TABLE 1.—Continued

Study	Species	Reinforcement Schedule	Main Finding	Comment
Spealman and Goldberg (1982)	Squirrel Monkey	Second order FI 1, 2, or 5 min. (FR 10 stimulus) and FI 5 min. schedules were tested. Several doses of nicotine and cocaine and saline were tested.	Nicotine and cocaine maintained similar patterns of responding on the schedules. Nicotine, but not cocaine S-A, decreased to saline-like rates when animals were pretreated with mecamylamine.	Nicotine's reinforcing efficacy was comparable to that of cocaine.
Risner and Goldberg (1983)	Beagle Dog	FR 15 followed by 4 min. timeout. Several doses of nicotine, cocaine, and saline were tested. Progressive ratio schedule was used.	Nicotine and cocaine maintained qualitatively similar patterns of responding and were reinforcers relative to saline. Mecamylamine pretreatment reduced nicotine but not cocaine S-A.	Cocaine maintained substantially greater response rates than nicotine.
Henningfield, Miyasato, and Jasinski (1983)	Human	FR 10 followed by 1 min. timeout. Several doses of nicotine and saline were tested.	Number of nicotine injections generally exceeded number of saline injections and were inversely related to nicotine dose. Post-session cigarette smoking was suppressed by nicotine.	Nicotine produced subjective effects similar to those produced by intravenous cocaine and had both reinforcing and punishing effects.
Goldberg and Henningfield (1983)	Human and Squirrel Monkey	FR 10 followed by 1 min. timeout. Several doses of nicotine and saline were tested.	Patterns of responding were qualitatively similar in both species. Number of nicotine injections exceeded number of saline injections in 3 of 4 human and 3 of 4 monkey subjects.	In both the human and monkey subjects, there was evidence that nicotine functioned with both reinforcing and punishing properties.

support to the initiation of tobacco use may be even greater than with illicit drugs, because family members, other social models, and advertising often tolerate, approve, or promote tobacco use while disapproving the use of some nonprescription drugs *(24)*. Also, as is the case with addictive drugs, an accelerated pattern of development of tobacco use has been observed, which is followed by relatively stable drug intake. Initially, the level of consumption increases gradually from the first day of use until some point, perhaps several years later, when it becomes relatively stable over time. Although many factors can operate to produce such a biphasic pattern of intake, it is generally assumed that tolerance and learning factors account for the gradual acceleration and that a level of optimum drug effect combined with toxicity and adverse effects at higher doses takes over to produce the stabilization phenomenon. A preliminary survey, conducted at Johns Hopkins University, indicates that nicotine, whether administered as cigarette smoke or smokeless tobacco, does not differ from other drugs in this regard. That is, tobacco users tend to begin smoking a few cigarettes a day or consume a portion of a container of smokeless tobacco each day and gradually increase consumption levels over a period of months or even years before they stabilize the amount they finally use (personal communication, J.E. Henningfield).

Patterns of Tobacco Self-Administration Are Orderly

Daily patterns of cigarette smoking are orderly. Addicted smokers tend to smoke their first cigarette within 30 minutes of waking from a night of sleep and find it difficult to abstain from tobacco use for more than a few hours *(25)*. If smoking behavior is relatively unconstrained, regular patterns develop that closely resemble those of psychomotor stimulant self-administration in animals *(20)*. Similar orderly patterns of tobacco self-administration are evident with cigarette smoking by humans. Several studies have demonstrated that across successive puffs on a cigarette, puff duration decreases and interpuff intervals tend to increase *(26,27,28,29)*, although these changes are multifactorially determined *(30)*. Anecdotal reports by smokeless tobacco users suggest that while consumption patterns are necessarily different (e.g., some keep a plug in their mouth almost continually during their waking hours) they are no less regular and orderly.

Tobacco Self-Administration Varies as a Function of Nicotine Dose

The effective dose of a substance may be varied by changing the quantity of drug per unit (the unit dose), by pretreating the individual (animal or human) with either an agonist or antagonist, or by altering the rate of elimination of the substance. Studies that involve these three manipulations have been done extensively with other drugs and more recently with nicotine. The results across study, drug, and species are remarkably similar. For general reviews of human and animal studies

see Griffiths, Bigelow, and Henningfield *(20)* and Henningfield, Lukas, and Bigelow *(31)*. See Gritz *(32)* and Henningfield *(33)* for recent reviews of the nicotine-specific literature. Over a wide range of dose levels, frequency of self-administration is inversely related to dose but drug intake is directly related to dose, reflecting partial compensatory changes *(26,32)*. Pretreatment with other agonists (or forms of nicotine) reduces drug taking, e.g., decreases cigarette smoking, *(34)* and reduces preferred nicotine concentration of tobacco smoke *(35)*. Pretreatment with antagonists initially increases drug self-administration. For example, the centrally and peripherally acting ganglionic blocker, mecamylamine, but not the peripherally acting blocker, pentolinium, increases subsequent smoking rates and increases preferred nicotine concentrations of tobacco smoke *(36,37)*. In addition, altering the elimination rate of nicotine alters the amount of nicotine that is self-administered in the form of tobacco smoke *(38)*.

There has been debate over the degree to which smokers regulate their nicotine intake, i.e., the "titration" hypothesis. It is now generally agreed that smokers do not precisely titrate their nicotine intake any more than animals titrate their intake of reinforcing drugs (except under extremely limited conditions) or humans titrate their intake of other reinforcing drugs *(20)*. However, when dose manipulations are observed and objective, sensitive dependent variables are measured in both animals and humans *(26,32,33)*, most of the studies demonstrate an increase in smoking as cigarette nicotine content falls below accustomed levels and a decrease in smoking when cigarette nicotine content is unusually high *(32)*. Kozlowski and his coworkers describe these findings in terms of a "boundry" model of dose compensation *(39)*.

Tolerance of Nicotine Develops With Repeated Use (Neuroadaptation)

The administration of most drugs of abuse results in neuroadaptation as measured by tolerance to the repeated administration of the drug and a subsequent rebound (withdrawal) when drug administration is terminated *(3)*. Tolerance to drug effects is determined either by the diminished response to repeated doses of a drug or the requirement of increasing doses to achieve the same drug effect. Tolerance to the behavioral and physiologic effects of nicotine has been studied for decades *(33)*. As is the case with other drugs of abuse, a variety of mechanisms accounts for tolerance to many of nicotine's effects, including metabolic *(40)*, behavioral *(41-43)*, and physiologic tolerance *(44-46)*. More recently, studies have shown that the effects of nicotine that are suspected to be critical to the addiction process also show tolerance with repeated dosing *(47,48)*.

Physiologic dependence on drugs is determined by showing that termination of drug administration produces a syndrome of effects that is generally opposite to those produced by drug administration. This syndrome is reversible, at least in its early stages, by administration of the

drug. Prolonged drug abstinence (detoxification) results in ultimate return to baseline (normal) values of behavioral and physiologic functions. It is now clear that repeated tobacco administration produces physiologic dependence that is specifically due to nicotine administration. Recent data that confirm this fact are reviewed in the section on Dependence Potential of Nicotine.

Nicotine Produces Therapeutic Effects

Most drugs of abuse have specific therapeutic applications; nicotine is no exception *(48-50)*. The degree to which the therapeutic effects of nicotine depend upon the individual's history of nicotine use, as opposed to the possibility that nicotine is efficacious for preexisting conditions, remains to be investigated. Similar issues are true for other drugs of abuse as well. Pomerleau and his coworkers *(51)* have studied a variety of mechanisms by which the possibly weak, initial reinforcing effects of nicotine can be greatly strengthened by subtle effects on mood, cognition, and normal physiologic and behavioral functioning. For instance, as will be described below, nicotine may produce a small, but important, enhancement of work performance. These effects appear to be mediated by the effects of nicotine on hormonal release and regulation. The following is a brief summary of some of the effects of nicotine, considered therapeutic by tobacco users, that have been investigated.

Several studies have shown that nicotine enhances performance on a variety of cognitive tasks that involve speed, reaction time, vigilance, and concentration *(52-55)*. These effects are strongest in cigarette smokers who are deprived of cigarettes. However, such performance enhancement was also evident after the administration of nicotine to nonsmokers and was produced by increasing the nicotine dose in persons who were already smoking. Nicotine may also be a useful mood regulator by virtue of its release of norepinephrine from the adrenal medulla *(56)*. Norepinephrine release is also stimulated by excitement, exercise, sex, antidepressant drugs, and other drugs of abuse, suggesting that cigarette smoking may function pharmacologically to alleviate boredom and stress. Finally, as an anoretic *(57-60)*, nicotine appears to function in three ways: by decreasing the efficiency with which food is metabolized *(61,62)*; by reducing the appetite for foods that contain simple carbohydrates (sweets) *(63)*; and by reducing the eating that may occur in times of stress *(64)*. Nicotine may also function as an anxiolytic by reducing responsiveness to stressful stimuli and enhancing mood *(56)*. In addition, nicotine reduces aggressive responses in experimental situations *(65)*.

A well-documented therapeutic role for nicotine as a drug is evident in the treatment of tobacco abstinence for many individuals following dependent patterns of tobacco use, e.g., as assessed by the Fagerstrom Tolerance Questionnaire *(25)*. This test provides both scientific and practical evidence of the role of nicotine in tobacco dependence. It is well

established that abstinence from tobacco in heavy cigarette smokers produces signs and symptoms of rebound that can be reversed by resumed tobacco use and at least partially reversed by other forms of nicotine administration *(66)*. For example, nicotine gum treatment for cigarette smoking is efficacious, although a variety of factors limit success rates *(34)*.* This drug substitution strategy is analogous to those obtained when intravenous opioid users are treated with other opioids given via other routes. For example, methadone administration may reverse signs and symptoms of opioid withdrawal, while leaving the patient feeling partially treated yet likely to relapse if not provided with an adjunctive behavioral treatment *(67)*.

Although the euphoriant properties of drugs can stand apart from collateral therapeutic actions (as is the case with morphine, amphetamine, and alcohol), attention to such drug effects may enhance the efficacy of treatment. Because nicotine, in the form of tobacco, is widely available, is relatively inexpensive, and is in a convenient form for precise dose regulation, it provides an ideal means of self-medication. These effects may contribute to the abuse liability of tobacco and are of demonstrable significance in the treatment of tobacco addiction *(51)*.

Similar Strategies Are Involved in the Treatment of Tobacco Addiction and Other Forms of Drug Addiction

If tobacco use is a form of drug addiction, then strategies of treatment of other forms of drug addiction should be applicable. Most available information and existing strategies for treatments of tobacco use are based on nonpharmacologic approaches. Such approaches have been no more useful in the treatment of tobacco dependence than in the treatment of dependence of opioids, stimulants, sedatives, or alcohol. On the contrary, experience in the treatment of drug addiction disorders makes clear the importance of addressing the pharmacologic components of the addiction *(67)*. This conclusion is strengthened by the observation that persons being treated for opioid addiction regard tobacco to be as necessary as methadone *(68)* and that persons successfully treated for other kinds of drug addiction are unable to give up tobacco *(69)*. This provides the support for the fundamental premise that tobacco addiction generally constitutes an independent health-impairing disorder. Specific treatment implications relating to cigarette smoking as a form of drug abuse are considered below.

To the extent that tobacco use is similar to other forms of drug abuse, treatment strategies that are used for drug abusers may be applied to the treatment of cigarette smoking. Although it is not the purpose of this chapter to describe in detail the treatment for cigarette smoking, a

* These therapeutic effects are produced by nicotine chewing gum, an orally administered form of nicotine that is approved by the Food and Drug Administration (FDA). The gum is obtainable in the United States by prescription only and is commonly used by physicians to help individuals quit smoking.

few commonalities, as well as differences, are worth mentioning. Four basic pharmacologic treatments for drug abuse provide the advantage of licit administration of an agent controlled by a certified clinician. These involve substitution therapy (e.g., methadone for opiate dependence) in which a more manageable form of the drug is provided according to a prearranged maintenance protocol; blockade therapy (e.g., naltrexone for opiate dependence) in which the effects of the abused drug are blocked by pretreatment with an antagonist; and nonspecific supportive therapy in which the patient is treated symptomatically, exemplified by the temporary use of benzodiazepines during alcohol detoxification *(67)*. All three approaches have been used in the treatment of cigarette smoking with varying degrees of success *(48)*. A fourth strategy of pretreating the patient with a drug that results in adverse side effects when the subsequent abused drug is taken (e.g., treatment of alcoholism with disulfiram) has not been systematically explored with tobacco.

The most recent, widely used treatment for cigarette smoking, and the first of those recognized as efficacious by the FDA, is modeled directly after the treatment of heroin addiction by methadone substitution. This treatment is nicotine gum substitution *(70)*. It is a practical application of the postulate that tobacco use is basically a form of drug addiction on nicotine. This recognition is especially relevant here, because smokeless tobacco is an oral form of nicotine. All of the relevant therapeutic data support the premise that compulsive tobacco use entails nicotine addiction, which in the form of tobacco exposes the user to health hazards, and that therapeutic strategies paralleling those for other forms of drug abuse are effective in treatment. Differences appear to be principally related to the social tolerance of tobacco addiction, relative to other forms of drug addiction, which contribute to greater difficulty in treating this form of drug abuse.

Summary of Commonalities Between Tobacco and Prototypic Addictive Drugs

The preceding review has shown that tobacco shares many points in common with prototypic addictive drugs. These similarities provide a strong conceptual basis for the categorization of tobacco as an addictive drug. The behavioral process is orderly, tobacco self-administration results in the delivery of a centrally active drug (nicotine), and the drug appears to be the major determinant in the control of the compulsive behavior of tobacco self-administration. These findings are consistent with those expected with animal and human subjects, as determined across a broad range of studies of drugs of abuse *(20)*.

In summary, tobacco, opium, and coca produce different effects but share a number of important similarities. Whereas large doses of opioids can produce a debilitating sedation, high doses of coca alkaloids (cocaine HCl) produce levels of behavioral excitation that are not nor-

mally produced by tobacco; but the intake of all of these substances leads to compulsive use. Compulsive use and the other commonalities described in the preceding subsections provide compelling evidence that tobacco use can be a form of drug dependence or addiction. The next major question is what element(s) of tobacco are critical to controlling the behavior of the user. The conceptual leap from habitual behavior to drug abuse and addiction can be made only on the basis of evidence that a specific psychoactive drug is critical to the behavior. The next section on the abuse liability and dependence potential of nicotine will address this question.

Experimental Studies of the Abuse Liability and Physical Dependence Potential of Nicotine

The comparison of tobacco to prototypic addictive drugs is the basis for concluding that compulsive tobacco use is a form of drug dependence behavior in which nicotine plays an important role. To test this hypothesis further, it should be possible to show that nicotine is an abusable substance even in the absence of the many stimuli associated with cigarette smoking. This can be done by evaluating nicotine in accordance with methods and criteria that have been used to assess any substance that is suspected of causing abuse and physical dependence. One-half century of research at the NIDA Addiction Research Center, and research in other laboratories, has produced valid and reliable experimental methods to evaluate a substance's potential to cause abuse and to produce physical dependence. The methods are empirically based on generally accepted examples of drug addiction, most notably opioid dependence (e.g., morphine) and, to a lesser degree, psychomotor stimulant dependence (e.g., cocaine) and sedative dependence (e.g., barbiturates and alcohol). These methods encompass standards for assessing the two dimensions of drug addiction—abuse liability and physical dependence potential. The evidence that is related to the abuse liability and physical dependence potential of nicotine is presented below.

Abuse Liability of Nicotine

Abuse liability refers to drug effects that contribute to compulsive self-administration, often in the face of excessive financial cost, physical and social dysfunction, and the exclusion of more socially acceptable behaviors *(5,6)*. In other words, it entails those effects of a substance that contribute to diminution of voluntary control over the use of the substance by the individual.

Objective methods to assess abuse liability are available and have been used to assess diverse agents *(5)*. These methods have been readily adapted to studies of nicotine abuse liability, with consideration given to the fact that nicotine has more rapid effects than many other drugs of abuse.

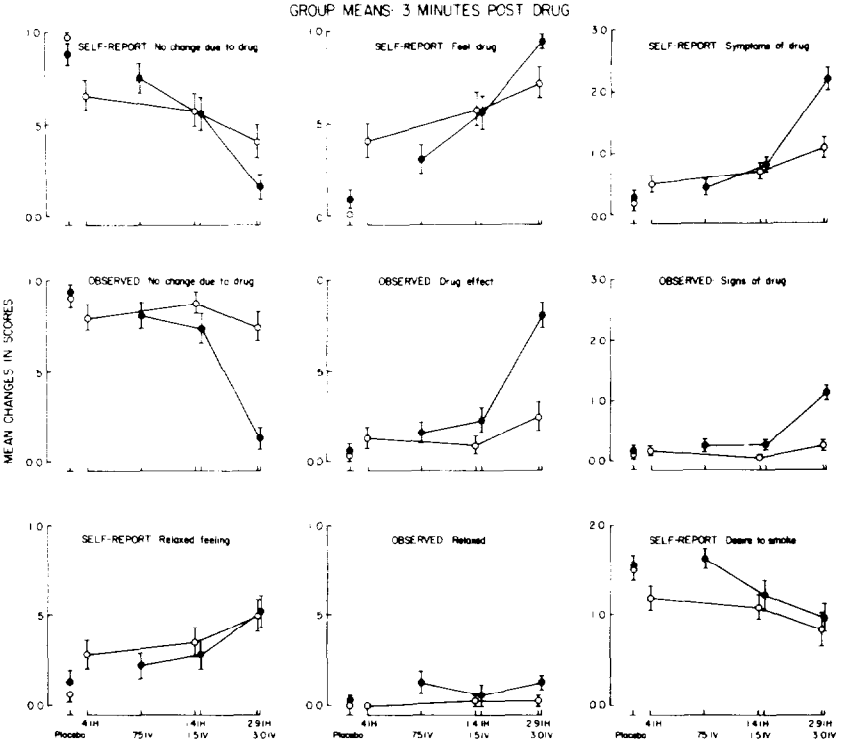
The hypothesis is that nicotine is psychoactive and serves as a euphoriant and reinforcer. Psychoactivity and euphoria are determined by assessing the pharmacodynamic subjective effects of single doses of the drug ("single-dose" or "abuse liability" studies) and are validated by observed behavioral and physiologic responses. Reinforcing efficacy is determined by assessing the ability of the drug to strengthen and maintain orderly patterns of behavior when the subject is permitted access to the drug (i.e., the prototypic "self-administration" study).

Pharmacodynamic Effects of Nicotine. In human studies of nicotine-related psychoactivity, volunteers are given a range of doses of the test compound and placebo under double-blind conditions. Persons with histories of drug abuse are used because they can accurately discriminate compounds with a potential for abuse and can compare the effects of the compounds to those of abuse drugs *(5)*. In one study, three doses of nicotine were given both intravenously and in the form of tobacco smoke under controlled conditions *(71)*. Nicotine produced a similar profile of effects (figure 1). Self-reported (subjective), observer-reported (behavioral), and physiologic variables were measured before, during, and after drug administration. In brief, nicotine was shown to be psychoactive, as evidenced by the reliable discrimination of nicotine from placebo. Self-reported effects of nicotine peaked within 1 minute after administration (by either route) and dissipated within a few minutes: peak and duration of response were directly related to the dose.

The two hallmark indicators of euphoria in such studies are the Liking Scale (Single Dose Questionnaire) and the Morphine Benzedrine Group (MBG) Scale (Addiction Research Center Inventory [ARCI]) (5). Responses on the 5-point Liking Scale, which asked how much the drug was liked (0 = "not at all," 4 = "an awful lot") are presented in figure 2. Nicotine produced responses on the Liking Scale similar to those of morphine and *d*-amphetamine. MBG Scale scores of the ARCI were consistent with the Liking Scale data, confirming that nicotine, given by both routes of administration, was a euphoriant. In another comparison between drugs, subjects more frequently identified nicotine injections as cocaine.

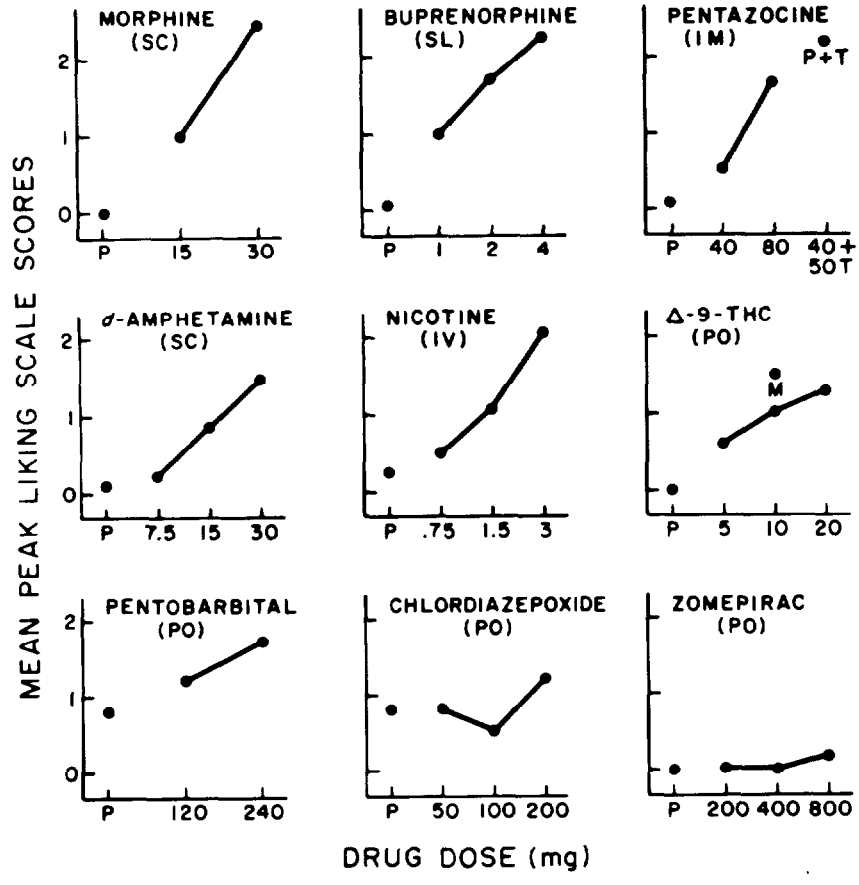
Similar results for intravenous and inhaled nicotine were also obtained on several physiologic measures, including pupil diameter, blood pressure, and skin temperature. These data confirmed that nicotine, given in either tobacco smoke or intravenously, was the critical pharmacologic compound accounting for these effects of tobacco smoke. A subsequent study showed that nicotine's subjective and physiologic effects could be partially blocked by pretreating the subjects with the antagonist mecamylamine *(18)*. Results of studies with animals also indicate that nicotine produces discriminable effects, and the data suggest that animals identify nicotine as being more similar to cocaine than to placebo or pentobarbital, but not identical to cocaine *(17)*.

FIGURE 1.—This figure is a summary of the data from a study of the liability of nicotine delivered as tobacco smoke (filled symbols-IN) or intravenous injections (open symbols-IV). Dose is presented on the horizontal axes. Even with a controlled smoking procedure, nicotine dose administration via cigarette smoke is more variable (producing flatter dose-response functions) than when given intravenously. Also, important effects of nicotine are covert though reliable and orderly (e.g., relaxed feelings, symptom scores). The finding that a low dose of tobacco smoke was more effective in reducing desire to smoke than a low dose of intravenous nicotine is consistent with the fact that satisfaction from smoking is also due to stimuli provided by the cigarette and the smoke.



Self-Administration of Nicotine. The second abuse liability dimension uses the "self-administration" procedure to examine the conditions under which a subject will voluntarily take the drug. Self-administration studies determine whether the drug serves as a biologically effective, positive reinforcer (or reward). Variants of these strategies are conducted in both animal and human subjects, thereby providing a means of establishing the biologic generality of the phenomena, while controlling the possible confounding influence of personality, social, or cultural variables. A high degree of concordance between findings from animal

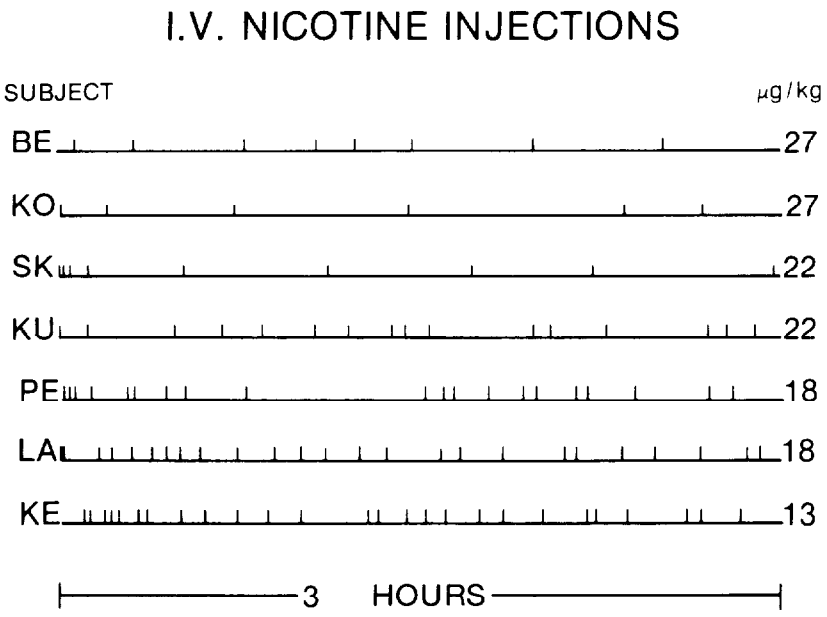
FIGURE 2.—This figure presents data from a series of abuse liability studies conducted at the Addiction Research Center. The findings that Liking Scale scores are directly related to dose and exceed placebo values are important in identifying dependence-producing drugs. Intravenous nicotine produced the same elevated dose-response function as highly addictive narcotics (e.g., morphine) and a prototypic stimulant (*d*-amphetamine). These data are also consistent with the lower abuse liability of chlordiazepoxide and almost negligible abuse liability of zomepirac. Administration of intravenous cocaine results in a function similar to that shown for intravenous nicotine, except that the cocaine dose levels must be increased by a factor of 5 to 10.



and human studies has been established over a wide range of drugs *(20)*. Therefore, this section focuses on the results of studies using human volunteers.

The methods developed in animal studies can be used to assess whether the pharmacologic activity of a drug maintains self-administra-

FIGURE 3.—This figure shows the patterns of nicotine self-administration that occurred when volunteer cigarette smokers were given the opportunity to take injections of nicotine, but not smoke cigarettes, during 3-hour tests. The amount of nicotine available was roughly comparable to that obtained by smoking cigarettes. The subjects smoked less following sessions in which they took nicotine than following sessions in which only saline (the placebo) was available.



tion paralleling drug seeking and drug taking by individuals in the natural environment or "real world." The strategy is particularly useful in studies of nicotine, because it precludes confounding by other stimuli that are associated with tobacco smoke inhalation (e.g., the tobacco brand, smell of the smoke, and lighting-up rituals).

In one such study, tobacco-deprived volunteers were tested during 3-hour sessions in which 90 presses on a lever resulted in either a nicotine or placebo injection *(72)*. All six subjects voluntarily self-administered nicotine (figure 3). Patterns of self-administration (injections) were similar to those observed when human subjects smoke cigarettes and when rhesus monkeys take intravenous amphetamine injections in comparable experimental situations *(20)*.

One subject, who lacked a history of drug abuse, exhibited an acquisition pattern of nicotine self-administration that developed gradually over several sessions. The pattern was a prototypic example of drug

abuse development. Double-blind substitution of saline for nicotine resulted in cessation of the self-injection behavior of subject KO (figure 3). Subjects who were given access to both nicotine and placebo concurrently (by pressing alternate levers) chose nicotine, confirming that nicotine had come to serve as a positive reinforcer *(73)*. These data indicate that the pharmacologic activity of nicotine was critical to the maintenance of the behavior.

Nicotine self-administration has been studied in a variety of nonhuman species under a variety of experimental conditions *(74)*. As noted earlier, recent results confirm that nicotine can function as an effective reinforcer although the conditions under which it serves as a reinforcer for animals are more restricted than those for morphine or cocaine *(21)*. Nicotine self-administration via cigarette smoke or smokeless tobacco may provide ideal confluences of conditions for the establishment and maintenance of nicotine dependence in humans *(33)* with the presence of immediate and abundant peripheral taste and olfactory stimuli *(75)*.

Implications of Pharmacodynamic and Self-Administration Studies. The results of the pharmacodynamic and self-administration studies provide direct evidence that nicotine itself, and apart from its being presented in combination with all of the orosensory properties of tobacco smoke, is an abusable drug. That is, nicotine meets the criteria of being psychoactive: it serves as a euphoriant and as a reinforcer. These findings strongly suggest that nicotine parallels other drugs (e.g., morphine in opium use, cocaine in coca leaf use, and ethanol in alcoholic beverage consumption) in its ability to maintain self-administration. The findings are of sufficient strength that the relevant public health implications have already been incorporated into issues of public health policy by the former Director of the National Institute on Drug Abuse, Dr. W. Pollin *(76)*, the U.S. Public Health Service *(77)*, and the former Secretary of the Department of Health and Human Services, Mrs. M. Heckler *(78)*.

Physical Dependence Potential of Nicotine

Physical dependence potential (also referred to as physiological dependence potential) pertains to the direct physiologic effects that are produced by the repeated administration of a drug that results in neuroadaptation *(3,4)*. Neuroadaptation is characterized by demonstrated tolerance to the effects of the drug and the occurrence of physiologic withdrawal signs following the termination of drug administration.

Physical dependence potential studies are conducted according to standardized tests, using methods such as the substitution approach in which an active drug is removed and replaced with either a placebo or another form of the drug *(5)*. Although many studies on the effects of tobacco abstinence on mood, behavior, and physiologic functions have been conducted, until recently, the classic "direct addiction" or "substitution" methodologies had not been used to study the physical dependence potential of nicotine *(79)*.

The absence of such studies and the fact that many critical markers of tobacco abstinence are not overt or easily measured (e.g., change in affect, EEG, and cognitive performance impairment) have led to questions about the severity of the tobacco withdrawal syndrome *(33)*. However, as shown below, abstinence from chronic tobacco or oral nicotine use is followed by a syndrome of behavioral and physiologic changes that are orderly, replicable, specific to nicotine, and of functional consequence in relapse to tobacco following abstinence. The apparent absence of withdrawal symptoms among some people is not inconsistent with the finding that nicotine has the *potential* to produce physical dependence. As is true for users of opiates (e.g., heroin), the magnitude of the withdrawal syndrome is related to a variety of factors such as dosage and individual predispositions *(80)*.

Definition of Tobacco Withdrawal. There are abundant data indicating neuroadaptation to tobacco use, showing that this adaptation is at least partially nicotine specific and that termination of chronic tobacco use produces a behavioral and physiologic rebound or withdrawal syndrome *(33)*. This has been stated in the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (APA) as follows *(81)*:

> Tobacco Withdrawal (APA, DSM, III, 1980). The essential feature is a characteristic withdrawal syndrome due to recent cessation of or reduction in tobacco use that has been at least moderate in duration and amount. The syndrome includes craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, headache, drowsiness, and gastrointestinal disturbances. It is assumed that this syndrome is caused by nicotine withdrawal, since nicotine is the major pharmacologically active ingredient in tobacco.
>
> Withdrawal does not occur with all smokers; but in many heavy cigarette smokers, changes in mood and performance that are probably related to withdrawal can be detected within two hours after the last cigarette. The sense of craving appears to reach a peak within the first 24 hours after the last cigarette, thereafter gradually declining over a few days to several weeks. In any given case it is difficult to distinguish between a withdrawal effect and the emergence of pychological traits that were suppressed, controlled, or altered by the effects of nicotine.

This definition by the American Psychiatric Association represents a reasonable consensus from various reviews of the literature on cigarette smoking and physiologic dependence on tobacco *(3,13,32,82,83)*. It is based on experimental data and clinical observations from cigarette smoking treatment studies demonstrating that certain signs and symptoms are of unusually high prevalence during the first few days of abstinence. Decreased heart rate and blood pressure have been studied experimentally *(84)*, as well as changes in cortical EEG potentials *(85,86)*,

changes in urine catecholamine excretion *(87)*, and weight gain *(57)*. Other possible concomitants of tobacco withdrawal reported clinically include headaches, gastrointestinal disturbances, insomnia, and fatigue *(82,87)*. A variety of behavioral effects occurs when tobacco or nicotine administration is abruptly terminated in human and animal subjects, including increased irritability, aggressiveness, and anxiety; performance also is impaired in various psychomotor and learning tests such as simulated driving, vigilance, and paired-associate learning *(88-90)*. Self-reported desire to smoke cigarettes ("craving") increases sharply for about 1 day following abstinence, then gradually declines over the course of about 1 week to a lesser level *(91)*. Most of these signs and symptoms of withdrawal subside over 1 to 2 weeks; however, some former tobacco users report that the desire to smoke may recur for many years and may be evoked by specific environmental stimuli that were previously associated with smoking, such as after meals or in selected social situations. This, too, parallels the powerful conditioning phenomena that are reported to be associated with other drugs of abuse *(92)*.

Evidence of Tobacco Withdrawal Symptoms. There is compelling evidence that acute tobacco abstinence produces a rebound (withdrawal) syndrome. This evidence comes from studies of two laboratories in which increases in low-frequency EEG bands and decreases in cortical activity were observed during the first day of tobacco abstinence *(85,86)*. These effects were immediately reversed when the subjects were allowed to smoke two cigarettes.

In a study of self-reported withdrawal symptomatology, 40 participants completed four 25-item questionnaire forms daily for 2 weeks *(93)*. Subjects were divided into two groups: totally abstinent and partially abstinent whose smoking levels were maintained at an average of 60 percent. Four symptom clusters emerged: (1) drowsiness in both groups declined over the first week and then increased over the second week, forming a U-shaped function; (2) physical symptoms (e.g., headaches and gastrointestinal disturbances) in both groups declined rapidly the first week and then remained stable across the second week; (3) psychological symptoms (e.g., anxiety and irritability) in both groups paralleled physical symptoms; and (4) craving symptoms in the totally abstinent group closely paralleled physical and psychological symptoms, whereas craving levels of the partially abstinent subjects remained elevated across the 2 weeks. The finding that partial abstinence is accompanied by persistent craving symptomatology is similar to the results of studies on the treatment of illicit opioid dependence with methadone. In these studies, low-dose methadone maintenance is associated with a persistent opioid craving *(94)*.

An important series of studies on the dependence potential of nicotine has recently been completed at the University of Minnesota *(95,96,97)*. The goals of these studies were to determine reliable and valid indicators

of tobacco withdrawal by examining physical, subjective, and behavioral reactions to tobacco deprivation. The first three studies of this series evaluated the dependence potential of tobacco and established a reliable battery of measures. In a residential study, 27 smokers resided for 7 days on a research ward *(95)*. Following baseline, they were assigned to abstain from smoking or to continue smoking for 4 days. Physiologic, subjective, and behavioral measures were obtained and analyzed. The second study was conducted on a nonresidential basis to assess tobacco withdrawal in the nonlaboratory environment *(96)*. In this study, signs and symptoms of tobacco withdrawal were measured in 100 smokers. Following baseline measurements, subjects were randomly assigned to either nicotine or placebo gum, to be chewed at each subject's own rate. The subjects returned on three different occasions for assessment. The third study assessed the reliability of the tobacco withdrawal syndrome within subjects *(97)*. This study employed a modified, within-subject experimental design; baseline smoking, tobacco deprivation, return to baseline smoking, and tobacco deprivation were assessed in each subject.

The results of all three studies demonstrated that the syndrome of withdrawal that occurs reliably and consistently in chronic smokers after tobacco deprivation includes decreased heart rate, increased caloric intake/eating, an increased number of awakenings during sleep, an increased desire to smoke cigarettes, and increased confusion. Other changes that were found, but not consistently, included increased irritability and decreased vigor. A prospective examination of data from both residential and nonresidential studies revealed that there were no statistically significant differences between men and women in either number or severity of tobacco withdrawal symptoms *(98)*.

A subsequent study was designed to assess the relationship between tobacco withdrawal symptoms and pre- and post-cigarette blood nicotine levels, pre-cigarette cotinine levels, change in nicotine level from pre- to post-cigarette, half-life of nicotine, and total smoke exposure *(99)*. Twenty subjects were required to smoke cigarettes for 3 days using a portable recorder that allowed measurements of smoking topography in a nonlaboratory environment. Blood samples were drawn to determine blood nicotine and cotinine levels. Subjects abstained from cigarettes for the next 4 days. A battery of tests to measure tobacco withdrawal symptoms was administered. In general, results showed an inconsistent relationship between measures of nicotine intake and tobacco withdrawal. The most consistent finding was the relationship of the desire to smoke cigarettes to blood nicotine and cotinine levels and change in nicotine from pre- and post-cigarette; that is, the higher the nicotine and cotinine level and "nicotine boost," the greater the desire for cigarettes during abstinence.

The three initial studies that were conducted at the University of Minnesota *(95,96,97)* systematically examined the physiologic depen-

dence produced by chronic tobacco use. This work represents a major advance in furthering the understanding of tobacco dependence. The NIDA Addiction Research Center is also nearing the completion of a series of studies on the physical dependence potential of tobacco and the degree to which oral nicotine treats the abstinence syndrome. Preliminary data analysis confirms the findings from the Minnesota studies.

Implications of Physical Dependence Potential Studies. These recent studies confirm and extend the findings of earlier investigations that demonstrated that nicotine had the potential to produce physiologic dependence. It is now known that the syndrome is orderly and is due to the administration and withdrawal of nicotine. The overt signs are more subtle than those marking opioid and sedative withdrawal, but these signs are not necessarily less important to the individual. For instance, withdrawal effects such as mood changes, performance deficits, and weight gain may be of considerable importance to the normal functioning of the individual. It is anticipated that just as detoxification and treatment of opioid and sedative dependence have benefited from improved understanding of these syndromes of withdrawal, so also may detoxification and treatment of tobacco withdrawal benefit.

Evidence That Orally Delivered Nicotine (Including Via Smokeless Tobacco) Has a Liability for Abuse and a Potential to Produce Physical Dependence

As previously indicated, moist snuff contains as much as 15.1 mg nicotine per gram; plug tobacco contains 17.2 mg per gram *(100,101)*. Lower-nicotine-containing brands exist. However, marketing efforts encourage (and users demonstrate) graduation to the higher-nicotine-containing products *(1)*. These levels of nicotine are substantial, since the relative potency of nicotine is 5 to 10 times greater than that of cocaine in producing discriminable subjective effects (1 to 2 mg of nicotine given intravenously, orally, or inhaled produces reliable behavioral and physiologic effects).

Two studies have confirmed that typical patterns of smokeless tobacco use result in the delivery of quantities of nicotine that produce plasma nicotine elevations comparable to those produced when cigarettes are smoked *(102,103)*. These studies also found that smokeless tobacco use reflected several of the indices of abuse liability and physical dependence potential. Smokeless tobacco users self-administered substantial quantities of nicotine; the patterns of smokeless tobacco use were orderly and stable; and subjective and behavioral effects may be produced from such use. More recently, a new form of smokeless tobacco, moist brown tobacco in tea bag-like pouches, was also shown to deliver pharmacologically active quantities of nicotine to the central nervous system *(104)*.

Reinforcing Properties of Nicotine in the Form of Chewing Gum

There is growing evidence that nicotine is reinforcing and has the potential to produce dependence even when absorbed through the buccal mucosa (and therefore more slowly) via chewing gum (nicotine polacrilex). One recently completed study involved the self-administration of either a nicotine- or placebo-containing chewing gum by smokers who had quit smoking *(105)*. When given a choice between placebo and nicotine chewing gum, subjects preferred nicotine to placebo and self-administered the nicotine gum throughout each day.* These data are particularly compelling, because nicotine, in the form of the nicotine polacrilex, is in an ion-bound complex. In this preparation, the nicotine is released and absorbed slowly compared to the nicotine in smokeless tobacco; and the polacrilex form of nicotine administration appears to be of relatively low abuse liability. This study also demonstrated that instructions by a physician can alter patterns of gum use and preference *(105)*. These data, which suggest that instructions can modulate the self-administration of orally delivered nicotine, are in keeping with the well-known fact that physicians control their patients' use of narcotics, sedatives, and stimulants.

Physical Dependence Potential of Smokeless Tobacco

Hatsukami and coworkers, at the University of Minnesota, studied neuroadaptation (physiologic dependence) in smokeless tobacco users *(106)*. All 16 subjects in the study used moist snuff and no other nicotine-delivering product. Measures of mood, feeling, behavior, and physiologic function were compared at baseline and during abstinence. Subjects showed significant signs and symptoms of nicotine withdrawal as measured by decreased resting pulse, attenuated orthostatic pulse changes, and increases in tobacco seeking ("craving"), eating, sleep disruptions, and confusion.

A study with nicotine gum showed orally delivered nicotine may cause physical dependence *(107)*. The subjects that were tested had been treated for tobacco dependence with nicotine gum that they used on a daily basis for at least 1 month. Eight subjects were then tested over the course of 4 weeks. They were given nicotine-containing gum during the first and fourth weeks; during the second and third weeks, they received nicotine gum for 1 week and placebo gum for the other. During the week that placebo gum was presented, seven subjects showed signs and symptoms of withdrawal, and two subjects relapsed to smoking or nicotine-containing gum. This study confirms that orally given nicotine has the potential to produce physical dependence. These findings were most recently confirmed by another study that showed development of physical dependence to nicotine gum in patients treated for tobacco dependence *(108)*.

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* Self-administration took place at an average rate of 7.4 pieces compared to an average of 1.2 pieces of placebo gum per day.

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PHYSIOLOGIC AND PATHOGENIC EFFECTS OF NICOTINE AND SMOKELESS TOBACCO

The user of smokeless tobacco is systematically exposed to significant amounts of nicotine, a potent multisystem pharmacologic agent. This chapter addresses the physiologic effects of nicotine upon the cardiovascular, nervous, and endocrine systems and the possible roles of nicotine in the pathogenesis of a variety of diseases.

Nicotine is described in pharmacology textbooks as a stimulant of autonomic ganglia and skeletal neuromuscular junctions (i.e., nicotinic muscarinic receptors). However, in vivo the actions of nicotine are far more complex depending on the dose, target organ, prevalent autonomic tone, and previous exposure history (tolerance) *(1,2)*. For purposes of this review, the focus is on the effects of nicotine in humans. Where human data are lacking and animal studies provide important information about physiologic effects, those studies are also discussed.

Most data on the actions of nicotine in humans derive from studies of the effects of cigarette smoking, comparing cigarettes with and without nicotine, and studies of the effects of intravenous nicotine. These studies provide the basis for our understanding of the human pharmacology of nicotine. However, as noted previously, actions of nicotine from smokeless tobacco and nicotine via inhalation or intravenous infusion may differ.

Physiologic Effects of Nicotine

Cardiovascular System

The predominant cardiovascular actions of nicotine result from activation of the sympathetic nervous system. Smoking a cigarette increases the heart rate (10 to 20 BPM), blood pressure (5 to 10 mmHg), cardiac stroke volume and output, and coronary blood flow *(3-5)*. Smoking may have different effects in smokers with coronary heart disease. It may reduce left ventricular contractility and cardiac output *(6)*, effects that are believed to be related to myocardial ischemia due to smoking-mediated tachycardia and the effects of carbon monoxide. Coronary blood flow may also decrease after smoking, which possibly is related to a nicotine-mediated increase in coronary vascular resistance *(7,8)*. Smoking, or nicotine intake, causes cutaneous vasoconstriction that is associated with a decrease in skin temperature, systemic venoconstriction, and increased muscle blood flow *(9-11)*.

Smoking results in increased circulating concentrations of norepinephrine, consistent with neural adrenergic stimulation, and epinephrine, indicating adrenal medullary stimulation *(3)*. Circulating free fatty acids, glycerol, and lactate concentrations increase. Cardiovascular and metabolic effects are prevented by combined alpha and beta adrenergic blockade, which indicates that the cardiovascular effects of cigarette smoking are mediated by activation of the sympathetic nervous