CHAPTER IV

TOBACCO USE
AS DRUG DEPENDENCE

CONTENTS

Introduction

This Chapter reviews the evidence that tobacco is a pharmacologically addicting substance and that tobacco use can be considered a form of drug addiction. Specific criteria to identify a substance as pharmacologically addicting are discussed in Chapters I and V. In brief, the criteria are: (1) that highly controlled or compulsive patterns of drug taking occur, (2) that a psychoactive or mood-altering drug is ingested by use of the substance and is involved in the resulting patterns of behavior, and (3) that the drug is capable of functioning as a reinforcer that can directly strengthen behavior leading to further drug ingestion. Addicting drugs can be characterized by other properties that include the following: they can produce pleasurable effects in users, they can cause tolerance and physical dependence, and they can have adverse or toxic effects. Drawing upon data from studies of tobacco and nicotine, involving both humans and animals, the present Chapter reviews the evidence that tobacco meets the criteria as a pharmacologically addicting substance. A specific comparison of tobacco to other pharmacologically addicting substances is provided in Chapter V.

Cigarette Smoking: Controlled Drug Self-Administration

Highly controlled or compulsive drug use refers to drug-seeking and drug-taking behavior that is driven by strong, often irresistible urges. It can persist despite a desire to quit or even repeated attempts to quit.

Basic observations and experimental research indicate that cigarette smoking is not a random or capricious behavior that simply occurs at the will or pleasure of those who smoke. Rather, smoking is the result of behavioral and pharmacologic factors that lead to highly controlled or compulsive use of cigarettes. The highly consistent patterns of cigarette smoking illustrate the controlled nature of the behavior. For example, following initiation of smoking the individual gradually increases cigarette intake over time until he or she achieves a level that remains stable, day after day, during the smoker's lifetime (Schuman 1977; US DHHS 1987a). The dependent smoker tends to adopt a pattern in which the initial cigarette of the day is smoked soon after waking (Fagerstrom 1978) and in which smoking throughout the day is regular from day to day (Griffiths and Henningfield 1982; Griffiths, Henningfield, Bigelow 1982). "Occasional" cigarette smoking (or "chipping") occurs just as does occasional use of other addicting drugs (see Chapter V); however, the 1985 National Health Interview Survey showed that only 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 1987a).

Strong evidence that cigarette smoking is a highly controlled or compulsive behavior is provided by survey data showing that a majority of smokers have tried to quit or at least would like to quit. For example, several Gallup surveys have shown that a large majority of smokers report a desire to quit smoking; in fact, the proportion of smokers who would like to quit increased from 66 percent in 1977 to 77 percent in 1987 (Gallup 1987), perhaps because of a declining social acceptability of smoking and the growing awareness of the health hazards of smoking. In addition, the 1986 Adult Use of Tobacco Survey (US DHHS 1987b) showed that 65 percent of cigarette smokers had made at least one serious attempt to quit; another 21 percent said that they would try to quit "if there were an easy way to do so" (Fiore et al., in press; US DHHS 1986).

The compulsive nature of cigarette smoking is most apparent in extreme cases: for example, the laryngectomized patient who, having already suffered severe consequences of smoking, continues to smoke through a tracheostomy hole. Similarly, 50 percent or more of patients recovering from surgery for a smoking-related disease (e.g., cancer, cardiovascular disease) resume smoking while in the hospital or shortly after discharge (Burling, Singleton et al. 1986; West and Evans 1986).

In this Section, the behavioral process of cigarette smoking and the factors which determine the course of the behavior are described. Evidence that cigarette smoking is repetitious and stereotypic, common features of compulsive drug use, is reviewed in this Section, as well as evidence that actions of nicotine are responsible for patterns of smoking behavior. Initially, however, it is necessary to briefly review the methods by which the behavioral process of cigarette smoking is studied, as well as the main findings from such studies.

Measurement of Cigarette Smoking

Cigarette smoking behavior may be analyzed at different levels ranging from epidemiological surveys to the analysis of cigarette puffing. In fact, many thousands of scientific articles have been published in which some aspect of cigarette smoking is described. Much of this research has been reviewed in the tobacco research compendia of Larson and his colleagues (Larson, Haag, Silvette 1961; Larson and Silvette 1968, 1971, 1975), a previous report of the Surgeon General (US DHEW 1979), several monographs of the National Institute on Drug Abuse (NIDA) (Jarvik et al. 1977; Krasnegor 1978, 1979a,b,c; Grabowski and Bell 1983; Grabowski and Hall 1985) and in articles by others (Russell 1971, 1976; Gritz 1980; Henningfield 1984).

It is characteristic of drug dependence that the drug-seeking and self-administration behaviors become stereotypical and automatic in

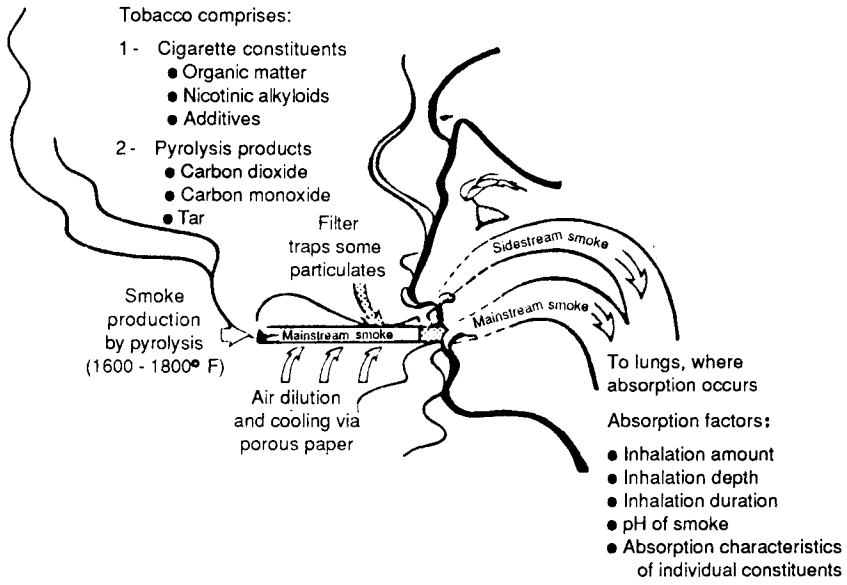

FIGURE 1.—Production and fate of cigarette smoke constituents

NOTE: Description of complexity of process by which nicotine is extracted from cigarette. Amount of nicotine ultimately absorbed is as much a function of smoker behavior as of cigarette characteristics.

SOURCE: Henningfield (1984).

appearance; cigarette smoking is no exception. The behavior of lighting, smoking, and extinguishing cigarettes, including puffing and inhaling, also becomes regular in smokers over time. The measurement techniques that permit such conclusions, however, must address a complex behavior. There are many variables (e.g., number of puffs, depth of inhalations) that might change and thereby affect the intake of tobacco smoke and its various constituents (e.g., nicotine, tar, carbon monoxide (CO)). As shown in Figure 1, the process of producing cigarette smoke constituents itself is complex (see US DHEW 1979; US DHHS 1981, for a more thorough discussion of these factors). This complexity emphasizes the importance of the use of careful measurement and multiple measures to ensure accurate characterization of cigarette smoking.

Quantification of cigarette smoking behavior has improved with the development of automated measurement techniques. These techniques permit the measurement of puffing and inhalation both in the laboratory (Gust, Pickens, Pechacek 1983; Epstein, Dickson, Stiller et al. 1982; Creighton, Noble, Whewell 1978; Herning, Hunt,

Jones 1983; Henningfield and Griffiths 1979; Puustinen et al. 1987) and outside the laboratory (Henningfield et al. 1980; Grabowski and Bell 1983). Puffing behavior is generally measured by having subjects smoke through cigarette holders that measure air flow by use of either temperature-sensitive thermistors (Gritz, Rose, Jarvik 1983; Fagerstrom and Bates 1981) or pressure-sensing transducers (Henningfield and Griffiths 1979; Gust, Pickens, Pechacek 1983a; Rawbone et al. 1978). Inhalation behavior has been measured by a variety of techniques, including mercury strain gauge pneumography (Rawbone et al. 1978; Herning et al. 1983), head- and arms-out whole-body plethysmography (Adams et al. 1983), and impedance (Nil, Buzzi, Battig 1986) and inductive plethysmography (Herning, Hunt, Jones 1983; Tobin and Sackner 1982; Tobin, Jenouri, Sackner 1982). Other methods include the use of inert gas radiotracers to determine the amount of smoke inhaled (Sheahan et al. 1980; Woodman et al. 1986) and a sensor for directly measuring the concentration of smoke particles in the holder before puffing (Jenkins and Gayle 1984).

These procedures have proved to be valuable and reliable methods of measuring smoking behavior (Woodman et al. 1984; Herning, Hunt, Jones 1983). Comparisons of data obtained when simply observing smokers to data obtained when using the mechanical devices indicate that such automated measuring techniques are valid. Such comparisons reveal consistent findings on measures such as number and duration of puffs and even of patterns of puffing within cigarettes (Henningfield and Griffiths 1979; Griffiths and Henningfield 1982). However, other research suggests that the devices may alter certain characteristics of smoking such as intensity of puffing (Tobin and Sackner 1982; Ashton, Stepney, Thompson 1978; Ossip-Klein, Martin et al. 1983). In addition, some smoking behaviors, such as blocking the ventilation holes of filters of low-yield cigarettes (which can markedly influence nicotine and tar intake from the cigarette) are thwarted by the use of a cigarette holder. Nonetheless, such measurements are useful and appear to provide valid means of evaluating the effects of specific experimental manipulations.

Measurement of the intake of cigarette smoke constituents may also be obtained by analysis of various biological fluids (saliva, urine, or blood) and expired air. Chapter II reviewed the methods and practical issues of using such specimens to assess resulting levels of nicotine, cotinine (a nicotine metabolite), CO, and other tobacco-associated compounds (see also Jarvis et al. 1987; Benowitz 1983).

Use of the methods described above has led to a much better understanding of how cigarettes are smoked and factors that affect intake of smoke constituents such as CO and nicotine. In addition, these methods permit conclusions regarding which aspects of smok-

ing are most robust across individuals, which aspects are strongly influenced by pharmacologic factors, and which aspects appear to be determined by other factors. Some of these findings are reviewed in subsequent sections.

Characterization of Cigarette Smoking Behavior

Although the process of smoking a cigarette may appear to be a simple behavior, it is actually a complex series of events; a full characterization requires the measurement of a variety of interdependent indices of frequency, duration, and volume. Even the act of taking a single puff is complex. Typically, a smoker puffs a volume of smoke into the mouth, where it is held for a short period of time (Guillerm and Radziszewski 1978; Medici, Unger, Ruegger 1985). The puff itself can occur at any point during inhalation, although most commonly it occurs toward the beginning of an inhalation (McBride et al. 1984; Guillerm and Radziszewski 1978). During inhalation, the puff is diluted with ambient air which may be inhaled through the nose, the mouth, or both (Rodenstein and Stanescu 1985; McBride et al. 1984; Adams et al. 1983). The postpuff inhalation is generally longer and larger in volume than normal inspirations (Rodenstein and Stanescu 1985; McBride et al. 1984). After a variable period of breath holding, the smoker exhales, usually through the mouth (Rodenstein and Stanescu 1985).

All of the above-mentioned behavioral factors can alter nicotine absorption. The likely impact of some factors is obvious (e.g., number of puffs taken) (Kozlowski 1981); others are much more subtle (e.g., puff shape, which is a function of the air flow rate over time) (Creighton and Lewis 1978b). Analogous but distinct from puffing factors are inhalation factors (e.g., depth and duration, dilution of the puff with ambient air) which can also determine the amount of tobacco smoke constituents which are absorbed. Table 1 lists several measures of cigarette smoking that have been objectively defined and measured.

The relationships among these behavioral measures have been studied. For instance, duration and volume of puffing are generally highly correlated although they vary somewhat from smoker to smoker (Gust and Pickens 1982; Epstein et al. 1982; Adams et al. 1983; Nemeth-Coslett and Griffiths 1985; Gust, Pickens, Pechacek 1983b; Gritz, Rose, Jarvik 1983). Peak smoke flow rate has been reported to be moderately correlated with puff volume and weakly correlated with puff duration (Gritz, Rose, Jarvik 1983). The relationship between puff volume and interpuff interval is much more variable (Adams et al. 1983; Gust, Pickens, Pechacek 1983b), and puffs per cigarette and puff duration have been found to be inversely related (Lichtenstein and Antonuccio 1981).

TABLE l.--Behavioral measures of cigarette smoking

Puffing behavior	Inhalation behavior
Puffs/cigarette	Inhalation volume
Interpuff interval	Inhalation duration
Puff duration	Breathhold duration
Butt length (weight)	Lung exposure duration
Puff volume	Percent of puff inhaled
Puff shape	
Puff flow rate (puff intensity)	
Peak flow rate (pressure)	
Latency to peak flow rate (pressure)	
Percent puffing time	

When the smoking of individual cigarettes is studied, the measures of cigarette smoking behavior and the resulting levels of biochemical markers have also been found to be highly correlated. For example, four studies found positive correlations between one or more of the behavioral measures and plasma nicotine levels (Pomerleau, Pomerleau, Majchrzak 1987; Sutton et al. 1982; Bridges et al. 1986; Herning et al. 1983). Using another approach, Zacny and associates (1987) independently varied three aspects of smoking-puff volume, inhalation volume, and lung exposure duration. They found that increases in puff volume (from 15 to 60 mL) produced proportional increases in plasma nicotine level, whereas increases in inhalation volume (from 10 or 20 to 60 percent of vital capacity) or lung exposure duration (from 5 to 21 sec) had no such effect.

CO intake (measured either from expired air or blood samples) also tends to be positively related to measures of smoking behavior, including total puff volume (Gust and Pickens 1982; Guillerm and Radziszewski 1978; Nil, Buzzi, Battig 1984; Woodman et al. 1986) and mean puff volume (Zacny et al. 1987; Zacny and Stitzer 1986). McBride and coworkers (1984) found moderate correlations (r=0.36 to 0.45) between CO boost and other measures of ventilation (tidal volume, minute ventilation, and prepuff expiratory volume). These studies illustrate some of the ways that specific aspects of cigarette smoking can affect absorption of smoke constituents. These measures have been used to scientifically describe many features of cigarette smoking. A summary of findings that have emerged from such studies is presented in the next Section.

Patterns of Puffing and Inhaling

Several studies have characterized the behavior of cigarette smoking in and outside the laboratory. The values of the most frequently measured variables are shown in Table 2. Despite a wide range of variations among studies, including differences in subject population (age, gender, smoking history, type of cigarette smoked), experimental setting, method used to collect the measurements, apparatus calibration procedures, and operational definitions of the measured variables, the findings among studies are strikingly consistent.

Over the course of smoking each cigarette there are striking consistencies from cigarette to cigarette, both within and between individuals. For example, during the smoking of a single cigarette, the duration of each puff tends to decrease and/or the time between each puff (interpuff interval) tends to increase (Graham et al. 1963; Griffiths and Henningfield 1982; Nemeth-Coslett and Griffiths 1985; Herning et al. 1981; Gust, Pickens, Pechacek 1983b; Woodman et al. 1986; Buzzi, Nil, Battig 1985; Adams et al. 1983; McBride et al. 1984; Chait and Griffiths 1982a). These trends were also found in nonlaboratory observations by Schulz and Seehofer (1978).

Although these observations reflect a tendency to decrease overall intensity of smoking over the course of the cigarette, the specific factors which produce such effects remain to be fully elucidated. The pattern has been hypothesized to be related to the nicotine dose per puff (Rickert et al. 1983; Russell et al. 1975; Chamberlain and Higenbottam 1985), because the nicotine concentration of smoke increases as the cigarette is smoked (Kozlowski 1981). However, experimental studies suggest that within-cigarette changes in puff intensity are not a simple function of the nicotine dose per puff (Nemeth-Coslett and Griffiths 1984a,b, 1985). Furthermore, puff volume may not be controlled by the same factors as puff duration (Nemeth-Coslett and Griffiths 1985). Thus, the orderliness of the behavior may be due to a variety of factors.

Various other aspects of puffing and inhaling during the smoking of single cigarettes have been studied and provide further information that helps to characterize this complex behavioral process. For example, puff shape (puff intensity over time) (McBride et al. 1984), latency to peak puff pressure (Buzzi, Nil, Battig 1985), and inhalation volume and duration (Adams et al. 1983) did not change over the course of smoking single cigarettes. The volume expired from puff to puff during and immediately after puffing (before inhalation) was lower for early puffs than for later puffs (Adams et al. 1983). Woodman and colleagues (1986) reported that the amount of smoke actually inhaled (range, 46 to 88 percent of puff volume) decreased proportionately with puff volume as cigarettes were smoked. Finally, significant changes from cigarette to cigarette in puff volume and

TABLE 2.--Published values of common measures of smoking

Study	Number of subjects	Puffs/ cigarette	Interpuff interval (sec)	Cigarette duration (sec)	Puff duration (sec)	Puff volume (mL)	Peak flow (mL/sec)	Inhalation volume (mL)
Rawbone et al. (1978)	12	10	41		1.8			
Rawhone et al. (1978)	9	10	35		2.1	43		
Woodman et al. (1986)	9	13	18	254	1.9	49		413
Nemeth-Coslett et al. (1986a)	8	8	64	414	1.8			
Nemeth-Coslett et al. (1986b)	8	8	47	362	1.4			
Nil, Woodson, Battig (1986)	132	13	28		2.2	30	28	560
Jarvik et al. (1978)	9	10						
Russell et al. (1986b)	10	11	35					
Ashton, Stepney, Thompson (1978)	14		24		1.5			
Schulz and Seehofer (1978)	100	11	50		1.4			
Schulz and Seehofer (1978)	218	12	42		1.3			
Henningfield and Griffiths (1981)	8	10	39	351	1.0			
Stepney (1981)	19	13		400		38		
Battig, Buzzi, Nil (1982)	110	13	26		2.1	40		
Epstein et al. (1982)	63	13			2.4	21		
Russell et al. (1982)	12	15	26	324	2.3	40		
Gritz, Rose, Jarvik (1983)	8	9	47		2.2	66	48	
Ossip-Klein, Martin et al. (1983)	9	8		351	1.4			
Ossip-Klein, Martin et al. (1983)	9	12		339	1.9			
Guillerm and Radziszewski (1978)	8	12	41	390	1.9	39	35	918
Gust, Pickens, Pechacek (1983b)	8	9	48	393	1.6	44		

Study	Number of subjects	Puffs/ cigarette	Interpuff interval (sec)	Cigarette duration (sec)	Puff duration (sec)	Puff volume (mL)	Peak flow mL/sec)	Inhalation volume (mL)
Adams et al. (1983)	10		26		1.9	44		614
Moody (1984)	517	9	26	232	2.1	44		
Nil, Buzzi, Battig (1984)	20	15	26		1.6	40	40	
McBride et al. (1984)	9	16	25	352	2.1	42		
Medici, Unger, Ruegger (1985)	17	14	19		2.2	43	31	
Burling et al. (1985)	24	12	28	330	1.7			
Nil, Buzzi, Battig (1986)	117	13	22		2.1	42	36	450
Hughes et al. (1986b3	46	11			1.6			
Bridges et al. (1986)	108	11				56		
Puustinen et al. (1986)	11	13	22		2.3	44		
Hilding (1956)	27	10						
Mean		11	34	346	1.8	43	36	591
Median		11	28	351	1.9	42.5	35.5	560
Range		8-16	18-64	232-414	1.6-2.4	21-66	28-40	413-918

NOTE: Data were taken from the baseline phase (or placebo treatment) of studies involving an experimental manipulation, with at least eight subjects. Values are rounded off to the nearest unit, and in some cases. were calculated from other variables or estimated from data presented in figures; missing values indicate that the variable was not measured or was not presented in the published study.

inhalation volume, as well as their ratio, were reported for individual subjects over the course of a 4-hr smoking session (Herning, Hunt, Jones 1983).

Dose-Related Determinants of Tobacco Intake

As the preceding material shows, cigarette smoking is a complex but orderly behavior; it may be qualitatively and quantitatively described. Furthermore, the behavioral process of tobacco smoke self-administration substantially determines the amount of smoke that is actually consumed. Similarly, the behavior of smoking may change in response to factors related to the delivered smoke and/or nicotine dose. These interactions are described in the present section. Much of this research has addressed issues concerning the manipulation of some aspect of cigarette and/or nicotine dose level. Such data are relevant to comparing this form of drug self-administration with other forms of drug self-administration, because one of the basic findings in studies of drug-seeking behavior is that the dose may affect the behavior. For example, when the dose (quantity) of a psychoactive drug is high, fewer doses are generally taken compared to when the dose is very low (Griffiths, Bigelow, Henningfield 1980; Chapter V).

With regard to cigarette smoking, the control and measurement of cigarette dose level is more complex than is the case with most other forms of drug delivery. For example, in opioid and alcohol studies, the amount of the morphine injected and volume of alcohol consumed can be precisely measured, but cigarette smoke can vary in levels of CO, tar, nicotine, and many other potentially important constituents (see Figure 2). The total smoke dose is positively related to the number of puffs taken per cigarette. However, total smoke dose might be changed by diluting the smoke with air or changing the number of available cigarettes. Alternatively, the smoke concentrations can be kept constant while changes are made in the concentration of nicotine delivered. This Section reviews these and several other strategies used to investigate some form of tobacco/nicotine dose manipulation and the resultant effects on cigarette smoking.

Control of Nicotine Intake

Among the most robust findings in research on cigarette smoking is the stability of nicotine intake that occurs from day to day within cigarette smokers. Several studies have collected blood samples from cigarette smokers while they are smoking their own cigarettes (Russell, Jarvis et al. 1980; Benowitz et al. 1983; Gori and Lynch 1985). This research has shown that blood levels of nicotine and cotinine among different cigarette smokers are stable and are relatively independent of the machine-estimated nicotine yield of the

cigarettes. Similarly, there are generally only modest correlations between the number of cigarettes smoked per day and resultant blood nicotine levels. This finding occurs because smokers consume different amounts of nicotine from their cigarettes, according to how the cigarettes are smoked. Figure 2 presents data from one of these studies.

To explain why nicotine intake is not simply determined by the machine-estimated nicotine yield of the cigarettes or the number of cigarettes smoked, many other aspects of smoking have been measured. This research is described in the remainder of this Section.

Smoke Concentration

The concentration of tobacco smoke delivered to the lung can be changed by dilution with air. Such dilution is an important means by which the low smoking-machine-estimated ratings (e.g., Federal Trade Commission ratings) of tar and nicotine are achieved in the so-called "light" or "ultra light" cigarettes (Kozlowski 1981, 1982, 1986, 1987). One way to study the possible effects of smoke dilution is to use the ventilated cigarette holders which have been marketed for persons who are trying to quit smoking. In principle, the smoker gradually reduces his or her level of dependence to nicotine by using holders of gradually increasing ventilation level. Three laboratory studies have evaluated the effects of such holders on cigarette smoking behavior (Henningfield and Griffiths 1980; Sutton et al. 1978; Martin et al. 1980). The results of all three were consistent: smoking was more intense at lower smoke concentrations and less intense at the highest concentration. In fact, in one of the studies, expired air CO levels were similar at all four concentration levels, indicating that the changes in smoking intensity were sufficient to defeat the holders' intended purpose of reducing the dose taken (Henningfield and Griffiths 1980). Using a somewhat different strategy, Zacny, Stitzer, and Yingling (1986) studied cigarette smoking with commercially available ventilated cigarettes. When the experimenter systematically blocked the filter vents of "ultra" low-yield cigarettes, there were decreases in puffs per cigarette, puff volume, and puff flow rate, and increases in interpuff interval.

These laboratory findings are consistent with findings obtained outside the laboratory when the cigarette butts of vented cigarettes are examined following smoking. Kozlowski, Rickert, Pope, and Robinson (1982) found that the cigarette butts taken from people who blocked the ventilation holes (often inadvertently) were more stained by tar and nicotine, reflecting less effective dilution and hence greater amounts of smoke delivery to the smoker. Data from a laboratory study suggest that 40 percent or more of smokers may inadvertently block the holes (Kozlowski, Rickert, Pope, Robinson,

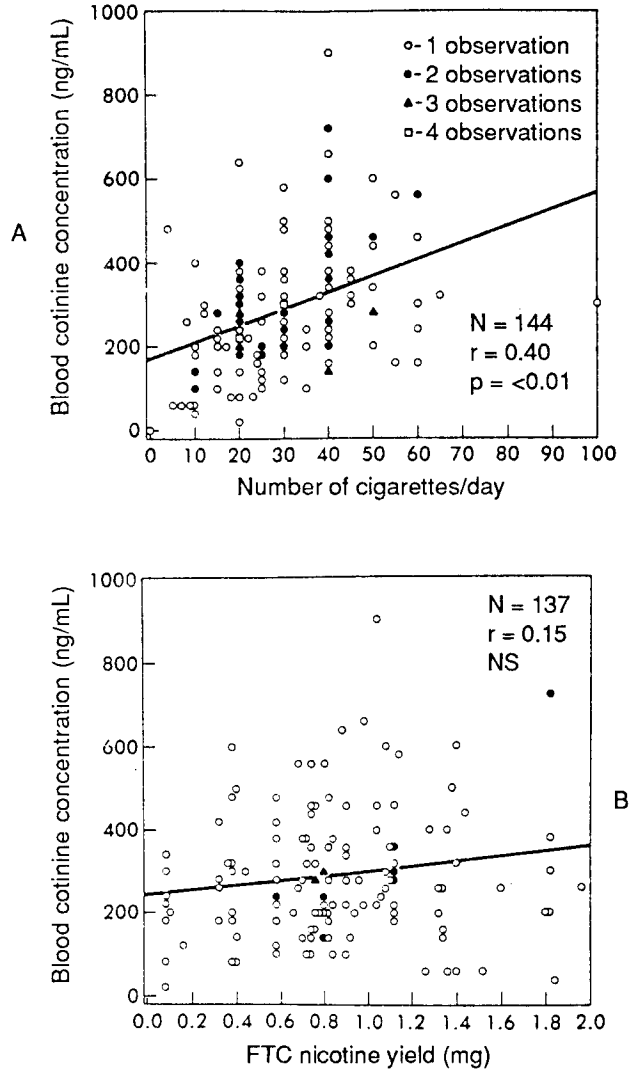

FIGURE 2.—Afternoon blood cotinine concentrations, compared by regression analysis with number of cigarettes smoked/day (A) and with U.S. Federal Trade Commission (FTC)-determined nicotine yield (B)

NOTE: The grouped smokers' values (observations 2–4) were so similar to individual values that plots overlapped. Total number of subjects in B is lower because data for a few subjects were incomplete. Morning blood cotinine concentrations (not shown) were on average slightly lower, but had similar correlations with number of cigarettes ($r = 0.45$) and FTC yield ($r = 0.06$).

SOURCE: Benowitz et al. (1983).

Frecker 1982). These findings imply that there is much greater exposure to cigarette smoke in the general population than one would expect based solely on the market share of ventilated cigarettes (US DHHS 1981; Kozlowski 1987).

Cigarette Length

When cigarettes are shorter, people smoke more of them (Ashton, Stepney, Thompson 1978; Goldfarb and Jarvik 1972; Gritz, Baer-Weiss, Jarvik 1976; Jarvik et al. 1978; Chait and Griffiths 1982b). Cigarette length may also affect how people smoke each cigarette. Ashton, Stepney, and Thompson (1978) found that smokers shortened their intervals between puffs and spent a greater proportion of time puffing on two-thirds-length cigarettes compared with full-length cigarettes. Russell, Sutton, and associates (1980) reported that smokers took relatively more puffs and left shorter butts when smoking shortened cigarettes. In another study, subjects smoking half-length cigarettes shortened the interval between puffs, but did not spend more time puffing on these cigarettes relative to full-length cigarettes (Chait and Griffiths 1982b). Puff duration and puff volume were inversely proportional to the length of the tobacco rod, even for the first puff of the cigarette (Chait and Griffiths 1982a; Nemeth-Coslett and Griffiths 1984a,b, 1985).

Cigarette Brand

Numerous studies have examined the effects of cigarette brand manipulations on cigarette smoking, and several reviews are available (Gritz 1980; Moss and Prue 1982; McMorrow and Foxx 1983). Such studies are of practical importance because smokers often switch to lower tar/nicotine yielding cigarette brands in an effort to reduce this exposure to toxins and to reduce their level of nicotine dependence (see Chapter VII). One finding of these studies is that the number of cigarettes smoked per day is only slightly increased when lower nicotine-yield brands are used. For this reason, it has been suggested that smokers switch to lower yield cigarette brands (1) to reduce exposure to smoke constituents and (2) to help them gradually reduce their dependence on nicotine (see discussion of these issues in US DHHS 1981 and in Chapter VII (nicotine fading)). However, as discussed earlier, several other studies indicate that there is little correlation between the nicotine rating of a cigarette and the plasma nicotine level of the smoker (Russell, Jarvis et al. 1980; Benowitz et al. 1983; Gori and Lynch 1985). Kozlowski (1981, 1982) has observed that increases of only one or two puffs per cigarette and possibly other more subtle changes in cigarette smoking (e.g., blocking ventilation holes and taking deeper inhala-

tions) may defeat the intended purpose of the brand-switching procedure.

Laboratory studies have provided information on the specific changes in smoking behavior that may reduce the intended impact of switching to lower yield brands of cigarettes. One confounding factor in such studies is that machine-estimated nicotine, tar, and CO yields do not necessarily change to the same degree or even in the same direction from one cigarette brand to the next (Tobacco Reporter 1985); thus, no definitive conclusions can be drawn about which specific smoke component was responsible for observed changes in smoking behavior. Nonetheless, some orderly and consistent findings emerge from a review of this literature. Several measures suggest that when tobacco smoke constituent ratings decline, smoking is more intense so that more smoke is delivered per cigarette; conversely, when tobacco smoke constituent ratings are higher, cigarette smoking becomes less intense (Frith 1971; Ashton, Stepney, Thompson 1979; Stepney 1981; Guillerm and Radziszewski 1978; Rawbone et al. 1978; Adams 1978; Creighton and Lewis 1978a; Ossip-Klein, Epstein et al. 1983; Russell et al. 1982; Ashton and Watson 1970; Epstein et al. 1981; Russell, Epstein, Dickson 1983; Tobin and Sackner 1982; Fagerstrom and Bates 1981; Woodman et al. 1987).

The consensus of the foregoing studies is that smokers tend to smoke in ways that minimize the effect of attempted reductions in nicotine intake; however, brand preferences can modulate nicotine intake. One study employing biochemical measures of smoke intake illustrated both of these phenomena (Benowitz and Jacob 1984). Subjects were permitted to smoke under each of three cigarette conditions: using their regular cigarette, using a higher nicotine-yield brand, and using a lower nicotine-yield brand. Subjects maintained significant nicotine intake under all three conditions, but the highest intakes of nicotine were with the subject's preferred brand. Nicotine intake from the lower nicotine-yield brands was somewhat lower than intake from the higher yield brands. Taken together, these studies indicate that brand switching may result in somewhat decreased levels of intake of nicotine and other constituents of tobacco smoke. However, because of compensatory changes in how cigarettes are smoked and in the number of cigarettes smoked, the decreases are substantially less than would have been predicted on the basis of the machine-estimated yield of the cigarettes.

Cigarette Yield of Nicotine

Research cigarettes which vary mainly in machine-estimated nicotine yield ratings but little in the yield of other constituents (e.g., tar, CO) have also been used in laboratory and nonlaboratory studies of cigarette smoking. This literature has been extensively reviewed (Russell 1971, 1976; Gritz 1980; Henningfield 1984; US DHEW 1979;

US DHHS 1981). The consensus of the literature indicates that as nicotine yield increases, the number of cigarettes smoked per day tends to decrease, although the converse relationship is not as robust (Russell 1979). Because few of these studies employed measures of smoking other than number of cigarettes smoked per day, the degree to which overall cigarette smoking behavior actually varied as a function of such manipulations may have been underestimated (Henningfield 1984).

Laboratory studies in which multiple behavioral measures of cigarette smoking were employed indicate that smoking is sensitive to nicotine dose manipulations. When cigarettes with higher nicotine yield ratings are smoked, there are decreases in measures such as puffs per cigarette, puff duration and puff volume, number of cigarettes, and expired air CO; and increases in interpuff and intercigarette interval (the specific measures were not identical for the three studies summarized) (Herning et al. 1981; Gust and Pickens 1982; McBride et al. 1984). These changes in smoking are consistent with the interpretation that intensity of smoking is inversely related to nicotine dose, indicating that compensatory changes in smoking could be affected by nicotine itself.

Urine pH

Because some nicotine is normally eliminated in the urine, manipulations of the rate of nicotine excretion might be expected to change cigarette smoking behavior (see Chapter II). Rate of renal excretion is partially determined by the acidity of the urine: lower pH values (higher acidity) increase the rate of nicotine excretion. One study showed that acidification of the urine of cigarette smokers resulted in small increases in cigarettes smoked per day, and alkalinization of urine was accompanied by only very small decreases in smoking (Schachter, Kozlowski, Silverstein 1977). A subsequent study in which urine pH was varied showed no change in cigarette smoking measures (Cherek, Mauroner, Brauchi 1982); another showed small but significant effects on nicotine intake in the expected direction (Benowitz and Jacob 1985).

The fact that there is a direct albeit weak relationship between rate of nicotine excretion and cigarette smoking has suggested to some that alkaline diets might be useful for persons trying to decrease their cigarette smoking (Fix and Daughton 1981; Fix et al. 1983; Grunberg and Kozlowski 1986). However, the relatively small amount of systemic nicotine which is eliminated by this route (approximately 2 percent in alkaline urine, 10 percent in urine without controlled pH) (Rosenberg et al. 1980; Benowitz and Jacob 1985; Chapter II) weakens its practical significance as a determinant of cigarette smoking behavior. The results of clinical studies suggest

that such therapies are not useful in the cessation of smoking (see also Grunberg and Kozlowski 1986; Schwartz 1987).

Tobacco Administration and Deprivation

When tobacco smoke itself is given or withheld, the tendency to smoke, as well as the way cigarettes are smoked, may be affected. Kumar and colleagues (1977) reported that pretreating smokers with a varying number of uniform puffs of tobacco smoke produced dose-related reductions in the subsequent number of puffs taken, volume per puff, and total puff volume during a 40-min period of smoking ad libitum. In a study of similar design, Chait, Russ, and Griffiths (1985) found that an increasing number of uniform pretreatment puffs decreased subsequent puffs per cigarette, cigarette duration, and total puff duration. Analogously, when the number of puffs available during any period of smoking (smoking "bout") during a given day was varied by the experimenter from 1 to 12 while the smokers were free to vary the interbout interval, the intervals between each smoking bout were directly related to the number of puffs that had been given (Griffiths, Henningfield, Bigelow 1982). These studies show that cigarette smoke intake is a function of time since the last cigarette or the smoke dose given at any smoking opportunity.

Whereas smoke pretreatment decreases several measures of cigarette smoke intake, other studies have found that deprivation for just 1 hr increases the tendency to smoke and elevates several measures of tobacco smoke intake (Henningfield and Griffiths 1979); furthermore, these effects were not due to "anticipation" by the subjects of the periods of smoke deprivation (Griffiths and Henningfield 1982). Several additional studies have confirmed that smoke deprivation increases one or more measures of cigarette smoking (Karanci 1985; Griffiths and Henningfield 1982; Zacny and Stitzer 1985; Epstein et al. 1981). Sutton and coworkers (1982) found a small, but statistically significant, positive correlation between time since the last cigarette and total puff volume on the subsequent cigarette. Similarily, when the interval between each smoking opportunity was varied from 7.5 to 120 min and subjects were free to take as many puffs per smoking bout as they pleased, the number of puffs per bout was directly related to the duration of the preceding interbout interval (Griffiths, Henningfield, Bigelow 1982). Restricting the number of cigarettes that may be smoked is another way to study tobacco deprivation. When smokers who on average smoked 37 cigarettes/day were permitted to smoke only 5 cigarettes/day, they consumed three times as much nicotine per cigarette compared with unrestricted smoking (Benowitz et al. 1986).

The results of studies of the effects of tobacco administration and deprivation on subsequent rates and patterns of cigarette smoking show that tobacco smoke can function as do other primary reinforc-

ers such as food, water, and dependence-producing drugs (Thompson and Schuster 1964). Such studies in themselves, however, do not reveal which of the many tobacco smoke constituents are critical. The next two sections will examine evidence that specific manipulations of nicotine and nicotine antagonists can produce analogous changes in cigarette smoking.

Nicotine Pretreatments

One of the basic ways to demonstrate that a psychoactive drug is controlling behavior is to determine if pretreatment with the drug leads to decreases in the amount subsequently taken. Such findings have been obtained with a variety of dependence-producing drugs (e.g., Griffiths, Bigelow, Henningfield 1980; Chapter V), and the strategy has been used to study the role of nicotine in cigarette smoking. These studies have shown that nicotine pretreatment by a variety of routes decreases the amount and/or intensity of subsequent cigarette smoking although the specific measures that have been reportedly affected vary across studies. It is possible that differences across studies reflect variations in sensitivity of measurement techniques and in the measures used.

Cigarette smokers may be pretreated with nicotine by giving them nicotine polacrilex gum to chew. The gum is available in similar tasting nicotine dose levels of 2 or 4 mg/piece. A similar tasting placebo preparation with no nicotine is also available. (In the United States, the placebo and 4-mg dose are only available for research.) With various combinations of nicotine gum doses it is possible to provide a wide range of dose levels. In one study, the chewing of nicotine polacrilex gum produced a dose-related (dose range = 0 to 8 mg nicotine) decrease in cigarette consumption during subsequent 90-min cigarette smoking sessions: Total puffs, total cigarettes, and expired-air CO levels were inversely related to nicotine dose; desire to smoke was also inversely related to dose but this effect varied considerably and was not statistically reliable (Nemeth-Coslett et al. 1987). Comparable findings have been obtained in several other studies, although dose manipulations were not as extensive as in the former study (Kozlowski, Jarvik, Gritz 1975; Nemeth-Coslett and Henningfield 1986; Brantmark, Ohlin, Westling 1973; Russell et al. 1976; Herning, Jones, Fischman 1985). Another study showed that nicotine given in capsule form also reduced subsequent cigarette smoking (Jarvik, Click, Nakamura 1970), although the low dose and poor systemic absorption of nicotine given by this route (see Chapter II) required that much higher dose levels be given (10 mg).

Two studies have also demonstrated that intravenous (i.v.) administration of nicotine decreases cigarette smoking (Lucchesi, Schuster, Emley 1967; Henningfield, Miyasato, Jasinski 1983). Another study found no change in smoking following i.v. nicotine infusions (Kumar

et al. 1977); however, the dose (equivalent to about 1.7 mg, given in 10 divided doses over 10 min) was probably inadequate, as suggested by results of other studies (Nemeth-Coslett et al. 1987). The finding that even i.v.-delivered nicotine can reduce subsequent cigarette smoking confirms that neither the tobacco vehicle nor the oral/respiratory route is necessary for nicotine to control behavior. The overall consistency of findings using a variety of forms of nicotine pretreatment is evidence for a specific effect of nicotine as a determinant of cigarette smoking.

Nicotine Antagonist Pretreatments

Another way to evaluate the specific role of nicotine as a determinant of rate and pattern of cigarette smoking is to administer drugs that block the effects of nicotine on the nervous system. Nicotine antagonists (ganglionic blockers) are available as drugs (e.g., pentolinium and hexamethonium) that do not readily enter the brain but are active in the peripheral nervous system, and as drugs (e.g., mecamylamine) that do enter the brain and thus work in both the peripheral and central nervous system (CNS) (Taylor 1985b). In theory, such drug administration should produce effects that are analogous to those that would be expected if the nicotine dose of cigarettes was decreased: that is, smoke intake should increase. Moreover, if smoke intake increases, but only when the centrally acting antagonist is given, such data would suggest the critical involvement of the effects of nicotine in the brain.

Three studies showed that pretreatment of smokers with mecamylamine produced increases in cigarette smoking that resembled those expected if the nicotine dose of the cigarettes had been decreased (Stolerman et al. 1973; Nemeth-Coslett et al. 1986a; Pomerleau, Pomerleau, Majchrzak 1987). In each of these studies, the short-term effect of the nicotine antagonists was studied. Similarly, mecamylamine pretreatment increased the preference for high nicotine-yield cigarette smoke (apparently by reducing its nicotinic effects) when subjects were tested with a device which blends smoke from high and low nicotine-yield cigarettes (Rose, Sampson, Henningfield 1985). The role of nicotine action in the brain was demonstrated in the study by Stolerman and colleagues (1973) in which a nicotine blocker (pentolinium) that does not readily enter the brain produced no effects on cigarette smoking.

Effects of Nonnicotinic Drugs on Cigarette Smoking

In addition to nicotine and nicotine antagonists, the effects of other psychoactive drugs on cigarette smoking have been studied in the laboratory. Such studies are important insofar as they constitute drug-interaction studies whereby it may be determined if the

behavioral and physiological actions of nicotine are altered as a function of pretreatment with other drugs. In addition, studies of interactions of nicotine with other dependence-producing drugs are important because tobacco use generally precedes and accompanies use of many other dependence-producing drugs (Chapter V). Several classes of psychoactive drugs have been administered in studies in which cigarette smoking was specifically measured. In general, the results permit a categorization of these drugs into two groups: (1) those drugs that produce increases in smoking under standard test conditions, and (2) those drugs that produce little reliable effect on cigarette smoking under standard test conditions.

Sedatives, opioid agonists, and psychomotor stimulants have been shown capable of producing robust and dose-related increases in cigarette smoking. Specifically, alcohol (ethanol) has been shown to increase cigarette smoke intake (Griffiths, Bigelow, Liebson 1976; Henningfield, Chait, Griffiths 1984; Nil, Buzzi, Battig 1984; Mintz et al. 1985; Mello et al. 1980b). In a study in which alcohol was found to increase smoking in all of five alcoholic subjects tested, pentobarbital (a depressant) was found to increase smoking in the two subjects with extensive histories of barbiturate use (Henningfield, Chait, Griffiths 1984). The effects of alcohol and pentobarbital were most robust in heavier drinkers and alcoholics (Henningfield, Chait, Griffiths 1983, 1984). The opioid agonists, heroin and methadone, increase cigarette smoking in opioid users (Mello et al. 1980a; Chait and Griffiths 1984). Methadone produced dose-related increases in number of cigarettes and puffs, and in puff duration in methadone-maintained smokers (Chait and Griffiths 1984). Analogously, number of cigarettes smoked per day gradually decreased as methadone-maintained clients had their daily methadone doses decreased over several weeks (Bigelow et al. 1981). Finally, the psychomotor stimulant *d*-amphetamine increases a variety of measures of cigarette smoking (Henningfield and Griffiths 1981; Chait and Griffiths 1983).

Three other drugs have been studied and found to produce little reliable effect on cigarette smoking. Caffeine is of interest because it might be predicted to either increase smoking by its general stimulant (amphetamine-like) effects (Rall 1985) or to decrease smoking by serving as a substitute for some of nicotine's stimulant effects (Kozlowski 1976). Laboratory studies, however, have found the effects of caffeine administration on cigarette smoking to be weak and inconsistent: two studies showed no reliable effect (Chait and Griffiths 1983; Nil, Buzzi, Battig 1984), another showed weak decreases in smoking (Kozlowski 1976), and a fourth showed weak increases in smoking following caffeine administration (Ossip and Epstein 1981).

The opioid antagonist naloxone (naloxone blocks effects of heroin-like opioids) is another drug of interest because of the possible role of endogenous opioids as mediators of some of the effects of nicotine (Chapter III; Pomerleau and Pomerleau 1984). In a test paradigm in which several drugs have been shown to produce orderly effects on cigarette smoking (Griffiths and Henningfield 1982), naloxone produced no consistent changes in cigarette smoking over a wide range of dose levels (Nemeth-Coslett and Griffiths 1986). Another study of the effect of naloxone which employed a single dose found a reduction in smoking (Karras and Kane 1980). No clear reconciliation of these disparate findings is evident. Finally, marijuana pretreatment was found to produce no reliable effect on tobacco intake (Mello et al. 1980b; Nemeth-Coslett et al. 1986b) or on the way cigarettes were smoked (Nemeth-Coslett et al. 1986b).

Effects of Nonnicotine Constituents of Tobacco Smoke and Citric Acid Aerosol

Chemicals presumed to act primarily in the respiratory tract and not in the central nervous system may also affect smoking. The region of the trachea just below the larynx is assumed to be a site of some cigarette smoke related sensations (Cain 1980). This site corresponds to the region 2 cm below the narrow opening of the larynx where particles entering the trachea change direction (Chan and Schreck 1980).

The components of cigarette tar and volatile gases in smoke contribute to the taste, olfactory, and tracheobronchial sensations elicited by cigarette smoke. In fact, minimal levels of tar are held by tobacco manufacturers to be important to maintain product satisfaction in smokers (Tobacco Reporter 1985; Gori 1980). Besides its causal role in lung cancer and other diseases (US DHHS 1982, 1983, 1984), tar may function to mask the harshness and irritation of nicotine (Herskovic, Rose, Jarvik 1986). Consistent with this hypothesis, nicotine aerosols delivering doses of nicotine similar to those in mainstream cigarette smoke are rated as extremely harsh and irritating by cigarette smokers (Russell 1986). Similarly, some gaseous components of smoke, such as acrolein and formaldehyde, are irritating and could also contribute to the tracheobronchial sensations elicited by smoke (Lundberg et al. 1983).

Levels of tar and other constituents may also contribute to brand preference and, conversely, to the difficulty in finding readily acceptable substitutes for the cigarettes normally smoked by individuals. For example, a nonmentholated cigarette may not be a desirable substitute for a mentholated one. Moreover, when given cigarettes made of lettuce or cocoa leaves, smokers complain about the unpleasant smell and taste (Goldfarb, Jarvik, Glick 1970; Herskovic, Rose, Jarvik 1986). Tobacco research cigarettes are often

found to be less palatable than commercial brands (Benowitz, Kuyt, Jacob 1982), indicating the importance of specific tobacco blends and/or additives in determining taste and brand preferences.

The precise nature of the sensations critical to smoking satisfaction has not been elucidated, and the relative roles of taste, olfaction, and tracheobronchial sensations are not clear. One way to assess the importance of local respiratory sensations in the subjective response to cigarette smoke is to block these sensations with a short-acting topical anesthetic. Two studies have used inhalation of a 4-percent lidocaine aerosol and mouth rinses and gargling with lidocaine solutions to assess the importance of airway sensations to cigarette smokers (Rose et al. 1984, 1985). In both studies, the desirability of puffs was decreased by local anesthesia of the respiratory tract. Additionally, the decline in reported craving for cigarettes that usually occurs after smoking was diminished by local anesthesia.

A study was also conducted in which smokers inhaled a refined tobacco smoke condensate (Rose and Behm, in press). The condensate produced a low overall nicotine yield (about 0.2 mg/10 puffs), while maintaining a higher ratio of nicotine to tar and a larger particle size than that of conventional cigarette smoke. Smoke generated in this fashion was rated as stronger and harsher than smoke of equivalent nicotine content delivered by smoking a conventional low-tar and low-nicotine cigarette (Rose and Behm 1987). The subjects also reported significantly greater satisfaction and diminished desire to smoke additional cigarettes after inhaling puffs of refined smoke compared with conventional low-nicotine cigarette smoke (Rose and Behm 1987). These studies demonstrate that local sensory effects of smoke may influence the short-term subjective responses to smoking.

The inhalation of aerosols containing citric acid is a standard method of eliciting coughing in human subjects (Pounsford and Saunders 1985). One study found that smokers inhaling puffs of a nebulized 15 percent aqueous solution of citric acid reported sensations of strength and harshness comparable to those produced by their own cigarette brand and considerably stronger than those elicited by an "ultra" low-tar, low-nicotine cigarette (Rose and Hickman 1987). Moreover, some pleasure was reported to be associated with these sensations, and desire for cigarettes was decreased, suggesting that mild irritation of the respiratory airways may be involved in satiation of smoking behavior and may have a role in smoking cessation efforts (Henningfield 1987c; Chapter VII).

Nicotine: Psychoactivity, Reinforcing and Related Behavioral Mechanisms of Nicotine Dependence

As the preceding sections have shown, cigarette smoking is an orderly behavioral and pharmacologic process clearly involving

maintenance of the desired levels of nicotine in the body. These data are sufficient to label tobacco use as a form of drug self-administration in which the role of nicotine in controlling tobacco self-administration functions as do morphine, ethanol, and cocaine in the use of opium-derived products, alcoholic beverages, and coca-derived products, respectively. However, the question may be asked whether the behavior-controlling pharmacologic properties of nicotine are similar to those of prototypic dependence-producing drugs when evaluated in standard laboratory tests. More specifically, the scientific question is whether nicotine itself shares critical dependence-producing properties with drugs such as morphine, cocaine, and alcohol. Standardized testing procedures can be used in both animal and human studies to objectively determine if a drug is dependence producing. These procedures, as well as a review of how addicting drugs control behavior, is presented in Chapter V. Chapter V also presents data obtained when drugs such as morphine, cocaine, and alcohol are tested by identical procedures.

In brief, four general kinds of behavior-modifying drug effects can be differentiated on the basis of the test procedure used. These drug effects are discussed in Chapter V and include the following: (1) Drugs may produce *interoceptive* stimulus effects; that is, they can produce effects that a person or animal can distinguish from the nondrug state. Although not identical in meaning, the following terms are often used to designate interoceptive drug effects: "psychoactive," "discriminative," "subjective," "self-reported." (2) Drugs may serve as *positive reinforcers* or *rewards,* the presentation of which produces repetition and strengthening of the behaviors which led to their presentation, i.e., "drug self-administration" or "drug seeking." (3) Drugs can *serve* as *unconditioned stimuli,* in which case they may directly elicit various responses; these responses may subsequently be elicited by stimuli which are associated with the drug (i.e., conditioned stimuli), including the presence of environmental, or even internal, cues. (4) Drug administration or abstinence can also function as *"punishers"* or *aversive* stimuli.

This Section will present data from studies of nicotine with each of the four testing procedures mentioned above. The convergence of findings from several distinct approaches provides compelling evidence that nicotine is a drug that can effectively control behavior, including behavior leading to its own ingestion (i.e., dependence or addiction).

Interoceptive, Discriminative, and Subjective Effects of Nicotine

Ingested chemicals can serve as stimuli by actions on either peripheral or centrally located receptors or by indirect effects mediated through the release of various biochemicals or neurohor-

mones. In general, the term "psychoactive" is reserved for those drugs whose discriminative effects are known to result from their actions in the brain. As described by Lewin (1931) and others (Thompson and Unna 1977) it is, in part, the nature of the discriminative stimulus effects of a drug within the body that sets the dependence-producing drugs apart from other non-nutritive substances. As shown in Chapter II, all commonly used forms of tobacco are effective means of delivering nicotine to the blood from which it is rapidly transported to the brain. Research with animals has shown that nicotine produces distinct effects in the central nervous system (CNS). In addition, nicotine has diverse peripheral and hormonal actions that could serve to intensify its CNS stimulus properties. The biochemical mechanisms of these effects are discussed in Chapter III.

Three procedurally distinct methods have been used to characterize the stimulus properties of nicotine and will be discussed in the following sequence: (1) discrimination testing in animals and humans, (2) assessing subjective effects in humans, and (3) testing for state-dependent learning effects in humans. Each method has been used to help characterize the stimulus properties of a variety of drugs including nicotine (Chapter V).

Drug Discrimination Testing in Animals

Animal studies of nicotine discrimination show that nicotine produces reliable effects that are readily identified by the subjects. Such studies indicate that fundamental biobehavioral mechanisms mediate the psychoactive properties of nicotine in humans, and that such effects are not unique to human psychological processes. These data also have implications for understanding and treating tobacco dependence and are summarized below.

Specificity of the Nicotine Stimulus

Although dependence-producing drugs may overlap, to some degree, in the nature of their effects on mood and feeling, each drug class and sometimes drugs within a class produce unique effects. As this Section shows, nicotine also produces some effects that permit it to be distinguished from most other psychoactive drugs. These studies are also useful for testing new drugs that are thought to produce nicotine-like effects.

Rats can learn to accurately discriminate nicotine from placebo regardless of the route of administration as long as the nicotine reaches the brain. Most researchers have utilized the subcutaneous (s.c.) route of administration (Rosecrans and Meltzer 1981); however, more recent studies have incorporated other routes of nicotine administration and have found that rats could learn to discriminate

nicotine when given nicotine by gavage (oral tube) in a dose of 0.5 mg/kg (Howard and Craft 1987). Oral nicotine-trained rats generalized to nicotine administered via either the s.c. or transdermal routes (nicotine solution was applied to a 1.5-cm circular area on the shaved back of the rat). There was little difference in dose potency between the oral and s.c.. routes; however, the transdermal route was much less potent and required eight times the oral dose to establish equivalent response patterns. Taken together, the results of these studies showed that nicotine given by a variety of routes produces time- and dose-related discriminative effects.

Several studies have compared nicotine with a variety of drugs by these drug discrimination testing procedures (Rosecrans and Meltzer 1981; Stolerman et al. 1987). Early research involved testing a wide variety of chemicals. These studies showed that nicotine-trained rats did not generalize to drugs of other classes such as the opioids, barbiturates, or hallucinogens (Rosecrans and Meltzer 1981). Of special interest was the prototypical stimulant *d*-amphetamine, because nicotine also has a variety of stimulant-like actions (Rall 1985). When nicotine-trained rats were tested with amphetamine, however, they only partially generalized to nicotine. In another study, Schechter (1981) observed higher levels of amphetamine generalization to nicotine in a group of rats trained to discriminate amphetamine from pentobarbital. Thus, nicotine may have some amphetamine-like effects which are unmasked under certain conditions.

Oxotremorine and arecoline are agonists of the cholinergic nervous system, but these drugs activate muscarinic, and not nicotinic, cholinergic receptors (Gilman et al. 1985). Consistent with the mechanisms of action of these cholinergic drugs are the findings that neither oxotremorine nor arecoline generalized to nicotine in nicotine-trained animals (Rosecrans and Meltzer 1981).

Nicotine analogs and metabolites have also been studied with the discrimination paradigm (Rosecrans and Chance 1977; Stolerman et al. 1987). Such research can help reveal the extent, if any, of the role of these nicotine-related or nicotine-derived chemicals in determining the nature of the discriminative effects that follow nicotine administration. In rats trained to discriminate 100 µg/kg of nicotine, the analogs cytisine and anabasine generalized to nicotine. The alkaloid nornicotine generalized partially to nicotine. Cotinine, the major metabolite of nicotine, was observed to generalize to nicotine only when the cotinine was given intraventricularly in relatively high doses to rats trained to discriminate relatively low dose levels (100 µg/kg) of nicotine. These data show that although metabolites of nicotine may share some stimulus properties with nicotine, the degree of generalization is weak, suggesting that the discriminative

stimulus effects of nicotine are mainly due to nicotine itself and not to the metabolites.

Synthetic analogs of nicotine have also been evaluated for their possible nicotine-like properties in discrimination studies (Rosecrans, Kallman, Glennon 1978; Rosecrans et al. 1978). Of the several compounds tested, only one, 3-methyl-pyridylpyrollidine, a chemical isomer of nicotine, was observed to generalize to the nicotine stimulus in nicotine-trained rats. This compound was observed to be 8 to 10 times less potent than nicotine. Its effects were significantly antagonized (reduced or blocked) by mecamylamine, which also antagonizes the stimulus generated by both S- and R-nicotine; the naturally occurring tobacco constituent, S-nicotine, is also 8 to 10 times more potent as a stimulus than R-nicotine. The results of these investigations indicate that the stimulus properties of nicotine are highly specific.

A finding relevant to pharmacologic treatment efforts (see Chapter VII) involved discrimination studies with lobeline (a constituent in several over-the-counter aids for quitting smoking). Lobeline is an alkaloid with some nicotine-like ganglionic effects in the peripheral nervous system (Gilman et al. 1985). Rosecrans and Chance (1977) found that lobeline was neither discriminated as nicotine nor did it block nicotine discrimination in nicotine-trained rats. These results do not support the use of lobeline-containing compounds as treatment aids for cigarette smoking (see also Schwartz 1987; Chapter VII).

Peripheral Versus Central Discriminative Stimulus Effects of Nicotine

The degree to which the stimulus is generated via peripheral rather than central nervous system (CNS or brain) actions is also important in understanding the nature of the nicotine stimulus. As discussed in Chapter III, nicotine has many peripheral autonomic nervous system (ANS) effects which might feed back to the CNS, thereby indirectly generating or contributing to stimulus effects. Thus, changes in blood pressure, heart rate, body temperature, and hormone release could be potential mediators of the effects. Several approaches have been utilized to address the role of peripheral actions of nicotine in the generation of the discriminative stimulus. One approach is to attempt to block nicotine with an antagonist not able to enter the CNS.

In one study, animals were trained to discriminate a dose of nicotine (Rosecrans and Chance 1977). Then they were pretreated with a series of nicotinic cholinergic antagonists and with muscarinic cholinergic antagonists. After pretreatment with an antagonist, the animals were retested with the training dose of nicotine. Mecamylamine, a centrally and peripherally acting nicotine antago-

nist, was the only drug observed to completely block the nicotine stimulus. As the dose of this antagonist was increased, percent correct responses on the nicotine-correct lever, after the injection of 200 or 400 µg/kg of nicotine, decreased to placebo response levels, indicating a complete antagonism of the nicotine stimulus. In a similar study, Stolerman, Pratt, and Garcha (1982) increased the nicotine dose in an attempt to overcome the actions of mecamylamine: the blockade was not overcome by any dose of nicotine. Thus, these data suggest that mecamylamine is not a competitive antagonist (blocking at the receptor itself) but rather may functionally antagonize nicotine's effects through another mechanism (Stolerman et al. 1987).

In other studies, a 331 µg/kg dose of mecamylamine antagonized the stimulus effects of 200 µg/kg of nicotine, while 835 µg/kg was required for similar antagonism of the 400 µg/kg dose of nicotine (Rosecrans and Meltzer 1981). All such studies found that the peripherally acting nicotinic antagonist, hexamethonium, did not affect nicotine discriminations. The muscarinic antagonist, atropine, was also without effect. The possible relationships of the nicotine stimulus to brain norepinephrine and 5-hydroxytryptamine (serotonin or 5-HT) systems were also investigated through the use of the appropriate antagonists/agonists. Similarly, a quaternary analog of nicotine, which does not enter the brain, was evaluated and found to produce no evidence of generalization in nicotine-trained rats (Rosecrans et al. 1978). Such studies do not support the involvement of peripheral systems in the generation of the nicotine stimulus.

Another strategy used to investigate the central nature of the nicotine stimulus compared concentrations of nicotine in the brain with the resulting stimulus effects of nicotine (Rosecrans and Chance 1977). It was assumed that if nicotine's stimulus effects are mediated in the brain, then such effects should be related to brain levels of nicotine. This hypothesis was confirmed. In fact, it was found that before nicotine functions as a stimulus, it must achieve a minimal drug level in the brain. In addition to relating drug level in the brain to the stimulus effect induced by nicotine, Rosecrans and Chance (1977) showed that systemically administered nicotine generalized to nicotine administered intraventricularly. Taken together, the foregoing studies show that the nicotine-generated discriminative stimulus is dependent on the actions of nicotine at central nicotine receptors in the brain.

Drug discrimination research has also examined the stimulus properties of the muscarinic cholinergic agonist, arecoline. Arecoline is a constituent of the betel nut mixtures commonly chewed in the East Indies (Taylor 1985a). Three approaches have been utilized to investigate the stimulus properties of arecoline. In the first study, arecoline served as a discriminative stimulus and thereby assumed

control of behavior (Rosecrans and Meltzer 1981). These effects of arecoline were blocked by pretreatment with the muscarinic antagonist, atropine, while the quaternary compound, methyl atropine (which does not readily cross the blood-brain barrier), was ineffective. These results indicate that the stimulus can also be exerted via muscarinic stimulation and confirm that the discriminative stimulus properties of muscarinic agonists, like those of nicotinic agonists, are centrally mediated. Additional studies indicated that mecamylamine was not able to antagonize the stimulus effects of arecoline (Rosecrans and Meltzer 1981). Finally, it was found that rats could be trained to discriminate between the muscarinic and nicotinic agonists, arecoline and nicotine. Thus, there appear to be two independent central cholinergic receptor systems (muscarinic and nicotinic), each of which can exert stimulus control over behavior when appropriately stimulated. These findings have been confirmed by Stolerman and colleagues (1987).

Interactions with Noncholinergic Neurons

In a preliminary study (Takada et al., 1988) two nicotine-trained squirrel monkeys recognized beta-carboline as nicotine. Beta-carboline induces symptoms resembling anxiety in animals; these symptoms can be reduced by administration of the anxiolytic, diazepam (Shephard 1986). In addition to this observation, Colpaert (1977) reported that nicotine can antagonize the diazepam cue, and Heath, Porter, and Rosecrans (1985) noted that nicotine antagonized the effects of diazepam on punished responding in rats. Mecamylamine was also found to attenuate the nicotine-induced antagonism of diazepam's antianxiety effect. Harris and coworkers (1986) found that metrazol (a convulsant) partially generalized (35 percent) to nicotine when tested in the discrimination paradigm in nicotine-trained animals. A greater degree of generalization of the metrazol cue to nicotine (50 percent) was observed 48 hr after the cessation of a 21-day chronic nicotine regimen in rats trained to discriminate metrazol (5 mg/kg) from saline; these generalizations were not antagonized by mecamylamine. Harris and colleagues (1986) suggested that the generalization of metrazol to nicotine was a function of a nicotine abstinence-induced withdrawal syndrome resembling anxiety. These studies suggest that nicotine may act at central receptors capable of eliciting a stimulus cluster which induces anxiety (Chapter III).

Subjective Effects of Nicotine in Humans

The extensive amount of nicotine discrimination research using a variety of animal species and several routes of administration confirms that nicotine is a potent drug that can induce alterations in

nervous system function that are distinct and readily identifiable. In addition, the similar findings observed in studies using different routes of nicotine administration are consistent with the hypothesis that the tobacco vehicle is not necessary to produce nicotine-associated changes of mood and feeling. The next Section examines data from analogous studies in which humans served as research subjects.

Psychoactivity of Nicotine

The animal research described above indicates that nicotine's psychoactivity is a result of basic biological actions. Human research on nicotine corroborates the validity of the animal research. Results from studies of the interoceptive effects of nicotine in humans are analogous to those obtained in animal studies described above.

One of the first human studies that used drug discrimination procedures, as had been developed with animal subjects, was a study of nicotine discrimination. The study involved the systematic manipulation of nicotine dose levels with research cigarettes which varied primarily in the amount of nicotine delivered (Kallman et al. 1982). This study demonstrated that nicotine, as delivered by the inhalation of tobacco smoke, produces discriminative stimulus effects. The degree and rate of acquisition of the discrimination appeared to be dose dependent. The ability of the subjects to make the discriminations did not appear to be related to either autonomic (e.g., heart rate) effects of nicotine or to nicotine's effects on other self-reported measures (e.g., taste of the cigarette).

The data from Kallman and associates (1982) are consistent with those of several other studies which have found that human volunteers can differentiate among cigarettes which vary mainly in the amount of nicotine which they deliver (Goldfarb, Jarvik, Glick 1970; Goldfarb et al. 1976; Herskovic, Rose, Jarvik 1986; Rose 1984; Griffiths, Bigelow, Henningfield 1980; Henningfield, Miyasato, Johnson, Jasinski 1985). Furthermore, the conclusion that centrally mediated effects of nicotine are important in such responsivity is supported by findings that pretreatment with mecamylamine reduced responsivity to nicotine dose levels of the cigarette (Stolerman et al. 1973; Nemeth-Coslett et al. 1986a; Pomerleau et al. 1987). The study by Stolerman and associates (1973) also showed that such antagonism of nicotine's effects was not obtained when peripherally acting pentolinium was given.

Other research has confirmed that the tobacco vehicle is not necessary to enable the interoceptive effects of nicotine. Several studies involving i.v. administration of nicotine in human subjects have found that humans readily differentiate among nicotine dose levels given intravenously. In the earliest of these studies, i.v. injections of nicotine were given to 35 volunteers, most of whom were cigarette smokers (Johnston 1942). The conclusions of Johnston

TABLE 3.--Summary of early observations regarding psychoactivity of intravenously delivered nicotine in humans

1.	"Psychic" effects are directly related to nicotine dose; nonsmokers are much more sensitive to toxic symptoms (e.g., nausea) than smokers
2.	Effect of nicotine is "specific and readily distinguished from that of cocaine or codeine"*
3.	Nicotine injections are "pleasant" to smokers, and are preferred by some over cigarette smoking
4.	Orally given nicotine (dissolved in water) also had "psychic" action, but appeared much less potent than intravenously administered nicotine; delayed onset of effect
5.	1-3 mg doses appeared tolerable and equivalent to smoking single cigarette; ~ 0.11 mg doses appeared to produce "subjective sensation" equivalent to one "deep" cigarette smoke inhalation

*More recent research indicates that higher dose levels of nicotine can produce cocaine-like effects (Henningfield, Miyasato, Jasinski 1985).

SOURCE: Johnston (1942).

that are especially relevant to characterization of the psychoactivity of nicotine are shown in Table 3.

Johnston's findings (Table 3) have been generally confirmed. Jones, Farrell, and Herning (1978) and Rosenberg and colleagues (1980) also found that human volunteers could differentiate i.v. nicotine at dose levels similar to those obtained by smoking cigarettes. In another study which extended the findings of Johnston (1942), both i.v. nicotine and nicotine inhaled from research cigarettes across a range of doses were administered to human volunteers with histories of using a variety of dependence-producing drugs (Henningfield, Miyasato, Jasinski 1985). Subjects clearly distinguished nicotine from a placebo, and the dose strength estimates were directly related to the nicotine dose level. A subsequent study showed that the immediate subjective effects of nicotine were diminished by pretreatment of subjects with mecamylamine (Henningfield et al. 1983).

In a study by Henningfield, Miyasato, Jasinski (1985), measures used to qualitatively describe the nature of the drug stimulus indicated that nicotine met criteria as a euphoriant. At higher doses nicotine was sometimes identified as a stimulant (cocaine or amphetamine); it elevated scores on the Morphine Benzedrine Group ("Euphoria" or "MBG") scale of the Addiction Research Center Inventory (ARCI) (Haertzen and Hickey 1987); and it produced dose-related increases in scores on a drug-liking scale. The high-dose cocaine/amphetamine identifications found in the study by Henningfield, Miyasato, and Jasinski (1985) were not observed by

Johnston, but such similarities between nicotine and cocaine may only be clearly identifiable by subjects experienced with both cocaine and nicotine.

Nicotine given in the polacrilex gum form has been evaluated with similar measures as described above. These studies involved giving various combinations of 2-mg- and 4-mg-nicotine pieces of polacrilex gum and placebo to cigarette smokers. Human volunteers were given the polacrilex gum to chew in doses ranging from 0 to 4 mg in one study (Nemeth-Coslett and Henningfield 1986) and 0 to 8 mg in another study (Nemeth-Coslett et al. 1987). Both studies showed that subject ratings of several effects (including "dose strength") were directly related to the total dose of nicotine that was given. In addition, similarity of the stimulus effects to those produced by cigarettes was a direct function of dose level. In these studies "liking" or "positive" effect scores were inversely related to dose level, suggesting that this nicotine delivery system has low potential for causing dependence when compared with that of cigarettes (Chapter VII). The role of centrally mediated nicotinic actions in the ability of humans to differentiate among polacrilex gum-delivered nicotine doses was confirmed in a study by Pickworth, Herning, and Henningfield (in press). These researchers found that mecamylamine pretreatment of human volunteers reduced both the EEG and subjective effects of nicotine polacrilex gum administration.

Like many other psychoactive drugs (Chapter V), nicotine can also produce unpleasant or dysphoric subjective effects that are related to the dose given and the route of administration. Such effects can be quantified by a psychological scale of the ARC1 that is sometimes referred to as the "dysphoria" scale (Jasinski, Johnson, Henningfield 1984) or the "LSD" scale because it was constructed from items found to be elevated when lysergic acid diethylamide (LSD) was given to volunteers (Haertzen 1966, 1974).

In one study, Henningfield, Miyasato, and Jasinski (1985) found that both inhaled (research cigarette smoke) and i.v. nicotine produced dose-related increases in LSD scale scores. In two other studies, nicotine polacrilex gum was tested (Nemeth-Coslett and Henningfield 1986; Nemeth-Coslett et al. 1987). LSD scale scores were at least slightly increased in both studies and were significantly increased in the study by Nemeth-Coslett and Henningfield (1986). These results with nicotine polacrilex gum, combined with no increases in MBG scale scores, are consistent with the observations described earlier suggesting a low overall dependence potential for this formulation.

Sensory Effects of Nicotine

As discussed earlier in this Chapter, nonnicotine constituents of tobacco smoke can produce functional sensory effects. Nicotine, too,

can produce peripherally mediated sensory effects which could contribute to the taste of the cigarette. Although not generally termed "psychoactive" drug effects, such effects could contribute to the control over behavior as they provide discrete cues which may be associated with centrally mediated nicotinic effects. For example, nicotine has a bitter taste, elicits burning sensations when placed on the tongue, and is irritating to the oral and respiratory mucosa (Windholz et al. 1976). Increasing the nicotine delivery of cigarettes while holding tar delivery constant leads to an increase in perceived strength and harshness. The possible effects of nicotine in the upper respiratory tract on subject ratings cannot be excluded in these studies. Nicotine also stimulates mechanoreceptors sensitive to pressure and stretch (Taylor 1985b), and this local action of nicotine may also contribute to the sensory characteristics of inhaled cigarette smoke.

Hexamethonium (the nicotine receptor antagonist that only acts peripherally) has been shown to block cigarette smoke-induced edema in the tracheobronchial mucosa of rats (Lundberg, Saria, Martling 1982). Another study showed that mecamylamine produced dose-related decreases in harshness ratings of individual puffs of cigarette smoke (Rose, Sampson, Henningfield 1985). In this study, subjects were asked to rate their preference at different nicotine concentrations of the smoke: mecamylamine pretreatment shifted preferences to higher smoke concentrations for individual puffs.

Another method of producing at least some of the nicotine-related sensations of cigarette smoke is to present nicotine in vapor or aerosol form without any components of tar. Nicotine vapor is likely to be deposited mainly in the mouth and pharynx (Russell 1986); thus it would be difficult to administer a pharmacologically effective dose of nicotine without producing excessive local irritation and bad taste. However, a low dose of nicotine delivered in this fashion might simulate the sensory effects of smoking, even if the pharmacologic effects are minimal. A low-dose nicotine aerosol delivering droplets 1 to 5 μm in size would be expected to provide respiratory sensations even more similar to cigarette smoking, as particles of this size would impact mainly in the tracheobronchial region.

Three studies have evaluated the effects of a commercially marketed nicotine vapor delivery system in human subjects. The delivery system was a version of that originally described by Jacobson, Jacobson, and Ray (1979); it was marketed as a "tobacco product" through February 1987, when the Food and Drug. Administration (FDA) required verification of "safety and efficacy" for continued marketing as a "nicotine delivery system" (see Chapter VII). It consisted of a cigarette-size plastic tube with a nicotine-containing polymer in the end distal from the user's mouth. It was used by sucking air through the tube and inhaling in a manner

similar to that when smoking cigarettes. When the system was used in this fashion, two studies found that plasma nicotine levels were not significantly elevated (Sepkovic et al. 1986; Henningfield 1986b). A third study found significant elevations in plasma nicotine following use of the nicotine tube (Russell et al. 1987). However, in the latter study subjects used what may be described as a heroic puffing procedure: they were instructed to puff 1 nicotine tube 10 times, at intervals of 40 sec; after a 4-min pause, subjects then "puffed and inhaled as hard and as frequently as possible, continously for the next 20 min, with changes every 5 min to fresh cigarette [nicotine tube]." Symptoms typical of those associated with higher levels of nicotine administration were observed, i.e., dizziness, lightheadedness, and in a few subjects, nausea (Russell et al. 1987).

In another study of the nicotine vapor inhaler, four tubes in which none, one, two, or four contained nicotine (the others being denicotinized) were simultaneously puffed on by volunteers through a specially designed cigarette holder (Henningfield 1986b, 1987a). In this study, despite the fact that measurable changes in plasma nicotine levels did not occur, several responses often associated with nicotine delivery were observed: (1) subject ratings of "harshness" were directly related to dose (number of nicotine-containing tubes); (2) post-puffing increases in heart rate occurred as a function of dose; (3) subjective effects were directly related to dose; and (4) desire to smoke tobacco cigarettes was inversely related to nicotine dose level. Taken together, these results show than even with negligible systemic levels, nicotine can induce feelings of satisfaction and can reduce urges to smoke when it produces tobacco-like sensations of throat burn and harshness (Chapter VII).

Some of the short-term satisfaction derived from inhaling nicotine may explain the apparent short-term efficacy of the vapor inhaler in reducing desire to smoke despite negligible plasma nicotine levels. This is in contrast to findings obtained when nicotine is given either intravenously or in the polacrilex gum (Henningfield, Miyasato, Jasinski 1983; Nemeth-Coslett et al. 1987). Whether the effects of the nicotine vapor inhaler are conditioned responses, peripheral nicotinic actions, or both, it remains to be determined if such effects would provide long-term efficacy as tobacco replacement in the nicotine-dependent tobacco user (Chapter VII). Such effects may not be satisfactory for long-term treatment (i.e., they may not satisfactorily alleviate tobacco withdrawal), although they may prove important in providing sources of pleasure and reduction of urges in people trying to quit smoking (Henningfield 1987b).

State-Dependent Learning

The potential of nicotine to induce state-dependent learning effects as well as how such effects are studied are discussed in

Chapter VI. In the present Section, findings are summarized in so far as they are relevant to assessing the dependence potential of nicotine. In brief, state-dependent learning refers to the phenomenon whereby behavior learned in one set of cues or stimulus conditions (context) is most reliably performed when subsequently attempted in the same context and/or is adversely affected when attempted in a novel context (Chapter VI). Psychoactive drugs can produce state-dependent learning effects, apparently by providing a recognizable context based on the interoceptive stimulus cues provided by the drug (see also Chapter V). Several studies have shown that nicotine exposure can lead to state-dependent learning effects. For example, a series of studies conducted by Andersson and colleagues (Andersson 1975; Andersson and Hockey 1977; Andersson and Post 1974) and by others (Peters and McGee 1982; Warburton et al. 1986) showed that nicotine exposure in the form of tobacco smoke could induce state-dependent learning effects in humans. In a study by Lowe (1985), nicotine's part in the state complex produced by alcohol and nicotine together was also evaluated.

There are two implications of the above findings regarding the dependence potential of nicotine. The first is that state-dependent learning could contribute to the dependence potential of cigarettes, in that optimal cognitive/behavioral performance may come to depend upon the continued self-administration of tobacco. These actions might also contribute to the strength of the reinforcing effects of nicotine by producing effects on learning and/or performance (see also Chapter VI).

Nicotine as a Positive Reinforcer

The primary biobehavioral mechanism by which dependence-producing drugs maintain drug seeking is by functioning as positive reinforcers (Thompson and Unna 1977; Thompson and Schuster 1968). That is, drugs can serve as stimuli that strengthen behavior leading to their own presentation (Skinner 1953; Thompson and Schuster 1968). As discussed in Chapter V, studies in the 1960s used the drug self-administration techniques developed to study morphine and other dependence-producing drugs in animals (Weeks 1962; Thompson and Schuster 1964; Chapter V). In the first such study with nicotine, Deneau and Inoki (1967) found that monkeys would also self-administer nicotine intravenously. However, some investigators considered these findings equivocal (Russell 1979; Griffiths, Brady, Bradford 1979). In 1981, Goldberg, Spealman, and Goldberg showed conclusively that nicotine itself could function as an efficacious positive reinforcer for animals, although the range of conditions under which it was effective was somewhat more limited than for drugs such as cocaine and amphetamine. Analagous studies with humans in the 1980s (e.g., Henningfield, Miyasato, Jasinski

1983) demonstrated that intravenously administered nicotine is a reinforcer. The results leading to the foregoing conclusions are summarized in the present Section.

Animal Studies of Nicotine as a Reinforcer

Whether a drug functions as a reinforcer can depend critically on the dose of drug, the previous exposure of the subject to that or other drugs, the behavioral history of the subject, and perhaps most importantly, the immediate contingencies relating responses and subsequent injections of drug (contingencies are often referred to as schedules of reinforcement) (Barrett and Witkin 1986; Chapter V). Nicotine differs from some dependence-producing drugs (e.g., cocaine) (Griffiths, Brady, Bradford 1979) in that for animals, the conditions under which it maintains high rates of self-administration behavior appear to be more limited; however, there are other dependence-producing drugs which also serve as reinforcers under a fairly limited range of conditions (e.g., alcohol) (Mello 1973; Meisch 1977).

Table 4 (modified from Henningfield and Goldberg 1983b) is a summary of the early studies that found i.v. nicotine injection to be ineffective or marginally effective as a reinforcer as well as more recent studies that conclusively demonstrated the capacity of nicotine to function as a positive reinforcer. The studies listed in this Table employed a variety of species (ranging from rats to human volunteers), different types and parameters of drug injection schedules, a variety of training histories, and a wide range of nicotine doses. Much of the research has been reviewed in greater detail elsewhere (Goldberg and Henningfield, 1988; Swedberg, Henningfield, Goldberg, in press). The present Section only reviews some of the more recent studies that have experimentally evaluated nicotine's reinforcing effects.

Until 1981, most experiments of nicotine self-administration involved continuous reinforcement schedules in which each response by an individual subject resulted in the i.v. injection of nicotine (Table 4). Under these continuous reinforcement schedules, (1) rates of responding were very low, ranging from about 0.008 to 0.0005 responses/set in different studies; (2) changes in nicotine dose produced only small and inconsistent changes in rates of responding; (3) the differences in rates of responding maintained by nicotine compared with saline were generally small; and (4) marked intersubject differences in self-administration of nicotine were often reported. In one series of studies (Lang et al. 1977; Singer, Simpson, Lang 1978; Latiff, Smith, Lang 1980; Smith and Lang 1980) a concurrent schedule of periodic deliveries of food pellets to food-deprived rats was found to increase rates of nicotine self-administration responding (Chapter V). The concurrent food reinforcement schedule ap-

TABLE 4.--Summary of reports in which nicotine was available under intravenous drug self-administration (S-A) procedures

Study	Species	Reinforcement schedule	Main findings	Comments
Deneau and Inoki (1967)	Rhesus monkey	FR 1; several nicotine doses tested	Two monkeys initiated S-A; others required priming procedure	Currently accepted reinforcing efficacy assessment criteria not achieved
Clark (1969)	Hooded rat	FR 1; several nicotine doses and saline tested	Nicotine a reinforcer relative to saline	No quantitative data (from study abstract)
Yanagita (1977)	Rhesus monkey	Experiment 1: FR 1; several nicotine, caffeine, and saline doses substituted for SPA	Nicotine and caffeine not reinforcers, compared with saline or SPA	(preliminary report, Yanagita et al. (1974) studies)
		Experiment 2: FR 1; several nicotine doses continuously available	Nicotine S-A rates stable in most subjects, but not clearly dose related	No direct reinforcing efficacy test
		Experiment 3: PR procedures; two nicotine doses, saline, and three cocaine doses tested	0.2 mg/kg nicotine and lowest cocaine dose (0.03 mg/kg) maintained similar response rates, which slightly exceeded rates maintained bv saline	Nicotine marginally reinforcing compared with saline and higher cocaine doses
Lang, Latiff, McQueen, Singer (1977)	Hooded rat	FR 1; nicotine and saline tested in food-sated and food-deprived rats	In food-deprived (not food-sated1 rats, nicotine a reinforcer, compared with saline	
Singer, Simpson, Lang (1978)	Hooded rat	CONC [(FR 1:nicotine)(FT 1 min:food pellet)] in food-deprived rats; rats subsequently food-sated	Food satiation decreased nicotine S-A rate, but nicotine a reinforcer in both conditions	Results similar to ethanol testing results

TABLE 4.--Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Griffiths, Brady, Bradford (1979)	Baboon	FR 160 followed by 3-hr timeout; several nicotine doses and saline substituted for cocaine	Number of nicotine injections/day did not exceed saline	Caffeine, ephedrine, and various other similarly tested stimulants were reinforcers relative to saline
Hansen, Ivester, Moreton (1979)	Albino rat	FR 1; several nicotine doses and saline tested	Mecamylamine (centrally acting antagonist). not pentolinium (peripherally acting antagonist), altered S-A behavior	Group data suggest nicotine as a reinforcer; no clear dose-effect curve
Latiff, Smith, Lang (1980)	Hooded rat	CONC [(FR 1:injection)(FT 1 min:food pellet)]; several nicotine doses and saline tested	Nicotine a reinforcer, relative to saline; mild effects of urine pH manipulations on S-A rate only during initial nicotine exposure	S-A rate inversely dose related during initial nicotine S-A behavior acquisition, not after establishment
Smith, and Lang (1980)	Hooded rat	FR 1; one nicotine dose and saline tested	Nicotine a reinforcer with and without CONC food delivery schedule in food-deprived, but not food-sated, rats	
Goldberg, Spealman, Goldberg (1981)	Squirrel monkey	Second-order schedule FI 1 or 2 min (FR l0:stimulus), followed by 3-min timeout; one nicotine dose and saline tested	Nicotine maintained high rates of responding; rates decreased markedly when (1) saline replaced nicotine, (2) brief stimuli omitted, (3) subjects mecamylamine pretreated	Demonstrated importance of ancillary environmental stimuli in maintaining high rates of responding

TABLE 4.--Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Dougherty, Miller, Todd, Kostenbauder (1981)	Rhesus monkey	FI 16 and second-order FI 1 min (FR 4:stimulus); several nicotine doses and saline tested	Nicotine maintained higher S-A rates than saline under FI and second-order schedules, but only a marginally effective reinforcer when continuously available	Establishing nicotine as reinforcer required several months, using procedures that establish cocaine or codeine as reinforcers in few days
Goldberg and Spealman (1982)	Squirrel monkey	FI 5 min followed by 1-min timeout; several nicotine and cocaine doses and saline tested	Nicotine and cocaine qualitatively similar reinforcers, compared with saline; cocaine maintained higher rates of responding in 1 of 2 monkeys; mecamylamine pretreatment reduced nicotine S-A rates	Showed nicotine can be punisher, similar to electric shock
Singer, Wallace, Hall (1982)	Long-Evans rat	CONC [(FR 1:nicotine)(FT 1 min:food pellet)]; one nicotine dose tested	Lower nicotine S-A rates in rat group with 60-OHDA lesions in nucleus accumbens than in sham-lesions group	Range of lesion-inhibited scheduled-induced behaviors extended
Spealman and Goldberg (1982)	Squirrel monkey	Second-order FI 1, 2, or 5 min (FR 10:stimulus) and FI 5-min schedules tested; several nicotine and cocaine doses and saline tested	Nicotine and cocaine maintained similar rates of responding and patterns; nicotine, not cocaine, S-A decreased to saline-like rates when mecamylamine pretreated	Under both schedules, nicotine and cocaine reinforcing efficacy comparable

TABLE 4.--Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Ator and Griffiths (1983)	Baboon	Experiment 1: FR 2 followed by 15-sec timeout; several nicotine doses, cocaine, and saline tested	Nicotine marginally reinforcing, compared with saline across narrow dose range	Inverted U-shaped initial dose-response curve; flat final curve (earlier abstract, Ator and Griffiths (1981))
		Experiment 2: FI 5 min followed by 1-min timeout; several nicotine and cocaine doses and saline tested; FI duration varied l-11 min	Nicotine maintained higher rates of responding than saline, but much lower than cocaine or food	Nicotine and injections/session responding rates little changed with varied FI duration
Goldberg and Henningfield (1983a, b)	Human and squirrel monkey	FR 10 followed by l-min timeout; several nicotine doses and saline tested	Monkey and human patterns of responding qualitatively similar; nicotine injection number exceeded saline injection number in 3 of 4 of both humans and monkeys	In both humans and monkeys, evidence of nicotine having both reinforcing and punishing effects (from study abstracts)
Henningfield, Miyasato, Jasinski (1983)	Human	FR 10 followed by l-min timeout; several nicotine doses and saline tested	Nicotine injection number generally exceeded saline injection number; nicotine injection number inversely related to nicotine dose; nicotine suppressed postsession cigarette smoking	Nicotine and intravenous cocaine subjective effects similar; nicotine had both reinforcing effects and punishing effects

TABLE 4.--Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Risner and Goldberg (1983)	Beagle dog	FR 15 followed by 4-min timeout: several nicotine, cocaine, and saline doses tested: PR schedule also used	Nicotine and cocaine maintained qualitatively similar patterns of responding and were reinforcers relative to saline; mecamylamine pretreatment reduced nicotine, not cocaine, S-A	Substantially greater response rates maintained with cocaine than nicotine
Cox, Goldstein, Nelson (1984)	Wistar rat	FR 1; several nicotine doses and saline tested: a second inactive lever available to assess nonspecific activity-increasing nicotine effects	Nicotine S-A rates higher than saline, but result in part of nonspecific activity increases	Active lever responding rates low (±40 responses/12 hrs), only about twice as high as inactive lever rates
Prada and Goldberg (1985)	Squirrel monkey	FR 30 followed by 4-min or 10-sec timeout; one nicotine dose tested	At 4-min timeout, overall nicotine-maintained response rate range 0.3-2.4 responses/sec; at 10-sec timeout, responding poorly maintained	Nicotine iv injections and food pellet delivery maintained similar high response rates (from study abstract)
Slifer and Balster (1985)	Rhesus monkey	Experiment 1: FR 1 and CONC [(FR 1:nicotine)(FT 5-min:food pellet)]; several nicotine doses and saline tested	At CONC condition, nicotine S-A at rate higher than saline; at FR 1 condition, nicotine S-A without CONC food	At some doses, nicotine maintained higher S-A rates than at FR 1 condition saline (preliminary report, Slifer (1983))
		Experiment 2: FR 10; saline and several nicotine doses substituted for cocaine	Nicotine a reinforcer relative to saline, but response rates low relative to single cocaine dose tested	Nicotine dose changes produced only small response rate changes

TABLE 4.--Continued

Study	Species	Reinforcement schedule	Main findings	Comments
Goldberg and Henningfield (1986)	Human and squirrel monkey	Monkeys: FR 10-200, with l-, 2-, or 4-min timeouts Humans: FR 10-800, with l-, 5-, l0, or 20-min timeouts	Nicotine maintained about l.0/sec overall rate of FR responding at high FR and timeout, in both humans and monkeys	(from text of talk)
Naruse, Asami, Ikeda, Ohmura (1986)	Rat	FR 1, FR 4, FR 8; several nicotine doses and saline tested	Higher nicotine injection doses (10 and 30 µg/kg) maintained responding above saline control levels	Nicotine a relatively weak reinforcer after 15day availability
De la Garza and Johanson (1987)	Rhesus monkeys	FR 10; saline and several nicotine, d-amphetamine, diazepam, and perphenazine doses substituted for cocaine	Nicotine a reinforcer relative to saline, but response rates very low relative to cocaine and d-amphetamine	Food deprivation significantly increased response rate for low nicotine dose in only 1 of 3 monkeys

NOTE: FR, fixed ratio; SPA, l-2 diphenyl-l-dimethyl-aminoethane-HC1; progressive ratio; FT, fixed time; FI fixed interval; CONC, concurrent

peared to hasten acquisition of the nicotine self-administration (Smith and Lang 1980).

Since 1981, methodology for studying the reinforcing effects of nicotine has shifted away from continuous reinforcement schedules and toward schedules of self-administration in which responses are only intermittently reinforced by nicotine injection (Goldberg et al. 1983). Such intermittent schedules appear to more closely approximate the patterns of human cigarette smoking behavior in which nicotine is taken in intermittent small doses (puffs) and with even greater intervals between dosing resulting from periods of time between cigarettes (Henningfield 1984). On a variety of intermittent schedules, i.v. nicotine was shown to function as an effective reinforcer, maintaining overall rates of responding ranging from 0.1 to more than 1 response/sec (Table 4). These increases in behavioral responses maintained by nicotine were obtained without the use of food deprivation or concurrent inducing schedules of food delivery.

In one series of experiments with squirrel monkeys, Goldberg and Spealman (1982) and Spealman and Goldberg (1982) utilized a fixed-interval schedule in which the first response to occur after a 5-min interval elapsed produced an i.v. injection of nicotine followed by a l-min period of drug nonavailability ("timeout"). Responses during the 5-min intervals had no specified consequences, and daily sessions ended after 10 intervals or 2 hr. Under these conditions, nicotine functioned as an effective reinforcer: (1) peak rates of responding maintained by nicotine ranged from 0.1 to 0.3 response/sec and were similar to those maintained by cocaine; (2) as nicotine dose per injection was increased from 3 to 300 mg/kg, rates of responding first increased and then decreased; (3) rates of responding maintained by nicotine were about fourfold to eightfold higher than those maintained during saline substitution; and (4) daily intramuscular treatment with 1 mg/kg of mecamylamine reduced rates of responding maintained by nicotine to saline-control levels but had no effect on responding maintained by cocaine. Thus, nicotine satisfied all the criteria discussed in Chapter V as an effective reinforcer. Particularly striking was the finding that although injection doses of nicotine above 30 mg/kg produced vomiting during the session, one or more of these higher doses continued to be maintained near maximal rates of responding in four of the six monkeys studied.

The results of Goldberg, Spealman, and Goldberg (1981) showing nicotine to be an effective reinforcer have been extended in subsequent studies. For example, high rates of responding were maintained on reinforcement schedules of nicotine injection in which the number of responses per injection was fixed at some intermediate level (e.g., 1 injection/l5 responses; such contingencies are termed fixed-ratio schedules). Risner and Goldberg (1983) used a 15-response fixed-ratio schedule of nicotine injection with 4-min

timeout periods following each injection in beagle dogs. Nicotine was an effective reinforcer in all dogs: (1) peak rates of responding were about 0.3 response/sec, but higher rates of responding were maintained by cocaine; (2) as the injection dose of nicotine increased from 10 to 100 mg/kg, response rates first increased and then decreased at the highest dose; (3) peak rates of responding maintained by nicotine were about fifteenfold greater than those maintained by saline; and (4) rates of responding maintained by nicotine but not by cocaine were reduced to saline levels by presession treatment with mecamylamine. Although cocaine maintained higher rates of responding than nicotine in the dog, fixed-ratio patterns of responding maintained by nicotine and cocaine were similar: a pause in responding at the start of each fixed ratio was followed by a change to steady responding at a high rate until nicotine or cocaine was injected.

In other studies Goldberg and Henningfield (1983a,b, 1986) used 10- to 30-response fixed-ratio schedules of i.v. nicotine injection in squirrel monkeys. When a 1-min timeout followed each injection, nicotine maintained rates of responding higher than did saline, although overall rates of responding were very low. When the timeout value was increased to 4 min (Prada and Goldberg 1985; Goldberg and Henningfield 1986) making maximum frequency of nicotine injection comparable to that of earlier studies by Goldberg and colleagues, nicotine maintained high rates of responding that ranged from 0.3 to 2.4 responses/sec in different monkeys.

Differences between nicotine and cocaine in their overall efficacy as intravenously delivered reinforcers have been found when the drugs are compared on progressive-ratio schedules. Risner and Goldberg (1983) studied beagles under a schedule in which the fixed-ratio requirement was increased daily until responding was no longer maintained. Cocaine maintained higher fixed-ratio values than did nicotine on this progressive-ratio schedule, although maximal fixed-ratio values for nicotine were well above those for saline. Yanagita (1977) obtained similar findings on a progressive-ratio schedule of i.v. nicotine or cocaine injection in rhesus monkeys (Chapter V).

Nicotine was also studied in the baboon using an intermittent schedule of reinforcement and was found to be a weak reinforcer. Ator and Griffiths (1983) used a 5-min fixed-interval schedule of i.v. nicotine injection in baboons with 1-min timeout periods. Peak rates of responding were higher than rates maintained during saline substitution. However, rates of responding maintained by nicotine were much lower than those maintained by i.v. injection of cocaine. In addition, as the injection dose of nicotine was increased from 10 to 560 mg/kg, rates of responding first increased and then decreased at the highest doses in one baboon. With the other two baboons, rates of responding either showed little change or decreased as injection dose

was increased. These variable dose-response data were consistent with the conclusion that nicotine was only a weak reinforcer in the baboons.

When cigarettes are smoked, a variety of environmental stimuli are intermittently associated with the pharmacologic actions of nicotine (e.g., pleasure and relief from withdrawal). These stimuli themselves appear important in controlling and strengthening repetitive cigarette smoking (e.g., removal of the sight and smell of cigarette smoking) (Gritz 1978). An experimental model for investigating the role of drug-associated stimuli is the second-order schedule of drug reinforcement. Second-order schedules of reinforcement involve the intermittent pairing or association of an environmental stimulus with the primary reinforcer; these stimuli are used as "secondary" or "conditioned" reinforcers to maintain chains of behavior leading eventually to the delivery of the primary reinforcer (Goldberg, Kelleher, Morse 1975; Katz and Goldberg, in press). These schedules add an additional component of relevance to the study of cigarette smoking: cigarette smoking involves the pairing of many such environmental stimuli (visual, olfactory, taste, and tactile) with the effects of nicotine administration.

Studies of i.v. nicotine on second-order schedules of reinforcement have shown that (1) nicotine can establish previously neutral stimuli (e.g., colored lights) as conditioned reinforcers when injections are paired with light presentations, (2) such schedules can result in high and persistent rates of drug-seeking behavior, and (3) the presentation of the stimuli themselves (in the absence of nicotine injections) could sustain substantial amounts of drug-seeking behavior. Goldberg, Spealman, and Goldberg (1981) and Spealman and Goldberg (1982) used a second-order schedule of nicotine injection in which completion of each 10-response fixed ratio during a 2-, 3-, or 5-min interval produced a brief visual stimulus; the first fixed ratio completed after the specified fixed interval elapsed produced both the visual stimulus and i.v. injection of drug. In these studies, nicotine functioned as a powerful reinforcer: (1) peak rates of responding maintained by nicotine ranged from 0.8 to 1.7 responses/sec and were similar to those maintained by cocaine; (2) as nicotine dose increased from 3 to 100 mg/kg, rates of responding first increased and then decreased; (3) rates of responding maintained by nicotine were twofold to eightfold greater than those maintained during saline substitution; and (4) rates of responding maintained by nicotine, but not by cocaine, were reduced to saline control levels by presession administration of 1 mg/kg of mecamylamine; (5) the brief visual stimuli functioned as conditioned reinforcers, as demonstrated by the finding that rates of responding fell markedly when they were omitted during the intervals.

Taken together, the results of the studies described in this Section confirm that nicotine is self-administered in several animal species and in the absence of either tobacco or unique human cultural factors. It appears to be most effective as a reinforcer when intermittently available and when environmental stimuli are paired with nicotine delivery. Under these conditions, nicotine injections functioned to motivate behavior as did cocaine injections; however, cocaine injections maintained more total work output than did nicotine. Finally, studies with nicotine antagonists further confirmed that effects of nicotine in the brain were necessary to maintain its reinforcing actions.

Human Studies of Nicotine as a Reinforcer

The methods developed in animal studies have also been used to demonstrate the reinforcing effects of i.v. nicotine injections in human volunteers (Henningfield, Miyasato, Jasinski 1983; Henningfield and Goldberg 1983a; Goldberg and Henningfield 1983a,b, 1986). In these studies all subjects had histories of tobacco use and subjects were not allowed to smoke 1 hr before or during 3-hr sessions: During test sessions every 10th lever press produced an i.v. injection of either nicotine or saline followed by a 1-min timeout. In one study (Henningfield, Miyasato, Jasinski 1983), nicotine was available on some days, while saline was available on other days. In other studies (Henningfield and Goldberg 1983a; Goldberg and Henningfield 1983a,b), nicotine and saline were concurrently available for responding on alternate levers. With both approaches, all of the subjects initiated self-administration of nicotine. Nicotine injections were regularly spaced throughout each session, and the rate of self-administration was inversely related to dose. When saline was substituted for nicotine, rates of responding usually decreased; responding that did occur for saline occurred predominantly at the start of each session and was erratic in temporal patterns.

In another study, the fixed-ratio value was then increased to 100; following each injection, subjects then had to wait 20 min before another injection could be obtained (Swedberg, Henningfield, Goldberg, in press). Under these conditions rates of responding increased and ranged from 0.4 to 2 responses/sec, similar to those seen with squirrel monkeys and dogs in the studies previously described. These studies of i.v. nicotine self-administration demonstrated conclusively that nicotine itself can serve as an effective reinforcer in humans.

Nicotine as an Aversive Stimulus

Even dependence-producing drugs do not have invariant positive reinforcing effects; they may be aversive under some conditions (see Chapter V). Furthermore, aversive effects are an additional mechan-

ism by which drugs can modify behavior and may be important in gradually increasing the total amount of control which is exerted by the drug over the individual. Such effects of nicotine could be important in limiting the total amount of cigarette smoking or even in determining when the cigarette is discarded.

The potential effects of nicotine to produce severe discomfort and thereby limit further intake have been part of the history of nicotine which has developed over the centuries (Lewin 1931; Dixon and Lee 1912). Two types of laboratory studies have been conducted to assess possible aversive effects of nicotine. The studies, involving animals and/or humans, showed that nicotine (at high levels) can serve as a punisher to suppress behavior leading to the delivery of another reinforcer, and as an aversive stimulus or negative reinforcer to maintain behavior that either terminates or prevents injections of nicotine.

In one series of studies (Goldberg and Spealman 1982, 1983), squirrel monkeys responded on a two-component fixed-ratio schedule of food presentation. In both components, every 30th lever press produced a food pellet. In the punishment component, which was signaled by a red light, the first response in each fixed ratio produced an i.v. injection of nicotine. When responding produced 10- or 30-mg/kg injections of nicotine during the punishment component, responding was selectively suppressed in that component in a dose-related manner. When saline was injected, however, rates of responding for food were no longer suppressed. Similar findings were obtained when electric shock was compared with nicotine in the same studies. Administration of mecamylamine, but not hexamethonium, reduced the punishing effects of the nicotine, showing that the effects were centrally mediated. Futhermore, these antagonists did not reduce the aversive effects of the electric shock, confirming that the effects of nicotine were due to nicotine actions at nicotinic receptors and not to more general possible effects of nicotine.

The potential aversive effects of nicotine have been experimentally demonstrated in human subjects in a preliminary experiment by Henningfield and Goldberg (1983a). Human volunteers who had been recruited for studies of i.v. nicotine self-administration and who did not self-administer nicotine during initial sessions were tested under a concurrent schedule of nicotine avoidance and nicotine self-administration. Two levers were present, and injections of nicotine were programmed to occur every 15 or 30 min. Pressing the left lever 10 times avoided the impending injection, while pressing the right lever 10 times produced an injection. Higher doses of nicotine (1.5 to 4 mg/injection given over 10 sec) resulted in increased rates of pressing on the left lever, and fewer injections occurred. Subjects never completed the 10 responses on the alternate lever required to produce an injection. When saline was substituted for nicotine,

responding decreased and the number of injections received markedly increased. Analogously, in these same subjects scores on a visual line analog scale for rating "negative or undesirable" effects were directly related to nicotine dose, and declined to zero when saline was substituted for nicotine.

Nicotine as an Unconditioned Stimulus

The preceding studies have largely evaluated the effects of nicotine administration on some behavior which was associated with the drug by a specific behavioral contingency. But drugs can also directly elicit responses which then might become conditioned to occur in the presence of whatever stimuli were associated with those effects. The effects may be seen as positive or negative and may be associated with either increasing or declining drug levels in the body (i.e., drug taking or drug withdrawal).

Two general conditioning paradigms are used to evaluate the unconditioned stimulus effects of drugs and have been used to test nicotine: the conditioned place preference and aversion paradigm, and the conditioned taste aversion paradigm. In addition to a discussion of these paradigms, data obtained from the practical application of such findings in the treatment of tobacco dependence will be summarized.

Conditioned Place Preference and Aversion

The place preference and aversion paradigm has been increasingly used to evaluate the potential of drugs to produce dependence (Bozarth 1983). It may be used to assess the positive and negative subjective states induced by drugs and other chemicals. In the place-conditioning procedure, an animal is exposed to the effects of a drug in a novel, distinctive environment. Another environment is paired with the administration of the drug vehicle (e.g., saline). Subsequently, the subject is given a free choice of both environments while not under the influence of the drug. It is currently hypothesized that the formation of place preferences or place aversions depends on the association of the interoceptive drug effect with an external stimulus (e.g., the particular environmental context of the place-conditioning apparatus). Nicotine has been shown to condition both positive and negative effects in this paradigm.

The first published study of the place-conditioning effects of nicotine (Fudala, Teoh, Iwamoto 1985) indicated that nicotine, at doses from 0.1 to 1.2 mg/kg administered s.c. to rats, produced both a place preference and place aversion depending upon the dose. As discussed in Chapter V, the ability to condition both place preferences as well as place aversions is characteristic of several dependence-producing drugs. A dose of 0.8 mg/kg was found to condition a

place preference for previously nicotine-paired environmental cues in the greatest proportion of animals. At the lowest effective place-conditioning dose of nicotine, 0.1 mg/kg, an almost equal proportion of animals exhibited place preferences and place aversions. This investigation also indicated that mecamylamine, but not hexamethonium, blocked the place preference-producing effects of nicotine, suggesting that this nicotine-induced effect was centrally mediated.

Subsequent studies have extended the findings of Fudala, Teoh, and Iwamoto (1985) discussed above. Using a more conservative classification method in categorizing their subjects, Fudala and Iwamoto (1986) observed that nicotine produced a conditioned place preference only within the dose range previously tested. Furthermore, nicotine conditioned a place preference when the drug was administered immediately prior to conditioning sessions, but not when administered from 20 to 120 min prior to conditioning. Depending on the timing of nicotine administration, either place preferences or place aversions may be produced. For example, at doses between 0.2 and 0.8 mg/kg, a dose-dependent place aversion was induced when nicotine was administered 5 min or less following an animal's exposure to the conditioning environment (Fudala and Iwamoto 1987). One other group of investigators, Clarke and Fibiger (1987), using the same dose range of nicotine as in the two aforementioned studies, found no nicotine-induced conditioned place preference in rats. However, the two investigative groups used experimental methods that differed considerably, including differences in apparatus design, olfactory cues, number of conditioning trials performed, and time of conditioning relative to nicotine administration. The finding that nicotine administration can lead to conditioned responses in animals provides additional evidence of nicotine's potential to control behavior by this basic learning process (i.e., Pavlovian or classical conditioning, see Chapter V).

Conditioned Taste Aversion and Rapid Smoking

During conditioned taste aversion experiments, the presentation of an aversive stimulus after the consumption of a distinctively flavored solution causes rejection of the solution when it is presented at a later time (Palmerino, Rusiniak, Garcia 1980; Chapter V). A variety of dependence-producing drugs have been found to be effective at inducing taste aversions (for example, Wise, Yokel, DeWit 1976; Suzuki et al. 1983; Hunt and Amit 1987; Chapter V). Findings specific to nicotine are presented here.

Etscorn (1980) reported that a large intraperitoneal (i.p.) dose of nicotine, 2 mg/kg, conditioned taste aversions to 20 percent (weight per volume) sucrose in Swiss-Webster mice with the two-bottle choice test paradigm. Etscorn and colleagues (1986) also reported that i.p. injections of 1, 3, and 9 mg/kg of nicotine in golden Syrian hamsters

induced dose-related conditioned taste aversions to 0.1 percent sodium saccharin solutions with a single-bottle choice paradigm.

Kumar, Pratt, and Stolerman (1983) reported that s.c. injections of nicotine bitartrate could condition taste aversions to either 0.1 percent sodium saccharin or 0.9 percent sodium chloride solutions at doses as low as 0.08 mg/kg in Lister hooded rats with a two-bottle choice paradigm. The conditioned taste aversion was induced by nicotine in a dose-related manner; stronger taste aversions were induced by nicotine after four conditioning trials than after one or two trials. The S-nicotine (the nicotine form normally delivered in cigarette smoke) was approximately five times as potent as its stereoisomer in conditioning taste aversions. Mecamylamine, 0.1 to 2 mg/kg administered before each conditioning trial, blocked the development of taste aversions produced by 0.4 mg/kg of nicotine; hexamethonium, 1 to 10 mg/kg, had no effect.

Other studies have confirmed the pharmacologic specificity of nicotine-induced taste aversions; that is, Iwamoto and Williamson (1984) also found that the development of nicotine-conditioned taste aversions could be prevented in rats by pretreatment with mecamylamine, 3 mg/kg, but not with 1 mg/kg of hexamethonium. In an analogous study, the pharmacologic specificity of apomorphine-(dopamine agonist chemically derived from morphine) conditioned taste aversions was investigated in rats by establishing the response to both apomorphine and nicotine following pretreatment of the animals with pimozide (Kumar, Pratt, Stolerman 1983). Pimozide is a dopamine antagonist that blocks many of the effects of apomorphine. Pimozide pretreatment reduced the strength of the conditioned test aversions to apomorphine but not to nicotine, confirming a certain degree of pharmacologic specificity of the conditioning effects of these two chemicals. Finally, an intraventricular microinjection of 5 mg/kg of the quaternary nicotinic cholinergic ganglionic antagonist, chlorisondamine, in hooded Lister rats blocked the development of conditioned taste aversions to 0.1 percent sodium saccharin or 0.9 percent sodium chloride induced by nicotine injected 9 to 16 days after the chlorisondamine (Reavill et al. 1986).

These data indicate that nicotine, like some other drugs, is capable of conditioning taste aversions in a dose-related manner in rodents (see Chapter V). Because mecamylamine, but not hexamethonium, blocks nicotine-conditioned taste aversions, the mechanism by which nicotine conditions taste aversions appears to be centrally mediated. Conditioned taste aversion studies in which various combinations of nicotinic agonists and antagonists are given have also been useful in helping to identify specific brain mechanisms of nicotine's behavior modifying properties (see review by Stolerman, in press; also see Chapters III and V).

The fact that nicotine can be used to elicit aversive effects has been put to practical application in the treatment of cigarette smoking (Chapter V), generally to associate aversive effects of high doses of nicotine with the taste, smell, and inhalation of cigarette smoke. Variations on this procedure have been termed "rapid" smoking or "aversive" smoking procedures; the clinical results of these procedures have been mixed (see Chapter VII).

Nicotine: Withdrawal Reactions (Physical Dependence)

The preceding Sections have shown that cigarette smoking is an orderly form of drug self-administration. The role of nicotine in controlling this behavior is similar to the role of other psychoactive drugs in the determination of other forms of drug dependence (see Chapter V). Nicotine can serve as a highly effective positive reinforcer, and deprivation of cigarette smoking and presumably of nicotine itself can increase the reinforcing efficacy of cigarettes (Henningfield and Griffiths 1979). If longer periods of deprivation are associated with a discomforting withdrawal syndrome, this would constitute an additional mechanism by which the reinforcing efficacy of nicotine would be further increased. The drug effect which enables such discomforting withdrawal is physical dependence. Physical dependence refers to physiological and behavioral alterations that become increasingly manifest after repeated exposure to a pharmacologic agent. The primary indication of physical dependence is an abstinence-associated withdrawal syndrome, although tolerance is a frequent concomitant (Kalant 1978; Cochin 1970; Kalant, LeBlanc, Gibbons 1971; Eddy 1973; Clouet and Iwatsubo 1975; Yanagita 1977). Physical dependence and tolerance are discussed in greater detail in Chapter V.

Tolerance to nicotine has been studied since the 19th century and is well documented (Langley 1905; Dixon and Lee 1912; Gillman et al. 1985). As reviewed in Chapters II and V, nicotine produces tolerance to a variety of behavioral and physiological responses. Until the 1970s, however, physical dependence on tobacco was not rigorously studied, although there was evidence for a syndrome of withdrawal that could accompany abstinence from chronic cigarette smoking (Lewin 1931; Weybrew and Stark 1967) and that was significantly involved in attempts to quit smoking (Dorsey 1936). The clinical significance of the tobacco withdrawal syndrome has also been formally recognized by professional organizations such as the American Psychiatric Association (APA) (1980, 1987) and the American College of Physicians (1986). These observations, along with the evidence that nicotine produces tolerance (Chapter II), led to the conclusion that nicotine exposure produced physical depen-

dence (Jaffe 1985; Jaffe and Jarvik 1978; US DHHS 1986b; APA 1980).

Conclusions that nicotine exposure produced physical dependence were also consistent with early data which suggested that i.v. nicotine delivery seemed to relieve withdrawal from cigarettes and may have produced physical dependence in a nonsmoker (Johnston 1942). Other supporting observations included the finding that abrupt reduction of the nicotine in cigarettes (i.e., low nicotine-yield cigarettes) resulted in behavioral and physiological withdrawal signs including discomfort and the seeking of regular cigarettes (Finnegan, Larson, Haag 1945; Knapp, Bliss, Wells 1963). However, the rigorous scientific methods of the kind that were developed to evaluate withdrawal from opioids and sedatives (Himmelsbach 1942; Isbell 1948; Isbell et al. 1955; Chapter V) were not applied to the study of the tobacco withdrawal syndrome until the late 1970s. Therefore, the data available at the time of the 1964 Report of the Surgeon General's Advisory Committee on Smoking and Health were not considered conclusive (US DHEW 1964). The present Section reviews characteristics of physical dependence on nicotine, including the relationship of nicotine intake to the magnitude of withdrawal signs and symptoms, and the role of both environmental and pharmacologic factors which influence the course of the withdrawal syndrome.

Criteria for Physical Dependence on Nicotine and Clinical Characteristics of the Withdrawal Syndrome

Similar kinds of phenomena characterize withdrawal syndromes from all drugs that produce physical dependence. If physical dependence on nicotine occurs, these same phenomena should be observed (see Chapter V; Martin 1977; Thompson and Unna 1977; Woods, Katz, Winger 1987). Based on these phenomena, criteria for establishing that physical dependence on nicotine occurs include the following: (1) Termination of cigarette smoking should be accompanied by changes in mood, behavior, and physical functioning. (2) Some of these changes should be in a direction which is opposite to those produced by cigarette smoking and should return to the baseline levels observed during chronic tobacco administration ("rebound effects"). (3) Physiological withdrawal effects should be reversible by nicotine administration.

The tobacco withdrawal syndrome as described by the APA in the revised Diagnostic and Statistical Manual (DSM III-R) (APA 1987), provides a clinical description (Table 5). Several of the symptoms of the nicotine withdrawal syndrome correspond to effects of nicotine that are either known or suspected to promote tobacco dependence as discussed in Chapter VI. It should be noted that the sequelae of tobacco abstinence include a range of responses which do not share the same underlying mechanisms. For example, some symptoms are

transient responses which are opposite those produced when nicotine is given and which subside within a few days or weeks of nicotine abstinence; such responses are presumed to reflect a physiological rebound occurring in the absence of chronic drug exposure. Other responses are also opposite those produced by nicotine administration but appear to primarily reflect the removal of nicotine exposure, and which may occur whether or not sufficient nicotine had been taken to produce physical dependence. An example of the latter type of response is body weight. Nicotine can directly suppress appetite and body weight, often below the value at which it would have been had nicotine not been taken; removal of nicotine is then accompanied by a stable increase in body weight.

Various lines of scientific evidence are available to characterize physical dependence on tobacco and to evaluate the specific role of nicotine. These data include surveys, treatment studies, and experimental laboratory studies and are briefly reviewed in this Section.

Retrospective Survey Data

Retrospective studies have been conducted with ex-smokers who were participating in major surveys (Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987) or who were patients with chronic respiratory problems (Burns 1969; Mausner 1970). Other studies were conducted using subjects who responded to advertisements in newspapers (Pederson and Lefcoe 1976) or were contacted by word of mouth (Trahir 1967). The subjects in these studies had either quit smoking recently, had quit smoking for more than 1 year, or had at least one episode of remaining abstinent for 24 hr. Although the reliability of these data is limited because they are from retrospective self-reports, they provide information on the prevalence and nature of symptoms which may be experienced by smoke-deprived persons and acutely abstinent smokers.

Symptoms reported by significant numbers of ex-smokers included: “craving” for tobacco (Hughes, Gust, Pechacek 1987; Trahir 1967; Burns 1969; Mausner 1970; Pederson and Lefcoe 1976); restlessness, nervousness, or irritability (Trahir 1967; Wynder, Kaufman, Lesser 1967; Burns 1969; Mausner 1970; Hughes, Gust, Pechacek 1987); anxiety (Hughes, Gust, Pechacek 1987); impatience (Hughes, Gust, Pechacek 1987); difficulty concentrating (Trahir 1967; Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987); somatic or physical complaints (Hughes, Gust, Pechacek 1987; Pederson and Lefcoe 1976); increased appetite (Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987); increased food intake (Wynder, Kaufman, Lesser 1967); and weight gain (Trahir 1967; Wynder, Kaufman, Lesser 1967; Mausner 1970; Pederson and Lefcoe 1976).

Measures of the incidence and magnitude of signs and symptoms vary across studies, at least partly because of the diversity of the

TABLE 5.--Diagnostic categorization and criteria for nicotine withdrawal

Nicotine-induced organic mental disorder

292.00 Nicotine Withdrawal

The essential feature of this disorder is a characteristic withdrawal syndrome due to the abrupt cessation of or reduction in the use of nicotine-containing substances (e.g., cigarettes, cigars, and pipes, chewing tobacco, or nicotine gum) that has been at least moderate in duration and amount. The syndrome includes craving for nicotine: irritability, frustration, or anger: anxiety; difficulty concentrating; restlessness; decreased heart rate; and increased appetite or weight gain.

In many heavy cigarette smokers, changes in mood and performance that are related to withdrawal can be detected within 2 hours after the last tobacco use. The sense of craving appears to reach a peak within the first 24 hours after cessation of tobacco use, and gradually declines thereafter over a few days to several weeks. In any given case it is difficult to distinguish a withdrawal effect from the emergence of psychological traits that were suppressed, controlled, or altered by the effects of nicotine or from a behavioral reaction (e.g., frustration) to the loss of a reinforcer.

Mild symptoms of withdrawal may occur after switching to low tar/nicotine cigarettes and after stopping the use of smokeless (chewing) tobacco or nicotine gum.

The diagnosis of Nicotine Withdrawal is usually self-evident from the person's history, and disappearance of the symptoms if smoking is resumed is confirmatory. However, withdrawal from other psychoactive substances may take place simultaneously, and produce similar symptoms.

Diagnostic Criteria for Nicotine Withdrawal

A. Daily use of nicotine for at least several weeks

B. Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by at least four of the following signs:
   (1) Craving for nicotine
   (2) Irritability, frustration, or anger
   (3) Anxiety
   (4) Difficulty concentrating
   (5) Restlessness
   (6) Decreased heart rate
   (7) Increased appetite or weight gain

SOURCE: Condensed from the American Psychiatric Association (1987)

measuring instruments and techniques used, questions asked, and populations examined. Collectively, the results of many such studies suggest that most nicotine-deprived cigarette smokers experience at least one symptom of the tobacco withdrawal syndrome, that between one-fourth and one-half show significant withdrawal, and that about one-fourth report no withdrawal at all (Pederson and Lefcoe 1976; Wynder, Kaufman, Lesser 1967; Hughes, Gust, Pechacek 1987; Gritz 1980; Henningfield 1984). Of those persons who retrospectively report experiencing no withdrawal symptoms, it is unclear whether they were not physically dependent, whether the assessment instruments were not sufficiently sensitive, or whether

some persons are less impaired or discomforted by withdrawal symptoms.

Prospective Data from Laboratory and Nonlaboratory Studies

Cigarette smokers have been studied both in laboratory and nonlaboratory settings using a variety of self- and observer-administered tests measuring subjective, behavioral, and physiological signs and symptoms that accompany tobacco deprivation. The studies have examined changes in functioning resulting after periods of tobacco deprivation ranging from 1 hr to 21 days. Most studies have obtained both baseline and deprivation measures; a few studies have incorporated a control group of continuing smokers or nonsmokers; and a few have obtained data after smokers resumed smoking or were given nicotine polacrilex gum. The studies included ones which were conducted while the subjects were residing on a research ward, were living in their usual environment, or were paying occasional visits to a clinic for smoking cessation treatment. The symptoms reported in these studies were similar to those obtained from the retrospective studies, demonstrating generality across method and setting. These symptoms included the following: "craving" for tobacco (Gritz and Jarvik 1973; Hatsukami et al. 1984; Gilbert and Pope 1982; Shiffman and Jarvik 1976; Cummings et al. 1985; Hughes and Hatsukami 1986), irritability or anger (Myrsten, Elgerot, Edgren 1977; Elgerot 1978; Weybrew and Stark 1967; Hughes and Hatsukami 1986), anxiety and tension (Mrysten, Elgerot, Edgren 1977; Hughes and Hatsukami 1986), restlessness (Hughes and Hatsukami 1986), impatience (Hughes and Hatsukami 1986), depression (Hatsukami et al. 1984), problems with concentration (Hatsukami et al. 1984; Weybrew and Stark 1967; Myrsten, Elgerot, Edgren 1977; Frankenhaeuser et al. 1971; Hughes and Hatsukami 1986), drowsiness or fatigue (Weybrew and Stark 1967), sleep disturbances (Hatsukami et al. 1984; Larson, Haag, Silvette 1961; Weybrew and Stark 1967; Myrsten, Elgerot, Edgren 1977; Hughes and Hatsukami 1986), and increased hunger or appetite (Myrsten, Elgerot, Edgren 1977; Hughes and Hatsukami 1986).

In one study (Hughes and Hatsukami 1986), each subject had a spouse, relative, or friend rate some of the symptoms of withdrawal to verify self-report. These observer ratings of irritability, anxiety, restlessness, drowsiness, fatigue, impatience, and somatic complaints were all significantly related to their respective subject's ratings, thus adding to the validity of reports of these symptoms. These researchers found that the most common self-report symptoms were increased irritabilit,y (80 percent), anxiety (87 percent), difficulty concentrating (73 percent), restlessness (71 percent), impatience (76 percent), insomnia (84 percent), and craving for tobacco (62 percent).

Seventy-eight percent of the subjects reported four or more DSM-III criteria. This degree of prevalence was higher than that found in a retrospective study conducted by Hughes, Gust, and Pechacek (1987), possibly reflecting differences in the measuring instruments or the populations themselves.

The physiological changes which have been found to occur after cigarette deprivation include decreased heart rate (Knapp, Bliss, Wells 1963; Murphee and Schultz 1968; Parsons, Avery et al. 1975; Benowitz, Kuyt, Jacob 1984; Hatsukami et al. 1984; Weybrew and Stark 1967; Gilbert and Pope 1982; Hughes and Hatsukami 1986; West and Russell 1987; Elgerot 1978; West, Jarvis et al. 1984; Henningfield 1987a) and decreased cortical arousal as evidenced by decreases in peak alpha frequency and increases in low frequency activity which appear to be associated with drowsiness and decreased vigilance (Knott and Venables 1977, 1979; Ulett and Itil 1969; Herning, Jones, Bachman 1983; Herning 1987). Knott and Venables (1978) have also found that the visual evoked response in tobacco-deprived smokers showed faster latencies and larger amplitudes for low-stimulus intensities than among nondeprived smokers and nonsmokers. They concluded that deprived smokers experience CNS hypersensitivity and, as a result, may experience visual stimulus input more easily and strongly. Hall and colleagues (1973) reported reduced auditory evoked response (AER) amplitudes during tobacco withdrawal. Blood pressure (Benowitz, Kuyt, Jacob 1984; Murphee and Schultz 1968; Knapp, Bliss, Wells 1963) and respiratory rate (Parsons et al. 1976) have also been found to decrease during abstinence. Studies have also reported an increase in skin temperature among tobacco-deprived smokers (Gilbert and Pope 1982; Myrsten, Elgerot, Edgren 1977) or no change (West and Russell 1987), and either a decrease (Fagerstrom 1978) or no significant change (Hatsukami et al. 1984) in body temperature among those who are classified as more dependent. Although some studies have reported insomnia and sleep disturbance following tobacco deprivation, tobacco-deprived smokers' total sleep time may be longer during withdrawal (Soldatos et al. 1980). Reported changes in sleep pattern include decreased latency to rapid-eye-movement (REM) sleep (Kales et al. 1970), decreased latency to light (delta electroencephalogram (EEG) wave) sleep onset (Parsons, Luttrell et al. 1975; Parsons and Hamme 1976), and increased total REM sleep time (Soldatos et al. 1980; Kales et al. 1970; Parsons, Avery et al. 1975).

Another physical change found among tobacco-deprived smokers is an increase in weight (Grunberg 1986; see also Chapter VI). Weight increase has also been found among those who quit smoking in a number of longitudinal survey studies (Bosse, Garvey, Costa 1980). This increase in weight has been attributed to increased caloric intake (Hatsukami et al. 1984; Grunberg 1982; Myrsten, Elgerot,

Edgren 1977; Burse et al. 1975; Gilbert and Pope 1982; Wack and Rodin 1982), decreased basal metabolism (Glauser et al. 1970; Wack and Rodin 1982), decreased energy expenditure (Hofstetter et al. 1986), or increased activity of lipoprotein lipase (Carney and Goldberg 1984) (see also Chapter VI).

Several studies have examined the effects of cigarette deprivation and administration on reaction time and psychomotor performance. These are reviewed in detail in Chapter VI and are only briefly summarized here. Two early studies each found considerable across-subject variability, with some subjects showing distinct deprivation-induced performance impairments which were reversed by tobacco administration, and other subjects showing impairments under the tobacco administration conditions (Bates 1922; Carver 1922). Since the studies by Bates and Carver, investigators have developed increasingly sophisticated methods of performance assessment which have led to a clearer understanding of the performance-related effects of nicotine administration and deprivation (see details in Chapter VI). For example, Heimstra, Bancroft, and DeKock (1967) used a simulated driving task and found that deprived smokers made significantly more errors on tracking and vigilance tasks than did nondeprived smokers or nonsmokers, who did not significantly differ from each other. Other research has demonstrated that smokers who were allowed to smoke cigarettes during the experimental session exhibited either no decrease or an improvement in speed and accuracy in reaction time, cognitive tests, and/or vigilance performance tasks, whereas deprived smokers most frequently show some impairment in performance tasks (Myrsten et al. 1972; Frankenhaeuser et al. 1971; Elgerot 1978; Kleinman, Vaughn, Christ 1973; Andersson 1975; Wesnes and Warburton 1984; Edwards et al. 1985; Snyder and Henningfield, in press; Henningfield 1986a, 1987a).

A recent study using a computerized battery of such tasks found clear impairments beginning within 8 hr of the last cigarette and improving only somewhat across 10 consecutive days of tobacco deprivation; resumption of smoking was accompanied by complete restoration of performance (Henningfield 1987a). The specificity of these performance effects of nicotine was confirmed by the findings that administration of nicotine in the polacrilex gum form produced a dose-related reversal of all performance impairments (Snyder and Henningfield, in press; Henningfield 1987a); this effect was not related to satisfaction or reduction of "craving" because the gum produced dose-related decreases in "liking" scores and produced no reliable decrease in "desire to smoke" (Henningfield 1987a).

Other changes occurring in tobacco-deprived cigarette smokers include increases in aggression scores on the Buss aggression machine (Schechter and Rand 1974) and increases in frequency of spontaneous jaw contractions (a putative analog of aggression)

(Hutchinson and Emley 1973). Analogously, monkeys withdrawn from chronic oral nicotine exposure (nicotine was placed in their drinking water) exhibited an increase in frequency of post-shock biting (Hutchinson and Emley 1973).

The magnitude of tobacco withdrawal is related to the environmental context (see Chapter V for a comparison to other dependence-producing drugs). For example, Hatsukami, Hughes, and Pickens (1985) reported that smokers who were deprived of cigarettes on an outpatient basis experienced more withdrawal symptoms than those who underwent withdrawal on a clinical research ward. These findings are consistent with those of Suedfeld and Ikard (1974), who found that deprivation of normal sensory stimulation reduced tobacco abstinence-associated discomfort. It has also been observed that the diurnal variation of withdrawal discomfort found among abstinent smokers (greater discomfort in the evenings) appears to be associated with diurnal variation in the social environment (e.g., meals, departure from work, or social contact) (Shiffman 1979).

Time Course of Responses to Nicotine Abstinence

Drug withdrawal syndromes generally include some signs and symptoms which are opposite those produced by administration of the drug and which then return to approximately the same values observed when drug intake was stable (rebound phenomena). The time course of different responses varies (Chapter V). The most recent studies show that several signs and symptoms of withdrawal appear to rebound within the first few days following cigarette abstinence; these signs and symptoms include increases in the urge to use tobacco, anxiety, problems with concentration, increased caloric intake, sleep disturbance, performance impairment, and general subjective distress (Hatsukami et al. 1984; Hughes and Hatsukami 1986; Schneider and Jarvik 1984; Cummings et al. 1985; Henningfield 1987a). Heart rate has been found to decrease to levels found among nonsmokers (Weybrew and Stark 1967) and may include some rebound, returning to stable levels between those maintained during normal cigarette smoking and those recorded during the first week of abstinence (Henningfield 1987a). The P300 response, a cognitive evoked potential component which is related to the ability to evaluate auditory stimuli (i.e., differentiate one sound from another by counting only certain sounds), showed a rebound (decrease in amplitude), with values returning to preabstinence (cigarette smoking) levels after about 3 to 5 days (Herning 1987). West, Russel, Jarvis, Pizzey, and Kadam (1984) reported that urinary epinephrine concentrations rebounded with a significant decrease during the first 3 days of abstinence followed by a significant increase. Finally, in the squirrel monkey study of nicotine abstinence-associated biting, Hutchinson and Emley (1973) found a

distinct rebound pattern in some subjects with biting levels sharply increasing and then returning to the levels observed during chronic oral nicotine administration.

Other signs and symptoms associated with tobacco abstinence do not return to levels observed during cigarette smoking. For example, weight gain has persisted for long periods of time (Blitzer, Rimm, Giefer 1977) and has also been reported to approach levels of nonsmokers (Khosla and Lowe 1971; Lincoln 1969; Chapter VI). In addition, some levels of performance impairment and associated reduction of a cognitive evoked cortical potential (N100), which is related to attention, persist at least 10 days and may last longer (Henningfield 1987a; Herning 1987).

As the preceding studies suggest, the duration of withdrawal reactions varies among studies and as a function of the measure (Shiffman 1979; West 1984). Urges to smoke cigarettes among ex-smokers have been reported to occur intermittently, although sometimes with great intensity, for up to 9 years after cessation of cigarette smoking. These reported symptoms may represent conditioned responses to environmental stimuli associated with either cigarette smoking or deprivation, may represent a protracted physiological phase of withdrawal, or both (e.g., Wikler 1965; Jasinski 1981; Chapter V).

Alleviation of Withdrawal Symptoms by Cigarette Smoking

Several studies have demonstrated that the signs and symptoms resulting from cigarette deprivation are alleviated by the resumption of cigarette smoking. These signs and symptoms include heart rate (Murphee and Schultz 1968; Weybrew and Stark 1967; Henningfield 1987a), blood pressure (Murphee and Schultz 1968), skin temperature (Myrsten, Elgerot, Edgren 1977), epinephrine and norepinephrine levels (Myrsten, Elgerot, Edgren 1977), EEG changes (Ulett and Itil 1969; Herning 1987), weight (Noppa and Bengtsson 1986), desire for food (Burse et al. 1975), hand tremor (Myrsten, Elgerot, Edgren 1977), desire to smoke (Gritz and Jarvik 1973), and fatigue, irritation, sleeplessness, problems with alertness and concentration (Weybrew and Stark 1967), and performance (Henningfield 1987a).

Hughes, Hatsukami, Pickens, and Svikis (1984) examined the consistency of tobacco withdrawal signs and symptoms using an experimental design in which periods of cigarette smoking and abstinence were alternated in the same subjects. This study demonstrated both the consistency of the withdrawal symptomology within subjects as well as the efficacy of resumed smoking in reversing it. The most consistent withdrawal effects across subjects were supine heart rate changes, insomnia, caloric intake, irritability, restlessness, drowsiness, general mood disturbance (measured by the

Profile of Mood States), and withdrawal discomfort. Furthermore, the intensities of the withdrawal discomfort of subjects during the two deprivation periods were similar. Similarly, a study at the Addiction Research Center (Baltimore, Maryland) showed that resumption of cigarette smoking after 10 days of tobacco abstinence was accompanied by a return to preabstinence levels of all measures including EEG, evoked cortical electrical potentials, heart rate, behavioral performance, and measures of mood (Henningfield 1987a; Herning 1987).

Relationship Between Preabstinence Nicotine Intake and Magnitude of Withdrawal Syndrome

The observation that the magnitude of tobacco withdrawal reactions is directly related to preabstinence levels of nicotine intake provides specific evidence that nicotine is the pharmacologic cause of the physical dependence. The clinical significance of these relationships is that both the magnitude of the tobacco withdrawal syndrome and difficulty in quitting smoking are directly related to the daily levels of nicotine that were being ingested. The relationship has not always been observed, however, when only crude indices of nicotine dosing were used. For example, correlations between number of cigarettes smoked per day (a poor marker of nicotine intake) (Benowitz 1983; Abrams et al. 1987; Chapter II) and withdrawal reaction severity are mixed across studies. Some investigators have observed a positive correlation between the number of cigarettes smoked per day and withdrawal severity (Wynder, Kaufman, Lesser 1967; Shiffman 1979; Burns 1969; Hall, Ginsburg, Jones 1986). Others have reported no differences in severity of craving or other measures of withdrawal between light and heavy smokers or as a function of number of cigarettes smoked (Gritz and Jarvik 1973; Shiffman and Jarvik 1976; Myrsten, Elgerot, Edgren 1977; Mausner 1970). Cummings and coworkers (1985) reported that although heavy smokers reported more withdrawal symptoms than light smokers, differences between heavy and light smokers were statistically significant only with respect to irritability.

The most reliable measure of day-to-day nicotine exposure appears to be cotinine in biological specimens or nicotine itself (Benowitz 1983; Chapter II). Recent studies using such measures have found significant relationships between either nicotine or cotinine levels and severity of withdrawal reactions. Pomerleau, Fertig, and Shanhan (1983) divided subjects by their baseline plasma cotinine levels (high or low quartiles). They found that subjects in the low-cotinine quartile exhibited less withdrawal change on the Shiffman Craving and Perception of Physical Signs subscales compared with subjects in the high-cotinine quartile. They also found a significant correlation between preabstinence baseline plasma cotinine levels and absti-

nence-associated craving for cigarettes. Hatsukami, Hughes, and Pickens (1985) established a similar significant correlation between craving for tobacco and plasma nicotine level, as well as nicotine boost. Zeidenberg and associates (1977) found that preabstinence serum cotinine was correlated significantly with the degree of difficulty in smoking cessation among males but not females. Finally, West and Russell (1985b) determined that whereas preabstinence plasma nicotine levels significantly predicted craving, hunger, restlessness, inability to concentrate, and overall withdrawal severity, preabstinence rates of daily cigarette consumption did not significantly predict any withdrawal effects.

Smokeless Tobacco Withdrawal Syndrome

A study of withdrawal reactions accompanying abstinence from smokeless tobacco products helped to determine that the syndrome did not require inhalation of smoke and its constituents, which are not present in smokeless tobacco (e.g., tar and CO.). This study showed that signs and symptoms of smokeless tobacco deprivation are similar to those occurring in smokers after cigarette deprivation (Hatsukami, Gust, Keenan 1987). In persons who had been using a high nicotine containing brand of chewing tobacco, Hatsukami, Gust, and Keenan (1987) measured a number of potential withdrawal signs and symptoms over a 6-day period. Baseline data were collected during 3 days of regular smokeless tobaco use. The significant changes which occurred during smokeless tobacco deprivation relative to the baseline included decreased heart rate and an increase in craving for tobacco, confusion, eating, number of awakenings, and total scores on a withdrawal symptom checklist for both self-rated and observer-rated measures. These changes were similar to those found among cigarette smokers who underwent a similar experimental protocol, although the smokeless tobacco withdrawal syndrome appeared to be less severe than the cigarette withdrawal syndrome (Hatsukami, Gust, Keenan 1987).

Nicotine Polacrilex Gum: Treatment and Physical Dependence

Nicotine polacrilex gum has been used to evaluate the specific role of nicotine in tobacco dependence. Experimental research and clinical observations of the ability of nicotine in the polacrilex gum form to alleviate tobacco withdrawal symptomatology provide conclusive evidence that the tobacco withdrawal syndrome is pharmacologically determined by physical dependence on nicotine. To the extent that the tobacco withdrawal phenomena described above are specific to nicotine and not characteristic of the delivery system (e.g., cigarette smoke), alternate forms of nicotine delivery should be able to sustain the physical dependence. This would be evidenced by (1)

blockade of signs and symptoms of withdrawal by nicotine delivery and (2) subsequent emergence of a tobacco withdrawal-like syndrome upon abrupt abstinence from nontobacco-delivered nicotine.

Treatment of Withdrawal Symptoms

Clinical trials and experimental studies in which nicotine polacrilex gum is evaluated as a means to alleviate signs and symptoms of tobacco withdrawal are of relevance to the treatment of tobacco dependence (Chapter VII). In addition, however, such data are analogous to data from the classic "substitution" study methodology used to help determine the pharmacologic specificity of withdrawal reactions following use of opioids, sedatives, and alcohol (described in Chapter V). In brief, however, the objective is to determine if the withdrawal reaction from the primary substance upon which the person is dependent can be alleviated by administration of a test drug.

Several studies have examined the effects of nicotine polacrilex gum on tobacco withdrawal (Jarvis et al. 1982; Schneider, Jarvik, Forsythe 1984; West, Jarvis et al. 1984; Hughes, Hatsukami, Pickens, Krahn et al. 1984; Snyder and Henningfield, in press; Henningfield 1987a). These studies have examined two groups of cigarette smokers who were assigned in a double-blind fashion (with the exception of West, Jarvis, and colleagues (1984), who used a single-blind design) to receive 2-mg polacrilex gum or placebo. The duration of cigarette deprivation during which the polacrilex gum (or placebo) was used varied from 24 hr to 6 weeks. In general, the results consistently showed an attenuation of withdrawal signs and symptoms. For example, nicotine polacrilex gum significantly reduced irritability (Jarvis et al. 1982; Hughes, Hatsukami, Pickens, Krahn et al. 1984; West, Jarvis et al. 1984), total withdrawal discomfort (Schneider, Jarvik, Forsythe 1984; Hughes, Hatsukami, Pickens, Krahn et al. 1984), somatic complaints (Hughes, Hatsukami, Pickens, Krahn et al. 1984), sleepiness (Jarvis et al. 1982), unsociability (West, Jarvis et al. 1984), cognitive performance deficits (Snyder and Henningfield, in press; Henningfield 1987a), heart rate decreases (Schneider, Jarvik, Forsythe 1984; West, Jarvis et al. 1984; Henningfield 1987a), and EEG effects including changes in cortical evoked potentials (Herning 1987; Pickworth, Herning, Henningfield, 1988).

Other measures were less reliably alleviated; these included depression (Jarvis et al. 1982; West, Jarvis et al. 1984), anxiety/tension (Jarvis et al. 1982; Hughes, Hatsukami, Pickens, Krahn et al. 1984), difficulty concentrating (Hughes, Hatsukami, Pickens, Krahn et al. 1984; West, Jarvis et al. 1984), and restlessness (Hughes, Hatsukami, Pickens, Krahn et al. 1984; West, Jarvis et al. 1984). The urge to smoke cigarettes has not been found to be reliably alleviated

by nicotine polacrilex gum administration (West and Schneider 1987; West 1984; Henningfield 1987a; Hughes, Hatsukami, Pickens, Svikis 1984) except possibly at high dose levels (Nemeth-Coslett, Henningfield, O'Keefe, Griffiths 1987). Interpretation of such data is complicated by the diverse strategies used to measure the urge to smoke or "craving" as discussed further in this Section.

Of these studies, two showed nonsignificant effects of nicotine polacrilex gum on hunger (Hughes, Hatsukami, Pickens, Krahn et al. 1984; West, Jarvis et al. 1984) and one showed significant effects in decreasing hunger (Jarvis et al. 1982). More recent research shows that the anorectic effect of nicotine polacrilex gum during tobacco abstinence is directly related to the dose level (i.e., number of doses taken per day) (Stitzer and Gross 1988; Fagerstrom 1987; Chapter VI). The dose-response relationship may explain the diversity in results when studies are compared; in some of these studies, dosing was either poorly controlled or not reported, or there was no verification of subject compliance with a dose regimen.

As would be expected, depending on the dose administered, the efficacy of nicotine polacrilex gum for most measures of withdrawal symptomology ranges from complete reversal of withdrawal to no effect. In a study in which periods of tobacco abstinence (3 days) were alternated with periods of cigarette smoking (4 days), subjects were given either 0-, 2-, or 4-mg-nicotine-containing pieces of the polacrilex gum (Henningfield 1987a). The subjects were given the polacrilex gum at 1-hr intervals (for 12 hr), and they chewed under the direction of research staff. Blood nicotine and cotinine levels confirmed that this procedure resulted in dose-related nicotine administration; plasma cotinine and nicotine levels at 4 mg were similar to those obtained during cigarette smoking (ad libitum smoking); plasma levels at 2 mg were between those at 4 and 0 mg. Measures included cognitive performance, heart rate, EEG, and self-reported symptomology. At 4 mg, all signs and symptoms of withdrawal were reduced or completely reversed except the desire to smoke. The 2-mg dose produced partial reversal of withdrawal effects.

Maintenance of Physical Dependence

Two studies have examined withdrawal effects after deprivation of nicotine polacrilex gum. West and Russell (1985a) conducted a study in which they examined withdrawal symptoms in six people who used nicotine polacrilex gum for at least 1 year. Baseline measures of possible withdrawal effects were collected during days that the subjects were chewing 2-mg pieces of nicotine polacrilex gum. These days were the first and third days of a 4-day experiment. On the second and fourth days, subjects were given either 0.5 mg unbuffered polacrilex gum (nicotine absorption is negligible in the unbuffered

formulation) to chew or no polacrilex gum. West and Russell (1985a) found significant changes for measures of withdrawal symptomology including irritability, ability to concentrate, and heart rate and for composite subjective withdrawal scores. Withdrawal reaction magnitude was slightly, but not significantly, less in the unbuffered gum than in the no gum condition.

Hughes, Hatsukami, and Skoog (1986) extended the findings of West and Russell (1985a) with a longer period of observation (1 week) and a double-blind, placebo-controlled design. In the study by Hughes, Hatsukami, and Skoog (1986), eight former smokers who had been using nicotine polacrilex gum for at least 1 month participated. The main finding was that when the maintenance dose levels (2-mg polacrilex gum) were replaced with placebo, reliable symptoms of withdrawal were produced. The effects included "craving" for tobacco, irritability/hostility, anxiety, depression, restlessness, impatience, difficulty concentrating, hunger, and total withdrawal discomfort; reports from observers verified several of the effects (i.e., observer estimates of irritability, anxiety, restlessness, impatience, and total withdrawal discomfort). The scales used to measure withdrawal discomfort in the study by Hughes and colleagues were similar to those used in a previous study of cigarette withdrawal conducted by the same investigators (Hughes and Hatsukami 1986), thus enabling an across-study comparison between abstinence from cigarettes and abstinence from nicotine in the polacrilex gum form. Intensities and numbers of withdrawal symptoms, except heart rate and insomnia, were similar.

Taken together, the results of the above-described studies with nicotine polacrilex gum have helped to confirm that tobacco withdrawal is pharmacologically caused by physical dependence on nicotine. Furthermore, the results of such work are of clinical significance because they indicate that much of tobacco withdrawal symptomology can be treated with nicotine polacrilex gum. Two studies show that nicotine polacrilex gum can maintain physical dependence; this emphasizes the importance of *gradually* giving up use of the gum to minimize the abruptness and severity of withdrawal symptoms (see Chapter VII).

Tobacco Craving

The measurement of self-reported craving for tobacco and interpretation of resulting data are among the more complicated issues in tobacco research. Findings discussed in this Chapter that nicotine polacrilex gum administration can suppress cigarette smoking and alleviate physical signs of tobacco withdrawal while having little effect on the urge to smoke indicate that such urges are not solely determined by nicotine deprivation. Similar observations regarding urges to use other dependence-producing drugs are discussed in

Chapter V (see also Childress et al., in press). The elicitation and alleviation of the urge to use tobacco, as for other dependence-producing substances, can be effected by a variety of pharmacologic and other environmental stimuli as well as changes in the physiological and/or behavioral state of the person (Chapter V).

Conclusions regarding the measurement and treatment of urges to use drugs are complicated because the questions about urges have been worded differently among studies. For example, subjects are somtimes asked to report their "craving." Unfortunately, subjects vary widely in their interpretations of the word "craving" and in their answers to questions about it (Kozlowski and Wilkinson 1987; Ludwig and Stark 1974). In addition, results concerning "craving" are sometimes discussed when the word was not even used in study questionnaires, and sometimes craving was inferred from other observations (e.g., self-reported discomfort or drug abstinence) (Kozlowski and Wilkinson 1987). These and other problematic issues have been discussed in several recent papers (Kozlowski and Wilkinson 1987; Shiffman 1987; West 1987; Hughes 1987; Marlatt 1987; Stockwell 1987; Henningfield 1987b; Henningfield and Brown 1987; West and Schneider 1987). One consensus that seems to emerge is that the term "craving" be replaced with "urge" or "desire" to smoke, and that subjects be asked to report the "strength" of such responses and not simply whether or not the response occurred (Kozlowski and Wilkinson 1987; Henningfield 1987b).

In consideration of the above reports and commentaries and the data reviewed in the present Chapter, the following conclusions may be drawn regarding the urge to smoke. Many means of measuring urges are reliably associated with early abstinence from tobacco; however, urges can also be elicited by a variety of other stimuli including cigarette smoking itself, tobacco-associated stimuli (e.g., sight, smell, advertisements), consumption of other psychoactive drugs, food deprivation, and mood changes. Furthermore, although urges are reliably associated with tobacco abstinence, the levels to which plasma nicotine must fall to produce it are unclear; for example, West, Russell, Jarvis, and Feyerbend (1984) found that smokers who switched to a low-nicotine cigarette reported only slight craving for their usual brand in spite of a drop in nicotine intake of around 60 percent. In addition, as discussed earlier, some sensory stimuli are effective at eliciting urges, whereas other sensory cues accompanying the inhalation of cigarette smoke may be effective at diminishing such urges (Rose et al. 1985). Chapter V provides a discussion of these issues in the context of analogous observations which have been made with other dependence-producing drugs and Chapter VII discusses the implications for replacement therapy used in treating tobacco dependence.

Alternate Nicotine Delivery Systems

Certain effects of nicotine depend little upon the specific type of delivery system that is used (see also Chapters, II, III, and VI). For instance, it appears likely that all forms of nicotine delivery resulting in systemic absorption are capable of producing tolerance and maintaining physical dependence (see also Chapter II). Similarly, it follows that a variety of nicotine delivery systems have potential utility in the treatment of cigarette smoking by the alleviation of withdrawal symptoms. However, the safety, including the potential to produce dependence, may vary considerably as a function of characteristics of the nicotine delivery system itself.

Kinds of Nicotine Delivery Systems

Because nicotine is well absorbed through the common routes of drug delivery and because the commonly used tobacco vehicle is not necessary to efficaciously deliver nicotine, nicotine can potentially be placed in a variety of vehicles and administered via a variety of delivery systems (Chapter II; Benowitz 1986; Jarvik and Henningfield, 1988). The nicotine delivery systems thus far discussed in this Chapter are tobacco smoke, nicotine polacrilex gum, i.v. nicotine, transdermal nicotine, and a nicotine vapor inhaler. Other potential therapeutic nicotine delivering systems under development include a nasal spray (Perkins et al. 1986) and nasal nicotine solutions given in droplet form (Russell, Jarvis, Feyerabend, Ferno 1983), both of which have been discussed by Russell (1988). Two other nicotine delivery systems are a chewable food product (Tobacco International 1987) and a "toothpaste" formulation which contains ground tobacco. Other nicotine delivering systems (in which the tobacco may be incidental and not necessary for nicotine delivery) are under development or consideration for over-the-counter retail marketing (R.J. Reynolds "Smokeless Cigarette" European Patent Application 1985, 1986; Cleghorn 1987; Mintz 1987).

As noted earlier, the nicotine vapor inhaler was removed from the retail market in February of 1987 by the FDA because it was a "nicotine delivery system intended to satisfy nicotine dependence" which had not been tested for safety and efficacy (Slade and Connolly 1987). At least through the end of 1987, the toothpaste-like formulation was available as an over-the-counter product but was under review by the FDA (FDA letter to Congressman Waxman); this formulation is distributed in Indian food stores. The chewable nicotine delivering product marketed by Pinkerton Inc. was test-marketed as a "tobacco product" for approximately 6 months during 1987. The FDA removed it from the market ruling that it was a "food product" ["chewing gum"] which was "unlike traditional smokeless tobacco products," and contained a "food additive [tobacco] deemed

unsafe" for human consumption (FDA letter to Congressman Waxman).

Safety of Alternate Nicotine Delivery Systems

Alternate nicotine delivery systems may be evaluated with respect to at least three categories of safety issues. These are: (1) short- and long-term toxic effects resulting from use of the system; (2) the ease and convenience of using the system; and (3) the dependence potential of the system. All of these factors can affect initiation and maintenance of nicotine dependence.

The first safety issue is related to the direct behavioral and physiological toxicity of the preparation itself. In the moderate nicotine doses that each of these and previously marketed systems deliver, acute nicotine toxicity would not appear to be a significant health risk. However, adverse health effects from chronic exposure to nicotine may occur (see Appendix B), and other potentially absorbed constituents of the system (e.g., tar) are markedly toxic.

Existing nicotine delivery systems vary widely in their potential overall toxicity. One product was found to meet FDA criteria for safety as well as efficacy (i.e., nicotine polacrilex gum). On the other hand, cigarette smoking is a cause of lung cancer and other cancers, emphysema, heart disease, and a variety of other diseases; smokeless tobacco use causes oral cancer and other forms of gum and mouth disease (US DHEW 1979; US DHHS 1982, 1983, 1984; US DHHS 1986b).

Traditional tobacco products have historically been considered by the FDA to be outside its regulatory purview (Action on Smoking and Health vs. Harris 1980). New products, which contain either small amounts of tobacco (e.g., tobacco-containing food products) or which appear to contain possibly nonessential amounts of tobacco (e.g., possibly the case with the R.J. Reynolds smokeless cigarette (European Patent Application 1985, 1986)) and which are not regarded as traditional tobacco products, may not be exempt from such review.

The second safety issue is the potential for the product to actually sustain tobacco use by alternating use of the substitute with use of the traditional tobacco product. This is analogous to the nonmedically approved use of methadone by opioid-dependent individuals when their drug of choice (e.g., heroin) is not available, and they are not involved in treatment for opioid dependence. The use of non-tobacco nicotine products to sustain tobacco use is, similarly, medically contraindicated and hence a form of nicotine abuse (Slade 1986; Richards 1987). While any alternative nicotine delivery system can theoretically be used for this purpose, two commercial products (the chewable nicotine-delivering "food" product and the nicotine vapor inhaler) were marketed specifically as temporary substitutes for

cigarettes when it was inconvenient to smoke (Bosy 1986; Tobacco International 1987). In contrast, the instructions for use of nicotine polacrilex gum clearly specify that this preparation should not be used along with cigarettes (Physicians' Desk Reference 1988). In addition to product design and formulation, factors such as labeling, packaging, marketing, retail distribution, and regulatory oversight might influence the degree to which any particular preparation is associated with an individual's continued use of the nicotine delivery system.

The third potential safety concern is related to the dependence potential of the system. As shown in Chapter V, the potential of a drug to addict users is associated with its effects on mood, feeling, and behavior; such effects are related to the bioavailability of the drug. Systems with a controlled rate of bioavailability or a lesser rate of absorption than is obtained from conventional tobacco products may have a lesser dependence potential than tobacco products. Other factors related to availability of the preparation and cost (both economic and behavioral) may also affect the likelihood that dependence will develop in users. For example, nicotine polacrilex gum is available by prescription only, and use of the gum is recommended as a temporary treatment aid. Active chewing is required to extract the nicotine, and swallowing the nicotine too quickly reduces the amount absorbed. These factors appear relevant to the observation that less than 10 percent of all subjects entering smoking treatment trials continue to use nicotine polacrilex gum after 1 year (Tonnesen et al. 1988; Jarvis et al. 1982). Among people who have used the polacrilex gum to quit smoking and who have maintained their tobacco abstinence for 1 year or more, a higher percentage of polacrilex gum use has been reported (13 to 38 percent); however, it is not clear to what degree such use may be necessary for some people to avoid relapse to tobacco use (see further discussion of these issues in Hughes 1988; Jasinski and Henningfield 1988; Hall et al. 1985; Tonnesen et al. 1988; Chapter VII). In contrast to nicotine polacrilex gum, smokeless tobacco products (particularly one in which finely ground snuff is placed in a small tea bag-like pouch) readily lend themselves to initiating as well as to maintaining nicotine dependence (US DHHS 1986b).

Table 6 compares nicotine polacrilex gum and cigarettes on a number of dimensions, most of which have been reviewed in either Chapters II, V, or VII. As shown in the Table, there is considerable disparity between these two delivery systems: the polacrilex gum provides a generally safe and medically beneficial form of nicotine delivery; cigarettes are a known cause of substantial amounts of death and disease each year (Chapter I; US DHEW 1979; US DHHS 1981, 1982, 1983, 1984, 1985). Such a disparity in potential safety

TABLE 6.--Comparison of tobacco cigarettes and nicotine polacrilex gum on indices related to safety, including potential to cause dependence

Characteristic	Tobacco cigarettes	Nicotine polacrilex gum
Proven carcinogen	Yes	No
Availability	Widely available consumer product, including vending machine availability	Prescription only
Taste	Carefully formulated with flavor enhancers	Not formulated to provide desirable taste
Ease of nicotine extraction	Readily available with little effort	Much effort required
Nicotine kinetics	Rapid uptake	Slow uptake
Initiation of dependence	Highly effective	No reported problem
Psychoactivity	Dose-related "liking"	Dose-related "disliking"
Reinforcing effects	Powerful	Weak
Withdrawal symptoms associated with abstinence	Yes	Yes
Social factors	Often used in social settings as part of social interactions	Used for specific therapeutic benefit
Primary regulatory oversight	U.S. Bureau of Alcohol, Tobacco, and Firearms	US. Food and Drug Administration

across systems would suggest that any new system be submitted to evaluations of safety including dependence-potential testing.

Conclusions

1. Cigarettes and other forms of tobacco are addicting. Patterns of tobacco use are regular and compulsive, and a withdrawal syndrome usually accompanies tobacco abstinence.
2. Nicotine is the drug in tobacco that causes addiction. Specifically, nicotine is psychoactive ("mood altering") and can provide pleasurable effects. Nicotine can serve as a reinforcer to motivate tobacco-seeking and tobacco-using behavior. Tolerance develops to actions of nicotine such that repeated use results in diminished effects and can be accompanied by increased intake. Nicotine also causes physical dependence characterized by a withdrawal syndrome that usually accompanies nicotine abstinence.

3. The physical characteristics of nicotine delivery systems can affect their toxicity and addictiveness. Therefore, new nicotine delivery systems should be evaluated for their toxic and addictive effects.

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