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and physiological functioning requires continued drug administration and that disruption will occur when the drug is withdrawn.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).

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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

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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), Schasre (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 Biernacki (1979), Vaillant (1964, 1970)
Financial problems	Cahalan (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), Jorquez (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), Jorquez (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

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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.

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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

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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

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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.

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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).

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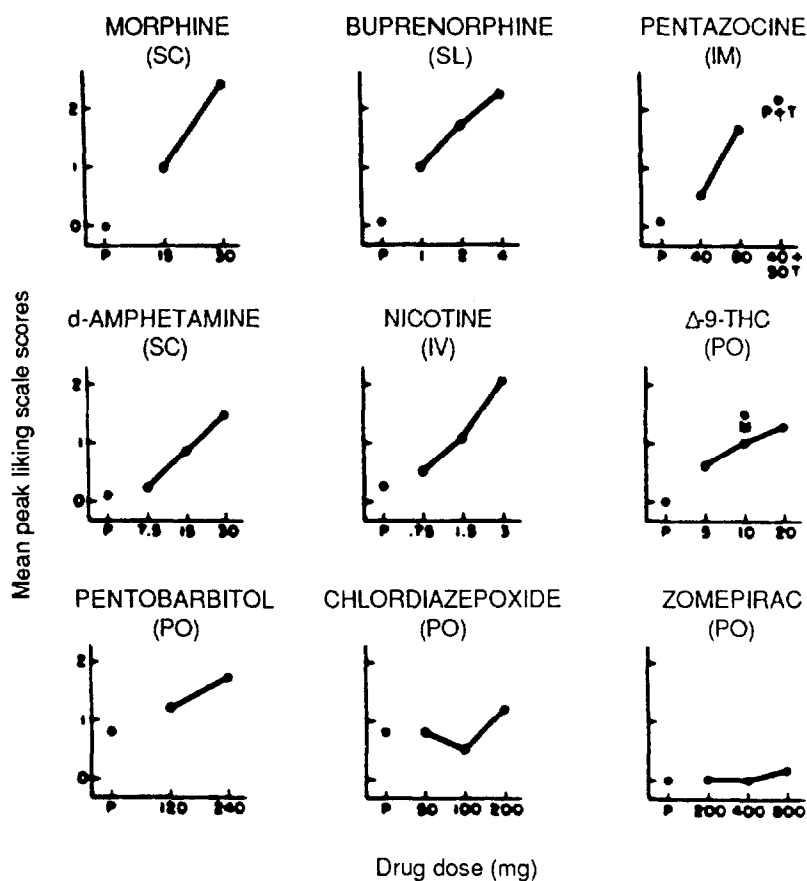
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FIGURE 1.—Liking scale scores of the single-dose questionnaire

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; Henningfield, 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

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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; Järbe 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