CHAPTER V

TOBACCO USE COMPARED TO OTHER DRUG DEPENDENCIES

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Introduction

The present Chapter compares cigarette smoking and nicotine with other forms of drug dependence and addicting drugs. Other chapters in this Report describe the behavior of cigarette smoking, the known biobehavioral mechanisms and modulators of nicotine's actions, and techniques for achieving abstinence from smoking. As is evident from this Report, cigarette smoking is most usefully explained and characterized as a drug dependence process in which nicotine is the identified drug of dependence. It is also evident that by either the World Health Organization (WHO) definition of "drug addiction" that was issued in the 1950s (WHO 1952) or by the definitions of "drug dependence" issued since the 1960s (WHO 1964, 1969, 1981), nicotine is appropriately categorized as an addicting or dependence-producing drug. Its designation as a drug is also consistent with the definitions provided by the WHO (1981) and the Food and Drug Administration (FDA) (1987). Nicotine-delivering tobacco preparations (which include all currently marketed tobacco preparations) could, therefore, be appropriately categorized as addicting or dependence-producing drugs. In addition to evaluating nicotine with respect to definitions of dependence-producing drugs, it is also useful to compare features of tobacco dependence and the pharmacologic properties of nicotine to other drug addictions and addicting drugs, respectively. This comparison is the purpose of the present Chapter.

Two of the most widely studied drug addictions provide standards to which other addictions may be compared. They are the addictions to the opium-derived or related substances ("opioids," e.g., morphine, heroin, methadone, codeine) and to alcohol. For nearly a century, it has been widely accepted that use of these substances could lead to addictive behavior and to adverse effects. Moreover, such consequences of use develop in a sufficient number of persons that there have been recurrent regulatory efforts to restrict access and conditions of use. Cocaine and related psychomotor stimulants (e.g., amphetamine) provide an additional important standard by which to judge suspected and known addicting chemicals. These stimulants have been accepted as standards by which to evaluate the addicting potential of other stimulants since the 1950s.

It is beyond the scope of the present Chapter to review all aspects of drug dependence in detail. Rather, this Chapter summarizes primarily the pharmacologic aspects of drug dependence. In particular, the Chapter provides information that permits a comparison of the pharmacologic basis of tobacco dependence, as described in the other Chapters, with the pharmacologic basis of other forms of drug dependence. More extensive reviews of the topics to be discussed have emerged from various review panels sponsored by the National Institute on Drug Abuse (NIDA) (Krasnegor 1978, 1979a,b,c; Thompson and Johanson 1981; Grabowski, Stitzer, Henningfield 1984;

Sharp 1984) and the National Academy of Sciences (Levison, Gerstein, Maloff 1983); other reviews have been held under the

ter 1973; Thompson and Unna 1977; Balster and Harris 1982; Taylor

determinants and consequences of drug dependence are more

1983; Tims and Ludford 1984; Petersen 1978; Bell and Battjes 1985;

1979; Lettieri, Sayers, Pearson 1980; Crowley and Rhine 1985).

Clinical Characteristics of Drug Dependence

Drug Dependence Defined

Before the 1960s it was fairly common to invoke factors such as "criminality," "character deficit," "immorality," and "weakness of will" in the clinical diagnosis of "drug addiction." In addition, these factors often included various social connotations. In part, it was because these attributes were not objective or scientifically based that the WHO in 1964 recommended that the term "addiction" be replaced with "drug dependence" in an effort to be more precise and descriptive in definition (WHO 1964, 1981).

According to current conceptualizations, the central and common element across all forms of drug dependence is that a psychoactive drug has come to control behavior to an extent that is considered detrimental to the individual or society (WHO 1981; APA 1987). Although the precise wording varies, the central concept of drug-dependence definitions refers to the behavior of the individual who has come under the control of a psychoactive drug, and this concept has provided the cornerstone of most definitions of dependence/addiction for at least a century (Berridge 1985) and arguably for several centuries (Murray et al. 1933; Austin 1979; Levine 1978). The involvement of a psychoactive drug is the critical feature that distinguishes drug addictions from other habitual behaviors.

In principle, the term "drug dependence" might be used to characterize any form of drug ingestion; however, the term is generally reserved for use when the chemical meets criteria as a "psychoactive" drug. These criteria are based on drug-induced changes in brain function; such changes may involve alterations in mood, feeling, thinking, perception, and other behavior. In this Chapter the term "drug dependence" or "drug addiction" refers to self-administration of a psychoactive drug in a manner that demonstrates that the drug controls or strongly influences behavior. In other words, the individual is no longer entirely free to use or not use the substance. Often times, this reduction in the degree to which use

TABLE l.--Diagnostic criteria for psychoactive substance dependence

A. At least three of the following:

(1) Substance often taken in larger amounts or over a longer period than the person intended

(2) Persistent desire or one or more unsuccessful efforts to cut down or control substance use

(3) A great deal of time spent in activities necessary to get the substance (e.g., theft), to take the substance (e.g., chain smoking), or to recover from its effects

(4) Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home (e.g., does not go to work because of hangover, goes to school or work "high," intoxicated while taking care of own children), or when substance use is physically hazardous (e.g., drives when intoxicated)

(5) Important social, occupational, or recreational activities given up or reduced because of substance use

(6) Continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance (e.g., continuing heroin use despite family arguments about it, cocaine-induced depression, or ulcer made worse by drinking

(7) Marked tolerance: need for markedly increased amounts of the substance (i.e., at least a 50 percent increase) to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount

(Note: The following items may not apply to cannabis, hallucinogens, or PCP)

(8) Characteristic withdrawal symptoms (see specific withdrawal syndromes under Psychoactive Substance-Induced Organic Mental Disorders)

(9) Substance often taken to relieve or avoid withdrawal symptoms

B. Some symptoms of the disturbance persistent for at least 1 month, or occurrent repeatedly over longer period of time

SOURCE: American Psychiatric Association (1987).

is considered "voluntary" is described as "habitual" or "compulsive" drug use.

Diagnostic Criteria for Drug Dependence

The Diagnostic and Statistical Manual (DSM-III-R) of the American Psychiatric Association (APA 1987) provides a useful example of the objective criteria currently used to define drug dependence. As stated in DSM III-Revised: "The essential feature of this disorder is a cluster of cognitive, behavioral, and physiological symptoms that indicate that the person has impaired control of psychoactive substance use and continues use of the substance despite adverse consequences." Specific diagnostic criteria for psychoactive substance dependence are shown in Table 1.

The APA designated 10 classes of psychoactive substance for which use may lead to dependence: alcohol; amphetamine or similarly acting sympathomimetics; cannabis; cocaine; hallucino-

gens; inhalants; nicotine; opioids; phencyclidine (PCP) or similarly acting arylcyclohexylamines; and sedatives, hypnotics, or anxiolytics. The fact that dependence criteria are the same for all classes of drug use highlights the assumption that dependence processes are functionally similar across substances with different pharmacologic profiles.

Features of Drug Dependence

Behavior that leads to drug ingestion, as well as the various behavioral and physiological sequelae resulting from the ingestion, are determined by both drug (pharmacologic or agent) and nondrug (behavioral or environmental) factors which will be discussed in this Chapter. The nondrug determinants include characteristics of the individual ("host" characteristics) such as age, genotype, and personality.

Highly Controlled or Compulsive Drug Use

Highly controlled or compulsive drug use indicates that drug-seeking and drug-taking behavior is driven by strong, often irresistible urges. It can persist despite a desire to quit or even repeated attempts to quit. Compulsive drug use may take precedence over other important priorities.

The extent to which compulsive behavior is apparent varies across individuals and is most easily detected in extreme cases. For example, to maintain daily drug intake laryngectomized patients may smoke cigarettes through their tracheostomy hole, cocaine users may take cocaine at the risk of loss of family and job, and prostitution has been observed to occur in exchange for a variety of drugs for which availability was low or price was high.

The drug-seeking behavior itself ranges from the routine and licit procurement of cigarettes or alcohol, to the possibly more extensive behavioral repertoire necessary to obtain prescriptions for certain drugs, to the highly intricate chains of behavior required to procure many illicit drugs. Drug-seeking behavior is not determined entirely by the specific pharmacologic properties of a particular drug, however. For instance, when alcohol or tobacco has been prohibited, procurement has at times involved as much risk and involvement as the procurement of illicit drugs in the 1980s (Austin 1979; Brecher 1972).

A drug may be taken to avoid withdrawal symptoms and other undesirable sequelae of drug abstinence. This factor may contribute to the level of compulsivity which develops. Addicting drugs often provide some therapeutic benefit or otherwise useful effect (Chapter VI); these effects may also contribute to the compulsive nature of drug use. Whether or not such benefits are considered to be more

important than the adverse effects of drug taking, this factor is important because it may have been prominent in initial exposure to the drug, it may have strengthened the control of the drug over behavior, and it may constitute a potential cause for relapse.

Physical Dependence and Tolerance

The observation of a withdrawal syndrome that accompanies abstinence from chronic drug exposure is the primary index of physical dependence induced by the drug (Martin 1965; Kalant 1978). Drug withdrawal syndromes are behavioral and physiological sequelae of abstinence from chronic drug administration. Tolerance refers to the diminished responsiveness to successive administration of a drug; it may occur independently of physical dependence but is a frequent concomitant (Kalant 1978). The magnitude of tolerance and physical dependence is directly related to the frequency and magnitude of the drug-dosing regimen; thus, low or infrequent drug dosing may not produce measurable levels of tolerance or physical dependence. Tolerance may develop in the absence of physical dependence; for example, infrequent dose administration may result in decreased responsiveness even though no measurable withdrawal reaction accompanies drug abstinence.

Whereas initial drug exposure may have caused marked behavioral and physiological disruption, the development of physical dependence implies that a relatively normal appearing behavioral and physiological functioning requires continued drug administration and that disruption will occur when the drug is withdrawn. For example, at certain doses, opioids, sedatives (including alcohol), and nicotine can produce marked intoxication in nontolerant individuals. As tolerance develops, these same dose levels may produce no readily observable signs of intoxication, and in the case of opioids and nicotine only extremely high doses or sudden abstinence are accompanied by disruption of ongoing behavior.

The development of tolerance to repeated drug exposure and of the onset of a withdrawal syndrome may be observed following a period of repeated drug exposure and drug abstinence, respectively, but these factors do not in themselves define a drug dependence syndrome requiring intervention to prevent relapse to drug use. It is possible to establish tolerance and physical dependence by repeated drug administration even when the animal or human never actually self-administered the drug. In animals, this is often done in experimental studies; human patients requiring pain relief may become tolerant to and physically dependent on opioid analgesics in hospital settings. Such animals and humans do not necessarily exhibit drug-seeking behavior when drug administration is terminated. Another such instance is the fetal opioid syndrome, in which treatment of the withdrawal reaction might be indicated but no

drug-seeking behavior would be present for which an intervention would be needed (Weinberger et al. 1986). Although not always essential for the occurrence of addictive drug-seeking behavior, tolerance and withdrawal phenomena are important in principle because they can serve to strengthen the control of the drug over behavior. Specifically, tolerance development can result in increased drug intake in an attempt to maintain the desired drug effects, and the onset of a drug withdrawal syndrome may constitute an aversive state which is alleviated by drug taking.

Harmful Effects

The concept that some sort of harm or disadvantage to the individual or society is a consequence of drug use is another element in most definitions of drug dependence. This concept is complex and socially determined, however. For example, drug seeking may result in illicit production and trafficking as currently occurs for illicit drugs (Drug Abuse Policy Office 1984), and had occurred for tobacco at various times when it was banned (Austin 1979; see also Warner 1982 for a discussion of recent cigarette-smuggling issues). Administration of drugs, or abstinence in the physically dependent person, may directly produce adverse behavioral and psychiatric effects ("psychotoxicity"). Finally, toxicity may also be a direct physiological effect of the addicting drug itself (e.g., liver damage caused by alcohol) or to associated toxins (e.g., transmission of the human immunodeficiency virus by needle sharing among i.v. drug users, or carcinogens delivered by tobacco smoke).

These forms of drug-associated damage can result in a variety of societal costs such as health care of drug users (including cigarette smokers), lost productivity of the work force (including tobacco-use-associated losses in productivity), and criminal justice system burdens associated with illicit drug use. Such adverse effects of drug use constitute the "liability" of drug use and may also be factors in the determination that drug use constituted "drug abuse" (Yanagita 1987). These societal aspects of drug dependence frequently invoke debates which pit the "right" to self-damage against the "right" of society to protect itself from the direct damage or costs incurred as a consequence of the individual's behavior. A historical appraisal of psychoactive substance use reveals that societies have often moved cautiously to restrict the use of drugs when there was little assumption of drug-use-associated damage.

Course of Drug Dependence

The chronic nature of drug ingestion in the severely dependent individual suggests that drug dependence processes themselves may be long lasting and resistant to termination. In contrast, the direct

effects of psychoactive drugs are generally limited to a few hours or days at most. Peak physical withdrawal signs and symptoms from opioids, sedatives, alcohol, and tobacco appear to last for about 1 to 2 weeks. However, at least for the opioids, a secondary stage of withdrawal may last for 1 year or more; this has been termed protracted withdrawal (Martin 1965; Jasinski 1981). As discussed in Chapters III and VI, an analogous protracted abstinence syndrome appears to exist in tobacco dependence and to be of importance for treatment efforts. Therefore, despite the relatively short-term duration of the effects of drug administration or withdrawal, the clinically relevant duration of drug dependence is much longer.

A major implication of post-1960s definitions of drug dependence is that drug dependence is not an absolute phenomenon, but rather may vary in degree (Jaffe 1965, 1985; Miller 1979). Often, within an individual the level of severity increases over time ("progressive" characteristic). The course may be quite variable, however. For example, an initially rapidly developed high level of use may be followed by long-term or transient remissions, while some individuals never progress at all beyond levels of use of a given drug that are sometimes considered safe and acceptable (Vaillant 1970, 1982). Such low or intermittent levels of drug use are sometimes referred to as "occasional," "controlled," "recreational" or "social" drug use or "chipping"; such use may still be problematic because there may be acute adverse consequences (e.g., auto accidents following drinking), as well as a transition to chronic drug use (as is characteristic following occasional tobacco use) and the possibility that any use involves illicit behavior (e.g., procurement of alcohol and tobacco by minors or possession of marijuana).

There are differences among drugs in the relative incidence of occasional users compared to regular daily users who meet criteria for dependence. For example, it is generally estimated that less than 15 percent of those who consume alcoholic beverages are dependent (Miller 1979). Analysis of opioid data are more problematic (Zinberg and Jacobson 1976); however, observations such as those made of Vietnam veterans show that opioid chipping is not only a well-documented phenomenon but may also be common in some social and environmental settings. Robins and colleagues found (1) that opioid chipping was a common occurrence among enlisted men in Vietnam, (2) that 88 percent of heroin-addicted Vietnam veterans used heroin occasionally upon their return to the United States, and (3) that most (approximately 90 percent) were able to avoid readdiction (Robins et al. 1977; Robins and Helzer 1975; Robins, Helzer, Davis 1975; Robins, Davis, Goodwin 1974; Robins, Davis, Nurco 1974; see also Zinberg 1972, 1980). In contrast, however, chipping appears relatively rare among tobacco users: the 1985 National Health Interview Survey showed that 10.6 percent of current smokers

smoke 5 or fewer cigarettes/day (unpublished data, Office on Smoking and Health; see also Russell 1976 and US DHHS 1987).

Polydrug Dependence and Multiple Psychiatric Diagnosis

Another feature of drug dependence is the common use of multiple substances, including tobacco, by dependent individuals. In fact, the most consistent feature of such multiple drug use is the high rate of co-occurrence of tobacco dependence along with dependence on opioids, alcohol, stimulants, and even gambling (Taylor and Taylor 1984). In addition, drugs used by individuals may sometimes vary and be interchanged as price and availability vary (e.g., cocaine is preferred by many but individuals may use opioids, or even sedatives, when cocaine is unavailable) (Kliner and Pickens 1982). Several drugs may also be taken simultaneously; for instance, heavy consumption of nicotine, alcohol, and marijuana is common. Finally, most surveys indicate that use of drugs such as cocaine, alcohol, opioids, and marijuana is accompanied (and usually preceded) by use of nicotine (US DHHS 1987).

Tobacco use concurrent with other drug dependencies is so prevalent that it is not generally considered to be of diagnostic significance or considered as a basis of multiple drug dependence diagnosis. Recently, the possible interactive nature of co-dependencies to nicotine and other drugs has been given increasing attention in drug treatment programs (Taylor and Taylor 1984; Kozlowski et al. 1984). These data are discussed later in this Chapter, as well as the issue of whether nicotine serves as a "gateway" to the use of illicit drugs.

Also of clinical significance is the concurrence of drug dependence and some other psychiatric disorder. This phenomenon is termed multiple or dual diagnosis (Meyer 1986; McLellan, Woody, O'Brien 1979; Allen and Frances 1986; Rounsaville and Kleber 1986; Jaffe and Ciraulo 1986). In general, dependence on opioids, alcohol, cocaine, and nicotine is often associated with elevated rates and levels of antisocial tendencies and extraversion, but such trends are not generally regarded as multiple diagnoses (for a review of several forms of multiple diagnosis, see Taylor and Taylor 1984). The designation of multiple diagnosis is reserved for the concurrent appearance of a clinically significant psychiatric disorder and drug dependence; the most common of such disorders would appear to be depression, anxiety, and antisocial personality (McLellan, Woody, O'Brien 1979; Rounsaville et al. 1982; Woody, McLellan, O'Brien 1984).

Spontaneous Remission

It is characteristic of drug dependence that some persons discontinue use of the drug while not engaged in a formal treatment program (i.e., "on their own") although they may have participated in a treatment program at some earlier point in time (Stall and Biernacki 1986). Spontaneous remission refers to intentional and unintentional cessation of drug use, variously referred to as "natural recovery," "maturing out," "burning out," or "self-quitting," but most frequently in current literature as "spontaneous remission." Such quitting is sometimes reported to be due to "will power" or "just deciding to quit." However, follow-up studies have revealed that significant environmental events are often associated with such quitting (for example, Vaillant 1970, 1982). Such data have suggested to some that the terms such as "self-quitting," "self-help," and "spontaneous remission" are misnomers (Fisher 1986; Fisher et al. 1988); nonetheless, because the term spontaneous remission is extant in the scientific literature, it will be used here. This Section provides a brief summary of available information comparing alcohol, opioids and tobacco with regard to their rates of spontaneous remission and of factors associated with remission from drug use.

In studies of spontaneous remission, a minimum criterion for abstinence, such as 1 year, is often imposed. Although the recorded history of drug dependence acknowledges that some people can achieve abstinence without benefit of formal intervention programs, there was little systematic study of spontaneous remission until the 1970s. Major motivations for the current interest in this phenomenon are to determine if the so-called spontaneous remitters differ in behavioral or physiological parameters from other drug-dependent persons, to identify factors which may be systematically applied in treatment settings, and to better understand the process of drug dependence itself.

The percentage of such spontaneous remitters reported in any given study appears to vary more as a function of population and study variables than as a function of drug class. For instance, data averaged across 10 studies show that approximately 30 percent of opioid-dependent persons spontaneously remit (Anglin et al. 1986) although estimates of remission rates vary from 2 percent to 65 percent (Harrington and Cox 1979; Winick 1962). On the other hand, approximately 90 percent of people who have quit smoking report that they quit without the aid of formal treatment programs or smoking cessation devices (Fiore et al., in press; see discussion of related issues in Fisher et al. 1988).

Deriving precise quantitative comparisons of rates of spontaneous remission across the various drug dependencies is problematic due to the differing criteria used to identify those who are spontaneous remitters. For example, in tobacco surveys, rates of spontaneous

remission are often estimated by retrospective self-reports from a sample of former smokers, whereas surveys of opioid and alcohol users generally include only those who were dependent enough to be involved in formal treatment programs at some time.

The factors which are associated with spontaneous remission appear to be similar across dependencies on alcohol, opioids, and tobacco (Stall and Biernacki 1986). Table 2 is a summary of findings which have been reported on factors related to spontaneous remission. As shown in the Table, influences such as health problems associated with use of the drug and social pressures are frequent precipitants of spontaneous remission among persons who were dependent on alcohol, opioids, or tobacco. Similarly, spontaneous remitters have often learned to better manage their drug "cravings" and to provide contingent reinforcement for quitting to themselves, and may even undergo significant lifestyle changes (Stall and Biernacki 1986).

These data regarding spontaneous remission support the conclusion, discussed earlier, that it is somewhat misleading to infer that spontaneous remitters are truly spontaneous or that they were not "really dependent" as is sometimes assumed (Fisher 1986; Fisher et al. 1988; US DHHS 1982). Rather, it seems more plausible that spontaneous remitters are largely those who have either learned to deliver effective treatments to themselves or for whom environmental circumstances have fortuitously changed in such a way as to provide a therapeutic situation (Fisher 1986; Stall and Biernacki 1986; Vaillant 1982, 1970). In addition, persons most likely to quit use of tobacco and opioids without benefit of formal intervention do tend to have shorter histories of use and/or be at lower levels of dependence (US DHHS 1987). Such issues, relating specifically to cigarette smoking, have been reviewed in considerable detail in a previous report of the Surgeon General (US DHHS 1982).

Chemical Detection Measures

Although drug dependence is not reliably diagnosed simply on the basis of amount of drug intake (Crowley and Rhine 1985; Jaffe 1985), it can be useful to determine whether or not a person has ingested a significant amount of a drug. For example, as is discussed later in this Chapter, many treatment programs require objective verification of drug-free patient status.

A potentially useful adjunct for objectively assessing exposure to drugs is to test for the presence of the drug in biological specimens (Walsh and Yohay 1987; Hawks and Chiang 1986). For instance, blood, urine, saliva, expired air, and other biological samples can be assayed for residual drug or drug-specific markers (e.g., metabolites). Such testing aids in determining that presumed drug-related effects were not actually symptoms of some other organic or mental

TABLE 2.--Studies concerning spontaneous remission behavior, by drug and commonly mentioned factors important to remission

Factor	Alcohol	Tobacco	Heroin
Health problems	Cahalan (1970), Goodwin et al. (1971), Knupfer (1972), Lemere (1953). Saunders et al. (1979), Stall (1983), Tuchfeld (1981)	Hecht (1978), Pederson and Lefcoe (1976)	Biernacki (1983)
Social sanctions	Cahalan (1970), Edwards et al. (1977), Goodwin et al. (1971), Knupfer (1972), Stall (1983), Thorpe and Perret (1959), Tuchfeld (1981), Vaillant (1982)	Perri et al. (1977)	Biernacki (1983), Schasm (1966), Vaillant (1966a,b, 1970)
Significant others	Edwards et al. (1977), Goodwin et al. (1971). Knupfer (1972), Saunders et al. (1979), Stall (1983), Tuchfeld (1981), Vaillant (1982)	DiClemente and Prochaska (1979). Hecht (1978), Pederson and Lefcoe (1976), Perri et al. (1977)	Biernacki (1983), Waldorf and Biemacki (1979), Vaillant (1964, 1970)
Financial problems	Cahahm (1970), Saunders et al. (1979), Stall (1983), Thorpe and Perret (1959), Tuchfeld (1981)	Hecht (1978)	Biernacki (1983)
Significant accidents	Knupfer (1972), Stall (1983), Tuchfeld (1981)	Perri et al. (1977)	Biernacki (1983), Jorques (1983). Waldorf and Biernacki (1981)
Management of cravings	Stall (1983)	Baer et al. (1977), DiClemente and Prochaska (1979), Hecht (1978), Pederson and Lefcoe (1976), Perri et al. (1977)	Biernacki (1983). Jorques (1983)

TABLE 2--.Continued

Factor	Alcohol	Tobacco	Heroin
Positive reinforcement for quitting	Edwards et al. (1977), Stall (1983)	Baer et al. (1977), DiClemente and Prochaska (1979), Pederson and Lefcoe (1976)	Biernacki (1983)
Internal psychic change/motivation	Edwards et al. (1977), Knupfer (1972), Saunders et al. (1979), Tuchfeld (1981)	Baer et al. (1977), Hecht (1978)	Biernacki (1983), Schasre (1966), Waldorf and Biernacki (1981)
Change in lifestyle	Edwards et al. (1977), Knupfer (1972), Saunders et al. (1979), Tuchfeld (1981)	DiClemente and Prochaska (1979), Hecht (1978)	Biernacki (1983), Jorquez (1983), Schasre (1966), Waldorf and Biernacki (1981)

SOURCE: Modified from Stall and Biernacki (1986).

disorder. One problem with such verification is that the drug level measured reflects recency as well as amount of drug use and thus may lead to either underestimation or overestimation of the typical level of drug use. Furthermore, absolute level of use does not necessarily determine whether use is pathological or detrimental. Another problem is that biochemical drug tests vary widely in both their specificity (correct drug identification) and sensitivity (minimum amount of drug detected) (see Grabowski and Lasagna 1987 and Walsh and Yohay 1987 for general reviews of such issues; and Benowitz 1983 and Muranaka et al. 1988 for a tobacco-related review; also see Chapter II).

Presently, verification of drug dependence is based largely on the behavioral factors as described below. The most useful application of testing for drug levels in the body remains the verification of compliance with treatment regimens in which drug abstinence is the goal. These and other issues regarding the methodologies and applications of chemical detection measures have been reviewed by a committee of the American Society for Clinical Pharmacology and Therapeutics (in press).

Patterns in the Development of Drug Dependence

When the relationships among drug dependencies have been studied in major epidemiological surveys (e.g., NIDA's National Household Survey (NHS) (US DHHS 1987)), two findings consistently emerge: persons who use dependence-producing drugs are often cigarette smokers, and cigarette smoking precedes and may be predictive of illicit drug use. Some of the data which have led to these conclusions are summarized in this Section.

Current Use of Cigarettes and Other Drugs

The association of current use of one drug with current use of other drugs has been studied extensively. One such study is the NHS conducted by NIDA (US DHHS 1987). The Eighth NHS, conducted in 1985, involved personal interviews with 8,038 persons 12 years of age and older, representative of the household population of the continental United States. Questions were asked about the age of respondents when they first tried a cigarette and age when they first started smoking daily. This distinction may be important when comparing cigarette use with the use of other drugs. Persons who do not make the transition from trying cigarettes to daily use may be less likely to use other drugs than those who do make this transition. A similar format was used with alcohol (i.e., age at which respondent first tried alcohol, not including childhood sips, and age of first using alcohol once a month or more). Questions about age at the onset of other drug use were limited to age at first use. In the NHS studies,

TABLE 3.—Current use of alcohol, marijuana, and cocaine among "current" cigarette smokers and nonsmokers by age group (percentages)

Age group, current drug use	"Current" cigarette use	
	No	Yes
Alcohol		
12–17	23.5	74.2
18–25	64.7	82.6
26–34	62.5	81.0
≥35	52.5	68.6
Marijuana		
12–17	5.8	47.3
18–25	13.7	35.4
26–34	10.6	26.0
≥35	1.7	3.5
Cocaine		
12–17	0.4	8.8
18–25	3.9	13.9
26–34	4.1	9.2
≥35	0.4	0.6

NOTE: Current use is any use reported in the 30 days prior to the interview.
SOURCE: National Household Survey on Drug Abuse, 1985. (in preparation)

current drug use is defined as any use of the drug during the 30 days preceding the interview.

Based on data from the 1985 NHS on Drug Abuse, Table 3 shows associations among use of various psychoactive substances. As shown in the table, rates of current use (i.e., during the past 30 days) of marijuana, alcohol, and cocaine are much higher among "current" cigarette smokers than among others. For example, among 12- to 17-year-olds, almost three-fourths of "current" smokers were current alcohol users compared with less than one-fourth of the youths who were not "current" smokers. Approximately 47 percent of the "current" cigarette smokers report being current marijuana users compared with 5.8 percent of the youths who were not "current" smokers.

Differences as large as those shown in Table 3 represent very strong correlations between use of cigarettes and use of other drugs. The strength of the correlation between use of cigarettes and use of other drugs, licit and illicit, suggests the potential importance of directing prevention efforts to the early gateway drugs: cigarettes and alcohol (Kandel and Yamaguchi 1985; Clayton 1986; Clayton and Ritter 1985).

Epidemiological Studies of the Progression of Drug Use

Tobacco use has been found to play a pivotal role in the development of other drug dependencies. The classic descriptive model for initiation patterns of drug use was developed by Kandel (1975), who first divided drugs into two groups of availability: licit and illicit. Kandel concluded that virtually all persons who ever used illicit drugs such as marijuana and cocaine had previously used licit drugs such as cigarettes and alcohol. Kandel's developmental stages model is based on the assumption that there are relatively invariant patterns of onset of use. The stages are:

(1) No Use of Any Drugs
(2) Use of Beer or Wine
(3) Use of Cigarettes and/or Hard Liquor
(4) Use of Marijuana
(5) Use of Other Illicit Drugs

Although Kandel's model addresses the initiation or onset of drug use, it does not account for patterns of early use (e.g., frequency of occasions or quantity per occasion). Nonetheless, there is general agreement that the model accurately characterizes the drug initiation process in the United States as one that begins with use of licit drugs (tobacco and alcohol) and, if progression occurs, involves greater use of these substances (Kandel, Marguilies, Davies 1978; Huba, Wingard, Bentler 1981; O'Donnell and Clayton 1982). This pattern has also been observed in France and Israel (Adler and Kandel 1981).

In a longitudinal study of the progression of drug use, Yamaguchi and Kandel (1984a) gathered baseline data in 1971 from subjects in the 10th and 11th grade in New York State. This representative sample was followed up in 1981 when the average age was 24.7 years. The order of onset identified by Yamaguchi and Kandel (1984a) was alcohol, cigarettes, marijuana, illicit use of psychoactive or prescriptive drugs, and other illicit drugs. Among persons who had used both alcohol and cigarettes 10 times or more, alcohol use preceded cigarette use in 70 percent of the cases for males and 55 percent of the cases for females. Among persons who had used cigarettes and marijuana 10 or more times, 67 percent of the males and 72 percent of the females reported using cigarettes first.

Using a sophisticated statistical analysis, Yamaguchi and Kandel (1984a) derived several additional conclusions including the following:

(1) For men, the pattern of progression was one in which the use of alcohol preceded marijuana; alcohol and marijuana preceded other illicit drugs; and alcohol, cigarettes, and marijuana preceded the illicit use of other psychoactive drugs. Eighty-seven percent of the men were characterized by this pattern.

(2) For women, the pattern of progression was one in which either alcohol or cigarettes preceded marijuana; alcohol, cigarettes, and marijuana preceded other illicit drugs; and alcohol and either cigarettes or marijuana preceded the illicit use of psychoactive drugs. Eighty-six percent of women shared this pattern.

Tobacco Use as a Predictor of Other Drug Use

In an analysis of nationwide data from the high school senior class of 1980, Clayton and Ritter (1985) found that alcohol drinking and cigarette smoking were the most powerful predictors of the extent of marijuana use for both males and females. Cigarette use was a stronger predictor of marijuana use among females. Moreover, this role of cigarette smoking was especially pronounced when it had been initiated at age 17 or earlier. Similarly, data from the longitudinal study by Yamaguchi and Kandel (1984a,b) revealed that, among persons with some history of alcohol use, cigarette smoking was a powerful predictor of marijuana use.

Consistent with the above described findings regarding cigarette smoking, smokeless tobacco use has also been shown to be a predictor of other drug use, including cigarette smoking (Ary, Lichtenstein, Severson 1987). More than 3,000 male adolescents were interviewed twice, at an approximately 9-month interval, to determine their rates and levels of use of various psychoactive substances. The main findings were that (1) users of smokeless tobacco were significantly more likely to use cigarettes, marijuana, or alcohol than nonusers; (2) users of smokeless tobacco were significantly more likely to take up use of cigarettes, marijuana, or alcohol than nonusers; (3) smokeless tobacco users who were using these other substances at the time of the first interview showed substantially greater increases in levels of use of these other substances over the 6-month interval than did nonusers of smokeless tobacco; and (4) 71 percent of those who had been using smokeless tobacco at the first interview remained users at the second interview.

Cigarette smoking is also a predictor of cocaine use. White and colleagues (US DHHS 1987) began with a large sample of 12-, 15-, and 18-year-old adolescents in New Jersey and reinterviewed them at 3-year intervals. As reported in NIDA's Triennial Report to Congress (US DHHS 1987), White and coworkers found that there were several predictors of cocaine use in 18-year-olds who had been interviewed 3 years earlier: prior use of cigarettes, alcohol, and marijuana. Furthermore, at the time of the second interview (of the 18-year-olds), the cocaine users used cigarettes, alcohol, marijuana, and other drugs more often than did nonusers of cocaine.

Although alcohol use frequently precedes tobacco use, the use of alcohol only progresses to dependence (alcoholism) in about 10 to 15

percent of all drinkers (Miller 1979). Use of cigarettes, by contrast, almost inevitably escalates to a level characterized as dependent use (Russell 1976; US DHHS 1987). This is consistent with the observation that although some use of alcohol may precede tobacco use, it is prior use of tobacco and not alcohol that emerges in the above-cited studies as the stronger predictor of illict drug use.

The 1985 High School Senior Survey by NIDA (US DHHS 1987) showed that the first dependence-producing drug tried among users of alcohol and illicit drugs was often tobacco. For example, among all respondents 12 years of age and older, first use of tobacco and alcohol occurred in the same year for 18 percent of the sample; cigarettes were used first by 62 percent of the sample, and alcohol was used first by 20 percent. Among those who tried both cigarettes and marijuana, 14 percent first tried these drugs in the same year, 75 percent tried cigarettes first, and 11 percent tried marijuana first. Among those who tried both cigarettes and cocaine, 95 percent used cigarettes first, 3 percent used them first the same year, and only 2 percent used cocaine before cigarettes. These observations show that when cigarettes and another of these dependence-producing drugs have been used by the same individual, cigarette use usually is the first of the two drugs used. One difference between cigarette smoking and the use of other common substances (e.g., milk, sugar, or aspirin) that may also precede the use of illicit drugs is that nicotine itself is a drug that produces the tolerance, physical dependence, and drug-seeking behavior that meet the criteria of a drug-dependence syndrome.

Frequency of Use of Cigarettes and Other Drugs

Measures of frequency of drug use also yield important findings. The data presented in Table 4 show the percentage of persons in three groups (never smoked, tried cigarettes but never used them daily, used cigarettes on a daily basis) who report use of alcohol, marijuana, and cocaine. The criterion for alcohol use is 5 or more consecutive drinks during at least 1 day in the past 30 days; criteria for marijuana and cocaine use involve previous use of these drugs more than 10 times during the respondent's lifetime. These criteria were used to eliminate those who merely tried the drug on a few occasions ("experimental" use). The percentages are presented separately for four age groups.

The main finding shown in Table 4 is that those who become daily cigarette smokers are considerably more likely than others to report use of these other drugs, regardless of age group. For example, among the 12- to 17-year-olds, less than 0.5 percent of the never smokers report using marijuana more than 10 times compared with 3.3 percent of those who tried but never used cigarettes daily and 22.7 percent of those who have used cigarettes daily. These data

TABLE 4.—Use of alcohol, marijuana, and cocaine among "never" cigarette smokers, "occasional" cigarette smokers, and daily cigarette smokers, by age group (percentages)

Age group, drug use	Cigarette use pattern		
	Never smoked	Tried, never used daily	Smoked daily
Alcohol[1]			
12–17	2.7	15.9	38.5
18–25	12.3	31.9	49.6
26–34	9.8	23.0	41.3
≥35	5.6	9.2	20.1
Marijuana[2]			
12–17	0.2	3.3	22.7
18–25	3.3	8.3	37.4
26–34	2.8	12.9	30.3
≥35	0.6	1.8	3.8
Cocaine[3]			
12–17	0.2	0.8	6.4
18–25	1.3	4.5	14.2
26–34	1.8	7.2	15.6
≥35	0.2	0.3	1.9

[1] Drank five or more drinks in a row on at least 1 day in past 30 days.
[2] Used marijuana more than 10 times.
[3] Used cocaine more than 10 times.
SOURCE: National Household Survey on Drug Abuse, 1985. (in preparation)

extend those presented in Table 3: associations exist between cigarette smoking and other drug use when considering "current" use (any use in the past 30 days) (Table 3) or measures of frequency of drug use (Table 4). Similarly, a study of alcohol drinking and cigarette smoking among students in grades 7 to 12 in New York State showed a positive correlation between the frequency of consuming alcoholic beverages and both the likelihood of smoking cigarettes and daily cigarette consumption (Welte and Barnes 1987).

Initiation of Drug Use

Initiation of drug use often occurs through social contacts, independent of the pharmacologic actions of the drug. Drug seeking is then sustained and modulated through combined social and pharmacologic factors. With the possible exception of stimulants such as cocaine and amphetamine, initial exposure to many psychoactive drugs (including opioids, alcohol, and nicotine) is often associated with aversive consequences (Haertzen, Hooks, Ross 1981; Haertzen, Kocher, Miyasato 1983). For example, opioids may produce nausea; alcohol and nicotine not only produce nausea but may

produce initially aversive sensory effects in some preparations (e.g., high-concentration alcoholic beverages may taste "bad" and cigarette smoke may be "harsh"). As a consequence, lengthy periods of occasional ("experimental" or "social") drug use frequently precede the development of daily drug use.

These observations imply that nondrug factors are important in the initiation and maintenance of drug intake until dependence upon the drug itself develops (Crowley and Rhine 1985; Vaillant 1970, 1982; Marlatt and Baer 1988; Brown and Mills 1987). As discussed elsewhere in this Chapter, such factors can also modulate level of drug use as well as influence the frequency of quitting attempts and their likelihood of success (see also Chapters IV and VII in this volume and earlier Reports of the Surgeon General). The specific factors that have been identified and accepted as prominent in helping to establish initial exposure to drugs (Crowley and Rhine 1985) include availability of the drug, cost of the drug, social acceptability of the drug, and other environmental sources of pressure to use drugs.

The acceptability of the drug preparation itself can be manipulated by controlling the dose of the drug and increasing its sensory palatability. For example, the utility of some of the newer smokeless tobacco formulations as "starter" products for youth is held to be due in part to the lower concentrations of nicotine, formulations that facilitate use (e.g., snuff in pouches), as well as nontobacco flavorings (e.g., mint or cinnamon) (Henningfield and Nemeth-Coslett 1988; US DHHS 1986, 1987; Connolly et al. 1986). Such strategies of "starter product" manipulation are analogous to those used to initiate drug seeking in laboratory animals, described later in this Chapter. Such product acceptability factors, combined with the ready availability, peer pressure to use, perceptions that the products were safe, and marketing strategies aimed at increasing the social desirability of smokeless tobacco use, appear to have been largely responsible for the marked rise in use of smokeless tobacco by youth in the 1970s (Ary, Lichtenstein, Severson 1987; Christen and Glover 1987; Connolly et al. 1986; Connolly, Blum, Richards 1987; Glover et al. 1986; Guggenheimer et al. 1987; Kirn 1987; Kozlowski et al. 1982; Marty et al. 1986; Negin 1985; Silvis and Perry 1987; US DHHS 1979; Appendix A).

Vulnerability to Drug Dependence: Individual and Environmental Factors

Despite the complexity of the issues, it is useful to identify factors that differentiate individuals who appear more susceptible to drug dependence. These factors may collectively be termed vulnerability factors. Vulnerability factors are diverse, varying among individuals and within individuals at different times (Radouco-Thomas et al.

1980; Marlatt and Baer 1988; Brown and Mills 1987). Vulnerability may arise from genetic variation or from environmental sources including learning (Jones and Battjes 1985). Vulnerability factors are such that they do not necessarily compel a person to use a drug; in fact, they might be undetected in a person never exposed to a dependence-producing drug. Nonetheless, the presence of several vulnerability factors can increase the likelihood of the development of drug dependence, including cigarette smoking.

The concept of a predisposition to drug dependence arose from the observation that not all people are equally prone to becoming behaviorally dependent upon drugs (Mann et al. 1985; Radouco-Thomas et al. 1980; Jaffe 1985; M.N. Hesselbrock 1986; V.M. Hesselbrock 1986; Mirin, Weiss, Michael 1986). The multiple sources of differences in predisposition or vulnerability to drug dependence are not mutually exclusive. One is a genetic predisposition, shared by family members by virtue of their common biological heritage. Another is an experiential predisposition, shared by family members by virtue of their shared life experiences. For instance, children with parents who are dependent on drugs are at elevated risk of becoming dependent (Hawkins, Lishner, Catalano 1986; Begletier et al. 1984; Kumpfer 1987). For tobacco, the magnitude of the effect is greater when both parents smoke than when only one parent smokes (Borland and Rudolf 1975; Green 1979). Other types of vulnerability factors are physiologic (e.g., pain, sleep deprivation) and psychiatric (e.g., anxiety, depression) conditions that may constitute undesirable states for which relief is sought by use of a drug (Crowley and Rhine 1985). Finally, as discussed earlier in this Chapter, a variety of nonpharmacologic factors are important in the initiation and development of drug dependence (e.g., price, availability); such factors may be considered vulnerability factors in their own right.

A recent area under active investigation is the identification of specific vulnerability factors in youth (Brown and Mills 1987). For example, cigarette smoking has long been associated with juvenile behavior problems (Armstrong-Jones 1927; Welte and Barnes 1987; Kumpfer 1987); more recently, scientific data have confirmed the statistical association of increased rates of cigarette smoking among juveniles with a conduct disorder diagnosis (i.e., adolescent deviance) (Sutker 1984). A related observation is that children with conduct disorders are at elevated risk of using opioids, cocaine, alcohol, tobacco, and other psychoactive drugs (Baumrind 1985). In fact, Kellam, Ensminger, and Simon (1980) found that certain indices of mental health identified in first graders were highly predictive of the use of various psychoactive drugs (including alcohol, opioids, marijuana, and nicotine) when the children were restudied in their teenage years. These studies do not directly address the degree to which juvenile behavior problems are causes or consequences of drug

use. It is plausible that either drug use or other behavior problems can exacerbate each other, possibly alternately contributing to a gradual escalation of drug use, behavior problems, or both. These observations suggest that it is especially important to prevent initiation of drug use among individuals who appear to be at increased risk (vulnerability) to developing drug dependencies.

Pharmacologic Determinants of Drug Dependence

As discussed earlier in this Chapter and in Chapter I, it is the involvement of a dependence-producing drug that sets drug addictions apart from the so-called "addictions" to other substances (e.g., food) and activities (e.g., gambling). There are scientific methods to determine if use of a substance involves a dependence-producing drug. These methods, how they are applied to study drugs such as morphine, cocaine, and nicotine, and some of the main findings from such work are reviewed in this Section.

A wide range of drugs can be used to modify behavior (e.g., as used in psychiatric treatment); however, the term drug dependence is generally reserved for dependencies which involve drugs that can sustain repetitive drug self-administration by virtue of their transient effects on mood, feeling, and behavior. Drugs that exert such effects via alteration of functioning of the brain or central nervous system (CNS) are generally termed "psychoactive" (WHO 1981). When the psychoactivity of a given drug is frequently pleasant, it is referred to as a "euphoriant," as "reinforcing," or as an "abusable" drug, although these terms are not precisely interchangeable. This framework is consistent with that described by Lewin (1931); namely, that these drugs are chemicals which are "taken for the sole purpose of producing for a certain time a feeling of contentment, ease, and comfort." Drugs which produce such effects effectively control the behavior of a wide range of species, including humans.

How Drugs Control Behavior

Drugs cause addiction by controlling the behavior of users; that is, addicting drugs come to influence behavior leading to their own ingestion. The behavioral and pharmacologic mechanisms of such control have been reviewed elsewhere (Thompson 1984) and will only be briefly summarized in this Section. Behavior, including drug taking, is biologically mediated by the electrical and chemical stimuli which arise from the nervous system. These stimuli may originate within the body and brain of the individual, but they may also arise from environmental events and be detected by sensory processes such as vision and audition. Dependence-producing drugs control behavior by activating, inhibiting, or mimicking the existing chemical circuits of the nervous system. Dependence-producing

drugs are those that readily exert control over behavior by virtue of their stimulus properties. It is useful to distinguish among four kinds of stimulus effects produced by dependence-producing drugs.

(1) Drugs can produce *interoceptive* or *discriminative* effects that a person or animal can distinguish from the nondrug state. These effects may set the occasion for the occurrence of particular behaviors. For example, the taste of alcohol or the smell of tobacco smoke can set the occasion for social interactions, and the "priming" effects of a single dose of a drug can lead to subsequent drug seeking and relapse in animals or humans with a history of use (Griffiths, Bigelow, Henningfield 1980; Colpaert 1986).

(2) Drugs may serve as *positive reinforcers* or *rewards* which directly strengthen behavior leading to their administration. The reinforcing efficacy may be related to effects termed either "stimulating," "relaxing," "pleasant," "useful," "therapeutic," or "euphoriant" or may be related to providing relief of withdrawal symptoms or other undesirable states.

(3) Drug administration or abstinence can also function as *"punishers"* or *aversive* stimuli. For example, high-dose levels of most psychoactive drugs serve as an upper boundary level of intake; analogously, decreasing drug levels can also function as aversive stimuli contributing to the strength of drug taking as a means to avoid such aversive effects (Downs and Woods 1974; Goldberg et al. 1971; Henningfield and Goldberg 1983b; Kozlowski and Herman 1984). Aversive stimuli may function as negative reinforcers by strengthening behavior that removes the stimuli (Skinner 1953). Thus, drug withdrawal symptoms are sometimes referred to as negative reinforcers that increase drug seeking.

(4) Drug administration, or abstinence following a period of chronic administration, can serve as *unconditioned stimuli,* in which case they may directly elicit various responses, e.g., vomiting at high-dose levels of opioid administration or during opioid withdrawal, light-headedness produced by rapid smoking, and a strong urge to use a drug. As will be discussed later in this Chapter, repetition of such phenomena can lead to their elicitation by drug-associated stimuli, e.g., the sight or smell of drug-associated stimuli (O'Brien, Ehrman, Ternes 1986; Wikler 1965; Wikler and Pescor 1967).

All of these processes may occur whether or not the person has correctly identified their source, i.e., is "aware" of how the drug led to the behavior (Fisher 1986). Furthermore, the biological power and generality of these processes are evidenced by the findings that they also occur in animals (Young and Herling 1986; Spealman and Goldberg 1978; Johanson and Schuster 1981).

Drugs differ widely in their potential to control behavior via such mechanisms. Dependence-producing drugs usually readily control behavior in all of the above capacities. Quantification of such

characteristics is the cornerstone of testing for the likelihood that use of a drug will lead to addiction. Observers in the 19th and early 20th centuries (e.g., Lewin 1931) had correctly determined that it was the psychological (behavioral) effects (sometimes termed "psychic" or "mental" effects) of substances that led to their habitual use. Practical methods for evaluating the behavior-modifying properties of drugs did not emerge until the behavioral sciences themselves had become sufficiently sophisticated in the 1930s and 1940s. Prior to this time, dependence-producing drugs were identified on the basis of retrospective observations of their effects. Since the 1940s, however, drug testing has grown increasingly reliable at identifying ("screening") drugs for their potential to produce dependence prior to observations of dependence outside the laboratory. In fact, highly reliable information can now be obtained on the basis of animal testing alone (Martin 1971; Thompson and Unna 1977; Brady and Lukas 1984; Bozarth 1987b).

Methods for evaluating the behavior-modifying properties of drugs were largely developed beginning in the 1940s in studies with morphine-like opioids and cocaine-like stimulants, and have only recently been systematically used to evaluate nicotine. The methods will be described in the remainder of this Section, along with a comparison between the behavioral-pharmacologic actions of nicotine and those of other drugs.

Dependence Potential Testing: Psychoactive, Reinforcing, and Related Effects

To scientifically determine if a chemical is dependence producing, a series of scientific tests may be done. These tests are jointly termed dependence potential tests. In this Chapter, Dependence Potential Testing refers to laboratory tests which measure the behavioral and physiological responses of animals and humans to drug administration and to termination of chronic drug administration. Taken together, the results of these tests can be used to objectively predict whether a drug lends itself to self-administration by persons who are exposed. The focus of the present Section is on how the methods are applied to evaluate the potential of drugs to control behavior and to produce transient alterations in mood or feeling that are predictive of self-administration. Such effects have essentially defined the dependence-producing drugs and have set them apart from other medicinals and food; drugs with such effects are sometimes termed "psychotropic" or "behaviorally active" but most commonly as "psychoactive" (President's Advisory Commission 1963; WHO 1981).

Not all psychoactive drugs lead to dependence; many drugs used to treat behavioral and psychiatric disorders are considered to have minimal dependence potential (for example, tricyclic antidepressants) or may actually produce effects that substantially impair long-

term compliance with therapeutic regimens (for example, major tranquilizers). How dependence-producing drugs are distinguished from other psychoactive drugs will be described in this Section. The next Section will discuss methods used to measure test drugs for their potential to produce tolerance and physical dependence.

In reviews and proceedings from various expert committees, the procedures to be described have been referred to as testing for "Abuse Liability," "Psychic Dependence," "Abuse Potential," "Addiction Liability," "Behavioral Dependence," and "Dependence Potential" (Brady and Lukas 1984; Goldberg and Hoffmeister 1973; Thompson and Unna 1977; Seiden and Balster 1985; Thompson and Johanson 1981; Bozarth 1987b; WHO 1981). Whereas there are differences in focus that are evident when these methods are compared, the general goals and strategies are consistent. These will be briefly described in this Section. Detailed descriptions of these methods have been provided by an expert subcommittee of the Committee on Problems of Drug Dependence (Brady and Lukas 1984) and in numerous conferences involving world experts on such procedures (Goldberg and Hoffmeister 1973; Thompson and Unna 1977; Seiden and Balster 1985; Thompson and Johanson 1981; Bozarth 1987b). The results of the methods are also considered in the process of reviewing the national and international regulatory status of various drugs either known or suspected to be addicting by the FDA, the Drug Enforcement Agency (DEA), and the WHO (WHO 1981, 1987).

Effects of Drugs on Mood and Feeling (Psychoactivity)

Dependence-producing drugs can change the way a person thinks, feels, and behaves. The effects may be very subtle (e.g., feelings of relaxation), or they may be profound (e.g., intoxication and impaired cognitive abilities). The scientific assessment of the effects of drugs on mood and feeling (also referred to as "psychoactive," "psychological," "interoceptive," "subjective," "psychic," or "self-reported" effects) was essentially an extension of the methods developed to assess physiological actions of drugs. By the late 1940s, several drug dependence researchers had concluded that physical dependence potential testing was of limited value in predicting whether drug-seeking behavior would develop following exposure to a given drug (Isbell 1948; Isbell and Vogel 1948). These researchers used observational techniques to measure interoceptive drug effects. Later, the reliability and general applicability of the techniques were substantially enhanced by incorporation of the methods developed by Rao (1952) for assessing changes in subjective state and the methods developed by Beecher (1959) for the measurement of pain and analgesia in humans.

These methods contributed to the development of what are generally considered the first objective questionnaires for assessing addictive drug effects by Fraser and his colleagues (Fraser and Isbell 1960; Fraser et al. 1961). A prominent feature of the questionnaires was a series of scales to evaluate the ability to feel or discriminate a drug effect, to rate the liking of the drug effect, and to identify the drug that was given from a list of widely used and abused drugs.

The next major advance in the quantification of subjective drug effects was the development of the Addiction Research Center Inventory (ARCI) by Haertzen and his colleagues (Haertzen, Hill, Belleville 1963; Haertzen 1966, 1974; Haertzen and Hooks 1969; Haertzen and Hickey 1987). The ARCI contained scales that were empirically derived to be sensitive to the effects of specific drugs and drug classes (e.g., sedatives, stimulants, hallucinogens). One of the most useful scales was developed to measure the effects of morphine and benzedrine (a prototypical opioid and stimulant, respectively); this scale was subsequently referred to as the "Morphine Benzedrine Group" or "MBG" or "Euphoriant" scale, because morphine-like and benzedrine-like drugs increased the scale scores while simultaneously producing feelings often reported as pleasurable (Haertzen, Hill, Belleville 1963; Haertzen 1974). Scores on the MBG scale are also elevated by most other addicting drugs (Jasinski 1977; Jasinski, Johnson, Henningfield 1984; Henningfield 1984). More recently, the highly specific drug discrimination testing procedures (described below) have been added to the human drug dependence potential testing armamentarium (Chait, Uhlenhuth, Johanson 1984, 1985).

To the extent to which certain common features are identified using tests such as the above, they may be categorized together, e.g., as dependence-producing or addicting drugs. This is referred to as determining "pharmacologic" equivalence. Conversely, to the extent to which these same drugs differ in certain respects, they may also be subcategorized as, for instance, analgesics, sedatives, or stimulants. Such categorization must be viewed with caution, however, because overemphasis on any particular feature of a drug can be misleading. For instance, morphine, alcohol, and amphetamine can all produce behavioral and physiological effects that are stimulant-like as well as effects that are sedative-like (Gilman et al. 1985; Dews and Wenger 1977). Nicotine has been viewed as both a stimulant ("excitant") (Lewin 1931) and a sedative (Armstrong-Jones 1927). Most commonly nicotine is now categorized as more stimulant-like than sedative-like, but with an appreciation of its diverse range of potential effects, which depend upon the dose given and the measure used (Gilman et al. 1985).

Methods and Results

Assessment of the psychoactivity of drugs in humans essentially entails giving either drug or placebo to volunteers and then asking them to report the nature of effects produced. Replicability and objectivity are increased by using standardized questionnaires such as those described above (e.g., "liking" scales, ARCI). In practice, several procedural variations are used to further enhance the reliability and validity of the results. The dose of the drug is varied to assess the nature of the dose-effect relationships; for all dependence-producing drugs, ratings of dose strength or the percentage of accurate drug identifications is directly related to the dose given. Subjects with histories of use of a variety of drugs can be asked to report which, if any, of those drugs the test drug feels like; such testing is useful to determine the extent to which the test drug produces any effects on mood and feeling that resemble those of previously studied drugs. Subjects with histories of use of a variety of drugs and who report "liking" the effects of a range of drugs can be used to help assess the dependence potential of the test drug by rating how desirable they find it to be.

Incorporation of several of these methods can add considerably to the strength of conclusions which can be drawn. For example, morphine-like opioids, pentobarbital-like barbiturates, amphetamine-like stimulants (including cocaine), alcohol, and nicotine all produce rapidly onsetting and offsetting discriminative effects; the magnitude and duration of these effects are directly related to dose; all elevate scores on the liking and MBG scales; the effects of all are directly (though complexly) related to pharmacokinetic factors such as rate of systemic absorption; all produce discriminative effects that correspond to certain physiological changes; all produce effects that can be accurately identified by an observer; all are identified as known addicting drugs by subjects with a history of use of such drugs; pretreatment with antagonists may block these effects (only opioids and nicotine have been systematically studied on this dimension). Such orderly and consistent kinds of effects across drugs confirm that they are appropriately categorized together as addicting drugs.

The selectivity and sensitivity of such procedures are illustrated in Figure 1. As shown in the Figure, when persons with multiple drug dependence histories were given drugs under double-blind conditions, they rated placebo (unconnected data point on each graph) and the nonaddicting zomepirac at a minimal level of "liking" (Jasinski, Johnson, Henningfield 1984). As a direct function of dose, however, the known addicting drugs were rated with greater liking scores. As also illustrated in Figure 1, nicotine produced comparable dose-related increases in drug liking scores as did amphetamine, morphine, and pentobarbital. Studies with human volunteers have also

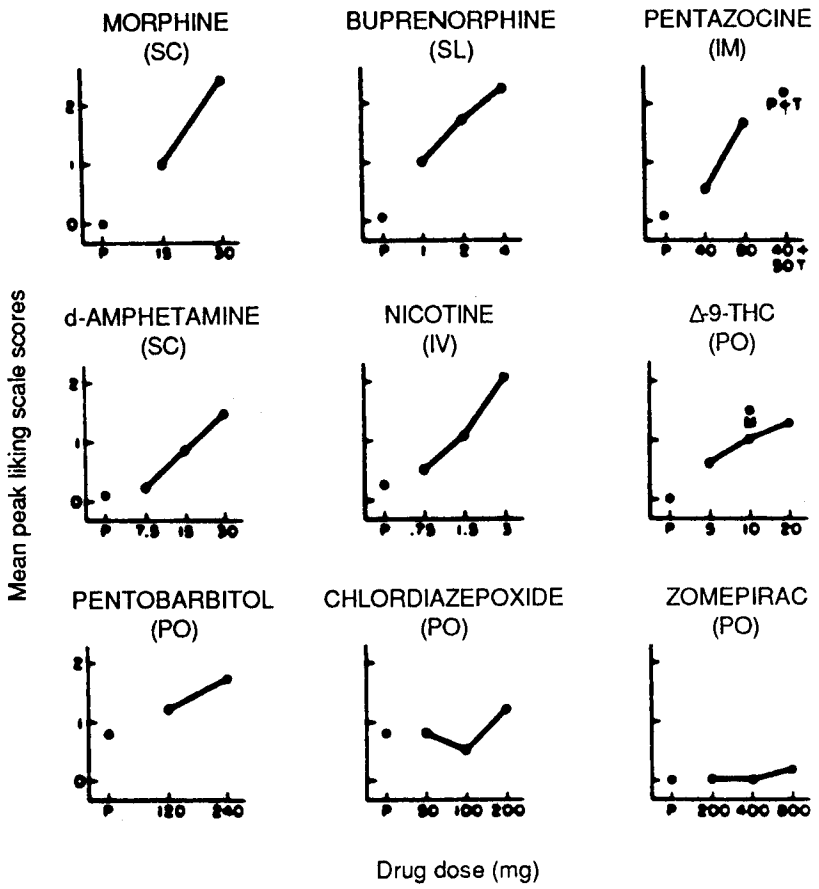

FIGURE 1.—Liking scale scores of the single-dose questionnaire

NOTE: Sample size ranges from 6 (pentobarbital and chlordiazepoxide) to 13 (d-amphetamine). The high dose of each drug (except zomepirac) produced significant ($p<0.05$) increases in scores above placebo. Data are peak response, which occurred from approximately 1 minute (nicotine) to 5 hours (buprenorphine). Morphine and zomepirac data are from the same group of subjects as pentobarbital and chlordiazepoxide data. The P + T point on the pentazocine graph is the score given to 40 mg pentazocine combined with 50 mg tripelennamine. The M point on the Δ-9-THC graph is the score, from the same subjects, obtained after smoking a marijuana cigarette containing 10 mg (1 percent by weight) Δ-9-THC.

SOURCE: Jasinski, Johnson, Henningfield (1984).

shown that most of the known addicting drugs (including nicotine) produced certain changes in mood and feeling that resemble those produced by morphine or benzedrine enough to significantly elevate the MBG scale scores (Griffiths, Bigelow, Henningfield 1980; Henning-field, Johnson, Jasinski 1987).

The validity of self-reported drug effects as objective indices of dependence potential has been tested using similar rating scales by observers who are blind to the condition. On the basis of their observations of subject behavior, observers report similar dose-related increases in scores on the strength of the drug effect and/or the level of drug liking for alcohol (Henningfield, Chait, Griffiths 1983), pentobarbital (Martin, Thompson, Fraser 1974; Henningfield, Chait, Griffiths 1983), morphine and heroin (Martin and Fraser 1961), amphetamine (Jasinski and Nutt 1972; Jasinski, Nutt, Griffith 1974), and a variety of other dependence-producing drugs (Jasinski 1977). A similar correspondence between subject and observer ratings was obtained when subjects were given either i.v. nicotine injections or research cigarettes which varied in nicotine dose (Henningfield, Miyasato, Jasinski 1985).

Effects on mood and feeling also correspond to a variety of physiological effects. Some of these physiological changes vary by drug class. For example, pupil diameter increases appear to correspond to early nicotine-induced subjective effects and to amphetamine and cocaine administration (Henningfield et al. 1983; Jaffe 1985), whereas pupil diameter decreases when morphine is given (Jasinski 1977). Other physiological effects show a greater degree of similarity across drug classes. For example, studies of ethanol administration in human subjects revealed that paroxysmal bursts of electroencephalogram (EEG) alpha activity paralleled subjective reports of euphoria during the ascending limb of the plasma ethanol curve (Lukas et al. 1986b,c), which also paralleled increases in plasma adrenocorticotropic hormone (ACTH) levels (Lukas and Mendelson, in press). Similar effects were observed following marijuana smoking (Lukas et al. 1985, 1986a) and acute i.v. nicotine administration (Lukas and Jasinski 1983). In turn, similar changes in EEG alpha activity have been shown to correspond with subject-reported pleasurable states which can occur in the absence of drug administration (Lindsley 1952; Brown 1970; Wallace 1970; Matejcek 1982).

Drug Discrimination Testing

Drug discrimination testing in animals is assumed to provide information analogous to the above-described procedures for assessing the effects of drugs on mood and feeling in humans (Goldberg, Spealman, Shannon 1981). Drug discrimination testing can provide two general kinds of information. First, the ability of dependence-producing drugs to control behavior by serving as positive reinforcers or punishers is associated with whether they produce interoceptive effects which are discriminated (or "felt"). Second, drugs can be compared with each other to determine the degree to which they are identified as similar or different. The methods used for drug

discrimination testing in animals were not systematized and widely utilized until the late 1960s and early 1970s (Overton 1971; Overton and Batta 1977; Schuster and Balster 1977; Jarbe and Swedberg 1982).

Extension of animal discrimination study results to humans is limited by species differences and by other unique human factors that may contribute to the dependence potential of a drug. Nonetheless, animal studies are an important advance because they permit relatively inexpensive and rapid testing of a broad range of compounds and allow evaluations to be made without the possible confounding social and cultural factors. Animal studies also provide a means of gauging the biological generality of the drug discrimination data (e.g., to determine if unusual genetic characteristics are necessary for certain drug effects).

Methods and Results

These procedures and variations have been described in greater detail elsewhere (Overton and Batta 1977; Colpaert 1986; Rosecrans and Meltzer 1981). In brief, the basic method is to train animals to emit one response when given one drug and to emit another response when given either no drug (i.e., placebo) or a different drug. The animals are usually trained with either food reinforcement or the withholding of electrical shock for "correct" responses. When the animals have been trained to a level of 80 or 90 percent correct responses, they are said to be discriminating drug from placebo. Then they are ready for the testing of different doses of the training drug or different drugs. This testing is often accomplished without the use of food or shock contingencies, so that it can be determined which response the animal will make when given the test drug.

A check on the validity is to give lower doses of the training drug; the lower the dose, the less the animal should respond on the drug lever and the more on the placebo lever. A similar effect is obtained when an antagonist is given before testing with the training drug; as the dose of the antagonist is increased, the ability of the animal to discriminate the training drug decreases and the animal emits more no-drug responses. These effects have been demonstrated with both the opioids and nicotine (Overton 1971; Colpaert 1986; Rosecrans and Meltzer 1981; Chapter III); i.e., decreasing the dose of the opioid or nicotine or pretreating with an opioid or nicotine antagonist can produce decreased drug lever responding.

The specificity of the stimulus produced by a drug can also be evaluated by testing drugs. The degree to which the animals make the "drug" responses or "mistake" the test drug for the training drug is termed "generalization" and indicates the level of similarity of effects between the drugs (Colpaert and Rosecrans 1978). Morphine analogs, amphetamine analogs, pentobarbital analogs, and nicotine

analogs produce substantial amounts of generalization to morphine, amphetamine, pentobarbital, and nicotine, respectively. The fact that there is less generalization across drug classes is an index of the specificity of the drug stimulus. The cross-drug classifications which have resulted from animal discrimination studies are generally consistent with human data (Goldberg, Spealman, Shannon 1981). For instance, if an animal has been trained to press one lever when given amphetamine and another lever when given pentobarbital, it tends to press the amphetamine lever more often than the pentobarbital lever following a nicotine injection (Schecter 1981). This finding is consistent with that obtained in a study in which human volunteers frequently identified nicotine injections as amphetamine or cocaine at higher nicotine dose levels but not at the lower levels and only rarely identified the nicotine injections as sedatives (Henningfield, Miyasato, Jasinski 1985).

A more recent development is the extention of the systematic drug discrimination procedures to use with human subjects. Similar methods are used, and initial findings with drugs such as nicotine and amphetamine are comparable to the results from animal studies (Kallman et al. 1982; Chait, Uhlenhuth, Johanson 1984). Specifically human volunteers can readily learn to differentially respond to the presence or absence of these drugs, and the effects are dose related.

Drug Self-Administration

When given the mechanical means to do so, animals self-administer addicting drugs (including nicotine) much like humans; that is, drugs that function as rewards or reinforcers for humans also tend to function as reinforcers for animals. The conceptualization of dependence-producing drugs as reinforcers provided the framework for a highly predictive test strategy, the self-administration study, whereby animals or humans are given the opportunity to take drugs under laboratory conditions (Thompson and Schuster 1968). This research strategy permitted scientific analysis of the single common link across all forms of drug dependence, namely that the addictive behavior (for whatever reason) is motivated or controlled by the drug's reinforcing (rewarding) properties (Goldberg and Hoffmeister 1973; Thompson and Unna 1977; Seiden and Balster 1985). Stimuli that can maintain and strengthen behavior leading to their presentation are termed "positive reinforcers" regardless of their hypothesized mechanism of action (e.g., alleviation of discomfort or production of pleasure) (Skinner 1953; Thompson and Schuster 1968). The reinforcing power or efficacy of a drug can be enhanced by a variety of conditions (e.g., deprivation of the drug which the organism had been repeatedly given, pain, food deprivation, social approval contingent on drug taking, and perceived useful effects) (Thompson and Schuster 1968; Thompson and Johanson 1981). Following

repeated exposure to a drug, a biologically mediated "drive" state can be established that did not preexist as do the drives for food, water, or sex.

The potential of a drug to serve as a reinforcer can be directly assessed and quantified in laboratory studies of drug self-administration. Essentially, a human or animal subject is given access to the drug; then his or her propensity to take the drug (i.e., to "self-administer" the drug) can be measured. The self-administration test provides the opportunity to rigorously study the main distinguishing feature of drug dependence, that is, drug-seeking behavior. As is the case in drug discrimination testing, animal data help to determine the generality of the biological basis of the addictive process for a given drug; for example, such data help to reveal if the process is unique to humans because of social, genetic, or other factors. If the drug is taken under a variety of prescribed conditions (summarized later in this Section), then it is said to be functioning as a "reinforcer" or "reward."

The validity and generality of self-administration test results were demonstrated by the observations that (1) there was a remarkable degree of consistency between patterns of drug self-administration among laboratory animals and observations concerning human drug dependence (Jasinski 1977; Griffiths, Bigelow, Henningfield 1980), (2) drugs that serve as reinforcers in self-administration studies also tend to be "liked" when given to humans, and (3) there was a high correlation among drugs which produced morphine-like euphoriant effects and those which were self-administered by animals (Griffiths and Balster 1979; Griffiths, Bigelow, Henningfield 1980; see related data in Schuster, Fischman, Johanson 1981).

Initiation of Drug Self-Administration

As discussed earlier in this Chapter, drugs cannot produce dependence without initial exposure to them. Initiation of drug use in humans is often mediated by social and other environmental sources of pressure. To determine if a drug will reinforce behavior in animals similarly requires some means of providing exposure to the drug. Strategies for establishing drug taking in animals are analogous in key respects to how humans may become dependent upon drugs. Four general categories of methods are most commonly used. The methods are not mutually exclusive and are sometimes used in combination.

The first method of establishing drug self-administration in animals is to provide initial doses ("priming" or "free sampling") and then to gradually increase the dose ("graduation"). For instance, i.v. drug infusions may be given to animals on a chronic basis while the animals are also given the opportunities to take the drug. This provides an opportunity to determine if simple exposure to the drug

is sufficient to result in drug seeking. A minor variation is to gradually increase the dose of each injection over time. This general procedure has been used to establish i.v. self-administration of *d*-amphetamine, morphine, alcohol, pentobarbital, cocaine, nicotine, and many other drugs (Deneau and Inoki 1967; Deneau, Yanagita, Seevers 1969; Yanagita 1977; Woods, Ikomi, Winger 1971; Brady and Lukas 1984; Griffiths, Bigelow, Henningfield 1980; Meisch 1987; Henningfield and Goldberg 1983a).

A second method of establishing drug self-administration is to substitute a new drug for one which was already serving as a reinforcer. Humans do this as a function of drug availability; they sometimes learn to like drugs which had not been taken previously and may even come to prefer the new drug. Using this method with animals provides a means of exposure to a new drug and may be useful in comparing one drug with another. In animal studies, cocaine is the most commonly used starter drug, because in animals (as in humans) cocaine seems to be a source of reinforcement and/or pleasure under an extremely broad range of conditions compared with most other drugs. Variations on this procedure have been used to evaluate the likelihood of self-administration of a wide range of drugs including amphetamine, barbiturates, alcohol, opioids, and nicotine (Griffiths et al. 1976, 1981; Woods 1980; Deneau 1977; Yanagita 1977; Griffiths, Bigelow, Henningfield 1980; Brady and Lukas 1984; Meisch 1987; Chapter III).

A third method is to induce the initial use of the test drug by prearranged environmental sources of "pressure" or "motivation." Induction of drug taking can be accomplished with very explicit contingencies. For example, presentation of food or withholding of electric shock can be made contingent on drug consumption (Mello and Mendelson 1971a,b). However, such direct contingencies often result in minimal response output (i.e., drug consumption) to obtain the positive reinforcer or to avoid the electric shock, and drug self-administration may not persist after the contingencies are removed (Mello 1973). For example, even when physical dependence on alcohol had developed in rhesus monkeys, the animals often rejected the drug when self-administration was not required to meet the contingency (Mello and Mendelson 1971a). Thus, these procedures have not been extensively used to generate animal models of human drug taking (Griffiths, Bigelow, Henningfield 1980).

The fourth procedure for establishing drug self-administration seems somewhat more analogous to how drug dependence may sometimes develop in humans outside the laboratory, and has been widely used to study drug self-administration in the laboratory; this method is termed the "adjunctive behavior" or "schedule-induced behavior" strategy (Falk 1983). The method involves a less direct means of inducing drug intake; in fact, the drug does not need to be

taken to obtain the reinforcer or to avoid the punisher. Rather, the animal is simply given the opportunity to take the drug; at the same time, the experimenter arranges conditions that are highly likely to engage the animal in cycles of work and breaking from work. For example, the animal may have to press a lever to obtain food. The result is that when the animal is unable to work on the food schedule (e.g., during the brief "timeouts" or "waiting" periods), the animal tends to take the drug. Eventually, the drug itself might come to function as a reinforcer in its own right, even in the absence of the environmental pressures that first led to its use. The dose level of the drug is then increased gradually over time. Variations on this procedure have been used to establish self-administration of alcohol (Falk, Samson, Winger 1972; Freed, Carpenter, Hymowitz 1970; Meisch 1975), pentobarbital (Meisch, Kliner, Henningfield 1981), nicotine (Singer, Wallace, Hall 1982), and a variety of other drugs (Brady and Lukas 1984; Meisch and Carroll 1981; Meisch 1987). Although many environmental conditions are present outside the laboratory that appear to function as do adjunctive schedules in the establishment of human drug dependence (e.g., boredom in occupational settings), there have been few experimental studies of adjunctive drug taking by humans (Falk 1983). One such study by Cherek (1982) showed that volunteers took more puffs per cigarette when they were given monetary reinforcers at regular intervals: the volunteers had to press a button to obtain the reinforcer, but their behavior did not decrease the time they had to wait for each reinforcer to become available.

Evaluation of Reinforcing Effects

Conclusive demonstration that the effects of the drug itself were the cause of the drug-seeking behavior is equivalent to showing that the drug itself is functioning as a positive reinforcer. The basic procedures were developed in animal studies (Pickens and Thompson 1968; Deneau 1977) and have been reviewed in detail elsewhere (Johanson and Schuster 1981; Balster and Harris 1982; Fischman and Schuster 1978; Yanagita 1980; Brady and Lukas 1984).

The most fundamental procedure is to verify that drug self-administration occurs under conditions in which it is "optional" or "voluntary"; that is, explicit contingencies for drug taking (e.g., to obtain food, to avoid shock, or to obtain preferred liquid) are not required. It is also necessary to ensure that the drug taking is not simply maintained by the characteristics of the vehicle (e.g., water or a flavored solution into which alcohol is placed, or the tobacco smoke in which nicotine is delivered to smokers).

If the drug is serving as a reinforcing stimulus, it should be capable of maintaining controlled behavior. For example, a complex chain of drug seeking (i.e., "procurement") might be required to

obtain the drug. An extension of this principle is to gradually increase the amount of work (i.e., the "cost") that must be expended to achieve drug delivery to determine how much the subject works ("pays") for a given drug or drug dose. For example, the ratio of lever press responses per drug injection is gradually increased in the "Progressive Ratio" procedure to determine the maximum ratio ("breaking point") that will be sustained (Yanagita 1977; Griffiths, Brady, Snell 1978a).

If the drug is serving as a reinforcer, then stimuli associated with drug administration should also come to serve as reinforcers ("conditioned reinforcers"). Of all dependence-producing drugs, the importance of this factor may be most pronounced with regard to nicotine because the various effects of nicotine may be associated with tobacco smoke and other stimuli hundreds of times each day over the course of many years of smoking. A fundamental observation is that even neutral-appearing stimuli can function as reinforcers in their own right when they are associated ("paired") with previously established reinforcers such as food, water, sex, or drugs (Skinner 1953; Thompson and Schuster 1968). For example, the taste and smell of alcohol are initially highly aversive to animals (Mello 1973), but in one study, the smell of alcohol was established as a conditioned positive reinforcer for animals: the smell of alcohol was enough to reinstate drug-seeking behavior even when the alcohol was not physically available (Meisch 1977). Seemingly arbitrary stimuli such as lights and tones can come to serve as reinforcers after association with i.v. self-administered drugs including cocaine-like stimulants, opioids, barbiturates, and nicotine (Goldberg 1970; Goldberg, Kelleher, Morse 1975; Griffiths, Bigelow, Henningfield 1980; Goldberg et al. 1983).

The basic methods described above are also used in human drug self-administration studies, although with various procedural adaptations which have been described in detail elsewhere (Nathan, O'Brien, Lowenstein 1971; Cohen, Liebson, Faillace 1971; Mello, McNamee, Mendelson 1968; Mello 1972; Meyer and Mirin 1979; Bigelow, Griffiths, Liebson 1975; Henningfield, Lukas, Bigelow 1986). As in the animal drug self-administration studies, the human volunteers must emit a measurable response that may lead to drug ingestion: for example, riding an exercise bicycle (Griffiths, Bigelow, Liebson 1979; Jones and Prada 1975) or pressing a button on a portable work station (Mello and Mendelson 1978). Such work requirements then become established as part of the chain of drug-seeking behavior. They have an advantage over non-laboratory drug-seeking behavior in that the amount of work can be carefully measured. Such data provide quantitative estimates of the time and/or work expended for drugs (see examples in the following studies and reviews: Johanson and Uhlenhuth 1978; Bigelow,

Griffiths, Liebson 1975; Mello and Mendelson 1978; Fischman and Schuster 1982; Henningfield and Goldberg 1983b; Jasinski, Johnson, Henningfield 1984).

Results from Drug Self-Administration Studies

Most categories of drugs which have been found to cause widespread drug dependence in the nonlaboratory setting have been tested with animals and humans in laboratory settings. Results of these studies have been reviewed in detail elsewhere (Griffiths, Bigelow, Henningfield 1980; Brady and Lukas 1984; Henningfield, Lukas, Bigelow 1986). Several categories of drugs have been found to be self-administered by humans and animals in the laboratory settings, to meet criteria as positive reinforcers, and to exhibit orderly relations as a function of drug dose, drug pretreatment, and other factors known to affect the intake of dependence-producing drugs. These include alcohol, morphine, pentobarbital, amphetamine, cocaine, and nicotine in the forms of cigarettes and i.v. injection.

Self-administration studies with animals are much more extensive and have also been reviewed in detail elsewhere (Johanson and Schuster 1981; Balster and Harris 1982; Fischman and Schuster 1978; Yanagita 1980; Brady and Lukas 1984; Young and Herling 1986). In brief, drug self-administration studies in animals in the 1960s showed that a range of drugs including opioids, amphetamines, barbiturates, certain organic solvents, alcohol, cocaine, and nicotine were self-administered (Weeks 1962; Thompson and Schuster 1964; Deneau, Yanagita, Seevers 1969; Deneau and Inoki 1967). All of these drugs were found to maintain powerful chains of drug-seeking behavior, even when insufficient drug was taken to produce a clinically significant degree of physical dependence (Goldberg, Morse, Goldberg 1976). Drugs that did not serve as reinforcers in these studies included caffeine, lysergic acid diethylamide (LSD), and the major tranquilizer chlorpromazine.

The speed of drug delivery can affect its reinforcing efficacy (Kato, Wakasa, Yanagita 1987). Thus, the inhaled form of cocaine (“crack”) is considered more reinforcing and dependence producing than other forms of cocaine delivery, with oral cocaine apparently among the least reinforcing of the commonly used routes of delivery (see also US DHHS 1987). Analogously, nicotine taken by the slow release oral preparation (nicotine polacrilex gum) appears to be much less reinforcing than nicotine taken by quicker release oral preparations (e.g., chewing tobacco) or cigarette smoke (Chapters IV and VII).

Research findings have continued to extend the early observations (Deneau, Yanagita, Seevers 1969) that the results with animals were remarkably consistent with observations regarding human drug dependence. For example, initial exposure of humans to drugs such

as opioids and stimulants led to addictive patterns of use, whereas chlorpromazine rarely did, and LSD infrequently did (Jasinski 1977; Griffiths et al. 1980). Earlier studies had suggested that alcohol, caffeine, and nicotine were not reinforcers in animals (Mello 1973; Russell 1979; Griffiths et al. 1986). However, by the early 1970s for alcohol (Meisch and Thompson 1971; Meisch 1977, 1982) and 1981 for nicotine (Goldberg, Spealman, Goldberg 1981), it had been confirmed that these drugs could also serve as effective reinforcers for nonhumans. The relatively little research done to assess the dependence potential of caffeine has not as conclusively demonstrated that it serves as a reinforcer in animals (Griffiths and Woodson 1988b).

Drug Dose as a Determinant of Drug Intake

Drug dose per administration is a major factor that affects self-administration of dependence-producing drugs. The resultant dose-response relationships are orderly, and the data have been reviewed extensively (Griffiths, Bigelow, Henningfield 1980; Johanson and Schuster 1981; Young and Herling 1986). In brief, the relationship between the dose size available and the number of doses taken is often referred to as an inverted U-shaped function because of the shape of a graph that results when the number of injections (y-axis) is plotted as a function of dose (x-axis) across a wide range of doses to which a subject is given access.

Over the range of doses which appear to be functioning as effective reinforcers, changes in dose are accompanied by compensatory changes in number taken such that total drug intake is somewhat stabilized. It appears that a determinant of such compensatory changes in drug self-administration is the apparent upper and lower "boundaries" or "thresholds" for aversive effects that might occur when either too much drug is obtained or when insufficient drug is obtained to prevent withdrawal responses (Kozlowski and Herman 1984). It should be noted, however, that in most studies, compensatory changes in drug intake as dose level is changed are almost never perfect and are frequently quite crude (Griffiths, Bigelow, Henningfield 1980). (See Yokel and Pickens 1974 for an example of a study in which drug intake was unusually stable across a range of amphetamine doses.) Thus, the usual observation related to drug dose is that as dose is increased, the rate of drug taking decreases somewhat but more total drug is obtained. This relationship is observed in studies of i.v. nicotine in animals (Goldberg et al. 1983) and humans (Henningfield, Miyasato, Jasinski 1983) and when tobacco smoke dose is manipulated in humans (Chapter IV).

A misinterpretation of dose-response relationships by tobacco researchers, largely in the 1970s, led to the controversy that marked the so-called "titration studies" of tobacco intake. Specifically, it was

assumed that if a drug was serving as a reinforcer, then compensation for changes in dose level should have been more effective than they appeared to be. Hence, some questioned whether nicotine was serving as a reinforcer because dose-response relationships in nicotine studies appeared very crude (Russell 1979). The question that arose was not whether cigarette smokers showed compensatory changes in responses to changes in dose level; they did. In fact, the nicotine dose-response relationship has probably been better studied and established, over a wider range of conditions and techniques of study, than have dose-response relationships with any other class of drugs which are self-administered by humans (Gritz 1980; Griffiths, Bigelow, Henningfield 1980; Henningfield 1984). The question was, rather, why compensatory changes in cigarette smoke intake often appear to be inadequate to maintain stable levels of nicotine intake. There are two main problems in interpreting these data, however. The first is that in the vast majority of human cigarette smoking studies, attempts to manipulate the dose delivered were not well controlled and the measures used to assess the possible effects of intended dose manipulations were not necessarily sensitive to compensatory changes (see Chapter IV and Henningfield 1984b). The second problem is that there is simply no basis for determining what degree of compensation *should* occur, because the degree of compensation observed in animal studies varies widely by drug and test condition, and because there are relatively few human data involving drugs other than nicotine to which such a comparison might be made (Griffiths, Bigelow, Henningfield 1980; Henningfield, Lukas, Bigelow 1986).

Cost of the Drug as a Determinant of Intake

Cost of the drug is a determinant of intake in both laboratory and non-laboratory settings. Evaluation of this phenomenon is objectively carried out in the laboratory in which the amount of work required to obtain the drug can be varied. From an economic perspective, this is similar to varying the price of the commodity which is available for purchase. Such manipulations with both humans and animals have shown that cost (e.g., amount of work required) affects drug intake: usually, the lower the cost, the greater the intake. In some studies manipulations of both cost and drug dose have been carried out (e.g., Moreton et al. 1977; Lemaire and Meisch 1985). These studies show that when the dose of the drug is reduced, drug-seeking behavior may increase at first and thereby maintain fairly stable intake, but if dose continues to decrease (or cost continues to increase), the behavior will not be maintained (Lemaire and Meish 1985). Early studies with cocaine, for example, showed that if access to cocaine was limited, either by time or work ("cost") requirements, cocaine self-administration could be maintained indef-

initely without serious apparent adverse effects (Pickens and Thompson 1968). However, if access to cocaine was nearly unlimited and the cost requirement low, monkeys might self-administer toxic dose levels (Deneau, Yanagita, Seevers 1969).

Use of tobacco in humans and intravenous nicotine self-administration by animals appear to be similarly affected by manipulations of cost as is use of other dependence-producing drugs. Specifically, as the amount of work required to obtain nicotine injections in animals is increased, the number of injections is decreased (Goldberg and Henningfield, 1988). Analogously, human cigarette smokers and other drug users can also be motivated with both positive and negative cost incentives (Bigelow et al. 1981; McCaul et al. 1984; Stitzer et al. 1982, 1986; Stitzer and Bigelow 1985). These laboratory findings with animals and humans correspond to the effects of changes in the price of cigarettes on cigarette sales (Lewit, Coate, Grossman 1981; Lewit and Coate 1982; Warner 1986a). Such relationships are also observed with other dependence-producing drugs including opioids, sedatives, alcohol, and amphetamines (Griffiths, Bigelow, Henningfield 1980; Yanagita 1977).

Place Conditioning Studies

Ingestion of dependence-producing drugs can lead to both positive and negative associations with the setting in which the drug effects were experienced. Whether the effects of a particular drug are positive or negative depends on the dose that was given and other factors that are discussed in this Section.

A scientific methodology for studying such phenomena is the "place-conditioning" or "place-preference-aversion" procedure (Bozarth 1987a). This procedure provides an indirect means of assessing the potential of a drug to establish drug seeking in the absence of any explicit contingencies on the behavior. These procedures determine if exposure to a drug in a given environmental setting enhances the preference of the animal for that setting. Conversely, the procedure can be used to determine if exposure to a drug in a specific environmental setting establishes an aversion of the animal to that setting.

Because of their convenient size and the general validity of their use as models for behavioral dependence potential testing, rats most commonly are used as subjects in place-conditioning studies. The general experimental procedure is to place the animal in one environment (e.g., one chamber of a multiple-chamber test apparatus) when a drug is given and in another environment (e.g., distinct in color, shape, or odor) when a placebo is given. Then, the animal is given access to both environments (i.e., placed in a connecting passage or placed in one chamber or the other) to determine which environment (chamber) it prefers (van der Kooy 1987; Bozarth

1987a), and, conversely, which environment it avoids. Studies have shown that conditioned preferences can be established for morphine (Bardo and Neisewander 1986), cocaine (Spyraki, Fibiger, Phillips 1982), alcohol (Stewart and Grupp 1985), and nicotine (Fudala, Teoh, Iwamoto 1985; Fudala and Iwamoto 1987; Chapter IV).

The relevance of place conditioning as a factor that increases the control of nicotine over behavior in human cigarette smokers may exceed that of other dependence-producing drugs. This possibility follows from the fact that the cigarette smoker has the ability to readily produce a critical environmental cue associated with smoking (cigarette smoke itself). Therefore, it should be possible for the smoker to "enhance" the reinforcing efficacy of a range of environments (Iwamoto et al. 1987); the highly discriminating sight, smell, and taste stimuli produced by tobacco smoke may effectively permit the smoker to establish a "preferred environment." This could contribute to the dependence potential of nicotine. The observation is also consistent with the finding that removal of the tobacco smoke-associated stimuli is accompanied by decreased pleasure and/or smoking (Gritz 1977; Goldfarb et al. 1976; Rose et al. 1987). As early as 1899 it was observed, for example, "that the pleasure derived from a pipe or cigar is abolished for many persons if the smoke is not seen, as when it is smoked in the dark" (Cushny 1899).

Constraints on Dependence Potential Testing

The main constraint on procedures used to evaluate the dependence potential of drugs is that they may fail to identify drugs which only lead to dependence under unusual or uniquely human circumstances. For example, LSD does not serve as an effective reinforcer for animals, and although its effects may be liked by humans under certain conditions, it also produce feelings of fear, paranoia, and other adverse effects (Griffiths, Bigelow, Henningfield 1980; Haertzen 1966, 1974). Caffeine provides an example of another kind of drug which is sometimes used in the face of adverse effects, even though the overwhelming majority of users do not use it in ways that are considered to be of significant adverse health effect (Gilbert 1976; Greden 1981). The anticholinergic drug atropine is another that is representative of a class of drugs that occasionally are used in nontherapeutic settings but do not appear to possess a marked dependence potential when objectively tested (Penetar and Henningfield 1986).

The wide range of factors that may result in occasional harmful use of some substances (e.g., caffeine) or which may contribute to the use of dependence-producing substances such as nicotine (Chapters IV and VI) is not routinely explored in current laboratory dependence potential tests. Thus, these drug dependence potential testing procedures appear more likely to underestimate than to overesti-

mate the pharmacologic potential of a drug to cause dependence outside of the laboratory. Furthermore, as discussed by Katz and Goldberg (1988), because a variety of drug and nondrug factors determine the actual prevalence of drug dependence outside of the laboratory, dependence potential data are most reliable when drawing qualitative conclusions. For example, such data are used to determine whether a drug is dependence producing, or whether it is more sedative- or stimulant-like.

Dependence Potential Testing: Tolerance and Withdrawal

In addition to taking control over behavior by virtue of reinforcing and other behavior modifying effects, many addicting drugs can also produce a physiological change termed physical dependence. Once physically dependent, the person may experience an even greater loss of control over use of a particular drug because abstinence from the drug may be accompanied by discomfort and heightened urges to take the drug (withdrawal syndrome).

Technically, physical dependence refers to physiological and behavioral alterations that become increasingly manifest after repeated exposure to a pharmacologic agent. As noted earlier, the primary indication of physical dependence is the observation of drug-abstinence-associated withdrawal signs and symptoms, although tolerance is a frequent concomitant (Kalant 1978; Cochin 1970; Kalant, LeBlanc, Gibbins 1971; Eddy 1973; Clouet and Iwatsubo 1975; Yanagita 1977). This phenomenon is also referred to as "neuroadaptation" or "physiological" dependence (WHO 1981; Woolverton and Schuster 1983). It should be noted that use of the term "physical" imports no greater degree of objectivity to phenomena associated with physical dependence than to the phenomenon of compulsive drug seeking: both physical dependence and drug seeking involve physiologically mediated drug receptor interactions that vary with the dose, kinetics, and type of drug. Furthermore, both of these kinds of drug-associated phenomena involve behavioral and physiological effects. For example, conventional measures of physical dependence include responses that are often considered behavioral (e.g., urge to use a drug, sleep time, food intake).

Research on opioid dependence in the 1940s focused largely on the physical dependence that developed when opioids were given to humans or certain animals (Martin and Isbell 1978). In particular, characterizing the level of tolerance that was acquired when morphine was repeatedly given, as well as the behavioral and physiological sequelae of abrupt termination of such administration, was a major contribution to the development of objective methods for testing dependence-producing drugs in general. Observations emerging from such research in the 1940s led to strategies that are still accepted as the definitive means to measure what may be termed the

TABLE 5.--Observations pertaining to the evaluation of physical dependence potential, derived from studies of morphine-like drugs

1.	Repeated drug administration leads to diminished responsiveness (i.e., tolerance) that is more or less complete, depending upon the response measured. Responsiveness might be at least partially overcome by increasing the dose. The degree of tolerance that develops is generally directly related to the overall dosing level, but varies widely across various possible measures.
2.	The establishment of tolerance to one opioid is shared among many opium-derived and related chemicals; the principle of "cross-tolerance" emerged as one means to further classify a dependence-producing chemical.
3.	Abrupt termination of use leads to behavioral and physiological responses that often tend to be opposite of responses produced by acute drug administration. When these opposite responses actually exceed normal baseline levels (e.g., opioid-induced constipation may be replaced by diarrhea for a few days). they are termed "rebound" responses; hence the frequent labeling of withdrawal as "rebound syndrome." Together, these responses are termed "the withdrawal syndrome."
4.	Severity of the withdrawal syndrome is related to the duration and dose levels of preabstinence exposure to the drug.
5.	During withdrawal, readministration of the chronically given opioid can reverse the signs and symptoms of the syndrome.
6.	A range of opioids can substitute for the one to which an organism was chronically exposed, thereby maintaining the level of physical dependence and preventing the onset of a withdrawal reaction. These same drugs can be used to reverse the syndrome of withdrawal precipitated by removal of the chronically given opioid. This observation provided the rational basis for the systematic development of "substitution" or "replacement" therapy for drug dependence.

NOTE: Details of the original experiments, and subsequent research upon which these observations follow. have been reviewed (Martin and Isbell 1978; Martin 1977; Sharp 1984; see also Deneau 1977).

"physical dependence potential" of a chemical (Jasinski 1977). Specifically, these tests could be used to evaluate the likelihood that (1) repeated use of a drug would lead to tolerance (physiological adaptation) such that effects of repeated use would diminish and (2) abrupt abstinence would be accompanied by a syndrome of behavioral and physiological disruption (withdrawal syndrome). Table 5 summarizes the prominent observations that emerged from these early studies (Martin and Isbell 1978; Martin 1977). These observations provide the conceptual framework within which physical dependence is assessed (Thompson and Unna 1977).

Tolerance

As noted earlier, repeated ingestion of most dependence-producing drugs leads to diminished effects unless larger doses of the drug are taken: this phenomenon is termed tolerance. One reason that tolerance is an important factor in drug dependence is that it may contribute to the escalation of drug self-administration that occurs over time. This relationship is often misinterpreted, however. Specifically, it is sometimes stated that tolerance results in a

continuous escalation of drug dose; however, lethal or aversive dose levels prevent indefinite escalation.

Procedures for assessing tolerance development rely heavily on procedures developed for assessing the direct effects of drugs (Kalant, LeBlanc, Gibbins 1971; Abood 1984). Because psychoactive drugs exert effects on numerous physiological systems and behavioral responses, almost any of a wide range of response measures can serve in studies. Perhaps the most fundamental strategy of tolerance assessment is to repeatedly present a given drug dose while measuring the subsequent responses to drug administration. When the response diminishes across drug presentations, tolerance to that response is said to have occurred. Among the most frequent measures of tolerance which have been used to assess psychoactive drugs are discrimination of drug administration, analgesia, heart rate, nausea, sedation, EEG activity, and performance on a behavioral task. Some measures (e.g., sedation from barbiturates) are more specific to certain drug classes, whereas others (e.g., pleasurable and dysphoric effects) are useful across a wider range of psychoactive drugs. A variation on the foregoing procedure is to increase the drug dose after responses have diminished to determine if the original response level can be partially or completely restored.

Cross-Tolerance

Cross-tolerance is demonstrated when pretreatment with one drug or formulation type produces tolerance to another drug or formulation type (Wenger 1983; Yanura and Suzuki 1977; Martin and Fraser 1961). For example, a person who is maintained on an adequate dose level of methadone will experience relatively little effect if he or she injects his or her usual dose of heroin (Kreek 1979). Similarly, persons given nicotine polacrilex gum may experience attenuated effects from cigarettes, including reduced satisfaction from smoking (Nemeth-Coslett et al. 1987).

Mechanisms of Tolerance

Several mechanisms of tolerance can be differentiated (Kalant, LeBlanc, Gibbins 1971; Abood 1984; Haefely 1986; Sharp 1984; WHO 1981). For instance, if a drug impairs the ability to perform a task that produces some form of reinforcement (e.g., humans working for money or animals pressing a lever for food), the performance may return to predrug exposure levels after repeated drug exposure over time. In this example, at least four distinct mechanisms of tolerance may have been operational; they are not mutually exclusive and may co-occur (Kalant, LeBlanc, Gibbins 1971; Abood 1984; Haefely 1986; Sharp 1984; WHO 1981; Eikelboom and Stewart 1979; Siegel 1975, 1976).

(1) The rate at which the drug was eliminated from the blood by metabolism (detoxification) or excretion (in urine, feces, sweat, or expired air) may have increased. This is frequently termed "dispositional" or "metabolic" tolerance. A general method used to assess dispositional tolerance is to measure the rate of decline in plasma drug levels after varying amounts of drug exposure.

(2) The response at the cellular level might have decreased as the drug receptor physiologically adapted to the drug or as the number of receptors was altered (thereby functioning as though the systemic dose had been reduced). This is frequently termed "functional" or "pharmacodynamic" tolerance. One method used to assess functional tolerance is to hold the plasma drug levels constant while measuring the response after varying amounts of drug exposure.

(3) The learning and motivational aspects of a behavioral situation may have resulted in compensatory behaviors that reduced the magnitude of the performance effects. This is frequently termed "behavioral" tolerance, "drug sophistication," or "behavioral adaptation." Behavioral tolerance can be assessed by presenting the drug at such long intervals so as to minimize the possible development of functional or metabolic tolerance (e.g., Stitzer, Morrison, Domino 1970), or by using a variety of other controlled procedures (Krasnegor 1978b).

(4) Another behavioral mechanism that can lead to the development of tolerance results from the classical or Pavlovian conditioning process that may occur where a drug is given. Pavlov (1927) found that drug administration could produce an unconditioned response that could subsequently occur as a conditioned response to an associated environmental stimulus. However, sometimes the conditioned response is opposite that of the drug response (Siegel 1975); when a drug-opposite response has been established, this conditioning mechanism may reduce the strength of the response to the drug itself (Goudie and Demellweek 1986).

The kinds of tolerance described above are sometimes categorized together as "acquired" tolerance, which emphasizes the fact that they have developed in an organism as a function of drug exposure (WHO 1981). Tolerance development can be affected by the unit drug dose, total daily dose, route of administration, prevailing environmental stimuli, and exposure dynamics (exposure dynamics refers to whether exposure to a drug is relatively continuous (Way, Loh, Shen 1969) or via multiple, discrete doses (Lukas, Moreton, Khazan 1982)) (see also, Dewey 1984; Adler and Geller 1984; O'Brien 1975; Bläsig et al. 1973; Okamoto, Rao, Walewski 1986). Acquired tolerance has been demonstrated to occur with opioids and with most nonopioid dependence-producing drugs, including nicotine (Martin 1977; Kalant, LeBlanc, Gibbins 1971; Abood 1984; Haefely 1986; Domino 1973; Chapter III). In fact, classic techniques of measuring tolerance

evolved in a series of studies involving nicotine by Langley, Dixon, and others near the end of the 19th century (Langley 1905; Dixon and Lee 1912); these researchers found that tolerance to nicotine was rapid and could be partially overcome by increasing the dose.

Constitutional Tolerance

Historically, although less commonly in recent years, tolerance has been used to differentiate individuals or populations with regard to their "preexisting" or "constitutional" level of drug responsiveness (Shuster 1984). This phenomenon has been designated "initial" tolerance by a subcommittee of the WHO (WHO 1981) and is also often referred to as "drug sensitivity" or "innate drug responsiveness." The mechanisms may be similar to those described above; for example, individuals may be born with differing numbers of receptors for a particular drug or with different abilities to detoxify a drug on the basis of enzymatic capacity of their liver. Analogously, for reasons that are not related to drug exposure, certain populations or individuals may be more effective in general at behaviorally compensating for impediments to learning or performance. Genetic, dietary, and early (including prenatal) developments are possible sources of such variation that are under study (Abood 1984).

Whereas a fairly wide range of variation among such preexisting levels of drug sensitivity has not been shown to affect the course of development of drug dependence, extreme or qualitative differences may have some impact. Such differences are sometimes held to alter the vulnerability of various individuals or populations to the development of drug addiction. One apparent example of such an effect is the markedly higher percentage of Oriental persons who, compared with most other populations in the United States, show an aversive reaction to alcohol ("flushing" response). This reaction results from slower metabolism of the alcohol metabolite, acetylaldehyde, in Orientals compared with many other ethnic groupings (Nagoshi et al. 1987). However, cultural factors also appear to strongly influence rates of alcohol use in Orientals so that even persons who show the flushing response may develop alcoholism (Sue 1987; Johnson et al. 1987).

Differences in constitutional levels of tolerance among individuals have been observed for all dependence-producing drugs, including nicotine (Chapter II). However, the importance of such individual and/or population differences remains unclear. In fact, a remarkable feature of opioids, sedatives (including alcohol), and stimulants (including nicotine) is the degree to which use has become entrenched in nearly any culture into which they have been introduced (Austin 1979). Similarly, initial exposure to opioids, sedatives, alcohol, cocaine-like stimulants, and nicotine has been shown for each to lead to drug-seeking behavior in a wide range of animal

species including primates, dogs, and rodents (Deneau 1977; Yanagita 1977; Woods, Ikomi, Winger 1971; Brady and Lukas 1984; Griffiths, Bigelow, Henningfield 1980; Meisch 1987; Meisch and Carroll 1981).

Withdrawal Syndromes

As discussed earlier, documentation of a drug withdrawal syndrome is the primary line of evidence used to decide whether a particular drug can cause physical dependence. The methods used to properly conduct such tests and provide definitive results are complex. This Section provides a summary of how such tests are conducted and some of the main findings from tests of drugs such as morphine, pentobarbital, and nicotine.

Measurement of drug withdrawal phenomena entails recording physiological, subjective, and behavioral responses that occur when drug administration is terminated, as well as those that occur following drug administration. If the organism has developed a sufficient degree of tolerance, such that levels of drug which formerly disrupted physiological and behavioral functioning have become necessary for relatively normal functioning, then the organism is said to be physically dependent. Such drug abstinence-induced disruption of functioning is termed a drug "withdrawal" or "abstinence" reaction or syndrome. The behavioral and physiological responses include some that are opposite those produced by drug administration. For instance, opioid-induced pupillary constriction, alcohol-induced muscle relaxation, and nicotine-induced tachycardia may be replaced by pupillary dilation, convulsive muscle activity, and bradycardia, respectively. Each drug withdrawal syndrome is unique to a particular drug class and animal species and also varies somewhat within individuals of a given species which are tested with the same drug. Both frequency and magnitude of withdrawal responses are typically measured.

In human studies, the range of measures available to assess withdrawal reactions is considerable. They may be designated by three categories: autonomic (e.g., blood pressure, pulse, core temperature, respiratory rate, pupillary diameter, diarrhea), somatomotor (e.g., nociception, neuromuscular reflexes, auditory and visual evoked potentials), and behavioral (e.g., irritability, sleep/awake cycle, hunger, urge to take the drug, i.e., "craving"). Himmelsbach and Andrews (1943) incorporated these distinctions into a weighted-point system used for rating the severity of these signs and symptoms of withdrawal (Fraser and Isbell 1960; Jasinski 1977). Refinements in the scaling of opioid withdrawal responses have continued (e.g., ARCI, weak opiate withdrawal scale) (Haertzen 1966; Bradley et al. 1987; Handelsman et al. 1987).

Opioid withdrawal phenonena remain the most rigorously studied and well characterized among the dependence-producing drugs. In part, this is because of the ready observability of many of the signs (e.g., dilated pupils, sweating, diarrhea). Other drugs for which withdrawal reactions are now known or suspected to occur in humans (e.g., amphetamine, cocaine, marijuana, phencyclidine) have been much less thoroughly studied than the opioids and sedatives (Mendelson and Mello 1984; Jones and Benowitz 1976). Studies with these drugs are also hindered by the fact that there are fewer readily observable signs of withdrawal, placing a greater burden on sophisticated technology (e.g., EEG and neurohormonal assessment) and procedures (e.g., performance assessment).

Two basic methods are used to measure withdrawal reactions. After a period of chronic drug administration, behavioral and physiological responses are measured following either abrupt drug abstinence ("spontaneous withdrawal") or the administration of a drug antagonist ("precipitated withdrawal") (Thompson and Unna 1977; Martin 1977).

Spontaneous Withdrawal Syndromes

Experimental studies of spontaneous withdrawal reactions include two procedures for obtaining subjects which have been chronically exposed to the drug. One procedure, termed the "direct addiction" procedure, is to administer the drug to the subject at gradually increasing dose levels, then to stabilize the dose for a predetermined time interval. Drug administration is then abruptly discontinued, and withdrawal measures are taken. This method has been used to study withdrawal from opioids, barbiturates, benzodiazepines, stimulants, ethanol, PCP, and gaseous anesthetics in a number of animal species and humans (Brady and Lukas 1984). A variation on this procedure is to abruptly withdraw subjects from a drug which they had been chronically receiving in the nonlaboratory environment. In human subjects, withdrawal reactions following cessation of use of opioids, alcohol, nicotine, sedatives, and other drugs have been studied using this procedure (Brady and Lukas 1984; Chapter IV).

A second procedure, termed the "substitution procedure," involves maintaining subjects at a given dose level of a standard or baseline drug; periodically, doses of the standard drug are replaced with either a placebo or a test drug to determine if there are signs of withdrawal that occur before the next dose of the baseline drug (Fraser 1957). This procedure provides information analogous to that obtained from studies of cross-tolerance; namely, it permits determination of whether cross-dependence exists. If the test drug prevents the expected onset of a withdrawal syndrome that should have accompanied abstinence from the maintenance drug, then it is possible that the two drugs produce similar kinds of physical

dependence. Because it is possible to suppress certain withdrawal responses by using unrelated drugs (e.g., clonidine can suppress certain aspects of morphine and nicotine (Jasinski, Johnson, Henning-field 1984)), a variety of control procedures are necessary to identify the mechanism by which the replacement drug suppressed the withdrawal responses (Martin 1977; Deneau and Weiss 1968; Yanagita and Takahashi 1973; Okamoto, Rosenberg, Boisse 1975; Jones, Prada, Martin 1976; Yanaura and Suzuki 1977).

In human subjects, both the direct addiction and substitution strategies were used to evaluate withdrawal reactions from opioids, barbiturates, and alcohol at the Addiction Research Center in the 1940s and 1950s (Himmelsbach 1941; Himmelsbach and Andrews 1943; Isbell et al. 1950, 1955). However, since those classic studies, most dependence potential studies in humans have been conducted with subjects who had been using the drug in a nonexperimental setting prior to the study. The effects of abstinence from chronic administration of opioids, barbiturates, benzodiazepines, caffeine, and nicotine have been studied using these variations of spontaneous withdrawal assessment (Benzer and Cushman 1980; Charney et al. 1981; Jaffe et al. 1983; Griffiths and Woodson 1988a; Greden 1981; Hatsukami, Hughes, Pickens 1985; Chapter IV). A disadvantage of such approaches is that it is not always possible to stabilize the subjects at a known dose level, which results in considerable cross-subject variation. The consequence of such dose-related variability is that it can raise the threshold for the detection of significant effects. This source of variability probably contributed to some of the earlier inconsistent findings regarding the nature and severity of withdrawal reactions from tobacco (see further discussions in Murray and Lawrence 1984). Early in the 20th century, analogous seemingly inconsistent data led to debates about the existence of an alcohol withdrawal syndrome (Isbell et al. 1955).

Precipitated Withdrawal Syndromes

Precipitated withdrawal responses may occur when a drug antagonist abruptly displaces the dependence-producing drug from its binding sites on receptors. The viability of this approach depends on the availability of a specific receptor antagonist which does not have other actions that would preclude assessment of a withdrawal syndrome. The antagonist is often given parenterally (e.g., intravenously or intramuscularly) to maximize its rate of onset and hence the likelihood of precipitating a withdrawal reaction.

Because of the availability of specific opioid antagonists, precipitation of withdrawal phenomena associated with abstinence from the morphine-like drugs has been most thoroughly studied using this strategy (Martin et al. 1987). The studies have shown that the process that leads to physical dependence begins with the first dose

of morphine (Higgins et al. 1987; Bickel et al. 1988) although such low levels of physical dependence are not generally considered sufficient for the clinical diagnosis of physical dependence. Analogous studies have been conducted using the antagonists of the benzodiazepines (e.g., diazepam (Lukas and Griffiths 1982, 1984)) and are one element in the conclusive demonstration that these drugs do produce physical dependence (WHO 1981, 1987). With regard to tobacco or other forms of nicotine delivery, no such comparable studies have been conducted, although, as discussed in Chapter IV, preliminary and related data suggest the theoretical possibility that nicotinic antagonists may be used to precipitate nicotine withdrawal responses (Pickworth, Herning, Henningfield, 1988).

Variability in Withdrawal Syndromes

There are multiple determinants of the course and magnitude of the withdrawal reaction from a drug. Factors which have been studied in the laboratory are similar to those which affect the development of tolerance described earlier. These include the total daily dose of the drug that was given, specific drug type, the duration of exposure, the schedule of termination, genetic constitution, gender, and the prevailing environmental stimuli (Suzuki et al. 1987; Suzuki et al. 1983; O'Brien et al. 1978; Suzuki et al. 1985; Yanagita and Takahashi 1973; Yanagita 1973). In general, the magnitude of the withdrawal reaction is directly correlated with the dose level given, the duration of exposure, and the rapidity with which drug levels at the receptor sites decrease. Conversely, lower dose levels, shorter times of exposure, and gradual dose reduction (as opposed to abrupt abstinence) can attenuate the withdrawal syndrome (Kalant, LeBlanc, Gibbins 1971; Abood 1984; Jaffe 1985; Okamoto 1984).

Because withdrawal signs and symptoms vary among individuals using the same drug, the syndrome may not be apparent when a small number of individuals are studied. Lack of general understanding of such factors probably contributed to the fact that the nature of morphine withdrawal phenomena in humans was not rigorously documented until the studies by Himmelsbach and his coworkers in the 1940s (Himmelsbach 1941; Himmelsbach and Andrews 1943). Similarly, withdrawal responses from chronic alcohol administration were not conclusively characterized and demonstrated until the pioneering studies by Isbell and his coworkers in the 1950s (Isbell et al. 1955). Research involving comparable strategies of assessment of physical dependence on cocaine, amphetamine, marijuana, PCP, and nicotine, only began in the late 1970s. In the absence of such data, these drugs were sometimes held to be nonaddicting (e.g., President's Advisory Commission 1963). Nonetheless, for several of such drugs it had long been recognized that some drug withdrawal phenomena did occur (Jaffe 1970, 1976, 1980, 1985) and that such phenomena were

of clinical significance in the treatment of persons who were attempting to abstain from them (Jaffe 1970, 1976, 1980, 1985; Zweben 1986). For example, even prior to the rigorous studies of tobacco withdrawal phenomena in the early 1980s (Chapter IV), the Tobacco Withdrawal Syndrome had been recognized by the American Psychiatric Association (APA) as an Organic Mental Disorder in its Diagnostic and Statistical Manual (DSM) of Mental Disorders (APA 1980) on the basis of the extensive clinical observations and other sources of information prior to the 1980s (Chapter IV). The specificity of tobacco withdrawal to nicotine itself was acknowledged in the revised DSM III (APA 1987).

Cravings or Urges

Among the most frequently discussed aspects of drug dependence is the recurrent and often persistent urge to use drugs in drug-dependent persons. The urge or desire to use a drug is widely termed "craving." However, how craving is defined and how craving-related data are interpreted comprise one of the most problematic areas in drug dependence research. For example, the term craving has been used in such a variety of ways that its use may actually impede accurate communication (Kozlowski and Wilkinson 1987; Henningfield 1987). In the present Report, where possible, the term "craving" has been replaced by more descriptive terms and phrases such as "strength of an urge to use a drug" wherever the original meaning of the referent material is not changed.

Whereas the urge to use a drug is a correlate of drug abstinence, it is not an invariant one. For example, although urges to take drugs reliably increase during early abstinence from morphine- and pentobarbital-like (short-acting sedatives-hypnotics) drugs, they are not a necessary concomitant of withdrawal reactions from other opioids (e.g., cyclazocine) (Martin et al. 1965; Jasinski 1978), and alcoholics often "voluntarily" abstain and undergo withdrawal even when alcohol is available (Mello 1968; Mendelson and Mello 1966). Moreover, such urges are also evoked by stimuli associated with drugs and even by administration of the drug itself (O'Brien, Ehrman, Ternes 1986; Childress et al., in press). Thus, urges to use drugs also occur (often at high levels) when there is little other evidence that physical dependence is present (e.g., many years after drug abstinence) or when drug intake is sufficient so that no other withdrawal signs or symptoms are present.

Because drug abstinence is only one of many factors that can evoke the urge to use a drug and because such urges are not necessarily alleviated by suppressing physiological withdrawal signs, conclusions based upon such data must be carefully considered and appropriately qualified. For instance, although methadone can block withdrawal responses (at adequate dose levels), it does not reliably

diminish urges to use other opioids or opioid self-administration (Jones and Prada 1975; Grabowski, Stitzer, Henningfield 1984; Henningfield and Brown 1987). It would not be appropriate to conclude that methadone did not effectively block withdrawal reactions from morphine-like drugs simply because it did not eliminate such urges, because by other measures, methadone is effective at blocking opioid withdrawal (Kreek 1979; Jaffe 1985; Jasinski and Henningfield 1988). Analogously, as reviewed in Chapters IV and VII, most tobacco withdrawal responses are effectively suppressed by nicotine replacement even though urges to use cigarettes are not reliably diminished (see also Henningfield and Jasinski 1988).

Constraints on Physical Dependence Potential Testing

There are both practical and conceptual constraints on physical dependence potential testing. The practical constraints have been discussed above and are related to the multiple sources of variability in the intensity of withdrawal responses, which can result in failure to detect withdrawal or in unreliable data.

The main conceptual constraint is that physical dependence is neither a necessary nor sufficient condition to establish or maintain drug-seeking behavior. For instance, drug-seeking and drug-taking behaviors can persist at small doses of cocaine or morphine which produce no significant degree of physical dependence in animals (Schuster and Woods 1967; Deneau, Yanagita, Seevers 1969; Johanson, Balster, Bonese 1976; Jones and Prada 1977; Bozarth and Wise 1981) or in human subjects (Zinberg 1979). Conversely, animals in the laboratory and humans in hospitals can be made physically dependent on drugs such as opioids and barbiturates and yet never display controlled or addictive drug-seeking behavior (WHO 1981; Bell 1971). Similarly, compounds such as propranolol, cyclazocine, and nitrites have clear physical dependence potentials in that tolerance develops after repeated dosing and an abstinence syndrome appears upon cessation, yet drug-seeking or drug-taking behavior does not reliably occur (Myers and Austin 1929; Crandall et al. 1931; Rector, Seldon, Copenhaver 1955; Jasinski 1976; Jaffe 1985).

Another constraint is the difficulty in determining whether abstinence-associated symptomology is specific to an individual or to an underlying medical disorder that became evident upon removal of the drug (Woody, McLellan, O'Brien 1984; Zweben 1986; Kosten, Rounsaville, Kleber 1986; Stitzer and Gross 1988). For instance, an opioid might alleviate depression in a person with primary affective disorder. In general, as will be described below (see also Chapter IV), withdrawal responses may be distinguished from other abstinence-associated symptomology by their relative consistency among indi-

viduals, by their transient nature, and by the direct relationship between their magnitude and the level of preabstinence drug intake.

Finally, although the magnitude of the withdrawal syndrome is a widely used index for assessing the degree of physical dependence, it should be noted that this single measure is not always sufficient. For instance, several studies have demonstrated that spontaneous withdrawal from chronic levo-alpha-acetylmethadol (LAAM) or buprenorphine administration failed to result in pronounced signs of withdrawal (Jasinski, Pevnick, Griffith 1978; Young, Steinfels, Khazan 1979). Such observations could lead to the false conclusion that LAAM and buprenorphine do not produce significant degrees of physical dependence, when in fact a variety of other lines of evidence confirm that they do. For example, administration of an opioid antagonist such as naloxone precipitates a marked and intense withdrawal syndrome in LAAM-maintained animals (Young, Steinfels, Khazan 1979). Analogously, Dum, Bläsig, and Herz (1981) performed a substitution type of experiment demonstrating that chronic administration of buprenorphine also results in physical dependence. The explanation for the misleadingly weak spontaneous withdrawal phenomena for LAAM and buprenorphine seems to be the slow elimination of these drugs from the plasma, which permits the body to adjust more gradually to drug abstinence. The long elimination half-life of LAAM's active metabolites (Kaiko and Inturrisi 1975) and buprenorphine's unique affinity for the opiate receptor and long elimination half-life (Cowan, Lewis, MacFarlane 1977) contribute to the lack of observed withdrawal signs after chronic exposure is terminated. A similar example exists for the long-acting benzodiazepine, diazepam. A delayed and relatively mild withdrawal syndrome appears after spontaneous withdrawal, but administration of the benzodiazepine receptor antagonist, Ro15-1788 (flumazenil), precipitates an immediate, intense abstinence syndrome (Lukas and Griffiths 1982, 1984). Analogous results are produced when the daily dose level of shorter acting drugs is gradually decreased.

A practical application of the finding that the magnitude of withdrawal reactions tends to be inversely related to rate of drug elimination is the gradual elimination of drugs from individuals who are suspected of being highly physically dependent. Such gradual elimination reduces the magnitude of the withdrawal syndrome. This is the basis of the gradual withdrawal of morphine, alcohol, or nicotine after a period of chronic intake at high dose levels (Jaffe 1985). Although gradual dose reduction of opioids and nicotine reduces the magnitude of most aspects of the withdrawal syndrome, it is not clear that such an approach improves overall treatment outcome compared with much more rapid drug cessation (i.e., "cold turkey") (Jasinski and Henningfield 1988; Chapter VII).

Therapeutic or Useful Effects of Dependence-Producing Drugs

With many dependence-producing drugs, the same biological properties that are important in their dependence-producing properties may also lend them to therapeutic application. In fact, most classes of drugs which cause dependence, including opioids, sedatives, alcohol, cocaine-like drugs, and nicotine, have been used as medicinals to treat specific medical disorders and human discomforts. Descriptions of the approved and general uses are available in the American Hospital Formulary Service (1988), the Physician's Desk Reference (Medical Economics Company 1988), the United States Pharmacopeia (Griffiths, Fleeger, Miller 1986), and Goodman and Gilman's Pharmacological Basis of Therapeutics (Gilman et al. 1985) (see also Table 6).

Although each of the drugs listed in Table 6 has a range of potential or actual therapeutic applications, past and current uses are often related to their effects on mood, feeling, and behavior. For instance, the stimulants may be used to modulate arousal level, the opioids to alleviate pain, the sedatives to alleviate anxiety; the drugs are sometimes systematically used to treat the dependence which may have previously developed on them or on another drug in the same class. Nicotine is no exception to these observations. Historically, tobacco was used to treat a range of disease states, although usually without evidence of efficacy (Corti 1931; Austin 1979). Nicotine in the polacrilex gum form is a drug approved by the FDA for treatment of nicotine dependence (see Chapter VII).

The therapeutic effects of dependence-producing drugs not only illustrate an important point of commonality among these drugs, but these effects also may be important in the drug dependence process itself. Such potential drug actions can be important in the initiation, maintenance, and relapse to drug dependence. The dependence process may have been precipitated by the therapeutic use (medically approved or self-initiated) of a drug. The dependence process may be exacerbated by the real or perceived benefit of the drug to the individual as such actions strengthen the reinforcing power of the drug. The therapeutic actions of a drug may be associated with relapse to drug use after many years of abstinence. These aspects of dependence potential as they pertain to nicotine are discussed in Chapter VI.

Adverse and Toxic Drug Effects

As discussed earlier, adverse drug effects are important clinical features of drug dependence. These effects may be used as factors in objective determinations of the overall liability associated with a drug (Yanagita 1987; Griffiths et al. 1985). For instance, chronic administration of sedatives or alcohol can produce intoxication and

TABLE 6.--Effects that may be produced by addicting drugs

Attribute	Nicotine *	Cocaine	Morphine-like	Alcohol
Discriminable interoceptive (subjective) effects	+ Henningfield and Goldberg (1985), Morrison and Stephenson (1969)	+ Fischman et al. (1976)	+ Terry and Pellens (1970)	+ Carpenter (1962)
Produce dose-related increases in self-reported "liking" scores	+ Henningfield, Miyasato, Jasinski (1985)	+ Henningfield et al. (1987)	+ Martin and Fraser (1961)	+? Mello (1968)
Produce elevated response on MBG (euphoria) scale of ARC inventory	+ Henningfield, Miyasato, Jasinski (1985)	+ Fischman et al. (1976)	+ Haertzen et al. (1963)	+ Henningfield et al. (1984). Stitzer et al. (1981)
Positive reinforcer in animal drug self-administration studies	+ Goldberg, Spealman, Goldberg (1981), Deneau and Inoki (1967), Ando and Yanagita (1981). Henningfield and Goldberg (1983a)	+ Pickens and Thompson (1968). Deneau et al. (1969)	+ Headlee, Coppock, Nichols (1955), Thompson and Schuster (1964)	+ Deneau et al. (1969), Winger and Woods (1973)
Positive reinforcer in human drug self-administration studies	+ Henningfield, Miyasato, Jasinski (1983)	+ Fischman and Schuster (1982)	+ Jones and Prada (1975)	+ Bigelow et al. (1975), de Wit et al. (1987)

TABLE 6.--Continued

Attribute	Nicotine *	Cocaine	Morphinelike	Alcohol
Place conditioning	+ Fudala, Teoh, Iwamoto (1985)	+ Spyraki, Fibiger, Phillips (1982)	+ Bardo and Neisewander (1986)	Stewart and+Grupp (1985)
Physical dependence develops such that withdrawal accompanies abrupt abstinence	+ Hatsukami et al. (1984), Hughes and Hatsukami (1988)	+? Carroll and Lac (1987), Jones (1984)	+ Light and Torrance (1929a), Kolb and Himmelsbach (1938), Himmelsbach (1941)	+ Iabell et al. (1955)
Tolerance develops	+ Langley (1905), Domino (1978), Marks, Burch, Collins (1983), Jones, Farrell, Herning (1978)	+ Tatum and Seevers (1929), Downs and Eddy (1932), Woolverton and Schuster (1978), Wood and Emmett-Oglesby (1987)	+ Light and Torrance (1929b)	+ Goldberg (1943)
Therapeutic use in treatment of medical disorder	+ AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+[2] AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+[3] AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+-[4] AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others

TABLE 6.--Continued

Attribute	Caffeine	Marijuana	Lysergic acid diethylamide	Chlorpromazine
Discriminable interoceptive (subjective) effects	+ Gilbert (1976), Griffths and Woodson (1988b)	Siler et al. (1933)	+ Hofmann (1975)	+ Griffths, Bigelow, Liebson (1979)
Produce dose-related increases in self-reported "liking" scores	+ - Griffiths, Bigelow, Liebson et al. (1986), Chait and Griffiths (1983) †, Griffiths and Woodson (1988b)	+ Higgins and Stitzer (1986), Cone et al. (1986)	?	?
Produce elevated response on MBG (euphoria) scale of ARC inventory	+ - Chait and Griffiths (1983)	Higgins and Stitzer (1986), Cone et al. (1986)	Haertzen et al. (1963)	Stitzer et al. (1981)
Positive reinforcer in animal drug self-administration studies	-? Deneau et al. (1969), Griffiths and Woodson (1988b)	Harris et al. (1974)	Hoffmeister and Wuttke (1976)	Hoffmeister and Goldberg (1973), Hoffmeister (1975), Deneau et al. (1969)
Positive reinforcer in human drug self-administration studies	+ ? Griffiths, Bigelow, Liebson et al. (1986), Griffiths, Bigelow, Liebson (1986), Griffiths and Woodson (1988b)	+ Mendelson and Mello (1984)	?	Griffiths, Bigelow, Liebson (1979)
Place conditioning	?	?		?

TABLE 6.--Continued

Attribute	Caffeine	Marijuana	Lysergic acid diethylamide	Chlorpromazine
Physical dependence develops such that withdrawal accompanies abrupt abstinence	+ Griffiths, Bigelow, Liebson (1986), Dreisbach and Pfeiffer (1943), Horst et al. (1934), Griffiths and Woodson (1988a)	+? Jones and Benowitz (1976), Mendelson et al. (1984), Ford and McMillan (1972), Beardsley et al. (1986)	Isbell et al. (1956)	Baldessarini (1980)
Tolerance develops	+ Carney (1982), Eddy and Downs (1928), Griffiths and Woodson (1988a)	+ McMillan et al. (1970), Weil et al. (1968), Babor et al. (1975), Cone et al. (1986)	+ Isbell et al. (1956)	? Baldessarini (1980)
Therapeutic use in treatment of medical disorder	+[5] AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+[6] AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	?[7] AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others	+[8] AMA (1983), Gilman et al. (1985), Medical Economics Company (1987), and others

NOTE: + indicates that drug administration produces the effect; - indicates that drug administration does not produce the effect; ? indicates that available scientific data are inadequate to draw a conclusion.

* Further discussion can be found in other chapters of this Report.

[1] As aid to stop cigarette smoking and to treat nicotine dependence.

[2] As topical anesthetic (rarely used) for ear, nose, eye. and throat.

[3](1) As strong analgesics for treatment of both acute and chronic pain, (2) treatment for myocardial infarction (analgesia, anxiolysis, and reduced left ventricular work-load and myocardial oxygen requirements), (3) for obstetric analgesia, (4) as preanesthetic medication to smooth induction, (5) treatment for pulmonary edema, (6) as cough suppressant, (7) treatment for severe diarrhea.

[4](1) As antiseptic agent on skin, (2) intravenously to treat premature labor (uterine relaxant), (3) treatment of spasticity by local or intrathecal injection of dilute absolute alcohol solution, (4) as vehicle in dermatologic preparations (antiseptic action, astringent action, cooling effect), (5) treatment of alcohol withdrawal.

[5](1) Incorporated with over-thecounter analgesics (e.g., aspirin) to treat ordinary headache and relieve inflammatory pain (scant scientific data to substantiated, (2) in combination with ergot alkaloid to treat migraine headache, (3) in combination with sympathomimetic agents possessing anorectic properties in weight-loss medications, (4) as stimulant, (5) treatment (clinical trials) for preterm infant apnea of undetermined origin, (6) rarely for treatment of central nervous system depressant poisoning.

[6](1) As antiemetic for cancer chemotherapy patient, (2) glaucoma treatment.

TABLE 6.—Continued

[7] None at present, but several proposed in past: (1) as psychotherapy aid, (2) as adjunct in alcohol and opioid addiction treatment, (3) as adjunct in terminal cancer patient therapy to reduce opioid analgesic need and induce tranquility.

[8] (1) Management of psychotic disorder manifestations, (2) treatment for nausea and vomiting, (3) relief of presurgery restlessness and apprehension, (4) treatment for acute, intermittent porphyria, (5) as adjunct in tetanus treatment, (6) to control mania manifestations in manic-depressive illness, (7) treatment for intractable hiccups, (8) treatment of children's severe behavioral disorders characterized by combativeness or hyperexcitable behavior, (9) possible second-line treatment for nonpsychotic anxiety.

† "Liking" was not measured, but the increased scores on a tension and anxiety scale suggested dose-related "disliking."

severe mood swings (Mello and Mendelson 1970; Mello 1968; Isbell et al. 1950); erratic supplies of opioids may be associated with sociopathic drug-seeking and withdrawal-related mood effects (Jasinski 1977); erratic supply of tobacco can also result in disruption of ongoing activities in an effort to obtain tobacco or as a consequence of withdrawal symptoms.

Consideration of multiple factors such as the dependence potential of a drug, the extent of its actual use, and the degree to which it produces adverse effects can be used to assess the overall liability associated with the use of a drug (i.e., "abuse liability") (Brady and Lukas 1984; Griffiths et al. 1985; Yanagita 1987). For example, caffeine produces only minimal (if any) disruptive behavioral or physiological effects and is not generally regarded as posing a serious public health problem even though self-administration may be widespread (e.g., caffeine in tea or coffee) (Griffiths and Woodson 1988a,b). In contrast, drugs which produce disruptive physiological and behavioral changes even when self-administered infrequently may be considered to represent a more serious health hazard (e.g., LSD). Drugs may fall anywhere on the continuum defined by these parameters, and the relative impact on health is most effectively determined by a comprehensive assessment of these interactive behavioral and physiological dimensions (Griffiths, Brady, Snell 1978b; Griffiths et al. 1985; Brady and Lukas 1984; Yanagita 1987).

Identification of Dependence-Producing Drugs

Independent of whether use of a substance has been observed to lead to addiction, it is possible to directly and objectively test a chemical to determine if it is addicting. Such tests provide data used by Federal (e.g., FDA, Drug Enforcement Administration) and International (e.g., WHO) agencies as to how to regulate chemicals. In fact, new drugs are usually evaluated and regulated ("scheduled") before they are ever made available for medical application. Such decisions rely heavily upon the known properties of addicting drugs and on the methods used to test for such properties (both described in this Chapter). Although the physicochemical structure of the drug is one determinant of the stimulus effects produced by drug administration, simply knowing the drug structure is rarely sufficient to predict the nature and magnitude of possible drug effects (Barnett, Trsic, Willette 1978); behavioral and physiological testing in animals and humans is usually necessary. When there is convergent evidence from multiple measures of dependence potential, then the drug is appropriately regarded as addicting or dependence producing. Whether humans outside the laboratory actually become addicted will depend on additional factors such as availability, price, and social acceptability of the drug (US DHHS 1987; also see discussion by Katz and Goldberg 1988).

Table 6 provides a comparison of several drugs in terms of the major measures that have been reviewed in this Chapter. As shown in the table, drugs known to produce widespread problems in a given population are characterized by positive responses with most of these measures (cocaine, morphine-like drugs, alcohol, and nicotine). Conversely, drugs not contributing to such problems have fewer positive responses on the various tests (cholorpromazine). Intermediate drugs are associated with intermediate levels of difficulty in management of use.

Comparison Among Drugs

Within a given class of drugs, it is sometimes possible to rate their relative efficacy as reinforcers by how much behavior was affected (e.g., how many lever presses would occur or how much money would be paid) (Griffiths et al. 1981; Yanagita 1987). For instance, the slower onsetting/offsetting formulations of opioids, barbiturates, stimulants, and nicotine appear to have a lower dependence potential than the quicker onsetting and offsetting formulations (Jaffe 1985).

The practical generality of such comparisons, however, is limited because many other factors determine the overall level of dependence that might develop, the extent of social and/or personal damage, and the resulting level of social concern (Yanagita 1987; Katz and Goldberg 1988). For example, the increasing availability and decreasing relative price of cocaine in recent years are major factors contributing to increased levels of use and resultant social damage (US DHHS 1987). Analogously, the widespread ready availability and the relatively low cost of tobacco products and alcohol have probably contributed to the much higher rates of addiction and mortality associated with alcohol and tobacco than with drugs such as cocaine, even though cocaine may appear to be a more effective reinforcer in animals. Social or cultural factors may also contribute to the spread and levels of drug use. For example, sensational press reporting may have contributed to the popularization of barbiturates in the 1960s (Brecher 1972), and the mass marketing and advertising of tobacco products is likely to have contributed to the use of these products, especially among women and especially in the case of smokeless tobacco products (Ernster 1985, 1986; Warner 1986b; Davis 1987; Tye, Warner, Glantz 1987).

Four examples of drugs associated with striking changes in the prevalence of use among various populations as well as associated morbidity are: alcohol, for which use and associated diseases decreased during the Prohibition years early in the 20th century; lysergic acid diethylamide (LSD), for which use and associated hospitalizations were elevated during the 1960s; cocaine, for which use and associated hospitalizations increased during the 1970s

(Crowley and Rhine 1985; Levine 1984; Nahas and Frick 1981; DuPont, Goldstein, Brown 1979; Holder 1987; US DHHS 1987); tobacco, in which consumption of smokeless tobacco products increased among youth in 1970s and cigarette consumption increased sharply among women in the 1950s and 1960s (US DHHS 1981,1986; Appendix A). As discussed in the aforementioned references, the changes in use of these drugs were not due to changes in the pharmacologic actions of the drug or sudden changes in genetic constitution of the populations, but rather to changes in factors such as availability, cost, social acceptability, regulatory controls, marketing efforts, and general perceptions about the risks associated with use.

Finally, various other factors contribute to the level of social concern and may be only indirectly related or unrelated to the pharmacologic properties of the drug itself. For instance, the observations on transmission of AIDS by way of shared needles among i.v. drug users and on cancer caused by tobacco smoke carcinogens have greatly increased the liability of use attributed to these drugs in recent years.

Environmental Determinants of Drug Dependence Including Behavioral Conditioning

A common feature of use of all dependence-producing drugs is that the positive (satisfaction symptoms) and negative (e.g., withdrawal symptoms) effects may become conditioned responses to associated environmental stimuli. The implications of this are important for understanding the chronic and self-sustaining nature of drug dependencies. Such conditioning is a powerful behavioral mechanism by which the drug comes to control an increasing amount of the behavior of the drug user (Thompson and Schuster 1968; Goldberg 1976a).

Some of the important environmental determinants of drug dependence are discussed elsewhere in this Chapter in the context of drug self-administration studies. These factors include: (1) the behavioral or economic cost of the drug itself or of taking the drug, (2) direct pressure to take the drug by making other reinforcers contingent upon drug taking, and (3) the other ongoing activities of the person (e.g., demanding work schedule) that tend to enhance drug taking. The focus of the present Section is on environmental stimuli that may contribute to drug dependence by evoking urges to use drugs, and by eliciting bodily responses that mimic the usual effects of either drug taking or drug withdrawal reactions.

Drug Taking as a Learned Behavior

The interface between a drug and its effects is the behavior of obtaining and ingesting the drug. Such behavior is learned behavior, and as discussed earlier in this Chapter, many of the factors that modulate this behavior are similar to those which modulate other learned behaviors including eating, exercise, and occupational skills (Thompson and Schuster, 1968). Technically, drug taking is "operant behavior" and includes "respondent" or "classically conditioned" components. The basic governing principle of operant behavior is that it occurs in the context of certain stimuli and is either strengthened or weakened by the nature of the consequence (a positive reinforcer strengthens the response and a punisher weakens the response) (Skinner 1938, 1953). Thus, for example, a friend might offer a drug (antecedent stimulus); the drug is ingested (operant behavior or response); and the effects of the drug strengthen the behavior (positive reinforcement). Respondent conditioning occurs simultaneously and further contributes to the strength of the behavior (Bouton and Swartzentruber 1986). A drug might serve as an unconditioned stimulus which elicits a relatively involuntary response (e.g., nicotine and morphine can elicit feelings of pleasure and/or nausea); when physical dependence has occurred, drug abstinence can also elicit certain responses (e.g., anxiety and urges to take the drug). Any environmental or even internal stimulus can become part of this conditioning process by repeated association with the elicited response. For example, the taste of alcohol, the smell of smoke, "thinking" about use of the substance, and the sight of cocaine- or opioid-associated paraphernalia can elicit feelings associated with either the administration or withdrawal of the drug (Childress, McLellan, O'Brien 1986a,b; Ludwig 1986; Ludwig and Stark 1974; Erben 1977; Gotestam and Melin 1983; Pickens, Bigelow, Griffiths 1973; Rickard-Figueroa and Zeichner 1985; Levine 1974).

The simultaneous operation of both operant and respondent conditioning can converge to generate and maintain powerful chains of behavior over which the individual may have little control. As shown earlier in this Chapter, highly addicting drugs are those which are very effective at reinforcing behavior and eliciting responses. Their power can be increased by factors such as drug deprivation, which may be associated with a discomforting withdrawal syndrome. In the presence of withdrawal, the person may behave in a way to relieve the discomfort of a withdrawal syndrome; in this case the withdrawal syndrome itself may be said to be functioning as a negative reinforcer. When drugs are readily available, as with tobacco for most people or opioids for physicians, these behavioral conditioning processes may be very subtle because the drug can be taken in a pattern that avoids excessive discomfort. For example, early interoceptive or subjective withdrawal cues that

are evident upon waking in the morning signal that "it is time to smoke a cigarette," and thus the smoker neither "forgets to smoke" nor experiences pronounced withdrawal symptoms.

As implied by the foregoing discussion, the strength and persistence of drug-seeking behavior are not just functions of the drug itself or of withdrawal. Rather, they are determined by many factors, such as the number of times that certain responses are associated with certain stimuli, the presence or absence of such stimuli, the subjective discomfort occurring as part of withdrawal, and the availability of the drug. The convergence of so many environmental and subjective forces can result in extremely persistent behavior that may appear disproportionate to the pleasure actually experienced when the drug is taken (e.g., the few minutes of pleasure from the postdinner cigarette or when heroin is taken after 8 to 12 hr of deprivation). In fact, the subjective pleasure itself may be very mild, and the person may describe the role of the drug as "simply maintaining feelings of normalcy or comfort" and not as "getting high" per se. The scientific basis for these observations has been actively and systematically studied since the pioneering work of Wikler and others (Wikler 1973) and has been reported and reviewed in detail elsewhere (Goudie and Demellweek 1986; O'Brien, Ehrman, Ternes 1986; Grabowski and Cherek 1983; Grabowski and O'Brien 1981; Childress, McLellan, O'Brien 1986a,b; McLellan et al. 1986; Wikler 1973; Meyer and Mirin 1979).

Drug-Associated Stimuli Modulate Drug Seeking

Stimuli associated with drug effects may come to elicit ("trigger") those same effects or sometimes opposite effects (withdrawal responses). For example, increased heart rate induced by stimulant administration may become associated with multiple environmental stimuli-the color of the tablet, the individual who provided it, and the office environment in which the drug was taken. These stimuli may act alone or in concert. One stimulus may produce a slight heart rate change; two such stimuli may produce a larger change; and the presentation of many such stimuli may have a synergistic effect. Other stimuli may counteract or facilitate these effects (Schindler, Katz, Goldberg, in press).

The response produced in relation to environmental correlates may differ qualitatively from the direct drug effect. For instance, the direct effect of a drug may be a heart rate increase, whereas the conditioned or learned response to drug-associated stimuli may be either a decrease or an increase in heart rate. Changes may be particularly evident for agents with biphasic effects such as nicotine. Whatever the direction of change in response value, the events may be of physiological and behavioral significance (for example, see Childress, McLellan, O'Brien 1986a,b; O'Brien, Ehrman, Ternes

1986; Stewart, de Wit, Eikelboom 1984; Grabowski and O'Brien 1981; Childress et al., in press). These complex conditioning processes which can function to precipitate drug taking appear to function similarly for a variety of drugs including opioids and tobacco (Ternes 1977).

Since the 1960s many researchers have shown that the role of associated stimuli is important for diverse biological reinforcers such as drugs, food, and sex. For example, Thompson and Schuster (1964) demonstrated that environmental stimuli paired with drugs could themselves come to generate drug seeking in monkeys. Schuster and Woods (1968), Davis and Smith (1976), and Carnathan, Meyer, and Cochin (1977) demonstrated that stimuli previously associated with drug taking could generate much drug-seeking behavior in animals during extinction of use when the drug is no longer available. Similar findings were obtained in a study of i.v. cocaine self-administration in which human volunteers emitted high rates of lever pressing in the presence of cocaine-associated stimuli when the drug was not available (Katz and Goldberg 1988).

Goldberg (1976b) reported that environmental stimuli associated with drug taking could help sustain substantial behavioral repertoires in monkeys often far in excess of the behavior that was maintained when just the drug was given. Similarly, Meisch found that the taste and smell of alcohol, which were normally found to be highly aversive to rats, became highly effective stimuli in their own right in the maintenance of alcohol-seeking behavior, even when alcohol was not actually available for the rats to consume (Meisch 1977). La1 and colleagues (1976) demonstrated that environmental stimuli previously associated with drug effects could, by producing drug-like responses, attenuate opiate withdrawal signs in rats. These and many other studies have shown conclusively that specific environmental stimuli associated with drug taking exert control over drug seeking, drug taking, and characteristics of the drug response itself.

Environmental conditions in many forms can contribute to sustained drug use, and specific stimulus conditions can have well-defined drug-like properties. This phenomenon, which has been well documented in laboratory settings, is recognized as being powerful in clinical pharmacology, in which "placebo" effects (conditioned responses to drug-taking conditions) may be dramatic and difficult to separate from so-called direct drug effects. Both direct drug effects and those established through learning influence physiology and behavior, thereby contributing to the strength of addictive behaviors. Recent reports suggest that conditioned effects can be attenuated for some individuals through effective treatment specifically designed to extinguish, or alter through learning, these responses (Childress, McLellan, O'Brien 1986a,b; McLellan et al. 1986).

The stimuli associated with drug effects also may generate further drug seeking and drug taking. Wikler (1973) and more recently Meyer and Mirin (1979) contributed substantially to both the conceptual framework and the data describing these complex phenomena. These investigators found that environmental stimuli which correlated with direct drug effects are pertinent to the acquisition, maintenance, and elimination of opioid taking by humans. Similar findings were observed in an intensive study of an alcoholic subject: alcohol-associated stimuli produced orderly responses including urges to drink and even drinking itself (Pickens, Bigelow, Griffiths 1973). A series of studies by Goldberg and his colleagues (Goldberg 1970; Goldberg, Kelleher, Morse 1975; Goldberg and Kelleher 1977; Goldberg, Spealman, Kelleher 1979) showed that environmental stimuli occasionally associated with morphine injections or with early withdrawal effects could lead to increased drug seeking and/or drug taking.

Conditioned Withdrawal Symptoms May Precipitate Drug Seeking

Wikler (1948) first described the discomfort of long-abstinent patients on their return to environments in which they had previously used drugs and experienced withdrawal symptoms. Subsequently, Wikler (1973), O'Brien (1975) and colleagues (O'Brien, Ehrman, Ternes 1986; O'Brien et al. 1975), and several other researchers (Siegel 1975, 1976, 1978; Eikelboom and Stewart 1979; Stewart, de Wit, Eikelboom 1984; Childress et al., in press) have made fundamental contributions to the identification of the complex interplay of factors modulating the physiological and behavioral components of abstinence. These and other studies have shown that the conditions established by abrupt withdrawal after chronic administration of a drug can serve as setting conditions which may result in further drug taking. In other words, for some individuals the onset or anticipation of abstinence symptoms may be strongly linked to reinitiation of drug self-administration. In turn, the drug effect reinforces the reinitiation of drug taking (Stewart, de Wit, Eikelboom 1984). Withdrawal symptoms and drug taking may thus become closely associated with a range of environmental stimuli. These stimuli then come to elicit abstinence symptoms and generate drug taking through a variety of powerful biobehavioral mechanisms. In fact, McNeill and colleagues (1986) have concluded that the pattern of abstinence symptoms itself may be in part determined by conditioning factors.

Environmental stimuli can lead to drug seeking by eliciting distressing conditioned withdrawal effects. Several thorough reviews on conditioning factors in drug dependence indicate that correlated behaviors and stimuli dramatically alter drug effects, withdrawal

symptoms, and other features of substance use behaviors (Goudie and Demellweek 1986; O'Brien, Ehrman, Ternes 1986; Grabowski and Cherek 1983; Grabowski and O'Brien 1981). These interacting factors have also been described in a number of prominent medical and scientific texts (Jaffe 1986, 1987), as well as in the recent Second Triennial Report to Congress from the Secretary, Department of Health and Human Services (US DHHS 1987).

One of the clearest observations of the contribution of environmental factors in tobacco withdrawal was made by Hatsukami, Hughes, and Pickens (1985). They noted that the number of withdrawal signs increased substantially when cessation occurred in the natural environment. Parallels exist in both laboratory research and naturalistic observation. Stitzer, Bigelow, and McCaul (1983) reviewed this literature and noted that individuals restrained from access to drugs for prolonged periods tend to return to use when the agents are again available; the implication is that environmental stimuli contribute to relapse. In a laboratory study, Thompson and Ostlund (1965) found that relapse to self-administration occurs rapidly for animals removed from, and then after extended periods returned to, the original environment but not for animals that undergo extinction of self-administration within that environment. In a reverse situation in humans, Robins, Davis, and Goodwin (1974) reported that individuals who experienced initial drug use in the stressful and ready-access conditions of the Vietnam war tended not to continue use on return to the United States.

Relapse to Drug Dependence

For many drug-dependent persons, achieving at least brief periods of drug abstinence is a readily achievable goal. Maintaining abstinence, or avoiding relapse, however, poses a much greater overall challenge. There is a substantial base of data for these conclusions. Treatment outcome reviews concerning opioid (Platt 1986), alcohol (Miller and Hester 1986a; Peele 1987), and tobacco (Brownell et al. 1986; Lichtenstein 1982; Schwartz 1987) dependence show that clinical interventions are often successful in producing short-term cessation of drug use but that relapse to use is a frequent posttreatment occurrence (Hunt, Barnett, Branch 1971; Brownell, Marlatt et al. 1986).

An important issue in the contemporary study of addictions is the degree to which relapse and recovery are generalizable across categories of substances (US DHHS 1986; Tims and Leukefeld 1986; Marlatt 1979; Miller and Hester 1986a,b; Schwartz 1987). This Section examines rates and predictors of relapse across drug classes with emphasis on comparisons among alcohol, opioids, and tobacco.

Implications of these observations for the prevention of relapse will be described in the next Section of this Chapter.

Definition of Relapse

In general, relapse refers to resumption of drug use following abstinence from such drug use; however, the criterion for abstinence and resumption of drug use must be specified. Principles for such specification are generally similar among drugs; however, there are drug-specific issues which complicate comparisons of data and will be discussed in this Section. Only when an individual has achieved criteria for abstinence is he or she "eligible" for the possibility of relapse. Defining abstinence over some time period as the eligibility criterion is useful because it permits distinctions to be drawn between continuous users and those who are able to "quit" drug use, however briefly. Definitions of "quit episodes" differ dramatically among published studies, leading to quite different interpretations of subsequent relapse. With regard to tobacco, a consensus conference, held under the auspices of the National Heart, Lung, and Blood Institute, recommended 24 hr of continuous abstinence from tobacco as the criterion for defining a quit episode and establishing eligibility for relapse to tobacco use (see Chapter VII). With regard to other dependence-producing drugs, patients of residential alcohol and drug abuse treatment facilities are usually deemed eligible for relapse at discharge without reference to the duration of treatment or abstinence.

Two general ways of defining relapse after a period of abstinence have appeared in the literature. Relapse has been defined as a discrete event occurring with the single use of a drug or as a process developing over time (Wesson, Havassy, Smith 1986). When relapse is defined as a discrete event, distinction is often made between first use of the primary drug of dependence and first use of any other psychoactive agent. Return to use of the primary drug holds clear potential for return to addiction (Hubbard and Marsden 1986). However, there has been less consensus regarding whether use of a substitute drug should be defined as relapse. When relapse is defined as occurring over time, the endpoint of the process has been variously defined as daily drug use for a specified period, a return to drug use at or above pretreatment or baseline level, a consequence of drug use such as readmission for treatment, a return to dependence defined by one or more diagnostic instruments, or a return to drug use at levels above criteria specified in terms of quantity and/or duration of drug use (APA 1987; Litman et al. 1983; Ossip-Klein et al. 1986; Simpson and Marsh 1986).

The choice of definition is also influenced by the treatment modality being evaluated and by the theoretical orientation of the investigator. For example, relapse is usually discretely defined in

clinical applications of aversive counterconditioning to treatment of alcohol and tobacco dependence (Boland, Mellor, Revusky 1978; Schwartz 1987). In contrast, investigations of skills training approaches to alcohol, tobacco, and other drug use treatment typically employ continuous or process measures of relapse, e.g., number of days of abstinence (Chaney, O'Leary, Marlatt 1978; Marlatt and Gordon 1985) because new skills are not lost after a slip but rather could be used repeatedly to reestablish abstinence (Catalano and Hawkins 1985).

Measurement of Relapse

Relapse is usually assessed by one of two measurement procedures (Wesson, Havassy, Smith 1986). Current drug use measures ascertain drug use at selected posttreatment intervals (e.g., 3, 6, and 12 months). Intermittent drug use occurring between these time intervals may not be captured by this procedure. Continuous status measures ascertain whether there was drug use at any point in the posttreatment interval. Current use measures typically yield higher abstinence rates than continuous status measures, because of the variable course of drug abuse careers (Pickens et al. 1985). Current use measures provide point-in-time estimates of relapse status among a sample of treated users, while continuous status measures allow for determining the percentage of individuals who have managed to achieve relatively enduring abstinence (Ossip-Klein et al. 1986). The implications of different measurement approaches for interpretation of relapse phenomena have been reviewed (Wells, Hawkins, Catalano, in press; Brownell et al. 1986).

While self-reported drug use status has been the primary method of detecting relapse, detection of the drug in biological fluids or in expired air is being used as an adjunct with increasing frequency (Wesson, Havassy, Smith 1986). As discussed earlier in this Chapter, biochemical methods of assessing drug use vary widely in their sensitivity and in the period during which drug use can be detected (Walsh and Yohay 1987).

Rates of Relapse

Hunt and his colleagues were the first to investigate commonalities in relapse processes among substances (Hunt, Barnett, Branch 1971; Hunt and Bespalec 1974; Hunt and General 1973; Hunt and Matarazzo 1970). They compared relapse rates for clients discharged from opiate, alcohol, and tobacco dependence treatment programs and noted the remarkable similarity of the relapse curves they obtained (Figure 2). Relapse was defined as any use of the primary drug of abuse. They then formulated a learning theory of relapse that was presumed to operate in alcohol, opioid, and tobacco dependence.

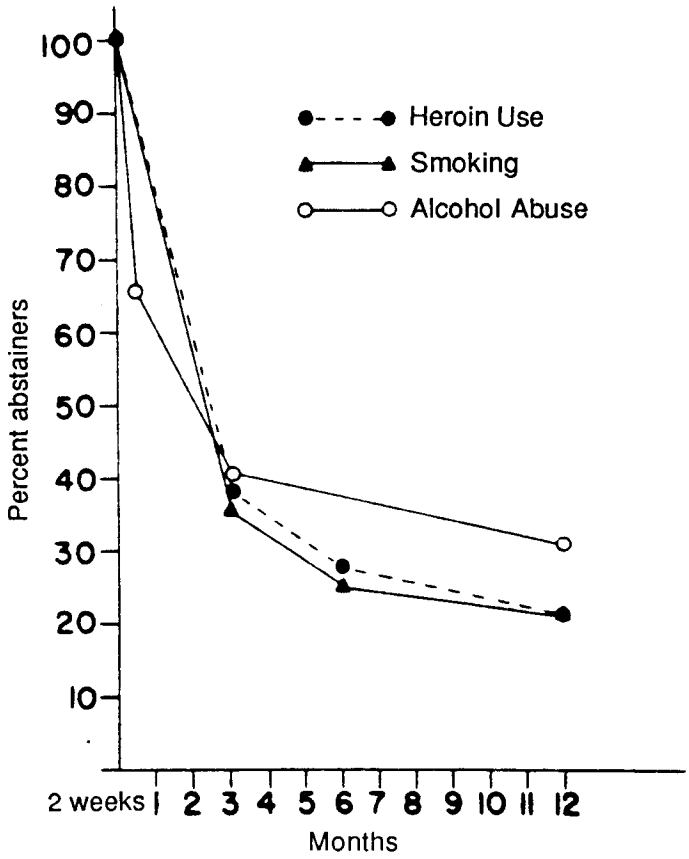

FIGURE 2.—Relapse over time for heroin use, smoking, and alcohol abuse

SOURCE: Hunt et al. (1971).

Although attempts to base theories of relapse on cumulative survival curves, such as those depicted in Figure 2, are complicated by a variety of factors (Litman, Eiser, Taylor 1979; Sutton 1979; Brownell et al. 1986), such curves do possess heuristic value. They indicate that abstinence rates fall precipitously in the early post-treatment period; that most treated smokers, alcoholics, and heroin addicts relapse to at least single use of the primary drug of use by 3-month followup; and that those who have maintained abstinence for at least 6 months are much less likely to relapse.

Similar large-scale reviews of relapse rates for multiple substances have not been published in recent years. Instead, a voluminous

literature has accrued regarding treatment effectiveness (Schwartz 1987; Miller and Hester 1986a; Platt 1986; Simpson and Sells 1982). However, data from studies of alcohol, opioid, and tobacco relapse consistently support the similarities in relapse rates and patterns across these three forms of drug dependence, as well as the operation of similar determinants of relapse. For instance, high rates of relapse characterize most treatment programs for dependence to opioids (Maddux and Desmond 1986; Platt 1986; McAuliffe 1975; McAuliffe et al. 1986; Waldorf 1983), alcohol (Belasco 1971; Bruun 1963; Robson, Paulus, Clarke 1965; van Dijk and van Dijk-Koffeman 1973; Vaillant 1982; Imber et al. 1976; Kendell and Staton 1966; Orford and Edwards 1977), and tobacco (Brandon, Tiffany, Baker 1986; Erickson, Rugg, Tunstall, Jones 1984; Hunt and Matarazzo 1973; Marlatt and Gordon 1985; Shumaker and Grunberg 1986; Schwartz 1969; see also Chapter VII). The remainder of this Section will address the parallel in the correlates of relapse to these three substances.

Correlates of Relapse

Factors found to be associated with relapse fall into three domains. Background or pretreatment factors are those that seem to heighten the individual's vulnerability to relapse (Shiffman et al. 1986). These variables may be measures of fixed pretreatment characteristics such as demographics and drug use history. Pretreatment factors appear to account for between 10 and 20 percent of the variance in posttreatment relapse (Cronkite and Moos 1980; Simpson, Savage, Lloyd 1979; Simpson and Sells 1982). Variables measured during treatment are also thought to influence the probability of relapse at posttreatment. These include treatment length, intensity, setting, type, and compliance with treatment. Treatment factors appear to account for 15 to 18 percent of the variance in drug abuse outcome studies (Simpson, Savage, Lloyd 1979). Posttreatment factors are those associated with the subject's posttreatment environment or internal state. These include degree of family support, drug use among peers, involvement in work and leisure activities, and emotional states. Posttreatment factors have been shown to account for roughly 50 percent of the variance in posttreatment relapses (Finney, Moos, Mewborn 1980) and thus may be the most important focus for relapse prevention efforts. The rest of this Section will review prominent relapse factors that have been systematically studied for opioids, alcohol, and tobacco.

Pretreatment Correlates of Relapse

Severity of Drug Dependence

Severity of pretreatment drug dependence is one determinant of the likelihood of relapse. Several studies have found that light

smokers are more likely to succeed at abstinence than heavy smokers (see Table 7 and Chapter VII). Similarly, with regard to opioid dependence, a shorter pretreatment period of dependence is associated with better posttreatment outcomes (Riordan et al. 1976), and level of drug craving was directly related to the amount of variance in relapse (McAuliffe et al. 1986). Estimating the contribution of severity of alcohol dependence to relapse is more problematic because there has been such a wide variety of measures (e.g., severity of social harm, illness, withdrawal, or craving) used among studies. Thus, the seven alcohol studies cited in Table 7 provide equivocal results, and it is unclear whether there is actually no relationship or whether variability in measurement among studies precludes meaningful conclusions. Furthermore, there is some evidence that predictions of relapse based on severity of dependence are moderated by age, marital status (Polich, Armor, Braiker 1981), and gender (Hesselbrock et al. 1983).

A factor that complicates the relationship between duration of drug dependence (as a measure of severity) and likelihood of relapse is that the age of the individual is directly related to remission (see discussion of spontaneous remission earlier in this chapter). Millman, Khuri, and Nyswander (1978) reported that length and intensity of addiction were positively associated with relapse, except that older opioid-dependent persons were more successful at avoiding relapse than younger ones. In a followup study of 38 treated methadone clients, Riordan and colleagues (1976) found that relapsed subjects were more likely than nonrelapsed subjects to have been addicted longer prior to treatment.

Psychiatric Impairment

As previously discussed, both depression and anxiety are commonly observed as dual diagnoses in persons dependent on alcohol and other psychoactive drugs. These diagnoses are also predictive of high rates of relapse and poor treatment outcomes. As shown in Table 7, several studies suggest that overall severity of psychiatric symptomatology may be an important predictor of treatment outcome. For example, McLellan and colleagues (1983) evaluated 6-month posttreatment outcomes for 460 alcoholics and 282 opioid addicts drawn from 6 rehabilitation programs. Using an intervention-based assessment of the severity of psychiatric symptomatology, they observed that patients with low psychiatric severity improved in every treatment program, while patients with high psychiatric severity showed almost no improvement in any treatment program. Patients with midrange severity levels of psychiatric disorder showed differential responses as a function of treatment modality.

TABLE 7.--Studies showing evidence for factors associated with relapse, by substance

Factors	Studies		
	Tobacco	Opioids	Alcohol
Pretreatment			
Degree of dependence	Hall, Herning et al. (1984), Pomerleau et al. (1978), Jarvik (1979), Shiffman (1979, 1984)	McAuliffe et al. (1986), Millman et al. (1978). Riordan et al. (1976)	Foy et al. (1984), Heather et al. (1983). Hesselbrock et al. (1983), Kivlihan et al. (in press), Litman et al. (1984), Orford et al. (1976). Polich, Armor, Braiker (1980)
Psychiatric impairment	No studies	Mclellan et al. (1983), Rounsaville et al. (1985)	Abbot and Gregson (1981), Gregson and Taylor (1977). Heilbrun and Tarbox (1978), O'Leary et al. (1979). Donovan et al. (1984), Mclellan et al. (1983) Rouneaville et al. (1987)
Criminality	No studies	Simpson and Sells (1982). DeLeon (1985)	No studies
Demographics	Tucker et al. (1985), Swan et al. (1985). Eisinger (1971), Campbell (1983)	Tucker et al. (1985), Simpson and Sells (1982)	Tucker et al. (1985). Pemberton (1967), Armor et al. (1978), Voegtlin and Broz (1949), Fox and Smith (1970)

TABLE 7.--Continued

Factors	Studies		
	Tobacco	Opioids	Alcohol
Treatment			
Length	No studies	Simpson and Sells (1982), DeLeon et al. (1982)	Miller and Hester (1986b)
Modality	Row et al. (1980), Foxx and Brown (1979), Elliott and Denney (1978), Erickson et al. (1983), Tiffany, Martin, and Baker (1986)	Simpson and Sells (1982), Bale et al. (1980)	Emrick (1974), Miller and Hester (1986a)
Use of drugs/Involvement in crime	No studies	Simpson and Sells (1982)	No studies
Positive expectations of outcome	Brandon, Tiffany, Baker (1986)	Simpson and Sells (1982)	Eastman and Norris (1982)
Posttreatment			
Family	Marlatt and Gordon (1980), Horwitz et al. (1985), Coppotelli and Orleans (1985), Mermelstein et al. (1983)	Dell Orto (1974), Levy (1972), Stanton, Todd, Steir (1979) Rhoads (1983), Wellisch and Kaufman (1975), Harbin and Mazier (1975), Hejinian and Pittel (1978), Kaufman (1985), Stanton (1978, 1979)	Finney et al. (1980). Moberg et al. (1982), Burton and Kaplan (1968). Moos and Moos (1984), Marlatt and Gordon (1980), Billings and Moos (1982a. b), Moos et al. (1979) Orford et al. (1976)
Peers	Cummings et al. (1980), Shiffman (1982), Evans and Lane (1981), Lichtenstein et al. (1977), Marlatt and Gordon (1980), Cummings et al. (1980)	Hawkins and Fraser (1987), Chaney et al. (1982), Marlatt and Cordon (1980, 1985)	Chaney et al. (1978), Marlatt (1978, Marlatt and Gordon (1980)
Isolation	No studies	Hawkins and Fraser (1987)	Stead and Viders (1979)
Lack of involvement in work		Ronnberg (1979), Savage and Simpson (1979), Simpson (1981), Simpson et al. (1986), Simpson and Lloyd (1979)	Bromet and Moos (1977), Finney et al. (1980)

TABLE 7.--Continued

Factors	Studies		
	Tobacco	Opioids	Alcohol
Lack of active leisure	Shiffman (1984)	Simpson et al. (1981), NIDA (1980)	Finney et al. (1980), Moberg et al. (1982), Moos et al. (1979), Stead and Viders (1979), Tuchfeld (1981). Tuchfeld et al. (1983)
Negative emotional states	Hatsukami et al. (1984), Marlatt and Gordon (1980), Lichtenstein et al. (1977), Mermelstein (1983), Mermelstein et al. (1986), Shiffman et al. (1986), Lichtenstein (1986)	Stephens and Cottrell (1972). Cummings et al. (1980), Marlatt and Gordon (1980), Hatsukami et al. (1981). Chaney et al. (1982)	Ludwig (1982), Marlatt (19781, Chaney et al. (1978), Finney et al. (1980), Slater and Linn (1982-1983), Pickens et al. (1985), Samsonowitz and Sjoberg (1981), Sandahl (1984), Hatsukami et al. (1981)
Negative physical states	Pomerleau (1979), Shiffman (1979)	Khatami et al. (19791, Chaney et al. (1982), Marlatt and Gordon (1989), Martin (1972)	Finney et al. (1980), Moos et al. (1979)
Skills deficits	Marlatt and Gordon (1980), Shiffman (1982, 1984), Curry and Marlatt (1985)	Brill (1963), Cheek et al. (1973), Fort (19661, Catalano and Hawkins (1985)	Miller et al. (1974), O'Leary et al. (19761, Rosenberg (1983), Miller and Eisler (1977)
Negative life events	Etringer et al. (1984)	Judson and Goldstein (1983), Rhoads (1983)	Moos et al. (1979, 1981), Finney et al. (1980), Rosenberg (1983), Hull and Young (1983), Vuchinich and Tucker (1985)
Lack of needed services	No studies	Ogborne (1978), Hawkins and Catalano (1985), McAuliffe et al. (1985)	Feit (1980), Ashley et al. (1976), Ogborne (1978), Ahles et al. (1983), Ito and Donovan (1986)

Demographic Factors

Demographic correlates of relapse have been widely studied. Consistent demographic predictors of relapse, either within or among substances, have not been identified (Tucker, Vuchinich, Harris 1985 and see Table 7). It is possible that the wide historical diversity of methods and definitions used contributes to greater apparent diversity when data are evaluated both within and among drug classes.

Treatment Correlates of Relapse

In treatment studies of opioid-dependent persons, it has been found that treatment type and duration as well as treatment expectancies affect posttreatment relapse. Length of time in treatment has been positively associated with outcomes across modalities of drug dependence treatment (McLellan et al. 1983; Simpson and Sells 1982). In addition, treatment completers have shown more positive outcomes than those who do not complete treatment regimens (DeLeon, Wexler, Jainchill 1982). Expectations of positive treatment outcome have also been related to lower relapse rates (Simpson and Sells 1982). Finally, modality of treatment has been related to treatment outcome in opioid addicts. Methadone maintenance, long-term inpatient treatment, and outpatient drug-free programs have all produced better outcomes than detoxification treatment or no treatment in both a followup study (Simpson and Sells 1982) and a prospective study (Bale et al. 1980). In the alcohol treatment literature, however, few differences have been detected among the most popular treatment techniques, including residential and outpatient modalities (Emrick 1974, 1975; Miller and Hester 1986a).

Schwartz (1987) has recently examined the effectiveness of more than 20 types of smoking cessation interventions (see Table 2 in Chapter VII). Seven methods showed good short-term results: educational techniques, nicotine chewing gum when combined with behavioral treatment, group hypnosis, physician intervention with cardiac patients, rapid smoking, satiation, and contingency contracting. Multicomponent programs that combined several interventions appeared to produce especially encouraging outcomes.

Expectations regarding alcohol's effects may enhance susceptibility to relapse. Eastman and Norris (1982) examined this relationship in 89 persons participating in outpatient treatment for alcohol dependence. At a 2-month followup, 71 percent of subjects with positive expectations about alcohol's effects had relapsed (any level of consumption was the criterion), compared with only 7 percent of subjects with negative expectations about the effects of alcohol. Analogously, in cigarette smokers, expectations regarding one's

ability to successfully abstain may also predict relapse to tobacco use (Brandon, Tiffany, Baker 1986; Chapter VII).

Posttreatment Correlates of Relapse

Evidence from a number of sources suggests that posttreatment experiences are particularly important to the relapse process. For example, Finney, Moos, and Mewborn (1980) found posttreatment factors to account for roughly half of all variance in treatment outcome. Further, recent investigations of the effectiveness of aftercare in the treatment of drug and alcohol abuse suggest that interventions which target the posttreatment interval may be particularly effective (Ahles et al. 1983; Catalano and Hawkins 1985; Catalano et al., in press; Marlatt and Gordon 1985). Specific categories of posttreatment factors associated with relapse are described below.

Family Support Factors

Family support has been a strong predictor of posttreatment success for opioid users, alcoholics, and cigarette smokers (Table 7). For example, Orford and colleagues (1976) found a marital cohesion factor to predict treatment outcome for drinking variables measured 12 months later. Similarly, in a survey of 219 subjects who were interviewed at l-year followup after treatment in a minimal intervention smoking cessation program, abstainers reported significantly more support from spouses, parents, family, and friends than did relapsers (Horwitz et al. 1985). Similarly, Orford and colleagues (1976) found that high marital discord was a predictor of relapse drinking at the 12-month followup among treated alcoholics, whereas Burton and Kaplan (1968) found reduction in the number of areas of disagreement between the alcoholic and his or her spouse to be associated with improvement in drinking behavior. These observations are consistent with the retrospective reports of relapsed subjects indicating that interpersonal conflict that was family or peer related was a trigger for drug use following a period of abstinence (Marlatt and Gordon 1980). Taken together, these data suggest that family support plays an important role in preventing relapse to substance use and that family conflict and lack of support for posttreatment recovery may increase levels of relapse for treated users of alcohol, opioids, and tobacco.

Drug Use Among Peers

Relapse to drug use following a period of abstinence after treatment often occurs when there is peer pressure to use drugs or when drugs are offered by the nonabstinent peer. A series of reports by Marlatt, Chaney, and their associates (Chaney, O'Leary, Marlatt

1978; Chaney, Roszell, Cummings 1982; Marlatt 1979; Marlatt and Gordon 1980, 1985) examining determinants of relapse for various substances suggested that social pressure is a factor for approximately 15 to 40 percent of relapse episodes among alcohol and opioid users. In a followup study of treated heroin users, Hawkins (1979) found that 69 percent of those who returned to heroin use after drug treatment reported that they did so in response to informal pressure from peers, suggesting an even stronger effect of social factors on relapse among opioid users. Similarly, living with smokers (Shiffman 1982) and failure to avoid smoking peers (Graham and Gibson 1981) are related to relapse in treated smokers. Specifically, Shiffman (1982) found that 30 percent of the relapse cases of 183 ex-smokers were associated with the presence of other people smoking. Other investigators have also found the presence of other smokers (Lichtenstein, Antonuccio, Rainwater 1977) or social pressure to smoke (Cummings, Gordon, Marlatt 1980) to be a risk factor for relapse (Chapter VII).

Involvement in Work and Leisure Activities

Although active employment and involvement in leisure activities may be distinguished (as shown in Table 7), there are similarities in their effects on relapse. Furthermore, the factors are similar in that both may be incompatible with active involvement with some dependence-producing drugs. In brief, research on posttreatment experiences of both opioid users and alcoholics has shown a consistent positive relationship between involvement in active recreational leisure activities (sports, hobbies, crafts, and volunteer work) and reduced use of opioids, alcohol, and tobacco (Table 7). Similarly, unemployment is associated with relapse to opioids and alcohol (Table 7).

Negative Emotional States

One of the most consistent findings from retrospective studies of relapse is the involvement of negative emotional states in relapse episodes. Data supporting this conclusion regarding tobacco use are discussed in detail in Chapters VI and VII and are only briefly summarized in this Section to enable a comparison of findings with opioids and alcohol. Ludwig (1972) interviewed 161 relapsed alcoholics and reported that 25 percent relapsed in response to "psychological distress." Marlatt (1978) interviewed 48 alcoholics who relapsed within 90 days of discharge from treatment and found that 10 percent relapsed in negative mood states and 29 percent in situations arousing frustration or anger. Negative emotional states are also prominent determinants of relapse to cigarette smoking. For instance, Marlatt and Gordon (1980) reported that 43 percent of the

relapse episodes of 35 subjects who had completed a smoking cessation program were in response to negative mood states.

Drug use has also been reported as a means of alleviating negative emotional states. For example, Stephens and Cottrell (1971) studied 236 opioid users who had received 6 months of inpatient methadone treatment. One-quarter of the clients they studied relapsed, reportedly using the drug to alleviate stress or to combat personal faults or depression. Consonant with these findings, reports of former drug users suggest that approximately one-fourth to one-third of the incidents of first drug use following treatment are precipitated by negative emotional states (Cummings, Gordon, Marlatt 1980; Marlatt and Gordon 1980).

Potential sources of negative emotions cited by relapsers include stressful interpersonal interactions (e.g., anger, frustration) and negative life events such as death, illness, job loss, or change. The role of negative life events has long been recognized as an important factor that can influence psychopathology, illness, and drug dependence; recently, systematic studies of these latter factors have also been conducted (Bloom 1985). For example, Moos, Finney, and Chan (1981) found that relapsed alcoholics reported nearly twice as many negative events and approximately one-half as many positive events as either recovered alcoholics or controls (Hull and Young 1983; Vuchinich and Tucker 1985).

Another potential source of negative emotions is illness or somatic discomfort from a variety of sources. In this regard, drug dependence researchers have documented the tendency of some drug users to use drugs as a form of self-medication (see Chapter VI for tobacco-specific data). For instance, opioid dependence may develop during the course of treatment for chronic pain (Khatami, Woody, O'Brien 1979) and other forms of somatic discomfort (Marlatt and Gordon 1980; Chaney, Roszell, Cummings 1982). Similarly, physical symptoms, including allergies, back pain, headache, and insomnia, during the posttreatment period were related to opioid and alcohol use in a sample of treated alcoholics (Finney, Moos, Mewborn 1980; Moos et al. 1979). A possibly related finding is the suggestion from a number of studies that protracted withdrawal symptoms are factors in relapse to opioid (Martin 1972) and tobacco (Pomerleau 1979; Shiffman 1979) use.

As shown in this Section, relapse is characteristic among persons treated for opioid, alcohol, nicotine, and other forms of drug dependence. Rates and patterns of relapse appear to vary more as a function of treatment characteristics, client parameters, and posttreatment environmental factors than as a function of drug type when alcohol, opioids, and nicotine are compared.

Posttreatment factors appear to be the most important determinants of treatment success and relapse avoidance for users of

tobacco, opioids, and alcohol. These are summarized in Table 7. Specifically, the most common predictors, similar for alcohol, opioids, and nicotine, include posttreatment family support factors, peer substance use factors, leisure and recreational activities, and occurrence of stressful or negative affect situations in the form of intrapersonal mood states, somatic complaints, negative life events, or stressful interpersonal interactions. Additional factors that appear important include pretreatment severity of use (tobacco and opioids), length of treatment (opioids), and type of treatment (tobacco and opioids).

Treatment of Drug Dependence

Scientifically based methods of helping drug dependent persons to achieve and maintain drug abstinence are available and can be efficacious. The methods are being continually refined, however, as new data are collected on how to better address the needs of clients or patients and how to make treatments more readily available and acceptable for those who want help. This Section briefly reviews some of the kinds of treatment approaches that are available for the various drug dependencies.

Treatment strategies designed to address dependence on opioids, alcohol, nicotine, and many other dependence-producing drugs are remarkably similar. This phenomenon provides additional evidence that the processes that determine addiction are similar for the various dependence-producing drugs. Some of the differences in treatment are related to variations in detoxification strategies, which depend on the route of drug administration and on differences in the duration of drug action. There is also need to tailor the content and/or intensity of treatment delivered to groups with different substance dependencies. For example, the need for medical intervention to alleviate acute withdrawal symptoms varies among and within drug classes as a function of the physical dependence level. This Section will discuss the goals of treatment for drug dependence and three types of interventions that are commonly employed: (1) pharmacologic substitution therapy designed to suppress withdrawal, (2) interventions designed to redress deficits in skills and/or deficits in social support that are potentially related to relapse, and (3) interventions designed to bolster or sustain motivation for abstinence. These kinds of intervention strategies are not mutually exclusive, and are often used in combination to yield better overall rates of success than any single approach (Grabowski et al. 1984).

Goals of Treatment

Reducing or eliminating self-administration of the substance to which the person is dependent is the primary goal of treatment. Traditionally, there has been a tendency for treatment programs to rely on a goal of complete abstinence rather than reduction of use to manageable or nonproblematic levels. The appropriateness of this goal may, in part, vary by drug class, as well as by severity of dependence. For example, problems associated with alcohol use vary considerably, and it would appear that many persons with low levels of dependence are able to maintain stable levels of "social drinking," whereas persons with more severe levels of dependence must maintain total abstinence (Miller and Joyce 1979; Miller 1979). Because it has been estimated that only about 10 to 15 percent of adults (United States) who drink warrant the designation "problem drinker" and only a subset of these warrant the designation "alcoholic," such variation in treatment goals is not surprising (Cahalan 1970; Miller 1979). Analogously, it appears that only a small fraction of caffeinated beverage (e.g., coffee and tea) drinkers display distinct adverse consequences and apparent loss of control over caffeine intake (Griffiths and Woodson 1988)--observations consistent with the rapidly growing decaffeinated beverage market. On the other hand, with drugs for which any nonprescription use is illicit (e.g., opioids) or on which the overwhelming majority of users are dependent (e.g., only 10.6 percent of current smokers smoke 5 or fewer cigarettes/day according to the 1985 National Health Interview Survey (unpublished data, Office on Smoking and Health)), a goal of reduction of use may be especially problematic (Chapter VII). Two additional problems with low-level cigarette use as a therapeutic goal are that no level of cigarette smoking has been found safe (US DHHS 1986) and that even if the smoker is only smoking a few cigarettes, by taking more puffs per cigarette and by inhaling the smoke more deeply, the smoker might actually maintain substantial levels of tobacco toxin intake and nicotine dependence (Kozlowski 1981; Benowitz et al. 1983; Chapter IV). The percentage of persons using amphetamine or cocaine who are unable to control their intake is unknown, but because nonmedical use of these drugs is illicit and because animal and human research indicates that these drugs are powerful reinforcers (US DHHS 1987), total abstinence is similarly recommended (US DHHS 1987).

Maintenance of abstinence or avoidance of relapse is another major treatment goal. Because relapse factors can remain functional for many years in individuals who are abstaining from use of a drug to which they had been dependent (Chapters VI and VII), designing a long-range program to minimize the impact of such factors is an integral part of many drug treatment programs (e.g., Thompson, Koerner, Grabowski 1984; Stitzer et al. 1984). These factors may

include some assumed to be physiologically related to the drug dependence process (e.g., anxiety or stress), while others are assumed to function at more of a behavioral level (e.g., the sight of drug-associated stimuli).

Types of Treatment for Drug Dependence

Treatment approaches can be divided into those which involve the administration of drugs (Pharmacologic Treatment Approaches) and those which do not (Nonpharmacologic or Behavioral Treatment Approaches). Sophisticated methods involving both pharmacologic and behavioral approaches are more recent developments and show considerable promise for the treatment of dependence to alcohol, opioid, cocaine-like drugs, and nicotine (Grabowski, Stitzer, Henningfield 1984). Although considered separately in this Section, pharmacologic and behavioral treatment approaches are commonly combined and may be most effective when used in combination (Grabowski, Stitzer, Henningfield 1984; Crowley and Rhine 1985). Combined treatment approaches specific to cigarette smoking are discussed in Chapter VII.

Pharmacologic Treatment of Drug Dependence

Four pharmacologically based approaches for the treatment of drug dependence can be differentiated: (1) *replacement* or *substitution therapy* (e.g., methadone for opiate dependence), in which a more manageable (and ideally, less addicting) form of the drug is provided; (2) *blockade therapy* (e.g., naltrexone for opiate dependence), in which the behavior-controlling effects of the abused drug are blocked by pretreatment with an antagonist; *(3) nonspecific pharmacotherapy,* in which the patient is treated symptomatically (e.g, use of clonidine during opioid detoxification); and (4) *deterrent therapy,* in which administration of the treatment drug results in the occurrence of aversive effects when the abused drug is subsequently taken (e.g., the use of disulfiram to treat alcoholism (Grabowski, Stitzer, Henningfield 1984; Jaffe 1985). Each of these approaches has been described in greater detail elsewhere and will be only briefly described below (Cooper, Altman, Brown, Czechowicz 1983; Bigelow, Stitzer, Liebson 1985; Jaffe 1985; Jasinski, in press; Jasinski and Henningfield 1988; Jarvik and Henningfield, in press).

Replacement Therapy

The most widely investigated and evaluated pharmacologic treatment approach for drug dependence is replacement therapy. The general principle of replacement therapy is to provide the patient with a safer and more manageable form of drug that directly alleviates signs and symptoms normally suppressed by the substance

upon which the patient is dependent (Jaffe 1985, 1987; Jasinski and Henningfield 1988). Ideally, it should also be of lower dependence potential so that its use may be more readily discontinued than use of the original form on which the person is dependent.

Replacement therapies function through four general actions: (1) they block the onset of the physiologically mediated aspects of withdrawal; (2) they maintain a level of tolerance that attenuates the reinforcing properties of the abused chemical; (3) they treat ("suppress") other signs and symptoms such as dysphoria that may constitute vulnerability and pose an impediment to normal functioning and well-being; (4) they directly suppress drug-taking behavior, much as caloric loading can suppress eating.

The drugs that are widely used to alleviate withdrawal symptoms by providing some level of pharmacologic replacement are the following: methadone for opiate withdrawal (Cooper, Altman, Brown, Czechowicz 1983), benzodiazepines for alcohol withdrawal (Sellers et al. 1983; Newsome and Seymour 1983; Liskow and Goodwin 1987), and nicotine polacrilex gum for tobacco withdrawal (Chapters IV and VII). The potential effectiveness of these agents in prevention or relief of withdrawal symptoms has been well documented (Jaffe 1985). However, relief of early withdrawal symptoms does not necessarily yield improved overall treatment outcomes. Primary withdrawal symptoms for all dependence-producing drugs are time limited, and their duration does not span the entire high-risk period for postcessation relapse. These observations are consistent with the finding that withdrawal symptomology is only one of several potential relapse determinants.

Besides relief of withdrawal symptoms, there are several other functions that a replacement therapy might serve that would make continued long-term treatment beneficial. One of these functions is a reduction in the need for the primary addicting drug, along with a similar reduction in drug seeking. Just as importantly, the replacement therapy may reduce or eliminate symptomology (e.g., anxiety, antisocial behavior, inability to concentrate on tasks) that may interfere with the person's ability to perform in occupational settings and maintain social relationships. Analogously, nicotine replacement therapy during cigarette abstinence can reduce or eliminate tobacco intake and symptoms that interfere with normal social or occupational activities, even though urges to smoke may not be eliminated (Chapter VII).

The constraints on the efficacy of replacement therapies are generally similar across drug classes. Most importantly, the clinical application of replacement therapies is impeded by the influence of nonpharmacologic factors, which vary among individuals and/or situations (e.g., the specific drug delivery system customarily used and ritualistic aspects of the behavior). Pharmacologically related

differences may also mitigate acceptability of the replacement drug; e.g., orally administered replacements are generally not as satisfying to the user as i.v. or inhalation systems, such as the "crack" form of cocaine or tobacco smoke. In addition, replacement therapies do not reliably diminish the urge to use the drug or specific drug formulation (e.g., cigarette brand or alcoholic beverage) to which a person is accustomed. (Issues related to craving are discussed in greater detail in Chapters IV and VII; Childress et al., in press; Henningfield and Brown 1987.)

Blockade Therapy

A pharmacologic alternative to replacement therapy is to produce a pharmacologic blockade of receptors which mediate the reinforcing as well as the toxic effects of the drug (Jaffe 1985). For opioid agonists such as morphine and heroin, the short-acting antagonist naloxone can be used to reverse the effects of an overdose of the opioid agonist. The longer acting antagonist naltrexone can be given on a daily basis to opioid users to prevent them from experiencing the reinforcing and toxic effects of opioid agonists. Unfortunately, clinical trials have shown that there is frequently poor compliance with blockade therapy (Ginzburg 1986). Lack of compliance results in limited clinical utility. No clinically tested antagonist treatments are currently available for the treatment of alcohol or nicotine dependence, although experimental research with the nicotine blocker, mecamylamine, suggests that such an approach may hold promise (Chapter VII; Jarvik and Henningfield, in press).

Nonspecific Pharmacotherapy or Symptomatic Treatment

Administration of and abstinence from dependence-producing drugs produce a cascade of effects involving a variety of neurochemical and physiological effects. As discussed with regard to nicotine in Chapters III and VI, such drug actions mediate many of the desirable and undesirable effects. In principle, it is possible to target treatment approaches on a symptomatic basis.

One example of such an approach is the use of an antidepressant (desipramine) to help achieve and maintain abstinence from cocaine (Gawin and Kleber 1984); cocaine abstinence is often accompanied by symptoms of depression. Somewhat analogous is the use of clonidine to treat opioid withdrawal symtomology (Gold, Dackis, Washton 1984). Clonidine seems to exert its primary actions by suppressing aspects of opioid withdrawal that are mediated by the activity of the sympathetic nervous system (SNS). In one study, clonidine was just as effective as morphine in the reduction of certain physiological signs of opioid withdrawal (Jasinski, Johnson, Kocher 1985); however, in that study, clonidine did not reduce the self-reported

"discomfort" as effectively as did morphine. These observations are consistent with the conclusion that some but not all of the effects of the opioid withdrawal syndrome are mediated by the SNS and that treatment of these effects may provide limited but objective benefit. An analogous approach has been explored for application of clonidine in the treatment of tobacco withdrawal (Glassman et al. 1984, 1988), but conclusions are only suggestive of the possible viability of this approach (Chapter VII; Jarvik and Henningfield, in press).

Pharmacologic Deterrents

Drug taking can sometimes be reduced or eliminated if the consequences are immediate and/or severe enough (Crowley and Rhine 1985). There has been some effort to develop pharmacologic treatments that ensure immediate, reliable, and highly aversive (but safe) effects following self-administration of the drug of dependence. Only one such agent has provided a near approximation of these criteria: disulfiram, which is used in the treatment of alcoholism (Jaffe and Ciraulo 1985; Miller and Hester 1986a). When disulfiram has been taken, a small amount of alcohol can produce rather severe discomfort and acute illness. Reviews of controlled treatment outcome studies (Miller and Hester 1986a) suggest that many of the therapeutic effects of disulfiram may also derive from placebo effects. Thus, in some studies (e.g., Fuller and Roth 1979), outcomes have been similar for placebo and active drug groups, with only medication-compliant individuals (about 20 percent in each group) showing good outcomes.

No deterrents comparable to disulfirum in potential efficacy have been clinically tested for treatment of dependence on opioids or nicotine (see also Chapter VII). As with antagonists, a practical problem in treatments using deterrents is compliance, i.e., maintaining adequate levels of use of the medication itself. A deterrent is ineffective if it is not taken, and development of contingencies to ensure that the patient takes the deterrent has proceeded slowly (Bigelow, Stitzer, Liebson 1984, 1985; Stitzer, Bigelow, Liebson, McCaul 1984). Therefore, even if theoretically effective deterrents become available for treatment of other drug dependencies, their utility might be limited.

Behavioral Treatment Strategies

Despite the powerful sequelae which may accompany both drug administration and drug abstinence, most drug-dependent persons (possibly excluding opioid users) are not systematically treated with pharmacologic approaches. Drug dependent persons may eventually "spontaneously remit" (discussed earlier in this Chapter), but many others enter formal treatment programs that provide supportive and

behavioral therapy. Behavioral treatment approaches have a heterogeneous array of theoretical bases and means of implementation (Stitzer, Bigelow, McCaul 1983). Although the term "behavioral treatment" is often reserved for approaches which involve the systematic application of behavior modification, it is sometimes applied to any nonpharmacologic approach. Thus, behavioral strategies may involve group support, individual counseling, skills training, or family intervention (Krasnegor 1979a; Grabowski, Stitzer, Henningfield 1984). The present Section will provide a brief review of behavioral approaches aimed largely at relapse prevention.

The major challenge in the treatment of drug dependence is no longer in the initial attainment of abstinence; rather it is in the maintenance of abstinence. In fact, it is worth noting that the shift in emphasis from achievement of abstinence to the maintenance of abstinence is an important advance in treatment efficacy in itself (McAuliffe et al. 1986). This current focus has resulted in the development of nonpharmacologically based approaches aimed at what is often termed relapse prevention. In the past decade, relapse prevention interventions have been increasingly founded on empirical investigations of situational precipitants of relapse and/or have addressed factors known to predict relapse that can be manipulated (Catalano and Hawkins 1985; Catalano et al., in press; Hawkins and Catalano 1985; Marlatt and Gordon 1985; Tucker, Vuchinich, Harris 1985; Brownell et al. 1986; Todd, 1984).

A specific goal of approaches to relapse prevention is to increase the impact of those factors that are negatively associated with relapse and to decrease the impact of factors that are positively associated with relapse. These approaches have led to the development of a number of techniques that hold promise for prevention of posttreatment relapse. Some of the better documented approaches are summarized below.

Relapse Prevention Skills

Marlatt and his associates (Marlatt and Gordon 1980, 1985; Cummings, Gordon, Marlatt 1980) have developed a cognitive behavioral model of relapse which includes skills training for each phase of the relapse process. They advocate training: (1) to recognize "apparently irrelevant decisions leading to relapse"; (2) to identify and cope with personal high-risk relapse situations; (3) to practice behaviors which increase perceptions of self-efficacy and control such as reading, relaxation, and meditation; (4) to recognize the negative effects in biphasic drug action which follow immediate positive effects; (5) to cope with a slip; and (6) in some cases, to practice a relapse under controlled circumstances called a "programmed relapse" (although the general efficacy of this approach has not been confirmed).

Reports of skills training with alcoholics far outnumber reports of similar training with users of other drugs. Treatment in these studies usually involves assertion/social skills training, problem-solving training, and/or practice of high-risk situations using a combination of methods, including didactic presentation, modeling, role play, feedback, generation and evaluation of alternative problem solutions, and homework assignments. Skills improvement has been achieved as indicated by role play, self-report, and questionnaire measures, and a positive impact of skills training procedures has been shown in the treatment of alcohol use (Watson and Maisto 1983; Van Hasselt, Hersen, Milliones 1978) and cigarette smoking (Shiffman 1982; Hall, Rugg et al. 1984).

The effectiveness of skills training with users of drugs other than alcohol has not been as thoroughly evaluated as for alcohol. In five single-case and uncontrolled group studies involving primarily opioid users, two reported reduced drug use at followup (Cheek et al. 1973; Polakow and Doctor 1973); four found self-reported improvements in social functioning (Cheek et al. 1973; Matefy 1973; Polakow and Doctor 1973; Wolpe 1965); and one reported improved role play performance (Callner 1973). Four studies of users of a variety of illicit drugs (Callner and Ross 1978; Hawkins, Catalano, Wells 1986; Smith 1982; Lin et al. 1982) have reported improvements in skills related to high-risk relapse situations, and one found decreased use of marijuana (Smith 1982). In one study, skill changes generalized to untrained situations and were maintained l-year posttreatment (Hawkins, Catalano, Wells 1986). As discussed in Chapter VII, preliminary studies suggest that skills training strategies may be of some utility in the treatment of tobacco dependence. For example, Hall, Rugg, Tunstall, and Jones (1984) found that smokers receiving relapse prevention skills training were significantly less likely to relapse than smokers assigned to a discussion control condition. Subsequent studies and reviews indicate mixed results (Hall et al. 1985; Schwartz 1987).

Leisure Activity Skills

In recognition of the association of relapse with an absence of active leisure activity, a number of aftercare programs have attempted to increase participation of clients in organizations beyond work or treatment (Catalano and Hawkins 1985; McAuliffe et al. 1986; Nurco et al. 1983; Wolf and Kerr 1979). Controlled studies have shown that drug users can be encouraged to participate in voluntary community organizations and activities following inpatient treatments and that these contacts can be maintained over a l-year period following treatment, but in these studies there were no beneficial effects in reducing relapse rates (Catalano and Hawkins 1985; Hawkins and Catalano 1985).

For alcoholics and cigarette smokers, physical exercise has been examined as a potential relapse prevention strategy. Murphy, Marlatt, and Pagano (1986) found that problem drinkers trained in running reported greater reductions in drinking at followup than did drinkers trained in meditation. In a retrospective self-report study, Koplan, Powell, Sikes, Shirley, and Campbell (1982) found at l-year followup that of the 2,500 runners competing in the 10K Peachtree Road Race in Atlanta and returning questionnaires, 81 percent of males and 74 percent of females who smoked cigarettes before they started running had stopped smoking after they began running.

Stress Management Skills

As discussed earlier in this Chapter and in Chapters VI and VII, negative emotions associated with stressful events or interpersonal interactions have been strongly implicated in relapse precipitation. In principle, such emotional states can be addressed through stress management training, relaxation, meditation, or other "lifestyle" interventions (Marlatt and Gordon 1985; Charlesworth and Dempsey 1982). Although stress reduction techniques are frequently included as a part of drug abuse treatment, there are a surprisingly small number of well-controlled studies addressing the effectiveness of anxiety-reduction techniques with drug-abusing clients (Marlatt and Gordon 1985). As indicated earlier in this Section, there is evidence that programs which may reduce anxiety by use of aerobic exercise or relaxation practice can bring about significant reductions in alcohol use among heavy drinkers (Marlatt and Marques 1977; Marlatt et al. 1984; Murphy, Marlatt, Pagano, 1986). Further research is needed to assess the effectiveness of these techniques in reducing the use of substances following treatment for alcohol, opioid, and tobacco dependence.

Motivation Enhancing Treatments

Treatment interventions in which the primary purpose is to improve or bolster motivation for continued abstinence can take many forms. Many drug-dependent persons enter treatment as the result of some form of pressure from friends, employers, family, medical practitioners, or legal agencies. Sometimes treatments can be designed that incorporate these sources of community pressure and support for abstinence. The present Section will focus on interventions that involve social support from professional therapists, peers, and family.

Social support strategies designed to bolster environmental support for abstinence include enlistment of support from families and existing social networks, the creation of new primary social support such as self-help groups or linkages with community volunteers, and

supportive services provided by professional human service workers. Only preliminary systematic research has been conducted utilizing such interventions; however, the approach appears of similar applicability and utility in the treatment of opioid, alcohol, and tobacco dependence (Ashery 1979; Nurco et al. 1983; Leach 1973; Madsen 1974; Janis and Hoffman 1970).

Professional contact is a special kind of support strategy which has been used in drug use treatment. Typically, it involves ongoing contact with professionals from the primary treatment program. This approach may include booster sessions of individual or group counseling, followup phone calls or letters from therapists, or followup visits by counselors to former clients in the community to review progress and problems. Fitzgerald and Mulford (1985) found that bimonthly phone calls to alcoholic patients by an alcohol counselor did not affect drinking outcome. Pokorny and others (1973) found that weekly group therapy sessions following 60-day inpatient treatment for alcoholism produced relapse results equivalent to more expensive 90-day inpatient treatment with no followup. Colletti and Supnick (1980) found that weekly contact with therapists during the first month following treatment for smoking resulted in better smoking outcomes at 6 months than when subjects received no aftercare, though these differences were not maintained at 12-month followup. Chapter VII describes additional analogous strategies used to treat tobacco dependence.

Family support is a potentially cost-effective and long-lasting form of motivation enhancement. The potential importance of family support is emphasized by the correlation between stable family environment and good treatment outcomes previously discussed. In recognition of this relationship, self-help groups to assist family members of addicts and alcoholics have proliferated since the early 1970s. They include Alcoholics Anonymous (AA), Narcotics Anonymous (NA), and Families Anonymous groups for families coping with alcoholism and drug abuse (Ashery 1979; Brown and Ashery 1979), and service-agency-based aftercare groups for families (Dunlop, Skorney, Hamilton 1982). Agencies which have also focused on broader informal social networks have also arisen (Collins and Pancoast 1976; Gottlieb 1981; Speck and Attneave 1973; Whittaker and Garbarino 1983). A study by Stanton, Todd, and Steier (1979) provides support for the benefits of involving the families of opioid users in treatment. They found that in families of opioid users which received structured family therapy, there were more days free of the use of opioids, nonopioid illegal drugs, and alcohol than for opioid users whose families did not receive such treatments. While not reporting drug use outcomes, others have enlisted family members and close friends of drug dependent persons as supportive sponsors in drug treatment programs (Sorensen and Gibson 1983; Callan,

Garrison, Zerger 1975). Such networks are being increasingly developed in recent years to help tobacco dependent persons (Chapter VII; see also Schwartz 1987).

Peer support constitutes a potentially powerful motivation-enhancing approach. A difficulty of peer support is that it often involves establishing a new peer group for the drug dependent person if his or her current peer group continues to support drug use. Self-help groups such as AA and NA, for example, provide former substance abusers with a new social support network of individuals in like circumstances (Ashery 1979; Nurco et al. 1983). Descriptive followup studies of non-probability samples of AA members have suggested that AA is an effective approach for assisting some recovering alcoholics to maintain their sobriety (Leach 1973; Madsen 1974; Maxwell 1962). Several studies of the effectiveness of residential AA programs have also found better outcomes associated with participation (Alford 1980; Smith 1984, 1985). However, these studies have either failed to utilize control groups or utilized "matched" comparison groups that differ on pretreatment criteria which may influence outcome. Thus, these studies do not provide conclusive efficacy data.

A few studies have attempted to create or enhance existing peer social support, with mixed results. For example, a volunteer sponsor program for "skid-row" alcoholics was described by Fagan (1986), in which sponsor groups from churches were assigned alcoholics in a rehabilitation program. This program was not evaluated in a controlled manner. Janis and Hoffman (1970) investigated the effects of a self-help social support intervention on relapse following smoking cessation treatment. Clients paired in a high-partner-contact condition (daily calls for 5 weeks) were more successful in maintaining abstinence at l- and lo-year followups than were clients in low-contact or control conditions. The critical dimension appeared to be quality of peer support.

Conclusions

1. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.
2. Environmental factors including drug-associated stimuli and social pressure are important influences of initiation, patterns of use, quitting, and relapse to use of opioids, alcohol, nicotine, and other addicting drugs.
3. Many persons dependent upon opioids, alcohol, nicotine, or other drugs are able to give up their drug use outside the context of treatment programs; other persons, however, re-

quire the assistance of formal cessation programs to achieve lasting drug abstinence.

4. Relapse to drug use often occurs among persons who have achieved abstinence from opioids, alcohol, nicotine, or other drugs.
5. Behavioral and pharmacologic intervention techniques with demonstrated efficacy are available for the treatment of addiction to opioids, alcohol, nicotine, and other drugs.

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