National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Residual Effects of Abused Drugs on Behavior

101

U.S. Department of Health and Human Services • Public Health Service • National Institutes of Health

Residual Effects of Abused Drugs on Behavior

Editors:

John W. Spencer, Ph.D.
Division of Clinical Research
National Institute on Drug Abuse

John J. Boren, Ph.D.
Division of Clinical Research
National Institute on Drug Abuse

Research Monograph 101
1990

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402

Residual Effects of Abused Drugs on Behavior

ACKNOWLEDGMENT

This monograph is based on the papers and discussion from a technical review on "Residual Effects of Abused Drugs on Behavior: Clinical-Research Integration" held on February 23 and 24, 1989, in Rockville, MD. The review meeting was sponsored by the Office of Science and the Division of Clinical Research, National Institute on Drug Abuse.

DHHS publication number (ADM)90-1719
Printed 1990

NIDA Research Monographs are indexed in the *Index Medicus. They* are selectively included in the coverage of *American Statistics Index, BioSciences Information Service, Chemical Abstracts, Current Contents, Psychological Abstracts,* and *Psychopharmacology Abstracts.*

Contents

Preface

During the past decade, there has been a disturbing rise in the abuse of various addictive drugs. What has become increasingly clear is the complexity of use of substances such as methamphetamine, marijuana, phencyclidine, cocaine or crack, and alcohol; often two or more drugs are taken concurrently at high doses. Not only is the degree of possible toxicity poorly understood, but so are the residual central nervous system and behavioral effects following drug discontinuation.

Determining long-term drug effects is important if their possible adverse consequences to physical and mental functioning are to be fully understood. For example, the extent to which long-term drug use specifically impairs cognition, e.g., the ability to think and reason, or exacerbates a long-lasting psychiatric or dementialike disorder is either not known or the information is incomplete. The ramification of residual drug effects extends beyond the individual to include the family, various legal and educational institutions, and even newborn infants. Estimates of the financial costs of treatment and rehabilitation of indigent substance abusers as well as postnatal care given to babies born to addicted mothers are escalating yearly.

A technical review entitled “Residual Effects of Abused Drugs on Behavior: A Clinical-Research Integration” was held at the National Institute on Drug Abuse in Rockville, MD, on February 23 and 24, 1989. The two major goals were: (1) to evaluate the current state of knowledge on the residual effects of chronic substance abuse on behavior, and (2) to foster an interdisciplinary research effort to study and understand long-term drug effects by involving both laboratory researchers and clinicians.

The papers presented at this technical review form the basis for the present monograph.

John W. Spencer, Ph.D.
John J. Boren, Ph.D.

Clinical and Behavioral Pharmacology Branch
Division of Clinical Research
National Institute on Drug Abuse
Rockville, MD 20857

Why Evaluate for Residual Drug Effects

John W. Spencer

INTRODUCTION

If illegal drugs such as cocaine and crack, phencyclidine, marijuana, or methamphetamine are repeatedly abused for an indefinite period of time, are there long-lasting effects on behavior following discontinuation of use? Can either temporary or permanent brain damage or brain dysfunction be described? If some type of behavioral deficit does exist, can it be *directly* attributable to the use of the drug itself? Despite over 20 years of research, answers to these questions are either not known or are incomplete.

What has been described in the research literature is that following alcohol withdrawal and, to some extent, inhalant abuse, certain individuals may have a behavioral, cognitive impairment in the initiation and flexibility of thinking and reasoning, a loss in memory function, or both (Nathan, this volume). These longer lasting, persistent impairments in behavior extending beyond any detoxification period have been termed "residual effects." Studies that have attempted to establish whether residual effects exist for any illegal drug of abuse have been more equivocal (Reed and Grant, this volume).

The major points that will be described and developed in this chapter are that, following repeated abuse of any substance, it will first be necessary to evaluate and establish whether residual drug effects exist; then the careful profiling or classifying of residual effects into type, degree of severity, and duration of effect or recovery for a specific population (children, adults) can provide a directed focus of research into the consequences of long-term illegal drug usage.

STEPS IN CLINICAL EVALUATION

Clinically, it is important to describe the presence of any detrimental behavioral deficits following long-term substance abuse. The neuropsychologist is

often presented with assessment referrals that request evaluation of detoxified drug abusers. A major job is the thorough indexing of performance impairments. Data collected helps to describe behaviorally what tasks the individual can or cannot perform. It is useful to analyze both level and quality of performance. This information can reveal how deficient the client is when compared to a drug-nonabusing subject, as well as reflecting the degree of accuracy and speed on specific items. Areas that need to be measured include motor dexterity, sensory processing (visual, auditory, and tactile), reaction time, attention and concentration, language functioning and verbal reasoning, visual-spatial analysis and construction, verbal and nonverbal memory, and degree of abstraction, planning, and problem-solving skills. Many of these perceptual and cognitive functions overlap in the skills required for successful performance. Memory may involve both verbal stimuli and visual-spatial configurations and depend upon adequate sensory processing ability. Concentration deficits can impair the ability to reason, as well as the ability to make judgments. Motivational deficits also may contribute to impairment at all levels of functioning. As will be discussed later in this chapter, more specific types of neurobehavioral responses may need to be evaluated. Neuropsychological evaluations should not only help describe cognitive impairments but should also list performance strengths that are not adequately used by the abstinent substance abuser.

It is equally important to ascertain not only if drug abusers understand certain abstractions but if they can access this ability to function adaptively. For example, in addition to simply indexing cognitive performance deficits, the relationship of these deficits to practical, everyday life situations should be made. Schaffer and Parsons (1987) demonstrated that sober middle-aged alcoholics who initially learned to match each face of six men and six women with a given name and then were required to recall the name after the face was again presented were less accurate than age- and education-equated controls. These learning deficits suggest a type of impairment in current adaptive behavior as, in the same study, the face-naming test predicted significant positive correlations between task performance and therapist ratings for the clients on various components of treatment behavior and treatment benefit, e.g., ability to plan ahead. The Adaptive Skills Battery (ASB) may be another type of test that has some degree of clinical relevance to the evaluation of cognition in detoxified drug abusers. Responses are scored in terms of competency of coping skills in a variety of common situations in the workplace and in marital, peer, and social relations. The respondent records what he or she would do in a given situation and, second, records what the very best response or action would be. Patterson et al. (1988) showed that detoxified alcoholics produced lower competency scores than controls' scores in a "give your typical response" set; however, in "give your best response" set, alcoholics and nonalcoholics did not differ, suggesting that it is in the execution of the cognitive or problem-solving skills and not in the capacity for such skills that drug abusers have the

most difficulties. This interpretation was strengthened because there was no significant correlation between performance on impersonal neuropsychological tests, e.g., nonverbal conceptualization, and competency of responding on the ASB. Through the use of adaptive behavior tests, the residual effects of drugs on certain aspects of cognition, such as interpersonal problem solving, may be elucidated. This information may be used to begin to make more accurate predictions of success in treatment, likelihood of relapse, and quality of posttreatment competency.

RESEARCH NEEDS

In many clinical referrals, specific questions are often asked. For example, "Is there evidence of brain damage?" or "What is the prognosis?" The implied assumption is that long-term drug abuse either directly or indirectly alters brain functioning. Research indicates that alcohol abuse can result in a pattern of behavioral impairments suggestive of central nervous system (CNS) damage (Tarter et al., this volume). Alcoholics demonstrate a pattern of generalized cognitive impairments in the areas of concept formation, perceptual-motor performance, and complex learning. These deficits are thought to be related to a diffuse pattern of cortical impairment, although some investigators suggest that frontal-limbic circuits are more susceptible. Alcoholics also show a type of residual memory deficit that may become severe enough to produce Korsakoff's syndrome, which is thought to be related to a more diencephalic subcortical pathology. Additionally, the extent to which long-term drug abuse may potentially hasten a form of organic brain disorder such as dementia, while presently not understood, becomes a challenging research issue in the study of residual drug effects, as it has clinical-prognostic significance.

Separation of Effects

A related research issue is that if residual drug effects exist, performance testing procedures should describe and separate the transient from the longer term effects. This information has implications for accurately describing and predicting the clinical course of recovery and for interfacing assessment and treatment. Early in treatment, substance abusers may be cognitively impaired to the extent that information processing cannot be adequately performed. Repeated neuropsychological assessments can help describe the degree to which the patient's mental functioning is recovering, as well as measuring recovery in general. Longer lasting deficits, particularly those involving memory loss, need to be documented, and appropriate adjustments made in the treatment plan. For example, teaching new skills or alternative activities to replace impairments caused by the drug-taking behavior may not be as easy to accomplish if memory processes are not intact.

Developmental Effects. At present, there is no concentrated research effort describing and subsequently tracking performance deficits in children who have stopped abusing drugs. It would be useful to determine if any residual drug effects can be found in this population, because it is at this age that various components of cognition, including planning, evaluation, and abstracting skills, undergo major developmental changes. A need exists to present data concerning the possible deleterious effects of a specific drug or drug combinations that might occur at a particular developmental stage in the formation of intelligence, emotional functioning, or social functioning. This information might be of help in remediation programming. If it can be demonstrated, for example, that a particular drug has a long-lasting residual effect on a specific behavior such as learning, impulse control, or motor activity, the parent or teacher's early knowledge of this information may help in understanding the child's maladjustment or difficulty in coping.

Analysis of Subcomponents of Behavior. If residual drug effects can be found in drug-abstinent children or adolescents, it is then useful to evaluate the components of certain cognitive skills, such as types of memory deficits, that may provide important information concerning the ways drug-abstinent children differ from drug-nonabusing children. Of paramount importance is the complete description of types of specific performance errors. For example, brain-impaired individuals can have many cognitive memory deficits, but these failures may occur for different reasons. Korsakoff's patients have difficulty recognizing information (declarative memory) but can acquire new skills (procedural memory), whereas persons with Huntington's disease show a generalized impairment in memory but fail because of deficits in procedural learning rather than failures in recognition (Mat-tone et al. 1984). Oscar-Berman (this volume) provides additional descriptions of types of errors made by Korsakoff's patients. Further, information of specific learning deficits in drug-abusing children may help uncover potential differences between the maturing right and left hemispheres. Adult alcoholics have difficulty performing visual-spatial tasks, which are the hallmark of right hemisphere damage in patients with documented pathology of this brain area. Yet most research has provided little evidence of greater right- than left-hemisphere damage. It remains to be clarified whether drug-abstinent children, whose cortices are less mature, make the same types of errors that reflect a generalized brain dysfunction in adults.

Many subclinical or "soft" signs seen in abstinent drug abusers may be more readily demonstrated if specific tests or a standardized and computerized neuropsychological test battery were available. Traditional testing batteries such as the Halstead-Reitan or Luria-Nebraska, used primarily for brain-damaged individuals, may be insensitive to drug-induced impairments. Lucki and Rickels (1986) have demonstrated that psychometric tests such as symbol copying and digit span did not reveal any significant deficits in subjects who had been taking benzodiazepines (BZ) chronically for at least 5 years. A test that measures visual perception thresholds, critical flicker

fusion, did reveal significant changes in long-term BZ users. Ability-specific tests may be more useful than gross performance measures, which are not demanding and focused enough to detect impairments. What appears to be needed is the investigation of elementary components of complex behavior. Instead of evaluating logical memory and language by a simple recall of a story or sentences, Zurif (1980) suggested the use of a lexical decision task that breaks language down into separate functions. Another example of the reduction of behavioral components to help evaluate total performance can be seen in a model developed by Sternberg and Gardner (1983). Verbal analogies are solved in a stepwise progression that involves encoding, inferring, applying, comparing, justifying, and responding. This type of "componential analysis" of analogical reasoning can help describe specific processes that may be adversely affected by long-term drug abuse. Remediation can then be directed at these deficits and not at other processes that are functioning normally. A measurement process needs to be developed that begins at the sensory transduction level and terminates with motor output. Both capacity and efficiency of performance plus speed in responding should be described. Neurologically impaired patients can be accurate but very slow to process cognitive information. Whether this same relationship exists for drug abstinent patients remains to be clarified.

Individual Differences. Describing individual differences regarding the presence or absence of residual drug effects in children or adults may help explain why some individuals are especially vulnerable to developing substance abuse habits. Predrug-use measures that list the presence or absence of developmental delays, head injuries, attention deficits, minimal brain dysfunction, hyperactivity, as well as cognitive and learning disabilities, should be well documented. Neuropsychological deficits may reflect a long-standing weakness in a particular cognitive process rather than revealing the effects of only recent drug use on CNS functioning. The importance of such research design issues can be illustrated by the strong suggestion that individuals with childhood histories of hyperactivity or attention-deficit disorder are at increased risk for the development, later in life, of psychiatric illness, including the tendency to abuse drugs. Knop et al. (1985) have documented that sons of alcoholic fathers were reported by their teachers to experience a more disturbed school career and have poorer impulse control as well as deficient verbal proficiency. An understanding of predrug behavior, when available, can help substantially in interpreting residual drug effects.

Use of Animal Studies

Because of the complexities of interpretation of data in many clinical studies, animal models can be useful for testing hypotheses regarding residual drug effects on cognition or other neurobehavioral processes. Among the difficulties in evaluating human research has been relating long-term drug abuse to brain dysfunction, which then may cause cognitive

impairment (causal hypothesis) or in demonstrating that with increased drug use, performance impairments become correspondingly more severe (Parsons et al. 1986).

By controlling diet and preventing nutritional deficiencies, the direct toxic effects of repeatedly administered abused drug(s) on learning or performance studies in animals may be evaluated over a specific time course. Important variables such as drug dose, frequency and length of drug administration, as well as the effect of age or gender, can be partialed out and quantified in parametric studies. The repeated administration of drugs to animals over time provides for a controlled way to evaluate hypotheses relating to residual drug effects. Determination of the relevance to clinical studies remains an inherently difficult but necessary task.

CLINICAL EVALUATIONS' CONTRIBUTION TO RESEARCH

Finally, evaluation for the presence of subtle residual drug effects may help stimulate and develop a more comprehensive clinical and research methodology. As one example, Ciesielski et al. (1985) were able to show abnormalities in the visual evoked response of long-term substance abusers. The human evoked potential (EVP) is an electrophysiological measurement in which a sensory or cognitive signal "evokes" or stimulates a response that is detected from the scalp and presumably represents brain responsiveness to a stimulus. The EVP is reproduced as an averaged tracing with latency (stimulus onset to response) and amplitude (height of response) within a series of generated waveforms. Differences indexed in the Ciesielski study included decreases in the amplitude of N2-P3 potentials. Some lateralizing effect(s) were observed. Longer EVP latencies occurred over the right rather than left hemisphere. No significant abnormalities were observed for various psychometric tests, e.g., logical memory, visual reproduction, and visual short-term memory. This finding suggested to the authors that not only were the brain potentials a more sensitive indicator of cerebral impairment than were behavioral tests, but the finding might also indicate that brain dysfunction physiologically can precede observable behavioral impairment. However, the assumption made in this study was that the psychological tests used were valid for the behavior studied. Other tests evaluating for memory dysfunction might have revealed different results. Certainly, noninvasive techniques such as the EVP, sleep-stage electrophysiology, and autonomic measures of galvanic skin response, vagal responsiveness, and neuromuscular physiology (tremors, balance) may be useful as adjunct indicators for describing possible residual drug impairment. For example, Harbin (1985) has reported that a late positive component of the event-related cortical potential can be correlated with memory (exponentially decaying; long-term or recent) or response speed, two indicators of neurological status and possibly of long-term drug effects. Porjesz et al. (1987) have also shown that the EVP (P3) appears to be reduced in voltage in abstinent alcoholics but not controls, when the subjects were engaged in

tasks that measured attention. The suggestion was made that multiple system deficits were involved, including frontal or medial temporal lobe sites, proposed generators for P3 wave forms. Continued research needs to clarify whether these interpretations are correct and to document the clinical relevance of observed changes in the EVP during drug abstinence.

CONCLUSION

To summarize, it first needs to be established that residual effects do exist following long-term drug abuse. It also remains to be clarified whether long-term drug abuse produces irreversible brain damage or more subtle reversible brain dysfunction. By the careful analysis of various types of learning and performance strengths and weaknesses, treatment planning strategies may begin to be made. This is especially true in cases in which there is a dual diagnosis of a mental disorder coexisting with the substance abuse, e.g., schizophrenia, depression, or dementia. It is important to know how long-term drug abuse can produce symptoms similar to these disorders as well as how the disorders control the drug-taking habit. A better understanding of the long-term performance deficits *and* any psychiatric disability may help in formulating an appropriate followup and lessen the occurrence of drug relapse. The study for possible residual drug effects in children and adolescents may help describe the types of learning, social, and emotional problems they can be expected to have in school and in the home. In this population, any neuropsychological assessment should include tests that are valid and appropriate for each developmental stage. A challenge for future research is to develop a new technology for indexing subtle, subclinical deficits occurring as a result of long-term drug abuse. One critical variable that investigators will need to attend to is the degree to which predrug deficits may interact with or influence outcome in the evaluation for residual drug effects. Animal models may be especially useful and appropriate.

ORGANIZATION OF THE MONOGRAPH

In the remaining chapters of this monograph, both the methodological and clinical research studies investigating residual drug effects on behavior are discussed. All the studies reveal the presence of some form of residual drug effect on behavior. Mr. Reed and Dr. Grant provide a comprehensive review of neuropsychological studies devoted to analyzing residual drug effects focusing on the importance of valid and reliable measurements and appropriate research designs to index behavioral deficits. Of special interest is the tracking mechanism necessary to keep drug abusers in longitudinal studies. A method of evaluating animal behavior, using complex operant baselines, is suggested by Dr. Paule to be amenable to evaluating residual drug effects. Data are presented that show various response-recovery rates in animals previously exposed to certain drugs. Dr. Woody reviews the clinical manifestations of stimulant and opiate residual effects. Of interest

is the possible biological alteration in the endocrine system of opiate abusers and the corresponding changes in certain behavioral-affect rating scales. Dr. Howard reviews her clinical findings, which show that in a small group of black, disadvantaged women, abuse of phencyclidine has residual effects on adaptive behavior 12 to 24 months after discontinuation of drug use. The profound effect of phencyclidine used in conjunction with other drugs appears to also influence sensory, motor, and play behavior of infants born to these drug-abusing women. Dr. Block presents data that show that heavy marijuana use may have residual effects on certain language-mediated tasks. The design of this study includes a predrug measurement, a component lacking in many residual studies. Investigations concerned with residual effects of alcohol have been going on for 20 years. Researchers in this area have both knowledgeable and valuable contributions to make to the field of polydrug abuse. Chapters by Drs. Nathan, Tarter, and Oscar-Berman review the effects of long-term alcohol abuse on various social and cognitive tasks. Alcohol abuse may produce a neurotoxic effect involving the liver and vitamin E absorption, which may be partially responsible for observed cognitive deficits. Learning deficits in alcoholics are suggested to be related to a diffuse cortical damage, whereas memory deficits may be more related to subcortical damage. Dr. Pryor utilizes an animal model to demonstrate that behavioral measurements of grip strength, stride length and width, and foot splay can be used to evaluate the subtle residual effects of toluene in the rat. This finding shows how a drug that is thought to act in an area of the brain responsible for motor control does in fact impair motor behavior. Reporting on the residual effect of cocaine, Dr. Herning uses a combined information-processing and reaction-time paradigm with an electrophysiological measurement (event-related potential) to demonstrate subtle residual drug effects, and Dr. O'Malley reviews the clinical abstinence symptomatology of cocaine and presents neuropsychological data that reveal some mild impairments. Of interest is that the length of cocaine abstinence correlates with performance on tests that discriminated cocaine abusers from normals.

REFERENCES

Ciesielski, K.T.; Madden, J.S.; Bligh, J.G.; and Schopflocher, D. Long term brain impairment in chronic alcoholics: N2-P3 cognitive potentials in a template matching memory task. *Alcohol Alcohol* 20:903-408, 1985.

Harbin, T. The late positive component of the evoked cortical potential: Application to neurotoxicity testing. *Neurobehav Toxic Teratol* 7:345-350, 1985.

Knop, J.; Teasdale, T.; Schulsinger, F.; and Goodwin, D. A prospective study of young men at high risk for alcoholism: School behavior and achievement. *J Stud Alcohol* 46:273-278, 1985.

Lucki, I., and Rickels, K. The behavioral effects of benzodiazepines following long-term use. *Psychopharmacol Bull* 22(2):424-433, 1986.

Mat-tone, M.; Butters, N.; Payne, M.; Becker, J.T.; and Sax, D. Dissociations between skill learning and verbal recognition in amnesia and dementia. *Arch Neurol* 41:965-997, 1984.

Parsons, O.A., and Stevens, L. Previous alcohol intake and residual cognitive deficits in detoxified alcoholics and animals. *Alcohol Alcohol* 21(2):137-157, 1986.

Patterson, B.; Parsons, O.; Schaeffer, K.W.; and Errico, A.L. Interpersonal problem solving in alcoholics. *J Nerv Ment Dis* 176:707-713, 1988.

Potjesz, B.; Begleiter, H.; Bihari, B.; and Kissin, B. Event related brain potentials to high incentive stimuli in abstinent alcoholics. *Alcohol* 4(4):283-287, 1987.

Schaeffer, K.W., and Parsons, O. Learning impairment in alcoholics using an ecologically relevant test. *J Nerv Ment Dis* 175:213-218, 1987.

Sternberg, R.J., and Gardner, M.K. Unities in inductive reasoning. *J Exp Psycho1 [Gen]* 112:80-116, 1983.

Zurif, E. Language mechanisms: A neuropsychological perspective. *Am Sci* 68:350-361, 1980.

AUTHOR

John W. Spencer, Ph.D.
Division of Clinical Research
National Institute on Drug Abuse
Parklawn Building, Room 10A-
5600 Fishers Lane
Rockville, MD 20857

The Long-Term Neurobehavioral Consequences of Substance Abuse: Conceptual and Methodological Challenges for Future Research

Robert J. Reed and Igor Grant

INTRODUCTION

In this chapter, we discuss issues that need to be considered and directions that might be taken in the investigation of central nervous system (CNS) consequences of the long-term chronic abuse of psychoactive drugs. In so doing, we will consider the current status of work in this area, several conceptual issues influencing such work, theoretical models for understanding and guiding the development of sound research strategies, methodological issues important to the implementation of repeated measures designs, and some of the current neurodiagnostic methods that could be incorporated into future multidisciplinary research.

Overview

In the 1960s, there began the well-documented upsurge in the nonmedical use of pharmaceutical and nonpharmaceutical psychoactive chemicals, which has yet to abate, some 25 years later. In the early 1970s, a number of often contradictory reports began to appear in the literature describing the findings of neuropsychological (NP) investigations of marijuana and hallucinogen use. The appearance of these articles signalled a caution that one could not repeatedly expose the brain to psychoactive agents without ultimately paying a price. Simultaneously, the number of drug users whose preferred substances included the barbiturate and nonbarbiturate CNS depressants and stimulants began to increase. Prevalence of heroin abuse also escalated as many military personnel who were initially exposed to this drug in Vietnam came home and continued to seek out and use opiates. During this decade, it also became clear that the concept of the "pure" heroin

addict or the "pure" marijuana abuser was losing its validity, since the majority of substance abusers had begun to avail themselves of several different drugs; hence the term "polydrug user" (Wesson et al. 1978).

Toward the end of the 1970s, the Nation was beginning to experience the fallout from the large-scale introduction of cocaine into American society, as production and distribution centers in Central and South America became more sophisticated. The 1980s saw the advent of free-base cocaine and crack as well as the spread of human immunodeficiency virus (HIV) infection through the use and sharing of dirty needles by intravenous (IV) abusers of cocaine, heroin, and amphetamines. Thus, even the recent history of substance abuse has many eddies and currents.

In the following review of research on neurobehavioral consequences of substance abuse, especially the NP findings, we attempt to define the limits of our knowledge in this area and point out the problems in methods and measurement that have made interpretation of data difficult.

Current Status of Work in the Area

During the 1960s and 1970s, a number of studies on the CNS consequences of chronic substance abuse were completed. These were mainly NP investigations, the results of which have been summarized by Grant and Mohns (1975), Parsons and Farr (1981) Grant and Reed (1985), and Carlin (1986).

In brief, the best designed controlled studies of heavy marijuana use (Mendelson and Meyer 1972; Grant et al. 1973; Rubin and Comitas 1975; Miras and Fink 1972; Satz et al. 1976; Stefanis et al. 1977) found no indications that NP abilities were adversely affected. Other clinical studies and some case reports (Campbell et al. 1971; Kolansky and Moore 1971; Kolansky and Moore 1972; Soueif 1971; Wig and Varma 1977; Mendhiratta et al. 1978) repotted NP deficits and computed tomography (CT)-measured atrophy in cannabis users. Several of the latter studies were uncontrolled, however, or other clinical conditions were prevalent among their subjects, which could account for the reported dysfunction.

More recently, there have been indications that both acute and longer term dysfunction in attention, information processing, and memory may result from marijuana use (Belmore and Miller 1980; Wetzel et al. 1982; Block and Wittenbom 1984; Hooker and Jones 1987; Page et al. 1988). The report from Page and colleagues comes from a followup in Costa Rica of the study originally reported by Satz and associates (1976). In the earlier study, no significant differences were found to exist among Costa Rican nationals who had been smoking marijuana heavily for more than a decade on average and a group of nonusers matched for socioeconomic status. The followup, however, included both the previously used measures and a new set of tests designed to assess attention and concentration and the learning

and retrieval components of memory. Twenty-seven of the forty-one original users and 30 of 41 original nonusers were successfulIy reevaluated. Again, there were no between-group differences on the original NP measures and, perhaps more interestingly, there were no meaningful performance changes between first and second evaluations for either group. The using group, however, by then having histories of more than 25 years of heavy cannabis use, was uniformly and significantly more impaired on the new tests of attention, concentration, and memory. Page and colleagues note that, although these differences were real and significant, they were sufficiently subtle to have been classified as subclinical. Interestingly, users had worse social functioning in several areas. They tended to have less demanding jobs and were more likely to have spent time in prison.

Page and associates do not address the possibility that their cannabis-using group may have been exposed to greater drug-use- and drug-nonuse-related risks for NP deficit in the interval between the first and second NP evaluations. As it is frequently the case that U.S. alcoholics and drug abusers are exposed to greater neuromedical risk (head injury, loss of consciousness, nutritional deprivation, hepatic disease, chronic obstructive pulmonary disease) than are nonabusers, and as such events have been shown to explain a significant portion of the variance in NP test results in both alcoholics (Adams and Grant 1986) and polydrug abusers (Grant et al. 1978b), it is possible that the same confounds might have been operating in this Costa Rican sample.

Hooker and Jones (1987) administered a series of memory and information-processing measures to subjects in a counter-balanced double-blind crossover design. These subjects were males between 19 and 22 years of age and averaged 14.8 years of education, with a range from 13 to 17 years. In the year prior to the experiment, the subjects' marijuana experience ranged between once per month and once per week. Two subjects had a lifetime frequency of marijuana use of over 1,000 occasions. Subjects were tested after smoking either one active or one placebo marijuana cigarette. Second assessments were made 1 to 3 weeks later. Analyses indicated that acute marijuana intoxication was related to the more frequent appearance of intrusions in a delayed free-recall verbal-memory procedure and to poorer performance on the Stroop color-word interference test.

Although Hooker and colleagues did not focus in this study on residual deleterious effects of marijuana, it is possible that 6 of the 12 subjects (those who received active cannabis at baseline) actually could have demonstrated residual effects at followup. If indeed there were residual effects, differences between placebo and cannabis groups might be expected to attenuate or disappear at followup, resulting in a significant treatment-by-time interaction in repeated measures analyses. Such a result did not occur, thus there is a tentative indication that marijuana use will not have residual effects. This conclusion is not compelling, however, given that the distribution of values

for potentially confounding subject attributes, i.e., prior drug and alcohol use, educational achievement, and IQ, were not described for the marijuana-first and placebo-first groups. The facts that the subjects smoked only one marijuana cigarette during the experiment and that the sample was very small also limit our ability to form generalizable conclusions about residual effects.

Thus, although the best early work with marijuana suggested that it was a relatively innocuous agent from a neurological standpoint, the more recent data tentatively suggest that it may have both acute and residual effects on some abilities that generally were not assessed in the earlier studies. Data on residual effects remain inconclusive, however.

Phencyclidine (PCP) was first synthesized in 1956. Used and then abandoned as a surgical anesthetic in humans, PCP has also served as an experimental drug in producing model psychoses and as a veterinary tranquilizer. It first appeared as an illicit street drug in 1965 and, according to some national surveys, has been consumed by more than 8 million Americans (Young et al. 1987). Its application as a surgical anesthetic was marred by postoperative psychotic reactions and acute agitation. It has frequently been linked with violent behavior in clinical case reports and in the popular press, but Brecher and associates (1988) state that, in many of these reports, other factors that may relate to violent behavior, such as simultaneous intoxication from other substances, are not dealt with. They further suggest that little empirical data exist that support the putative link between this substance and violence. There is no denying, however, that persons acutely toxic on this agent can present with a host of bizarre symptoms.

Acutely intoxicated PCP abusers frequently demonstrate both the active (hallucinations, fixed delusions, paranoia) and passive (thought disorder, withdrawal, apathy, catatonia) symptoms of schizophrenia (Javitt 1987). French (1988) reported that chronic exposure to PCP among rats did not diminish the drug's ability to activate mesolimbic neurons, which are thought to be implicated in the etiology of schizophrenia. He speculates that this absence of a tolerance effect may partially underlie the biological mechanism by which chronic use of larger doses of PCP can lead to psychotomimetic symptoms. These recent findings and others suggest that PCP might provide a more encompassing chemical model for schizophrenia than do the hallucinogens or the amphetamines.

In early NP reports, PCP abusers demonstrated acute and postacute sensory and motor disabilities as well as anterograde amnesia (Davies 1961; Luby et al. 1959; Luisada 1978). PCP-using polydrug abusers appeared in one study to be more impaired neuropsychologically than polydrug users who did not use PCP (Ware 1978), while another study of similar design did not find significant differences (Carlin et al. 1979).

In sum, the residual effects of PCP are not understood. PCP must remain, however, high on the list of substances that might have long-lasting deleterious neurobehavioral effects; the severe acute and subacute (lasting days to weeks) behavioral disruption it is known to cause make this a plausible inference. Furthermore, PCP's lipophilic properties favor its remaining in the body for prolonged periods, thereby lengthening the potential for long-term toxic effects.

CNS depressants have been associated with postabstinence NP impairment that resembles the pattern seen among alcoholics (Adams et al. 1975; Judd and Grant 1975; Bergman et al. 1980; Grant et al. 1978a). Hendler and colleagues (1980) and Petursson and associates (1983) reported NP impairment in chronic benzodiazepine users on the Wechsler Adult Intelligence Scale, and Golombok and colleagues (1988) found impaired visual-spatial ability and impairment of sustained attention among British patients prescribed this same class of psychoactive agents for at least 1 year.

Bergman and associates reported, in a followup of their 1980 study (Bergman et al. 1989), that 30 of their original 55 sedative-hypnotic-abusing subjects showed slight but significant improvement in NP functioning 4 to 6 years later. These investigators partitioned their sample on the basis of relapse vs. abstinence during the interim. While both subgroups improved significantly on seven out of nine measures at the second evaluation, relapsed sedative-hypnotic abusers performed more poorly on a block design measure, on the Trailmaking Test, and on a measure of field dependence than did the abstinent subgroup. Interestingly, the relapsed group demonstrated greater improvement than the abstinent group on both the Trailmaking and the Witkin Rod and Frame Tests. Bergman and colleagues suggest that, because of the extremely poor scores obtained at baseline by the relapsers, they had more room for improvement at second testing. It is also possible that those who relapsed did so because they were impaired prior to onset of drug use. Comparisons made of the abusers' data, both at baseline and at followup, with socioeconomically matched normative data indicate that despite the pooled sample within-group improvement, the sedative-hypnotic abusers continued to demonstrate significant NP impairment 4 to 6 years after treatment.

Volatile substances are abused recreationally by a relatively small percentage of the population, but are of significant concern because many persons are at risk for their effects through contact with such substances as toluene, acrolein, n-hexane, and methylbutylketone in their occupations or through the increasing presence of these agents in the ambient environment. The research so far suggests that some of these substances, particularly toluene, can produce both neuropsychological and neuroradiological abnormalities (Arlien-Soborg et al. 1979; Bruhn et al. 1981); others, mostly the ketones, may cause peripheral neuropathy (see review by Grant and Reed 1985).

Animal models of addiction indicate that cocaine and the amphetamines produce more persistent drug-seeking behavior than does any other class of psychoactive chemical (Gawin and Ellinwood 1988). Thus, it is not surprising that stimulant addiction, to cocaine in particular, has grown rapidly. Despite this widespread exposure, little is known about long-term effects on brain function. Some very early studies and clinical case reports described vasculitis, necrotizing angitis, and cerebrovascular accidents in abusers of CNS stimulants (Citron et al. 1970; Weiss et al. 1970; Kane et al. 1969). Rylander (1972) suggested that disturbances in memory, concentration, and certain types of abstract thinking occurred as long-term sequelae of stimulant abuse, but there were no reports that spoke of stimulant toxicity manifesting as NP impairment following abstinence. Grant and associates (1978a), for example, found no association between use of CNS stimulants and NP performance in their sample of 151 polydrug abusers.

On the other hand, human and animal neuropharmacologic studies raise concerns that there may be irreversible CNS effects of stimulant abuse. For example, long-term administration of stimulants to animals indicates that there is depression in the mesolimbic and mesofrontal cortical reward systems of the brain. This depression might correspond to the anhedonia demonstrated during withdrawal in humans (Colpaert et al. 1979; Leith and Barrett 1976; Kokkinidis and Zacharko 1980). A stimulant-induced supersensitivity of the inhibitory autoreceptors on the dopamine (DA) neuron has been suggested as the primary neurophysiologic substrate of cocaine withdrawal (Gawin and Ellinwood 1988).

As yet, however, it has not been conclusively shown that there is a long-term or permanent impairment of ability to experience reward because of chronic perturbation of the dopaminergic system through stimulant abuse. There is evidence in the animal literature that amphetamine is neurotoxic if elevated brain levels are sustained for very long. This toxicity can result in histopathological and neurochemical changes, including degeneration of nigrostriatal presynaptic DA terminals and striatal DA depletion. Postsynaptic neurons appear to be affected by repeated and sustained exposure to amphetamine as well (Robinson and Becker 1986). In some animals, notably the cat, DA depletion can persist for up to a year following as few as three injections (Levine et al. 1980). The issue of whether amphetamines or cocaine effectively reduce the number of pre- and postsynaptic DA receptors is a controversial one (see Robinson and Becker 1986 for a comprehensive review of this area). But, if long-term or permanent changes in the dopaminergic system are a consequence of amphetamine abuse, these changes could lead to NP and information-processing impairments and to decreased social and occupational functioning, via decreased ability to anticipate rewards.

Although some early investigations found NP dysfunction in hallucinogen abusers, other investigations did not (Cohen and Edwards 1969; McGlothlin

et al. 1969; Acord 1972; Wright and Hogan 1972; Acord and Barker 1973). These early lysergic acid diethylamide (LSD) studies were compromised in many ways (small sample sixes; absence of, mismatched, or inappropriate control groups; uninterpretable or unreported drug consumption metrics; use of poorly understood, possibly invalid measurement instruments; and failure to estimate premorbid ability level of participants). But these contradictory and unreliable findings, combined with the Collaborative Neuropsychological Study of Polydrug Users' (CNSP) failure to find a relationship between reported hallucinogen use and CNS deficit, suggest that deficit, if it exists, is more subtle than can be assessed by existing NP measures.

The recreational use of inhalants such as amyl and butyl nitrite has become more common in the last decade. We are not aware of any data to suggest direct neurotoxicity associated with the abuse of these substances. The use of these agents to facilitate sexual enjoyment is commonly acknowledged in gay subpopulations. HIV infection is prevalent among homosexual men, and AIDS-related dementia occurs in a smaller subset of these persons. It is not clear whether the nitrites play any role in facilitating CNS complications in such groups.

Opiates have been studied neuropsychologically since 1974, when Fields and Fullerton first reported an absence of Halstead Reitan Battery (HRB) performance differences in groups of heroin addicts and medical controls. In a report by Grant and colleagues (1978a), polydrug users who reported using a relatively greater amount of opiates, including heroin, opium, and synthetic narcotics, were more likely to be judged impaired on clinical NP evaluation than polydrug users who used relatively little of this class of drug. Thus these two early studies present conflicting information on the effect of opiates on CNS function. Hill and Mikhael's 1979 report of a 40-percent impairment rate in a small sample of heroin abusers came from a controlled study as well, but did not resolve the issue because of failure to include data on length of abstinence in the heroin abusers. Rounsaville and associates (1980) compared NP functions in heroin addicts and epileptics. Eighty percent of the addicts and 86 percent of the epileptics were classified as impaired, but 43 percent of the heroin addicts had abused significant levels of other drugs, including alcohol and cocaine. In the end, these results were also confounded by the fact that only 20 of the 72 addicts were drug free at the time of testing. In a continuation of this investigation (Rounsaville et al. 1982), the same sample of heroin addicts was compared with Comprehensive Employee Training Act (CETA) employees: essentially no differences were found except that heroin abusers performed better than the controls on simple motor tasks. The fact that both groups performed in the mildly impaired range suggests that other factors (e.g., educational deprivation) needed to be considered in assessing these NP data. More recently, Guerra and associates (1987) assessed attention, memory, and verbal fluency in a controlled, repeated-measures investigation of NP performance in 93 opiate-dependent individuals. Testing was accomplished prior to and

following a l-week detoxification. Initially, the performance of the opiate abusers was significantly more impaired than that of the socioeconomically matched controls. At followup, the opiate addicts showed significant improvement relative to their first testing and, when compared again with the first evaluation data obtained from controls, were not significantly different. Since the controls were not retested, however, it is not possible to discern whether the observed recovery was due to practice effects, to the controlled withdrawal from narcotics, or to some interaction of the two.

In summary, this brief review indicates that a moderately large body of data has been collected and reported over the past two decades on the relationship between chronic drug abuse and brain disorder. In spite of some excellent efforts, relatively little is known about long-term NP effects that goes beyond the facts of acute intoxication and withdrawal. Much of what is known is tentative and confounded by a host of factors that, if not addressed in future neurodiagnostic investigations, will leave us in the same position two decades hence. Bearing this in mind, in the next section we discuss several conceptual issues central to fostering more definitive results in the future.

CONCEPTUAL ISSUES

Defining CNS Effects: The Notion of Neurobehavioral Phenomena

The alterations that psychoactive drugs can produce can be appreciated, at least theoretically, at several levels of abstraction. At the most basic level, there will be biochemical and macromolecular changes, some evanescent, some more lasting. Some of these changes might translate into reversible (loss of dendritic spines; fluid shifts; inflammatory changes; demyelination) or irreversible (cell loss) structural damage. At the macro level there may be neurological, cognitive, affective, and behavioral alterations, both reversible and irreversible.

Methods for detecting these events are many. When animal models are used, increasingly precise information can be obtained in the living organism, as, for example, the relating of single-cell recordings, or samplings of neurotransmitter products from selected brain regions in behaving, drug-treated animals (Kuczenski and Segal 1989). Such designs move beyond correlations of antemortem behavior and postmortem neuroanatomy, towards simultaneous, *in vivo* observations of behavioral and neurophysiological changes produced by various psychoactive drugs.

With living human beings, such elegant but invasive “brain-behavior” correlative experiments are obviously infeasible. Therefore, we can only infer CNS effects through indirect measures. Until recently, NP testing, which samples behavior thought to be particularly dependent on CNS integrity, represented the most sensitive noninvasive approach to detecting brain

dysfunction. With the advent of advanced electrophysiological techniques, e.g., brain electrical activity mapping (BEAM) and functional neuroradiological methods, e.g., positron emission tomography (PET); single photon emission computed tomography (SPECT), it becomes possible to study physicochemical brain changes *in vivo*, and to relate these to behavior. These techniques permit the term "neurobehavioral" to embrace drug-related CNS phenomena that might be observed from multiple vantage points, including the neurologic, psychiatric, radiologic, electrophysiologic, and neuropsychologic.

The Natural History Concept as a Guiding Frame of Reference

In medicine, the temporal evolution of a pathologic phenomenon is known as its natural history. Although the notion that drug-associated neurobehavioral phenomena occur in the context of a natural history is implicit in most research, the failure to address this concept explicitly has led in the past to erroneous (or premature) conclusions regarding issues such as the supposed "safety" of an agent, or, alternatively, its permanent toxicity. We think that the design of future research in this area will be better served by a conscious and accurate understanding of what is known of the natural history of drug-related brain disorder.

Several years ago we proposed a general model in time-line format for the natural history of brain disorder as related to alcohol and drug abuse (figure 1) (Grant et al. 1980). In this model, the basic epochs of the phenomenon include, in order, a prenatal period, a preexposure period (birth to first exposure), a latent period, an occult period, a preclinical period, and a clinical period. These six periods are bracketed by conception and death. During both the prenatal and preexposure periods, the model presumes the individual is both healthy and developmentally normal.

The latent period begins at the time of first exposure to the toxic substance. Between this first exposure and the observation of the first clinical neurobehavioral signs, the first neurotoxic event occurs (destruction of dopaminergic cells or microinfarcts following amphetamine use). This first toxic event may occur sooner or later following initiation of use depending on (1) the toxicity of the substance and (2) the relative amount consumed over time. Theoretically it is possible that this prodromal (latent, occult, and preclinical) period could extend indefinitely if a very mildly toxic substance were used infrequently by the healthy individual, i.e., having no predisposing risk or vulnerability.

Viewing the previously reviewed substance abuse literature in the context of the natural history model points out that most of what we know now relates only to the short-term effects of drug abuse, i.e., to drug effects on brain function during acute intoxication, during the period directly following cessation of use (abstinence), and during the immediate postabstinence phase. Only with respect to alcoholism have we even begun to appreciate the

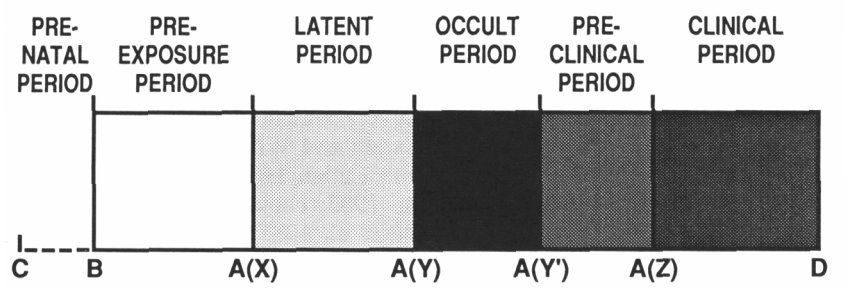

FIGURE 1. *Model for the natural history of neurotoxin-induced brain disorder*

KEY: C=conception; B=birth; A(X)=age at first exposure to drug; A(Y)=age at which first irreversible neuronal changes begin; A(Y')=age at first positive findings on mast sensitive test; A(Z)=age at first clinical signs; and D=death.

complexities of long-term effects. Even with alcoholism, much of what has been reported has come from cross-sectional rather than longitudinal investigations or from a few followup studies from which it may be premature to generalize.

Without such prospective studies, guided by a natural history framework, we shall fail to develop information that can be ordered in time, an essential prerequisite to the testing of causal models.

Reversible and Irreversible Deficits

The natural history model (figure 1) was made intentionally simple for didactic purposes. For instance, it permitted no recovery from CNS-related substance abuse effects. However, recent studies on the NP sequelae of alcoholism indicate that there is recovery of some NP function in some alcoholics with continuing abstinence (abstinence beyond a few weeks). We have observed that long-term (minimum 18 months) abstinent alcoholics do not differ on most NP measures from age- and education-matched controls and that such long-term abstainers are significantly less impaired than recently detoxified alcoholics (Grant et al. 1979; Grant et al. 1984). These cross-sectional studies are supported by more recent longitudinal data. On 2-year followup evaluation of a sample divided into four groups (continuing alcoholic drinkers, short- and long-term sober alcoholics, and controls), continuing drinkers were rated as neuropsychologically worse more often than was the short-term sober group. In the short-term sober group, 16 percent were rated as improved, while in the continuing drinker group, only 9 percent were so rated. Interestingly, 19 percent of the long-term sober group (abstinent by then a minimum of 4 years) showed significant improvement.

Such data raise the possibility of very long-term, slow recovery (Grant et al. 1987).

Other reports of NP and CT-measured recovery among abstinent alcoholics (Adams et al. 1980; Carlen et al. 1978; Carlen and Wilkinson 1980, Wilkinson and Carlen 1980a; Wilkinson and Carlen 1980b; Wilkinson and Carlen 1983; Wilkinson 1987; Brandt et al. 1983; Fabian and Parsons 1983; Goldman 1983a; Goldman 1983b; Goldman et al. 1985; Grant et al. 1986; Grant 1987) and the hint that NP recovery may occur among polydrug users who maintain abstinence (Grant et al. 1978a) suggest that longer term recovery may occur for substance abusers as well. These data indicate that the simple natural history time line originally proposed needs refinement. Through that refinement process we can determine whether recovery may be total partial permanent, or temporary.

A Proposed Nosology for Subclinical and Reversible Neurobehavioral Disorders Associated with Substance Abuse

The cross-sectional and, especially, the longitudinal data on NP recovery in alcoholism reviewed above indicate that at least some neurobehavioral disturbance is slowly reversible. Since there is no nomenclature in the Diagnostic and Statistical Manual for Mental Disorders (DSM III-R) (American Psychiatric Association 1987) under which these phenomena are described, we have proposed for future revisions (DSM IV) criteria along the lines shown in tables 1 and 2. These criteria, first presented for alcoholism in Grant et al. (1986) and Grant et al. (1987), will permit the diagnosis of intermediate duration (slowly reversible) neurobehavioral disorders associated with substance abuse. Additionally, since some substance-abuse-related CNS disorders may never reverse fully, yet may stop short of major impairment typified by the label "dementia," we recommend a category of subclinical or subsyndromal neurobehavioral disorder (table 3).

Premorbid Status of Substance Abusers

Do persons who become substance abusers, whether of alcohol or other psychoactive drugs, come from a subsample of the population that would appear neurobehaviorally abnormal if examined before they were exposed to the drug? To answer this question would require prospective longitudinal studies that begin data collection in at-risk samples before substance abuse begins.

Most neurodiagnostic studies on substance abuse have been cross-sectionally organized. In cross-sectional NP studies in which premorbid status is thought to be important but not concurrently evolving, it has been typical to rely on markers such as educational achievement or history of early childhood risk factors in an attempt to control for these influences. Markers such as these are better than none at all. These retrospectively obtained

TABLE 1. *Diagnostic criteria for intermediate-duration neurobehavioral disorder associated with substance abuse*

Presumptive Diagnosis

1. Neurobehavioral disorder is evident following prolonged heavy ingestion of the substance.
2. Disorder is evident as early as the first week of abstinence and persists for months or even several years after cessation of substance ingestion.
3. Disorder is not due to other causes of slowly reversible organic mental disorder (for example, head injury, hypothyroidism).
4. The severity and features of the disorder do not meet the criteria for delirium or dementia.

Definitive Diagnosis

1. Repeated evaluations show improvement in neurobehavioral disorder related to abstinence or reduced consumption.

SOURCE: Grant et al. 1986, copyright 1986, American Psychiatric Association.

TABLE 2. *Definition of neurobehavioral disorder*

A. Subjective sense of reduced intellectual acuity or capacity (more difficult to learn new things, remember, handle more complex information) or observations by significant others that the individual is more forgetful or has shown other evidence of intellectual decline.

B. One of the following objective signs:

   1. Neurocognitive deficit (abstracting ability, perceptual motor skills, memory below expectations for age- and education-matched controls) observed on structured neuropsychiatric exam or neuropsychological testing.

   2. Laboratory evidence of structural or functional brain abnormality indicated by one or more of the following:

      a. computed-tomographic or magnetic-resonance-scan evidence of abnormally widened sulci or ventricular dilatation compared with age-matched norms;

      b. electroencephalographic evidence of diffuse disturbance (slowing of alpha, increase of theta activity); and

      c. abnormalities on dynamic brain imaging (PET, SPECT) compared to age-, education-, and sex-matched norms.

SOURCE: Grant et al. 1986. copyright 1986. American Psychiatric Association.

TABLE 3. *Diagnostic criteria for subclinical neurobehavioral disorder associated with substance abuse*

Presumptive Diagnosis

1. Neurobehavioral disorder is evident following prolonged heavy consumption of the substance.
2. Disorder is evident a minimum of 1 year after cessation of consumption.
3. Disorder is not due to other causes of subclinical dementia (late sequelae of head injury, permanent effects of hypothyroidism).
4. The severity and features of the disorder do not meet the criteria for delirium or dementia.

Definitive Diagnosis

1. Repeated evaluation shows no significant improvement in neurobehavioral disorder in relation to continuous abstinence beyond 1 year.

SOURCE: Grant et al. 1986, copyright 1986, American Psychiatric Association.

predictors, however, probably cannot have the validity of concurrently witnessed events.

Thus, in spite of the significant financial and operational challenges, the birth to earth (more practically, midchildhood to early adulthood) prospective study of persons at risk for substance abuse offers the most convincing means to answer questions important to the natural history of brain disorder as it relates to abuse. Key questions related to the predrug-use status of such individuals, such as whether drug abuse causes brain damage, or brain damage causes drug abuse, which have obscured the conclusions of earlier studies, could be answered directly. Even though prospective designs would be difficult to implement, it is worth the effort to attempt them. The determination of outcomes for different patterns of substance abuse, while accounting for coexisting factors known to influence brain function, is of inestimable importance to the development of treatment and prevention.

MEASUREMENT CONSIDERATIONS

Useful, important, and scientifically well-founded theories cannot be evaluated properly when basic measurement factors, on which evaluation of such theories depends, are ignored. Research on the neuropsychology of substance abuse has sometimes suffered from insufficient concern for the basic psychometric principles of validity, reliability, sensitivity, and specificity.

Although many readers will be well versed in these matters, a brief reminder of these concepts may be useful.

Validity

For our purposes, neurobehavioral strategies chosen to investigate CNS effects of drugs should demonstrate three forms of validity. First, the procedure should have construct validity, that is, it should be known to measure the ability or property it is thought to measure. For example, the Minnesota Multiphasic Personality Inventory (MMPI), which might validly reflect certain aspects of personality, is not a valid measure of attention, memory, or other NP abilities. Similarly, digit span, though an NP test, is not a test of memory in the usual sense of the word, since performance on digit span tends to be unrelated to performance on traditional tests of memory; furthermore, patients with amnesia tend to perform reasonably well on digit span.

Second, procedures should also have concurrent validity. If NP tests are used to infer brain damage, then performance on such tests should correlate with other, nonpsychometric indicators of brain damage, e.g., other behavioral measures, neurologic examinations or neuroradiologic findings. This requirement puts constraints on the overly enthusiastic use of new and theoretically interesting applications. For example, computer-assisted performance measures might have appeal in developing theories of information processing. But until they are shown to have concurrent validity, their use as the sole indicator of CNS disturbance in substance abuse research would be ill-advised.

Third, the neurobehavioral techniques should have predictive validity. The term predictive validity has been used in several ways, sometimes with connotations resembling concurrent validity. For this discussion, we prefer to limit this concept to temporal prediction, that is, the method in question should be capable of predicting a neurobehaviorally relevant outcome. For example, poor performance on certain very sensitive NP tests may occur in the absence of other indicators of CNS disturbance at a particular point in time. If the test is valid, however, then continued exposure to the same toxic influence should lead ultimately to abnormality on other indicators, behavioral, electrophysiologic, or radiologic.

Reliability

Since it is through longitudinal repeated-measures studies that the residual effects of chronic drug abuse on brain function will be best illuminated, it is necessary to consider measurement reliability before choosing instruments for assessment. Reliability in this case refers to a test's consistency or correlation with itself. Internal reliability refers to the degree to which the scores for any randomly selected subset of a test's items would correlate

with the score obtained for all the items. Stability, or "test-retest" reliability, refers to the degree to which scores obtained on the same test over a specified period of time correlate with one another.

High test reliability-stability does not guarantee that a test will be valid, but low reliability-stability does guarantee low test validity. In general, test-retest reliability decreases as a function of the interval between testings and increases between early adolescence and adulthood as CNS development reaches asymptote. Although it is important to consider inter-item reliability when selecting instruments for research purposes, it is test stability that is more relevant in the context of repeated-measures research in substance abuse.

It is important that the time-related variability in performance on a test be well understood before the test is employed in repeated-measures fashion. It is not necessary to select measures that do not vary from one point in time to another, all other factors being equal (most NP tests are subject to learning by persons who are not afflicted with rapidly progressive degenerative diseases of the CNS or subject to other significant trauma between assessments). It is necessary, however, to understand a test's properties with respect to a subject's ability to learn strategies and tactics for succeeding at it, after repeated exposures. Repeat performances on tests that are vulnerable to learning are interpretable, but only by taking into account the expected learning curve.

In repeated-measures studies in which it is desirable to minimize learning and for which the interest interval is relatively short, alternative forms can be used to manage the learning curve, so that the specifics of a test are manipulated but not the strategic concept. Needless to say, alternate forms must be highly intercorrelated with one another to maintain a clear concept of what is being measured.

One might also choose a learning saturation model, in which the same or highly correlated alternate forms are readministered frequently enough at baseline to bring the learning curve to asymptote before treatment is implemented. If alternate forms are used, scores when asymptote is achieved must leave room for improvement as a function of treatment (recovery). Despite such precautions, we find that "practice effect" remains a formidable issue; in one experiment, we noted an effect for time even after a dozen administrations of a brief battery of tests containing alternate forms over an 8-week assessment (Huey et al., unpublished data).

Sensitivity and Specificity

The usefulness of valid measures will be circumscribed by their ability to detect both strong and weak signals (sensitivity) and to detect only those signals that are relevant, ignoring "noise" (specificity). Tests that are highly

sensitive will correctly identify brain dysfunction in most persons who have it but will, to varying degrees, produce false alarms. Highly specific tests, which trade off sensitivity for accuracy, may produce misses.

In neuropsychology, sensitivity and specificity are influenced by test difficulty and complexity. Difficulty refers to the demand placed on information processing of a specific type. For example, one can have hard and easy motor tests, span tests, and discrimination tests. More difficult tests can be sensitive to subtle dysfunction, but may be less specific.

Complexity refers to the variety of information, or information-processing strategies, that must be deployed. A problem-solving test, such as the Category test from the HRB is one example. Greater complexity can correlate positively with higher sensitivity and negatively with specificity. That is, sensitive tests generally measure abilities that are highly multidetermined, in the sense that successful performance may require the coordination of several more or less complex mental operations, which in turn may depend upon the neurobiological resources of several different loci in the brain. Specific tests often measure more discrete abilities, which are in turn often more highly localizable in the brain.

General Vs. Specific Indicators

Some NP tests, usually those with high complexity, can be seen to be "general" indicators of cerebral dysfunction, in the sense that virtually any form of brain disease, be it generalized or localized, will be reflected in poorer performance. The Category test is a case in point. Few truly brain-damaged persons score well on this test. Tests that are more specific, for example, word fluency, will tend to reflect left anterior frontal lobe function and can be normal in brain pathology that does not involve that region.

There is obviously room in the field for the employment of both sensitive and specific measures, provided that their respective propensities toward false positive and false negative classification are taken into account. We would argue, however, that our knowledge regarding the NP consequences of the abuse of many classes of drugs is relatively limited at this point. Therefore, we think the field would profit most at the outset from the employment of sensitive tests that can provide broad parametric coverage across a wide spectrum of intellectual abilities.

Normative Samples

Except for test development per se, tests with known psychometric properties, i.e., tests that have proven criterion and predictive validity and demonstrated reliability across time (for repeated-measures designs) are preferable to inventing new tests or employing unstudied variations of existing measures. Adopting well-studied measures, for which age- and

education-stratified normative data exist, makes sense even when studies include separately enrolled control groups or when study subjects are used as their own controls. The existence of norms for behavioral tests allows the investigator to account for important sources of variation in performance while affording better opportunities for cross-study comparisons.

Selection of tests and test batteries will depend upon the research questions to be answered. To diagnose and describe the features of adaptive change related to drug abuse, a battery that provides broad parametric coverage is needed. For some hypotheses, however, such as in studies of short-term memory and learning, this approach may be inappropriate.

Among NP measures, the HRB and the Luria-Nebraska, although not the only normed test batteries in existence, are probably the two most frequently employed in a variety of clinical research settings. The facts that the HRB subtest scores have been normed in the past decade (Heaton et al. 1986; Filley et al. 1989; Braff et al., in press), that its whole set of scores can be rated clinically by trained neuropsychologists (Heaton et al. 1981; Grant et al. 1978b; Grant et al. 1979; Grant et al. 1982), and that it provides, in the form of the expanded HRB (Grant et al. 1987), coverage of the spectrum of NP abilities recommend its use. The HRB takes from 5 to 8 hours to administer completely, and this has been seen as a shortcoming because of concerns about fatigue. We think that subject stress and time of administration, not to mention increased costs related to increased staff labor, are valid concerns. However, through an appropriate division of testing sessions into smaller time blocks, the full HRB has been used without incident even in severely ill COPD patients (Grant et al. 1982), as well as by multiple drug users (Grant et al. 1978b). The lengthy time it takes to complete the expanded HRB is offset by the richness of the data it provides, as well as by its common use in many distinct clinical samples. Comparability across clinical samples is a highly desirable outcome, which has been achieved too infrequently. When accomplished, however, information can be obtained on brain-behavior relationships, which may be difficult for any one study to accomplish. Grant et al. (1987) describes results from merging of HRB data taken from two multicenter studies.

Standardized Methods of Administration

Another consideration related to the selection of measures is the notion of standardized methods of administration. A test can be valid, reliable, and sensitive; but if it is administered in a nonstandard manner, the resultant scores will reflect variance unrelated to the subject's ability, thereby confounding interpretation.

A simple examiner-provided prompt during the delayed recall of previously learned information can change a free-recall memory paradigm into a recognition paradigm, which tends to be easier than the free recall of

information. The speed at which the pages are turned in the booklet version of the Category test can drastically change the number of correct responses and fail to reflect the subject's true abstracting ability.

Choosing appropriate tests and assuring their reliable administration can be challenging to any single laboratory; multicenter studies face the additional difficulty of establishing interlaboratory reliability. One valuable precaution, employed in several large multicenter studies (the CNSP, the Nocturnal Oxygen Therapy Trial, and the Diabetes Control and Complications Trial) involved the centralized training of neuropsychometrists at the outset. To maintain consistency, senior neuropsychometrists from coordinating centers periodically performed site visits at each data collection center to observe actual testing and to critique examiners. In this way, standardized methods were established and maintained over the course of the investigations. In the future, similar vigilance will be required to establish confidence in our knowledge of cognitive functioning in substance abusers. It will be difficult to achieve such confidence if different investigators, apparently using the same tests, turn out to have used different methods of administration or interpretation.

These psychometric considerations are of obvious but often insufficiently acknowledged importance. Decisions regarding whether to fund future proposals in substance abuse research should in part be based on the degree of soundness of the psychometric foundations of the measures proposed, as well as on the commitment by investigators to follow standardized methods of administration.

CONFOUNDS AND COFACTORS NOT RELATED TO MEASUREMENT

Figure 2 is a structural model depicting some of the factors that neuropsychologists have wme to understand during the past 30 years as having influence on NP performance at any point in a subject's lifetime (Grant 1987). The influence of some of these factors has been demonstrated empirically, e.g., age and education. Others are as yet only theoretically associated with brain-behavior relationships, e.g., "constitution," genetic endowment. In this model, influences on NP function are multiple, complex, and interactive; any investigation, regardless of design or of clinical population studied, must control for or at least consider these factors, if results from such studies are to be unambiguous.

Some factors that will need to be taken into consideration in future research are demographic in nature, some ate related to the metrics utilized to express drug consumption, and some are associated with unique characteristics of substance-abusing populations.

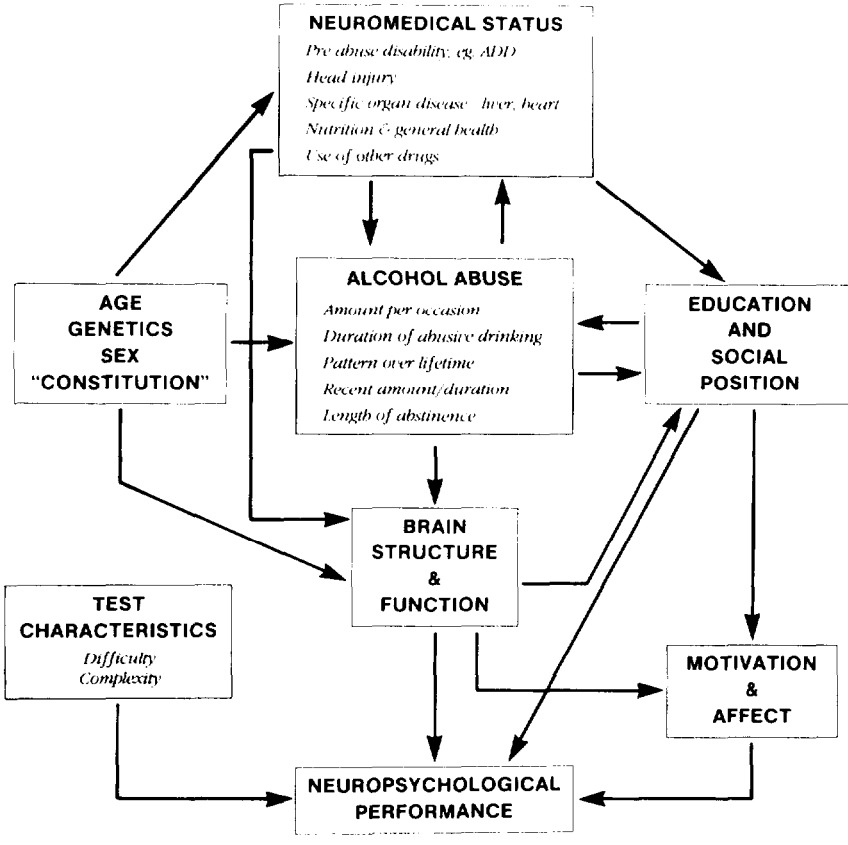

FIGURE 2. *Variables to consider in any causal model of alcohol-associated neuropsychological deficit*

Age and Education

Empirical evidence shows that the demographic variables of age and education are, by themselves, strongly predictive of NP performance (Finlayson et al. 1977; Parsons and Prigatano 1978; Heaton et al. 1986, Filley et al. 1989). Thus, to the extent possible, we must control for these factors in research. Age and educational status of individuals are also likely to influence whether or not they abuse alcohol or other substances, and at what level. -l-he existence and level of substance abuse may in turn affect educational achievement and social position, if the abuse begins early enough. The point is that, while both demographics and substance abuse are related to NP performance, they are also related to each other, and therefore may

relate to NP status directly, indirectly, or interactively, in fairly complex ways.

The problem of controlling for age or education is not one that is generally solvable through after-the-fact statistical manipulation. In some earlier controlled studies of alcoholism, in which nonalcoholics were better educated than alcoholic subjects, analysis of covariance (ANCOVA) was employed in an attempt to rectify the case-control mismatch. The problems here were, first, that the strict assumptions underlying the appropriate use of the ANCOVA procedure were sometimes violated; and, second, that ANCOVA often undercorrects, so that persisting group differences might still be a function of the wvariate (Adams et al. 1985). An additional complication arises because the true meaning of the wvariate score, especially in the case of education, may be complex. For instance, are subjects poorly educated because of (a) attendance at poor schools, (b) lack of financial support for college, (c) absence of opportunity, (d) poor adult models, (e) poor native intellectual endowment, or (f) early brain insults (Adams et al. 1985)? There are other cautions for the application of statistical control, but they amount to an admonition that preexisting study and control group differences along these demographic dimensions are to be avoided.

Multiple Substance Abuse

In Grant and colleagues' 1978a study of 151 polydrug abusers, correlations of .3 and above were found for 11 of 15 possible pairs of substance classes. This indicated that a significant portion of the sample did indeed use more than one drug at abuse levels. While this is not surprising, given that multiple substance abusers constituted the target population, similar findings were noted in a group of medical students whose intensity of drug use was much lower-i.e., with the possible exception of use of alcohol and marijuana, those who indicated experience with any other single drug tended to have experience with numerous other drugs (Rochford et al. 1977). More recent investigations of the prevalence of multiple vs. single drug abuse continue to show that most drug abusers employ more than one substance (Mehrabian and Straubinger 1989; Rainone et al. 1987). This means that, in efforts to understand the neurobehavioral consequences of a particular drug, researchers must be prepared to contend with the additive or interactive effects of other substances. Data must be gathered in a manner conducive to effective use of multivariate approaches.

Quantitation of Drug Use

Multivariate assessment works best with interval or continuous data derived from estimates of consumption levels that yield nontrivial distributions. To collect such data, studies need to use structured-interview questionnaires administered by trained personnel. The collection of categorical data on drug use (yes-no or low, moderate, or heavy) is a less satisfactory

alternative for several reasons. For one thing, the meaning of such classification within, as well as between, studies is usually obscure. In past reports, alcohol use, for example, has been described categorically; i.e., subjects are designated as heavy, moderate, light, or social drinkers. If these terms are not operationally defined, e.g., grams or ounces of ethanol consumed in a specified time period, then it becomes difficult to determine potential dose-effect or quantity-frequency relationships within the study and difficult to compare findings from different studies.

Whereas yes-no responses can be useful as classification factors in multivariate statistical procedures, they cannot legitimately serve as dependent variables in the analysis of variance model, because they are not continuous. Using a yes-no response to create types or subtypes has its place in substance abuse research, but for questions relating to the dose-effect relationship, such lower order data can only create additional cells and increase degrees of freedom. The often impractical solution to this problem is enrollment of larger numbers of subjects. Finally, lower order categorical and ordinal data can always be derived from higher order continuous data, while the reverse is not true.

Attempting to quantitate consumption from the outset is a better choice even if it represents only an imperfect estimate of consumption. Clearly, error will be introduced by forgetting (heightened by drug-induced acute or chronic cognitive deficit) or motivated distortion. Nevertheless, reports by alcoholics of their wnsumption indicate that such estimates can be reasonably accurate (Fine et al. 1978; Maisto et al. 1979; Sobel and Sobel 1978; Rohan 1976). The value of the quantitative approach has also been underscored by successful cross-study comparisons in the alcohol literature (Adams et al. 1981).

To keep the number of cells in multivariate statistical procedures to a manageable minimum, use of many specific abusable agents can be reduced through a table of equivalencies into several classes. For example, in the CNSP, the sedative class included all the barbiturates, methaqualone, ethchlorvynol, methyprylon, glutethimide, all of the benzodiazepines, and chloral hydrate. All the stimulants were reduced to milligrams of dextroamphetamine. The hallucinogens, even though known to act on the CNS in different ways, were reduced to occasions of use.

Examples of aspects of drug consumption that should be recorded include dates of first and last use (which yields duration of use); frequency of use (per day, per week, per month) during different epochs in a subject's life; quantities or dosages typically used; duration of periods of intercurrent abstinence between first and last use; amount consumed per occasion, per day, week, or month during the period when use was maximal; and duration of the peak use period.

Types of Preparations and Methods of Ingestion

It may be useful to obtain some notion of preferred drug or drugs and some notion of the relative priority given by the subject to the various classes of drugs abused (ranked order of preference vs. ranked order of actual use; or primary use of pharmaceutically manufactured chemicals vs. primary use of street or illicitly manufactured substances such as methamphetamine or any of the so-called "designer" drugs).

It is important to document the route of administration, since there are differential risks to the CNS from different methods of use. The varieties of ways in which polydrug users from the CNSP reported introducing the many drugs they used into their bodies were impressive. Oral ingestion of drugs that came in pill or capsule form was most common, but nonpharmaceutically manufactured methamphetamine, cocaine, heroin, and various street barbiturates were frequently repotted to have been injected both intravenously and subcutaneously. Of wurse for marijuana, smoking was the preferred method, but Vietnam veterans reported smoking heroin as well, when the powdered substance was sprinkled on marijuana or even on ordinary cigarettes. Heroin, crystal methamphetamine, and cocaine were all reported to have been insufflated. One individual reported manufacturing his own amphetamine suppositories, and several devotees of hallucinogens reported introducing LSD, in solution, through eyedrops.

The IV route can add CNS risks secondary to introduction of infectious agents or impurities into the circulatory system. Currently, the possibility of infection with HIV, which can result in a dementing disorder, must be considered seriously in the neurobehavioral evaluation of the IV drug user.

In addition, illicitly manufactured drugs may be bound by filler substances that do not dissolve properly. If injected, such particulate matter may wind up lodged in the lungs and serve as foci for infection or microemboli to the CNS. These can cause small structural lesions observable through magnetic resonance imaging (MRI) scanning. The so-called "rush" associated with the injection of crystal methamphetamine or cocaine is actually an assault on the heart and on the cerebral vascular system, which can result in both microinfarcts and frank, full-blown cerebrovascular accidents. Spasm of cerebral vessels and small aneurysms have also been associated with IV amphetamine administration.

Indirect Indicators of Drug Immersion

Amount of drug consumed and frequency of use within a defined time frame are two benchmarks of drug immersion. Other benchmarks are behaviors whose occurrence can be used to infer the effect of drug use on a person's life. These qualities might be referred to as the biosocial concommitants of drug use. Some of these biosocial characteristics have shown

promise in predicting differences in NP status. For example Carlin and colleagues (1980) classified 79 polydrug-abusing subjects who were part of the CNSP as either "streetwise" or "straight," based on whether they appeared to abuse drugs for self-medication or for recreation. Multivariate analyses confirmed the presence of two different types of neuropsychologically impaired polydrug users in the sample. Streetwise subjects abused larger amounts of most substances, alcohol and heroin in particular. Their NP impairment was more likely to be related to the amount of alcohol and heroin reported. Straight subjects abused fewer classes of drugs, but were more likely to report high levels of CNS depressant use; additionally, they had significantly greater premorbid and concurrent medical risk scores. Their NP impairments tended to be related to CNS depressant use. This study pointed out that the earlier findings of no association between alcohol abuse and NP impairment in the same sample of polydrug users reported by Grant et al. (1978a) may have been premature, perhaps because, in the aggregated sample, the relationship was obscured. The typologies identified by Carlin and associates point to the broader information base that may be required to develop better models of neurotoxicity associated with drug abuse.

Premorbid and Concurrent Medical Risk

The structural model presented in figure 2 points out that NP performance can be adversely affected, sometimes permanently, by many illnesses and trauma. Sources of NP morbidity can include perinatal and early childhood illness or injury, early childhood and latency age learning disability, loss of consciousness due to head injury or other experience such as near-drowning or drug overdose at any time, exposure to environmental toxins such as carbon monoxide or petrochemical solvents, and other neurological, hepatic, or metabolic disease. Major psychiatric illness likewise needs to be taken into account in studies of substance abuse, because of the high prevalence of psychopathology among substance abusers and because the negative effect that serious psychiatric illness can have on NP performance may be difficult to distinguish from drug effects alone.

That NP impairment in alcoholics may be explained as much by exposure to such medical events as by the potential direct neurotoxicity of alcohol has been reported by many groups (De Obaldia and Parsons 1984; Goldstein et al. 1983; Loberg 1986; Tarter et al. 1984a; Tarter et al. 1984b; Tarter et al., this volume; Smith and Smith 1977; Ryan and Butters 1984; Rehmstrom et al. 1977; Gilberstadt et al. 1980; Irwin et al. 1989; Butters et al. 1987; Grant et al. 1984; Adams and Grant 1984). NP function in substance abusers has been shown to be similarly affected by premorbid medical risk exposure. In 151 polydrug abusers from the CNSP sample (Grant et al. 1978b), 4 medical risk items accounted for 20 percent of the variance in Halstead's Impairment Index.

It should also be remembered that such neuromedical risk need not be independent of drug abuse. Rather, the drug abuse lifestyle is likely to expose users to such added risk, e.g., head injury or HIV exposure, further complicating interpretation of NP outcome.

Attrition

Although polydrug-abusing subjects who were not successfully followed up during the CNSP (Grant et al. 1978a) were neuropsychologically indistinguishable at baseline from those who were successfully reevaluated at 3 months postbaseline, they were less well educated and apt to have abused larger amounts of sedative hypnotic drugs. Given the finding in this study of a significant baseline association between abuse of depressants and NP dysfunction, it is possible that the unfollowed subjects, perhaps having a less substantial native endowment, as suggested by their lower educational achievement, would ultimately have diverged from that part of the group that was followed successfully in terms of the incidence of NP impairment.

The CNSP experience points out that selective attrition wuld influence the results of any repeated measures investigation. It also points out that attrition is probably an unavoidable fact in substance-abusing samples, for many reasons. It is well known that this population tends to be very mobile. Subjects involved in criminal behavior might remain in hiding to avoid contact with the criminal justice system. Those whose drug use has led to the development of psychopathological syndromes may become sequestered in the mental-health-care delivery system.

Clearly, longitudinal studies must be acutely concerned with minimizing attrition. Crucial to minimizing attrition is budgeting for adequate numbers of well-trained and properly paid followup workers. Such persons need to understand the drug use subculture as well as the scientific mission of the project. They should be able to move about inside the subculture, to keep track of, contact, and reenroll subjects who are needed for further evaluation. Investigative groups need to request and set aside sufficient funds for encouraging and rewarding subject compliance with the followup protocol. Even the wiliest and most accomplished followup workers will fail if they can do nothing but appeal to the noblest instincts of their subjects to obtain compliance.

It is useful to think of successful followup as emanating from, first, good subject retention policies, which seek to maintain contact with subjects so that they do not get lost; and second, astute subject-locating procedures that help reestablish contact with persons who, for one reason or another, do get lost to followup. A specific and detailed set of followup and subject-retention procedures needs to be built in (and budgeted for) in all longitudinal studies of substance abuse. It can be organized around the principle of employing the easiest, most efficient retention tactics first, followed by the

successively more difficult and time-consuming search tactics. Figure 3 shows a followup tracking algorithm depicted in flowchart style, developed in our Veterans Administration-based study on alcohol abuse and NP impairment. The depicted path generally might apply to reestablishing contact with subjects who are already lost rather than to maintaining contact with subjects whose whereabouts are known. Following such a path systematically and persistently will ultimately yield higher followup rates. Pursuing followup in any less systematic way will guarantee lower subject retention and compromise ultimate interpretation of findings.

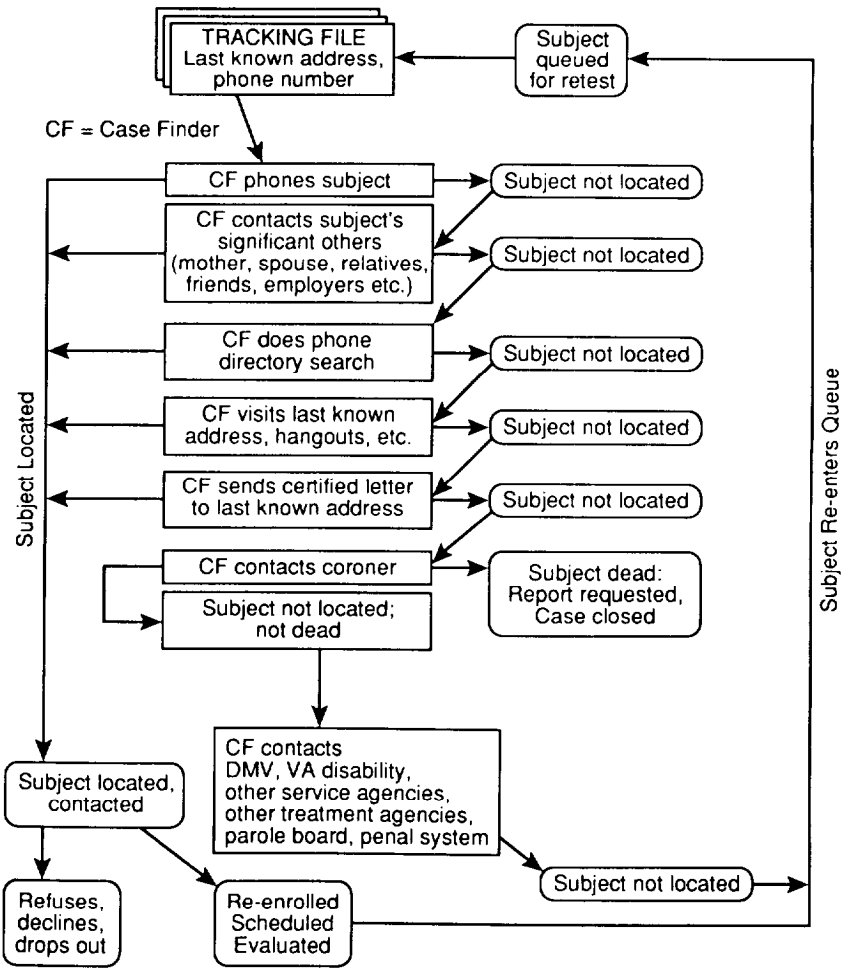

FIGURE 3. *Followup studies: Subject-tracking flow chart*

SUMMARY OF CONCEPTUAL AND METHODOLOGICAL ISSUES

Future researchers would do well to think in global concepts about their work before designing their protocols. The many and complex interacting subsystems of the brain, appreciated by an increasingly sophisticated array of neurodiagnostic techniques, can be described in terms of "neurobehavioral" phenomena. An understanding of drug abuse effects in terms of the natural history model can provide a conceptual base from which to work. It is possible that neurobehavioral abnormalities found among long-term chronic substance abusers may be reversible; these questions of reversibility are legitimate and important, given the data on NP recovery among alcoholics.

We have attempted to focus on methodological solutions rather than merely report the many methodological problems that limit current knowledge of the CNS consequences of substance abuse. Future investigations will fail to clarify the important issues if the principles of measurement are not borne in mind by researchers in any neurobehavioral discipline, including neuropsychology. Controlling for a complex array of premorbid and intercurrent neuromedical, socioeconomic, and demographic influences on neurobehavioral status will make future investigations more difficult. But ignoring the need to account for these sources of variance would leave us with a confusion of contradictory findings and an inadequate increase in sorely needed knowledge.

NEW METHODS

Having reviewed the conceptual and methodological issues that seem relevant to investigations of substance abuse effects on cerebral functioning, we will review a series of neurodiagnostic methods that, to date, have seen only limited application in substance abuse research. In general, we discuss them to stimulate interest among researchers and to suggest that several or all of these methods could be brought together in assessment of the same sample to shed light on the important links between dynamic and structural CNS changes and external behavioral deficits.

Methods for Investigating Brain Structure

Methods for appreciating the structure of the human brain *in vivo* include CT and MRI. Both methods create digital as well as negative film images of the brain (and other parts of the body). The digital images are produced first and may be stored on magnetic tape. The film images are then produced by the translation of the digitally recorded data. The principle underlying CT is that different tissue and fluid types have differing x-ray absorption rates. This absorption rate variation allows for a photographic reconstruction of those tissues exposed to x-rays. MRI relies on the fact that, in the presence of a magnetic field, the nuclei of various atoms present

in the human body can be made to absorb and emit electromagnetic energy. These emissions reflect various components of atomic movement after they are perturbed by radiofrequency waves; such movement depends in turn on the molecules in which such atoms are located. As different tissues have different chemical compositions, it is possible to translate digitally recorded information on changes in atomic movement into film images.

CT is the older, less expensive, and more frequently utilized technology. Its limitations relative to MRI are that it exposes patients to radiation and its images lack the resolution of MRI and can be confounded by bone artifact. MRI images are better resolved than CT images, permitting greater visual discrimination of white and grey matter and of distinct neuroanatomical structures. It is also possible with MRI to obtain brain images in axial, sagittal, and coronal planes; CT provides only axial images. The major limitations of MRI are that it is much more costly than CT, patients are placed in a relatively confined tubelike structure during the procedure, which may provoke claustrophobic reactions in at-risk persons; and the equipment produces a knocking sound that some people find disconcerting. Depending on the number of different planes in the protocol, MRI procedures may take more than an hour to complete.

In the clinical setting, film images from both CT and MRI procedures are reviewed, usually by trained neuroradiologists, to determine the absence, presence, nature, and severity of abnormalities and their locations within the brain. When clinical inspection is incorporated into formal research procedures, ordinal scales rating various tissue and fluid parameters are frequently applied. Ventricular size, degree of sulcal atrophy in various locations, and, at times, summary indices such as the ratio of ventricular width to total brain width are reported. MRI, because of its greater resolution, permits a greater appreciation for abnormalities in grey vs. white matter and reveals areas of high signal intensity, sometimes referred to as “UBOs” or unidentified bright objects. Increased resolution also makes the MRI procedure more sensitive to very small or punctate lesions (small spots) of varying etiology in parenchymal (functional organ) tissue, which CT might fail to reveal.

To our knowledge, formal investigations of the stability of these methods in depicting the structural status of the brain over time do not appear in the literature. The repeated exposure of healthy persons to the radiation of CT and the cost of obtaining serial MRIs from such persons impose constraints on such work. It is well known, however, that even the healthy brain changes with increasing age, and these changes are consistently reflected in reports obtained from samples of differing ages.

Of increasing interest has been the development of image-processing computer software for both CT- and MRI-generated data. These algorithms can produce objective volume estimates of normal and abnormal brain structures

and fluid compartments. MRI algorithms, because of the procedure's greater resolution, can produce tissue data for grey and white matter as well as distinguish between cerebrospinal fluid (CSF) and tissue.

CT- and MRI-imaging studies of substance abusers are desperately needed. For example, the literature includes many reports of the catastrophic consequences of amphetamine and cocaine-related cerebrovascular accidents (Levine et al. 1987; Kaye and Fainstat 1987; Golbe and Merkin 1986; Chasnoff et al. 1986, Brust and Richter 1977; Schwartz and Cohen 1984; Mody et al. 1987). These complications include subarachnoid and intracerebral hemorrhage, cerebral ischemia, and stroke. Clinical reports have revealed such abnormalities in as many as 31 separate cases to date (Jacobs et al. 1989). In all of these reports, CT provided evidence for various structural insults to the brain.

Although such catastrophic consequences are important, future investigations that employ neuroradiological methods ought to focus on substance abusers who escape these more drastic effects. Investigations should be concerned initially with describing the presence, absence, and incidence of microinfarcts, microaneurysms, and other small lesions that might reflect infection or demyelination. A preliminary report by Volkow and colleagues (1988) points in the direction to be taken. Her group looked in multidisciplinary fashion at MRI, PET, and clinical neurological data from seven stimulant abusers. Three of the seven showed white matter hyperintensities suggesting demyelination on MRI; two who had normal brain structure revealed seventh-cranial-nerve paresthesia on neurological exam; and one other, normal on MRI, showed abnormal cerebral blood flow on PET examination. The computer-assisted processing of MRI images, which involves classifying pixels (graphic image units) based on variations in signal strength, also offers the possibility of looking for subtle, diffuse changes in white matter. If a greater incidence of small structural lesions is found in concert with the abuse of any particular class of substance, other questions regarding the role that such lesions may play in NP dysfunction and recovery can then be addressed.

Methods for Studying Dynamic Intracerebral Processes

Regional Cerebral Blood Flow and Metabolism. Inspection of the physiology of the living brain has become increasingly feasible since the advent of two highly sophisticated technologies: SPECT and PET. SPECT is able to measure photon emission from radiolabeled substances. With SPECT, xenon, krypton, and technetium microsphere inhalation have all been used in the study of cerebral blood flow (Hill et al. 1982). Parenteral introduction of ^{123}iodoamphetamine (IMP) and ^{123}iodobenzyl (HIPDM) permits the study of both flow and uptake. Both amines are lipophilic, move easily across the blood-brain barrier, and are nearly completely extracted during a single passage through the brain. IMP is at less than 50 percent peak activity and

HIPDM is at 75 percent within 2 minutes of injection. Maximum brain activity continues with both tracers for between 30 and 60 minutes. Peak activity for IMP is substantially higher than for HIPDM (Holman et al. 1984). The greater utilization of IMP makes its use with the less sensitive rotating gamma-ray camera more practical. The relatively extended activity time for IMP and HIPDM allows concurrent behavioral challenges for studying regional differences in activity, depending on the nature of the behavioral task.

When SPECT is used, several recording instruments are available, including a rotating gamma-ray sensitive camera, a multidetecting scanning tomograph, and an Anger camera, the images from which are subjected to planar scintigraphy. SPECT, utilizing the xenon-inhalation technique, has an acceptable test-retest reliability (Blauenstein et al. 1975; McHenry et al. 1978). One limitation is that central brain structures are masked to SPECT if multiple external collimeters are used to measure regional flow.

The SPECT methodology has recently been used to assess regional cerebral blood flow (rCBF) alterations in persons acutely intoxicated on benzodiazepines, alcohol, and marijuana (Mathew et al. 1985; Mathew and Wilson 1986; Mathew et al. 1989) and has been employed in studies of detoxifying alcoholics (Berglund et al. 1980). The Berglund study found a steady decrease in the variability of rCBF, a normalization of the expected assymetry of blood flow between right and left hemispheres, and specific right hemispheric rCBF increases in the superior frontal and parieto-occipital areas. They also found statistically significant correlations between improvement on the Trailmaking test and increased blood flow in bilateral fronto-temporal areas. The Berglund investigation is instructive for its repeated-measures design, in which both NP and rCBF measures were obtained from each subject at 1, 3, 5, and 7 weeks postabstinence.

PET studies of cerebral blood flow, blood volume, oxygen, and glucose consumption are often conducted utilizing glucose labeled with isotopes of carbon (^{11}C), oxygen (^{15}O), nitrogen (^{13}N), or radiolabeled oxygen by itself. Brain phannacokinetics are studied using any of a number of molecules (ligands), which can be labeled with carbon, fluorine (^{18}F), bromide (^{76}Br), and other elements that can exist as isotopes (Frackowiak 1986).

With PET, a gamma-sensitive camera transversely collects images of the positron-labeled material as it flows through the cerebral vascular system, transports through the blood-brain barrier, and perfuses the CNS tissue, which metabolizes it. When such labeled molecules, e.g., ^{18}F deoxyglucose, emit positrons, they collide with electrons, resulting in annihilation and emission of two gamma particles, at roughly 180-degree angles, at the site of the collision. The gamma camera, with computer assistance, can reconstruct the location of this event, thereby allowing digitally encoded

information on gamma transmission to be translated into an image of the brain regions involved in uptake of the radiolabeled substance.

PET scanning is considerably more expensive than SPECT, because it requires a cyclotron in the manufacture of radiolabeled tracers and extensive technical staff to run the scanner. SPECT is a relatively more available and less expensive technique. Because they can measure abnormalities in blood flow and metabolism, PET and SPECT might be more sensitive to certain early neurophysiological changes related to substance abuse than are MRI and CT.

The potential of PET for substance abuse research can be appreciated from a brief look at related neuroscientific applications. Animal studies involving the rat have examined both acute and chronic effects on glucose metabolism of amphetamines (Orzi et al. 1983), tricyclic antidepressants and MAO inhibitors (Gerber et al. 1983), and antipsychotics (McCulloch et al. 1982). In several controlled human investigations, PET has, among other things, successfully distinguished between the ratio of frontal to posterior uptake of deoxyglucose in persons with both schizophrenic and affect disorders vs. age- and sex-matched controls (Buchsbaum et al. 1982; Buchsbaum et al. 1984; Delisi et al. 1985a; DeLisi et al. 1985b). In the latter case, the investigation was longitudinal; a group of nine schizophrenics were scanned twice, with 9 months elapsing between first and second scans. Initially, the patients had undergone a minimum 2-week neuroleptic washout. At follow-up, the subjects had all been restored to their medication regimens for a minimum of 2 weeks. A significant increase in total cortical uptake of deoxyglucose was noted among the schizophrenics treated with various common neuroleptics at followup, but the "hypofrontal" frontal-posterior ratio remained unchanged.

Depressivelike symptoms occur following cessation of amphetamine and cocaine exposure in both animals and humans. This suggests that at least transient pathophysiological changes might occur in the central nervous subsystems that are thought to be associated with depression (Barrett and White 1980; Carroll and Lac 1987; Kokkinidis and Zacharko 1980; Kokkinidis et al. 1986; Kokkinidis 1988; Leith and Barrett 1976; Leith and Barrett 1980; Wood and Lal 1987; Woolverton and Kleven 1988; Siegel and Kuczenski, unpublished data). Current evidence implicates serotonergic, noradrenergic, and dopaminergic systems in the actions of cocaine and amphetamine (Barrett and White 1980; Dackis and Gold 1985; Dackis et al. 1985; Goeders and Smith 1983; Kokkinidis 1988; Koob and Bloom 1988; Pitts and Marwah 1987; Sibley et al. 1982; Wyatt et al. 1988) and suggests the importance of future PET studies employing appropriate ligands.

Formal PET studies of substance abusers as a diagnostic category and of stimulant abusers, in particular, are only recently appearing in the literature. Volkow and associates (1988) reported that rCBF was decreased in the

regions of the lateral prefrontal and left anterior temporal cortex of cocaine abusers. However, Baxter and colleagues (1988), using ^{18}F-6 fluoro-L-dopa and PET did not find evidence of abnormal flow and metabolism in preliminary studies of nondepressed withdrawing cocaine abusers. In fact, Baxter's cocaine abusers were comparable to nonpatient controls and better than cocaine-nonabusing bipolar and unipolar depressed subjects on measures of rCBF.

One recently proposed longitudinal investigation, to be jointly carried out by the San Diego and Los Angeles campuses of the University of California medical schools, will use ^{18}F-6 fluoro-L-dopa to study the uptake of L-dopa in the brains of stimulant abusers at 2 to 3 days and at 4 to 6 weeks post-withdrawal. Using the ratio of dopa uptake in the striatum vs. the cerebellum in stimulant abusers and drug-nonusing controls, some light may be shed on the question of whether presynaptic DA dysfunction, which can occur in stimulant abuse, remediates with continued abstinence.

The potentially important relationship between NP performance and dynamic brain processes is beginning to be illuminated by the conjoint use of NP and PET methods. Chase and associates (1984) repotted significant correlations between performance on the 11 subtests of the Wechsler Adult Intelligence Scale and the uptake of ^{18}F fluorodeoxyglucose in various regions of the brains of a small mixed sample of elderly normals and Alzheimer's disease patients. Although this was a small study, with some limitations related to the low resolution of the PET images obtained, the cross-validation of two neurodiagnostic methods is important and can serve as a model for future research in substance abuse.

Fully exploring the possibility that psychoactive chemicals may permanently alter receptor number and function or produce other long-standing metabolic brain changes could be of considerable import in shaping future research and treatment strategies, as well as in the development of general public policy regarding drug abuse. For example, if, through longitudinal radiolabeled ligand studies, it was determined that amphetamine abuse permanently reduced the number of functioning DA receptors or damaged the neurons responsible for DA production, this finding could have a significant effect on the development of neuropsychopharmacological treatment for drug abusers. Such studies also have the potential to contribute significantly to knowledge of the physiometabolic underpinnings of major psychiatric illnesses such as schizophrenia and mood disorders.

Electrophysiology: EEG and Evoked Potentials. Electrophysiological methods such as BEAM and neurometrics constitute two other means by which dynamic brain processes may be studied *in vivo.* They have common roots in clinical electroencephalography (EEG). With the recent advent of computer-based data collection and processing, EEG methods have

undergone considerable improvement, facilitating a greater understanding of brain electrical phenomena.

Neurometrics, as developed by Drs. Leslie Prichep and E. Roy John at New York University (NYU), is a method that estimates the probability that the quantitative data derived from qualitative features of brain electrical activity reflect dysfunction. Recordings of the resting EEG and various sensory-evoked potentials are obtained by computer under standardized testing conditions. Computer algorithms extract quantitative features from these recordings, which are then compared with a normative data base (normative data in the brain research laboratory at NYU have been obtained from more than 750 subjects between 6 and 90 years of age), using multivariate statistical procedures. The real-time value of any feature is replaced with an estimate of the probability that this value in an individual patient might be found in a healthy, normal functioning person of the same age (Prichep and John 1986). Such methods lend themselves readily to the creation of elec trophysiological profiles for clinically identifiable disease states. Recent attempts at discriminant function classification by Prichep and John resulted in 77, 72, 80, and 79 percent correct group assignment in normal, primary depressive, alcoholic, and demented patients all considered simultaneously (chance correct assignment was 25 percent), based on 11 quantitative indices features extracted from their neurometric profiles. An independent replication resulted in an even greater total correct classification.

Evoked potential work by Duffy and colleagues at the Children's Hospital in Boston has been evolving in roughly the same direction as that of Prichep and John. Duffy has pioneered in what he refers to as BEAM (brain electrical activity mapping). Using a statistically based method, he has developed rules for the diagnosis, from an analysis of topographic maps of brain electrical activity, of dyslexia in young patients. As with Prichep and John's method, there is considerable individual variation in brain electrical output across trials, even in healthy individuals. To develop his own normal data base, Duffy employed sophisticated statistical algorithms that sampled mean variance in the same normal subjects across repeated trials, thereby accumulating substantial knowledge, not only of actual performance, but of variance across trials in his age-stratified normal sample. An interesting joining of this methodology with pharmaceutical challenge for purposes of testing the validity of BEAM was demonstrated when 13 patients with known supratentorial (above the tentorium of the cerebellum) brain lesions were administered IV sodium thiopental and monitored via BEAM technology. The purpose was to better visualize electrical abnormalities. Thiopental is known to induce fast background activity across a number of EEG-sensitive electrical frequencies. When atrophic or space-occupying lesions are present, alterations in beta activity are noted in the presence of thiopental. Using the statistical probability mapping procedures developed at Children's Hospital, it was possible to demonstrate electrical abnormalities on the BEAM map that corresponded accurately to the CT-scan-established

location of the lesion in question in 12 of the 13 cases. This occurred after the first injection of thiopental and was replicated on the second injection (Duffy et al. 1984).

Duffy and his group have also applied BEAM in studies of lecithin's effects on the electrophysiology of the brains of Alzheimer's disease patients (Duffy et al. 1987) and in the aforementioned investigations of dyslexia (Duffy et al. 1980a; Duffy et al. 1980b; Duffy et al. 1984). The group at NYU's brain research laboratory have applied their methods in studies of normal developmental equations for the electroencephalogram, in the EEG correlates of various neurological abnormalities in children (John et al. 1980; John et al. 1983), in the study of quantitative EEG irregularities among depressives (Prichep et al. 1986), and in investigations of dementia (Prichep et al. 1983). Others, utilizing the same or similar methods, have studied cerebral ischemia (Jonkman et al. 1985).

Thus, the past 10 years have produced an increased sensitivity in the EEG through the application of sophisticated computer-assisted statistical averaging, within-subject sampling methods, and the development of substantial normative data bases. John et al. (1988) and Duffy et al. (1984) imagine that the development of complete taxonomies for the electrophysiological correlates of many psychiatric illnesses is not far in the future.

In research on substance abuse, several applications of computed electrophysiology are apparent. First, as normative data bases evolve, it should be possible to describe the differential EEG characteristics of different abusable substances and the time course for changes in electrical activity of the brain, in relation to withdrawal and abstinence. Second, the patterns of abnormality, for example regional changes, can be explored. Third, it should be possible to link electrical and NP studies to examine alterations in information processing caused by acute intoxication with, withdrawal from, and longer term phenomena associated with particular drugs. Fourth, electrical, metabolic (PET or SPECT), and NP studies of the same drug users at various times can elucidate the relationship of drug- or withdrawal-induced biochemical alterations, electrical activity, and cognitive behavioral outcomes.

Information Processing and Performance Paradigms. Earlier, we described NP methods of assessing drug abusers. Neuropsychometry is, of course, only one approach to behavioral assessment. Additional strategies have evolved under the general rubric of information processing (IP) and performance paradigms.

IP abilities and performance are thought to underlie higher level and more complex NP functions. They include measures of the speed and efficiency or accuracy with which an individual perceives a stimulus, manipulates its representation in the CNS, and offers response. IP measures are frequently

described as being process sensitive rather than outcome sensitive. Performance on most IP tasks is relatively unconfounded by educational and social background. Constructs that are operationally defined and tested with such measures include simple and choice reaction time, inspection time, movement time, simple attention, divided attention, and concentration. Often, several of these parameters arc assessed within the same procedures and much of the literature in which such methods are reported is concerned with the determination of the fundamental psychological abilities associated with intelligence.

The Hick paradigm (Jensen 1982) is a basic and commonly applied example of a combined simple and choice reaction-time measure. Whether presented via computer or by a dedicated reaction-time device, the task samples reaction (or "inspection") time and movement time. Subjects are presented with one, three, or five choice conditions. Open squares on a CRT screen for example, may be used as stimulus lights, and subjects are required to respond by pressing the appropriate key as quickly as possible after a square becomes illuminated. Multiple trials are obtained for each choice condition. At the beginning of each trial, the subject rests a forefinger of his or her dominant hand on the space bar without depressing it. At random intervals of 1.5 to 2.5 seconds, one of the stimulus squares is illuminated. The subject must first press the space bar and then press the key directly below the illuminated light. Reaction time is recorded as the number of milliseconds between the onset of stimulus and the instant the subject presses the space bar. Movement time is the interval between pressing the space bar and pressing the response key.

The Arrows Test (Larson 1985) is another example of a reaction-time paradigm. Again, a subject facing a CRT is asked to fixate on two small circles placed 1/2 inch apart in the center of the screen. In each trial, one circle is replaced by an arrow and, depending on the arrow's direction and position, the subject must press either a right or left key on the keyboard. If the arrow points downward, its position (replacing right or left circle) indicates the appropriate response. A right- or left-pointing arrow, regardless of position, indicates the appropriate response. The position and direction of the arrows are varied randomly. Median response latencies and comprehensive standard deviations for the differing conditions are typical scores used in assessing performance.

One common example of an inspection-time paradigm is the Inspection Time with Lines Test (Saccuzzo et al. 1986). In this test, subjects are briefly shown two horizontal lines of unequal length, presented in the center of a CRT screen. Subjects are to select the longer line in the pair on each trial. A record is kept of accuracy, and subjects are given performance feedback by the computer. The display of lines is terminated by the superimposition of another line that masks the test item and limits viewing time (this is termed visual backward masking). The length of the test lines

remains constant; therefore, duration of the stimulus is the chief source of item difficulty. In this particular paradigm, five separate durations are applied, and 50 trials are administered, with 10 trials per duration. The purpose is to learn at which duration the subject obtains the maximal number of correct responses, i.e., how much inspection time the brain requires to respond correctly.

In one example of an application of these strategies to the study of psychoactive drugs, the relationship of monoaminergic overactivity to IP abilities was examined. Braff and colleagues at the University of California, San Diego Medical School employed a variation of the visual backward masking paradigm in an investigation using methylphenidate to induce a monoaminergic surge in nonpsychotic psychiatric inpatients (Braff and Huey 1988). In this study, a tachistoscope, rather than a computer, controlled duration and sequence of stimulus presentations. A target was first presented at a duration long enough for patients to discriminate and report it (critical stimulus duration), in a forced-choice letter identification task. After an interval, a pattern-masking stimulus was presented, which erased or interfered with the registration of the target in the subject's brain. As the interstimulus interval increased between target and mask, the target at some point escaped the disruptive effects of the mask. Methylphenidate was found to induce schizophrenialike IP dysfunction in this double-blind crossover investigation of nonpsychotic inpatients. Specifically, when treated with methylphenidate, the subjects were impaired on measures of attention and IP, compared with their performance while treated with oxazepam or placebo. These findings support the well-documented vulnerability of schizophrenics to masking even at relatively long interstimulus intervals (Steronko and Wood 1978; Brody et al. 1980; Braff 1981; Ruff et al. 1985; Saccuzzo et al. 1986) and the hypothesis that schizophrenia is, at least in part, a result of a perturbed DA system in the brain.

If we accept that the paradigms described above assess the early IP that underlies more complex cognitive events such as perception; storage and retrieval of information; manipulation of concepts; and decision making, then the importance of including IP measures in studies of the longer term effects of drug abuse become obvious. Because the alterations in IP noted in some schizophrenic patients might reflect changes in dopaminergic function, IP techniques are of special interest in studies of drugs that directly or indirectly affect DA neurones. Such agents include cocaine, the amphetamines, and phencyclidine. Indirect effects on DA function may also be produced by the opiates and by withdrawal from CNS depressants. The enduring nature of alteration in fundamental IP clearly requires study.

CONCLUSION

In summarizing this brief review of promising neurodiagnostic methods that could be applied in studies of substance abuse, we return to our plea for

multidisciplinary research. Through multidisciplinary investigations, the products of brain activity (cognition, measured by NP and IP tests) can perhaps be linked to underlying neurobiological processes (electrophysiology, blood flow, metabolism) and brain structure. While the multidisciplinary approach is not the only way to continue to develop an understanding of substance-abuse.-related brain disorder, it is an approach that does greater justice to the complexity of brain-behavior relationships than any univariate strategy. It is an approach that, if implemented properly, can spare us many of the problems associated with the piecemeal, "two steps forward, one step back" methods that have often been used in the past, mostly out of necessity.

REFERENCES

Acord, LD. Hallucinogenic drugs and brain damage. *Milit Med* 137:18-19, 1972.

Acord, L.D., and Barker, D.D. Hallucinogenic drugs and cerebral deficit. *J Nerv Ment Dis* 156:281-283, 1973.

Adams, K.M.; Brown, G.G.; and Grant, I. Analysis of covariance as a remedy for demographic mismatch of research subject groups: Some sobering simulations. *J Clin Exp Neuropsychol* 7(4):445-462, 1985.

Adams, K.M., and Grant, I. The influence of premorbid risk factors on neuropsychological performance in alcoholics. *J Clin Exp Neuropsychol* 8:362-370, 1986.

Adams, K.M.; Grant, I.; Carlin, A.S.; and Reed, R.J. Cross-study comparisons of self-reported alcohol consumption in four clinical *groups. Am J Psychiatry* 138(4):445-449, 1981.

Adams, K.; Grant, I.; and Reed, R. Neuropsychology in alcoholic men in their late thirties: One year follow-up. *Am J Psychiatry* 137:928-931, 1980.

Adams, K.M.; Rennick, P.M.; Schooff, K.G.; and Keegan, J.F. Neuropsychological measurement of drug effects: Polydrug research. *J Psychedelic Drugs* 7:151-160, 1975.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders—R.* 3d ed. Washington, DC: the Association, 1987.

Arlien-Soborg, P.; Brunn, P.; Gyldensted, C.; and Melgaard, B. Chronic painters' syndrome: Chronic toxic encephalopathy in house painters. *Acta Neurol Scand* 60:149-156, 1979.

Barrett, R.J., and White, D.K. Reward system depression following chronic amphetamine: Antagonism by haloperidol. *Pharmacol Biochem Behav* 13:555-559, 1980.

Baxter, LR.; Schwartz, J.M.; Phelps, M.E.; Mazziotta, J.C.; Barrio, J.; Rawson, R.A.; Engel, J.; Guze, B.H.; Selin, C.; and Sumida, R. Localization of neurochemical effects of cocaine and other stimulants in the human brain. *J Clin Psychiatry* 49(suppl 2):23-26, 1988.

Belmore, S.M., and Miller, LL Levels of processing and acute effects of marijuana on memory. *Pharmacol Biochem Behav* 13:199-203, 1980.

Berglund, M.; Bliding, G.; Bliding, A.; and Risberg, J. Reversibility of cerebral dysfunction in alcoholism during the first seven weeks of abstinence: A regional cerebral bloodflow study. *Acta Psychiatr Scand* 119-127, 1980.

Bergman, H.; Borg, S.; Engelbrektson, K.; and Vilander, B. Dependence on sedative hypnotics: Neuropsychological impairment, field dependence and clinical course in a 5-year follow-up study. *Br J Addict* 84:547-553, 1989.

Bergman, H.; Borg, S.; and Holm, L. Neuropsychological impairment and the exclusive abuse of sedatives or hypnotics. *Am J Psychiatry* 137:215-217, 1980.

Blauenstein, U.W.; Halsey, H.J.; Wilson, E.M.; Willis, E.L.; and Risberg, J. The 133 Xe inhalation method: Analysis of reproducibility. In: Harper, A.M.; Jennet, W.B.; Miller, J.D.; and Rowan, R.O., eds. *Blood Flow and Metabolism in the Brain.* New York: Churchill Livingstone, 1975.

Block, R.I., and Wittenborn, J.R. Marijuana effects on semantic memory: Verification of common and uncommon category members. *Psychol Rep* 55:503-512, 1984.

Braff, D.L. Impaired speed of information processing in nonmedicated schizotypal patients. *Schizophr Bull* 7:499-508, 1981.

Braff, D.L.; Heaton, R.K.; Cullum, C.M.; Grant, I.; and Zizook, S. The general pattern of neuropsychological deficit in outpatient schizophrenics with relatively normal Wisconsin Card Sorting results. *Arch Gen Psychiatry*, in press.

Braff, D.L., and Huey, L. Methylphenidate-induced information processing dysfunction in nonschizophrenic patients. *Arch Gen Psychiatry* 45:827-832, 1988.

Brandt, J.; Butters, N.; Ryan, C.; and Bayog, R. Cognitive loss and recovery in chronic alcohol abusers. *Arch Gen Psychiatry* 40:435-442, 1983.

Brecher, M.; Wang, B.W.; Wong, H.; and Morgan, J.P. Phencyclidine and violence: Clinical and legal issues. *J Clin Psychopharmacol* 8(6):397-401, 1988.

Brody, D.; Saccuzo, D.P.; and Braff, D.L. Iconic memory dysfunction in schizophrenia and the elderly. *J Abnorm Psycho1* 89:617-622, 1980.

Bruhn, P.; Arlien-Soborg, P.; Gyldensted, C.; and Christensen, E.L. Prognosis in chronic toxic encephalopathy. *Acta Neurol Scand* 64:259-272, 1981.

Brust, J.C.M., and Richter, R.W. Stroke associated with cocaine abuse? *NY State J Med* 77:1473-1475, 1977.

Buchsbaum, M.S.; DeLisi, L.E.; Holcomb, H.H.; et al. Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psychiatry* 41:1159-1168, 1984.

Buchsbaum, M.S.; Ingvar, D.H.; Kessler, R.; et al. Cerebral glucography with positron tomography. *Arch Gen Psychiatry* 39:251-259, 1982.

Butters, N.; Grant, I.; Smith, T.; Reed, R.; and Schuckit, M.A. Predictors of cognitive performance of alcoholic inpatients at intake, discharge and three-month follow-up. *Alcohol: Clin Exp Res* 11:266, 1987.

Campbell, A.M.G.; Evans, M.; Thompson, J.L.G.; and Williams, M.J. Cerebral atrophy in young cannabis smokers. *Lancet* 2:1420, 1971.

Carlen, P.L., and Wilkinson, D.A. Alcoholic brain damage and reversible deficits. *Acta Psychiatr Scand* 62:103-118, 1980.

Carlen, P.L; Wortzman, G.; Holgate, R.C.; Wilkinson, D.A.; and Rankin, J.G. Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomography scans. Science 200:1076-1078, 1978.

Carlin, AS. Neuropsychological consequences of drug abuse. In: Grant, I., and Adams, K.M., *eds. Neuropsychological Assessment of Neuropsychiatric Disorders: Clinical Methods and Empirical Findings. New* York: Oxford University Press, 1986. pp. 478-497.

Carlin, A.; Grant, I.; Adams, K.; and Reed, R. Is phencyclidine (PCP) abuse associated with organic mental impairment? *Am J Drug Afcohof Abuse* 6:273-281, 1979.

Carlin, A.S.; Strauss, F.F.; Grant, I.; and Adams, K.M. Drug abuse style, drug use type, and neuropsychological deficit in polydrug users. *Addict Behav* 5:229-234, 1980.

Cat-toll, M.E., and Lac, S.T. Cocaine withdrawal produces behavioral disruptions in rats. *Life Sci* 40:2183-2190, 1987.

Chase, T.N.; Fedio, P.; Foster, N.L.; Brooks, R.; Giovanni, D.; and Mansi, L. Cortical localization by fluorodcoxyglucose F 18—positron emission tomography. *Arch Neurol* 41:1244-1247, 1984.

Chasnoff, I.J.; Bussey, M.E.; Savich, R.; and Stack, C.M. Perinatal cerebral infarct and maternal cocaine use. *J Pediatr* 108:456-459, 1986.

Citron, B.P.; Halpern, M.; McCarron, M.; Lundberg, G.D.; McCormick, R.; Pincus, I.J.; Tatter, D.; and Haverback, B.J. Necrotizing angitis associated with drug abuse. *N Engl J Med* 283:1003-1011, 1970.

Cohen, S., and Edwards, A.E. LSD and organic brain impairment. *Drug Depend* 2:1-4, 1969.

Colpaert, E.C.; Niemegeers, C.J.E.; and Janssen, P.A.J. Discriminative stimulus properties of cocaine: Neuropharmacological characteristics as derived from stimulus generalization experiments. *Pharmacol Biochem Behav* 10:535-546, 1979.

Dackis, C.A., and Gold, M.S. New concepts in cocaine addiction: The dopamine depletion hypothesis. *Neurosci Biobehav Rev* 9:469-477, 1985.

Dackis, C.A.; Gold, M.S.; and Davies, R.K. Bromocriptine treatment as treatment of cocaine abuse: The dopamine depletion hypothesis. *Int J Psychiatry Med* 15:125-135, 1985.

Davies, B.M. Oral semyl in obsessive states. *J Ment Sci* 109:1-14, 1961.

DeLisi, L.E.; Buchsbaum, M.S.; Holcomb, H.H.; et al. Clinical correlates of decreased anteroposterior gradients in positron emission tomography (PET) of schizophrenic patients. *Am J Psychiatry* 142:78-81, 1985a.

DeLisi, L.E.; Holcomb, H.H.; Cohen, R.M.; et al. Positron emission tomography (PET) in schizophrenics with and without neuroleptic treatment. *J Cereb Blood Ffow Metab* 5:201-206, 1985b.

De Obaldia, R.D., and Parsons, O.A. Reliability and validity of the Primary/Secondary Alcoholism Classification Questionnaire and the HK/MBD Childhood Symptoms Checklist. *J Clin Psycho1* 40:1257-1263, 1984.

Duffy, F.H.; Denckla, M.B.; Bartels, P.H.; and Sandini, G. Dyslexia: Regional differences in brain electrical activity by topographic mapping. *Ann Neurol* 7:412-420, 1980a.

Duffy, F.H.; Denckla, M.B.; Bartels, P.H.; Sandini, G.; and Kiessling, L.S. Dyslexia: Automated diagnosis by computerized classification of brain electrical activity. *Ann Neurol* 7:421-428, 1980b.

Duffy, F.H.; Jensen, F.; Erba, G.; Burchfiel, J.L.; and Lombroso, C.T. Extraction of clinical information from electroencephalographic background activity: The combined use of brain electrical area mapping and intravenous sodium thiopental. *Ann Neurol* 15:22-30, 1984.

Duffy, F.H.; McAnulty, G.; Albert, M.; Durwen, H.; and Weintraub, S. Lecithin: Absence of neurophysiologic effect in Alzheimer's disease by EEG topography. Neurol 37:1015-1019, 1987.

Fabian, M.S., and Parsons, O.A. Differential improvements of cognitive functions in recovering alcoholic women. *J Abnorm Psycho1* 92:81-95, 1983.

Fields, F.R.J., and Fullerton, J.R. The influence of heroin addiction on neuropsychological functioning. In: Newsletter for *Research in Mental Health and Behavioral Science.* Washington, DC: Department of Medicine and Surgery, Veterans Administration, 1974.

Filley, C.M.; Heaton, R.K.; Nelson, L.M.; Burks, J.S.; and Franklin, G.M. A comparison of dementia in Alzheimer's disease and multiple sclerosis patients. *Arch Neurol* 46(2):157-161, 1989.

Finlayson, M.A.J.; Johnson, K.A.; and Reitan, R.M. Relationship of level of education to neuropsychological measures in brain-damaged and nonbrain-damaged adults. *J Consult Clin Psycho1* 45:536-542, 1977.

Fine, E.W.; Steer, R.A.; and Stoles, P.E. Relationship between blood alcohol concentration and self reported drinking behavior. *Q J Stud Alcohol* 39:466-472, 1978.

Frackowiak, R.S.J. An introduction to positron tomography and its application to clinical investigation. In: Trimble, M.R., ed. *New Brain Imaging Techniques and Psychopharmacology.* Oxford: Oxford University Press, 1986.

French, E.D. Effects of acute and chronic administration of phencyclidine on the A10 dopaminergic mesolimbic system: Electmphysiological and behavioral correlates. *Neuropharmacology* 27(8):791-798, 1988.

Gawin, F.H., and Ellinwood, E.H. Cocaine and other stimulants. *N Engl J Med* 318(18):1173-1182, 1988.

Gerber, J.C.; Choki, J.; Brunswick, D.J.; Reivich, M.; and Frazer, A. The effect of antidepressant drugs on regional cerebral glucose utilization in *the* rat. *Brain Res* 269:319-325, 1983.

Gilberstadt, S.J.; Gilberstadt, H.; Zieve, L.; Buegel, B.; Collier, P.O.; and McClain, C.J. Psychomotor performance defects in cirrhotic patients without overt encephalopathy. *Arch Intern Med* 140:519-521, 1980.

Goedets, N.E., and Smith, J.E. Cocaine dopaminergic involvement in cocaine reinforcement. *Science* 221:773-774, 1983.
Golbe, L.I., and Merkin, M.D. Cerebral infarct in a user of free-base cocaine ("crack"). *Neurology* 36:1602-1604, 1986.
Goldman, M. Reversibility of psychological deficits in alcoholics: The interaction of aging with alcohol. Presented at the eleventh annual meeting of the International Neuropsychology Society, Mexico City, 1983a.
Goldman, M.S. Cognitive impairment in chronic alcoholics: Some cause for optimism. *Am Psychol* 38:1045-1054, 1983b.
Goldman, M.S.; Klisz., D.K.; and Williams, D.L. Experience-dependent recovery of cognitive functioning in young alcoholics. *Addict Behav* 10:169-176, 1985.
Goldstein, G.; Tarter, R.E.; Shelly, C.; Alterman, A.I.; and Petrarulo, E. Withdrawal seizures in black and white alcoholic patients: Intellectual and neuropsychological sequelae. *Drug Alcohol Depend* 12:349-354, 1983.
Golombok, S.; Moodley, P.; and Lader, M. Cognitive impairment in long-term benzodiazepine users. *Psychol Med* 18:365-374, 1988.
Grant, I. Alcohol and the brain: Neuropsychological correlates. *J Consult Clin Psycho1* 55:310-324, 1987.
Grant, I.; Adams, K.; Carlin, A.; Rennick, P.; Judd, L.; and Schooff, K. The collaborative neuropsychological study of polydrug users. *Arch Gen Psychiatry* 35:1063-1074, 1978a.
Grant, I.; Adams, K.; Carlin, A.; Rennick, P.; Judd, L.; Schooff, K.; and Reed, R. Neumpsychological effects of polydrug abuse. In: Wesson, D.R.; Carlin, A.S.; Adams, K.M.; and Heschner, G., eds. *Polydrug Abuse: The Results of a National Collaborative Study. New* York: Academic Press, 1978b.
Grant, I.; Adams, K.; and Reed, R. Normal neuropsychological abilities of alcoholic men in their late thirties. *Am J Psychiatry* 136:1263-1269, 1979.
Grant, I.; Adams, K.; and Reed, R. Aging, abstinence and medical risk factors in the prediction of neuropsychological deficit among long-term alcoholics. *Arch Gen Psychiatry* 41:710-718, 1984.
Grant, I.; Adams, K.; and Reed, R. Intermediate duration (subacute) organic mental disorder of alcoholism. In: Grant, I., *ed. Neuropsychiatric Correlates of Alcoholism.* Washington, DC: American Psychiatric Press, 1986.
Grant, I.; Heaton, R.K.; McSweeny, A.J.; Adams, K.M.; and Timms, R. Neuropsychological findings in chronic obstructive pulmonary disease. *Arch Intern Med* 142:1470-1476, 1982.
Grant, I., and Mohns, L. Chronic cerebral effects of alcohol and drug abuse. *Int J Addict* 10(5):883-920, 1975.
Grant, I.; Prigatano, G.P.; Heaton, R.K.; McSweeny, A.J.; Wright, E.C.; and Adams, K.M. Progressive neuropsychological impairment in relation to hypoxemia in chronic obstructive pulmonary disease. *Arch Gen Psychia*try 44:999-1006, 1987.

Grant, I., and Reed, R. Neuropsychology of alcohol and drug abuse. In: Alterman, A.I., ed. *Substance Abuse and Psychopathology.* New York: Plenum Press, 1985. pp. 289-341.

Grant, I.; Reed, R.; and Adams, K. Natural history of alcohol and drug related brain disorder: Implications for neuropsychological research. *J Clin Neuropsychol* 2:321-331, 1980.

Grant, I.; Rochford, J.; Fleming, T.; and Stunkard, A. A neuropsychological assessment of the effects of moderate marijuana use. *J Nerv Ment Dis* 156:278-280, 1973.

Guerra, D.; Sole, A.; Cami, J.; and Tobena, A. Neumpsychological performance in opiate addicts after rapid detoxification. *Drug Alcohol Depend* 20:261-270, 1987.

Heaton, R.K.; Grant, I.; Anthony, W.Z.; and Lehman, R.A.W. A comparison of clinical and automated interpretation of the Halstead-Reitan Battery. *J Clin Neuropsychol* 3:121-141, 1981.

Heaton, R.K.; Grant, I.; and Matthews, C.G. Differences in neuropsychological test performance associated with age, education and sex. In: Grant, I., and Adams, K.M., eds. *Neuropsychological Assessment of Neuropsychiatric Disorders: Clinical Methods and Empirical Findings.* New York: Oxford University Press, 1986. pp. 100-120.

Hendler, N.; Cimini, C.; Terence, M.A.; and Long, D. A comparison of cognitive impairment due to benzodiazepines and to narcotics. *Am J Psychiatry* 37:828-830, 1980.

Hill, T.C.; Holman, L.; Lovett, R.; et al. Initial experience with SPECT (Single Photon Computerized Tomography) of the brain using N-isopropyl-123 p-iodoamphetamine: Concise communication. *J Nucl Med* 23:191-195, 1982.

Hill, S.Y., and Mikhael, M.A. Computerized transaxial tomographic and neumpsychological evaluations in chronic alcoholics and heroin abusers. *Am J Psychiatry* 136:598-602, 1979.

Holman, B.L.; Hill, T.C.; Polak, J.F.; Lee, R.G.; Royal, H.D.; and O'Leary, D.H. Cerebral perfusion imaging with iodine 123-labeled amines. *Arch Neurol* 41:1060-1063, 1984.

Hooker, W.D., and Jones, R.T. Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. *Psychopharmacology* 91:20-24, 1987.

Irwin, M.; Smith, T.L.; Baird, S.; Schuckit, M.A.; and Butters, N. Graded neuropsychologic impairment and elevated gamma glutamyl transferase in chronic alcoholic men. *Alcohol: Clin Exp Res* 13:99-103, 1989.

Jacobs, I.G.; Roszler, M.H.; Kelly, J.K.; Klein, M.A.; and Kling, G.A. Cocaine abuse: Neurovascular complications. *Radiology* 170:223-227, 1989.

Javitt, D.C. Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia. *Hillside J Clin Psychiatry* 9(1):12-35, 1987.

Jensen, A.R. Reaction time and psychometric "g." In: Eysenck, H.J., ed. *A Model for Intelligence.* New York: Springer-Verlag, 1982.

John, E.R.; Ahn, H.; Prichep, L.S.; Trepetin, M.; Brown, D.; and Kaye, H. Developmental equations for the electroencephalogram. Science 210:1255-1259, 1980.
John, E.R.; Prichep, L.S.; Ahn, H.; Easton, P.; Fridman, J.; and Kaye, H. Neurometric evaluation of cognitive dysfunction and neurological disorders in children. *Prog Neurobiol* 21:239-290, 1983.
John, E.R.; Prichep, L.S.; Fridman, J.; and Easton, P. Neurometrics: Computer-assisted differential diagnosis of brain dysfunctions. *Science* 239:162-169, 1988.
Jonkman, E.J.; Poortvliet, D.C.J.; Veering, H.M.; DeWeerd, A.W.; and John, E.R. The use of neurometrics in the study of patients with cerebral ischemia. *Electroencephalogr Clin Neurophysiol* 61:333-341, 1985.
Judd, L.L., and Grant, I. Brain dysfunction in chronic sedative users. *J Psychedelic Drugs* 7:143-149, 1975.
Kane, F.J.; Keeler, M.H.; and Reifler, C.B. Neurological crises following amphetamine. *JAMA* 210:556-557, 1969.
Kaye, B.R., and Fainstat, M. Cerebm vasculitis associated with cocaine abuse. *JAMA* 258:2104-2106, 1987.
Kokkinidis, L. Neurochemical correlates of post-amphetamine depression and sensitization in animals. *Anim Mod Psychiatr Disord* 2:148-173, 1988.
Kokkinidis, L., and Zacharko, R.M. Response sensitization and depression following long-term amphetamine treatment in a self-estimation paradigm. *Psychopharmacology* 68:73-76, 1980.
Kokkinidis, L.; Zacharko, R.M.; and Anisman, H. Amphetamine withdrawal: A behavioral evaluation. *Life Sci* 38:1617-1623, 1986.
Kolansky, H., and Moore, W.T. Effects of marijuana on adolescents and young adults. *JAMA* 216:486-492, 1971.
Kolansky, H., and Moore, W.T. Toxic effects of chronic marijuana use. *JAMA* 222:35-41, 1972.
Koob, G.F., and Bloom, F.E. Cellular and molecular mechanisms of drug dependence. *Science* 242:715-723, 1988.
Kuczenski, R., and Segal, D. Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. *J Neurosci* 9(6):2051-2065, 1989.
Leith, N.J., and Barrett, R.J. Amphetamine and the reward system: Evidence for tolerance and post-drug depression. *Psychopharmacologia* 46: 19-25, 1976.
Leith, N.J., and Barrett, R.J. Effects of chronic amphetamine or reset-pine on self-stimulation responding: A model of depression? *Psychopharmacology* 72:9-15, 1980.
Levine, M.S.; Hull, C.D.; Garcia-Rill, E.; Erinoff, L.; Buchwald, N.A.; and Heller, A. Long-term decreases in spontaneous firing of caudate neurons induced by amphetamine in cats. *Brain Res* 194:263-268, 1980.
Levine, S.R.; Washington, J.M.; Jefferson, M.F.; Kieran, S.N.; Moen, M.; Feit, H.; and Welch, K.M.A. "Crack" cocaine-associated stroke. *Neurology* 37:1849-1853, 1987.

Loberg, T. Neuropsychologic findings in the early and middle phases of alcoholism. In: Grant, I., and Adams, K.M., *eds. Neuropsychological* Assessment of *Neuropsychiatric Disorders:* Clinical Methods *and Empirical Findings.* New York: Oxford University Press, 1986. pp. 415-440.

Luby, E.D.; Cohen, B.D.; Rosenbaum, G.; Gottlieb, J.S.; and Kelly, R. A study of a new schizophrenomimetic drug-semyl. Arch *Neurol Psychia*try 81:363-369, 1959.

Luisada, P.V. The phencyclidine psychosis: Phenomenology and treatment. In: Peterson, R.C., *ed. Phencyclidine Abuse: An Appraisal.* National Institute on Drug Abuse Research Monograph 21. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1978. pp. 241-253.

Maisto, S.; Sobel, L.; and Sobel, M. Comparison of self reports of drinking behavior with reports of collateral informants. *J ConsuIt Clin Psychol* 47:106-112, 1979.

Mathew, R.J., and Wilson, W.H. Regional cerebral bloodflow changes associated with ethanol intoxication. *Stroke* 17:1156-1159, 1986.

Mathew, R.J.; Wilson, W.H.; and Daniel, D.G. The effect of nonsedating doses of diazepam on regional cerebral bloodflow. *Biol Psychiatry* 20:1109-1116, 1985.

Mathew, R.J.; Wilson, W.H.; and Tant, S.R. Acute changes in cerebral bloodflow associated with marijuana smoking. *Acya Psychiatr Scand* 79:118-128, 1989.

McCulloch, J.; Savaki, H.E.; and Sokoloff, L. Distribution of effects of haloperidol on energy metabolism in the rat brain. *Brain Res* 2443:81-90, 1982.

McGlothlin, W.H.; Arnold, D.O.; and Freedman, D.X. Organicity measures following repeated LSD ingestion. *Arch Gen Psychiatry* 21:704-709, 1969.

McHenry, L.C.; Merory, J.; and Bass, E. Xenon-133 inhalation method for regional cerebral blood flow measurements: Normal values and test-retest tesults. *Stroke* 9:195-205, 1978.

Mehrabian, A., and Straubinger, T. Patterns of drug use among adults. *Addict Behav* 14:99-104, 1989.

Mendelson, J.H., and Meyer, R.E. Behavioral and biological concomitants of chronic marijuana smoking by heavy and casual *users. In: Marijuana: A Signal of Misunderstanding.* The Technical Papers of the First Report of the National Commission on Marijuana and Drug Abuse. Vol. 1. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., March 1972. pp. 69-246.

Mendhiratta, S.S.; Wig, N.N.; and Verma, S.K. Some psychological correlates of long-term heavy cannabis users. *Br J Psychiatry* 132:482, 1978.

Miras, C.N., and Fink, M. Investigation of very heavy, very long-term cannabis users: Greece. In: *Marijuana: A Signal of Misunderstanding.* The Technical Papers of the First Report of the National Commission on Marijuana and Drug Abuse. Vol. 1. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., March 1972. pp. 53-55.

Mody, C.K.; Miller, B.L.; McIntyre, H.B.; Mendoza, R.; and Goldberg, M.A. Neurologic complications of cocaine abuse (abstract). *Neurology* 37(suppl 1):193, 1987.

Orzi, F.; Dow-Edwards, D.; Jehle, J.; Kennedy, C.; and Sokoloff, L. Comparative effects of acute and chronic administration of amphetamine on local cerebral glucose utilization in the conscious rat. *J Cereb Blood Flow Metab* 3:154-160, 1983.

Page, J.B.; Fletcher, J.; and True, W.R. Psychosociocultural perspectives on chronic cannabis use: The Costa Rican follow-up. *J Psychoactive Drugs* 20:57-65, 1988.

Parsons, O.A., and Fan, S.P. The neuropsychology of alcohol and drug use. In: Filskov, S.B., and Boll, T.J., eds. *Handbook of Clinical Neuropsychology*. New York: Wiley, 1981. pp. 320-365.

Parsons, O.A., and Prigatano, G.P. Methodological considerations in clinical neumpsychological research. *J Consult Clin Psycho1* 46:608-619, 1978.

Petursson, H.; Gudjonsson, G.H.; and Lader, M.M. Psychometric performance during withdrawal from long-term benzodiazepine treatment. *Psychopharmacology* 81:345-349, 1983.

Pitts, D.K., and Marwah, J. Cocaine and central monaminergic neurotransmission: A review of electrophysiological studies and comparison to amphetamine and antidepressants. *Life Sci* 42:949-968, 1987.

Prichep, L.S.; Gomez-Mont, F.; John, E.R.; and Ferris, S.H. Neuromettic electroencephalographic characteristics of dementia. In: Reisburg, B., ed. *Alzheimer's Disease: The Standard Reference. New* York: Free Press, 1983.

Prichep, L.S., and John, E.R. Neurometrics: Clinical applications. In: da Silva, F.H.L.; van Leeuwen, W.S.; and Remond, A., eds. *Handbook of Electroencephalography and Clinical Neurophysiology*. Vol. 2. Amsterdam: Elsevier, 1986.

Prichep, L.S.; Lieber, A.L.; John, E.R.; Alper, K.; Gomez-Mont, F.; Essig-Peppard, T.; and Flitter, M. Quantitative EEG in depressive disorders. In: Shagass, E., ed. *Electrical Brain Potentials and Psychopathology*, New York: Elsevier, 1986.

Rainone, G.A.; Deren, S.; Kleinman, P.H.; Wish, E.D. Heavy marijuana users not in treatment: The continuing search for the "pure" marijuana user. *J Psychoactive Drugs* 19(4):353-359, 1987.

Rehmstmm, S.; Simert, G.; and Hansson, J. Chronic hepatic encephalography: A psychometrical study. *Scand J Gastroenterol* 12:305-311, 1977.

Robinson, T.E., and Becker, J.B. Enduring changes in brain and behavior produced by amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. *Brain Res Rev* 11:157-198, 1986.

Rochford, J.; Grant, I.; and LaVigne, G. Medical students and drugs: Further neuropsychological and use patterns. *Int J Addict* 12:1057-1065, 1977.

Rohan, W.P. Quantitative dimensions of alcohol use for hospitalized problem drinkers. *Dis Nerv Sys* 37:154-159, 1976.

Rounsaville, B.J.; Jones, C.; Novelly, R.A.; and Kleber, H. Neuropsychological functioning in opiate addicts. *J Nerv Ment Dis* 170:209-216, 1982.

Rounsaville, B.J.; Novelly, R.A.; and Kleber, H.D. Neuropsychological impairment in opiate addicts: Risk factors. *Ann NY Acad Sci* 362:79-80, 1980.

Rubin, V., and Comitas, L. *Ganja in Jamaica: A Medical and Anthropological Study* of *Chronic Marijuana Use.* The Hague: Mouton, 1975.

Ruff, R.M.; Cox, D.R.; Geyer, M.A.; and Braff, D.L. Attentional and information processing deficits in head injured and schizophrenic patients. *J Clin Exp Neuropsychol* 7:645-646, 1985.

Ryan, C., and Butters, N. Alcohol consumption and premature aging: A critical review. In: Galanter, M., ed. *Recent Developments in Alcoholism.* Vol. 2. New York: Plenum Press, 1984. pp. 223-250.

Rylander, G. Psychoses and the punding and choreiform syndromes in addiction to central stimulant drugs. *Psychiatr Neurol Neurosurg* 75:203-212, 1972.

Saccuzzo, D.P., and Braff, D.L. Information processing abnormalities in schizophrenic and psychotic patients: Trait and state dependent components. *Schizophr Bull* 12:447-459, 1986.

Sacuzzo, D.P., and Larson, G.E. Analysis of test-retest reliability for a battery of cognitive speed tests. Navy Personnel Research and Development Center. NPRDC TN-88-10. San Diego, CA, November 1987.

Saccuzo, D.P.; Larsen, L.; and Rimland, B. Visual, auditory and reaction time approaches to the measurement of speed of information processing and individual differences in intelligence. *Pers Individ Diff* 2:659-668, 1986.

Satz, P.; Fletcher, J.M.; and Sutker, L. Neuropsychological, intellectual and personality correlates of marijuana use in native Costa Ricans. In: Dombush, R.L.; Freedman, A.M.; and Fink, M., *eds. Chronic Cannabis Use. Ann NY Acad Sci* 282:266-306, 1976.

Schwartz, K.A., and Cohen, J.A. Subarachnoid hemorrhage precipitated by cocaine snorting. *Arch Neurol* 41:223-224, 1984.

Sibley, D.R.; Wienberger, R.; Segal, D.S.; and Creese, I. Multiple daily amphetamine administration decreases both [3H] agonist and [3H] antagonist dopamine receptor binding. *Experientia* 38:1224-1225, 1982.

Smith, H.H., and Smith, L.S. WAIS functioning of cirrhotic and noncirrhotic alcoholics. *J Clin Psychol* 33:309-313, 1977.

Sobel, L., and Sobel, M. Validity of self-reports in three populations of alcoholics. *J Consult Clin Psychol* 46:901-907, 1978.

Soueif, M.I. The use of cannabis in Egypt: A behavioral study. *Bull Narc* 23:17-28, 1971.

Stefanis, C.; Dombush, R.L.; and Fink, M. *Hashish: A Study of Long-Term Use.* New York: Raven Press, 1977.

Steronko, R.J., and Woods, D.J. Impairment in early stages of visual information *processing* in non-psychotic schizotypic individuals. *J Abnorm Psychol* 87:481-490, 1978.

Tarter, R.E.; Hegedus, A.M.; Van Thiel, D.; Schade, R.; Pollit-Heyl, A.; and Gavaler, J. Association between hepatic dysfunction and neuropsychological capacity of cirrhotic alcoholics. *Alcohol: Clin Exp Res* 8:123, 1984a.

Tarter, R.E.; Hegedus, A.M.; Van Thiel, D.; Schade, R.; and StarzI, T. Non-alcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence for hepatic encephalopathy. *Gastroenterology* 86:1421-1427, 1984b.

Volkow, N.D.; Valentine, A.; and Kulkarni, M. Radiological and neurological changes in the drug abuse patient: A study with MRI. *J Neuroradiol* 15(3):288-293, 1988.

Ware, L.A. Neuropsychological functioning in users and nonusers of phencyclidine. *Dissert Abst* Carbondale: Southern Illinois University, 1978. p. 124.

Weiss, S.R.; Raskind, R.; Morganstern, N.L.; Pytlyk, P.J.; and Baiz., T.C. Intracerebral and subarachnoid hemorrhage following use of methamphetamine ("speed"). *Int Surg* 53:123-127, 1970.

Wesson, D.R.; Carlin, A.S.; Adams, K.M.; and Beschner, *G. Polydrug Abuse: The Results of a National Collaborative Study. New* York: Academic Press, 1978.

Wetzel, C.D.; Janowsky, D.S.; and Clopton, P.L. Remote memory during marijuana intoxication. *Psychopharmacology* 76:278-281, 1982.

Wig, N.N., and Varma, S.K. Patterns of long-term heavy cannabis use in North India and its effects on cognitive functions: A preliminary report. *Drug Alcohol Depend* 2:211-219, 1977.

Wilkinson, D.A. C.T. scan and neuropsychological assessments of alcoholism. In: Parsons, O.A.; Butters, N.; and Nathan, P.E., eds. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment. New* York: Guilford Press, 1987.

Wilkinson, D.A., and Carlen, P.L. Neuropsychological and neurological assessment of alcoholism: Discrimination between groups. *J Stud Alcohol* 41:129-139, 1980a.

Wilkinson, D.A., and Carlen, P.L. Relationship of neuropsychological test performance to brain morphology in amnesic and nonamnesic chronic alcoholics. *Acta Psychiatr Scand [Suppl]* 286:89-101, 1980b.

Wilkinson, D.A., and Carlen, P.L. Recoverability in recently abstinent alcoholics: Results of repeated neuropsychological, EEG, CT scan and neurological examination. Presented at the annual meeting of the International Neuropsychology Society, Mexico City, 1983.

Wood, D.M., and Lal, H. Anxiogenic properties of cocaine withdrawal. *Life Sci* 41:1431-1436, 1987.

Woolverton, W.L., and Kleven, M.S. Evidence for cocaine dependence in monkeys following a prolonged period of exposure. *Psychopharmacology* 94:288-291, 1988.

Wright, M., and Hogan, T.P. Repeated LSD ingestion and performance on neuropsychological tests. *J Nerv Ment Dis* 154:432-438, 1972.
Wyatt, R.J.; Karoum, F.; Suddath, R.M.; and Hitri, A. The role of dopamine in cocaine use and abuse. *Psychiatr Ann* 18:531-534, 1988.
Young, T.; Lawson, G.W.; and Gacono, C.B. Clinical aspects of phencyclidine (PCP). *Int J Addict* 22(1):1-15, 1987.

AUTHORS

Robert J. Reed, M.S.
Igor Grant, M.D.

San Diego Veterans Administration
Medical Center and
School of Medicine
University of California, San Diego
La Jolla, CA 92020

Use of Complex Behavioral Baselines to Monitor Residual Drug Effects in Animals

Merle G. Paule

INTRODUCTION

The behavior of an animal represents the integrated output of the organism. It is an observable and therefore measurable activity that is generally mediated by the central nervous system (CNS), primarily the brain. Specific behaviors are thought to be associated with specific brain functions. Copulation is thought to subserve the function of reproduction; eating, the function of feeding; and so on. For the most part, it is yet unclear whether many specific behaviors and thus many specific brain functions can be correlated with specific anatomical substrates or specific neurotransmitter systems. The status of a specific function of the brain can, however, be inferred by observing specific behaviors that are thought to be associated with the specific function of interest.

Operant techniques are behavioral procedures requiring that subjects operate (hence the term "operant") specific manipulanda or instruments in response to specific environmental conditions or stimuli. These instruments may be levers, press-plates, keys, etc. Environmental conditions in a given operant situation can be organized such that the responses or behaviors emitted by subjects are thought to depend upon rather specific (albeit often poorly defined) functions of the brain. Examples of such functions include: learning; short- and long-term memory; attention or vigilance; sensory perception (color, sound, and position discrimination); temporal or time perception; reproduction; and motivation. Because operant techniques allow the design of experiments that generate behaviors thought to be indicative of the status of specific brain functions, such techniques are of tremendous interest to those studying the functional integrity of the brain. A major drawback to using operant techniques in the animal laboratory is that it takes time to train subjects to perform at stable (predictable) levels that are appropriate for use as behavioral baselines; it is not unusual for training to take several

months. Another problem associated with the use of operant techniques is the difficulty of routinely assessing the large numbers of experimental subjects that are desirable in many experiments. This is less of a problem now that highly automated systems administer the behavioral tasks and collect and store the data, often performing calculations or other data manipulations online.

Some investigators have a strong interest in assessing the functional integrity of the brain by monitoring behaviors generated using operant techniques, and there are other reasons why complex behaviors, in general, may be useful for studying effects (acute, chronic, residual, or other). Complex behaviors are thought to be subserved by multiple neurons and thus are dependent upon the integrity of multiple units. If the function of any of the units, or neurons, subserving or influencing a particular function is altered, the behavior dependent upon that function may also be altered. It is presumed that complex behaviors will usually be more sensitive to the effects of exogenous compounds than are more basic reflex behaviors, since reflex behaviors are generally subserved by a relatively small number of neurons (two in the simplest case). With operant behaviors in particular, it is advantageous to be able to elicit a specific type of complex behavior simply by putting a trained subject into the appropriate environment. Additionally, operant behaviors are under the control of the environment, and environmental variables can be strictly controlled; therefore, operant behaviors can also be controlled. Well-controlled behaviors are generally characterized by relatively small variabilities, and it has been noted that baselines with little variability may be more sensitive to experimental manipulation than baselines with great variability (Thompson 1974). For instance, to demonstrate that a specific manipulation had a significant effect on a behavioral baseline characterized by a large variability (a standard error of 20 percent of the mean) the manipulation would have to cause a relatively large effect. On the other hand, if the baseline data were characterized by a small variability (standard error of 2 percent of the mean), then a smaller effect could be detected, even if the means were the same for both baselines. In some cases, extremely stable behavioral baselines (such as those obtained after extensive repetition over long periods of time) can be some of the most difficult to affect by a given manipulation. The particular behaviors involved and the number of observations made (in obtaining both baseline and experimental data) will also have a profound effect on the ability of a particular behavior to detect the effect of an experimental manipulation, but this is true for any experimental measure. Another point in favor of operant behavioral assessment is that the experimenter's interaction with the subject is minimized, thus reducing or eliminating a potential source of experimental variability.

Because operant behaviors are not only useful but also interesting and meaningful, the more operant behaviors measured, the better. The more operant behaviors measured in the same subject, the better. Further, a recent approach to operant behavioral analyses in nonhuman primates used a

computerized operant test battery or OTB (Paule et al. 1988; Schulze et al. 1988). The OTB consists of five different tasks. Each task is performed by most experimental subjects, and each task is thought to engender responding that is dependent upon a different brain function. The specific functions modeled in these tasks include learning, color and position discrimination, motivation, short-term memory and attention, and time perception. The names of the operant tasks, or schedules, that generate behaviors thought to depend upon these functions are incremental repeated acquisition (IRA), conditioned position responding (CPR), progressive ratio (PR), delayed matching-to-sample (DMTS), and temporal response differentiation (TRD), respectively. The OTB may be used in complex behavioral studies, particularly since the advent of computerized task administration and data manipulation. The operant or behavioral panels used in such studies will vary according to the type of laboratory animal used and the number, type, and complexity of behavioral tasks administered to each subject.

STRATEGIES FOR STUDYING THE RESIDUAL EFFECTS OF DRUGS ON BEHAVIOR IN ANIMALS

There are various strategies for studying the residual effects of drugs on the behavior of animals, and a description of some of these strategies and examples of studies that have used them may help illustrate the possibilities. It is important to point out that laboratory-animal scientists have tremendous advantages over those investigators who strive to conduct studies in human populations. The laboratory-animal scientists do not have to concern themselves with the tremendous number of known confounding factors present in human subjects. Such confounding factors include, but are by no means limited to, socioeconomic status, age, sex, health status, diet, and previous drug use. The laboratory-animal scientist can rather easily control for these potentially confounding variables. The epidemiologists and clinicians often cannot control for these variables, and must rely on relatively sophisticated statistical procedures to try to factor out confounding variables.

Controlled studies on the residual behavioral effects of drugs in animals generally seek to answer the question: Is the behavior of a treated animal somehow different than it was prior to treatment and, if so, is the change a result of that treatment? Attempts to answer this question usually involve one of two approaches. In the first, each animal serves as its own control; in the other, treated animals are compared to untreated animals or those treated only with placebo or vehicle. The most comprehensive studies will use both approaches. Because it has usually been assumed that most therapeutic agents and drugs of abuse have reversible effects on behavior when given acutely, most studies on residual effects have involved the chronic administration of such compounds, and this discussion will be limited to studies involving chronic drug exposure. Recent reports, however, have demonstrated long-lasting behavioral effects of drugs (sensitization to subsequent drug exposure) in animals receiving very limited exposure to

some compounds, such as amphetamine (Kolta et al. 1985a; Kolta et al. 1985b).

For studies that compare treated animals to themselves, it is imperative to obtain some measure of behavior prior to the initial drug exposure. For complex operant behaviors, it is essential to establish a behavioral baseline prior to exposing the animal to the drug. This involves monitoring performance parameters, i.e., accuracy and rate of responding, repeatedly, long enough to establish predictable (near steady-state) levels of responding. Once a behavioral baseline has been established, it can be used to determine the magnitude and direction of subsequent drug effects on that behavior in that same animal. Paule and Killam (1986) used this strategy to examine the effects of chronic anticonvulsant administration on operant performance in the genetically epileptic baboon, *Papio papio (Ppa).* In these studies, performance in an incremental repeated acquisition task (IRA) was used as a model of learning behavior. In this task, subjects were required to respond on three response levers in a specified order to receive food reinforcers. The correct sequence of lever presses was changed each test session so that animals had to acquire a new series of lever presses each session. At the start of each session, animals were required to press only two levers in a specific sequence to obtain food. After a criterion of 20 errorless sequences was completed, the task difficulty was incremented such that the subjects had to complete a three-response series and so on, up to a sequence requiring five responses or to the animal's performance limit, whichever occurred first. An important performance measure was the percentage of the IRA task completed each session. This endpoint is a measure of the response sequence length mastered in a given session and is a function of both response rate and accuracy. Data obtained for the antiepileptic agents valproic acid (VPA) (figure 1) and ethosuximide (ESX) (figure 2) demonstrated that performance in the IRA task was sensitive to disruption by both agents, albeit at very different doses for the two compounds.

The drugs were given 7 days per week for 2 weeks in ascending doses. The data points presented are thus 2-week averages of performance in this task. This experimental design allowed examination of the effects of increasing doses of the drug during the active administration phase of the experiment, during the period of acute withdrawal from daily drug administration, and during a prolonged period of recovery from chronic drug administration. Observation of drug effects on behavior that occur during active exposure allows for the examination of early treatment effects, if there are any, and the examination of tolerance development to such effects, if it occurs. Evidence for active treatment effects were noted during VPA administration in three of six animals shown in figure 1 *(Ppa* 136, 131, and 137). The effects began at doses of 15, 30, and 240 mg/kg per day, respectively. Active treatment effects were noted during ESX administration in four out of four animals shown in figure 2 and began at doses of 15, 30,

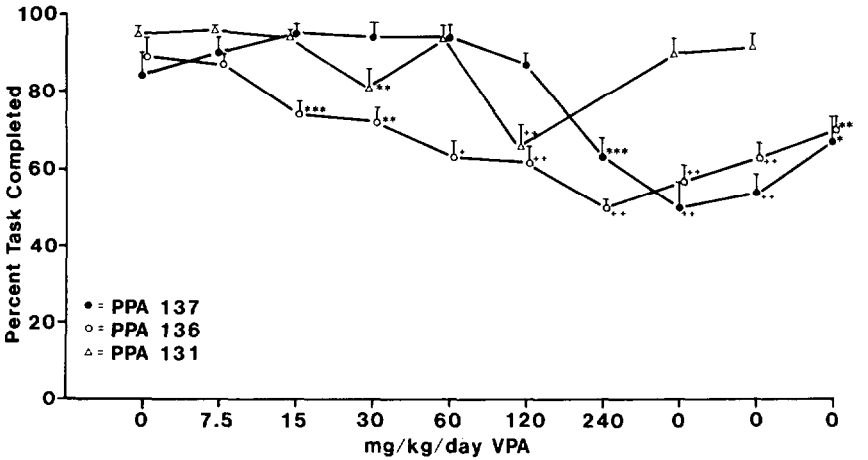

FIGURE 1. *Effects of chronic VPA administration in the baboon on percentage of IRA tasks completed*

KEY: *p<.05; **p<.025; ***p<.01; +p<.005; and ++p<.001, two-tailed *t* tests

NOTE: Data are means (+SEM) of 10 test sessions conducted over 2 consecutive weeks at each dose of drug or vehicle (0 mg/kg/day). Significance is measured against the control period immediately preceding the first dose given.

SOURCE: Paule and Killam 1986. copyright 1986, American Society for Pharmacology and Experimental Therapeutics.

and 60 mg/kg per day (for *Ppa* 101 and 131, 102, and 128, respectively). Evidence for tolerance development during VPA treatment was noted in *Ppa* 131 after an increase in daily dose from 30 to 60 mg/kg as evidenced by a return of performance to predrug levels at 60 mg/kg per day. Increasing the dose again to 120 mg/kg per day overcame the tolerance developed by this animal, as indicated by further decrements in its behavior at this dose. Evidence for tolerance development to the effects of ESX was noted in two animals whose performance improved at 30 mg/kg per day after being disrupted by doses of 15 mg/kg per day. This apparent tolerance was also overcome by the higher dose of 45 mg/kg/day. There appeared to be an absence of withdrawal effects in five of the six subjects in the VPA study, as abrupt cessation of daily VPA administration did not cause any additional adverse effects on this behavior. One animal exhibited a further decrease in the percentage of task completed during withdrawal *(Ppa* 137). However, it appeared that this change was simply a further deterioration of behavior resulting from the insult associated with the high daily dose of 240 mg/kg per day, as there were no precipitous changes in behavior that were associated with acute withdrawal. In the ESX study, no subject's behavior

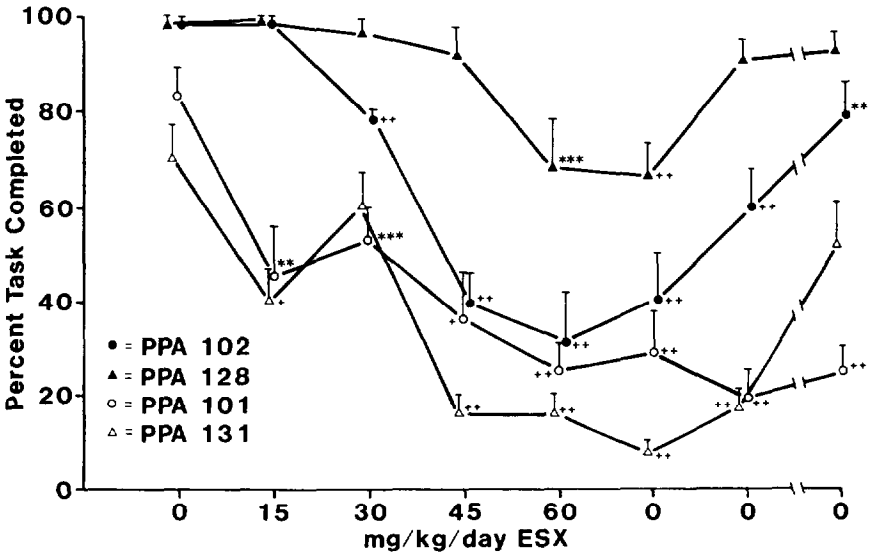

FIGURE 2. *Effects of chronic ESX administration in the baboon on percentage of IRA tasks completed*

KEY: **p<.025; ***p<.01; +p<.005; and ++p<.001.

NOTE: Data presented as described in figure 1. The break in the abscissa represents 4 weeks during which the animals were tested while receiving vehicle, but data were not collected. The last point on the graph thus represents data obtained during weeks 9 and 10 after drug treatment, during which vehicle was still being given.

SOURCE: Paule and Killam 1986, copyright 1986, American Society for Pharmacology and Experimental Therapeutics.

significantly worsened during the acute withdrawal phase either, but the relatively devastating behavioral effects caused by daily ESX treatment persisted for at least 10 weeks following cessation of treatment. For *Ppa* 101 there was little evidence of any recovery from the behavioral disruption caused by ESX even 10 weeks after cessation of treatment.

When it is pointed out that the most effective anticonvulsant doses for VPA and ESX are 7.5 to 30 and 60 or more mg/kg per day, respectively, it seems clear that the more behaviorally toxic of these two anti-petit-mal agents is ESX, since it causes rather profound behavioral disruption at doses well below those considered effective in the treatment of epilepsy. VPA, on the other hand, disrupted behavior only at doses generally higher than those considered to be effective in therapy.

The main point to be made from these data is that clear residual effects are detectable in a complex behavior that is thought to model learning. In the same studies (Paule and Killam 1986), it was found that in *Ppa* performing a different operant task (incremental fixed-ratio), neither VPA nor ESX caused consistent effects on behavior during or after chronic drug treatment. Thus, there are also clear differences in task sensitivity or susceptibility to drug effects. The adverse behavioral effects of drug treatment, noted as decrements in performance of the learning tasks, persisted for at least 6 weeks after the last dose of VPA and for up to 10 weeks and longer after the last dose of ESX. These residual effects were not likely due to the continued presence of drug, as neither compound was detectable in serum 1 week after the last dose. However, as brain levels of drug were not measured, the possibility that the residual behavioral effects were found because of the continued presence of these compounds or their metabolites in target tissue cannot be ruled out.

In studies conducted in exactly the same fashion (Paule and Killam 1980), the behavioral effects of chronic nordiazepam (NDZP, a major metabolite of diazepam) administration were examined over a similar time course, again in *Ppa*. Figure 3 shows data obtained from one of nine animals performing the IRA task during these studies. This was the only animal in which the effect was demonstrated. Were the data from this subject to be included in a group analysis of the effects of abrupt NDZP withdrawal, it would likely appear that there was a measurable effect on the group. These data are shown to demonstrate that individual subjects vary tremendously in their responses to drug administration and withdrawal. It is important to take this variation into consideration, as interpretation of group data alone may be misleading. Details of the exposure for this subject can be found in the figure legend.

The upward arrow (figure 3) indicates when daily NDZP administration began, and the downward arrow indicates when daily NDZP administration stopped. Note that during the exposure period, performance was not much different, if any, than it had been prior to treatment. However, soon after cessation of daily NDZP administration, performance in this task decreased dramatically, and for more than 1 year after the last dose of NDZP (about 50 weeks, shown in figure 3), this animal's performance never returned to levels noted prior to or during daily NDZP administration. In this subject, then, it appeared that acute withdrawal from chronic NDZP administration profoundly altered a complex behavioral response, and the alteration lasted for an extended period of time. This behavioral disruption continued long after that indicated in figure 3, and was unaltered by chronic administration of other anticonvulsants over wide dose ranges. The animal's general appearance during this time was not noticeably different than it was prior to the start of chronic NDZP administration. Thus, operant techniques demonstrated a rather profound behavioral effect, caused presumably by abrupt drug withdrawal, that might otherwise have gone completely unnoticed.

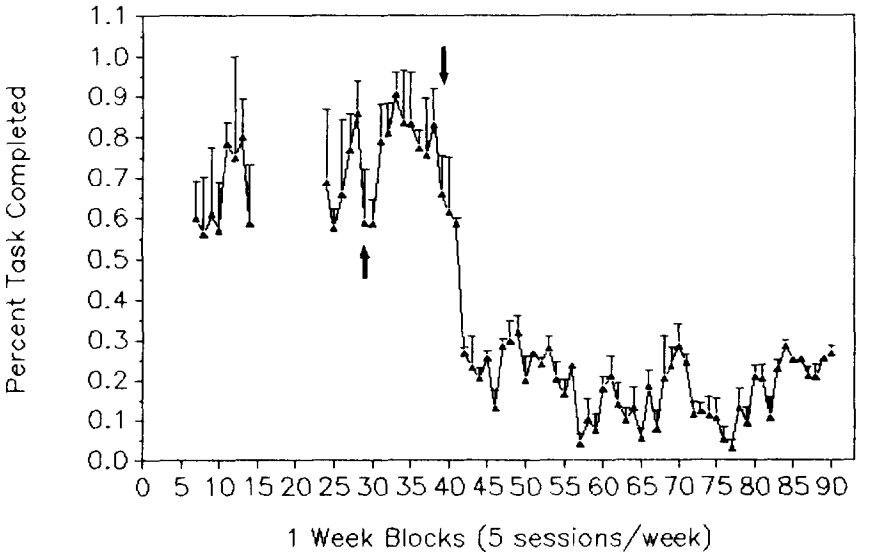

FIGURE 3. *Effects of acute withdrawal from chronic NDZP administration in the baboon on percent of IRA tasks completed*

NOTE: Data shown are weekly averages (+SEM) for one animal *(Ppa* 134) of nine that received the same treatment regimen. During weeks 5-13, the animal received various doses of NDZP vehicle (40% propylene glycol, 10% ethanol, 50% water, by volume) or saline given IM once per day or no treatment. During weeks 14-23 the animal was invoIved in acute dose-response studies on naloxone, data not shown. During weeks 24-28 the animal again received either IM saline injections or NDZP vehicle. Upward arrow indicates the beginning of daily NDZP administration: once. per day IM injections at doses of 0.125. 0.25, 0.5, 1.0, and 2.0 mg/kg. Doses were given in ascending order, each dose was given 7 days/wk for 2 weeks. Downward arrow indicates when acute NDZP withdrawal began: vehicle only was given for 4 weeks followed by saline administration for 3 weeks (to week 4.5). For the remainder of the time shown, the subject also received chronic treatments with various doses of valproic acid and carbamazepine.

The mechanism underlying this phenomenon is unknown, but its occurrence is important for a number of reasons. First, such an effect demonstrates again that complex behaviors may be very useful for detecting long-term or residual effects of drugs or drug withdrawal. Second, it demonstrates that acute drug withdrawal may have profound and apparently irreversible effects on complex behaviors in some subjects. Finally, it demonstrates a very important experimental reality: not all animals respond in the same manner to the same experimental manipulations. Eight other animals (one of which was the affected animal's half-brother) received essentially the same drug regimen as did the affected individual, and none of those animals exhibited the phenomenon just described.

The excellent work by Stiglick and Kalant (1982a) on the cannabinoids demonstrates another approach to examining the residual effects of drugs. Additional examples of this approach can be found in their other publications (Stiglick and Kalant 1982b; Stiglick and Kalant 1983; Stiglick and Kalant 1985; Stiglick et al. 1984). In these studies, laboratory rats were treated chronically (for 3 or 6 months) with marijuana extract. Two to three months after the last dose, the animals underwent a variety of complex behavioral assessments; their performance was then compared to that for rats that had received vehicle only. Animals that had been exposed to the marijuana extract demonstrated significant alterations in open field activity and significant deficits in the acquisition of a "time perception" (differential reinforcement of low-rate responding schedule or DRL) task (figure 4). After 2 to 3 weeks of training, the marijuana-extract-treated animals were significantly less efficient in responding in the DRL task than were the controls, irrespective of whether active exposure to the extract lasted for 6 (figure 4a) or for 3 (figure 4b) months. Likewise, recent studies by Holson et al. (1989) have demonstrated significant residual (2 months after the last dose) behavioral effects of delta-9-tetrahydrocannabinol (Δ^9-THC) in rats responding to a complex maze after chronic (90 day) oral administration. Thus, residual effects of cannabinoids have been clearly demonstrated in rodent models in studies in which no behavioral assessments were made during the active exposure phase of the experiment or for 2 to 4 months after the last treatment.

A study supported by the National Institute on Drug Abuse and conducted at the National Center for Toxicological Research has been designed specifically to examine the residual behavioral effects of chronic marijuana smoke exposure. Young male rhesus monkeys are serving as subjects in this large-scale experiment using complex operant behaviors as baselines for examining drug effects. An extensive amount of behavioral data have been gathered in this study and detailed analyses are under way for publication elsewhere. The experimental design represents a comprehensive approach to the study of residual behavioral effects of drugs.

As shown, monitoring behaviors prior to, during, and after the active-drug-exposure phase of a chronic drug study allows one to obtain data on residual as well as other drug effects (acute effects, tolerance development, withdrawal effects, etc.). However, it may be argued that in subjects allowed to perform the behaviors of interest during the active exposure phase of an experiment, tolerance may develop to any behavioral disruption caused by such treatment. Residual drug effects would then be masked by such tolerance and thus go undetected. For the chronic marijuana smoke study, all subjects were trained to perform in the operant test battery (OTB) described earlier for about 1 year. The subjects were then divided into two behavioral groups: one group was behaviorally assessed during the active exposure phase (1 year), while the other group was given cage rest throughout that period. Behavior was monitored again in the cage-rested group

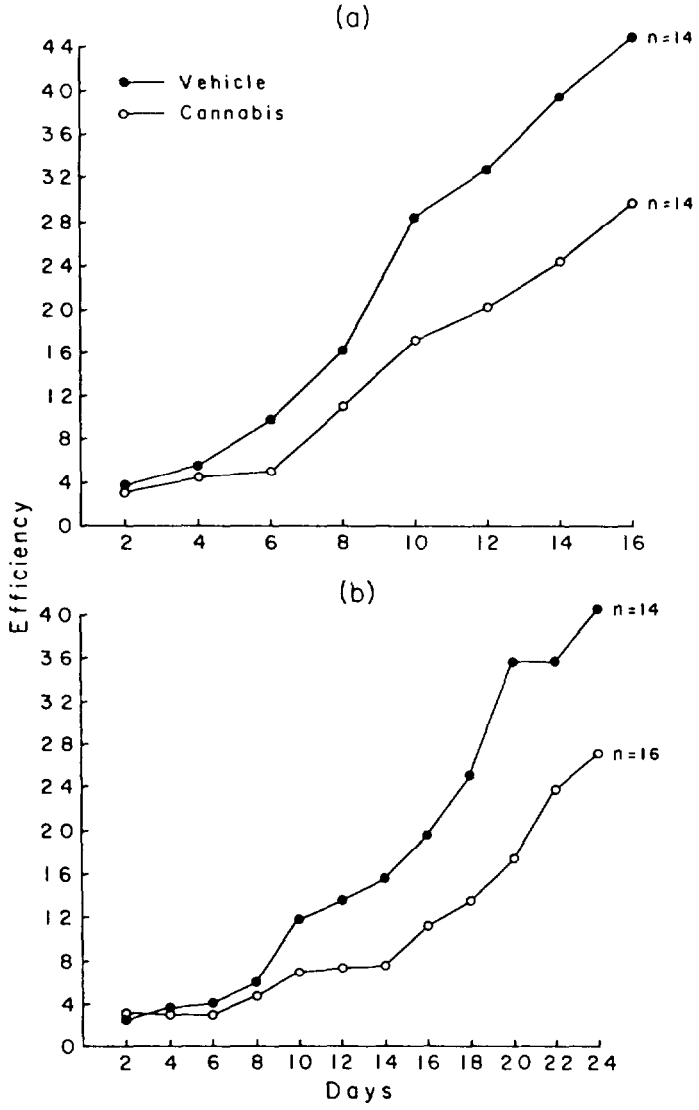

FIGURE 4. *Acquisition of DRL. performance by control rats or rats treated chronically with marijuana extract following either 6 months (a) or 3 months (b) of exposure (extract dose equivalent to 20 mg tetrahydrocannabinol/kg)*

NOTE: Testing began 97 and 113 days after the last treatment for the 6- and 3-month exposures, respectively. Efficiency is defined as the percent of responses reinforced.

SOURCE: Stiglick and Kalant 1982a, copyright 1982, Springer-Verlag.

beginning 2 months after the last exposure to marijuana smoke. Within both behavior groups, there were four treatment groups: a high-dose marijuana group (1 marijuana cigarette, approximately 2.5 percent Δ^9-THC per day, 7 days per week); a low-dose marijuana group (1 marijuana cigarette per day, only on Saturdays and Sundays, with sham exposures Monday through Friday); an extracted marijuana cigarette group (1 marijuana cigarette devoid of cannabinoids, 7 days per week); and a sham group (exposure to the dosing situation only, no smoke any day). Thus there were a total of eight different experimental cells: four exposure conditions X two behavioral conditions. It is important to the design that prior to marijuana exposure, the eight groups used to fill these cells were balanced with respect to performance in the five operant tasks contained in the OTB. That is, animals were sorted into groups such that there were no differences in group averages between measures of performance on each of the five operant tasks. This preparation prior to beginning active marijuana smoke exposure assured comparability of performance between experimental cells, i.e., differences in apparent baseline "abilities" between groups were eliminated. This experimental design also allowed for the use of the two different approaches mentioned previously in studying the residual behavioral effects of drugs: animals served as their own controls and they were compared to other control animals. Additionally, the behavior of some subjects was continuously monitored, whereas performance in others was monitored only long after exposure had ceased.

Preliminary findings from these studies have been reported elsewhere (Paule et al. 1988; Slikker et al. 1988). Briefly, it was shown that chronic marijuana smoke exposure does have detectable residual effects in some of the OTB tasks. These residual effects were found in both behavioral groups and in both the low- and the high-dose groups. Generally, when group effects were detected, such effects were attributable to only a few, or some times to one animal within the affected group. In affected animals that were behaviorally assessed throughout the exposure period, cessation of exposure was usually accompanied by a gradual return of performance toward that of sham or placebo animals. In affected animals that were cage-rested during the chronic exposure and withdrawal periods, noted residual effects did not appear to wane with the passage of time (figure 5). Thus, both approaches to the behavioral analysis of residual drug effects were effective.

CONCLUSION

It is clear that well-designed and controlled laboratory animal studies can specifically examine and detect residual drug effects. Such studies are free of the large numbers of confounding variables that cannot be controlled, or in some cases known, in human studies. Additionally, human studies often suffer from design flaws (Feinstein 1988). The relatively few numbers of laboratory animal investigations that have been performed specifically to

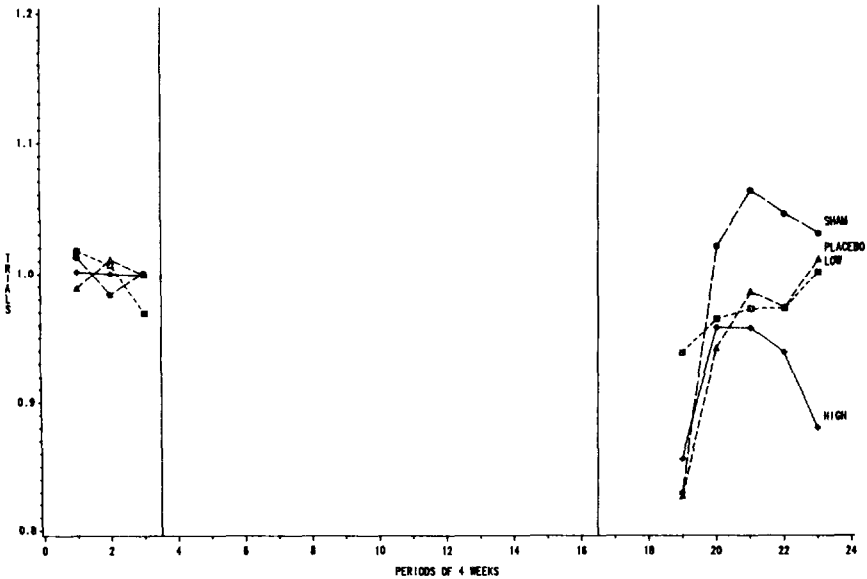

FIGURE 5. *Residual effects of chronic marijuana smoke exposure on performance of a conditioned position response (CPR) task in rhesus monkeys*

NOTE: The CPR task required subjects to respond at either a left or a right press-plate depending upon whether a center press-plate had been illuminated red or yellow (left correct) or blue or green (right correct). See Schulze et al. (1988) for details of the procedure. This group of animals was not allowed to perform the task during the active exposure portion of the study. The mean number of trials completed per session are plotted as ratios of the preexposure or baseline period. The first vertical line represents the start of 1 year of smoke exposure and the second vertical line the end of exposure. The data are means for each treatment group for periods of 4 weeks during which 10 CPR sessions generally occurred. Behavioral testing was reinstated 2 months after the last exposure; the performance of the sham, placebo, and low-dose groups was indistinguishable from one another within 5 months (by period #23). The performance of the high-dose group, however, remained significantly different from all other groups at this time, primarily because of the continued poor performance of one or two animals in that group. Additionally, the average performance of the high-dose group, when collapsed over periods 20-23, was significantly different from that of the sham group collapsed over the same periods.

assess residual behavioral effects of drugs may reflect the time and cost associated with these types of studies. Nonetheless, in light of the continuing drug abuse problem, it is becoming increasingly important to conduct appropriate studies to determine the probable long-term consequences of drug abuse on complex brain function. The public may then become better informed and thus better equipped to make decisions concerning drug abuse. There seems an urgent need to increase the emphasis on laboratory animal

studies so that useful information on the consequences of long-term drug abuse can be obtained in a timely fashion. It should be possible, using animal studies, to more rapidly identify those drugs with the greatest potential for causing adverse behavioral effects in humans. Examination of the behavioral effects of compounds with well-defined mechanisms of action, i.e., specific agonists, antagonists, depletes, and neurotoxicants for the various neurotransmitter systems, may provide valuable information concerning the participation of specific neurotransmitter systems in specific behaviors. As many drugs of abuse are known to interact with specific neurotransmitter systems, e.g., benzodiazepines and the GABA system, it may then be possible to predict which behaviors or classes of behaviors will be adversely, or otherwise, affected by a specific drug.

REFERENCES

Feinstein, A.R. Scientific standards in epidemiologic studies of the menace of daily life. *Science* 242:1257-1263, 1988.

Holson, R.R.; Ali, S.F.; Scallet, A.C.; Slikker, W., Jr.; and Paule, M.G. Benzodiazepine-like behavioral effects following withdrawal from chronic delta-9-tetrahydrocannabinol administration in rats. *Neurotoxicology* 10:491-500, 1989.

Kolta, M.G.; Shreve, P.; De Souza, V.; and Uretsky, N.J. Time course of the development of the enhanced behavioral and biochemical responses to amphetamine after pretreatment with amphetamine. *Neuropharmacology* 24(9):823-829, 1985a.

Kolta, M.G.; Shreve, P.; and Uretsky, N.J. Effect of methylphenidate pretreatment *on* the behavioral and biochemical responses to amphetamine. *Eur J Pharmacol* 117:279-282, 1985b.

Paule, M.G., and Killam, E.K. Improvement of repeated acquisition (learning) performance by chronic nordiazepam administration in the epileptic baboon. *The Pharmacologist* 22(3):292, 1980.

Paule, M.G., and Killam, E.K. Behavioral toxicity of chronic ethosuximide and sodium valproate treatment in the epileptic baboon, *Papio papio.* *J Pharmacol Exp Ther* 238(1):32-38, 1986.

Paule, M.G.; McMillan D.E.; Bailey, J.R.; Scallet, A.C.; Ali, S.F.; and Slikker, W., Jr. The effects of chronic marijuana smoke exposure on complex behavior in the rhesus monkey. *The Pharmacologist* 30(3):A115, 1988.

Paule, M.G.; Schulze, G.E.; and Slikker, W., Jr. Complex brain function in monkeys as a baseline for studying the effects of exogenous compounds. *Neurotoxicology* 9(3):463-470, 1988.

Schulze, G.E.; McMillan, D.E.; Bailey, J.R.; Scallet, A.C.; Ali, S.F.; Slikker, W., Jr.; and Paule, M.G. Acute effects of delta-9-tetrahydrocannabinol (THC) in rhesus monkeys as measured by performance in a battery of complex operant tests. *J Pharmacol Exp Ther* 245(1):178-186, 1988.

Slikker, W., Jr.; Paule, M.G.; McMillan, D.E.; Bailey, J.R.; Scallet, A.C.; and Ali, S.F. Assessment of complex behavior in the rhesus monkey: Effects of chronic marijuana smoke exposure. *Abst Soc Neurosci* 14(1):327, 1988.

Stiglick, A., and Kalant, H. Residual effects of prolonged cannabis administration on exploration and DRL performance *in rats. Psychopharmacol*ogy 77:124-128, 1982a.

Stiglick, A., and Kalant, H. Learning impairment in the radial-arm maze following prolonged cannabis treatment in rats. *Psychopharmacology* 77:117-123, 1982b.

Stiglick, A., and Kalant, H. Behavioral effects of prolonged administration of delta-9-tetrahydrocannabinol in the rat. *Psychopharmacology 80:325*-330, 1983.

Stiglick, A., and Kalant, H. Residual effects of chronic cannabis treatment on behavior in mature *rats. Psychopharmacology* 85:436-439, 1985.

Stiglick, A.; Llewellyn, M.E.; and Kalant, H. Residual effects of prolonged cannabis treatment on shuttle-box avoidance in the rat. *Psychopharmacol*ogy 84:476-479, 1984.

Thompson, D.M. Repeated acquisition of response sequences: Effects of d-amphetamine and chlorpromazine. *Pharmacol Biohem Behav* 2:741-746, 1974.

AUTHOR

Merle G. Paule, Ph.D.
Pharmacodynamics Branch
Division of Reproductive and Developmental Toxicology
National Center for Toxicological Research
Jefferson, AR 72079-9502
and
Department of Pharmacology and Toxicology, Slot 611
Department of Pediatrics, Slot 512
College of Medicine
University of Arkansas for Medical Sciences
4301 West Markham Street
Little Rock, AR 72205

Clinical-Behavioral Observations of the Long-Term Effects of Drug Abuse

George E. Woody, A. Thomas McLellan, and Charles P. O'Brien

INTRODUCTION

The topic of the long-term effects of drug abuse is one of the most difficult areas in substance abuse research to study, but also one of the most interesting and important. Of the many problems to emerge in exploring this area, one of the first is that of separating acute drug effects and withdrawal effects from underlying, nondrug conditions. The available studies that have tried to address this problem typically have many methodological flaws, and these are discussed in detail by Grant (this volume). One of the most vexing methodological difficulties is that of finding proper controls. An ideal study might measure a group of relevant variables before the onset of drug abuse or dependence in subjects who are matched on a range of variables (perhaps, ideally, twins). Half of these subjects would then become addicts; the variables would then be measured again at a later time after the abuse or dependence has ended. Such a design is possible with animals but probably impossible to even contemplate in humans. Nonetheless, in spite of the complex methodological problems that are part of studying this difficult area, studies have been done that provide interesting data leading to future research.

GENERAL OBSERVATIONS

One study that has examined the long-term effects of stimulants, depressants, and opiates is that done by McLellan and colleagues (1979). These investigators followed a group of patients who were readmitted to the substance abuse units of the Coatesville Veterans Administration Medical Center at least once every 6 months for a period of 6 years. Because of their history of repeated admissions, these patients were some of the most refractory and chronic substance abusers treated at that institution during the

years from 1972 to 1978, when the study was conducted. All subjects had a psychiatric interview upon admission and were administered the Minnesota Multiphasic Personality Inventory (MMPI) approximately 2 weeks after hospitalization. This 2-week interval was selected as being sufficient for most acute drug effects to have disappeared, thus minimizing the chances for acute effects to interfere with the MMPI scores or psychiatric assessments. The patients studied were grouped into three categories, based upon the class of drugs that they used: stimulants (mainly amphetamines), depressants (barbiturates, methaqualone, glutethimide, benzodiazepines), and narcotics (heroin, hydromorphone, methadone).

The findings were very interesting. Demographic variables and MMPI scores were similar for all subjects at their first admission. They differed only in the drugs that they typically abused at this early stage in their drug-taking careers. A much different picture emerged over the period of the study. The stimulant group developed significant increases in schizophrenic-like symptoms, especially paranoia. The sedative abusers developed increases in depressive symptoms, cognitive impairment (vocabulary and abstracting difficulties), and anxiety. The narcotic addicts had elevations in depression and sociopathy upon admission, and these symptoms remained unchanged over the 6-year period. These data are summarized in table 1.

The results were interpreted as indicating that prolonged use of stimulants was associated with the emergence of schizophreniclike symptoms over the 6-year period; depressants were associated with depression; and narcotic addiction resulted in no new psychiatric symptoms. These psychiatric effects were specific to the drug of choice and were not due to acute withdrawal effects, as the evaluations were done at least 2 weeks after admission. The tentative conclusions were that the specific drug that was used may have actually caused the observed psychiatric conditions, but these conclusions must remain tentative due to methodological problems. One of these problems was that of controls. Since the patients were observed only after the drug use had started, it was impossible to be certain that the effects occurred only because of the drug and not because of an underlying, nondrug condition that would have emerged even in the absence of drug abuse.

Amphetamine Effects

A second line of clinical data is that of toxicity from long-term amphetamine abuse, as reported by Swedish researchers. Unlike the situation in the United States, where polydrug use is the norm, amphetamine use in Sweden has occurred in an almost “pure” form since 1960. This has provided a better opportunity than that available in the United States for studies of long-term amphetamine effects. Several observations have been made.

TABLE 1. *Scores on psychologic tests in 1972 and 1978*

Test	Group 1 11 Men (Psycho-stimulants) 1972	1978	Group 2 14 Men (Psycho-depressants) 1972	1978	Group 3 26 Men (Opiates) 1972	1978
SILS						
Mean I.Q.	101	103	102	94†	104	102
Mean Cognitive Impairment	93	94	93	81†	92	91
MMPI*						
Validity	52	54	54	51	56	55
General Pathology	64	96†	58	78†	62	66
Hypochondriasis	61	67‡	61	72‡	59	61
Depression	55	58	60	94‡	64	66
Hysteria	60	71	54	58	54	54
Psychopathy	70	76‡	68	74‡	72	78
Male-Female**	64	70	60	58	62	62
Paranoia	63	84‡	57	55	59	61
Psychasthenia	56	57	58	62	58	62
Schizophrenia	66	98‡	60	63	64	61
Mania	64	87‡	63	66	65	59
Social Inversion	48	55	55	59	56	58

*MMPI values above 70 indicate severe problem areas.
**Inappropriate gender identification.
†$p<.01$ by paired t-test.
‡$p<.05$ by paired t-test.

SOURCE: McLellan et al. 1979, copyright 1979, *New England Joumal of Medicine.*

First, amphetamine abusers and addicts appear to diminish their use of this drug markedly after about 10 years; in this way, amphetamine dependence is more self-limited than other types of addiction, such as opiate dependence. The reason for this decrease in self-administration seems to be related to the second series of observations, which are that long-term amphetamine use produces central nervous system (CNS) toxicity.

Two kinds of toxic effects have been reported. One is paranoia with auditory or visual hallucinations. These symptoms are well-known adverse effects of amphetamine abuse and addiction, which seem to occur more rapidly and at lower doses after long-term use. This observation is

consistent with a kindling effect, as reported by Poet and colleagues (1976). The second toxic effect is the development of choreoathetosis. This may result from changes in dopamine receptors, as is seen with prolonged use of antipsychotic drugs. Choreoathetosis has not been a prominent complication of amphetamine abuse or dependence in America, but it is reportedly a well-recognized complication of long-term amphetamine use in Sweden (Lundh and Tunving 1981).

It is uncertain if long-term cocaine abuse will produce effects similar to those reported from Sweden with amphetamines. The data of Ricaurte and associates (1980), reporting damage to serotonin and dopamine receptors after administration of methylene-dioxy-methamphetamine (MDMA) to animals, suggests that long-term cocaine abusers should be studied for the emergence of similar effects.

Another observation, again from the Scandinavian literature, is that amphetamine abusers and addicts have a death rate of approximately 1 percent per year, compared to approximately 2 percent per year for opiate addicts. This is probably due to the respiratory depressant effects that are part of opiate administration but are not seen with stimulants (Tunving 1988).

Sedative Effects

There is an immense literature about the cognitive impairments and affective disturbances that are produced by alcohol (Parsons et al. 1987), and a less extensive but substantial literature on similar problems that are produced by sedative hypnotics. Most studies of long-term sedative abuse and dependence indicate that the sedative hypnotics cause depression, anxiety, and cognitive impairment, as indicated in the paper by McLellan and coworkers discussed earlier and summarized in table 1. Most of these effects diminish or disappear with prolonged abstinence. A more detailed description of these effects is included in the chapter by Grant (this volume).

Opiate Effects

Chronic effects of opiates include those that occur during self-administration and those that are observed in long-term addicts following detoxification.

Effects During Chronic Administration. Several studies have evaluated the effects of chronic methadone administration; one of the first was that by Martin and colleagues (1973). These authors examined a range of variables in six healthy prisoners who were serving Federal sentences for drug-related crimes in the addiction treatment and research program at Lexington, KY. Methadone was given for approximately 14 weeks. They found that methadone suppressed normal levels of testosterone, leuteinizing hormone (LH), and cortisol; produced sedation; decreased blood pressure, pulse, and pupil size; and caused hemodilution and peripheral edema. These effects were

similar to those observed with chronic morphine administration, and the researchers concluded that methadone's long-term effects were very similar to those of morphine.

Kreek (1973) studied a similar range of variables, but the subjects had been taking methadone chronically for 2 or more years as part of a methadone treatment program. She found no abnormalities in testosterone, LH, or cortisol. The only hormonal value that was different from normals among those she evaluated was prolactin, which rose shortly after receiving the daily methadone dose and remained elevated for several hours. She interpreted these findings as indicating tolerance to most of the endocrine effects of methadone. Her work does not contradict that of Martin and associates, as, in short-term studies, she found effects similar to those of Martin. Rather, it indicates that a long period of time is necessary for tolerance to develop to many of the abnormalities that are produced during short-term administration. Kreek also found that the edema and hemodilution observed by Martin and coworkers are caused by an increase in secretion of antidiuretic hormone that is caused by methadone and that, with long-term administration, tolerance also develops to this effect.

The only long-term medical problems observed by Kreek were increased sweating, observed in 48 percent of long-term methadone patients; constipation, seen in 17 percent; decreased libido, found in 22 percent; and difficulty obtaining an erection in 14 percent. Amenorrhea was usually observed early in treatment, but menses usually became normal after 4 to 6 months in treatment. Very slight decreases in polymorphonuclear leukocytes and in blood urea nitrogen levels and increases in lymphocytes were also seen with long-term maintenance treatment. No changes in liver function tests were seen, and vital signs were also within normal limits (Kreek 1973; Kreek and Hartman 1982).

One interesting clinical observation that has been reported occasionally but consistently is that of an apparent antipsychotic effect from methadone (McKenna 1982). The data are always clinical anecdotes that typically occurs as follows. A patient has been treated for months or years and has been observed to be somewhat impulsive, anxious, or depressed but does not seem to have a major psychiatric problem other than opiate dependence. For one reason or another, this patient is detoxified. Shortly before the detoxification is completed, or several days after the last dose of methadone is administered, the patient becomes much more anxious. Within hours or days, a full-blown schizophrenic disorder emerges. This requires psychiatric hospitalization and antipsychotic medication. In some cases, the patient was known to have schizophrenia; in other cases, there is no such history. In retrospect, it appears that the methadone was exerting an antipsychotic effect and that the emergence of the schizophrenia resulted from the loss of this effect during the latter stages of detoxification. Methadone can thus be seen as helping to "stabilize" or suppress schizophrenia in patients who are

free of acute symptoms. In this formulation, the removal of the methadone "unmasks" the underlying schizophrenic process. Another observation along these same lines is that schizophrenic addicts who are receiving methadone and antipsychotic medication appear to require less medication than non-addicted, nonmethadone-maintained schizophrenics (Woody and O'Brien, unpublished observations).

It is important to emphasize the very anecdotal and clinical nature of these observations. However, it is equally important to note that the authors have heard many similar reports and have personally observed several instances that demonstrate the points discussed above. The apparent antipsychotic effect of methadone (and other narcotics) may be related to dopamine blockade. As noted above, methadone elevates prolactin, an effect produced by neuroleptic medication and caused by blockade of dopamine receptors (Kreek and Hartman 1982).

Effects Following Detoxification. Dole's original theory stated that chronic opiate use caused permanent neurophysiological abnormalities (Dole et al. 1966). These alterations became clinically significant when addicts were drug free and resulted in a persistent craving for narcotics following detoxification. The abnormalities were postulated to be a significant contributor to the very high relapse rates following detoxification and other forms of drug-free treatment. Chronic addicts thus came to need opiates in much the way that diabetics need insulin, because they were physiologically abnormal as a result of changes that were produced by years of opiate use. This theory, along with that of "narcotic blockade" (raising the tolerance with high doses of methadone so that it is almost impossible to experience narcotic effects from heroin administration) provided much of the justification for the early experiments with methadone and for explaining its success. Though this theory is widely quoted and respected, it has never been proven. Other explanations for relapse have also been proposed and these include psychosocial (Khantzian 1982, Wurmser 1982) and conditioning factors (Wikler 1973; O'Brien et al. 1984).

Although the results can be considered only tentative, because of the methodological problems mentioned earlier, several recent studies have provided data that can be interpreted as supportive of Dole's theory. One is the work of Kreek (1989) who has shown abnormal responses to metyrapone in detoxified former heroin addicts. Metyrapone blocks the 11 beta-hydroxylation of the precursor of cortisol and thereby prevents its production by the adrenal cortex. Normal subjects will have a compensatory rise in ACTH and beta-endotphin levels following the administration of metyrapone, in response to the reduced levels of cortisol. Kreek has found that stabilized methadone-maintained patients have a normal rise in adrenocorticotrophic hormone (ACTH) and beta-endorphin following metyrapone but that detoxified former heroin addicts have a greatly exaggerated increase in the plasma levels of beta-endorphin. Kreek's work is preliminary and continuing, but it

suggests that detoxified opiate addicts may have an abnormally increased hormonal response to stress. This abnormality could be a result of physiological alterations produced by long-term opiate use, and it may contribute to relapse following detoxification.

A similar finding has resulted from a project that aimed to examine the relationships between endocrine secretion and affect in opiate addicts during methadone maintenance, detoxification, and long-term abstinence (Woody et al. 1988). Comparisons were made between chronic opiate addicts during four stages of treatment: stabilization on methadone for 3 to 4 months, termed early maintenance (n=27); stabilized for 2 or more years, termed long-term maintenance (n=10); successfully detoxified for 2 or more years, termed long-term drug free (n=15); and normal controls (n=15).

Subjects were males, the average age was 38, and the average number of years of opiate dependence was 7.5 years. Of the subjects, 68 percent reported a history of other drug abuse (usually benzodiazepine or amphetamine). Subjects who had serious medical problems, current psychiatric problems other than opiate dependence, who were currently taking any prescribed medication or illicit substance other than methadone were not recruited for the study. Long-term abstinence was verified by interview with an experienced research technician, by urinalysis, and by personnel who had treated the subjects in an abstinence-oriented group. Most of the long-term drug-free subjects were graduates of Eagleville, a nearby therapeutic community, and had been engaged in the followup program from that institution. Controls were recruited from the hospital police force and from housekeeping. They had no history of substance abuse and were of the same age and socioeconomic background as the methadone patients and drug-free group.

All subjects were admitted to the Philadelphia Veterans Administration Medical Center inpatient ward for testing. The procedures followed on all testing occasions and for all subjects were identical with one exception. This was that the methadone-maintained subjects were admitted to the unit 1 or 2 days before testing, to be certain that no other drugs were taken that would influence the measures of hormones and affect; controls and long-term drug-free subjects reported to the inpatient unit at 8 a.m. on the day of testing.

Blood samples were obtained by means of a Sigmamotor microflow blood withdrawal pump through an indwelling nonthrombogenic catheter placed in the left forearm. The pump, which provides an integrated plasma sample, was set at 10 ml per hour, and collecting tubes were changed at 30-minute intervals over the 7-hour period (8:30 a.m. to 3:30 p.m.). A total sample of approximately 120 ml of blood was taken on each testing occasion. All blood samples were centrifuged immediately after completion of each 30-minute interval, and the plasma was separated and stored at -25 °C until

analyzed. Hormone analyses were done by SmithKline Laboratories, using standard assays supplied by various companies. Testosterone was analyzed using the assays of the Diagnostic Products Corporation; prolactin assays were from Hybritech Corporation; cortisol assays were from Clinical Assays of Cambridge; and LH assays were from American Biotechnical Corporation.

All methadone subjects received their daily dose at 10 a.m. A battery of tests aimed to measure affect was administered between 9:15 and 10 a.m. and again between 2:30 and 3:15 p.m. These times were chosen to maximize the chances of finding differences before and after receiving the daily methadone dose. The same battery of measures were administered at identical times to the long-term drug-free subjects and the controls.

Preliminary work done on this project indicated that cortisol and prolactin were the most variable of the four hormones studied; analyses were performed on all 14 of the 30-minute samples for these substances. The other hormones were less variable over time; therefore, to conserve costs, the testostemne analyses were performed on seven of the half-hour samples, and LH analyses were computed on four of the samples. In both cases, analyses were spaced evenly over the 'I-hour time period. These multiple samples provided a profile of each hormone during the testing period. As the samples were collected directly into a distal tube (attached to the subject's waist), there was very little disruption, which might have been reflected in the hormonal analyses, for the patient. Upon completion of the testing procedure, the patients were discharged from the research ward and continued on maintenance or other followup treatment.

The hormone levels are seen in figures 1 through 4, and the affect scores, as measured on the Beck Depression Inventory, the Hopkins Symptom Checklist-90 (SCL-90), and the Profile of Mood Scales (POMS), are seen in figures 5 through 9.

Pmlactin levels showed the predictable rise and fall after the daily methadone dose for maintained subjects. There was some indication of tolerance, as the curve formed by the long-term maintenance subjects was lower than that of the early maintenance group; however, these differences were not significant. A similar finding is seen in the higher prolactin levels of the long-term drug-free group compared to the controls; again, these differences were not significant. Cortisol levels in the long-term drug-free and control subjects were almost identical, as seen in figure 2. Significant differences were evident, however, between long-term drug-free subjects and all other groups in the measured levels of testosterone and LH.

Significant differences were seen between the long-term drug-free subjects and all other groups on the SCL-90 anxiety and hostility scores and on the POMS tension and anger scores. No differences were seen between groups

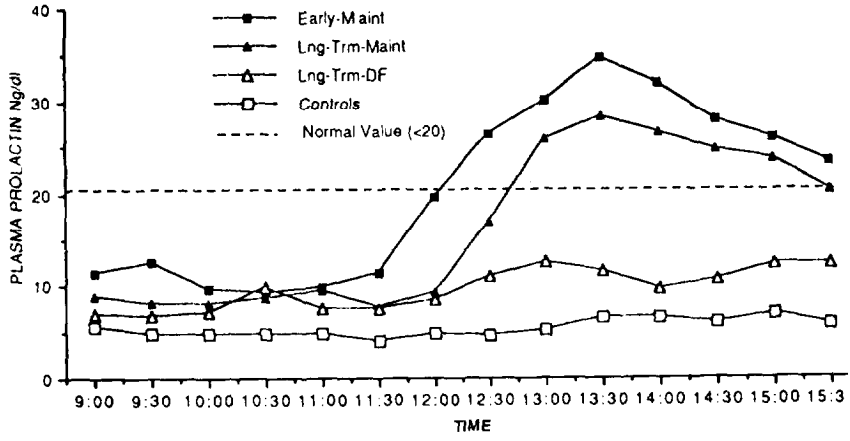

FIGURE 1. *Plasma prolactin levels by group*

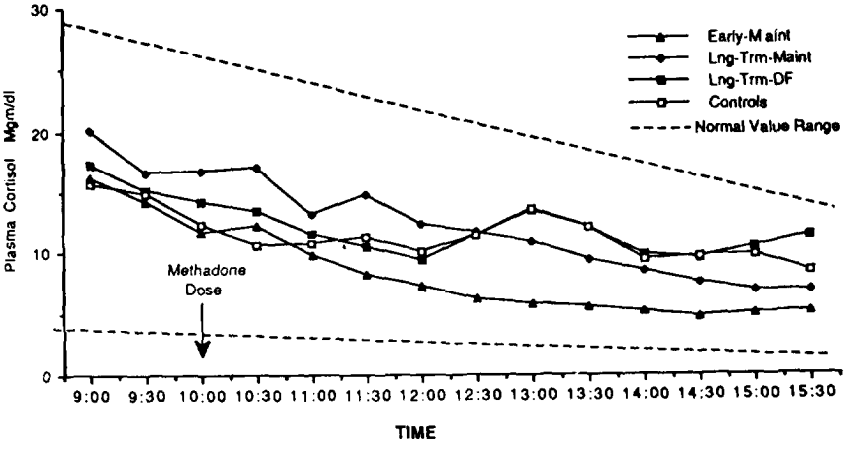

FIGURE 2. *Plasma cortisol levels by group*

on the Beck, nor were significant differences noted between the morning and afternoon psychological testing occasions, although there were trends for all scores to be lower in the afternoon. These differences suggested that the long-term drug-free subjects may have experienced subtle residual drug effects on one or more of the neurophysiological systems that regulate affect.

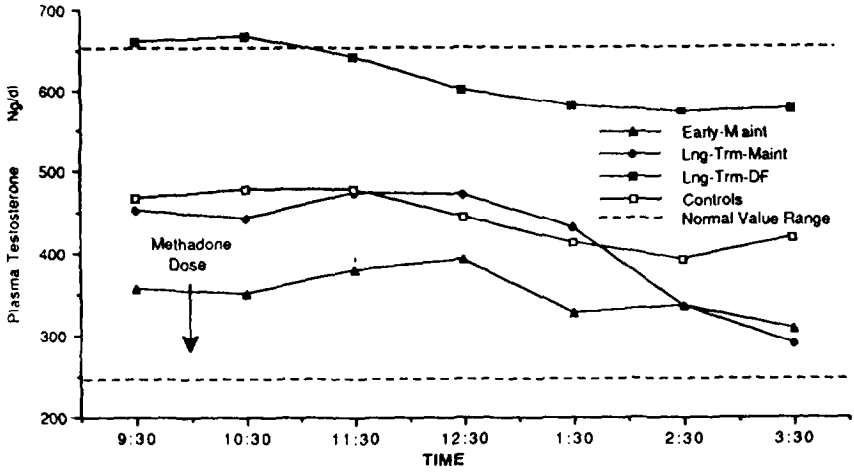

FIGURE 3. *Plasma testosterone levels by group*

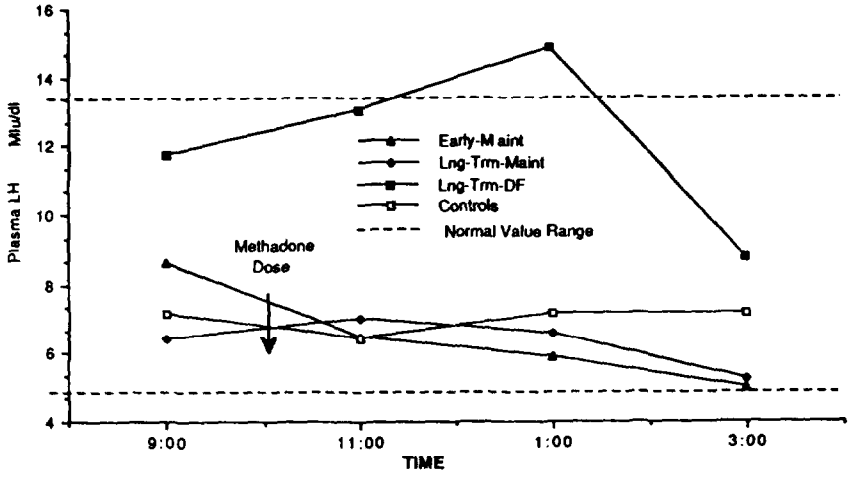

FIGURE 4. *Plasma LH levels by group*

As noted at the beginning of this chapter, methodological problems limit any conclusions made from the changes observed above. Among such problems is the comparability of groups. Those opiate addicts who succeed in becoming abstinent for 2 or more years may be biologically different,

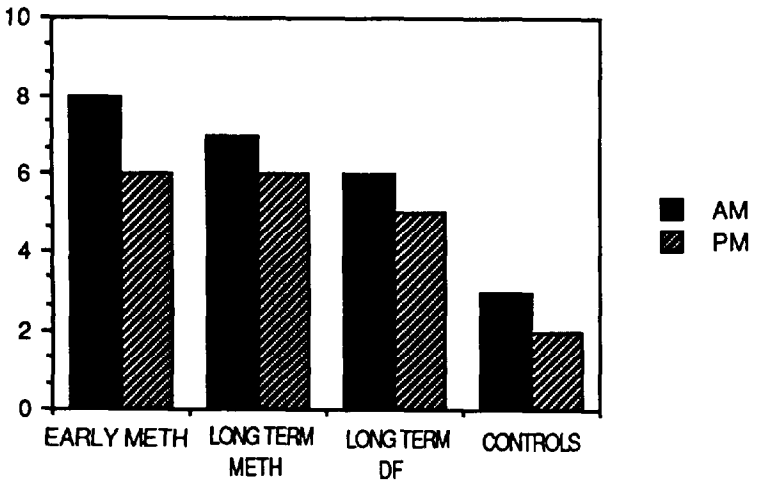

FIGURE 5. *Beck Depression Inventory in endocrine subjects*

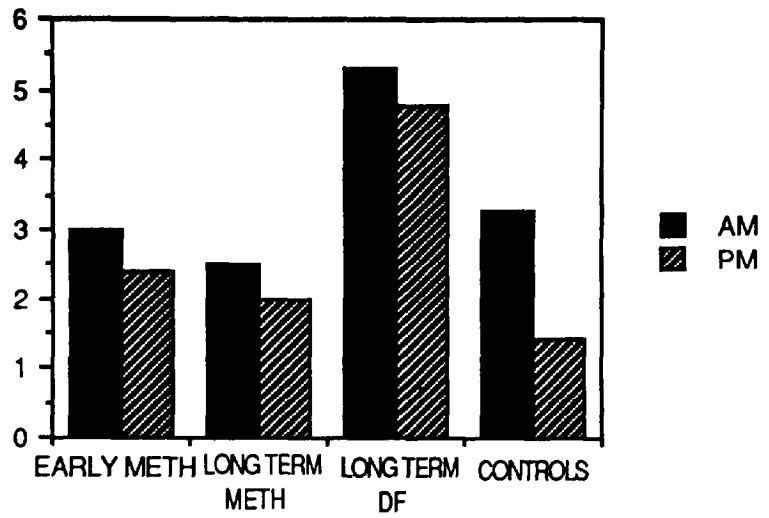

FIGURE 6. *SCL-90 data in endocrine subjects: Anxiety*

psychologically different, or both from those who remain on methadone and from nonaddict controls. The fact that the long-term drug-free subjects and controls were not kept on the inpatient testing unit overnight may have

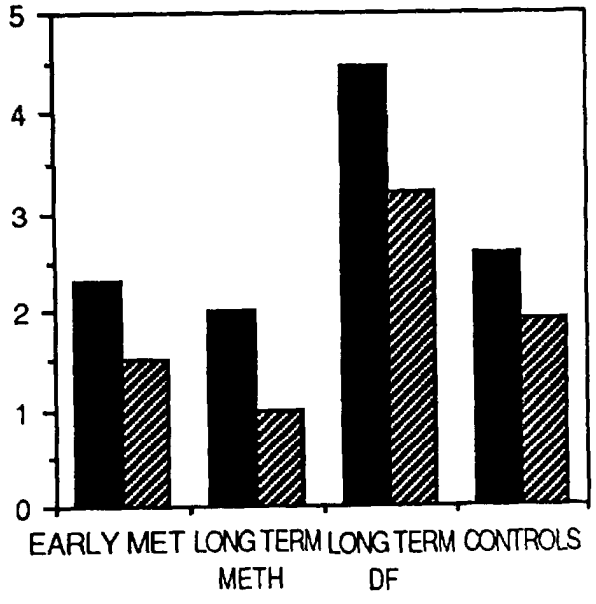

FIGURE 7. *SCL-90 data in endocrine subjects: Hostility*

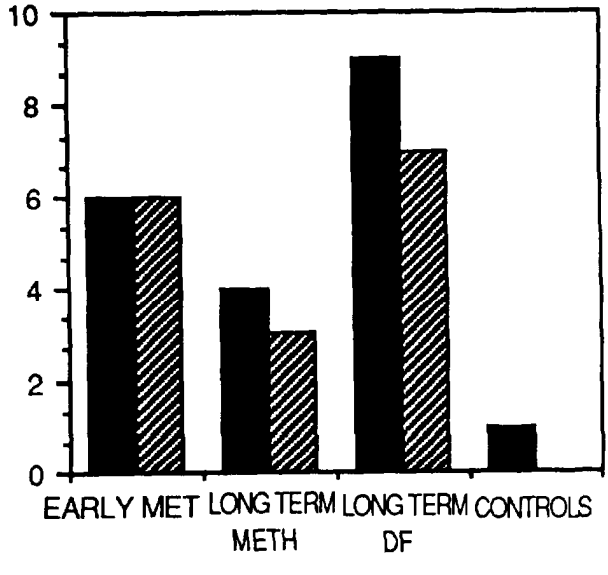

FIGURE 8. *POMS data in endocrine subjects: Tension*

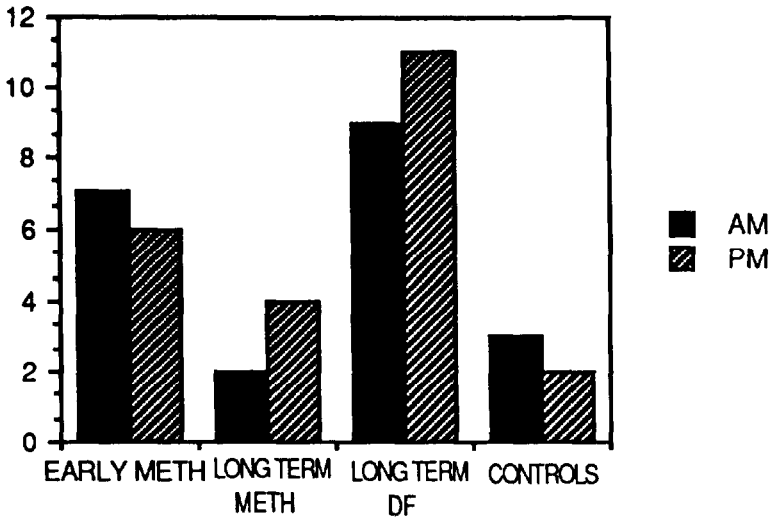

FIGURE 9. *POMS data in endocrine subjects: Anger*

influenced their LH and testosterone levels, along with their scores on the SCL-90 and the POMS. The fact that the opiate addicts had also abused other drugs may also be important; the differences observed could be a function of any number of drug effects and have nothing to do with the history of long-term opiate dependence.

Nevertheless, it must be noted that both studies (Kreek 1989; Woody et al. 1988) found neuroendocrine differences between the long-term drug-free opiate addicts and the other groups studied. The elevations in SCL-90 measures of anxiety and hostility and in the POMS ratings of tension and anger could reflect other aspects of this difference between normals and people with a history of chronic opiate addiction. These data could be interpreted as showing that long-term opiate use produces long-term biological alterations that are reflected in disruptions in the secretion of certain hormones of neurotransmitters that contribute to the regulation of affect, including anxiety, tension, hostility, and anger. These possible biological alterations could be related to the mechanisms involved in the antipsychotic and prolactin-elevating effects of opiates, which help to suppress symptoms of schizophrenia in addicts who have that disease.

CONCLUSION

The finding of one or more long-term biological alterations produced by chronic stimulant or opiate dependence would be consistent with the Swedish clinical reports and the theories of Dole. The methodological

problems inherent in studying these issues are formidable, but more biologically focused studies of stimulant and opiate addicts who have had extensive addiction careers that were followed by long-term abstinence may provide valuable information about these important questions.

REFERENCES

Dole, V.P.; Nyswander, M.; Kreek, M.J. Narcotic blockade. *Arch Intern Med* 118:304-309, 1966.

Khantzian, E.J. Psychological (structural) vulnerabilities and the specific appeal of narcotics. In: Verbey, K., ed. Opioids in mental illness: Theories, clinical observations, and treatment possibilities. *Ann NY Acad Sci* 398:24-32, 1982.

Kreek, M.J. Medical safety and side effects of methadone in tolerant individuals. *JAMA* 223:665-668, 1973.

Kreek, M.J. Effects of chronic opioid use. Presented at annual meeting of the American Society for Alcoholism and Other Drug Dependencies. Atlanta, GA, 1989.

Kreek, M.J, and Hartman, N. Chronic use of opiates and antipsychotic drugs: Side effects, effects on endogenous opioids, and toxicity. In: Verbey, K., ed. Opioids in mental illness: Theories, clinical observations, and treatment possibilities. *Ann NY Acad Sci* 398:151-172, 1982.

Lundh, H., and Tunving, K. An extrapyramidal choreiform syndrome caused by amphetamine addiction. *J Neurol Neurosurg Psychiatry* 44:728-730, 1981.

Martin, W.R.; Jasinski, D.R.; Haertzen, C.A.; Kay, D.C.; Jones, B.E.; Mansky, P.A.; and Carpenter, R.W. Methadone—A reevaluation. *Arch Gen Psychiatry* 28:286-295, 1973.

McKenna, G. Methadone and opiate drugs: Psychotropic effect and self-medication. In: Verbey, K., ed. Opioids in mental illness: Theories, clinical observations, and treatment possibilities. *Ann NY Acad Sci* 398:44-53, 1982.

McLellan, A.T.; Woody, G.E.; and O'Brien, C.P. Development of psychiatric disorders in drug abusers. *N Engl J Med* 301:1310-1313, 1979.

O'Brien, C.P.; Childress, A.R.; McLellan, A.T.; Termes, J.; and Ehrma, R.N. Use of naltrexone to extinguish opioid-conditioned responses. *J Clin Psychiatry* 45:53-56, 1984.

Parsons, O.A.; Butters, N.; and Nathan, P.E. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford, 1987.

Post, R.M.; Kotin, J.; and Goodwin, R.R. The effects of cocaine on depressed patients. *Am J Psychiatry* 131:511-517, 1976.

Ricautte, G.A.; Schuster, C.R.; and Seiden, L.S. Long-term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in the rat brain: A regional study. *Brain Res* 193:153-163, 1980.

Tunving, K. Fatal outcome in drug addiction. *Acta Psychiatr Scand* 77:551-566, 1988.
Wikler, A. Dynamics of drug dependence: Implications of a conditioning theory for research. *Arch Gen Psychiatry* 28:611-616, 1973.
Woody, G.E., and O'Brien, C.P. Unpublished clinical observations.
Woody, G.E.; O'Brien, CP.; McLellan, A.T.; Persky, H.; and Amdt, I.A. Hormonal secretion in methadone-dependent and abstinent subjects. In: Harris, L.S., *ed. Problems of Drug Dependence, 1987. Proceedings of the 49th Annual Scientific Meeting the Committee on Problems of Drug Dependence, Inc.* National Institute on Drug Abuse Research Monograph 81. DHHS Pub. No. (ADM)88-1564. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1988. pp. 216223.
Wurmser, L. The question of specific psychopathology in compulsive drug use. In: Verbey, K., ed. Opioids in mental illness: Theories, clinical observations, and treatment possibilities. *Ann NY Acad Sci* 398:33-43, 1982.

AUTHORS

George E. Woody, M.D.
A. Thomas McClellan, Ph.D.
Charles P. O'Brien, M.D., Ph.D.

Drug Dependence Treatment and Research Center
University of Pennsylvania
and
Philadelphia Veterans Administration Medical Center
39th and Woodland Avenue
Philadelphia, PA 19104

Adaptive Behavior in Recovering Female Phencyclidine/Polysubstance Abusers

Judy Howard, Leila Beckwith, and Carol Rodning

INTRODUCTION

Abuse of phencyclidine hydrochloride (PCP) continues to be a significant problem in urban areas of the United States. In Los Angeles County, PCP abuse reached its height in 1983. At that time, 30 percent of PCP abusers were women of childbearing age whose first use of PCP occurred at 20 years of age (Husson 1984). Currently, PCP abuse has moved from the south-central region of Los Angeles County to East Los Angeles.

PCP is inexpensive, readily obtainable, and generally used in combination with other drugs such as marijuana, heroin, and alcohol (Golden et al. 1982). Most recently, it has been used with cocaine and its derivative, "crack" cocaine. Polysubstance abuse was characteristic of the women in our study at the University of California, Los Angeles (table 1).

PCP can be injected, inhaled, or taken orally. In behavioral research, the pharmacological effects of PCP have been compared most often with those of amphetamines, sympathomimetic stimulants, pentobarbital, or central nervous system depressants (Balster and Baird 1979; Balster and Chait 1978; Balster and Wessinger 1983). PCP also has its own unique effects. For instance, adults who have been intoxicated with PCP describe numbness in their extremities and a feeling of dissociation of their limbs. Awareness of space is altered so that depth perception and the angles of floors, doors, and walls appear distorted (Balster 1980). Organization of sensory input-olfaction, temperature, pain, vision, and audition-also is impaired (Pender 1971). In human behavioral studies, high doses of PCP produced disturbing manifestations, including psychosis, increased irritability, and argumentative states (Pradhan 1984; Javitt 1987).

TABLE 1. *Percentage of drug, alcohol, and tobacco use in drug-abusing and drug-nonabusing mothers*

	Drug-Abusing n=47	Drug-Nonabusing n=38
PCP*	100%	0
Mean Years of Use†	6.3	–
Cocaine*	42%	0
Mean Years of Use†	1.8	-
Opiate*	3%	0
IV Drugs†	20%	0
Marijuana†	20%	0
Alcohol	75%	20%
Tobacco Cigarettes	60%	26%

*From infant toxicology screen.
†From maternal report.

AIM OF THE STUDY

Although this chapter focuses on the mothers' symptoms and behaviors during use and abstinence, the primary purpose of the study was to identify specific behavioral changes in the offspring of women who used PCP during pregnancy. Our specific aims were to do the following:

1. Compare PCP-exposed infants with matched groups of drug-nonexposed infants for attention regulation, social interaction, motor patterns, and cognitive development through year 2.

2. Compare PCP-exposed infants being reared in foster homes with PCP-exposed infants being reared by biologic parent(s) for attention regulation, social interaction, motor patterns, and cognitive development through year 2.

3. Assess the influence of other significant factors on development at 2 years, including maternal obstetrical problems; other drug, alcohol, and cigarette use; adequacy of prenatal care; neonatal complications; and the adequacy of the rearing environment.

Two groups of PCP-exposed infants were studied: (1) those placed by court order in foster homes, and (2) those discharged home to their parents after birth. In addition, a third group of drug-nonexposed infants reared by their biologic parents was selected. We provided intensive supportive services to caregivers of all subjects—both PCP-exposed and drug-nonexposed

infants—to reduce subject attrition, which is a significant problem in this population, and to promote stability within the caregiving environment. Table 2 provides a description of the sample population.

TABLE 2. *Sample description*

Mothers	Drug Abusers	Drug Nonusers
Recruited at Infant's Birth	47	38
Attrition*	6%	26%
Discharged†	11%	0
Maintained in Study	39	28
Drug Abusers in Recovery	20% (8 of 39)	0

*Attrition: Mother discontinued participation by own initiative.
†Discharge: Mother's participation was discontinued by project staff because of safety concems, despite mother's desire to continue involvement in the study.

RECOVERING ADDICTS IN STUDY

Among the 47 women in the study who were chronic addicts, there appeared to be 7 women who had stopped using drugs. These seven women had abstained from drug use for 1 or 2 years. The nonusing status of these women has been determined by maternal report to our support staff and by the staffs observations of the mothers' behaviors.

In the total addict sample of 47 women, 7 completed drug-treatment programs varying in length from 9 to 18 months and including both residential and outpatient formats. Seventeen attended but did not complete drug-treatment programs.

Of the seven women who completed drug-treatment programs, five are presently drug free. Of these five drug-free women, three completed 9-month outpatient drug-treatment programs, one completed a 9-month residential program, and one completed an 18-month residential program. One woman attended but did not complete a 9-month outpatient program and is presently drug free. The seventh woman who is drug free did not attend any drug-treatment program.

The length of drug use in the seven recovering addicts ranged from 5 to 20 years, with a mean of 10.25 years, while a mean of 6.3 years was found for the entire addict sample. Six of the seven women were polysubstance abusers, reporting use of as many as five different substances, including PCP, amphetamines, marijuana, cocaine, heroin, and alcohol. One woman reported using only PCP.

The mean age of the recovering women was 27.3 years, whereas the mean age for the total addict sample was 27.1 years. Formal education ranged from 8 to 14 years in the total addict sample, with a mean of 11 years for the seven drug-free women, compared with a mean of 11.1 years for the entire drug-using sample. Further maternal subject descriptions can be found in table 3. All drug-abusing mothers in the study received Aid to Families with Dependent Children.

TABLE 3. *Maternal subject description*

	Drug Abusers n=47	Drug Nonusers n=38
Mean Age*	27.1	21.9
Range	16-37	16-32
Mean Years Education*	11.1	12.3
Range	8-13	10-16
Welfare	94%	56%
Marital Status	95% single	69% single
Ethnicity	90% black	97% black
Prenatal Care at Any Time During Pregnancy	75%	97%
Prenatal Care in First Trimester	22%	63%
Mean Number of Pregnancies*	5.2	2.4
Mean Number of Deliveries*	2.7	1.2

*Groups significantly different, $p<.05$.

Of particular interest is the fact that, of the women in the total drug-using sample, the recovering addicts had the longest history of substance abuse. Furthermore, it is not clear why these seven women were able to abstain from drug use. Most had family histories of intergenerational substance abuse, as well as physical abuse or neglect during childhood. Other mothers in the drug-using sample had more responsive relationships with their children, better self-esteem, greater self-reflection, and better social skills; we would have predicted that they were more likely to achieve success in abstaining from substance abuse.

DESCRIPTIVE NARRATIVE OF BEHAVIOR IN THE SEVEN DRUG-FREE WOMEN

Sexual behavior and responsibility for birth control in the recovering addict group did not differ from that in the group that continued to abuse drugs.

Both the abstaining and substance-abusing mothers had a repeat pregnancy occurrence of 50 percent after their initial enrollment in our study. Clinically, a number of the women indicated a distaste for physical contact (including sexual intercourse) and a sensitivity to being touched when high on drugs. This sensitivity continued after the discontinuation of drug abuse, but did not appear to alter their sexual and birth-control behavior.

To determine behavioral impairment in these women during substance abuse and recovery, we administered two measures: (1) the Hopkins Symptom Checklist (Derogatis 1973); and (2) the Adaptive Skills Inventory (Jones and Lanyon 1973).

The Hopkins Symptom Checklist, a self-report screening questionnaire designed to detect psychiatric symptoms, was administered to all seven drug-free women. While using drugs, all seven reported somatic symptoms such as headaches, sweating, trembling, poor appetite, fast heart rate and pounding heart, and little sleep but no fatigue. These somatic symptoms abated during the recovery phase, when the women reported occasional headaches differing in intensity and improved appetite with subsequent weight gain. Symptoms of emotional lability-including crying easily, restlessness, low frustration tolerance, and unprovoked violence and aggression towards others (even towards individuals unknown to the subjects)--were present in all seven women when they were using drugs.

Examples of various women's responses to items on the questionnaire included the following:

- "I would have violent fights with my boyfriend . . . I had many injuries and caused many injuries."
- "I would fight anyone who touched me."
- "When high, I would attack people. I was extremely violent."
- "My head would tell me things that were not true or were not there. It seems someone was always after me."
- "I was on the race track all the time because the PCP told me we could conquer the world."
- "I didn't want anything, only drugs, didn't even want shoes."
- "My son begged me not to smoke. He was afraid I would die and then I could not take care of him."

Yet these women reported that, off drugs, their physical violence stopped and they felt more in control.

In summary, while on drugs, the level of symptoms reported by the women occurred at a level indicative of a psychiatric disorder. During the recovery period, the women reported 80 percent fewer symptoms.

The Hopkins Symptom Checklist provided useful information about the types of symptomatology—both somatic and psychological-experienced by these women on and off drugs. However, it was not sensitive to the continuing difficulties in daily functioning and organization that were apparent both to the women themselves and to the support staff.

Clinical staff continued to observe behavioral impairments in these women after the cessation of drug use. These deviant behaviors included an inability or an impaired ability to generalize information, a tendency to be overliteral in interpreting communications, childlike and self-referent responses in social situations, difficulties with short-term memory, and continuing problems with getting lost.

Many of these women had difficulty following simple, well-learned instructions on preparing a meal or finding a familiar place. They would report that they had to "think real hard" before answering questions, often finding it necessary to repeat words or phrases that had just been expressed to them. Some of the women reported difficulty distinguishing the time of day, week, month, or year, as well as difficulty remembering significant dates such as birthdays. One woman still reported nightmares (but not flashbacks), and all the women reported sleep difficulties, mostly in terms of a type of restlessness.

To explore further specifics regarding these women's behavior, three vignettes from the Adaptive Skills Inventory were administered. This inventory was designed to study chronic alcoholics' problems in handling day-to-day situations. We adapted the vignettes to make them more appropriate to our population. The three situations presented to these seven mothers were: (1) A fast-food restaurant serves you the wrong items-what do you do? (2) A friend betrays your confidence to another friend-what do you do? and (3) You have a dispute with your significant other-what do you do? Unlike their responses while on drugs, when off drugs the recovering addicts indicated that they would use strategies other than physical violence to resolve each of these problems. Examples of their responses include the following:

> Vignette 1, on-drug response: "I would jump on the person behind the counter and go off on her. I would make a big scene."
>
> Vignette 1, off-drug response: "I would ask her to change the order, maybe curse her out . . . if no response, I would call for the manager."

Vignette 2, on-drug response: "If I were still using, I would be throwing bottles and everything at that woman's house. They would probably have to call the police."

Vignette 2, off-drug response: "I would first say, 'I didn't say those things.' I would not still be her friend."

Vignette 3, on-drug response: "I'd get high, as usual, after a fight."

Vignette 3, off-drug response: "I'd probably be glad he left. If he can't act right, he needs to leave."

DISCUSSION

The information learned from these women's responses is preliminary and qualitative, yet useful. Even though our research design did not include a specific study of psychopathology in the mothers of the project infants, it was apparent to us through our clinical observations that the mothers' behaviors were deviant both on drugs and off. In addition, extensive interviews with family members indicated that these aberrant behaviors occurred following substance abuse.

We also found a neurological dysfunction for the infants of many of these PCP-abusing mothers. Neonatal symptomatology included greater apathy, jitters, irritability, and abnormalities in muscle tone and reflexes. Behavioral measurements at 6 and 15 months by the Gesell Developmental Examination showed language impoverishment and a significantly lower developmental quotient. Qualitative analysis of the PCP-exposed children's play indicated some ataxia; poor abduction and extension of fingers, hands, and arms, with some intentional tremor. Additional descriptive data are presented in table 4.

TABLE 4. *Infant subject description*

	Drug Exposed	Drug Nonexposed
Mean Gestational Age (weeks)	39.2	39.5
Range	34-42	34-42
Mean Birthweight* (gm)	2,919.8	3,383.1
Range	1,580-3,970	2,550-4,150
Mean Crown-Heel Length* (cm)	49.4	51.3
Range	41-56	46-54
Mean Head Circumference (cm)	32.7	33.5
Range	28-36	22-36

*Group significantly different, $p<.05$.

We believe that the problems of life adaptation that, in these women, seem to coincide with chronic substance abuse require further study. The preconceived psychiatric nosology used to describe and diagnose psychiatric illness did not seem appropriate for understanding the kinds of impairments we noted in these recovering addicts.

The behavioral descriptions recounted previously were difficult to capture using existing testing instruments. We had to adapt the few measures that seemed relevant and then fall back on self-report. Nonetheless, these measures-inadequate as they were-supported our clinical observations that recovering addicts have continued difficulties following discontinuation of drug use.

It is obvious, on the basis of both self-report and our behavioral observations, that these women acted less violently, were less impulsive, and had more self-control when off drugs. Yet, even though they functioned better during recovery, they reported residual difficulties with day-to-day functioning, including problems in providing a consistent routine for their children. For example, analysis (when the infants were 3 and 9 months old) of the interaction of previously drug-exposed infants with their caregiver indicated that mothers who had originally abused PCP and continued to care for their children were less accepting and sensitive to the needs of the children, as assessed by the Ainsworth sensitivity scale (Ainsworth et al. 1978). The interaction of the mothers with their children indicated that many of these mothers appeared very immature.

Interpretation of the cause for these deviant behaviors is of utmost importance. One obvious etiology would be the effects of environmental deprivation, with subsequent diminution in cognitive abilities. Another etiology would be chronic brain impairment caused by polysubstance abuse. Such a model is well documented in reports of the behavioral deterioration seen in chronic alcoholics.

We understand that recovering addicts must fight a daily battle against the physical and psychological urge to use drugs. However, this concentration on abstinence cannot be construed as the sole cause of recovering addicts' inability to solve problems and function consistently and independently. This preliminary evidence suggests a residual central nervous system impairment resulting from chronic polysubstance abuse. More strategies are needed to assess these impairments, as well as to assess behavioral strengths, if effective treatment programs are to be developed for substance-abusing individuals and their families.

REFERENCES

Ainsworth, M.; Bleher, M.; Waters, E.; and Wall, S. *Patterns of Attachment.* New Jersey: Lawrence Erlbaum, 1978.

Balster, R.L. The effects of phencyclidine and three analogues on motor performance in mice. *Pharmacology* 20:46-51, 1980.
Balster, R.L., and Baird, J.B. The effects of phencyclidine, D-amphetamine and pentobarbital on spaced responding in mice. *Pharmacol Biochem Behav* 11:617-623, 1979.
Balster, R.L., and Chait, L.D. The effects of phencyclidine on amphetamine stereotypy in rats. *Eur J Pharmacol* 48:445-450, 1978.
Balster, R.L, and Wessinger, W.D. Central nervous system depressant effects of phencyclidine. In: Kamenka, J.M.; Domino, E.F.; and Geneste, P., eds. *Phencyclidine and Related Arylcyclohexymines: Present and Future Applications.* Ann Arbor: NPP Books, 1983.
Derogatis, L.R.; Lipman, R.S.; Covil, L. SCL-90, An outpatient psychiatric rating scale—preliminary report. *Psychopharmacol Bull* 9:13-28, 1973.
Golden, N.L; Sokol, R.J.; Martier, S.; and Miller, S.I. A practical method for identifying angel dust abuse during pregnancy. *Am J Obstet Gynecol* 142:359-360, 1982.
Husson, B.S. Trends and epidemiology of drug abuse. In: U.S. Department of Health and Human Services. *Alcohol, Drug Abuse, and Mental Health.* Proceedings of Community Epidemiology Work Group. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., June 1984.
Javitt, D.C. Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia. *Hillside Journal of Clinical Psychiatry* 9(1):12-35, 1987.
Jones, S., and Lanyon, R.I. Relationship between adaptive skills and outcome of alcoholism treatment. *J Stud Alcohol* 42:521-525, 1983.
Pender, J.W. Dissociative amnesia. *JAMA* 215:1126-1130, 1971.
Pradhan, S.N. Phencyclidine (PCP): Some human studies. *Neurosci Biobehav Rev* 8(4):493-501, 1984.

ACKNOWLEDGMENTS

The following staff ensured the success of this research project: Eleanor Baxter, M.A., Jacquelyn Dickens, M.S.W., Clementine Royston, A.A., and Sarah Simpson, MA., provided comprehensive early intervention for project infants, their families, and foster parents. Rachelle Tyler, M.D., performed health and developmental examinations. The research for the study reported in this chapter was supported by National Institute on Drug Abuse grant R01 DA 4139.

AUTHORS

Judy Howard, M.D.
Professor of Clinical Pediatrics

Leila Beckwith, Ph.D.
Professor

Carol Rodning, Ph.D.
Assistant Research Professor

Department of Pediatrics
UCLA School of Medicine
23-10 Rehabilitation Center
Los Angeles, CA 90024

Long-Term Marijuana Use and Subsequent Effects on Learning and Cognitive Functions Related to School Achievement: Preliminary Study

Robert I. Block, Sara Farnham, Kathleen Braverman, Russell Noyes, Jr., and M.M. Ghoneim

INTRODUCTION

Adverse effects of chronic marijuana use on learning, memory, and cognition are of serious concern in view of the widespread use of this drug, especially as use has extended into progressively younger age groups. Clinical impressions of many observers suggest that chronic marijuana use impairs cognitive function (National Institute on Drug Abuse 1982). Surprisingly, although acute impairment of memory from single marijuana doses has been frequently and rigorously demonstrated, experimental studies of chronic marijuana effects on learning, memory, and cognition have generally been methodologically weak, ambiguous in outcome, or both. Of about a dozen such studies conducted in the United States and Canada (Entin and Goldzung 1973; Weckowicz and Janssen 1973) and a similar number elsewhere (Wig and Varma 1977), approximately one-fourth reported that chronic marijuana use adversely affected cognition (Soueif 1971); the rest did not find such effects.

One crucial requirement for evaluating the performance of chronic marijuana users is comparison with an appropriately matched group of nonusing subjects. Short of an extremely expensive longitudinal study that follows children over many years, the most desirable procedure is to match groups of users and nonusers on some measure of intellectual functioning obtained before the onset of drug use. Only one past study (Culver and King 1974) followed such a procedure. The absence of chronic marijuana effects in this study could be due to the minimal criteria set for marijuana use (use at

least twice a month for 1 year or more, with no use before entering college).

In a continuing study, we have been examining cognitive effects of chronic marijuana use by comparing the performance of marijuana users and nonusers. Scores during the fourth grade of grammar school on the Iowa Tests of Basic Skills (Hieronymus et al. 1982), standardized tests that have been administered to almost all grammar school children in Iowa for several decades, have been retrieved for all subjects. These scores will be used to establish that the marijuana users were comparable to the nonusers in their intellectual functioning before they began using marijuana. When completed, the study is expected to determine whether chronic marijuana use produces cognitive impairments and, if so, whether these impairments depend on the frequency of use.

Subjects in the study participated in two test sessions under nondrug conditions. In one session, they were administered the 12th-grade versions of the Iowa Tests (Iowa Tests of Educational Development), which emphasize basic, general intellectual abilities and academic skills and effective utilization of previously, i.e., preexperimentally, acquired information in verbal and mathematical areas. In the other session, subjects were administered computerized tests that emphasize learning and remembering new information, concept formation, associative processes, semantic memory retrieval and psychomotor performance. The 12th-grade Iowa Tests were administered to maximally exploit the advantage we had (relative to past studies) from equating the groups of marijuana users and nonusers on their fourth-grade Iowa Test scores. Iowa Test scores show considerable stability over time, with substantial correlations between individuals' scores in 4th and 12th grades obtained 8 years apart ($r=.68$ before and $r=.77$ after correction for attenuation because of dropout from the sample) (Scannell 1958). The computerized tests were developed with other goals in mind: we favored (1) tasks that were sensitive to acute effects of marijuana and other drugs in our preliminary studies (Block and Berchou 1984; Block and Wittenbom 1985); (2) tasks that other investigators had found sensitive to effects of marijuana, either acutely or (in the limited data available) following chronic use; and (3) tasks relevant to the skills required in school and work performance. Learning and remembering new information was a major focus because the only two American studies that suggested substantial adverse effects of chronic marijuana use involved memory tasks (Entin and Goldzung 1973; Gianutsos and Litwack 1976).

METHOD

Subjects and Screening

Volunteers were recruited through local news media and were paid for participation. During a preliminary screening visit, they provided permission to

retrieve their fourth-grade scores on the Iowa Tests of Basic Skills, a urine sample for drug screening, and information about their medical history, demographic characteristics, and use of marijuana and other drugs (Johnston et al. 1981). They were asked to classify their average weekly frequency of using marijuana or other cannabis products as "not at all," "less than once," "1 to 4 times," "5 to 6 times," or "7 or more times" and to indicate the duration of their use at this frequency. Portions of the Diagnostic Interview Schedule (DIS) Version III-A (Robins and Helzer 1985), a structured psychiatric screening interview for use by research staff, were administered.

So that their scores on the Iowa Tests could be retrieved, subjects were restricted to adults (age range 18 to 42 years) who had attended the fourth grade of grammar school in Iowa between 1956 and 1980. Marijuana users were restricted to individuals who had used marijuana or other cannabis products at least weekly for the last 2 years or more. Nonusers were restricted to individuals who had not used marijuana more than twice in their lives. Efforts were made to restrict subjects to individuals having limited experience with drugs other than marijuana, but the initial exclusion criteria concerning use of other drugs had to be relaxed to avoid rejecting an excessive percentage of "heavy" marijuana users.

Although the final sample for the study will consist of 144 marijuana users and 72 nonusers, the present report is based on 102 marijuana users and 89 nonusers who completed the study through January 1989. Since nonusers were relatively easier to recruit than marijuana users, an extra 17 nonusers were tested before curtailing their enrollment so that subsequent matching of groups on fourth-grade Iowa Test scores could be done primarily by dropping excess nonusers. No marijuana users were excluded or dropped based on their fourth-grade scores. Among the marijuana users, the reported frequency of using marijuana was 1 to 4 times weekly for 41, 5 to 6 times weekly for 23, and 7 or more times weekly for 38.

Procedure

Subjects were tested in two sessions. They agreed to obtain at least 7 hours sleep on the nights before the sessions and to abstain from caffeine and nicotine during the sessions, from alcohol on the days of the sessions and after 6 p.m. on the preceding evenings, and from marijuana and other drugs for 24 hours before the sessions.

In the first session, which lasted about 3 hours including a rest, the tests of Vocabulary, Correctness and Appropriateness of Expression, Ability To Do Quantitative Thinking, and Ability To Interpret Literary Materials from the Iowa Tests of Educational Development (Level II) were administered along with the Short Test of Educational Ability (Level 5) a test of general academic ability standardized with the Iowa Tests (Science Research Associates 1981). The tests were administered according to procedures specified in the

test manuals (Iowa Testing Programs 1987; Science Research Associates 1974). All were pencil-and-paper tests in multiple-choice format. The tasks involved were as follows:

1. Correctness and Appropriateness of Expression: (a) deciding which of several alternative versions of a specified portion of a short text best expressed the idea, made the statement grammatically correct or most precise, was worded most consistently with the style and tone of the text, or was correctly punduated or capitalized. The subject could refer to the text while answering the questions; and (b) picking which of several words was misspelled.

2. Ability To Interpret Literary Materials: answering questions assessing comprehension of a short text. The subject could refer to the text while answering the questions.

3. Ability To Do Quantitative Thinking: solving mathematical word problems drawn from practical realistic situations and answering questions assessing understanding of basic mathematical concepts.

4. Vocabulary: picking which of several words was the closest synonym for a specified word.

5. Short Test of Educational Ability: answering four types of questions involving vocabulary (as on the Vocabulary test), arithmetic reasoning (computation), letter series (recognizing the pattern in a specified series of letters and choosing the next letter in the series), and symbol manipulation (recognizing symbolic quantitative relations, e.g., "If AB=C and A decreases, does C increase or decrease?").

In the second session, which lasted about 2.5 hours, computerized learning and cognitive tests-free and constrained associations, paired-associate learning, text learning, Buschke's Selective Reminding Task, concept formation, and psychomotor performance (discriminant reaction time and critical flicker fusion)-were administered by an Apple II Plus computer system. Subjects viewed stimuli on a video monitor and other display devices and responded orally or by pressing buttons. A delayed memory test was then given.

Two alternate versions of the computerized tests using distinct but comparable stimuli and two equated forms of the 12th-grade Iowa Tests (Forms X-8 and Y-8) were each used with about half of the marijuana users and nonusers, as were two different sequences of administration of the tests.

Statistical Analyses

For preliminary analyses of the data, the small sample of subjects using marijuana five to six times weekly was pooled with the subjects using marijuana seven or more times weekly to form a group of "heavy" marijuana users for comparison with the "light" marijuana users (one to four times weekly) and nonusers. Differences between these groups on 12th-grade Iowa Test scores were examined by one-way analyses of variance; if significance was established, between-group differences were then analyzed by Tukey tests (Winer 1971). Similar analyses were done to examine the comparability of the groups on fourth-grade Iowa Test scores, age, and education. Their comparability on categorical demographic characteristics was checked by chi-square tests. A significance level of $p<.05$ was used for all tests.

RESULTS

Comparability of the Groups

Figure 1 shows the subjects' fourth-grade Iowa Test scores. Before the onset of drug use, the heavy users, light users, and nonusers were comparable on the Composite score averaged over all tests and on scores for four of the five individual tests. On one test, Language Skills, the nonusers performed better than either group of marijuana users. Table 1 shows the subjects' demographic characteristics. The heavy users, light users, and nonusers were comparable with respect to age, education, race, work status, annual income, and Hollingshead Occupational Scale scores, but not sex. Most marijuana users were men, while most nonusers were women. The percentage of men was 80 percent for both heavy users and light users but only 30 percent for nonusers.

Three heavy marijuana users and three nonusers met criteria on the Diagnostic Interview Schedule for a history of major depressive episodes, but none was currently depressed. No subjects met criteria on the Diagnostic Interview Schedule for a history of bipolar disorder or schizophrenia.

Marijuana Use

Heavy and light users reported using marijuana at their indicated frequencies for averages (means plus or minus standard errors) of 6.5±0.5 years and 6.2±0.7 years, respectively. They started use in similar grades: 9.9±0.3 and 10.0±0.4, respectively. Figure 2 shows frequency distributions for duration of marijuana use and grade of first use. After the study began, a question was added about the number of times subjects smoked marijuana on an average day. The 27 heavy users who were asked this question reported smoking marijuana 2.4±0.5 times on an average day.

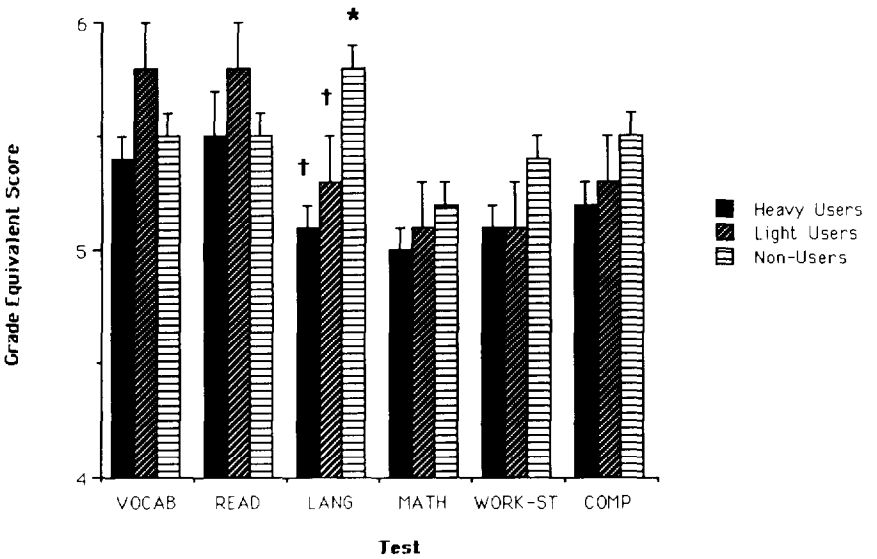

FIGURE 1. *Performance of subjects on the Iowa Tests of Basic Skills during the fourth grade of grammar school*

*F=7.7, p<.001 for difference between heavy users, light users, and nonusers in one-way analysis of variance.
†Differs from nonosers by followup Tukey tests, p<.05.

KEY: 4=fourth grade, 5=fifth grade, etc. VOCAB=Vocabulary, READ=Reading Comprehension, LANG=Language Skills, MATH=Mathematics Skills, WORK-ST=Work-Study Skills, COMP=Composite Score.

NOTE: Vertical lines indicate standard errors.

Of the nonusers, 96 percent reportedly never used marijuana, and 4 percent had tried it once or twice in their lives.

Use of Other Drugs

Figures 3, 4, and 5 show the lifetime experience of the participants with alcohol and illicit drugs other than marijuana. Data are shown for the heavy users, light users, and nonusers.

The light marijuana users had limited experience with other illicit drugs, and the nonusers had virtually none. None of the light users and nonusers met criteria for a history of dependence on other illicit drugs on the

Diagnostic Interview schedule, reported using any such drugs more than twice in the last month, or showed any other illicit drugs in urine specimens. Except for one light marijuana user, none of the light users and nonusers met criteria for a history of alcohol dependence on the Diagnostic Interview Schedule.

TABLE 1. *Demographic characteristics of subjects*

Characteristics	Heavy Users (n=61)	Light Users (n=41)	Nonusers (n=89)
Age (years, M±SE)	23.9±0.6	23.4±0.8	22.1±0.5
Education (years, M±SE)	14.3±0.2	14.5±0.3	14.1±0.2
Work Status (percent)			
Employed (nonstudents)	30	20	16
Employed (students)	41	37	47
Unemployed*	30	44	37
Annual Income (percent)			
Under $15,000	82	90	80
$15,000 to $35,000	18	10	20
Hollingshead Occupational Scale Score** (percent)			
1, 2, or 3	40	37	36
4 or 5	40	21	30
6, 7, 8, or 9	21	42	34
Sex (percent)			
Men	80	80	30
Women	20	20	70
Race (percent)			
White	100	98	99
Black or Asian	0	2	1

*All the unemployed subjects were students except for four heavy users and two light users.
**Excludes the unemployed and seven employed students who did not indicate their occupations. Occupations are scored on a nine-point scale. Lower scores indicate less status.

NOTE: Analyses of variance for age and education and chi-square tests for the categorical characteristics showed no significant differences among groups except for sex, $\chi^2=48.6$, $p<.001$.

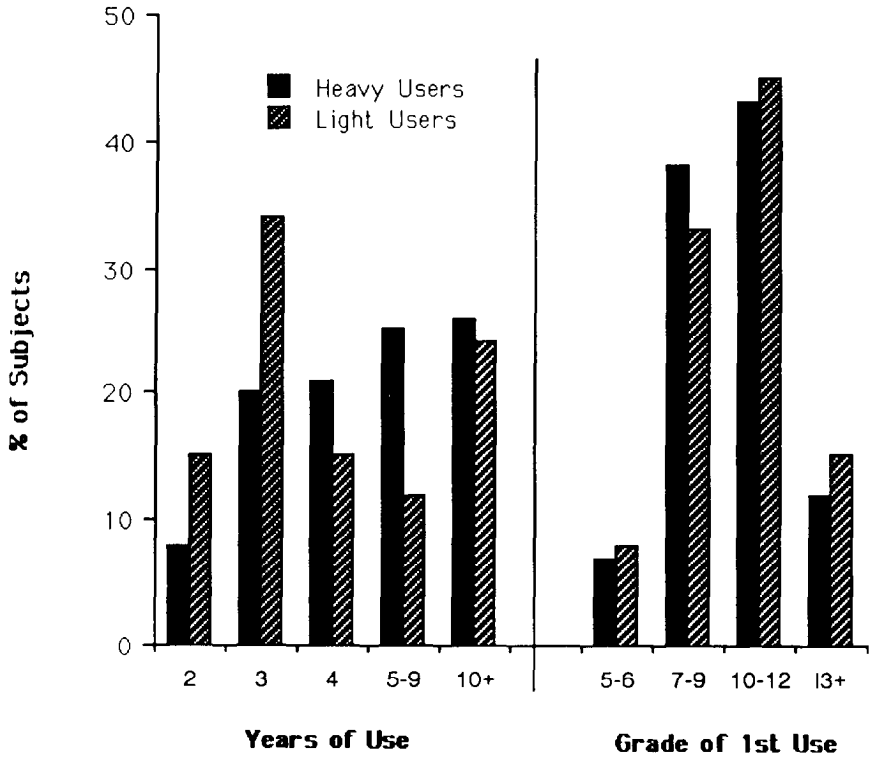

FIGURE 2. *Frequency distributions for marijuana use histories*

NOTE: Years of Use (left) shows how long the heavy and light marijuana users had reportedly been using marijuana at their indicated frequencies. *Grade of First Use* (right) shows the school year during which the heavy and light users first tried marijuana. Grade of first use was not provided by one heavy user and one light user.

Approximately two-thirds of the heavy marijuana users had no history of dependence on other illicit drugs, did not report using any such drugs more than twice in the last month, did not show any in urine specimens, and had no history of alcohol dependence. The remaining heavy marijuana users did show one or more (average 1.3) of these characteristics. Stimulants and psychedelics were the illicit drugs with which heavy marijuana users had the most other experience; they had considerably less experience with depressants (figure 3).

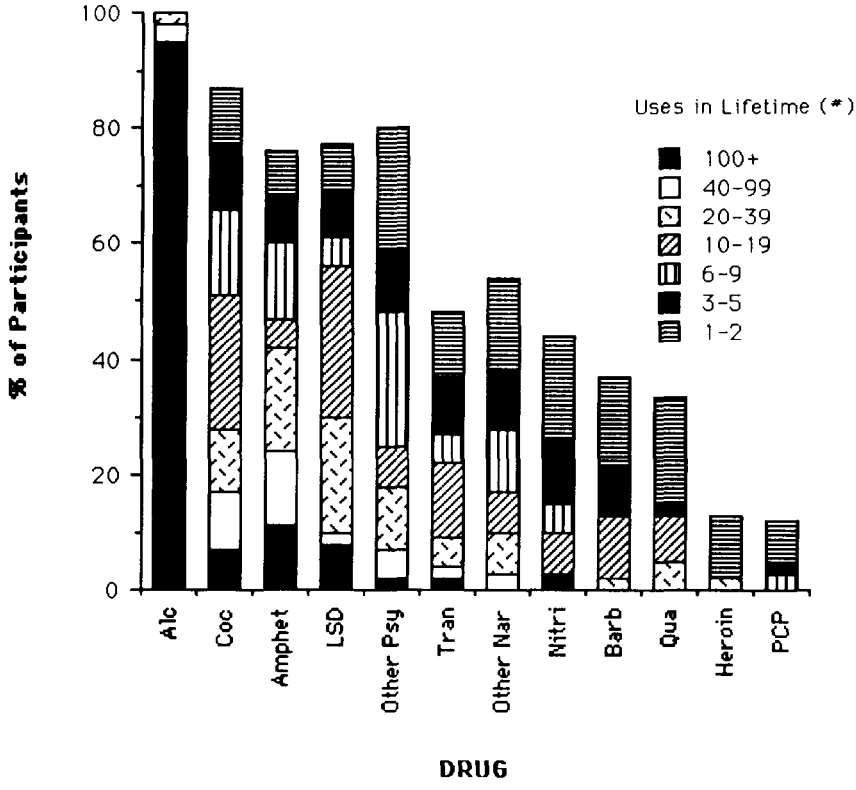

FIGURE 3. *Use of drugs other than marijuana by subjects who were heavy marijuana users*

KEY: Alc=alcohol, Coc=cocaine, Amphet=amphetamines, LSD=lysergic acid diethylamide, Other Psy=psychedelic drugs other than LSD, Tran=tranquilizers, Other Nar=narcotic drugs other than heroin, Nitri=amyl or butyl nitrites, Barb=barbituates, Qua=methaqualone (Quaalude), Heroin=heroin, PCP=phencyclidine.

NOTE: Areas within bars represent the percentages reporting use of that drug the indicated number of times in their lifetime.

Impairments From Marijuana Use

Figure 6 shows performance on the 12th-grade versions of the Iowa Tests and the Short Test of Educational Ability. The heavy users, light users, and nonusers performed comparably on four of the five tests. On the Expression test, the heavy users performed worse than either the nonusers or light users. The latter two groups did not differ.

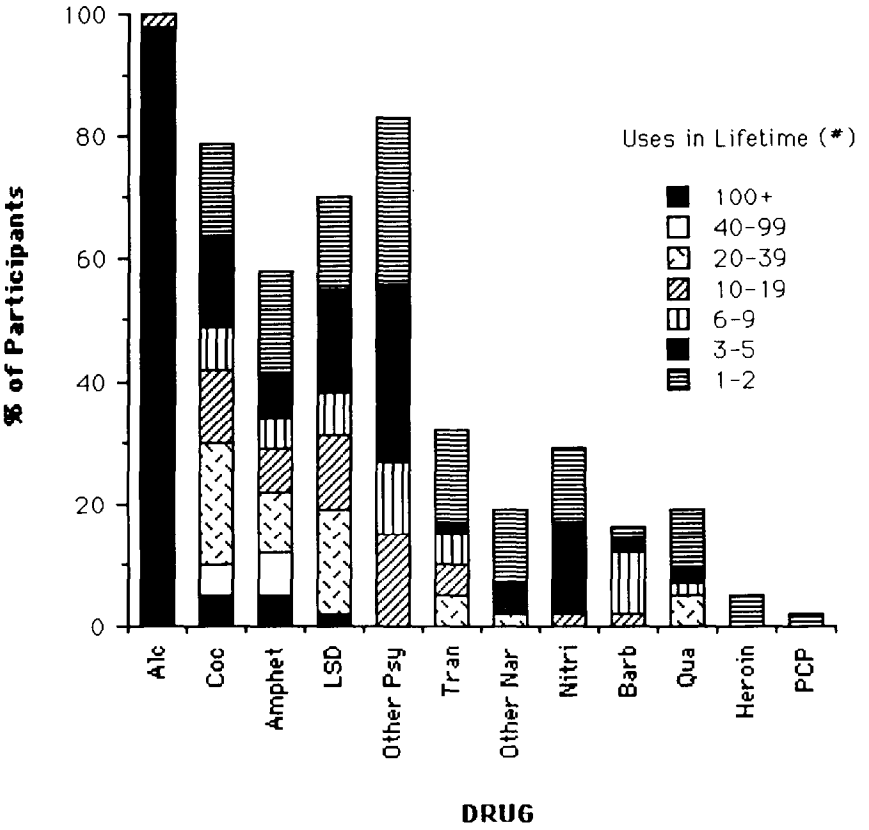

FIGURE 4. *Use of drugs other than marijuana by subjects who were light marijuana users*

NOTE: Format and abbreviation are the same as in figure 3.

DISCUSSION

If the study were complete and did not involve any measure of intellectual abilities before the onset of marijuana use or any computerized learning and cognitive tests, its conclusion would be that light, chronic marijuana use produces no cognitive impairment while heavy, chronic use produces a small but statistically significant impairment of verbal expressive skills without concomitant impairment of vocabulary, reading comprehension,

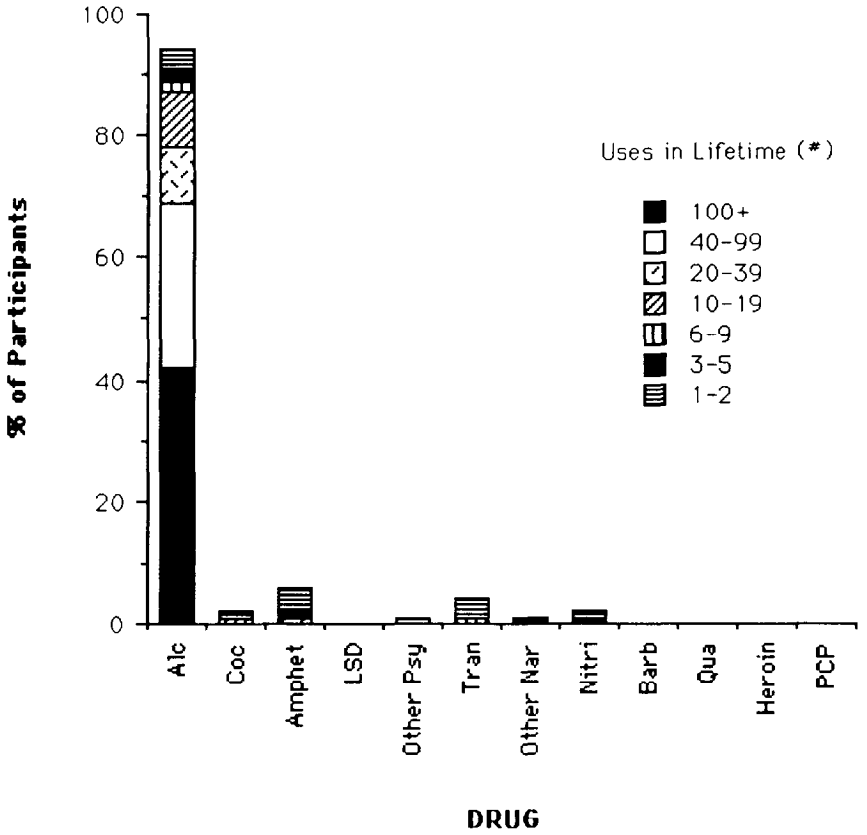

FIGURE 5. *Use of drugs other than marijuana by subjects who were nonusers of marijuana*

NOTE: Format and abbreviations are the same as in figure 3.

mathematical abilities, or general abilities. There are four main ways this conclusion must be hedged.

First, more marijuana users must be tested. Also, more male nonusers must be tested to make the users and nonusers comparable in sex distribution. These subjects might perform differently than those tested so far.

Second, among the 4th-grade tests, the only one that showed a difference between groups (Language Skills) was the one most closely related to Expression, the only 12th-grade test that showed a difference between

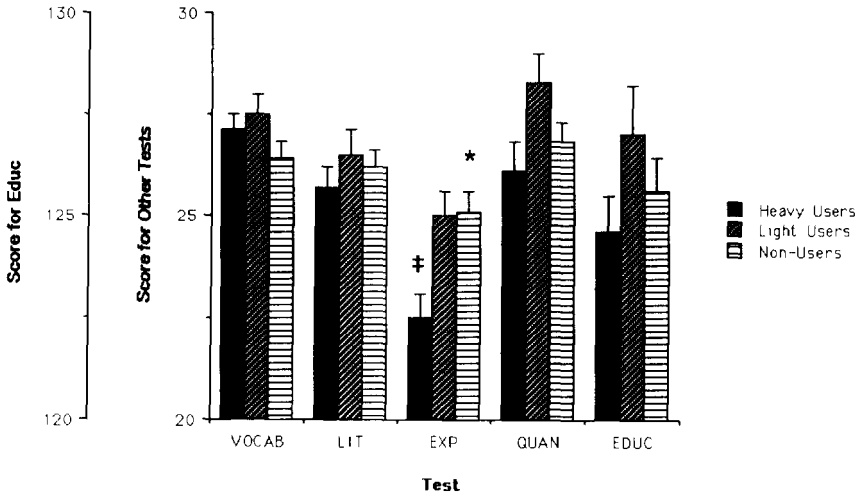

FIGURE 6. *Performance on the 12th-grade versions of the Iowa Tests of Educational Development (standard scores) and the Short Test of Educational Ability (quotient score)*

*F=6.8, p<.01 for difference between heavy users, light users, and nonusers in one-way analysis of variance.
*Differs from nonusers and from light users by followup Tukey tests, p<.05.

KEY: VOCAB=Vocabulary, LIT=Ability To Interpret Literary Materials, EXP=Correctness and Appropriateness of Expression, QUAN=Ability To Do Quantitative Thinking, EDUC=Short Test of Educational Ability.

NOTE: The fourth-grade tests most comparable to VOCAB, UT, EXP, and QUAN are Vocabulary, Reading Comprehension, Language Skills, and Mathematics Skills, respectively. Vertical lines indicate standard errors.

groups. Thus, the apparent impairment of the heavy marijuana users on Expression may disappear when the final groups of subjects, balanced on fourth-grade test scores, have been formed. The final selection of nonusers cannot be made until the remaining marijuana users have been enrolled in the study, since this selection will be determined by a metric matching the users and nonusers as closely as possible. To avoid leaving the question completely in limbo at this point, however, a quick selection of nonusers of the planned final group size (n=72) was made by deleting the extra 17 nonusers who had the highest Language Skills scores, except for those who were male or above the average age of all subjects (since the marijuana users were disproportionately male and slightly, albeit nonsignificantly, older than the nonusers). Reanalyses of the resulting groups showed that these deletions eliminated the significant differences between heavy users, light

users, and nonusers on Language Skills scores without introducing any new significant differences among groups on other fourth-grade test scores or demographic characteristics. The mean Language Skills score of the remaining 72 nonusers was 5.5±0.1. Reanalysis of scores on the 12th-grade Expression test continued to show a significant difference between groups, $F=4.7$, $p<.05$, the mean Expression score of the remaining nonusers being 24.4±0.5. As before, Tukey tests showed that the heavy users performed worse than either the nonusers or the light users, while the latter two groups did not differ from each other. This tentatively suggests that the apparent impairment of the heavy marijuana users on Expression may persist when the final groups of subjects have been formed.

Although the percentage of women remained lower among the marijuana users than among the nonusers even after deleting the extra 17 female nonusers, additional analyses suggested that the results were not just artifacts of sex differences: (1) although women performed slightly better than men on the 4th-grade Language Skills and 12th-grade Expression tests, neither the sex difference nor the interaction of sex with groups was significant for either test; (2) when all women were excluded and only the male heavy users, light users, and nonusers were analyzed, the groups did not differ on 4th-grade Language Skills scores but continued to show a significant difference on 12th-grade Expression scores, $F=3.2$, $p<.05$, despite the small number of male nonusers tested to date ($n=27$). For men, the mean scores for Language Skills were 5.1 for heavy users, 5.3 for light users, and 5.4 for nonusers. The corresponding scores for Expression were 22.2, 24.7, and 24.1, respectively. The corresponding scores for women were 5.1 for heavy users, 5.2 for light users, and 5.6 for nonusers for Language Skills and 23.8, 26.5, and 24.5 for Expression, respectively.

The third qualifier to the apparent conclusion is that the Iowa Tests generally emphasize utilization of previously (preexperimentally) acquired information and skills, while most of the computerized tests given in the second test session emphasize learning and remembering new information. One of the hypotheses of the study is that chronic marijuana use may more adversely affect learning and remembering new information than other cognitive functions, so that the computerized tests may be more sensitive than the Iowa Tests to adverse effects of marijuana use. Whether this hypothesis will be supported is unknown, since the results of the computerized tests have not yet been examined.

Finally, although the heavy marijuana users as a group were much more experienced with marijuana than with any other illicit drug, individuals who had experimented with other drugs had to be included to obtain enough subjects. Before concluding that any impairment shown by the heavy users was attributable to marijuana, additional analyses examining the possible contribution of other drug use will be necessary.

A "purer" group of exclusive users of marijuana might be obtained by recruiting in more densely populated areas than Iowa. However, heavy marijuana use is correlated with use of other drugs throughout the United States (Johnston 1980; Johnston 1981). Isolating the effects of individual drugs like marijuana on learning and cognitive function is crucial from a scientific viewpoint, but the combined effects of using multiple drugs may be of even greater practical concern. The general approach we have been using for examining cognitive effects of chronic marijuana use could profitably be applied in examining cognitive effects of chronic use of multiple drugs. Whatever drug or drugs are under investigation, selecting groups that are equated for intellectual functioning before the onset of drug use allows much greater confidence in the conclusions.

NOTES ADDED IN PROOF

When the study described in this chapter was completed, the reported frequency of using marijuana within the final sample of 144 marijuana users was 7 or more times weekly for 52, 5 to 6 times weekly for 28, and 1 to 4 times weekly for 64. These groups reported using marijuana at their indicated frequencies for means of 6.2, 5.8, and 5.5 years, respectively. To obtain a group of 72 nonusers for the final analyses who were comparable to the marijuana users in sex distribution, fourth-grade Iowa Test scores, and other characteristics, additional male nonusers were tested, and only a subset of the female nonusers (n=l5) was chosen for inclusion. These female nonusers were chosen so that the fourth-grade Iowa Test scores, age, and education were matched for the users and nonusers. Choices were made without reference to an individual's scores on the 12th-grade Iowa Tests. No marijuana users or male nonusers were excluded as part of the matching process. After matching, there were no significant differences between groups in fourth-grade Iowa Test scores (Vocabulary, Reading Comprehension, Language Skills, Mathematics Skills, Work-Study Skills, and Composite Score). The groups also showed no significant differences with respect to sex, age, education, work status, annual income, Hollingshead Occupational Scale score, or race. Of the 12th-grade Iowa Tests, 2 subtests, Correctness and Appropriateness of Expression and Ability To Do Quantitative Thinking, showed significant impairments in heavy marijuana users relative to nonusers. The other tests (Vocabulary, Ability To Interpret Literary Materials, and Short Test of Educational Ability) did not show impairments in heavy marijuana users. Less frequent marijuana use did not produce impairments on any test. Thus, the most important findings of the study are the impairments observed in verbal expression and mathematical skills following heavy marijuana use.

REFERENCES

Block, R.I., and Berchou, R. Alprazolam and lorazepam effects on memory acquisition and retrieval processes. *Pharmacol Biochem Behav* 20:233-241, 1984.

Block, R.I., and Wittenbom, J.R. Marijuana effects on associative processes. *Psychopharmacology* 85:426-430, 1985.

Culver, C.M., and King, F.W. Neuropsychological assessment of undergraduate marihuana and LSD users. *Arch Gen Psychiatry* 31:707-711, 1974.

Entin, E.E., and Goldzung, P.J. Residual effects of marihuana usage on learning and memory. *Psycho1 Rec* 23:169-178, 1973.

Gianutsos, R., and Litwack, A.R. Chronic marijuana smokers show reduced coding into long-term storage. *Bull Psychonom Soc* 7:277-279, 1976.

Hietonymus, A.N.; Lindquist, E.F.; and Hoover, H.D. *Manual for School Administrators, Iowa Tests of Basic Skills.* Chicago: Riverside Publishing, 1982.

Iowa Testing Programs. *ITED Examiner's Manual, Directions for Testing, Iowa Tests of Educational Development, Forms X-8 and Y-8.* Iowa City, IA: University of Iowa, 1987.

Johnston, L.D. The daily marijuana user. Presented at the 1980 meeting of the National Alcohol and Drug Coalition, Washington, DC, September 18, 1980.

Johnston, L.D. Frequent marijuana use: Correlates, possible effects, and reasons for using and quitting. Presented at the American Council on Marijuana Conference, Treating the Marijuana Dependent Person, Bethesda, MD, May 4, 1981.

Johnston, L.D.; Bachman, J.G.; and O'Malley, P.M. *Student Drug Use in America:* 1975-1981. DHHS Pub. No. (ADM)82-1221. Rockville, MD: National Institute on Drug Abuse, 1981.

National Institute on Drug Abuse. *Marijuana and Youth: Clinical Observations on Motivation and Learning.* Rockville, MD: the Institute, 1982.

Robins, L.N., and Helzer, J.E. *Diagnostic Interview Schedule (DIS) Version III-A.* St. Louis: Washington University School of Medicine, 1985.

Scannell, D.P. *Differential Prediction of Academic Success from Achievement Test Scores.* Ph.D. thesis. Iowa City, IA: University of Iowa, 1958.

Science Research Associates, Inc. *Examiner's Manual, STEA, Short Test of Educational Ability, Levels* 3-5. Chicago: Science Research Associates, Inc., 1974.

Science Research Associates, Inc. *ITED, Iowa Tests of Educational Development, Forms X5 and Y5, Technical Report Addendum: 1978 Standardization.* Chicago: Science Research Associates, Inc., 1981.

Soueif, M.I. The use of cannabis in Egypt: A behavioural study. *Bull Narc* 23:17-28, 1971.

Weckowicz, T.E., and Janssen, D.V. Cognitive functions, personality traits, and social values in heavy marijuana smokers and nonsmoker controls. *J Abnorm Psychol* 81:264-269, 1973.

Wig, N.N., and Varma, V.K. Patterns of long-term heavy cannabis use in north India and its effects on cognitive functions: A preliminary report. *Drug Alcohol Depend* 2:211-219, 1977.

Winer, B.J. *Statistical Principles in Experimental Design. 2d* ed. New York: McGraw-Hill, 1971.

ACKNOWLEDGMENTS

David A. Frisbie, Ph.D., Iowa Testing Programs, University of Iowa processed requests for transcripts of fourth-grade scores on the Iowa Tests of Basic Skills. Dr. Frisbie and others at Iowa Testing Programs, particularly Robert A. Forsyth, Ph.D., and A.N. Hieronymus, Ph.D., provided advice concerning the Iowa Tests of Basic Skills and Iowa Tests of Educational Development. Ms. Stacy Siegel and Ms. Wendy Walters assisted with the conduct of the research. James V. Himichs, Ph.D., Department of Psychology, University of Iowa provided advice concerning the study. The research was supported in part by U.S. Public Health Service grant 1 R01 DA 03988 from the National Institute on Drug Abuse to the first author and by grant RR59 from the General Clinical Research Centers Program, Division of Research Resources, National Institutes of Health to the Clinical Research Center, University of Iowa.

AUTHORS

Robert I. Block, Ph.D.
Assistant Professor
Department of Anesthesia

Sara Famham, B.A.
Research Assistant
Department of Anesthesia

Kathleen Braverman, B.S., R.N.
Research Assistant
Department of Anesthesia

Russell Noyes, Jr., M.D.
Professor
Department of Psychiatry

M.M. Ghoneim, M.D.
Professor
Department of Anesthesia

University of Iowa
Iowa City, IA 52242

Residual Effects of Alcohol

Peter E. Nathan

INTERACTIONS OF RESIDUAL EFFECTS WITH TOLERANCE AND WITHDRAWAL PROCESSES

Tolerance

Alcohol intoxication refers to the varied behavioral, neurological, and psychological sequelae of alcohol ingestion. The average-sized individual metabolizes between 7 and 10 grams of alcohol per hour, which corresponds to approximately 1 ounce of 90-proof spirits or 12 ounces of beer (Becker 1979). As the amount of alcohol ingested exceeds metabolic capacity, the level of alcohol in the blood increases. For the individual who has not developed a high degree of tolerance to alcohol, i.e., the social drinker, the degree of intoxication and the observed impairment correspond roughly to measured blood alcohol level (BAL: milligrams of alcohol per 100 ml of blood, or mg percent).

After one or hvo drinks, the nontolerant individual experiences only minor changes in coordination, behavior, or mood. However, as BAL increases above 100 mg percent (approximately five drinks in 1 hour for a 160-pound man), most social drinkers begin to demonstrate significant signs of intoxication, including impaired speech, ataxia, mood lability, impaired judgment, and memory and attention deficits. At dosage levels exceeding 200 mg percent, these symptoms intensify. Marked dysarthria and ataxia are accompanied by extensive impairment of judgment, psychomotor skills, attention and memory, and mood control. At dosage levels exceeding 300 mg of alcohol per 100 ml of blood, the anesthetic action of alcohol predominates, with the possibility of coma, respiratory failure, and death increasing dramatically at BAI.s between 400 and 700 mg percent.

In most States in the United States, the legal limit of alcohol intoxication for the operation of an automobile ranges between 80 and 100 mg of alcohol per 100 ml of blood. These alcohol concentrations, however, do not necessarily correlate with the actual level of impairment observed, especially for heavy alcohol consumers who have developed a high degree of tolerance

for alcohol. The final level of intoxication and resultant impairment is a function not only of BAL but also of the characteristics of the drinker (Mendelson and Mello 1985), as well as the pattern of consumption, general health and liver functioning, and presence of other drugs in the blood (Noble 1984). Characteristics of the drinker that influence intoxication and impairment include the drinker's age, weight, prior experience with alcohol, learned expectations concerning the effects of alcohol (Wilson et al. 1980), and degree of acquired tolerance for alcohol (Lipscomb and Nathan 1980).

The diagnosis of alcohol intoxication is complicated when tolerance for alcohol develops. Individuals who have developed a high degree of behavioral tolerance may not evidence the impairments or exhibit the overt signs of intoxication observed in individuals who drink socially (Mello 1972). Tolerant individuals have been found to perform quite well at BALs between 200 and 300 mg percent in tasks requiring psychomotor skills and good mentation (Mello and Mendelson 1978; Talland et al. 1964).

Laboratory studies of the metabolism of C^{14}-labeled ethanol have indicated that, although the chronic ingestion of alcohol results in an increased rate of metabolism in both alcoholic and nonalcoholic subjects, the general rate of metabolism does not differentiate the two groups (Mello 1972; Mendelson 1964; Mendelson et al. 1965). These data suggest that tolerance to alcohol is related to adaptive processes in the central nervous system rather than to alterations in the rate of metabolism of ethanol (Mendelson 1968).

Despite these findings, important questions concerning the extent to which tolerance is retained by sober alcoholics remain. Though some have reported "savings" in the rate at which tolerance is reacquired after a period of sobriety (Shapiro and Nathan 1986), the extent, nature, and prognostic significance of this residual phenomenon in sober alcoholics remains uncertain.

Relevant to this issue are data on the differential abilities of alcoholics and nonalcoholics to estimate their own BALs. Alcoholics have been found consistently to be less accurate than nonalcoholics in estimating their BALS both prior to and following training in internal cue discrimination (Huber et al. 1976; Lansky et al. 1978; Shapiro et al. 1980). Lipscomb and Nathan (1980) hypothesized that heightened tolerance in alcoholics may account for observed differences between alcoholics and nonalcoholics in the ability to utilize internal cues of intoxication for a variety of purposes, including moderation of drinking. To test this hypothesis, Lipscomb and Nathan (1980) grouped nonalcoholic subjects according to differences in body sway when intoxicated and when sober. Recognized as an extremely sensitive measure of intoxication, body sway is also viewed as a reliable measure of tolerance to ethanol (Moskowitz et al. 1974).

In the research by Lipscomb and Nathan, low-tolerance subjects evidenced marked differences in body sway between sober and intoxicated states;

high-tolerance individuals showed little difference in body sway between sober and intoxicated states. Following internal cue training, the low-tolerance subjects were found to be significantly more accurate than the high-tolerance subjects in their blood-alcohol estimates, a finding suggesting that increased tolerance may interfere with the utilization of internal intoxication cues.

If the residual effects of heavy alcohol use include the increased potential to redevelop tolerance more quickly, these data suggest that these effects may play a role in the heightened risk of heavy drinkers to go on to develop frank abuse and dependence.

Withdrawal

Alcohol withdrawal delirium—delirium tremens—constitutes one of the most serious residual effects of alcohol. The onset of this condition is usually preceded by mild to moderate, essentially normal, withdrawal symptomatology. The more severe symptoms occur within 1 week after the cessation or reduction of heavy drinking, and, a few days after normal withdrawal, symptoms have dissipated. The syndrome is characterized by confusion, disorientation, and a severe tremulous state. The course is variable, with alternating periods of agitation and calm, punctuated by vivid hallucinations and illusions and autonomic hyperactivity (fever, sweating, tachycardia, elevated blood pressure and respiration rates, and insomnia) (Victor 1976). The disorder is usually of short duration, with 15 percent of patients in remission after 24 hours and over 80 percent in remission in less than 3 days (Victor 1976; Victor and Adams 1953).

Although virtually all alcoholics experience at least some of the generally benign symptoms of withdrawal, only 5 percent of alcoholics hospitalized for major withdrawal experience alcohol withdrawal delirium (Victor and Adams 1953), with an estimated incidence among alcoholics ranging from 1 percent to 15 percent (Gross et al. 1974). Peak incidence of the disorder is between the ages of 30 and 50, with a decline in frequency after the age of 60. Improvements in the effective hospital management of the syndrome have resulted in a significant drop in mortality rates, with estimates ranging between 5 percent and 50 percent (typically 15 percent) to less than 1 percent (Gross et al. 1974; Pattison 1985).

Gross and his colleagues (1974) found significant differences between whites and blacks in the age of admission for symptoms of alcohol withdrawal delirium, with blacks on the average 8 years younger than whites. These age differences may be related to cultural differences in quantity and frequency of alcohol consumption (Cahalan 1977; Lex 1985). Men are at higher risk to develop the disorder than women, probably because of both the higher incidence of alcoholism in men and differences in drinking patterns between men and women (Tracey et al. 1976).

Data on recurrence rates of delirium tremens are in conflict. Feuerlein (cited in Gross et al. 1974) has suggested that the recurrence rate is low and decreases with subsequent episodes, while Gross and his colleagues (1974) reported a readmission rate for the syndrome of 43 percent. The latter finding suggests a residual effect of chronic alcohol abuse. Exploration of the mechanism responsible for this residual effect, if it does in fact exist, might well prove helpful to a fuller understanding of the pathophysiology of this important syndrome.

RESIDUAL EFFECTS OF ALCOHOL

Amnestic Disorders

Korsakoff first described the unique amnestic syndrome, which would subsequently bear his name, in 1887. In its acute phase, the syndrome is characterized by mental confusion and disorientation to time, place, or person; in its chronic stages, the confusional state subsides, and patients again become alert-but typically apathetic and lacking in spontaneity or self-direction. As indicated above, the memory function is severely disturbed: there is a marked deterioration in short-term memory, coupled with varying degrees of retrograde amnesia (Cermak 1987; Victor 1975). Confabulation is also frequently associated with Korsakoffs syndrome. However, the presence of confabulation is not required for the diagnosis (Victor 1976). In addition, these patients evidence deficits in a variety of conceptual and perceptual functions (Butters and Granholm 1987).

The onset of Korsakoff's syndrome is frequently preceded by an acute episode of Wemicke’s disease, an encephalopathy characterized by ataxia, ophthalmoplegia, nystagmus, and a global confused state (Victor et al. 1971).

The exact incidence of Korsakoffs syndrome is unknown, but estimates are that between 1 percent and 3 percent of alcohol-related problems requiring hospitalization can be traced to the disorder (Dreyfus 1974; Victor et al. 1971). In their classic study of 245 alcoholic patients, Victor and his colleagues (1971) reported age of onset for the disorder to be fairly evenly distributed among the ages of 30 to 70 years. A sex ratio of 1.7 males to 1 female was observed in this sample. However, these sex differences disappeared during the fifth and sixth decades of life.

The rate and extent of recovery from the symptoms of Korsakoff’s syndrome appear to be quite variable. Victor and colleagues (1971) reported that complete recovery occurred in 21 percent of 104 cases, with remaining patients showing significant but incomplete recovery (25 percent), slight improvement (28 percent), or permanent disability (26 percent). Rate of recovery also varied greatly. It ranged from 9 days to 1 year, with more rapid and complete improvement in neurological signs typically following

the administration of adequate thiamine, but slower resolution of cognitive-memory impairments (Donovan et al. 1987; Wilson 1987).

Korsakoffs syndrome and Wemicke's disease have been viewed as two clinically distinct aspects of the same disease entity, frequently termed the Wernicke-Korsakoff syndrome (Dreyfus 1974; Victor 1975). The etiology of this collective syndrome has generally been thought to be a profound deficiency of vitamin B_1 (thiamine). A number of lines of evidence implicate the role of a nutritional deficit in the etiology of Korsakoff's syndrome: (1) acute Wemicke's disease, malnutrition, and chronic Korsakoffs syndrome are consistently associated: 85 percent of Victor's patients presenting with Wemicke's disease subsequently exhibited the symptoms of Korsakoff's syndrome; (2) some improvement in the syndrome follows the administration of thiamine and vitamin therapy; (3) the lesions and other pathological changes that occur in Korsakoff's syndrome are essentially the same as those characterizing diseases of known nutritional etiology, e.g., Wemicke's disease (Victor et al. 1971).

Freund (1976) has noted, however, that much of the evidence for the nutritional hypothesis is based on correlational data and does not provide unequivocal proof of a cause-and-effect relationship. Unlike Wemicke's disease, which has been observed in patients suffering severe nutritional depletion unrelated to alcohol, Korsakoffs syndrome is extremely rare in cases of vitamin deficiency in the absence of alcohol consumption (Freund 1976). In addition, the response of Korsakoff's syndrome to thiamine therapy is slow and, in almost 80 percent of cases, incomplete (Victor et al. 1971). Further, the absence of controlled clinical trials makes it difficult to determine whether the observed changes reflect a response to vitamin therapy or a spontaneous recovery over time. As well, the pathological changes observed in Korsakoffs syndrome do not appear to be confined to brain areas characteristic of Wemicke's disease, e.g., the diencephalic areas (Butters and Granholm 1987; Freund 1976).

Nonetheless, the balance of evidence implicates a role for nutritional factors in the pathogenesis of Korsakoff's syndrome (Victor 1975; Victor et al. 1971). It is well known that chronic alcohol ingestion may result in vitamin deprivation by the displacement of food in the diet. In addition, the excessive intake of alcohol favors the development of a thiamine-deficient state by adding carbohydrate calories, which increases the need for thiamine. Finally, heavy alcohol ingestion impairs the ability of the gut to absorb thiamine and other nutrients (Victor 1975). But, regardless of the exact nature of the alcohol-nutritional interaction in this syndrome, effective treatment requires early identification to prevent the establishment of the irreversible memory deficits that characterize alcohol amnestic disorder (Cermak 1987).

This disorder is a particularly catastrophic consequence of chronic alcoholism for some. What remains unknown, however, is what inclines some

chronic alcoholics to develop the disorder and protects others, including those suffering from marked thiamine deficiency, from it. We also do not know whether lengthy periods of sobriety, in the midst of a lifetime of alcohol abuse, protects against or perhaps even sensitizes to the development of Korsakoff's syndrome. Both unanswered questions demand answers.

Dementia

Sometimes, persons with a history of chronic alcohol consumption develop dementia and consequent intellectual impairment. The differential diagnosis of dementia associated with alcoholism requires a history of prolonged and heavy alcohol use, persistence of dementia for at least 3 weeks after drinking ceases, and the exclusion, by appropriate means, of all other causes of dementia besides chronic alcohol consumption (Oscar-Berman 1987).

This condition must be differentiated from mild, alcohol-dependence-related cognitive deficits revealed only by neuropsychological evaluation (these conditions are discussed later in this chapter). Persons given the diagnosis of dementia associated with alcoholism, by contrast, must demonstrate at least some impairment in social or occupational functioning. The dementia can vary in severity from mild impairment in functioning to impairment in general functioning so severe that custodial care is required. Characteristic features of dementia include deterioration in previous intellectual abilities, short- and long-term memory deficits, and impairment in abstract thinking, judgment, and impulse control of sufficient magnitude to interfere significantly with work, usual social activities, or relationships with others.

Alcohol abuse likely plays both a direct and an indirect role in the etiology of this disorder (Victor et al. 1971). Alcohol contributes directly to the pathogenesis of the disorder through its toxic effects on the brain and indirectly by its interaction with vitamin deficiency, other alcohol-related diseases, and alcohol-related accidents causing damage to the brain (Freund 1976; Risberg and Berglund 1987).

Although the exact incidence of the disorder is unknown, it has been estimated that between 15 percent and 30 percent of nursing-home patients with organic brain syndrome are alcoholics whose alcohol-related organicity has become permanent (Schuckit 1979).

Changes in Social Interaction

Patterns of social interaction associated with alcohol consumption were a prime focus of the empirical laboratory studies of alcoholic drinking that my colleagues and I undertook at Boston City Hospital and Rutgers University. The initial impetus for this research came from data on the behavioral effects of chronic drinking reported by Mendelson and Mello in 1966. Their male chronic alcoholic subjects' social behavior seemed to vary

according to three factors: the amount of alcohol they had consumed, the nature of their drinking and living environments, and the history of their alcohol abuse. To undertake a detailed experimental analysis of these variables, my coworkers and I planned an around-the-clock comparative examination of the operant-choice behavior of groups of alcoholic and nonalcoholic males, during periods of social interaction and social isolation, crossed with periods of drinking and abstinence.

Our alcoholic subjects, most of them drawn from Boston's skid row, expended almost all of the points they earned for operant work to purchase alcohol, not to relieve social isolation (Nathan et al. 1970). Moreover, these men usually chase to remain isolated during nondrinking periods as well, especially toward the end of the 3-week drinking period.

O'Brien and I (Nathan and O'Brien 1971; Nathan et al. 1971) then directly compared the social behavior of alcoholic men with that of matched nonalcoholics. The nonalcoholic men turned out to be much more social than the alcoholic men; they spent many more reinforcement points for socialization before, during, and after periods of drinking than had their alcoholic peers. In a complementary study of women, Tracey et al. (1976) reported that female alcoholics in a similar operant-choice situation were more prosocial than the chronic alcoholic men who had been studied earlier.

Studying the drinking and social behavior of alcoholics who seemed largely comparable to the subjects my colleagues and I had investigated, Bigelow (1973) and Griffiths and colleagues (1975) reported most of their male chronically alcoholic subjects to be significantly more sociable on drinking days than on days when they could not drink. Additional support for the view that not all chronic alcoholics are social isolates when they are drinking-that, in fact, alcohol serves very often to increase their social interaction--came from a study by Thornton and colleagues (1975) in which alcohol dramatically increased social interaction among groups of alcoholics.

It may be, then, contrary to my own early findings, that chronic alcoholics may actually become more rather than less isolated interpersonally when they drink. Among the apparent factors influencing alcohol's effect on interpersonal behavior are the likelihood that being with others during drinking periods threatens the continued availability of alcohol (skid-row alcoholics cannot afford to share), whether the person has good social skills to begin with (many skid-row alcoholics are social isolates, drunk or sober), and whether social skills were reinforced in the past (middle-class alcoholics are more likely to value social skills).

Unlike some of the other behaviors that follow alcohol ingestion, the effect of alcohol-related expectancies on social interaction has not been examined intensively. Indirect explorations contrasting drug and expectancy effects on social anxiety, however, indicate that expectancy does play an important

role in determining alcohol's effect on social anxiety (Lipscomb et al. 1980; Wilson and Abrams 1977; Wilson et al. 1980). These findings suggest that believing that alcohol relaxes, facilitates communication, and enhances self-esteem is important to alcohol's role as a social facilitator.

Changes in Cognitive Processes

Chronic alcohol abuse causes deficits in cognitive functioning. In some instances, these deficits are severe and disabling enough to meet the diagnostic criteria for dementia associated with alcoholism. In others, especially when accompanied by nutritional deficiency, profound cognitive deficits may signal Korsakoff's syndrome. Most of the time, though, the deficits in cognitive functioning that accompany chronic alcohol abuse are not severe enough in and of themselves to justify a separate diagnosis. Instead, for the most part, these deficits are simply seen as correlates or consequences of a long period of (generally) abusive drinking.

The well-known deficits associated with alcohol intoxication include balance, coordination, judgment, and cognitive-perceptual impairments (Jones and Vega 1971; Jones and Parsons 1975). Less well known is that, although the social drinker returns to intact cognitive-perceptual functioning shortly after all alcohol has cleared from the body, the alcoholic or problem drinker who attains sobriety does not return to normal cognitive functioning for a longer period of time, depending on such factors as age (Goldman 1982), alcohol consumption pattern (Sanchez-Craig 1980), and quantity and frequency (Eckhardt et al. 1978). Typical deficits associated with chronic alcohol abuse affect problem solving, nonverbal abstracting, and perceptual-spatial motor performance. Memory and new learning skills may also be depressed. Finally, although general verbal intelligence often shows no impairment, linguistic skills of a more demanding nature may be impaired in chronic alcoholics (Parsons 1987).

An interesting recent series of studies (reviewed by Goldman 1987) revealed that the most important determinant of recovery from the cognitive deficits associated with prolonged drinking may be age. Heavy drinkers and alcoholics under the age of 40 generally recover from virtually all cognitive deficits by 2 to 3 weeks after drinking has ceased, regardless of drinking history. Alcoholics over 40, by contrast, take much longer to recover functioning and, even after 3 months or more without a drink, may show residual deficits in visual-perceptual functioning. These findings suggest that certain of the deteriorative processes associated with aging interfere with the recovery of the cognitive functioning that takes place in younger individuals, regardless of the quantity of alcohol consumed.

It is interesting to speculate on the role of age in other residual effects of chronic alcohol abuse. Do the possible residual effects of chronic alcohol abuse on tolerance and withdrawal, possibly even susceptibility to delirium

tremens, vary as a function of age? Do older alcohol abusers maintain residual effects that younger ones lose? The role of age raises most interesting questions, which should certainly be explored.

REFERENCES

Becker, C.E. Pharmacotherapy in the treatment of alcoholism. In: Mendelson, J.H., and Mello, N.K., eds. *The Diagnosis and Treatment of Alcoholism.* New York: McGraw-Hill, 1979. pp. 283-304.

Bigelow, G. Experimental analysis of human drug self-administration. Presented at the annual meeting of the Eastern Psychological Association, Philadelphia, PA, May 1973.

Butters, N., and Granholm, E. The continuity hypothesis: Some conclusions and their implications for the etiology and neuropathology of alcoholic Korsakoff's syndrome. In: Parsons, O.A.; Butters, N.; and Nathan, P.E., eds. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford Press, 1987. pp. 176-206.

Cahalan, D. Subcultural differences in drinking behavior in U.S. national surveys and selected European studies. In: Nathan, P.E., and Marlatt, G.A., eds. *Alcoholism: New Directions in Behavioral Research and Treatment.* New York: Plenum Press, 1977. pp. 235-254.

Cermak, L.S. Models of memory loss in Korsakoff and alcoholic patients. In: Parsons, O.A.; Butters, N.; and Nathan, P.E., *eds. Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford Press, 1987. pp. 207-226.

Donovan, D.M.; Walker, R.D.; and Kivlahan, D.R. Recovery and remediation of neuropsychological functions: Implications for alcoholism rehabilitation. In: Parsons, O.A.; Butters, N.; and Nathan, P.E., eds. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford Press, 1987. pp. 339-360.

Dreyfus, P.M. Diseases of nervous system in chronic alcoholics. In: Kissin, B., and Begleiter, H., eds. *The Biology of Alcoholism.* Vol. 3. New York: Plenum Press, 1974. pp. 265-290.

Eckhardt, M.J.; Parker, E.S.; Noble, E.P.; Feldman, D.H.; and Gottschalk, LA. Relationship between neuropsychological performance and alcohol consumption in alcoholics. *Biol Psychiatry* 13:551-565, 1978.

Freund, G. Diseases of the nervous system associated with alcoholism. In: Tarter, R., and Sugarman, A., *eds. Alcoholism: Interdisciplinary Approaches to an Enduring Problem.* Reading, MA: Addison-Wesley, 1976. pp. 171-202.

Goldman, M.S. Reversibility of psychological deficits in alcoholics: The interaction of aging with alcohol. In: Wilkinson, D.A., *ed. Cerebral Deficits in Alcoholism.* Toronto: Addiction Research Foundation, 1982. pp. 79-105.

Goldman, M.S. The role of time and practice in recovery of function in alcoholics. In: Parsons, O.A.; Butters, N.; and Nathan, P.E., eds. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford Press, 1987. pp. 291-321.

Griffiths, R.R.; Bigelow, G.; and Liebson, I. Effects of ethanol self-administration on choice behavior: Money *vs.* socializing. *Pharmacol Biochem Behav* 3:443-446, 1975.

Gross, M.M.; Lewis, I.; and Hastey, S. Acute alcohol withdrawal syndrome. In: Kissin, B., and Begleiter, H., *eds. The Biology of Alcoholism.* Vol. 3. New York: Plenum Press, 1974. pp. 191-290.

Huber, H.; Nathan, P.E.; and Karlin, R. Blood alcohol level discrimination by non-alcoholics: The role of internal and external cues. *J Stud Alcohol* 37:27-39, 1976.

Jones, B.M., and Parsons, O.A. Alcohol and consciousness—Getting high, coming down. *Psychol Today* 8:53-58, 1975.

Jones, B.M., and Vega, A. Cognitive performance measured on the ascending and descending limb of the blood alcohol *curve. Psychopharmacologia* 23:99-114, 1971.

Lansky, D.; Nathan, P.E.; and Lawson, D.M. Blood alcohol level discrimination by alcoholics: The role of internal and external cues. *J Consult Clin Psychol* 46:953-960, 1978.

Lex, B.W. Alcohol problems in special populations. In: Mendelson, J.H., and Mello, N.K., eds. *The Diagnosis and Treatment of Alcoholism.* 2d ed. New York: McGraw-Hill, 1985. pp. 89-188.

Lipscomb, T.R., and Nathan, P.E. Effect of family history of alcoholism, drinking pattern, and tolerance on blood ethanol level discrimination. *Arch Gen Psychiatry* 37:577-582, 1980.

Lipscomb, T.R.; Nathan, P.E.; Wilson, G.T.; and Abrams, D.B. Effects of tolerance on the anxiety-reducing function of ethanol. *Arch Gen Psychiatry* 37:577-582, 1980.

Mello, N.K. Behavioral studies of alcoholism. In: Kissin, B., and Begleiter, H., eds. *The Biology of Alcoholism.* Vol. 2. New York: Plenum Press, 1972. pp. 219-292.

Mello, N.K., and Mendelson, J.H. Alcohol and human behavior. In: Iversen, L.L., and Snyder, S.H., eds. *Handbook of Psychopharmacology.* Vol. XII. New York: Plenum Press, 1978. pp. 235-317.

Mendelson, J.H. Experimentally induced chronic intoxication and withdrawal in alcoholics. *Q J Stud Alcohol* 2:1-126, 1964.

Mendelson, J.H. Ethanol 1-C^{14} metabolism in alcoholics and nonalcoholics. *Science* 159:139, 1968.

Mendelson, J.H., and Mello, N.K. Experimental analysis of drinking behavior of chronic alcoholics. *Ann NY Acad Sci* 133:828-845, 1966.

Mendelson, J.H., and Mello, N.K. Diagnostic criteria for alcoholism and alcohol abuse. In: Mendelson, J.H., and Mello, N.K., eds. *The Diagnosis and Treatment of Alcoholism.* 2d ed. New York: McGraw-Hill, 1985.

Mendelson, J.H.; Stein, S.; and Mello, N.K. Effects of experimentally induced intoxication on metabolism of ethanol 1-C^{14} in alcoholic subjects. *Metabolism* 14:1255, 1965.

Moskowitz, H.; Daily, H.; and Henderson, R. *Acute Tolerance to Behavioral Impairment of Alcohol in Moderate and Heavy Drinkers.* Report to the Highway Research Institute of the National Highway Safety Administration, Department of Transportation, Washington, DC, 1974.

Nathan, P.E., and O'Brien, J.S. An experimental analysis of the behavior of alcoholics and nonalcoholics during prolonged experimental drinking. *Behav Ther* 2:455-476, 1971.

Nathan, P.E.; O'Brien, J.S.; and Lowenstein, L.M. Operant studies of chronic alcoholism: Interaction of alcohol and alcoholics. In: Roach, M.K.; McIsaac, W.M.; and Creaven, P.J., eds. *Biological Aspects of Alcohol.* Austin, TX: University of Texas Press, 1971. pp. 341-370.

Nathan, P.E.; Titler, N.A.; Lowenstein, L.M.; Solomon, P.; and Rossi, A.M. Behavioral analysis of chronic alcoholism. *Arch Gen Psychiatry* 22:419-430, 1970.

Noble, E.P. Pharmacotherapy in the detoxification and treatment of alcoholism. In: *Psychiatry Update.* Vol. III. Washington, DC: American Psychiatric Association, 1984. pp. 346-359.

Oscar-Berman, M. Neuropsychological consequences of alcohol abuse: Questions, hypotheses, and models. In: Parsons, O.A.; Butters, N.; and Nathan, P.E., eds. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford Press, 1987. pp. 256-272.

Parsons, O.A. Neuropsychological consequences of alcohol abuse: Many questions—Some answers. In: Parsons, O.A.; Butters, N.; and Nathan, P.E., eds. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford Press, 1987. pp. 153-175.

Pattison, E.M. The selection of treatment modalities for the alcoholic patient. In: Mendelson, J.H., and Mello, N.K., eds. *The Diagnosis and Treatment of Alcoholism.* 2d ed. New York: McGraw-Hill, 1985. pp. 189-294.

Risberg, J., and Berglund, M. Cerebral blood flow and metabolism in alcoholics. In: Parsons, O.A.; Butters, N.; and Nathan, P.E., eds. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford Press, 1987. pp. 64-75.

Sanchez-Craig, M. Drinking pattern as a determinant of neuropsychological deficits. *J Stud Alcohol* 41:1082-1090, 1980.

Schuckit, M.C. *Drug and Alcohol Abuse.* New York: Plenum Press, 1979.

Shapiro, A.P., and Nathan, P.E. Human tolerance to alcohol: The role of Pavlovian conditioning processes. *Psychopharmacology* 88:90-95, 1986.

Shapiro, A.P.; Nathan, P.E.; Hay, W.M.; and Lipscomb, T.R. Influence of dosage level on blood alcohol level discrimination by alcoholics. *J Consult Clin Psychol* 48:655-656, 1980.

Talland, G.A.; Mendelson, J.H.; and Ryback, P. Experimentally induced chronic intoxication and withdrawal in alcoholics: Part 5. Tests of attention. *Q J Stud Alcohol* 2:74-86, 1964.

Thornton, C.C.; Alterman, A.I.; Skoloda, T.E.; and Gottheil, E. Drinking and socializing in "Introverted" and "Extraverted" Alcoholics. Presented at the annual meeting of the National Council on Alcoholism, New York, April 1975.

Tracey, D.; Karlin, R.; and Nathan, P.E. Experimental analysis of chronic alcoholism in four women. *J Consult Clin Psycho1* 44:832-842, 1976.

Victor, M. Nutrition and diseases of the nervous system. *Progr Food Nutr Sci* 1:145-172, 1975.

Victor, M. Treatment of alcohol intoxication and the withdrawal syndrome: A critical analysis of the use of drugs and other forms of therapy. In: Boume, P.G., *ed. Acute Drug Emergencies: A Treatment Manual.* New York: Academic Press, 1976. pp. 242-556.

Victor, M., and Adams, R.D. Effects of alcohol on the nervous system. In: Merritt, H.H., and Hare, C.C., eds. *Metabolic and Toxic Diseases of the Nervous System.* Baltimore: Williams & Wilkins, 1953. pp. 526-573.

Victor, M.; Adams, R.D.; and Collins, G.H. *The Wernicke-Korsakoff Syndrome.* Philadelphia: F. Davis Company, 1971.

Wilson, G.T. Cognitive processes in addiction. *Br J Addict* 82:343-353, 1987.

Wilson, G.T., and Abrams, D.B. Effects of alcohol on social anxiety and physiological arousal: Cognitive versus pharmacological processes. *Cogn Ther Res* 1:195-210, 1977.

Wilson, G.T.; Abrams, D.B.; and Lipscomb, T.R. Effects of intoxication levels and drinking pattern on social anxiety in men. *J Stud Alcohol* 41:250-264, 1980.

AUTHOR

Peter E. Nathan, Ph.D.
Center of Alcohol Studies
Rutgers-The State University of New Jersey
New Brunswick, NJ 08903

Hepatic, Nutritional, and Genetic Influences on Cognitive Process in Alcoholics

Ralph E. Tarter, Howard Moss, Amelia Arria, and David Van Thiel

INTRODUCTION

Cognitive science is the study of conscious experience. It encompasses the study of phenomena ranging from introspection to the mechanisms underlying sensory information processing.

Neuropsychology is concerned with relating cognitive process to brain organization. When injury to the brain occurs, as, for example, following chronic use of drugs, it is important to ascertain how the central nervous system (CNS) pathology affects the structure and operations of cognition. This information may help better to understand and predict the behavior of the person.

This discussion addresses three questions. (1) Does chronic substance abuse disrupt cognitive capacities? (2) What are the potential mechanisms of action by which drug abuse compromises CNS integrity? (3) Are individuals who are at high risk for substance abuse differentiable from the rest of the population with respect to cognitive capacities?

EFFECTS OF CHRONIC SUBSTANCE ABUSE ON COGNITION

Alcohol and substance abuse rank among the three most prevalent psychiatric disorders (Myers et al. 1984). Comparatively little is known, however, regarding the long-term neurobehavioral consequences of chronic drug use. Sampling and methodologic problems are major mitigating factors in conducting research in this complex problem area. For example, inhalant abusers, benzodiazepene abusers, and opiate abusers comprise somewhat distinct populations with respect to socioeconomic status, gender, and race. Hence, generalization with respect to comparative neurotoxicity is difficult

because individuals who select a particular drug are not representative of the population at large. Furthermore, pattern of drug use and underlying motivation for drug use are not the same for all members within a population using a certain drug. The occasional recreational drug user is quite different from the person who uses drugs for self-medication or the person who is physically addicted with respect to the acute and cumulative effects of the substance on the brain. Also, individuals who use one drug preferentially are inclined to use other drugs occasionally, and, not infrequently, consume two or more drugs conjointly. This behavior, which is generally referred to as polydrug abuse, makes it difficult to ascertain the neurobehavioral effects of specific drugs in humans.

The acute and chronic effects of drug interaction on cognition are entirely unknown, hence it is not readily feasible to determine a specific drug effect on neuropsychological test performance. Thus, although the available evidence implicates the presence of neurobehavioral deficits for users of alcohol, inhalants, benzodiazepenes, as well as certain other drugs having abuse liability (Tarter and Edwards 1987), it is not possible to relate unequivocally the neuropsychological sequelae to the effect of the particular drug. To date, data have not been presented relating such fundamental variables as frequency, patterns, and quantity of drug use to level of neuropsychologic test performance.

The research conducted to date has been almost entirely desaiptive. The findings suggest that the prolonged consumption of certain types of drugs is associated with decrements in neuropsychologic test performance. However, the paucity of studies published in which the above-noted factors are controlled mitigates against any general conclusions regarding the mechanisms underlying the chronic and lasting effects of drugs on cognition. Nonetheless, the available evidence indicates that not all drugs having abuse liability cause neuropsychologic impairment. For example, there is no convincing evidence that heroin and marijuana abusers perform deficiently on neuropsychological tests (Parsons and Farr 1981). Where disturbances are observed, they are reflected by cognitive deficits in both capacity and efficiency and are manifest on tests of attention, memory, visual-motor, and abstracting processes. The extent to which the structure of cognition in terms of the representational systems or schemata are disrupted has not been investigated. From the perspective of neuropsychology, it is not inconceivable that the brain can become pathological to the extent that representational systems are impaired. For example, pervasive cortical atrophy and ventricular dilation have been described in chronic alcoholics (Ron 1983). Such profound structural change can be expected to impair brain functioning such that sensory input cannot be transduced and coded into the representational systems comprising cognition. As yet, no research has been conducted relating the effects of drug abuse to cognitive schemata and brain integrity using neuropsychologic tests.

The empirical evidence accrued regarding the effects of abused drugs on the brain has focused on processes of cognition rather than on the representational structures of cognitive schemata. By far, the drug most studied has been alcohol. With respect to the cognitive consequences of alcoholism, substantial evidence indicates that detoxified alcoholics (sober for up to 1 month) exhibit deficits on tasks measuring abstracting, memory, and visual-spatial capacities (Tarter and Edwards 1985). These deficits were found in up to 75 percent of alcoholics drawn from clinical populations. However, cognitive deficits tend to be absent when neuromedical history is normal (Grant et al. 1984). The severity of cognitive deficits, when present, is modest compared to that observed in persons with acute neurologic injury, and these deficits can be grouped into two broad syndromes (Wilkinson and Carlen 1980). One syndrome presents as an amnesic disorder that in its most severe manifestations qualifies for a Wernicke-Korsakoff diagnosis. The second syndrome presents as a somewhat benign dementia. These two neuropsychologic sequelae are not mutually exclusive inasmuch as there. are overlapping features with respect to manifest cognitive impairment. Investigations have not yet been conducted to delineate different neuropsychologic syndromes concomitant to drug abuse.

Although a substantial literature has emerged describing the type, severity, and reversibility of neuropsychologic deficits in alcoholics, remarkably little research has tried to identify the biological mechanisms that may be etiologically significant. The neurotoxicity of alcohol is well established. Additionally, chronic alcohol excess is associated with a disruption of multiple biological systems, which, besides the direct neurotoxic effect of alcohol, can induce CNS injury. Research conducted in our laboratory indicates that liver disease and vitamin-E-absorption disorder may contribute significantly to the cognitive deficits observed in alcoholics. The following brief discussion examines these two mechanisms potentially underlying the etiology of neurologic pathology concomitant to alcohol abuse.

MECHANISMS UNDERLYING CNS INJURY

Liver Disease

Hepatic injury and dysfunction are common sequelae of chronic alcohol abuse. Up to 30 percent of alcoholics develop cirrhosis, which, independently of alcohol consumption, is associated with a chronic hepatic encephalopathy (Rehnstrom et al. 1977). This liver-disease-induced neuropsychiatric disorder is commonly believed to be the consequence of the liver's failure to catabolize circulating neurotoxins, particularly nitrogenous substances (Duffy and Plum 1982). Hepatic encephalopathy caused by conditions other than alcoholism is commonly associated with the same types of neuropsychologic deficits as is commonly found in alcoholics (Tarter et al. 1988). As table 1 illustrates, when alcoholics and nonalcoholics are compared, both groups having biopsy-confirmed cirrhosis, they perform very similarly on

most neuropsychologic tests. On tests that measure short-term memory, eye tracking, and eye-finger coordination, the alcoholics do, however, perform more poorly, indicating that not all of the CNS disturbance can be ascribed to the effects of hepatic encephalopathy. The causes of these latter deficits are not possible to discern; they may reflect the additional toxic impact of alcohol on the brain or be the consequence of medical and biological factots other than liver disease that are common in alcoholics.

TABLE 1. *Neuropsychologic test results*

Test	Control	Nonalcoholic Cirrhotic	Alcoholic Cirrhotic	F
Token Test	1253	11.53	11.55	1.3
Rey Figure Copy	35.84	35.01	35.39	2.5
Rey Figure Delay	50.92	49.36	48.42	0.0
Trailmaking A	28.91	34.61	43.31	3.9*
Trailmaking B	60.46	81.84	112.22	6.6*
Block Design	36.51	34.70	31.07	1.6
Stroop—Color	12.93	15.92	16.52	1.7
Stroop—Word	8.68	9.32	10.53	2.6
Stroop—Interference	18.46	30.20	30.93	5.5*
Animal Naming	24.48	20.33	22.35	1.9
Symbol Digit	53.52	40.94	39.11	10.9*
Digit Span Forward	7.27	6.24	6.38	3.5*
Digit Span Backward	4.44	4.63	4.29	0.4
Digit Supraspan	2.90	1.83	2.59	2.2
Benton Visual Retention Test	8.21	6.85	6.87	4.2*
Brown Peterson Memory Test	41.98	37.31	33.04	3.6*
Finger Tapping—Dominant	50.92	49.36	48.42	0.4
Finger Tapping—Nondominant	47.21	44.73	44.53	1.1
Grooved Pegboard-Dominant	68.96	84.79	95.59	4.0’
Grooved Pegboard—Nondominant	77.16	94.42	111.28	2.8
Pursuit Rotor—Dominant	16.98	14.82	13.19	2.9
Pursuit Rotor—Nondominant	16.16	14.10	13.52	1.3
Static Ataxia—Eyes Open Lateral	4.65	3.28	3.15	0.8
Static Ataxia—Eyes Open Front-Back	9.59	10.02	11.60	0.5

TABLE 1. (Continued)

Test	Control	Nonalcoholic Cirrhotic	Alcoholic Cirrhotic	F
Static Ataxia—Eyes Closed Lateral	6.59	4.67	8.56	0.6
Static Ataxia—Eyes Closed Front-Back	14.90	23.50	20.72	1.8

*p<.05

NOTE: Data are group means, adjusted for age and education level. F values represent main effects.

The demonstration that liver disease in alcoholics may underlie certain of the cognitive deficits has important ramifications. First, it suggests that effective medical management of the liver disease may ameliorate the cognitive deficits. Preliminary data employing pharmacologic (Conn and Lieberthal 1978) and surgical (Tarter et al. 1988) procedures support this possibility. Second, because the liver subserves a number of essential biological functions (nutrition, immune regulation, detoxification, manufacture of plasma proteins), it may be that specific aspects of hepatic disturbance contribute to particular types of cognitive impairment. The biochemical variables listed in table 2, upon factor analysis, reduced into three categories of liver processes: liver injury, liver dysfunction, and protein synthesis in the liver. As can be seen in the table, various aspects of liver disease are differentially associated with different types of cognitive processes.

In summary, emerging evidence links hepatic disease to neuropsychologic impairment in alcoholics (Tarter et al. 1986). The extent to which recovery of cognitive capacity, often seen in alcoholics, is the product of a corresponding improvement in liver status concomitant to sobriety is unknown. Also, it is unclear whether liver disease consequential to other types of drug use, either directly from the drug or indirectly by disease resulting from intravenous self-administration, e.g., hepatitis, underlies the CNS pathology. The investigations conducted on alcoholics suggest that how liver disease affects brain functioning may be an important topic for research concerned with documenting the residual effects of other types of substance abuse on cognitive capacity.

Nutrition

The water soluble B-complex vitamins are integral to maintaining normal mental functioning. Chronic and severe intake deficiencies in these vitamins are associated with an organic brain syndrome (Roe 1979). The best known of these is a thiamine deficiency, which, in a subset of alcoholics, results in

TABLE 2. *Linear multiple regression analysis of hepatic injury variable-s and neuropsychologic test variables adjusted for age*

Neuropsychologic Test	Biochemical Variables*	r	Percent of Variance Predicted	p<
Block Design	(1) globulin (2) prothrombin time (3) ICG clearance	.37	13.8	.05
Trailmaking Test A	(1) albumin (2) prothrombin time (3) ICG clearance	.37	12.8	.05
Trailmaking Test B	(1) prothrombin time	.27	7.0	.05
Symbol Digit Modalities	(1) albumin (2) prothrombin time (3) globulin (4) ICG clearance (5) ammonia	.47	21.9	.0l
Animal Naming	(1) albumin (2) prothrombin time (3) ammonia (4) globulin (5) ICG clearance	.55	29.8	.00l
Digit Span Forward	(1) ICG clearance (2) albumin (3) globulin (4) prothrombin time	.39	15.0	.05
Digit Span Backward	(1) albumin (2) globulin (3) ammonia	.38	14.2	.05
Supra Span	(1) albumin (2) prothrombin time (3) ammonia (4) ICG clearance (5) globulin	.47	21.8	.0l
Tokens Test	(1) prothrombin time (2) albumin (3) ammonia (4) ICG clearance	.40	15.6	.05

*Numbers in parentheses indicate order of variable entry in regression equation.

an acute encephalopathy. This is often referred to as Wemicke's syndrome. In its chronic state, the Wemicke Korsakoff syndrome is the most profound neurologic sequela of alcoholism. Other B-complex vitamin deficiencies have also been shown to induce or exacerbate an organic brain syndrome.

The effects of a fat-soluble vitamin deficiency has been the subject of research in our laboratory (Arria et al., in press). In one study, we found that 52 percent of alcoholics met criteria for a vitamin E deficiency. This may be important for elucidating the neural mechanisms underlying the cognitive deficits in alcoholics. Vitamin E is an antioxidant and, as such, functions to protect membrane phospholipids from peroxidation by free radicals. The absence of the protective function of vitamin E in alcoholics may catalyze membrane destruction. It is noteworthy that alcohol administration to animals results in increased membrane permeability; thus one potential mechanism for CNS injury may relate to cell membrane injury or destruction consequential to a vitamin-E-absorption disorder.

Table 3 summarizes the findings from a recently completed study in our laboratory on a nonalcoholic sample. The findings demonstrate the potential importance of vitamin E on psychomotor capacity.

In summary, the residual cognitive deficits associated with chronic alcohol or drug abuse may be due in part to disturbed nutritional intake or absorption. Inadequate intake of essential nutrients may be intrinsic to the lifestyle of the destitute drug addict; this inadequacy, added to the drug's effects on the brain, exacerbates the cognitive impairment. In addition, a disruption of biological systems regulating absorption of essential nutrients may contribute to the CNS pathology. Thus, drug abuse may be associated with persisting cognitive impairment owing to the combined influences of direct action on the brain, indirect effects of drug use (lifestyle), or disruption of organ-system integrity (liver, pancreas, heart), and infection.

COGNITIVE DEFICIT PRESAGING SUBSTANCE ABUSE

children of alcoholics and children of drug abusers may manifest neurodevelopmental and cognitive deficits concomitant to either drug teratogenicity or genetic predisposition. Evidence presented in the past several years suggests that children of alcoholics exhibit cognitive impairments compared to children of nonalcoholics (Tarter et al., in press). Deficits have also been reported even when the children of alcoholics were raised away from their biological alcoholic parents. To date, no circumscribed cognitive syndrome has been delineated, although from the studies published, it appears that children of alcoholics may be deficient on tasks measuring planning, verbal memory, and abstracting (Tarter et al. 1989). It should be emphasized, however, that the results are preliminary and the presence, type, and severity of cognitive impairment observed are not consistent across all investigations.

TABLE 3. *Performance scores on neuropsychologic rests for normal healthy controls, primary biliary cirrhosis (PBC) patients with vitamin E deficiency, and PBC patients without vitamin E deficiency*

Neuropsychologic Test	PBC Vitamin E Deficient	Healthy Controls	PBC Vitamin E Sufficient
Visual-Motor Efficiency			
Trailmaking A	36.22±9.4*	26.87±6.7	34.71±11.0
Trailmaking B	98.0±31.8*	57.00±10.3	77.14±32.5
Symbol Digit	39.16±10.1*	55.60±7.2	44.07±6.0
Simple Motor Speed			
Finger Tapping (right and left hands)	82.94±13.9	84.50±11.2	84.29±8.8
Fine Motor Coordination			
Grooved Pegboard			
Dominant Hand	79.05±10.1*	61.80±8.3	76.67±22.1
Nondominant Hand	87.95±21.7*	65.43±7.3	85.00±22.6* (t=2.87)
Eye-Hand Coordination			
Pursuit Rotor			
Dominant Hand	12.64±2.9*	15.9±2.8	13.43±4.9
Nondominant Hand	1246±3.5	15.37±3.1	12.99±5.4

*p<.01, significantly different from normals.

NOTE Data represent means ± standard deviation.

The above findings, albeit tentative, implicate a disruption of CNS integrity in children predisposed to alcoholism. Indeed, approximately 25 percent of children of alcoholics become alcoholics themselves (Goodwin 1979). Similarly, a familial and possibly genetic basis for substance abuse has been documented, suggesting that there may also be cognitive deficits in children predisposed to drug abuse. One important research question concerns whether having a cognitive deficit significantly and directly contributes to the risk for developing a substance abuse disorder. Table 4 summarizes the key findings from our most recent study contrasting community-dwelling children of alcoholic (chosen solely on previous alcohol history) and nonalcoholic men. It can be seen that verbal intellectual capacity, achievement level on standardized tests of educational attainment, and certain aspects of short-term memory are deficient in male offspring of alcoholic fathers. It remains for future research to determine the relative

genetic and environmental contributions to these deficits and to ascertain how the manifest impairments affect outcome in adulthood.

TABLE 4. *Sons of alcoholics and nonalcoholics*

	Alcoholic Offspring (Mean)	Normal Men Offspring (Mean)	F	p <
Age	14.29	14.33	1.19	—
Grade	7.76	8.07	1.33	—
Peabody Individual Achievement Test				
Mathematics	102.31	116.70	14.14	.001
Reading Recognition	103.88	112.93	4.63	.05
Reading Comprehension	102.06	115.11	6.73	.0l
Spelling	94.56	108.44	13.83	.001
General Information	106.56	113.96	2.022	-
Total	102.19	116.78	12.4	.001
Dichotic Listening				
Right Ear	29.63	31.67	1.91	—
Left Ear	29.13	30.04	0.11	—
Symbol Digit Paired Association Learning				
Number Correct	22.25	23.37	1.14	—
Number Correct (delay)	5.94	6.37	0.77	—
Peterson Memory Test				
5 Seconds Interpolation	14.06	16.07	1.97	
15 Seconds Interpolation	10.31	13.56	5.93	.05
30 Seconds Interpolation	9.88	13.93	7.48	.01
Total Recall	34.25	43.56	7.83	.01
Peabody Picture Vocabulary Test				
Standard Score	103.56	119.30	8.29	.01

DISCUSSION

As society becomes increasingly complex and dependent on technologic sophistication, it is likely that even subtle cognitive impairment will have pronounced adverse effects on the individual's potential for adjustment. The

longstanding effects of drugs on the brain pose a major societal problem in light of current prevalence of drug use. The extent of permanent residual cognitive sequelae has not been researched, although, based on studies of alcoholics and polydrug abusers, it would appear that drug users are at heightened risk of suffering CNS injury both from the substance abused and from a lifestyle typified by deprivation, neglect of personal well-being, and traumatic injury. To date, answers to certain important questions are unavailable. For example: Which drugs have lasting neurotoxic effects? Which drugs produce CNS injury indirectly by impairing function of other organ systems? Does cessation of drug use early in life have a delayed effect on CNS functioning in later life? Does a cognitive deficit from drug use affect treatment prognosis? Are differential cognitive profiles associated with different types of drugs? How does cognitive deficit consequential to drug use relate to behavioral change and psychopathology? These pressing questions have practical implications for the treatment of substance abusers.

CONCLUSION

The available limited evidence suggests that alcoholism and certain types of drug abuse are associated with cognitive deficits. The deficits, although not severe in most cases, are nonetheless significant insofar as safety to self and others may be concerned. Subtle impairment in psychomotor speed and coordination may, for example, place the person at great risk when operating power machinery or performing a dangerous job. For this reason, an important area for future research would be to devise precise assessment methods to detect subtle CNS disturbance. Neuropsychologic tests using the precise measurement afforded by microcomputers may thus be useful for determining whether an individual is fit to perform a certain task. Such testing may provide a noninvasive method of accruing information about acute and chronic drug effects on functional capacity, which has direct ramifications for the safety and health of the individual.

REFERENCES

Arria, A.; Tarter, R.; Warty, V.; and Van Thiel, D. Vitamin E deficiency and psychomotor dysfunction in adults with primary biliary cirrhosis. *Am J Clin Nutr,* in press.

Conn, H., and Lieberthal, M. *The Hepatic Coma Syndrome and Lachtulose.* Baltimore: Williams and Wilkins, 1978.

Duffy, T., and Plum, F. Hepatic encephalopathy. In: Arias, L.; Popper, H.; Schacter, D.; and Shafritz, D., *eds. The Liver: Biology and Pathobiology.* New York: Raven Press, 1982. pp. 693-715.

Goodwin, D. Alcoholism and heredity. *Arch Gen Psychiatry* 36:57-61, 1979.

Grant, J.; Adams, K.; and Reed, R. Aging, abstinence, and medical risk factors in the prediction of neuropsychologic deficit among long-term alcoholics. *Arch Gen Psychiatry* 41:710-718, 1984.

Myers, J.; Weisman, M.; and Tischler, G. Six month prevalence of psychiatric disorders in three communities. *Arch Gen Psychiatry* 41:959-967, 1984.

Parsons, O., and Farr, S. The neuropsychology of alcohol and drug abuse. In: Filskov, *S.*, and Boll, T., eds. *Handbook* of *Clinical Neuropsychology*. New York: Wiley, 1981. pp. 320-365.

Rehnstrom, S.; Simert, G.; Hanson, G.; and Vong, J. Chronic hepatic encephalopathy. A psychometrical study. *Scand J Gastroenterol* 12:305-311, 1977.

Roe, D. *Alcohol and the Diet.* Westport, CT: AVI Publishing Co., 1979.

Ron, M. The alcoholic brain: CT scan and psychological findings. *Psycho1 Med* (Suppl 3); 1983.

Tarter, R., and Edwards, K. Neuropsychology of alcoholism. In: Tarter, R., and Van Thiel, D., eds. *Alcohol and the Brain: Chronic Effects.* New York: Plenum Press, 1985.

Tarter, R., and Edwards, K. Brief and comprehensive neuropsychological assessment of alcoholism and drug abuse. In: Hartlage, L.; Asken, M.; and Hornsby, L., eds. *Essentials of Neuropsychological Assessmenl.* New York: Springer, 1987. pp. 138-162.

Tarter, R.; Edwards, K.; and Van Thiel, D. Hepatic encephalopathy. In: Goldstein, G., and Tarter, R., eds. *Advances in Clinical Neuropsychology.* Vol. 3. New York: Plenum Press, 1986. pp. 243-264.

Tarter, R.; Erb, S.; Biller, P.; Switala, J.; and Van Thiel, D. The quality of life following liver transplantation. A preliminary report. *Gastroenterol Clin North Am* 17:207-217, 1988.

Tarter, R.; Jacob, T.; and Bremer, D. Cognitive status of sons of alcoholic men. *Alcohol: Clin Exp Res* 13:232-235, 1989.

Tarter, R.; Moss, H.; and Laird, S. Neuropsychological and neurophysiological characteristics of children of alcoholics. In: Windle, M., and Searles, J., eds. *Children of Alcoholics: A Critical Review of the Literature.* New York: Guilford, in press.

Tarter, R.; Van Thiel, D.; and Moss, H. Impact of cirrhosis on the neuropsychologic test performance of alcoholics. *Alcohol: Clin Exp Res* 12:619-621, 1988.

Wilkinson, D., and Carlen, P. Relationship of neuropsychological test performance to brain morphology in amnesic and non-amnesic chronic alcoholics. *Acta Psychiatr Scand* 285:89-101, 1980.

ACKNOWLEDGMENTS

Supported by U.S. Public Health Service grants AA 06936, AA 06601, and 1 P50 DA 0560555.

AUTHORS

Ralph E. Tarter, Ph.D.
Howard Moss, M.D.
Amelia Arria, B.S.

Department of Psychiatry
University of Pittsburgh Medical School
Pittsburgh, PA 15213

David H. Van Thiel, M.D.
Department of Medicine
University of Pittsburgh Medical School
Pittsburgh, PA 15213

Learning and Memory Deficits in Detoxified Alcoholics

Marlene Oscar-Berman

INTRODUCTION

To begin on common ground, this chapter will define three terms that will be used frequently: "learning," "memory," and "detoxified alcoholics." Next, it will relate the concepts of "learning" and "memory" to areas of brain damage associated with alcohol abuse in detoxified alcoholics. Similarities between alcoholics and chronologically older nonalcoholic subjects will be noted, both in terms of neuroanatomical and functional changes; special attention will be paid to the role of the right hemisphere. Finally, this chapter will review findings that suggest that learning deficits may be related to perceptual deficits, which, in turn, may be related to neocortical damage, and that memory deficits, especially those dependent upon short-term storage capacity, may be related to damage below the level of the cortex.

DEFINITIONS OF LEARNING AND MEMORY

The term "learning" usually refers to the processes by which new information is acquired, while "memory" usually refers to the storage of new and old information for later use (Corsini 1987). Learning is dependent upon sensory input; it is usually an incremental process that involves practice, and it usually requires some form of reinforcement. Learning theorists do not always agree on a definition of learning, although most do agree that it can be measured operationally in terms of changes in behavior over time (Bower and Hilgard 1981). Common operational measures of learning are decreases in errors with practice over time, and decreases in amount of time taken to perform a specific task.

Memory, in turn, can be dependent upon learning; memories can be stored for very short periods of time—seconds or even milliseconds, during which information is encoded and consolidated—or for long periods of time weeks, years, or a lifetime (Bugelski 1987; Tulving 1985). Conceptually,

there is a thin line between learning and memory, and a thin line between different stages or forms of memory. For example, it's hard to specify where short-term memory ends and long-term memory begins.

Table 1 represents one way of looking at human memory, which emphasizes temporal characteristics of the information being processed. Table 1 is intended to be descriptive only and, therefore, relatively atheoretical.

TABLE 1. *Forms of human memory*

	Sensory Memory	Immediate Memory	Short-Term Memory	Long-Term Memory
Terms Used	Iconic/ Acoustic storage	Primary memory	Secondary memory	Tertiary memory
Durations	Fractions of a second	up to about 45 seconds	Minutes to years	May be permanent
Examples	Subliminal perception	Digit span	A new song	Your name

Most of the early learning and memory research in alcoholism centered around the middle two aspects of memory listed in table 1, that is, primary and secondary memories, having temporal durations, respectively, of anywhere from several seconds to several years (Talland 1965; Victor et al. 1971). More recently, research on disorders of learning and memory have emphasized qualitative aspects of the information being acquired and stored (Mishkin and Applinzeller 1987; Squire and Butters 1984; Tulving 1985).

DETOXIFIED ALCOHOLICS

The term "detoxified alcoholic" has a specific meaning in the majority of studies to be reviewed in this chapter. Only male subjects have been employed in the research projects. The study of females brings in a host of variables that are beyond the scope of the present discussion, e.g., brain asymmetries are noted to be different in the two genders (Geschwind and Galaburda 1984). In the studies conducted in our laboratories, the alcoholic research participants consisted of men over age 20 who had used alcohol in excessive quantities, generally for at least 7 years, and whose drinking problems had been severe enough to meet criteria for alcohol abuse and alcohol dependence according to currently recognized diagnostic criteria

such as those of the DSM III (American Psychiatric Association 1980) and DSM III-R (American Psychiatric Association 1987). To be enrolled in our studies, alcoholics were required to be dry for at least 4 weeks before testing and to have no history of significant head injury, seizure disorder, stroke, or other serious neurological disease; no significant diabetes, heart disease, or other underlying medical illness; no serious psychiatric disturbance or ongoing psychological disability such as depression; no chronic polydrug abuse; and no current use of psychotropic medications. A fuller description of the research project and additional references can be found in Ellis and Oscar-Berman (1989).

We have also been interested in studying cognitive changes in detoxified alcoholics who have developed Korsakoff's syndrome, characterized most dramatically by severe anterograde amnesia or loss of short-term memory (Oscar-Berman 1980; Talland 1965). The exclusion criteria for our Korsakoff patients were essentially the same as those for non-Korsakoff alcoholics, and both alcoholic groups were equated as much as possible for education and verbal IQ scores. However, whereas the non-Korsakoff alcoholics had clinically normal memory ability (as measured by memory quotients derived from the Wechsler Memory Scale, generally being between 90 and 130), the memory quotients of the Korsakoff patients, by definition, were abnormally low (usually falling between 60 and 100). That is, one important requirement for a subject's inclusion as a Korsakoff patient in our laboratory, as well as in other laboratories, was that the patient's memory quotient be at least 20 points below his verbal IQ score (Squire and Butters 1984). Likewise, an important requirement for inclusion as a non-Korsakoff alcoholic was that the memory quotient be no more than 15 points below the verbal IQ score. A dichotomous, nonoverlapping requirement permitted us to describe group similarities-as well as group differences-with confidence.

AREAS OF BRAIN DAMAGE ASSOCIATED WITH ALCOHOL ABUSE

Although not all researchers agree, it can be stated that any brain damage that may be associated with long-term chronic alcohol abuse is fairly diffuse and involves the cerebral cortex (Lishman 1981; Wilkinson and Carlen 1982). Wilkinson and Carlen (1982) compared computerized tomography (CT) scans of non-Korsakoff alcoholics to those of neurological controls across five age decades. A striking characteristic of the brains of the alcoholics was abnormal ventricular enlargement at the level of the caudate, as well as sulcal widening in the cerebral cortex. Of special interest was the fact that the ventricles and sulci became increasingly wider with increasing age. In the 1950s, Courville described this feature of cerebral atrophy in the brains of alcoholics and likened it to brain shrinkage that occurs with normal chronological aging (Courville 1966). That is, alcoholics and normal aging individuals showed fairly uniform cortical atrophy, most

prominent over the dorsolateral frontal regions and extending posteriorly into the superior parietal lobule. From the observed similarities in the brains of alcoholic and aging individuals sprang the search for parallels in functional decline associated with alcoholism and aging, and a notion referred to as the "premature aging hypothesis" (Ryan 1982), which will be discussed in the following sections. First, however, one more item should be noted regarding neuroanatomy and alcoholism: if alcoholics have developed Korsakoff's syndrome, damage to subcortical areas becomes more and more prominent. Several of the subcortical areas implicated in the anterograde amnesia of Korsakoff's syndrome are: (1) diencephalic structures such as the mammillary bodies of the hypothalamus, and the dorsomedial thalamic region (Victor et al. 1971); (2) basal forebrain structures such as the nucleus basalis of Meynert (Arendt et al. 1983); and (3) medial temporal lobe structures such as the amygdala and hippocampus (Mishkin and Appenzeller 1987). Interestingly, Wilkinson and Carlen (1982) indicated that the cortical brain morphology scores of Korsakoff patients were not age related as they were in non-Korsakoff alcoholics; this suggests that Korsakoff alcoholics may be "immune" to premature aging. If true, it may be because Korsakoff patients already have suffered maximal alcohol-related brain damage, as though a "basement" effect for central nervous system (CNS) involvement had been reached.

PREMATURE AGING HYPOTHESIS

Researchers began to observe a distinct and important functional similarity between (non-Korsakoff) alcoholics and chronically older normal controls. That is, many laboratories reported selective deterioration by alcoholic or aging individuals in their abilities to solve a variety of nonverbal tasks, in contrast to their intact abilities on verbal tasks. Notable examples were the low scores of both groups on the performance subscales of IQ tests, but not on the verbal IQ subscales; however, there were many, many other examples (Ellis and Oscar-Berman 1989). The observation of similar nonverbal functional decline, together with the similarity in gross neuroanatomical findings of the two groups, led to the formulation of the "premature aging hypothesis" of alcoholism. There actually were two versions of the premature aging hypothesis; the second seems to have held up better under experimental scrutiny than the first. Figure 1 shows the two versions of the premature aging hypothesis.

According to the first version, labeled the "accelerated aging" hypothesis in the figure, chronic alcoholism leads to the precocious development of behavioral changes typically associated with advancing age (Noonberg et al. 1985; Ryan 1982; Ryan and Butters 1980). Thus, cognitively and neuroanatomically, alcoholics become old before their time. The second version, labeled the "age sensitivity" hypothesis in the figure, places the timing of the changes somewhat differently (Noonberg et al. 1985; Ryan 1982). This view holds that older brains are more vulnerable to the deleterious

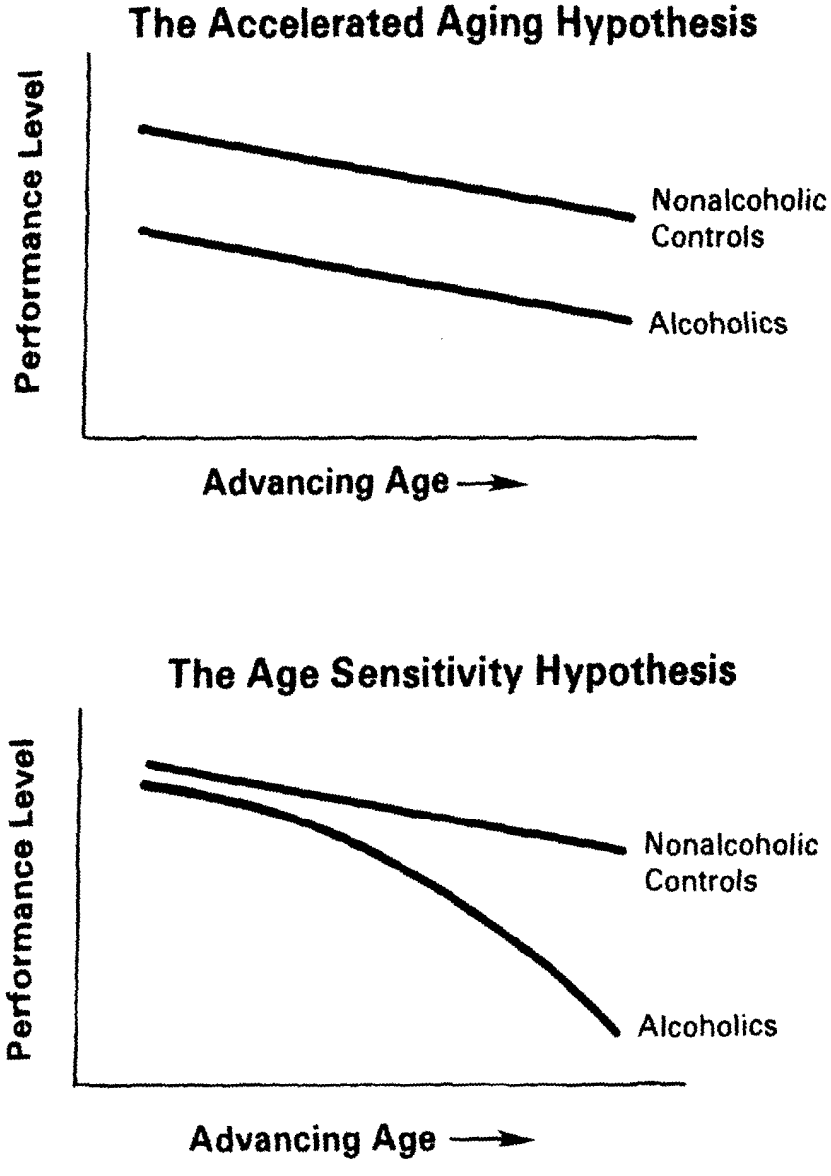

FIGURE 1. *Two versions of the premature aging hypothesis: Accelerated aging vs. age sensitivity*

SOURCE: Ellis and Oscar-Berman 1989, copyright 1989, American Psychological Association.

consequences of alcohol abuse than are the brains of younger adults. Therefore, it would be only after about the middle of the fourth decade—when the manifestations of normal chronological aging begin to appear—that alcoholics would begin to show greater impairments than their peers. As already noted, the age-sensitivity version of the premature aging hypothesis has stood up better than the accelerated-aging version. An example from a study recently completed in our laboratory is described in the following section (Oscar-Berman and Bonner 1989).

NONMATCHING-TO-SAMPLE (ODDITY) AND DELAYED NONMATCHING-TO-SAMPLE

This particular study (Oscar-Berman and Bonner 1989) is described in detail here for several important reasons. First, the results are prototypical for demonstrating a positive example of the age-sensitivity version of the premature aging hypothesis. Second, the study is distinctive in its capabilities for eliciting parallel functional deficits along several lines; perceptual processing, attention, learning, and short-term memory all can be assessed in the same experiment (Oscar-Berman and Bonner 1985). Third, the study exemplifies an approach that is gaining momentum in the search for understanding learning and memory deficits consequent to human brain damage; the approach simply employs the same behavioral paradigms that have been used successfully for decades in disclosing specific deficits that result from brain lesions in animals.

The tasks we employed were nonmatching-to-sample (NMTS) and delayed nonmatching-to-sample (DNMTS). Figure 2, borrowed from a textbook chapter on learning and memory in nonhuman primates (Harlow et al. 1971), shows the NMTS task being used with a monkey subject. For the monkey to earn a reinforcement, it must select the odd stimulus out of the three presented, thereby solving the problem "correctly." When the odd one is selected consistently, the monkey can be said to have learned the "nonmatching" or "oddity" strategy. For monkeys, the reinforcement usually is a raisin or a peanut. With human subjects performing the version of the task that we used (Maki and Leith 1973), pennies served as rewards.

The subjects in our study consisted of a total of 59 normal and alcoholic men, including 13 with alcoholic Korsakoff's syndrome. The normals and the non-Korsakoff alcoholics were equated for age within three age brackets: 35 to 45, 46 to 59, and 60 and older. Those six subgroups, each containing a minimum of seven subjects, formed the basis for one set of statistical comparisons that we used for assessing the separate contributions of aging and alcoholism to any observed deficits. Because there was not a sufficient number of Korsakoff patients in each of the three age brackets to permit a similar comparison (the age range of the 13 Korsakoff alcoholics was between 41 and 71), we matched them with 13

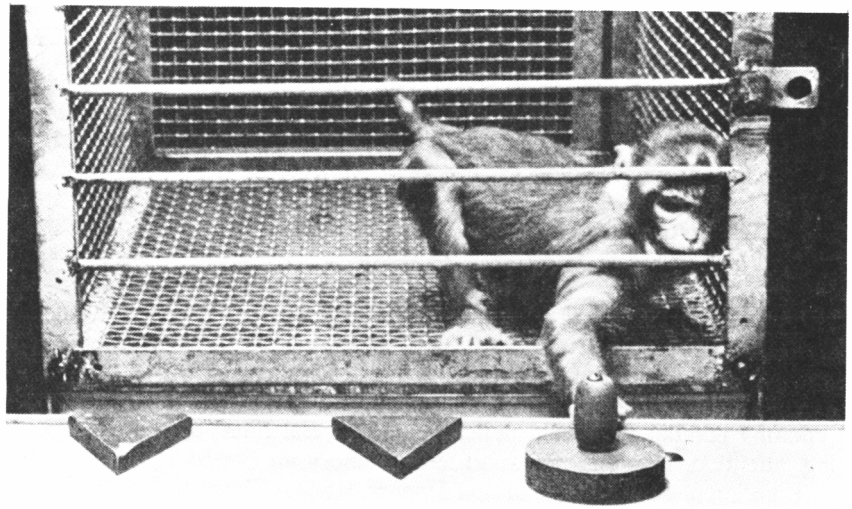

FIGURE 2. *A monkey performs the NMTS or oddity task*

SOURCE: Harlow et al. 1971, copyright 1971, Academic Press, Inc.

non-Korsakoff alcoholics and 13 normals of the same ages for the purpose of analyzing their data separately.

The experimental apparatus that we used is shown in figure 3. Subjects sat facing a panel containing three adjacent stimulus keys (also serving as manipulanda for responses). The stimuli were lights projected through filters from behind onto the stimulus keys, and consisted either of colors (red or green), or of white lines (oriented vertically or horizontally). It was also possible to compound the colors with the lines, thereby making red or green horizontal lines and red or green vertical lines. The sample stimulus was on the middle key, and the subjects' choices had to be made by pressing the right or the left stimulus key, whichever was the odd one of the three. The apparatus was run with the aid of a computer program that allowed us to obtain measures of four parameters: learning, attention, processing time, and short-term memory. Learning was measured simply in terms of the number of trials that it took each person to make 21 correct choices of the odd stimulus in a block of 24 trials. There were no statistically significant group differences by this measure. All groups, including the Korsakoff alcoholics, were equally capable of learning the simple nonmatching or oddity strategy.

Attention was manipulated by making the central stimulus simple or complex, thereby requiring the subjects to notice either one stimulus dimension

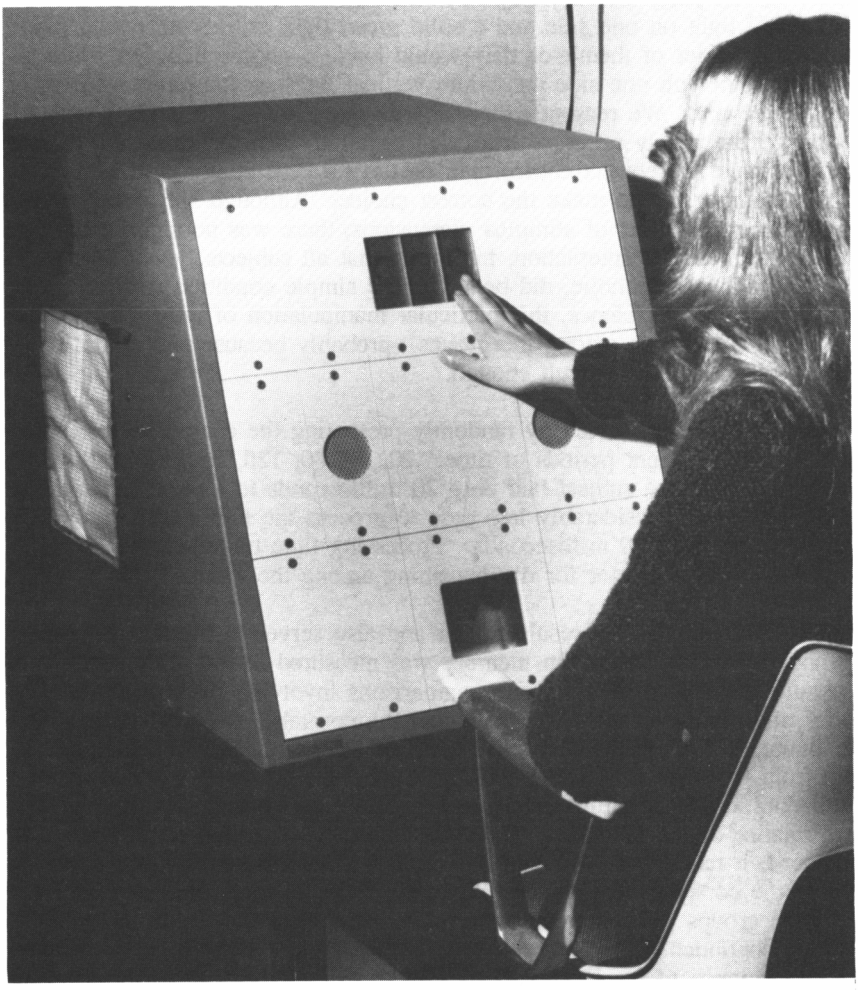

FIGURE 3. *A human subject performs the NMTS or oddity task in our neuropsychology laboratory*

NOTE: Colored lights or patterns are projected from behind onto the response panels.

or two stimulus dimensions. When the center stimulus was a simple one, it varied only in color, or only in line orientation. In that case, subjects would have to choose either between red and green or between vertical and horizontal lines. When the center stimulus was complex, however, it contained a combination of one of the colors with one of the line orientations.

e.g., red with horizontal, making a stimulus that appeared as red horizontal lines. In that case, the subjects still would have to make their choice from a solid red light on one side and a solid green light on the other side (with no lines in either of them), or they would have to choose between white horizontal lines on one side and white vertical lines on the other, with color being irrelevant. We reasoned that subjects with attentional deficits would perform more poorly on those trials that required them to notice two dimensions to make the correct choice than on trials where they had to notice only one dimension to make the correct choice. Although we found a significant main effect of stimulus dimensions, there was no significant group-by-dimensions interaction, indicating that all subjects, young and old, alcoholic and nonalcoholic, did better on the simple condition than on the complex condition. Hence, this particular manipulation of attention turned out not to distinguish among the groups—probably because two stimulus dimensions were not difficult enough.

Processing time was varied by randomly presenting the central sample stimulus for five different periods of time: 20, 40, 80, 120, and 500 milliseconds. Thus, if a subject had only 20 milliseconds to look at the sample stimulus, he had considerably less time to process the information than on a trial when he had 120 milliseconds. Processing time turned out to be a very important parameter for distinguishing among the groups.

Figure 4 summarizes the results so far and also serves to introduce the methods by which short-term memory was measured in the study. In figure 4, results are shown of the group comparisons involving the Korsakoff alcoholics, the non-Korsakoff alcoholics, and the normals. On the left side of the figure, it is clear that the non-Korsakoff alcoholics were indistinguishable from the normals. The Korsakoff alcoholics, however, were impaired at all durations of stimulus exposure except 500 milliseconds. Although the performance of the Korsakoff alcoholics improved as exposure duration increased, it reached the level of the controls only with the longest exposure (where the controls were at a ceiling level). On the right side of figure 4, the same groups were compared, and it remains clear that the Korsakoff patients continued to perform at lower levels than the other groups. In fact, the performance of the Korsakoff patients deteriorated, while performance of the other groups remained fairly steady. Nonetheless, the independent variable was not how long the center stimulus was available but how long was the delay between the center stimulus going off and the comparison stimuli coming on, allowing subjects to make a choice. This interstimulus delay was our measure of short-term memory. The subjects had to remember during the delay what they saw just before the sample stimulus went off. The right side of figure 4 actually shows the classic short-term memory deficit in alcoholic Korsakoff patients (Talland 1965). There were six different interstimulus delays, ranging from 0 to 30 seconds; they were randomly presented across trials and randomly intermixed with the different stimulus exposures mentioned earlier. For example, on one trial, a subject

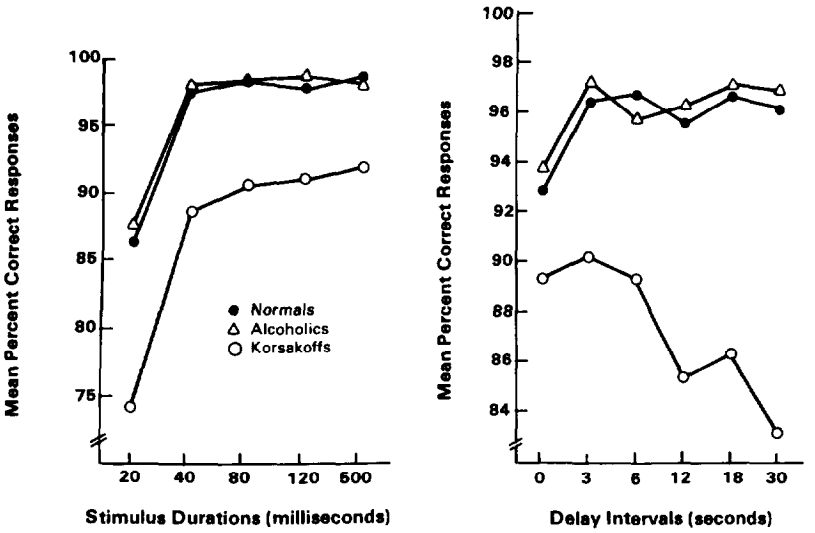

FIGURE 4. *Performance on the DNMTS tasks by alcoholic Korsakoff patients, non-Korsakoff alcoholics, and normal controls*

SOURCE: Oscar-Berman and Bonner 1989, copyright 1989, Psychonomic Society, Inc.

might have been given a red sample for 40 milliseconds, followed 30 seconds later by a choice between a red and a green stimulus (he should, of course, have chosen green). On another trial, he might have been given a set of green horizontal lines for 20 milliseconds, followed 12 seconds later by a choice between horizontal and vertical white lines (he should have chosen the vertical lines). The rule for correct responding never changed; only the specific experimental parameters changed. In that sense, the task actually was measuring two types of memory: memory for the rule of the task, which always stayed the same, and memory for the information displayed before the delay, which changed on every trial.

In the human memory field, memory for rules would fall under the category of "procedural" or "semantic" memories, and memory for specific bits of new information would fall under the category of "declarative" or "episodic" memories (Squire and Butters 1984; Tulving 1985). Results with the Korsakoff patients, showing intact oddity rule-learning, but impaired short-term memory, confirmed many findings, published in the last few years, that semantic or procedural memories are relatively spared in alcoholic amnesia, but that declarative or episodic memories are especially vulnerable in these subjects. Reviews may be found in Parsons et al. (1987) and

Squire and Butters (1984). What about detoxified alcoholics who did not have Korsakoff's syndrome?

Figure 5 shows the results for the comparisons of the six subgroups of age-matched non-Korsakoff alcoholics and normals. Figure 5 represents a refined breakdown of the two groups that were not distinguishable in figure 4; however, since the age range of the non-Korsakoff groups was wider than that of the Korsakoff alcoholics, the total number of alcoholic and normal subjects was greater. There was considerable overlap among the six subgroups except under the most difficult processing conditions (the shortest exposure durations), and under the most stringent demands on short-term memory (the longest interstimulus delays). Therefore, only the potentially discriminating data were analyzed. Generally, the older subjects, both the alcoholics and the normals, showed significant deficits in processing and significant deficits in short-term memory, although their deficits were not nearly as dramatic as the ones observed in the Korsakoff patients. There was also a statistically significant age-by-alcoholism interaction with processing time and delay interval. Even though figure 5 does not depict it, this four-way interaction, when teased apart statistically, indicated that when the experimental conditions placed increased demands upon processing and memory, the older alcoholics (ages 60 and over) did not perform as well as their younger counterparts; however, older normals were not significantly different from younger controls. The reasons that the compounding effect of alcoholism and aging is not apparent in figure 5 are that the effect was small and the intergroup comparisons were based on combined data for the three shortest durations and the three longest delays. Nonetheless, these results provided some support for the age-sensitivity version of the premature aging hypothesis, which placed emphasis upon the appearance of alcohol-related deficits in the older age range.

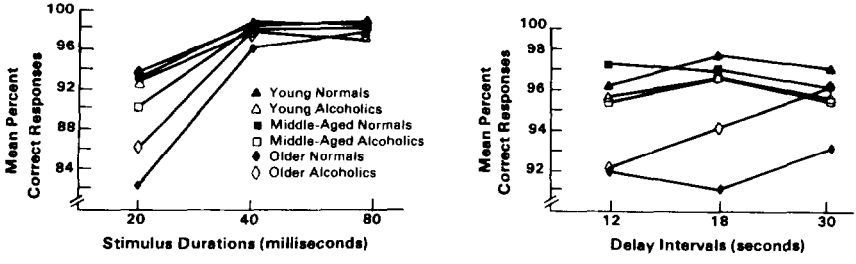

FIGURE 5. *Performance on the DNMTS tasks by non-Korsakoff alcoholics and normal controls in each of three age groups*

SOURCE: Oscar-Berman and Bonner 1959, copyright 1989, Psychonomic Society, Inc.

To summarize the findings so far: (1) all groups were capable of learning the simple NMTS strategy; (2) deficits in selective attention did not stand out in this study, although there is evidence from other studies of reliable attentional deficits in alcoholism and aging (Oscar-Berman 1980; Oscar-Berman 1984; Oscar-Berman and Ellis 1987); (3) semantic or procedural memories in alcoholic and aging groups were not compromised compared to shorter term declarative or episodic memories, where alcoholic Korsakoff patients and, to a lesser degree, the older groups showed deficits; (4) alcoholic Korsakoff patients, and—again to a lesser degreed—older subjects with and without an alcohol history were retarded in perceptual processing ability; and, finally, (5) the added characteristic of alcohol abuse compounded the effects of aging only in the most difficult experimental conditions (short stimulus durations and long interstimulus delays), thus lending some support to the age-sensitivity version of the premature aging hypothesis. These results emphasized a note of caution expressed by many other investigators: when studying behavioral phenomena in alcoholics, including attention, percaption, learning, and memory, it is important to consider the contributions of aging to any observed abnormalities (Grant 1986; Parsons et al. 1987; Riege 1987; Ryan 1982).

COMPARATIVE NEUROPSYCHOLOGY: THE USE OF COMPARABLE MEASURES OF PERFORMANCE IN BRAIN-DAMAGED HUMANS AND MONKEYS

The DNMTS task has been very popular for assessing the effects of brain damage in human and nonhuman primates, and deficits in monkeys have been reported following damage to brain structures implicated in human memory disorders. For example, several laboratories reported finding deficits after bilateral damage to diencephalic or medial temporal lobe structures (Aggleton and Mishkin 1983; Gaffan et al. 1984, Mahut et al. 1982; Mishkin 1978; Z&-Morgan et al. 1982). Goldman-Rakic and her group (Witt and Goldman-Rakic 1983) also reported DNMTS deficits in monkeys with experimentally induced thiamine deficiency—an animal model of Korsakoff's disease. Although those deficits were associated with brainstem lesions, the affected brainstem regions are known to project to cortical association regions, which in turn have been found to be important for normal performance on nonmatching types of tasks (Horel 1978; Lhermitte and Signoret 1976; Mishkin 1978; Oscar-Berman and Bonner 1985). Surprisingly, regions relatively spared by thiamine deprivation were the diencephalic and medial temporal areas typically implicated in human amnesia (mammillary bodies of the hypothalamus, dorsomedial thalamic nuclei, hippocampus, and amygdala). Patients with diffuse cortical atrophy, characteristic of Alzheimer’s disease, also have demonstrated DNMTS deficits (Albert and Moss 1984).

Based upon the patterns of results from the nonmatching studies reviewed so far, it appears that, in alcoholism, widespread cortical damage was

responsible for at least some aspects of the observed deficits (especially those related to processing), while other aspects of the deficits (especially in short-term memory) were related to subcortical damage. This conclusion is based upon relative contributions of cortical and subcortical damage, because one does not exist without the other in chronic neurological disease.

DNMTS is only one experimental paradigm successfully employed to disclose human impairments and directly comparable to animal models of cognitive deficits. Many more paradigms are being used with increasing frequency in behavioral neurology (Freedman and Oscar-Berman 1986b; Kish et al. 1988). For example, delayed-response and delayed-alternation tasks, which are sensitive to frontal system damage, have been used to differentiate among the dementias of Alzheimer's and Parkinson's diseases (Freedman and Oscar-Berman 1986b; Freedman and Oscar-Berman 1986c), Korsakoff's syndrome (Freedman and Oscar-Berman 1986a; Oscar-Berman et al. 1982) and olivopontocerebellar atrophy (El-Awar et al. 1988). Also used have been tactual discrimination learning tasks (Freedman and Oscar-Berman 1986b; Freedman and Oscar-Berman 1987). as well as visual and spatial discrimination learning tasks (Freedman and Oscar-Berman 1989; Oscar-Berman and Zola-Morgan 1980a; Oscar-Berman and Zola-Morgan 1980b; Squire et al. 1988; Zeaman and House 1963), which are sensitive to damage in other cortical association regions (including parietal and temporal cortex). Operant conditioning paradigms and probability learning tasks, which are sensitive to damage to frontal and limbic system structures, have been used for many years (Bitterman 1975; Oscar-Berman et al. 1976; Oscar-Berman et al. 1980). Further, Razran's 1971 review includes a description of the work of Ivanov-Smolensky in the 1920s. These and other paradigms are staple repertoires in the laboratories of experimental and physiological psychologists, and they have considerable promise for disclosing residual effects of abused drugs.

HEMISPHERIC ASYMMETRIES AND PERCEPTUAL LEARNING AND MEMORY

Prior to the discussion of NMTS tasks, note was made of a consistent finding of poor performance in alcoholic and aging groups on nonverbal tasks. Although the topic of nonverbal performance was described as one manifestation of the premature aging hypothesis of alcoholism, the topic has importance for another reason as well. That is, it also may shed light on learning and memory deficits in the same groups. The nonverbal tasks that alcoholic and aging subjects had trouble with were similar to the kinds of tasks that patients with damage to the right hemisphere were known to have trouble with (Goodglass and Kaplan 1979; Kaplan 1988). These observations led, independently, to the "right hemisphere hypothesis" in the alcoholism literature (Parsons 1975). and to the "right hemisphere hypothesis" in the aging literature (Klisz 1978). These two hypotheses actually erupted separately, and they were not immediately related lo the premature aging

hypothesis, which had derived from observed similarities in structural and functional decline of alcoholic and aging subjects. The right hemisphere hypothesis, whether applied to alcoholic or aging individuals, suggested simply that a disproportionate decline in nonverbal functions was due to a differential sensitivity of the functions subserved by the right hemisphere, to the biological onslaught of alcoholism and of aging. The hypothesis was descriptive rather than explanatory, because no specific mechanisms were postulated. In our laboratory, we tested the right hemisphere hypothesis directly, by employing tasks sensitive to functional asymmetries of the two cerebral hemispheres. As a class, these tasks are referred to as dichotomous stimulation tasks; they rely upon the simultaneous inputs from two separate sensory channels on the left and the right sides of the body—the two ears, the two visual half-fields, or the two hands, for example. Mainly because of the organization of our nervous system, with language lateralized to the left half of the brain and nonlanguage lateralized more or less to the right half of the brain, along with the predominance of crossed connections of the sensory fields with contralateral brain areas, under dichotomous stimulus input conditions (with the right and left input channels competing), the right input channel is superior to the left when verbal stimulus materials are used, and the left side is superior to the right with nonverbal stimulus materials. We administered the dichotomous stimulus tests with three different sensory input modalities (vision, touch, and audition), and we administered them under a variety of experimental conditions (Ellis and Oscar-Berman 1989; Oscar-Berman 1988). The majority of the findings from most of our experiments can be summarized as follows: there was some evidence. for certain changes occurring as a result of alcoholism only in older persons, whose brains may be increasingly susceptible to the effects of alcohol. However, the combined effects of alcoholism and aging were not nearly as apparent as the changes that occurred with aging alone. Furthermore, results did not support the hypothesis that alcoholism differentially affects right hemisphere function compared to left hemisphere function.

In reviewing most of the published research conducted in this area over the last 10 years, including our own, Ellis and Oscar-Berman (1989) concluded that the similarities between alcoholic and aging subjects extended beyond the realm of nonverbal tasks. The early emphasis on defective nonverbal performance appeared to be an artifact of at least two features of the nonverbal tasks employed: perceptual processing demands and demands related to formulating effective strategies for encoding information into short-term memory. Most simple verbal tasks, perhaps because they were easily processed, tended to be approached with simple strategies. Nonverbal tasks used materials that were less familiar than words, required more time to be processed, and were solved by elaborate strategies. When sufficient processing time was permitted and when strategies were simplified in one way or another, alcoholic and aging subjects performed on nonverbal tasks as well as they could perform on verbal tasks. Their total performance levels were lower than those of younger subjects, just as they were in the

DNMTS tasks, and probably for the same reasons-not because of greater right than left hemisphere decline. When Korsakoff patients were tested on dichotomous stimulation tasks, they showed the same asymmetries as everybody else, but their total levels of performance were even lower than everybody else's, just as they were in the DNMTS tasks and for the same reasons.

CONCLUSION

Two general conclusions emerge from these diverse experimental approaches to assessing learning and memory deficits in detoxified alcoholics. First, learning deficits may be related to perceptual processing deficits, which in turn may be related to diffuse neocortical damage associated with long-term alcohol abuse (sometimes compounded by aging); these deficits are not greater in the right hemisphere than in the left hemisphere. Second, memory deficits, especially those dependent upon short-term memory capacity, may be related to damage below the level of the cortex and probably are not as sensitive to age-related changes as the cortically mediated functions.

TOPICS FOR FUTURE RESEARCH

To go forward with an integrated clinical and research approach to understanding the residual effects of abused drugs on behavior, there must be interdisciplinary communication and a view toward the future (Oscar-Berman 1989). This volume contains contributions from representatives of diverse clinical and laboratory environments, to foster interdisciplinary communication. With an eye toward the future, six topic areas have been selected for special consideration; these areas likely would benefit considerably from a continued, cooperative venture between clinicians and researchers:

1. *Comparative Neuropsychology.* By employing sensitive tasks derived from experimental and physiological psychology, subtle attentional, perceptual, motivational, and learning and memory deficits (especially those related to damaged neocortical brain regions) may be detected and described.

2. *Affect,* Emotional changes have been reported subsequent to damage of diverse brain regions thought to be vulnerable in substance abuse, e.g., the prefrontal cortex, the right hemisphere, and the limbic system. Careful study of the topic of affective functions in substance abusers could shed light on the nature of their cognitive deficits.

3. *Polydrug Abuse.* Many abused substances are used concurrently by one individual. The separate, as well as interactive, contributions of abused drugs to behavioral changes need clarification.

4. *Gender Differences.* Because there are important gender differences in brain structure and function, and because males are less variable than females in hormonal and endocrine influences, more research has employed male than female subjects. It would be important to explore the contribution and nature of gender differences in response to abused substances.

5. *Subtypes.* "Alcoholism" is not a unitary concept. Several subtypes of alcoholics have been described, along with differing etiologies (Parsons et al. 1987; Vaillant 1983). Childhood hyperactivity and attentional deficit disorder especially have been implicated in etiology and in outcome. Knowledge of important etiological factors may help to define vulnerability, intervention, and prognosis.

6. *Neurotransmitter and Neuroimmune Systems.* The ways in which alcoholism affects neurotransmitter systems and immune systems are not well known. Likewise, the ways in which most neurological changes (including those associated with normal aging) are expressed in these systems are not well known. Clarification of the relationship of neurological changes in alcoholism to changes in neurotransmitters, as well as to changes in the immune system, would profit from further investigation.

REFERENCES

Aggleton, J.P., and Mishkin, M. Memory impairment following restricted medial thalamic lesions in monkeys. *Exp Brain Res* 52:199-209, 1983.

Albert, M., and Moss, M. The assessment of memory disorders in patients with Alzheimer's disease. In: Squire, L.R., and Butters, N., eds. *Neuropsychology* of *Memory.* New York: Guilford Press, 1984. pp. 236-246.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 3d ed. Washington, DC: the Association, 1980. 494 pp.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 3d ed.-Revised. Washington, DC: the Association, 1987. 567 pp.

Arendt, T.; Bigl, V.; Arendt, A.; and Tennstedt, A. Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans and Korsakoff's disease. *Acta Neuropathol (Berl)* 61:101-108, 1983.

Bower, G.H., and Hilgard, E.R. *Theories of Learning.* 5th ed. Englewood Cliffs, NJ: Prentice-Hall, 1981. 647 pp.

Bitterman, M. The comparative analysis of learning. Science 188:699-709, 1975.

Bugelski, B.R. Memory. In: Corsini, R.J., ed. *Concise Encyclopedia of Psychology.* New York: Wiley, 1987. pp. 701-703.

Corsini, R.J., *ed. Concise Encyclopedia of Psychology.* New York: Wiley, 1987. 1,242 pp.

Courville, C.B. *The Effects of Alcohol on the Nervous System of Man.* Los Angeles: San Lucas Press, 1966. 102 pp.

El-Awar, M.; Freedman, M.; Oscar-Berman, M.; and Kish, S. Selective delayed response deficits in olivopontocerebellar atrophy. *Neurology* 38(Suppl. 1):248, 1988.

Ellis, R.J., and Oscar-Berman, M. Alcoholism, aging, and functional hemispheric asymmetries. *Psycho1 Bull* 106:128-147, 1989.

Freedman, M., and Oscar-Berman, M. Bilateral frontal lobe disease and selective delayed-response deficits in humans. *Behav Neurosci* 100:337-342, 1986a.

Freedman, M., and Oscar-Berman, M. Selective delayed response deficits in Alzheimer's and Parkinson's disease. *Arch Neurol* 43:886-890, 1986b.

Freedman, M., and Oscar-Berman, M. Comparative neuropsychology of cortical and subcortical dementia. *Can J Neurol* Sci 13:410-414, 1986c.

Freedman, M., and Oscar-Berman, M. Tactile discrimination learning deficits in Alzheimer's and Parkinson's disease. *Arch Neurol* 44:394-398, 1987.

Freedman, M., and Oscar-Berman, M. Spatial and visual learning deficits in Alzheimer's and Parkinson's disease. *Brain Cogn* 11:114-126, 1989.

Gaffan, D.; Gaffan, E.A.; and Harrison, S. Effects of formix transection on spontaneous and trained non-matching by monkeys. *Q J Exp Psycho1* 36B:285-303, 1984.

Geschwind, N., and Galaburda, A.M., *eds. Cerebral Dominance: The Biological Foundations.* Cambridge, MA: Harvard University Press, 1984. 232 pp.

Goodglass, H., and Kaplan, E. Assessment of cognitive deficits in the brain-injured patient. In: Gazzaniga, M.S., ed. *Handbook* of *Behavioral Neurobiology.* Vol. 2. New York: Plenum Press, 1979. pp. 3-22.

Grant, I., *ed. Neuropsychiatric Correlates of Alcoholism.* Washington, DC: American Psychiatric Press, 1986. 141 pp.

Harlow, H.F.; Harlow, M.K.; Schiltz, K.A.; and Mohr, D.J. The effect of early adverse and enriched environments on the learning ability of Rhesus monkeys. In: Jarrard, L.E., ed. *Cognitive Processes of Nonhuman Primates.* New York: Academic Press, 1971. pp. 121-148.

Horel, J.A. The neuroanatomy of amnesia. A critique of the hippocampal memory hypothesis. *Brain* 101:403-445, 1978.

Kaplan, E. A process approach to neuropsychological assessment. In: Boll, T., and Bryant, B.K., *eds. Clinical Neuropsychology and Brain Function: Research, Measurement and Practice.* Washington, DC: American Psychological Association, 1988. pp. 125-167.

Kish, S.J.; El-Awar, M.; Schut, L.; Leach, L.; Oscar-Berman, M.; and Freedman, M. Cognitive deficits in olivopontocerebellar atrophy: Implications for the cholinergic hypothesis of Alzheimer's dementia. *Ann Neurol* 24:200-206, 1988.

Klisz, D.K. Neuropsychological evaluation in older persons. In: Storandt, M.; Siegler, I.C.; and Elias, M.F., eds. *The Clinical Psychology of Aging.* New York: Plenum Press, 1978. pp. 71-95.

Lhermitte, F., and Signoret, J.-L. The amnesic syndrome and the hippocampal mammillary system. In: Rosenzweig, M.R., and Bennett, E.L., eds. *Neural Mechanisms of Learning and Memory*. Cambridge, MA: MIT Press, 1976. pp. 49-56.

Lishman, W.A. Cerebral disorder in alcoholism: Syndromes of impairment. *Brain* 104:1-20, 1981.

Mahut, H.; Zola-Morgan, S.M.; and Moss, M. Hippocampal resections impair associative learning and recognition memory in the monkey. *J Neurosci* 2:1214-1229, 1982.

Maki, W.S., and Leith, C.R. Shared attention in pigeons. *J Eq Anal Behav* 19:345-349, 1973.

Mishkin, M. Memory in monkeys severely impaired by combined but not separate removal of amygdala and hippocampus. *Nature* 273:297-298, 1978.

Mishkin, M., and Appenzeller, T. Anatomy of memory. *Sci Amer* 256:80-89, 1987.

Noonberg, A.; Goldstein, G.; and Page, H.A. Premature aging in male alcoholics: "Accelerated aging" or "increased vulnerability." *Alcoholism: Clin Exp Res* 91:334-338, 1985.

Oscar-Berman, M. Neuropsychological consequences of long-term chronic alcoholism. *Am Sci* 68:410-419, 1980.

Oscar-Berman, M. Comparative neuropsychology and Alcoholic Korsakoffs disease. In: Squire, L., and Butters, N., eds. *Neuropsychology of Memory*. New York: Guilford Press, 1984. pp. 194-202.

Oscar-Berman, M. Normal functional asymmetries in alcoholism? *Aphasiology* 2:369-374, 1988.

Oscar-Berman, M. Links between clinical and experimental neuropsychology. *J Clin Exp Neuropsychol* 11:571-588, 1989.

Oscar-Berman, M.; Blumstein, S.; and DeLuca, D. Iconic recognition of musical symbols in the lateral visual fields. *Cortex* 12:241-248, 1976.

Oscar-Berman, M., and Bonner, R.T. Matching- and delayed-matching-to-sample performance as measures of visual processing, selective attention and memory in aging and alcoholic individuals. *Neuropsychologia* 23:639-651, 1985.

Oscar-Berman, M., and Ellis, R.J. Cognitive deficits related to memory impairments in alcoholism. In: Galanter, M., *ed. Recent Developments in Alcoholism.* Vol. 5. New York: Plenum Press, 1987. pp. 59-80.

Oscar-Berman, M.; Heyman, G.M.; Banner, R.T.; and Ryder, J. Human neuropsychology: Some differences between Korsakoff and normal operant performance. *Psychol Res* 41:235-247, 1980.

Oscar-Berman, M.; Sahakian, B.J.; and Wikmark, G. Spatial probability learning by alcoholic Korsakoff patients. *J Exp Psychol: Human Learn Memory* 2:215-222, 1976.

Oscar-Berman, M., and Zola-Morgan, S.M. Comparative neuropsychology and Korsakoff's syndrome. I: Spatial and visual reversal learning. *Neuropsychologia* 18:499-512, 1980a.

Oscar-Berman, M., and Zola-Morgan, S.M. Comparative neuropsychology and Korsakoff's syndrome. II: Two-choice visual discrimination learning. *Neuropsychologia* 18:513-526, 1930b.

Oscar-Berman, M.; Zola-Morgan, S.M.; Oberg, R.G.E.; and Bonner, R.T. Comparative neuropsychology and Korsakoff's syndrome. III: Delayed response, delayed alternation and DRL performance. *Neuropsychologia* 20:187-202, 1982.

Parsons, O.A. Brain damage in alcoholics: Altered states of unconsciousness. In: Gross, M., *ed. Alcohol Intoxication and Withdrawal II.* New York: Plenum Press, 1975. pp. 569-584.

Patsons, O.A.; Butters, N.; and Nathan, P., eds. *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment.* New York: Guilford Press, 1987. 414 pp.

Razran, G. *Mind in Evolution: An East-West Synthesis of Learned Behavior and Cognition.* Boston: Houghton Mifflin, 1971. 430 pp.

Riege, W.H. Specificity of memory deficits in alcoholism. In: Galanter, *M.,* ed. *Recent Advances in Alcoholism.* Vol. 5. New York: Plenum Press, 1987. pp. 81-109.

Ryan, C. Alcoholism and premature aging: A neuropsychological perspective. *Alcoholism: Clin Exp Res* 6:79-96, 1982.

Ryan, C., and Butters, N. Learning and memory impairments in young and old alcoholics: Evidence for the premature-aging hypothesis. *Alcoholism: Clin Exp Res* 4:288-293, 1980.

Squire, L.R., and Butters, *N.,* eds. *Neuropsychology of Memory.* New York: Guilford Press, 1984. 655 pp.

Squire, L.R.; Zola-Morgan, S.; and Chen, K.S. Human amnesia and animal models of amnesia: Performance of amnesic patients on tests designed for the monkey. *Behav Neurosci* 102:210-221, 1988.

Talland, G.A. *Deranged Memory.* New York: Academic Press, 1965. 365 pp.

Tulving, E. How many memory systems are there? *Am Psycho1* 40:385-398, 1985.

Vaillant, G. *The Natural History* of *Alcoholism.* Cambridge, MA: Harvard University Press, 1983. 359 pp.

Victor, M.; Adams, R.D.; and Collins, G.H. *The Wernicke-Korsakoff Syn*drome. Philadelphia: F.A. Davis, 1971. 206 pp.

Wilkinson, D.A., and Carlen, P.L. Morphological abnormalities in the brain of alcoholics: Relationship to age, psychological test scores and patient type. In: Wood, W.G., and Elias, M.F., *eds. Alcoholism and Aging: Advances in Research.* Boca Raton, FL: CRC Press, Inc., 1982. pp. 61-77.

Witt, E.D., and Goldman-Rakic, P.S. Intermittent thiamine deficiency in the Rhesus monkey. II. Evidence for memory loss. *Ann Neurol* 13:396-401, 1983.

Zeaman, D., and House, B.T. The role of attention in retardate discrimination learning. *In:* Ellis, N.R., ed. *Handbook* of *Mental Deficiency.* New York: McGraw-Hill, 1963. pp. 195-223.

Zola-Morgan, S.; Squire, L.R.; and Mishkin, M. The neuroanatomy of amnesia: Amygdala-hippocampus versus temporal stem. *Science* 218:1337-1339, 1982.

ACKNOWLEDGMENTS

Supported by the National Institute on Alcohol Abuse and Alcoholism Research Grant AA 007112 and by funds from the U.S. Department of Veterans' Affairs Medical Research Service.

AUTHOR

Marlene Oscar-Berman, Ph.D.
Division of Psychiatry and Department of Neurology
Boston University School of Medicine
and
Psychology Research Service
Department of Veterans' Affairs Medical Center
85 East Newton Street
Boston, MA 02118

Persisting Neurotoxic Consequences of Solvent Abuse: A Developing Animal Model for Toluene-Induced Neurotoxicity

Gordon T. Pryor

INTRODUCTION

Long-term, heavy users of various psychoactive substances run the potential risk of irreversible damage to the nervous system. The extent to which such irreversible damage represents a real threat is, however, debatable. In fact, clear examples of irreversible dysfunction and pathologic damage to neural structures that can be unequivocally attributed to the neurotoxic consequences of specific abused substances are relatively rare. The volatile organic solvents represent a class of abused compounds that engenders especially serious concern (Sharp and Brehm 1977; Sharp and Carroll 1978; Crider and Rouse 1988).

Intuitively, but perhaps naively, many people have assumed that heavy exposure to these lipophilic substances would dissolve neural tissue, or at least some of its constituents. In fact, only a small number of organic solvents have been unequivocally shown to cause neuropathologic damage to the nervous system in animals and humans, e.g., carbon disulfide, *n*-hexane, methyl n-butyl ketone, trichloroethylene (Spencer et al. 1985). Nevertheless, there is reason for real concern. The lack of definitive proof of the neurotoxicity of the majority of solvents can be attributed more to a lack of systematic and relevant investigation than to substantive negative data proving that they are innocuous. A case in point is toluene, which is found in a variety of abused products and that has been ascribed by many clinicians to be the agent responsible for causing "brain damage" in heavy solvent abusers.

Toluene is a significant component of many abused solvent products and is the only pure solvent that frequently has been reported to be inhaled for its

euphoric effects (Grabski 1961; Knox and Nelson 1966). Also, it has been demonstrated that primates will self-administer toluene by pressing a lever to produce the vapors, thus attesting to its rewarding properties (Wood 1978). Among the products reportedly abused for their euphorigenic effects are glues, cements, and adhesives; paint and lacquer thinners and removers; spray paints; degreasers and various cleaning fluids; typewriter correction fluid; gasoline; and toluene. These products are typically mixtures of various solvents formulated for their physicochemical properties. Specific brands become popular and are used almost exclusively for their euphoric effects as long as they are available. Toluene is contained in large proportions in the most frequently chosen products, and toluene is the only pure solvent to be frequently abused. Thus, toluene may be the sought-after component that most promotes the abuse of product mixtures.

If toluene is the major sought-after euphoriant in abused products, regardless of its own toxicity, then its presence may promote exposure of the solvent abuser to other constituents of the product that are unequivocally dangerous (n-hexane, metals). However, because toluene is a common component of various products used by heavy solvent abusers who require medical attention-because of neurologic or neurobehavioral symptoms, as well as renal dysfunction (Streicher et al. 1981)—many clinicians (and toxicologists) have concluded that toluene is, in fact, responsible. The evidence for this conclusion has been mainly circumstantial.

Toluene has received considerable attention by toxicologists. In reviews by Hayden and associates (1977) and Benignus (1981a; Benignus 1981b), it has gotten a surprisingly clean bill of health as a toxicant in general and as a neurotoxicant in particular. Why then is the notion so strong (as reflected in frequent literature citations, for example) that toluene is a major neurotoxicant associated with solvent abuse? The remainder of this chapter will be directed towards examining the evidence for this notion and recounting our own experience in trying to find the answer experimentally.

OTOTOXICITY OF TOLUENE

Our involvement with the National Institute on Drug Abuse in the area of solvent abuse began in 1976. This association resulted in some of the most extensive laboratory investigations conducted to date of the neurotoxicity of solvents. Toluene was a major focus of these investigations for the reasons cited above. Nonetheless, using a variety of behavioral and electrophysiologic methods that were designed, developed, and validated for the purpose of screening potentially neurotoxic substances (Pryor et al. 1983c; Rebert 1983), we were unable to find convincing evidence that toluene caused any persisting neurobehavioral or electrophysiologic dysfunction in rats (Pryor et al. 1983a).

Because of the results of these studies, we began to question whether toluene was really responsible for the neurotoxic consequences of heavy solvent abuse. In reexamining the clinical literature, it was evident that in most cases other solvents or other conditions could have been responsible for the reported dysfunctions. Moreover, it was not clear whether the symptoms reported were persistent or whether they cleared upon abstention. Finally, only in a few cases was the chemical composition of the abused products verified, and polydrug use was a frequent complication.

Nevertheless, there were a few reports that made it difficult to dismiss toluene as a neurotoxicant. Cases in which toluene appeared to be the only solvent used created the suspicion that our laboratory results with rats may not have been as definitive as they appeared. Perhaps we were using the wrong species or the wrong measures (our test battery was designed as a general screening method). In any event, although we were unable at that time to induce a persisting neurotoxic syndrome in our animal model, we were uncomfortable with the conclusion that toluene was totally innocuous.

One of the methods used in the studies cited above was a computer-automated multisensory conditioned avoidance response, in which visual, auditory, and somatosensory stimuli were used to assess sensorimotor function. It was designed to monitor function in the three sensory modalities in the same animals so as to detect specific sensory deficits. Because we had not, in fact, found such specific sensory effects in the many experiments done with a wide variety of chemicals over some 10 years (Pryor et al. 1983c), we began to question its ability to serve its intended purpose and set out to systematically examine its validity in this regard. For validation, we used chemicals or conditions that were known to affect specific sensory systems. For the auditory system, we used the ototoxic antibiotic kanamycin (Prosen et al. 1980). From human and animal studies, it was known that this drug caused damage to the hair cells in the cochlea and that the damage proceeds such that the areas receptive to high frequencies are affected first, followed by areas associated with decreasing frequency. With this in mind, and aware of the fact that the auditory sensitivity of the rat is at much higher frequencies than that of the human (Kelley and Masterton 1977), we used a 20-kHz-tone stimulus in these studies. In all previous applications, including those to examine the potential neurotoxic effects of toluene, we had used a 4-kHz tone. The validity of the procedure was clearly demonstrated by a progressive loss of the ability to perform the avoidance response to the 20-kHz tone by the rats treated with kanamycin, without any effect on performance of the avoidance response to the light and somatosensory shock stimuli.

Subsequently, for reasons unrelated to the solvent studies, we retested, using the 20-kHz-tone, a group of rats that had been exposed chronically to toluene more than 2 months earlier. Whereas these rats performed the response to the light and the somatosensory stimulus (low-intensity current to the

feet) at levels comparable to those of unexposed controls, they appeared unable to hear the tone. This serendipitous observation led us to conduct a series of tests in which the frequency of the tone was varied from 4 to 20 kHz, and estimates of sensitivity at each frequency were obtained by varying the intensity (Pryor et al. 1983b). The results suggested that the earlier exposure to toluene had caused a persisting and marked loss of auditory sensitivity that was clearly evident at the higher frequencies (8 kHz and above) with no apparent loss at 4 kHz, the frequency we had routinely used in the past. Suspicious of a possible behavioral artifact, we also tested rats using the brainstem auditory-evoked response (BAER). This procedure had also been used previously, using a click stimulus with a frequency spectrum centered around 5 kHz. For these later tests, we used tone pips of 8, 12, and 16 kHz in addition to the clicks. The results showed clear evidence of hearing loss that was greatest at the higher frequencies (Rebert et al. 1983). Moreover, analyses of these results suggested a peripheral rather than a central locus for the effect.

We then conducted a series of experiments to confirm and characterize the nature of the toluene-induced hearing loss and the exposure conditions that caused it (Pryor et al. 1987). The results of this extensive series of experiments indicated that: (1) weanling rats were more sensitive to the effect than young adults; (2) the hearing loss was frequency dependent; (3) there was damage to the peripheral receptors (hair cells in the cochlea); (4) the effect was concentration, duration, and exposure-schedule dependent; (5) subcutaneous injection of toluene was as effective as inhalation exposure, thereby demonstrating a systemic effect; and (6) related solvents such as xylenes and styrene were equally as effective or more effective than toluene, whereas unrelated solvents such as n-hexane, methylene chloride, and methyl ethyl ketone (MEK) were without effect (unpublished).

This discovery of a toluene-induced hearing loss in rats also led us to reexamine the clinical literature for evidence of a similar effect in humans. Indeed, hearing loss, although not a frequently reported symptom, was associated with exposure to toluene or toluene-containing substances in both industrial accidents (Biscaldi et al. 1981) and heavy solvent abusers (Ehyai and Freeman 1983).

THE CLINICAL SYNDROME ASSOCIATED WITH TOLUENE CONTAINING SOLVENT ABUSE

Reports continued to appear that made it more and more difficult to dismiss toluene as the agent causing moderate to severe neurologic dysfunction in heavy solvent abusers. The reports from two groups of investigators ***were*** especially convincing.

Fornazzari and colleagues (1983) described the symptomatology associated with a fairly large group of solvent abusers in Toronto, Canada. These

patients used almost exclusively a specific brand of contact cement that the authors stated contained primarily toluene. When we analyzed the composition of this cement, however, we found it to be a complex mixture that, in addition to toluene, contained significant amounts of the known neurotoxicant *n*-hexane and its reported synergist MEK (Altenkirch et al. 1978). Nevertheless, the symptomatology described by these investigators did not fit that expected from these latter solvents, i.e., it did not include a peripheral neuropathy. Instead, the major neurologic symptoms suggested primarily central damage, especially to cerebellar structure controlling motor coordination. Other prominent symptoms included cognitive dysfunction, pyramidal tract disorders, and sensory dysfunction, including hearing loss.

Similar results were reported by Rosenberg and coworkers (Hormes et al. 1986, Rosenberg et al. 1988) who had studied a fairly large number of patients in Denver, CO. In these cases, the product was a specific brand of spray paint that contained mainly toluene, but also contained significant amounts of methylene chloride and small amounts of xylenes. The results of this study were especially important because the investigators took care to ensure that most patients had been solvent free for several weeks to months at the time of examination, thus reducing the possibility of residual acute effects. Moreover, the BAER was used to provide objective evidence of central involvement, and magnetic resonance imaging of several patients appeared to indicate brain atrophy.

The common component in the two products from Toronto and Denver was toluene. Because both were mixtures, unequivocal identification of this solvent as the causative agent could not be made. Moreover, the possibility of interactions among the various components and the contribution of other factors, such as polydrug use, could not be discounted.

The following list presents the clinical signs and symptoms most commonly reported in patients who have, over a period of time, heavily abused solvents containing toluene.

- Short-term memory loss
- Emotional instability
- Cognitive impairment
- Slurred and "scanning" speech
- Wide-based ataxic gait
- Staggering or stumbling in trying to walk
- Nystagmus
- Ocular flutter
- Tremor
- Optic neuropathy
- Unilateral or bilateral hearing loss
- Loss of sense of smell
- Diffuse slowing of the EEG
- Abnormal or absent BAER
- Diffuse cerebral, cerebellar, and brainstem atrophy
- Enlarged ventricles and widening of cortical sulci, especially in the frontal or temporal cortex

When we next had the opportunity to study toluene, we used this list as a guide to select and develop behavioral tests that might reflect similar signs and symptoms in rats chronically exposed to toluene. Several of the clinical signs and symptoms form a cluster that neurologists refer to as "cerebellar ataxia." Therefore, we chose a series of tests that we thought would reflect various aspects of motor function that could be measured objectively:

- Forelimb and hindlimb grip strengths;
- Rotorod performance;
- Gait analysis-stride length, stride width, stride angle; and
- Landing hindlimb foot splay.

The tests of grip strength (Meyer et al. 1979) make use of strain gauges to measure the force required to break the rat's grip on a bar by both forepaws and hindpaws. These tests are sensitive to the peripheral neuropathy caused by n-hexane and related hexacarbons (Pryor et al. 1983a). The rotorod test is used to measure the rat's ability to balance and locomote on a rotating rod that is incrementally increased in rate of rotation until the rat falls off. To quantitate the rat's pattern of walking, its hind feet are linked, and it is allowed to walk down an alley covered with a blotter to record its steps (Jolicoeur et al. 1979). The pattern of walking is then analyzed in terms of the length, width, and angle of the steps taken. Similarly, the rat's reflexive response to being dropped from a short height is recorded as the distance between the hind feet on landing.

In the first experiment in this series, we exposed groups of weanling rats for 8 hours per day, 7 days per week to toluene (2,000 to 2,600 ppm), *n*-hexane (2,000 to 2,600 ppm), or a mixture of toluene, n-hexane, and MEK (2,000 to 5,200 total ppm in approximately equal amounts). *n*-Hexane was included as a positive control because we knew that the exposure schedule would induce a peripheral neuropathy that would be reflected in the measures of grip strength (Pryor et al. 1983a). The mixture was included as a preliminary test of possible interactions among three of the components that were found in the contact cement used in Toronto, Canada. The entire battery of tests was given periodically beginning after 7 weeks of exposure and for 6 weeks after the exposure ended.

The results clearly indicated that exposure to toluene had caused a persisting motor syndrome that was different from that caused by exposure to *n*-hexane. The expected decreases in grip strength were the major effects of exposure to *n*-hexane, whereas this effect was not seen in the rats exposed to toluene (figure 1). The nature of the toluene-induced syndrome can be seen in figure 2. The syndrome was characterized by a shortened

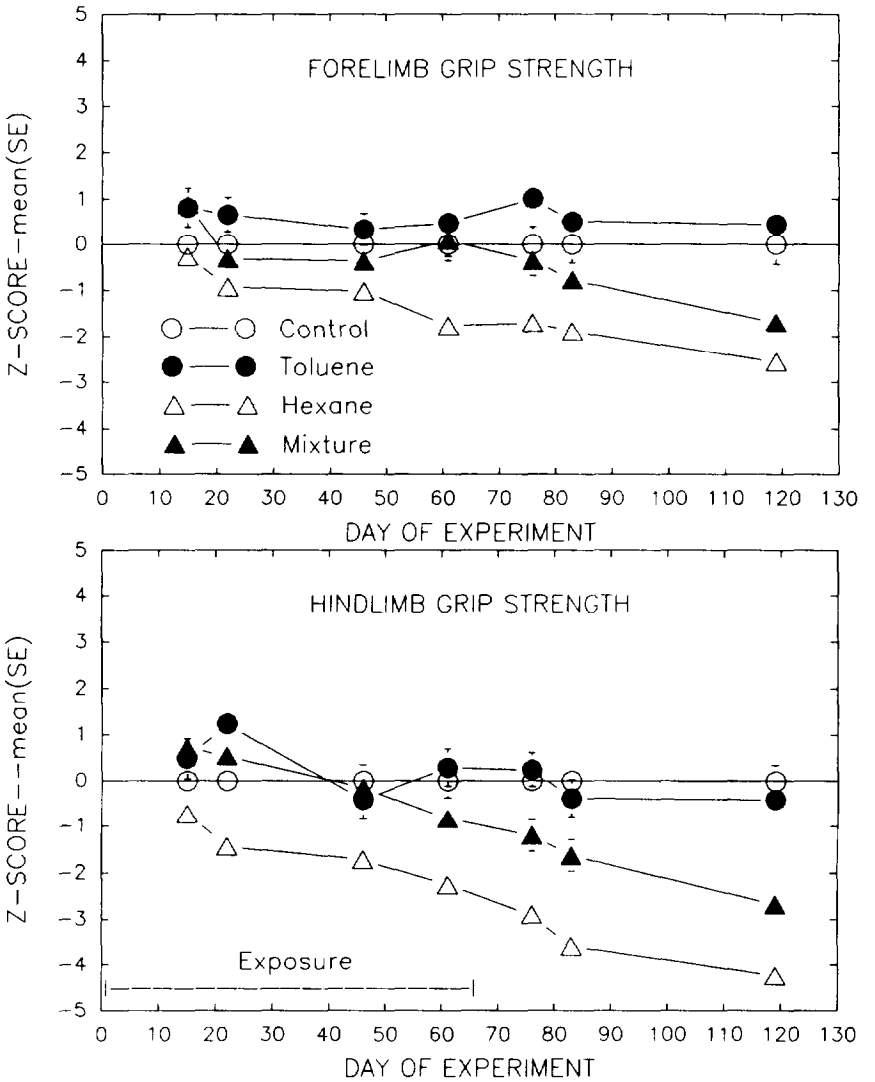

FIGURE 1. *Effect of toluene,* n*-hexane, or a mixture of tolune,* n*-hexane, and MEK on grip strength*

NOTE: Values are expressed relative to control means in variance units.

and widened gait and a widened landing foot splay. Such a pattern in the four-legged rat is at least suggestive of the "wide-based ataxic gait"

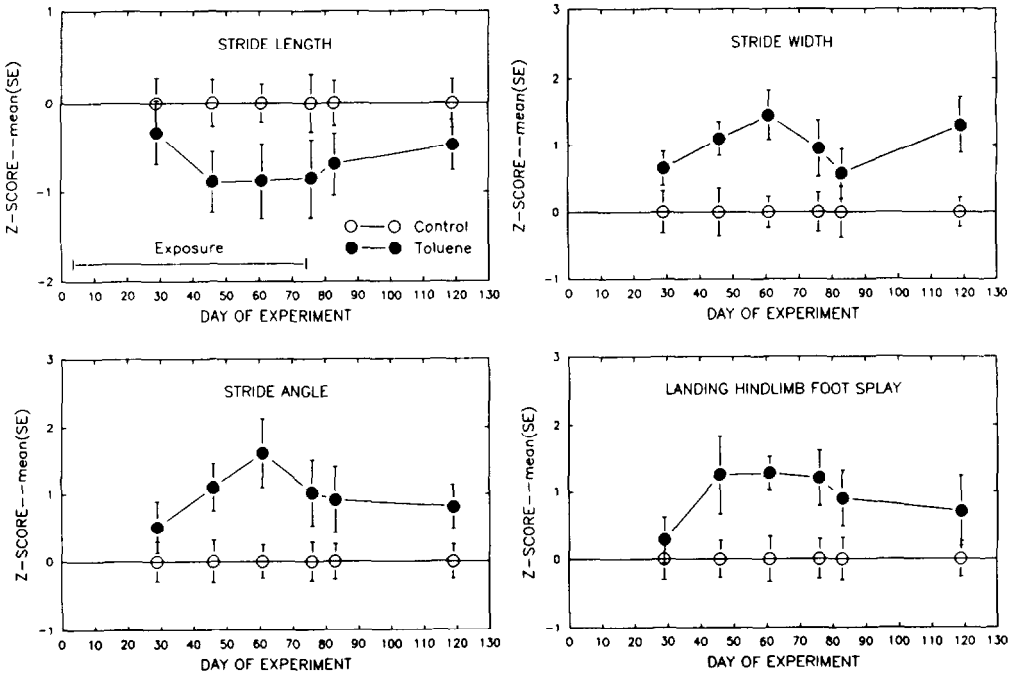

FIGURE 2. *Effect of toluene on a battery of tests of motor coordination*

NOTE: Values are expressed relative to control means in variance units.

associated with cerebellar ataxia in humans. Interestingly, the rats exposed to the mixture first took on some of the characteristics of the rats exposed to toluene, but the final outcome was a decrease in grip strength as in the rats exposed to n-hexane (figure 1).

The essential aspects of this experiment have now been replicated several times under various conditions in our laboratory (manuscripts in preparation), and the development of the syndrome appears to be robust and persisting. We have also looked at the effects of other solvents (methylene chloride and MEK), both alone and in combination with toluene, on this battery of tests. Thus, far, only toluene has caused the persisting motor syndrome just described.

CRITERIA FOR DEFINING A SUBSTANCE AS BEING NEUROTOXIC

Most, if not all, abused psychoactive substances may impair performance or result in socially unacceptable behavior because of their acute pharmacologic effects. Compulsive use may also result in behavior that is morally and legally unacceptable and may cause a progressive deterioration of family, work, and social relationships. At this time, the extent to which persisting

or permanent damage to the nervous system results from substance abuse is less clear. Spencer and associates (1985) have suggested the following criteria for defining a substance as the causative agent responsible for persisting nervous system damage:

1. There is a consistent pattern of neurologic dysfunction in humans associated with well-documented exposure to the substance.

2. The syndrome (all or in part) can be mimicked in animals by appropriate exposure to the substance.

3. Neuropathologic "lesions" can be demonstrated in the nervous system or the peripheral sense organs that satisfactorily account for the dysfunction in humans and animals.

In their view, "failure to satisfy any of these criteria leaves room for doubt that the suspect agent is capable of impairing the structure or function of the nervous system" (Spencer et al., p. 53).

A PARTIAL MODEL OF TOLUENE-INDUCED BRAIN DYSFUNCTION

If we assume that the motor syndrome in rats caused by exposure to toluene is analogous to the "cerebellar ataxia" observed in humans, then, along with the demonstration of tolueneinduced hearing loss in rats, we have a partial animal model of the syndrome associated with human abuse of toluene-containing solvents. In turn, these results with rats provide some of the necessary evidence, as defined by the criteria listed in the previous section, that toluene is in fact the toxicant responsible for at least part of the human syndrome. To the extent that all or most of the signs and symptoms listed are reflective of the effects of heavy toluene abuse in humans, our model is still incomplete. However, by designing tests to look specifically for some of these other dysfunctions, we are optimistic that they can be demonstrated in our rat model if they are caused by toluene. Regardless of the outcome of such further research, the results obtained thus far are sufficient to begin attempting to identify the brain structures and mechanisms involved. Again, clues from the clinical literature will be used to guide this search. Cerebellar involvement is clearly suggested, but we have not seen damage to this structure at the light microscopic level in hemotoxylin and eosin stained sections. The report of Rosenberg and colleagues (1988) based on magnetic resonance imaging suggests more subtle neuropathologic lesions involving myelin. Identification of such a locus in our rat model would provide needed support for this suggestion and would satisfy the final criterion for identifying toluene as a neurotoxicant.

REFERENCES

Altenkirch, H.; Stoltenburg, G.; and Wagner, H.M. Experimental studies on hydrocarbon neuropathies induced by methyl-ethyl-ketone. *J Neurol* 219:159-163, 1978.

Benignus, V.A. Health effects of toluene: A review. Neurotoxicology 2:567-588, 1981a.

Benignus, V.A. Neurobehavioral effects of toluene: A review. *Neurobehav Toxicol Teratol* 3:407-415, 1981b.

Biscaldi, G.P.; Mingardi, M.; Moglia, G.; and Bossi, M.C. Acute toluene poisoning. Electroneurophysiological and vestibular investigations. *Toxico1 Eur Res* 3:271-272, 1981.

Crider, R.A., and Rouse, B.A., eds. *Epidemiology of Znhalant Abuse: An* Update. National Institute on Drug Abuse Research Monograph 85. DHHS Pub. No. (ADM)88-1577. Washington, DC: Supt. of Docs., U.S. Print. Off., 1988.

Ehyai, A., and Freeman, F.R. Progressive optic neuropathy and sensorineural hearing loss due to chronic glue sniffing. *J Neural Neurosurg Psychiatry* 46:349-357, 1983.

Fornazzari, L.; Wilkinson, D.A.; Kapur, B.M.; and Carlen, P.L. Cerebellar, cortical and functional impairment in toluene abusers. *Acta Neurol Scand* 67:319-329, 1983.

Grabski, D.A. Toluene sniffing producing cerebellar degeneration. *Am J Psychiatry* 118:461-462, 1961.

Hayden, J.W.; Petersen, R.E.; and Bruckner, J.V. Toxicology of toluene (methylbenzene): Review of current literature. *Clin Toxicol* 11:549-559, 1977.

Hormes, J.T.; Filley, C.M.; and Rosenberg, N.L. Neurologic sequelae of chronic solvent vapor abuse. *Neurology* 36:698-702, 1986.

Jolicoeur, F.B.; Rondeau, D.B.; Hamel, E.; Butterworth, R.F.; and Barbeau, A. Measurement of ataxia and related neurologic signs in the laboratory rat. *Am J Neurol Sci* 6:209-215, 1979.

Kelley, J.B., and Masterton, B. Auditory sensitivity in the rat. *J Comp Physiol Psychol* 91:930-936, 1977.

Knox, J.W., and Nelson, J.R. Permanent encephalopathy from toluene inhalation. *N Eng J Med* 275(26):1494-1496, 1966.

Meyer, O.A.; Tilson, H.A.; Byrd, W.C.; and Riley, M.T. A method for the routine assessment of fore- and hind-limb grip strength of rats and mice. *Neurobehav Toxicol* 1:233-236, 1979.

Prosen, C.A.; Petersen, M.R.; Moody, D.B.; and Stebbins, W.C. Kanamycin ototoxicity in the guinea pig. *Neurotoxicology* 1:497-513, 1980.

Pryor, G.T.; Dickinson, J.; Howd, R.A.; and Rebert, C.S. Neurobehavioral effects of subchronic exposure of weanling rats to toluene and hexane. *Neurobehav Toxicol Teratol* 5:47-52, 1983a.

Pryor, G.T.; Dickinson, J.; Howd, R.A.; and Rebert, C.S. Transient cognitive deficits and high-frequency hearing loss in weanling rats exposed to toluene. *Neurobehav Toxicol Teratol* 5:53-57. 1983b.

Pryor, G.T.; Rebert, C.S.; and Howd, R.A. Hearing loss in rats caused by inhalation of mixed xylenes and styrene. *J Appl Toxicol* 7(1):55-61, 1987.

Pryor, G.T.; Uyeno, E.T.; Tilson, H.A.; and Mitchell, C.L. Assessment of chemicals using a battery of neurobehavioral tests. *Neurobehav Toxicol Teratol* 5:91-117, 1983c.

Rebert, C.S. Multisensory evoked potentials in experimental and applied neurotoxicology. *Neurobehav Toxicol Teratol* 5:659-671, 1983.

Rebert, C.S.; Sorenson, S.S.; Howd, R.A.; and Pryor, G.T. Toluene-induced hearing loss in rats evidenced by the brainstem auditory-evoked response. *Neurobehav Toxicol Teratol* 5:59-62, 1983.

Rosenberg, N.L.; Spitz, M.C.; Filley, C.M.; Davis, K.A.; and Schaumberg, H.H. Central nervous system effects of chronic toluene abuse-Clinical, brainstem evoked response and magnetic resonance imaging studies. *Neurotoxicol Teratol* 10:489-495, 1988.

Sharp, C.W., and Brehm, M.L., eds. *Review of Inhalants: Euphoria to Dysfunction* National Institute on Drug Abuse Research Monograph 15. DHHS Pub. No. (ADM)77-553. Washington, DC: Supt. of Docs., U.S. Print. Off., 1977.

Sharp, C.W., and Carroll, L.T., eds. *Voluntary Inhalation of Industrial Solvents.* National Institute on Drug Abuse. DHEW Pub. No. (ADM)79-779. Washington, DC: Supt. of Docs., U.S. Print. Off., 1978.

Spencer, P.S.; Path, M.R.C.; and Schaumberg, H.H. Organic solvent neurotoxicity: Facts and research needs. *Stand J Work Environ Health* 11(supp1 1):53-60, 1985.

Streicher, H.Z.; Gabow, P.A.; Moss, A.H.; Kono, D.; and Kaehny, W.D. Syndromes of toluene sniffing in adults. *Ann Intern Med* 94:758-762, 1981.

Wood, R.V. Stimulus properties of inhaled substances. *Environ Health Perspect* 26:69-76, 1978.

ACKNOWLEDGMENTS

This research was supported by U.S. Public Health Service contract numbers 271-77-3402, 271-80-3712, and 271-87-3132 from the National Institute on Drug Abuse (Dr. Charles W. Sharp, Project Officer). Dr. Charles S. Rebert, as a coinvestigator at SRI, collaborated extensively on these projects and provided helpful comments to this manuscript.

AUTHOR

Gordon T. Pryor, Ph.D.
Neuroscience Department
SRI International
333 Ravenswood Avenue
Menlo Park, CA 94025

Cognitive Deficits in Abstaining Cocaine Abusers

Ronald I. Herning, Barbara J. Glover, Bonnie Koeppl, William Weddington, and Jerome H. Jaffe

INTRODUCTION

Cocaine abusers may be cognitively impaired when they abstain from cocaine. Evidence for possible decrements in cognition comes indirectly from several sources. The descriptions of psychiatric sequelae occurring in patients withdrawing from cocaine include sleep loss and depression (Gawin and Kleber 1986; Baxter 1983). In cocaine nonabusers, attentional deficits and psychomotor retardation were observed during sleep deprivation and depression (Weiss and Laties 1962; Thier et al. 1986; Massiouri and Lesevre 1988). Cognitive alterations may accompany the sleep loss and depression observed during cocaine withdrawal. In addition, Melamed and Bleiberg (1986) reported a brief decrement in a maze task and persistent poor performance on the Paced Auditory Serial Addition test (PSAT) in patients treated for free-base cocaine abuse. Cocaine abusers had decreased relative cerebral blood flow in prefrontal cortical areas as compared to controls (Volkow et al. 1988). Sensitive neurophysiological and cognitive testing may document other alterations during abstinence. The use of event-related potentials (ERPs) coupled with cognitive performance testing has been one exquisitely sensitive approach (Callaway 1983).

Cognitive and performance deficits during cocaine withdrawal have important applied as well as theoretical implications in treatment and in the workplace. Specific cognitive deficits such as attentional problems or memory loss may hamper effective psychiatric treatment. Likewise, poor job performance may put the withdrawing user and the public at greater risk of an accident. Only two studies have investigated the possible cognitive impairment in heavy cocaine abusers (Melamed and Bleiberg 1986; Volkow et al. 1988). These studies were limited to the first 10 days of abstinence and had no control groups. Further research is clearly indicated.

The present study investigated cognitive information processing and performance in cocaine abusers before and during inpatient treatment. The focus was on the first few weeks of treatment. Because psychiatric counseling was the only treatment used in this study, drug-free assessment of cognitive function was possible. ERP measures as well as behavioral performance indices were used to quantify the possible impairments. The ERP methodology allows inferences to be made as to which aspects of cognition may be affected by cocaine abstinence. The study is currently in progress; data presented are from the patients and control subjects analyzed at the time of this report.

METHODS

Subjects

Twelve males seeking treatment for cocaine abuse were studied along with nine controls. No subjects had medical problems. The demographics, self-reported history of cocaine use, and the Addiction Severity Index (ASI) are presented in table 1. The ASI employment scale is slightly elevated for the controls. Besides a self-reported history of cocaine abuse that met DSM-IIIR criteria, each patient had a urine sample positive for cocaine on an outpatient visit. All but one subject, who snorted, self-administered cocaine intravenously. The axis I diagnoses other than substance dependence in the patient group included one patient with depression. Seven subjects in the patient group had axis II diagnoses of antisocial personality.

Cognitive Information Processing Tasks

Selected tasks from the Neurophysiological Workload Test Battery (NWTB) were administered to the subjects. NWTB provides a series of tasks that can be quickly learned and uses neurophysiologic and performance measures to assess impairment. The neurophysiologic measures included the amplitude and latency of ERP components elicited by task stimuli. The performance measures included correctness and reaction time as well as specialized measures for visual motor tracking. The tasks and measures are listed in table 2.

The auditory rare-event-monitoring task is a version of the P300 oddball task (Squires et al. 1977). The subject counted low-pitched (1,000 Hz) tones from a random series (a tone/second) of high- (2,000 Hz) and low-pitched tones. The low-pitched tones occurred about 20 percent of the time. The tones were presented every 2 seconds. After the subject listened to the series for 4 minutes, he reported his count to the researcher. N100 and P300 components were measured from the rare-tone ERP. The correctness measure was the ratio of the subject's count over the actual number of tones presented.

TABLE 1. *Demographic and drug use data for patients and control subjects (means±SD)*

Data	Patients (n=12)	Control Subjects (n=9)
Age	27.9±6.3	32.1±4.3
Education	12.1±3.2	11.2±1.9
Cocaine Use		
Age of First Use	19.2±5.8	—
Years Dependent	3.7±3.0	—
Amount/Week (grams)	6.7±3.9	—
Addiction Severity Index (0-9)		
Drug	9.0±0.0	0.0±0.0
Alcohol	0.0±0.0	0.0±0.0
Medical	0.0±0.0	0.0±0.0
Employment	3.7±2.0	1.10±1.20
Family and Social	4.8±1.2	0.0±0.0
Psychiatric	4.6±1.4	0.0±0.0
Legal	1.1±1.9	0.0±0.0

TABLE 2. *Neurophysiologic workload test battery tasks*

Task	Measure
Auditory Rare Event Monitoring	N100 and P300 components of ERP, correctness
Visual Rare Event Monitoring	Reaction time, correctness
Sternberg Memory (2 set sizes)	P300 component of ERP, reaction time
Visual Motor Tracking	RMS error, edge violations

During the visual rare-event monitoring task, the subject viewed a television monitor. Two squares and two triangles traveled in random directions across the screen, periodically flashing. The subject was to press a push-button when he observed a square change its direction. A square changed direction about 80 times during the 5-minute test. Percentage of correct detections and reaction time were performance measures for this task. Because the change of direction does not produce clear ERP, no ERP measurea were included.

The Sternberg (1969a; Sternberg 1969b; Sternberg 1975) memory task was presented on a television monitor. Two- and four-letter sets were used. For a given test, a two- or four-letter set was presented to the subject for 30 seconds. Single letters were then presented at the rate of one every 3 seconds. The subject pressed a pushbutton with the preferred hand if the letter was in the set that had been presented or another pushbutton with the other hand if the letter was not in the memory set. P300 amplitude and latency were measured from the ERP elicited by the in-set and out-of-set letters. The performance measure was reaction time.

The visual motor tracking task was also presented on a television monitor. An inverted "T" moved randomly in the vertical dimension. The subject's task was, by using a joystick, to stabilize the inverted "T" between two horizontal bars in the center of the screen. Root Mean Square (RMS) error and edge violations measures of tracking performance were calculated.

ERP Recording and Measurement

The electroencephalogram (EEG) was recorded from C_2 referred to A, with Grass, Model 7P511, amplifier using a half-amplitude bandpass from .1 to 100 Hz with a notch filter at 60 Hz. The electrocularogram (EOG) was also recorded and used for monitoring eye movement artifacts. Sensor Medics silver/silver chloride electrodes were used at all sites. Electrode impedances were below 3 Kohm. The NWTB averaged the raw single trial ERPs according to stimulus type (rare/frequent, in-set/out-of-set, etc.) and determined the amplitude and latency for the P300 component of the averaged ERP waveforms. The measurements were reviewed by a researcher and corrected if necessary. The researcher also manually measured the amplitude and latency of N100 in the auditory event-monitoring task.

Testing Procedure

On an outpatient visit to the Addiction Research Center, the subject was given an explanation of each NWTB task and then allowed to practice on each task. After each practice, the subject performed that task, and the EEG was recorded.

The subject was admitted to the inpatient research ward before 11 a.m. on the first inpatient day (day 1). The first inpatient day ranged from the first to the fourth day after the outpatient-test day. The inpatient tests were administered on day 1, day 2, day 3, day 4, about day 7, about day 14, and about day 21. All cognitive testing and EEG recording were performed while the subject sat in a comfortable reclining chair in an electrically shielded, sound-attenuated chamber. The auditory stimuli were delivered through earphones, and visual stimuli were presented on a video monitor 1 meter from the subject's face. The subject's behavioral responses were

obtained from a verbal response, pushbutton(s), or a handheld joystick, depending on the task.

Statistical Considerations

Difference scores, calculated by subtracting the outpatient score from each inpatient day, were used to control for possible baseline differences between the patients and control subjects. Limited missing data were approximated using the guidelines and procedures described by Winer (1962), so univariate analysis of variance could be performed. To ease the interpretability and to reduce the number of post hoc comparisons made, the simple effect and simple interaction procedures described by Winer (1962) were used to interpret significant higher order interactions. In these procedures, higher order interactions are reduced into multiple simple effects or simple interactions at individual levels of another factor, and Tukey type A post hoc comparisons are made only when significant simple effects or interactions are observed. A .05 probability level was chosen for statistical significance.

RESULTS

Auditory Rare-Event-Monitoring Task

No significant differences between the patient and control group were observed for N100 amplitude and latency of the target tone ERP or correctness in this task. There was a slight tendency for N100 latency for the patients to increase on day 14 and day 21. Perhaps with testing after day 21 this difference might continue to increase and become significant. N100 amplitude, likewise, did not differ between groups over the course of the hospital stay.

P300 latency was significantly increased compared to the latency of the control subjects (group by time interaction: $F(6,114)=2.18$, $p<.05$). The post hoc comparisons tests indicated that the increase was statistically significant only on treatment day 1 (figure 1). P300 amplitude did not change over the course of the treatment period for the patient or control group.

Visual Rare-Event-Monitoring Task

No significant differences between the patients and the control subjects for reaction time and correctness were found. The mean for reaction time is plotted in figure 2.

A significant treatment-day main effect was observed ($F(6,96)=2.61$, $p>.02$). That is, reaction time increased for both groups over the hospital stay. This increase is seen in figure 2. The percent correct detections in this task also increased over time, but no differences were observed between groups on this measure.

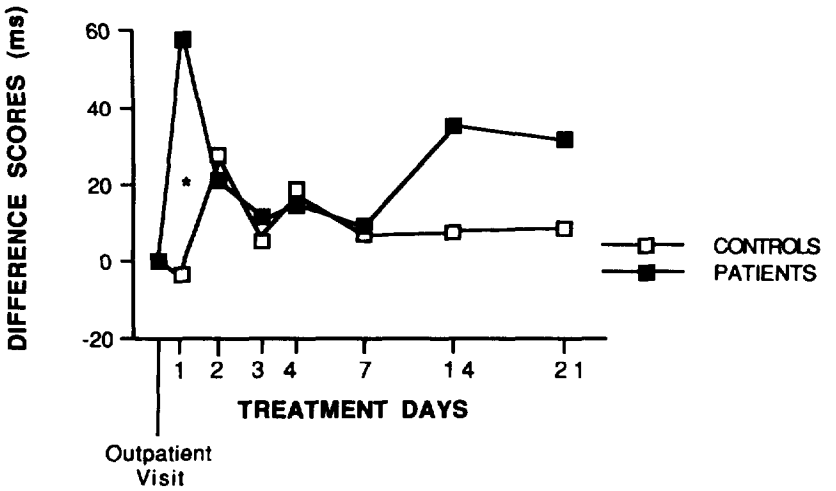

FIGURE 1. *P300 latency for the auditory rare-event-monitoring task plotted as difference scores*

*Significant difference between means using the Tukey (A) procedure.

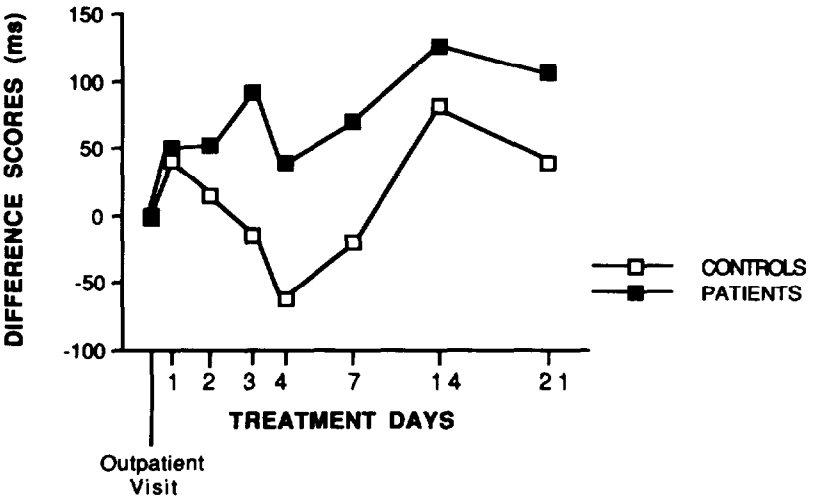

FIGURE 2. *Reaction times for the visual rare-event-monitoring task plotted as difference scores*

NOTE: No significant differences were found on this task.

Sternberg Memory Task

The Sternberg memory task was performed with two set sizes (two-letter and four-letter memory load). The main effect for group factor was significant for reaction time ($F(1,19)=4.591$, $p>.05$). The means averaged over all treatment days and experimental conditions are shown in figure 3.

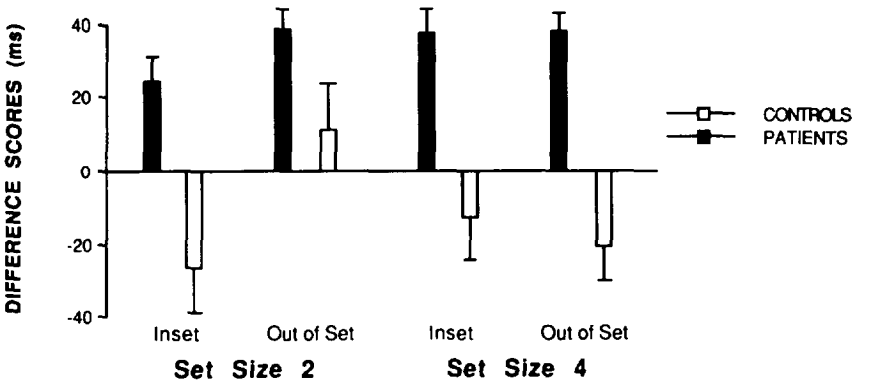

FIGURE 3. *Difference scores on the Sternberg memory task over test sessions for each condition*

NOTE: In all comparisons, the differences between groups are significant.

The performance of the patients worsened over the course of treatment compared to the control subjects. A significant time group by day by set size by response type (in- or out-of-memory set) was also significant for reaction time ($F(6,114)=3.207$, $p>.01$). The increased reaction time was observed over all conditions for the patients. The controls were faster over the hospital stay for all conditions except set size 2 when the probe letter was not the letter to be remembered. The time courses to these effects are plotted in figure 4 and figure 5. No significant changes were observed for P300 amplitude or latency on this task.

Visual Motor-Tracking Task

Neither tracking measure, RMS error or Edge Violations, was altered over the course of treatment.

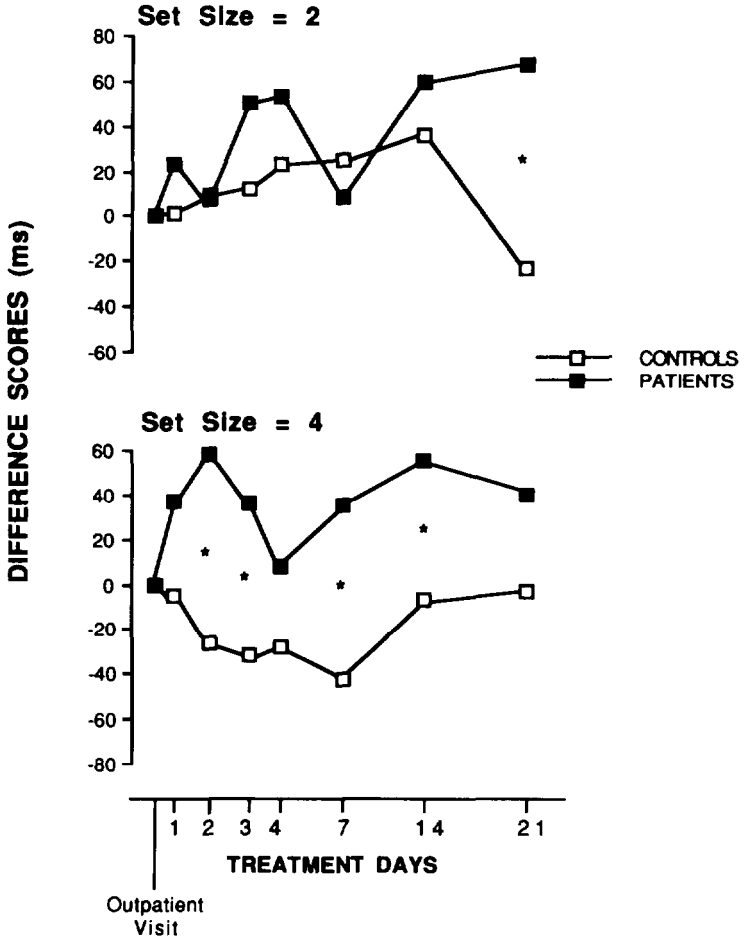

FIGURE 4. *Time course of the in-set reaction time difference scores on the Sternberg memory task over test days*

*Significant differences between means using the Tukey(A) procedure.

CONCLUSION

Specific cognitive decrements were observed when cocaine abusers abstained from cocaine. The decrement occurred at two different stages in the stimulus information-processing chain. A delay in stimulus evaluation as judged by P300 latency occurred on the first treatment day. The patients also had slowed reaction time on the Sternberg memory task for as long as they

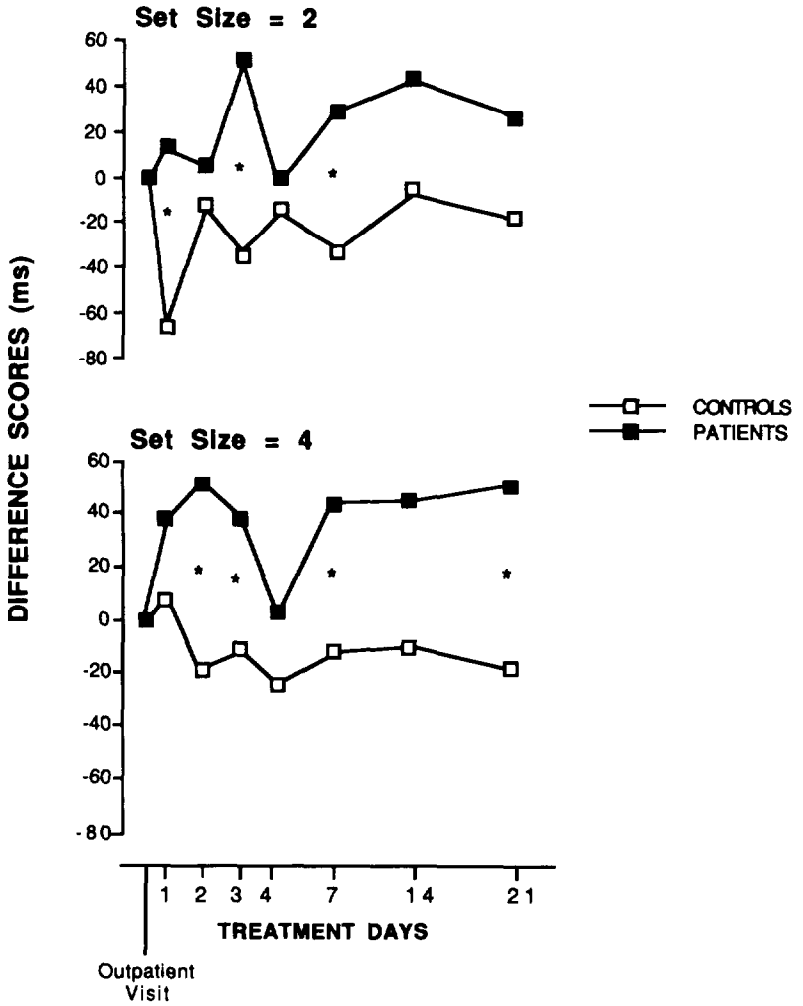

FIGURE 5. *Time course of the out-of-set reaction time difference scores on the Sternberg memory task over test days*

*Significant differences between means using the Tukey(A) procedure.

were tested. The time course of other measures was similar for both the patients and the control subjects. We did not test all aspects of cognition or performance in this study. Although the tasks were simple and the patients were not pushed to the limit of their performance capacity, deficits during cocaine abstinence were clearly observed.

In the present investigation we demonstrated that P300 latency was longer for abstinent cocaine abusers than for control subjects on the first treatment day. This increase in latency cannot be attributed to the more direct effects of stimulant drug administration. For example, acute intravenous and oral doses of cocaine reduce P300 amplitude but do not change latency (Heming et al. 1985). Methylphenidate decreases rather than increases P300 amplitude in drug nonusers (Brumaghim et al. 1987). One experimental manipulation that will produce delays in the P300 is the increase in stimulus complexity, which suggests that cognitive evoked potential latency may be a measure of stimulus evaluation time (Callaway 1983).

Persistent P300 latency delays can also be observed in dementia (Polich et al. 1986) and may be related to poor stimulus processing. The delays of P300 latency we observed appear to be more transient but may also reflect both brain impairment and corresponding deficit stimulus processing.

The time of last cocaine use before admission was not consistent across all patients. The time and the amount of cocaine use before admission needs to be verified against plasma levels of cocaine and its metabolites. However, the increase in P300 latency was large and very significant in spite of possible variability in time and amount.

The reaction-time delays observed in the Sternberg task might have been a result of clinical depression. There is evidence that reaction time can be delayed in depressed patients (Thier et al. 1986; Massiouri and Lesevre 1988), and depression appears to be observed with both cocaine abuse and abstinence (Gawin and Kleber 1986).

We suggest that depression did not act as a confound in this study. Severe depression was not observed in our patient group. First, only one patient was clinically depressed at admission, and Beck depression test scores were relatively low for the patient group during treatment. Second, both the patients and the control subjects differed on reaction time on the Sternberg memory task, but not on the visual rate-event-monitoring task. Third, on the Sternberg task there was a memory load; the subjects had to search recent memory before responding. No memory component was involved in the visual rare-event monitoring task. Also, the subjects were more impaired on the four-letter rather than the two-letter set as would be expected if short-term memory, instead of reaction time, was impaired.

The short-term memory deficit persisted over the period we tested the patients, with no improvement over 3 or 4 weeks. The Paced Auditory Addition Task used by Melamed and Bleiberg (1986) to evaluate cognition in free-base abusers also required short-term memory, and they found that performance deficits persisted over the 10 days of drug-free treatment. They had no outpatient test session, as we had. We presume our subjects used cocaine the day they came for the outpatient test, and on that day they

seemed less impaired than when they first entered treatment. How long the short-term memory deficit continues after the last dose of cocaine remains unclear.

At least three major interpretations of the memory decrement during abstinence are possible. This preliminary study cannot conclusively support any single explanation. The memory decrement may result from (1) a long-term readjustment in several neurotransmitter systems, (2) an unmasking of a residual functional neurological alteration produced by cocaine use, or (3) an unmasking of a preexisting constitutional cognitive alteration in the patients. Treatment of cocaine abusers with dopaminergic agonists such as bromocriptine or antidepressant drugs has become popular as an attempt to restore receptor balance, as well as to prevent the craving and depression associated with cocaine abstinence. Although similar to the first explanation, residual neurological alterations of a reversible nature are based on cocaine effects on plasma membranes and blood flow in the brain. Other transmitter systems may be affected. Finally, 7 of 12 subjects had a DSM-IIIR diagnosis of antisocial personality. We have reported that aggressive adolescent males have sensory and cognitive alteration throughout the auditory information-processing system (Heming et al. 1989). Abstinence from cocaine may unmask this deficit. Because not all subjects had the antisocial personality diagnosis, we favor the second explanation-that is, the memory decrement may be due to more generalized persistent functional neurophysiological alteration unmasked by cocaine abstinence. Such a decrement in cognitive function may be a contributing factor in relapse.

REFERENCES

Baxter, L.R. Desipramine in the treatment of hypersomnolence following abrupt cessation of cocaine use. *Am J Psychiatry* 140:1525-1526, 1983.

Brumaghim, J.T.; Klorman, R.; Strauss, J.; Lewine, J.D.; and Goldstein, M.G. Does methylphenidate affect information processing? Findings from two studies on performance and P3b latency. *Psychophysiology* 24:361-373, 1987.

Callaway, E. The pharmacology of human information processing. *Psychophysiology* 20:359-370, 1983.

Gawin, F.H., and Kleber, H.D. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. *Arch Gen Psychiatry* 43:107-113, 1986.

Heming, R.I.; Hickey, J.E.; Pickworth, W.B.; and Jaffe, J.H. Auditory event-related potentials in adolescents at risk for drug abuse. *Biol Psychiatry* 25:598-609, 1989.

Heming, R.I.; Jones, R.T.; Hooker, W.D.; and Tulunay, EC. Information processing components of the auditory event related potential are reduced by cocaine. *Psychopharmacology* 87:178-185, 1985.

Massiouri, F.E., and Lesevre, N. Attention impairment and psychomotor retardation in depressed patients: An event related potential study. *Electroencephalogr Clin Neurophysiol* 70:46-55, 1988.

Melamed, J.I., and Bleiberg, J. Neuropsychological deficits in freebase cocaine abusers after cessation of use. Presented at the annual meeting of the American Psychiatric Association, Washington, DC, August 1986.
Polich, J.; Ehlers, C.L; Otis, S.; Mandell, A.J.; and Bloom, F.E. P300 latency reflects the degree of cognitive decline in dementing illness. *Electroencephalogr Clin Neurophysiol* 63:138-144, 1986.
Squires, K.; Donchin, W.; Heming, R.I.; and McCarthy, G. On the influence of task relevance and stimulus probability on ERP components. *Electroencephalogr Clin Neurophysiol* 42:1-14, 1977.
Sternberg, S. The discovery of processing stages: Extensions of Donders' method. *Acta Psychologica* 30:276-315, 1969a.
Sternberg, S. Memory-scanning: Mental processes revealed by reaction time experiments. *American Scientist* 57:421-457, 1969b.
Sternberg, S. Memory scanning: New findings and current controversies. *Q J Exp Psychol* 27:1-32, 1975.
Thier, P.; Axmann, D.; and Giedke, H. Slow brain potentials and psychomotor retardation in depression. *Electroencephalogr Clin Neurophysiol* 63:570-581, 1986.
Volkow, N.D.; Mullani, N.; Gould, K.L.; Alder, S.; and Krajewski, K. Cerebral blood flow in chronic cocaine users: A study with positron emission tomography. *Br J Psychiatry* 57:641-648, 1988.
Weiss, B., and Laties, V.G. Enhancement of human performance by caffeine and the amphetamines. *Pharmacol Rev* 14:1-36, 1962.
Wirier, B.J. *Statistical principles in experimental design.* New York: McGraw-Hill, 1962.

ACKNOWLEDGMENT

Technical collaborative contributions were made by members of the Tri-Services Joint Working Group on Drug-Dependent Degradation in Military Performance. The views, opinions, and findings contained in this report are those of the authors and should not be construed as an official position of the Joint Working Group.

AUTHORS

Ronald I. Heming, Ph.D.
Barbara J. Glover, R.N.
Bonnie Koeppl, M.S.
William Weddington, M.D.
Jerome H. Jaffe, M.D.

Cognitive Studies and Human Performance Laboratory
Addiction Research Center
National Institute on Drug Abuse
Baltimore, MD 21224

Abstinence Symptomatology and Neuropsychological Impairment in Chronic Cocaine Abusers

Stephanie S. O'Malley and Frank H. Gawin

INTRODUCTION

As recently as 1980, cocaine was believed to be a relatively safe nonaddicting drug (Gvinspoon and Bakalar 1980). The lessons of previous stimulant epidemics in the 1890s, 1920s, 1950s and 1960s had been forgotten, and new users were aware only of the short-term positive mood effects of cocaine use. As a result, millions of people experimented with cocaine, and, by 1986, approximately 3 million were estimated to abuse cocaine regularly (Adams et al. 1986). Because the time period between initial stimulant use and the development of dependence is 2 to 5 years (Gawin and Kleber 1985), published reports of adverse consequences from cocaine abuse did not appear for several years (Gawin and Ellinwood 1988). Although a number of acute complications of stimulant abuse have been identified (Gold et al. 1985; Creglar and Mark 1986), this chapter reviews the evidence for adverse residual effects of cocaine use on affective and neuropsychological functioning.

ABUSE PATTERNS AND NEUROADAPTATION

An examination of potential residual effects of cocaine requires that patterns of abuse be considered. After initial experimentation and repeated episodes of cocaine use with higher doses, a shift from controlled to uncontrolled cocaine abuse takes place over the course of several years. Clinical consensus indicates that it is not until this shift has occurred that cocaine produces noticeable clinical consequences (Seigel 1982; Gawin and Kleber 1985; Ellinwood and Petrie 1977; Kleber and Gawin 1984).

The clinical hallmark of this shift is that use of cocaine in extended binges develops, during which abusers become unable to cease use until all supplies are exhausted. During binges, cocaine addicts have no interest in sex,

nourishment, sleep, safety, survival, money, morality, loved ones, or responsibilities. After the binge, they frequently go for 1/2 day to 5 days without any cocaine use (Gawin and Kleber 1986).

Abusers average one to three binges per week, lasting from 8 to 24 hours each. During binges, cocaine boluses are readministered every 15 minutes as users attempt to recreate the rush of cocaine euphoria (Seigel 1982; Gawin and Kleber 1986). This means that repeated insults to the brain's homeostatic mechanisms take place. In this context, it is likely that adaptation to cocaine's acute effects on mood takes place, with chronic clinical consequences (Gawin and Ellinwood 1988, Gawin and Ellinwood 1989). In addition, neuropsychological impairment may occur as a result of chronic hyper- or hypostimulation of specific brain regions, or by hemodynamic insults associated with cocaine use.

NEUROADAPTATION IN BRAIN REWARD SYSTEMS

Gross physiological withdrawal symptoms do not occur in cocaine dependence. Nonetheless, there is substantial consistency in the preclinical data indicating that cocaine causes adaptation in brain systems that regulate psychological processes. These data are fully reviewed and referenced else where (Gawin and Ellinwood 1988). Briefly, chronic stimulant exposure in animals causes subsensitivity of mesolimbic and mesocortical dopaminergic projections in animals. These projections are involved in reward. This subsensitivity provides an apparent parallel to the reward subsensitivity described by cocaine abusers, which is clinically termed anhedonia. Further, chronic cocaine administration produces multiple receptor alterations in these same systems. These receptor alterations, the decreases in sensitivity of reward systems, and the clinical withdrawal symptoms of anhedonia are all reversed by treatment with tricyclic antidepressants. In addition, behavioral depression after high-dose stimulants in animals parallels the time course for withdrawal anhedonia in humans. Multiple alterations in neurotransmitter concentrations, turnover, and metabolism also occur in animals and are paralleled by alterations in peripheral indices of central transmitter function in humans.

These data have led to the hypothesis that cocaine produces a true "physiological" addiction as a consequence of chronic, high-dose use, but one whose expression is "psychological." The clinical description of these psychological consequences is consistent among investigators (Gawin and Ellinwood 1988; Seigel 1982; Ellinwood and Petrie 1977; Gawin and Kleber 1986), but the symptom displays are often subtle, requiring development of precise instruments and methods for symptom assessment. Thus, the withdrawal consequences of cocaine have been only partially studied and verified by laboratory or hospital evaluations in humans.

ABSTINENCE SYMPTOMS

Gawin and Kleber (1986) have described a triphasic cocaine abstinence pattern that delineates the emotional consequences of long-term cocaine use. This pattern includes crash, withdrawal, and extinction phases. Figure 1 outlines the phases of abstinence following a cocaine binge.

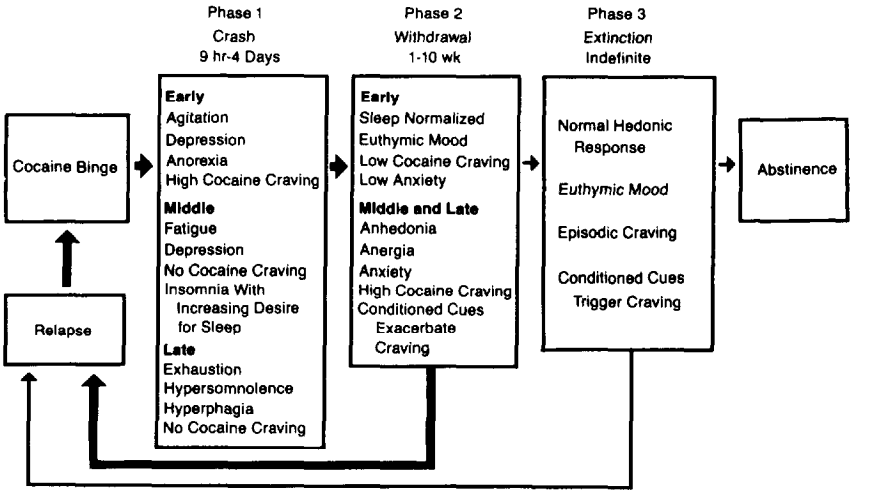

FIGURE 1. *Phases following a cocaine binge*

NOTE: Duration and intensity of symptoms vary depending on binge characteristics and coexisting psychiatric diagnoses.

SOURCE: Gawin and Kleber 1986 copyright 1986, American Medical Association.

Phase I: "Crash"

A "crash" of mood and energy immediately follows a cocaine binge. Cocaine craving, depression, agitation, and anxiety intensify. Within 1 to 4 hours, cocaine craving is replaced by desire for sleep. Sedatives, opiates, anxiolytics, or alcohol may be taken to induce sleep. Prolonged sleep may be punctuated by massive eating episodes. Hypersomnolence can last several days, followed by mood normalization.

Clinical recovery from the crash is, in part, accomplished by sleep, nutrition, and replacement of neurotransmitters depleted by the prior binge. Usual management is nutrition and rest, along with observation for possible suicide. The crash is similar to the acute withdrawal of the alcohol

hangover, rather than chronic withdrawal, in that it is minimally associated with cravings for the abused substance.

Crash symptoms resemble neurovegetative symptoms in major depression; therefore, assessments for psychiatric disorders or severity of chronic abstinence symptoms are delayed until crash symptoms have abated. Generally, sleep normalization and 1 to 3 days of confirmed abstinence assure that acute postuse symptoms have ended (Gawin and Kleber 1986).

Phase II: "Withdrawal"

A protracted dysphoric syndrome, including inactivity, listlessness, boredom, and pleasurelessness (anhedonia) occurs 1 to 5 days following the crash. These symptoms are less dramatic than the extreme depression during the crash and were not recognized by early observers. They are not as unremitting or severe as major mood disorders, but this pleasureless existence amplifies stimulant craving and leads to resumption of use. This withdrawal phase parallels withdrawal from other abused substances, except for its lack of gross physiological changes.

Clinicians observe that anhedonic symptoms abate within 1 to 10 weeks of sustained abstinence. Predisposing psychiatric disorders may prolong and amplify these withdrawal symptoms.

Phase III: "Extinction"

Months or even years after resolution of withdrawal, occasional periods of "conditioned" cocaine craving can occur, lasting only hours. Conditioned cocaine cravings result from objects or events (cues) that in the past had been paired with cocaine intoxication and that evoke associations to cocaine euphoria. Cues can be specific persons, locations, events, mild alcohol intoxication, interpersonal conflicts, adverse mood states previously soothed by cocaine, or the sight of objects linked to abuse (money, white powder, glass pipes, mirrors, syringes, single-edged razor blades, among many others) (Gawin and Ellinwood 1989). If the person does not yield to craving, the desire will abate; it diminishes on each subsequent exposure and gradually becomes extinct.

NEUROPSYCHOLOGICAL IMPAIRMENT

The possibility that cocaine abuse may also result in cognitive dysfunction is suggested by case reports of cocaine-induced intracranial hemorrhage and cerebral vasculitis (Kaye and Fainstat 1987; Tuchman et al. 1987; Levine et al. 1987). These vascular consequences are probably related to the vasoconstrictor properties of cocaine, in which both cardiac output and peripheral resistance are increased, resulting in transient hypertension. Neuropsychological impairment may also result from overstimulation of

dopaminergic pathways and subsequent hypoexcitability of these areas when cocaine administration is discontinued (Bauer 1989).

Research involving acute administration of cocaine and similar drugs (e.g., methylphenidate) suggests that cocaine's actions on the central nervous system (CNS) improve vigilance and motor functions (Fischman and Shuster 1980; Coons et al. 1981). Overstimulation of these functions with chronic cocaine administration, however, may potentially result in disrupted attention and impaired motor skills. Given that cocaine's actions involve the mesolimbic system, it is also likely that memory may be affected as well.

Despite the potential clinical significance of this issue, there are few controlled studies of the neuropsychological consequences of chronic cocaine use. In one study, O'Malley and colleagues (1988) compared 20 recently abstinent cocaine abusers with 20 age- and education-matched controls using the Wechsler Adult Category test, the Finger Oscillation test, and the Neuropsychological Screening Battery (NSB) (Heaton et al., in press; Franklin et al., in press). The cocaine abusers reported using, on average, 447.15 grams of cocaine over approximately 4 years. Their mean age and educational level were 27.6 (SD=7.17) and 13.2 (SD=1.61) years, respectively. Individuals were excluded who had a history of intravenous drug use, dependence on alcohol or drugs other than cocaine, significant head trauma, developmental problems, major medical disorders, a psychotic illness, or current use of medications that might affect the CNS.

On the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the cocaine abusers scored significantly lower than controls on the arithmetic subtest only. The results for the remaining neuropsychological measures are presented in table 1. As can be seen, cocaine abusers did worse on the Symbol Digit Modalities test, a measure of verbal forgetting (Story Memory), the Halstead Category test, and the summary score of the NSB. Mean scores for the cocaine abusers on the Symbol Digit Modalities test and the NSB summary measure were in the mild impairment range. These findings suggest that recent abstinence from cocaine is associated with problems in concentration, memory, and nonverbal problem solving and abstracting ability. One unexpected finding was higher oral fluency scores for the cocaine abusers. Perhaps the most striking result was that 50 percent of the cocaine abusers scored in the impairment range on the NSB summary score, in contrast to only 15 percent of the controls. Briefer periods of abstinence were related to poorer arithmetic performance and tended to be associated with greater impairment on the NSB summary measure and with more errors on the Halstead Category test.

In a second study, O'Malley and associates (1989) continued to examine the issue of residual effects of cocaine in a larger sample of cocaine abusers, using a more extensive neuropsychological assessment battery. Although

TABLE 1. *Cocaine abusers and normals compared on neuropsychological measures*

Measure	Cocaine Ss M	Cocaine Ss SD	Control Ss M	Control Ss SD	t	p
Impairment Index[a]	5.80	4.34	2.70	4.04	2.34	.02
Aural Comprehension[b]	11.80	.41	11.70	.57	64	.53
Commands[b]	22.20	2.09	22.30	1.49	-.17	.86
Oral Fluency[b]	14.85	5.07	11.15	2.85	2.84	.008
Written Fluency[b]	11.85	3.56	12.50	3.71	-.57	.56
Confrontation Naming[b]	17.85	2.06	17.90	.41	-.08	.94
Sentence Repetition[b]	4.65	.67	4.80	.41	-.85	40
Trails A[a]	25.90	6.00	22.00	9.68	1.53	.14
Trails B[a]	59.05	26.50	49.55	23.76	1.19	.24
Symbol Digit[b]	51.10	10.10	65.05	11.17	-2.66	.01
Story Learning[b]	6.35	4.17	7.06	3.25	-.60	.55
Story Memory[a]	10.20	9.32	4.80	6.14	2.16	.04
Figure Copy[b]	17.35	2.60	16.85	2.58	.61	.55
Figure Learning[b]	14.00	4.64	15.25	2.94	-1.02	.31
Figure Memory[a]	3.25	8.11	5.35	6.71	-.89	.38
Numerical Attention						
Time[b]	157.20	31.49	146.85	25.97	1.12	.27
Errors[b]	3.90	2.94	3.80	3.16	.10	.92
Reading Comprehension[a]	11.60	.68	11.85	.49	-1.33	.19
Category Test Errors[b]	40.60	22.74	25.80	15.90	-.08	.94
Finger Tapping						
Dominant[a]	53.90	6.59	55.76	4.43	-.99	.33
Nondominant[a]	48.70	7.34	49.83	5.80	-.54	.59

[a]Higher scores indicate poorer performance.
[b]Lower scores indicate poorer performancc.

NOTE: There was no evidence of speech articulation problems in any of the cocaine or control subjects. All subjects received a perfect score.

the first study was conducted with inpatients who were newly abstinent (mean=23 days), this investigation studied 25 outpatients who had accrued an average of 135 days of abstinence. The subjects were cocaine abusers (mean age=28.4 years) who had been interviewed with the Schedule for Affective Disorders and Schizophrenia as part of a diagnostic study. Based on this interview, subjects with a lifetime or current history of drug or

alcohol abuse other than cocaine or stimulants were excluded from participating. The remaining exclusion criteria were similar to those used by Adamse and colleagues (1988). Of the sample, 74 percent primarily smoked free-base cocaine; the remainder were intranasal users. On average, the sample had used a total of 522.7 grams of cocaine over 46.9 months. They were predominantly male (60 percent) and Caucasian (60 percent), with a mean educational level of 13.5 years (SD=1.7).

Cocaine abusers were compared with 25 age-, education-, sex-, and race-matched normal controls using the extended Halstead-Reitan Battery (Reitan 1986). Tests comprising this battery include the WAIS—R, category test, trail-making test, tactual performance test (TPT, time, memory, and location), rhythm test, speech-sounds perception, aphasia examination, sensory perceptual examination, finger-tapping test, grip-strength dynamometer, grooved pegboard test, and the Minnesota Multiphasic Personality Inventory. Heaton's adaptation of the Wechsler Memory scale was used to assess learning and memory for verbal and figural information (Heaton et al. 1978).

For data analysis, the various neuropsychological tests were classified according to the ability area tapped by the measure. The skill areas included measures of: (1) verbal skills, (2) abstraction and cognitive flexibility, (3) complex psychomotor skills, (4) learning and incidental memory, (5) memory, (6) attention and speed of information processing, (7) simple motor skills, and (8) simple sensory skills. The tests comprising each ability area are presented in table 2.

Multivariate analyses of variance were then used to compare the cocaine abusers and controls on these eight areas and on a group of summary measures, including Verbal IQ, Performance IQ, and the Average Impairment Rating. The areas in which the cocaine abusers performed more poorly than controls included complex cognitive motor skills, simple motor skills, and the summary measures. When individual tests were examined, the analyses revealed that the cocaine abusers performed more poorly on the following tests of cognitive-motor and simple motor skills: spatial relations, grooved pegboard, grip strength, and spatial relations. With regard to memory, the cocaine abusers showed a deficit in retaining nonverbal material. None of the individual summary scores discriminated between the two groups, although the multivariate analysis was significant. With the exception of grip strength and spatial relations, the cocaine abusers' scores were in the normal range on all tests.

ABSTINENCE AND RECOVERY OF FUNCTION

An extensive body of research on neuropsychological changes associated with alcohol abuse suggests that significant cognitive impairment is evident in recently detoxified alcoholics, but that slow recovery of function occurs

TABLE 2. *Ability areas and specific neuropsychological tests used to compare cocaine and normal subjects*

Ability Area	Tests
Summary Measures	Verbal I.Q.; Performance I.Q.; Average Impairment Rating
Verbal Skills	Vocabulary; Information; Comprehension; Similarities; Aphasia Errors
Abstraction and Cognitive Flexibility	Category Errors; Trail B
Attention and Speed of Information Processing	Rhythm Test; Digit Span; Arithmetic; Picture Completion; Speech Sounds
Learning and Incidental Memory	Story Learning; Figure Memory; TPT—Memory; TPT—Location
Memory	Story Memory; Figure Memory
Complex Psychomotor Skills	TPT—Minutes per block; Digit Symbol; Picture Arrangement; Block Design; Object Assembly; Spatial Relations
Simple Motor Skills	Finger Tapping; Grip Strength; Grooved Pegboard
Simple Sensory	Perceptual Errors

with long-term abstinence (Grant 1987). The findings from our research suggest that a similar process may conceivably occur with cocaine abuse.

In our study of recently abstinent cocaine abusers (O'Malley et al. 1988), length of abstinence correlated with performance on tests that discriminated cocaine abusers from normals. In addition, 50 percent of the cocaine abusers were found to be in the mildly impaired range in contrast to 15 percent of controls. In contrast, when we studied a sample of cocaine abusers who had been abstinent almost 4 months on average, their neuropsychological tests scores, although poorer than controls, were generally in the normal range. The patterns of impairment noted in the two studies suggest that disruptions in attention may recover more rapidly and that motor impairment may be more persistent.

The question of recoverability of function would be best addressed using a longitudinal design in which subjects are tested shortly after achieving abstinence and at several intervals over time. In an initial examination of this

question, Cummings and associates (1988) tested a group of 30 male cocaine addicts upon admission to an inpatient unit and 2 weeks later with the Peterson Short-Term Verbal Learning Test, the WAIS—R digit span, a digit-symbol substitution test, and a choice-reaction-time test. Preliminary results indicated that subjects' performance improved from baseline on digits backwards and on the 30-second trial of the Peterson Short-Term Learning Test. The contribution of practice effects to this improvement cannot be ruled out, however, in the absence of a control group. Using a different methodology, Volkow and colleagues (1988) failed to End improvement in cerebral blood-flow abnormalities when subjects were tested shortly after admission to treatment and 10 days later. The time between testings in both studies was relatively short and further research is needed to address whether significant improvement would occur with extended abstinence.

REMAINING QUESTIONS AND FUTURE DIRECTIONS FOR RESEARCH

Although our research reveals poorer performance by cocaine abusers, the degree of impairment is not as striking as that seen with alcoholics. Before minimizing the long-term effects of cocaine on cognitive functioning, however, a number of caveats should be made. First, it is important to note that current studies of cocaine abusers have used relatively young subjects who had abused cocaine for approximately 4 to 7 years on average. In studies demonstrating cognitive dysfunction in alcoholics, subjects are generally older with longer histories of abuse (Parsons and Farr 1981). As the population of long-term cocaine abusers increases, future research addressing whether more significant changes result from extended periods of abuse will be needed.

Perhaps a more important caution is that our samples of cocaine abusers were highly selective and consisted of subjects whose only abused substance was cocaine. This pattern of single-substance abuse is not typical of the majority of drug abusers. Cocaine abusers are often dependent on alcohol. Another subgroup combines cocaine and heroin in a "speedball" to produce a more tempered high. The preliminary results of a large diagnostic study of 300 treatment-seeking cocaine abusers (Rounsaville, personal communication) indicated that 61.7 percent met lifetime research diagnostic criteria for alcohol abuse or dependence. Given that alcohol dependence has been shown to be associated with substantial neuropsychological impairment, it is likely that cocaine abusers who also abuse alcohol or other drugs may be at particular risk for cognitive dysfunction. While studies of relatively "pure" cocaine abusers allow clearer inferences about the role of cocaine in any observed impairments, additional studies of cocaine abusers who also abuse other substances are required.

Although the evidence for residual effects of cocaine on cognitive and emotional functioning is accruing, much of our knowledge remains anecdotal.

In addition, the time course and nature of recovery of cognitive functioning following cocaine withdrawal can only be inferred from the current cross-sectional studies. At this juncture, longitudinal studies are needed in which abstinence symptomatology is assessed at specific time periods after cocaine use is discontinued. In research on cognitive functioning, traditional neuropsychological test batteries could be augmented with tests concentrating on specific areas hypothesized to be affected by cocaine. The existing research suggests that processes involved with vigilance, memory, and motor functioning may be particularly important.

REFERENCES

Adams, E.H.; Gfroerer, J.C.; Rouse, B.A.; and Kozel, N.J. Trends in prevalence and consequences of cocaine use. *Adv Alcohol Subst Abuse* 6:49-71, 1986.

Coons, H.W.; Peloquin, L.J.; Klorman, R.; Bauer, L.O.; Ryan, R.M.; Perlmutter, R.A.; and Salzman, L.F. Effect of methylphenidate on young adults' vigilance and event-related potential. *Electroencephalogr Clin Neurophysiol* 51:373-387, 1981.

Creglar, L.L., and Mark, H. Medical complications of cocaine abuse. *N Engl J Med* 315:1495-1500, 1986.

Cummings, C.; Gorelick, D.A.; and Marcus, M.M. Neuropsychological testing of male cocaine addicts. Presented at the annual meeting of the American Medical Society, Alcoholism and Other Drug Dependencies, Atlanta, GA, April 1989.

Ellinwood, E.H., and Petrie, W.M. Dependence on amphetamine, cocaine and other stimulants. In: Pradhan, S.N., ed. *Drug Abuse:* Clinical *and Basic Aspects.* New York: CV Mosby, 1977. pp. 248-262.

Fischman, M.W., and Schuster, C.R. Cocaine effects in sleep deprived humans. *Psychopharmacologia* 72:1-8, 1980.

Franklin, G.M.; Heaton, R.K.; Nelson, L.M.; Filly, C.M.; and Seibert, C. Correlation of neuropsychological and magnetic resonance imagery: Findings in chronic progressive multiple sclerosis. *Neurology,* in press.

Gawin, F.H., and Ellinwood, E.H. Cocaine and other stimulants: Actions, abuse, and treatment. *N Engl J Med* 318:1173-1182, 1988.

Gawin, F.H., and Ellinwood, E.H. Stimulant abuse treatment. In: Kleber, H.D., *ed. Psychiatric Treatment Manual: Substance Abuse.* Washington, DC: American Psychiatric Association, 1989.

Gawin, F.H., and Kleber, H.D. Cocaine abuse in a treatment population: Patterns and diagnostic distinctions. In: Kozel, N.J., and Adams, E.H., eds. *Cocaine Use in America: Epidemiologic and Clinical Perspectives.* National Institute on Drug Abuse Research Monograph 61. DHHS Pub. No. (ADM)85-1414. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1985. pp. 182-192.

Gawin, F.H., and Kleber, H.D. Abstinence symptomatology and psychiatric diagnosis in chronic cocaine abusers. *Arch Gen Psychiatry* 4:107-111, 1986.

Gold, M.S.; Washton, A.M.; and Dackis, C.A. Cocaine abuse: Neurochemistry, phenomenology, and treatment. In: Kozel, N.J., and Adams, E.H., eds. *Cocaine Use in America: Epidemiologic and Clinical Perspectives.* National Institute on Drug Abuse Research Monograph 61. DHHS Pub. No. (ADM)85-1414. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1985. pp. 130-150.

Grant, I. Alcohol and the brain: Neuropsychological correlates. *J Consult Clin Psycho1* 55:310-324, 1987.

Gvinspoon, L., and Bakalar, J.B. Drug dependence: Non-narcotic agents. In: Kaplan, H.I.; Freedman, A.M.; and Sadock, B.J., *eds. Comprehensive Textbook of Psychiatry.* 3rd ed. Baltimore: Williams and Wilkins, 1980.

Heaton, R.K.; Chelune, G.J.; and Lehman, R.A.W. Using neuropsychological and personality tests to assess the likelihood of patient employment. *J Nerv Ment Dis* 166:408-416, 1978.

Heaton, R.K.; Thompson, L.L.; Nelson, L.M.; Filly, C.M.; and Franklin, G.M. Brief and intermediate length screening of neuropsychological impairment in multiple sclerosis. In: Rao, S.M., ed. *Multiple Sclerosis: A Neuropsychological Perspective.* New York: Oxford University Press, 1990. pp. 149-160.

Kaye, B.R., and Fainstat, M. Cerebral vasculitis associated with cocaine abuse. *JAMA* 258:2104-2106, 1987.

Kleber, H.D., and Gawin, F.H. Cocaine abuse: A review of current and experimental treatments. In: Grabowski, J., *ed. Cocaine: Pharmacology, Effects, and Treatment of Abuse.* National Institute on Drug Abuse Research Monograph 50. DHHS Pub. No. (ADM)84-1326. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984. pp. 111-129.

Levine, S.R.; Washington, J.M.; Jefferson, M.F.; Kieman, S.W.; Moen, M.; Feit, H.; and Welsh, K.M. Crack cocaine-associated stroke. *Neurology* 37:1849-1853, 1987.

O'Malley, S.S.; Adamse, M.; Heaton, R.K.; and Gawin, F.H. Neuropsychological impairment in chronic cocaine abusers. Presented at the Annual Meeting of the Society of Psychologists in Addictive Behaviors, Atlanta, GA, August 1988.

O'Malley, S.S.; Gawin, F.H.; Heaton, R.; and Kleber, H.D. Cognitive deficits associated with cocaine abuse. Presented at the Annual Meeting of the American Psychiatric Association, San Francisco, CA, May 1989.

Parsons, E.S., and Farr, S.D. The neuropsychology of alcohol and drug use. In: Filskin, S.B., and Boll, T.S., eds. *Handbook of Clinical Neuropsychology.* New York: Wiley, 1981. pp. 320-365.

Reitan, R.M. Theoretical and methodological bases of the Halstead-Reitan Neuropsychological Test Battery. In: Grant, I., and Adams, K.M., eds. *Neuropsychological Assessment of Neuropsychiatric Disorders.* New York: Oxford University Press, 1986. pp. 3-30.

Seigel, R.K. Cocaine smoking. *J Psychoactive Drugs* 14:21-27, 1982.

Tuchman, A.J.; Daras, M.; Zalzal, P.; and Mangiardi, J. Intracranial hemorrhage after cocaine abuse. *JAMA* 257:1175, 1987.

Reitan, R.M. Theoretical and methodological bases of the Halstead-Reitan Neuropsychological Test Battery. In: Grant, I., and Adams, K.M., eds. *Neuropsychological Assessment of Neuropsychiatric Disorders.* New York: Oxford University Press, 1986. pp. 3-30.

Seigel, R.K. Cocaine smoking. *J Psychoactive Drugs* 14:21-27, 1982.

Tuchman, A.J. Daras, M.; Zalzal, P.; and Mangiardi, J. Intracranial hemorrhage after cocaine abuse. *JAMA* 257:1175, 1987.

Volkow, N.D.; Mullani, N.; Gould, L.; Adler, S.; and Krajewski, K. Cerebral blood flow in chronic cocaine users: A study with positron emission tomography. *Br J Psychiatry* 152:641-648, 1988.

Wechler, D. *Wechsler Intelligence Scale for Adults—Revised.* New York: The Psychological Corporation, 1981.

ACKNOWLEDGMENTS

Support was provided by National Institute on Drug Abuse Center grant P50 04060 and DA 05348 and by the National Institute on Alcoholism and Alcohol Abuse grant AA 07080.

AUTHORS

Stephanie S. O'Malley, Ph.D.
Department of Psychiatry
School of Medicine
Yale University
285 Orchard Street
New Haven, CT 06511

Frank H. Gawin, M.D.
Department of Psychiatry
University of California
Los Angeles, CA

National Institute on Drug Abuse Research

monograph series

While limited supplies last, single copies of the monographs may be obtained free of charge from the National Clearinghouse for Alcohol and Drug Information (NCADI). Please contact NCADI also for information about availability of coming issues and other publications of the National Institute on Drug Abuse relevant to drug abuse research.

Additional copies may be purchased from the U.S. Government Printing Office (GPO) and/or the National Technical Information Service (NTIS) as indicated. NTIS prices are for paper copy; add $3.00 handling charge for each order. Microfiche copies are also available from NTIS. Prices from either source are subject to change.

Addresses are:

NCADI
National Clearinghouse for Alcohol and Drug Information
P.O. Box 2345
Rockville, MD 20852

GPO
Superintendent of Documents
U.S. Government Printing Office
Washington, DC 20402

NTIS
National Technical Information Service
U.S. Department of Commerce
Springfield, VA 22161
(703) 487-4650

For information on availability of National Institute on Drug Abuse Research Monographs 1 through 24 (1975-1979) and others not listed, write to NIDA, Community and Professional Education Branch, Room 10A-54, 5600 Fishers Lane, Rockville, MD 20857.

25 BEHAVIORAL ANALYSIS AND TREATMENT OF SUBSTANCE ABUSE. Norman A. Krasnegor, Ph.D., ed.
GPO out of stock
NCADl out of stock
NTIS PB #80-112428/AS $31

26 THE BEHAVIORAL ASPECTS OF SMOKING. Norman A. Krasnegor, Ph.D., ed. (Reprint from 1979 Surgeon General's Report on Smoking and Health.)
GPO out of stock
NTIS PB #80-118755/AS $23

30 THEORIES ON DRUG ABUSE: SELECTED CONTEMPORARY PERSPECTIVES. Dan J. Lettieri, Ph.D.; Mollie Sayers; and Helen W. Pearson, eds.
GPO Stock #017-024-00997-1
NCADI out of stock
Not available from NTIS

31 MARIJUANA RESEARCH FINDINGS: 1980. Robert C. Petersen, Ph.D., ed.
GPO out of stock
NTIS PB #80-215171/AS $31

32 GC/MS ASSAYS FOR ABUSED DRUGS IN BODY FLUIDS. Rodger L. Foltz. Ph.D.; Allison F. Fentiman, Jr., Ph.D.; and Ruth B. Foltz.
GPO out of stock
NCADI out of stock
NTIS PB #81-133746/AS $31

36 NEW APPROACHES TO TREATMENT OF CHRONlC PAIN: A REVIEW OF MULTIDISCIPLlNARY PAIN CLINICS AND PAlN CENTERS. Lorenz K.Y. Ng, M.D., ed.
GPO out of stock
NCADI out of stock
NTIS PB #81-240913/AS $31

37 BEHAVIORAL PHARMACOLOGY OF HUMAN DRUG DEPENDENCE. Travis Thompson, Ph.D., and Chris E. Johanson, Ph.D., eds.
GPO out of stock
NCADI out of stock
NTlS PB #82-136961/AS $39

38 DRUG ABUSE AND THE AMERICAN ADOLESCENT. Dan J. Lettieri, Ph.D., and Jacqueline P. Ludford. M.S., eds. A RAUS Review Report.
GPO out of stock
NCADl out of stock
NTIS PB #82-148198/AS $23

40 ADOLESCENT MARIJUANA ABUSERS AND THEIR FAMILIES. Herbert Hendin, M.D.; AM Pollinger, Ph.D.; Richard Ulman. Ph.D.; and Arthur Carr, Ph.D., eds.
GPO out of stock
NCADI out of stock
NTlS PB #82-133117/AS $23

42 THE ANALYSIS OF CANNABINOIDS IN BIOLOGICAL FLUIDS. Richard L. Hawks, Ph.D., ed.
GPO out of stock
NTlS PB #83-136044/AS $23

44 MARIJUANA EFFECTS ON THE ENDOCRINE AND REPRODUCTIVE SYSTEMS. Monique C. Braude, Ph.D., and Jacqueline P. Ludford, M.S., eds. A RAUS Review Report.
GPO out of stock
NCADI out of stock
NTIS PB #85-150563/AS $23

45 CONTEMPORARY RESEARCH IN PAIN AND ANALGESIA, 1983. Roger M. Brown, Ph.D.; Theodore M. Pinkert, M.D., J.D.; and Jacqueline P. Ludford, M.S., eds. A RAUS Review Report.
GPO out of stock
NCADI out of stock
NTIS PB #84184670/AS $17

46 BEHAVIORAL INTERVENTION TECHNIQUES IN DRUG ABUSE TREATMENT. John Grabowski, Ph.D.; Maxine L Stitzer, Ph.D.; and Jack E. Henningfield, Ph.D., eds.
GPO out of stock
NCADI out of stock
NTIS PB #84-184688/AS $23

47 PREVENTING ADOLESCENT DRUG ABUSE: INTERVENTION STRATEGIES. Thomas J. Glynn, Ph.D.; Carl G. Leukefeld, D.S.W.; and Jacqueline P. Ludford, M.S., eds. A RAUS Review Report.
GPO Stock #017-024-01180-1 $5.50
NCADI out of stock
NTIS PB #85159663/AS $31

48 MEASUREMENT IN THE ANALYSIS AND TREATMENT OF SMOKING BEHAVIOR. John Grabowski, Ph.D., and Catherine Bell, M.S., eds.
GPO Stock #017-024-01181-9 $4.50
NCADI out of stock
NTIS PB #84-1451841/AS $23

50 COCAINE: PHARMACOLOGY, EFFECTS, AND TREATMENT OF ABUSE. John Grabowski, Ph.D., ed.
GPO Stock #017-024-01214-9 $4
NTIS PB #85-150381/AS $23

51 DRUG ABUSE TREATMENT EVALUATION: STRATEGIES, PROGRESS, AND PROSPECTS. Frank M. Tims, Ph.D., ed.
GPO Stock #017-024-01218-1 $4.50
NTlS PB #85-150365/AS $23

52 TESTING DRUGS FOR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. Joseph V. Brady, Ph.D., and Scott E. Lukas, Ph.D., eds.
GPO Stock #017-024-01204-1 $4.25
NTlS PB #85-150373/AS $23

53 PHARMACOLOGICAL ADJUNCTS IN SMOKING CESSATION. John Grabowski, Ph.D., and Sharon M. Hall, Ph.D., eds.
GPO Stock #017-024-01266-1 $3.50
NCADI out of stock
NTIS PB #89-123186/AS $23

54 MECHANISMS OF TOLERANCE AND DEPENDENCE. Charles Wm. Sharp, Ph.D., ed.
GPO out of stock
NCADI out of stock
NTlS PB #89-103279/AS $39

55 PROBLEMS OF DRUG DEPENDENCE, 1984: PROCEEDINGS OF THE 46TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis. S. Harris, Ph. D., ed.
GPO out of stock
NCADI out of stock
NTIS PB #89-123194/AS $45

56 ETIOLOGY OF DRUG ABUSE: IMPLICATIONS FOR PREVENTION. Coryl LaRue Jones, Ph.D., and Robert J. Battjes, D.S.W., eds.
GPO Stock #017-024-01250-5 $6.50
NTIS PB #39-123160/AS $31

57 SELF-REPORT METHODS OF ESTIMATING DRUG USE: MEETING CURRENT CHALLENGES TO VALIDITY. Beatrice A. Rouse, Ph.D.; Nicholas J. Kael, M.S.; and Louise G. Richards, Ph.D., eds.
GPO Stock #017-024-01246-7 $4.25
NTIS PB #8-248083/AS $23

58 PROGRESS IN THE DEVELOPMENT OF COST-EFFECTIVE TREATMENT FOR DRUG ABUSERS. Rebecca S. Ashery, D.S.W., ed.
GPO Stock #017-024-01247-5 $4.25
NTIS PB #89-125017/AS $23

59 CURRENT RESEARCH ON THE CONSEQUENCES OF MATERNAL DRUG ABUSE. Theodore M. Pinkert, M.D., J.D., ed.
GPO Stock #017-024-01249-1 $2.50
NTIS PB #89-125025/AS $23

60 PRENATAL DRUG EXPOSURE: KINETICS AND DYNAMICS. C. Nora Chiang. Ph.D., and Charles C. Lee, Ph.D., eds.
GPO Stock #017-024-01257-2 $3.50
NTIS PB #89-124564/AS $23

61 COCAINE USE IN AMERICA: EPIDEMIOLOGIC AND CLINICAL PERSPECTIVES. Nicholas J. Kozel, M.S., and Edgar H. Adams, M.S., eds.
GPO Stock #017-024-01258-1 $5
NTIS PB #89-131866/AS $31

62 NEUROSCIENCE METHODS IN DRUG ABUSE RESEARCH. Roger M. Brown, Ph.D., and David P. Friedman, Ph.D., eds.
GPO Stock #017-024-01260-2 $3.50
NCADI out of stock
NTIS PB #89-130660/AS $23

63 PREVENTION RESEARCH: DETERRING DRUG ABUSE AMONG CHILDREN AND ADOLESCENTS. Catherine S. Bell, M.S., and Robert J. Battjes, D.S.W., eds.
GPO Stock #017-024-01263-7 $5.50
NTlS PB #39-103287/AS $31

64 PHENCYCLIDINE: AN UPDATE. Doris H. Clouet, Ph.D., ed.
GPO Stock #017-024-01281-5 $6.50
NTIS PB #89-131858/AS $31

65 WOMEN AND DRUGS: A NEW ERA FOR RESEARCH. Barbara A. Ray, Ph.D., and Monique C. Braude, Ph.D., eds.
GPO Stock #017-024-01283-1 $3.50 NTIS PB #89-130637/AS $23

66 GENETIC AND BIOLOGICAL MARKERS IN DRUG ABUSE AND ALCOHOLISM. Monique C. Braude, Ph.D., and Helen M. Chao, Ph.D., eds.
GPO Stock #017-024-01291-2 $3.50 NCADI out of stock
NTlS PB #89-134423/AS $23

68 STRATEGIES FOR RESEARCH ON THE INTERACTIONS OF DRUGS OF ABUSE. Monique C. Braude, Ph.D., and Harold M. Ginzburg, M.D., J.D., eds.
GPO Stock #017-024-01296-3 $6.50 NCADI out of stock
NTIS PB #89-134936/AS $31

69 OPIOID PEPTIDES: MEDICINAL CHEMISTRY. Rao S. Rapaka, Ph.D.; Gene Bamett, Ph.D.; and Richard L. Hawks, Ph.D., eds.
GPO Stock #017-024-1297-l $11 NTlS PB #89-158422/AS $39

70 OPIOlD PEPTIDES: MOLECULAR PHARMACOLOGY, BIOSYNTHESIS, AND ANALYSIS. Rao S. Rapaka, Ph.D., and Richard L. Hawks, Ph.D., eds.
GPO Stock #017-024-1298-0 $12 NTIS PB #89-158430/AS $45

71 OPIATE RECEPTOR SUBTYPES AND BRAIN FUNCTION. Roger M. Brown, Ph.D.; Doris H. Clouet, Ph.D.; and David P. Friedman, Ph.D., eds.
GPO Stock #017-024-01303-0 $6 NTIS PB #89-151955/AS $31

72 RELAPSE AND RECOVERY IN DRUG ABUSE. Frank M. Tims, Ph.D., and Carl G. Leukefeld, D.S.W., eds.
GPO Stock #017-024-01302-l $6 NTIS PB #89-151963/AS $31

73 URINE TESTING FOR DRUGS OF ABUSE. Richard L. Hawks, Ph.D., and C. Nora Chiang, Ph.D., eds.
GPO Stock #017-024-01313-7 $3.75 NTIS PB #89-151971/AS $23

74 NEUROBIOLOGY OF BEHAVIORAL CONTROL IN DRUG ABUSE. Stephen 1. Szara. M.D., D.Sc., ed.
GPO Stock #017-024-1314-5 $3.75 NTIS PB #89-151989/AS $23

75 PROGRESS IN OPIOID RESEARCH. PROCEEDINGS OF THE 1986 INTERNATIONAL NARCOTICS RESEARCH CONFERENCE. John W. Holaday. Ph.D.; Ping-Yee Law, Ph.D.; and Albert Herz. M.D., eds.
GPO Stock #017-024-01315-3 $21 NCADI out of stock
Not available from NTIS

76 PROBLEMS OF DRUG DEPENDENCE, 1986. PROCEEDINGS OF THE 48TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01316-1 $16 NCADI out of stock
NTIS PB #88-208111/AS $53

77 ADOLESCENT DRUG ABUSE: ANALYSES OF TREATMENT RESEARCH. Elizabeth R. Rahdert, Ph.D., and John Grabowski, Ph.D., eds.
GPO Stock #017-024-01348-0 $4 NTIS PB #89-125488/AS $23

78 THE ROLE OF NEUROPLASTICITY IN THE RESPONSE TO DRUGS. David P. Friedman, Ph.D., and Doris H. Clouet, Ph.D., eds.
GPO Stock #017-024-01330-7 $6 NTIS PB #88-245683/AS $31

79 STRUCTURE-ACTIVITY RELATIONSHIPS OF THE CANNABINOIDS. Rao S. Rapaka, Ph.D., and Alexandros Makriyannis, Ph.D., eds.
GPO Stock #017-024-01331-5 $6 NTIS PB #89-109201/AS $31

80 NEEDLE SHARING AMONG INTRAVENOUS DRUG ABUSERS: NATIONAL AND INTERNATIONAL PERSPECTIVES. Robert J. Battjes, D.S.W.. and Roy W. Pickens, Ph.D., eds.
GPO Stock #017-024-0134.5-5 $5.50 NTIS PB #88-236138/AS $31

81 PROBLEMS OF DRUG DEPENDENCE, 1987. PROCEEDINGS OF THE 49TH ANNUAL SCIENTIFIC MEETING, THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01354-4 $17 NTIS PB #89-109227/AS
Contact NTIS for price

82 OPIOIDS IN THE HIPPOCAMPUS. Jacqueline F. McGinty, Ph.D., and David P. Friedman, Ph.D., eds.
GPO Stock #017-024-01344-7 $4.25 NTIS PB #88-245691/AS $23

83 HEALTH HAZARDS OF NITRITE INHALANTS. Harry W. Haverkos, M.D., and John A. Dougherty, Ph.D., eds.
GPO Stock #017-024-01351-0 $3.25 NTIS PB #89-125496/AS $23

84 LEARNING FACTORS IN SUBSTANCE ABUSE. Barbara A. Ray, Ph.D., ed.
GPO Stock #017-024-01353-6 $6 NTIS PB #89-125504/AS $31

85 EPIDEMIOLOGY OF INHALANT ABUSE: AN UPDATE. Raquel A. Crider, Ph.D., and Beatrice A. Rouse, Ph.D., eds.
GPO Stock #017-024-01360-9 $5.50 NTIS PB #89-123178/AS $31

86 COMPULSORY TREATMENT OF DRUG ABUSE: RESEARCH AND CLINICAL PRACTICE. Carl G. Leukefeld, D.S.W., and Frank M. Tims, Ph.D., eds.
GPO Stock #017-024-01352-8 $7.50 NTIS PB #89-151997/AS $31

87 OPIOID PEPTIDES: AN UPDATE. Rao S. Rapaka, Ph.D., and Bhola N. Dhawan, M.D., eds.
GPO Stock #017-024-01366-8 $7 NTIS PB #89-158430/AS $45

88 MECHANISMS OF COCAINE ABUSE AND TOXICITY. Doris H. Clouet, Ph.D.; Khursheed Asghar, Ph.D.; and Roger M. Brown, Ph.D., eds.
GPO Stock #017-024-01359-5 $11 NTIS PB #89-125512/AS $39

89 BIOLOGICAL VULNERABILITY TO DRUG ABUSE. Roy W. Pickens, Ph.D., and Dace S. Svikis, B.A., eds.
GPO Stock #017-022-01054-2 $5 NTIS PB #89-125520/AS $23

90 PROBLEMS OF DRUG DEPENDENCE, 1988. PROCEEDINGS OF THE SOTH ANNUAL SCIENTIFIC MEETING. THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
GPO Stock #017-024-01362-5 $17

91 DRUGS IN THE WORKPLACE: RESEARCH AND EVALUATION DATA. Steven W. Gost. Ph.D., and J. Michael Walsh, Ph.D., eds.
GPO Stock #017-024-01384-6 $10 NTIS PB #90-147257/AS $39

92 TESTING FOR ABUSE LIABILITY OF DRUGS IN HUMANS. Marian W. Fischman. Ph.D., and Nancy K. Mello, Ph.D., eds.
GPO Stock #017-024-01379-0 $12 NTIS PB #90-148933/AS $45

93 AIDS AND INTRAVENOUS DRUG USE: FUTURE DIRECTIONS FOR COMMUNITY-BASED PREVENTION RESEARCH. C.G. Leukefeld, D.S.W.; R.J. Battjes, D.S.W.; and Z. Amsel. Ph.D., eds.
GPO Stock #017-024-01388-9 $10 NTIS PB #90-148941/AS $39

94 PHARMACOLOGY AND TOXICOLOGY OF AMPHETAMINE AND RELATED DESIGNER DRUGS. Khursheed Asghar, Ph.D., and Errol De Sousa, Ph.D.. eds.
GPO Stock #017-024-01386-2 $11 NTIS PB #90-148958/AS $39

IN PRESS:

95 PROBLEMS OF DRUG DEPENDENCE, 1989. PROCEEDINGS OF THE 51ST ANNUAL SCIENTIFIC MEETING. THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.

96 DRUGS OF ABUSE: CHEMISTRY, PHARMACOLOGY, IMMUNOLOGY, AND AIDS. Phuong Thi Kim Pham, Ph.D., and Kenner Rice, Ph.D., eds.

97 NEUROBIOLOGY OF DRUG ABUSE: LEARNING AND MEMORY. Lynda Erinoff, ed.

98 THE COLLECTION AND INTERPRETATION OF DATA FROM HIDDEN POPULATIONS. Elizabeth Y. Lambert, M.S.. ed.

99 RESEARCH FINDINGS ON SMOKING OF ABUSED SUBSTANCES. C. Nora Chiang, Ph.D., and Richard L. Hawks, Ph.D., eds.

100 DRUGS IN THE WORKPLACE: RESEARCH AND EVALUATION DATA. VOL. II. Steven W. Gost, Ph.D., and J. Michael Walsh, Ph.D., eds.

101 RESIDUAL EFFECTS OF ABUSED DRUGS ON BEHAVIOR. John W. Spencer, Ph.D., and John J. Boren, Ph.D., eds.

102 ANABOLIC STEROID ABUSE. Geraline C. Lin, Ph.D., Lynda Erinoff, Ph.D., eds.

103 DRUGS AND VIOLENCE: CAUSES, CORRELATES, AND CONSEQUENCES. Mario De La Rosa, Ph.D.; Elizabeth Y. Lambert, M.S.; and Bernard Gropper, Ph.D., eds.

DHHS Publication No. (ADM)91-1719
Alcohol, Drug Abuse, and Mental Health Administration
Printed 1990