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

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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,

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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 wide-spread 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

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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

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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).

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(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

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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

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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, Henningfield 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

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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 (s   Chapter IV), withdrawal responses may be distinguished from ...e. .bstinence-associated symptomology by their relative consistency among indi-

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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	Morphine-like	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 (1986)	+? Carroll and Lac (1987), Jones (1984)	+ Light and Torrance (1929a), Kolb and Himmelsbach (1938), Himmelsbach (1941)	+ Isbell 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	+[1] 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