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 irritability (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 (Fagerström 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; Fagerström 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	U.S. 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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