Nicotine Dependence*
Interface between Tobacco and Tobacco-related Disease

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Tobacco and its smoke constitute environmental toxins that are the major preventable cause of death and disease in the United States, contributing to more than 300,000 deaths per year. Some exposure to tobacco and related toxins is "passive;" however, the highest levels of exposure occur in people who deliberately, repeatedly and chronically expose themselves to it. In fact, these individuals must devote considerable amounts of time and effort (several hours per day), spend money (hundreds of dollars per year), ignore health warnings and their own beliefs, sometimes risk the health of others (eg, companions or even the fetus of a tobacco-using woman), and possibly ignore social rules and even laws (eg, restrictions on smoking). In 1964, when the Surgeon General of the United States issued what may now be regarded as a conservative exposition of some of the health consequences of smoking, many thought that this would largely signal the demise of cigarette smoking; yet a generation later, nearly one-third of adult Americans continue to use tobacco products. Why? Other less well-established environmental causes of death and disease are avoided. People stop drinking water that has become contaminated, move their place of residence when it appears that toxic waste dumping even slightly increases their chance of developing cancer, and willingly pay higher taxes to remove asbestos from their children's schools.

Centuries ago the answer was known. Tobacco can addict those who sample it, and it can addict with the power of substances such as alcohol and opium. Addiction is the interface between tobacco as an environmental toxin and the multitude of diseases now known to be a function of repeated exposure. Without addiction, there would be no widespread exposure. Curiously in the Americas, the original site from which tobacco was disseminated, addictive aspects of tobacco do not appear to be well understood by the public. In fact, although seen by some and commercially utilized by the tobacco industry, the role of nicotine in the addiction has not been as widely acknowledged as the facts would indicate it should be. Perhaps the extent to which the hazards of tobacco are underscored by its allure are due, in part, to considerable efforts of the tobacco industry to promote tobacco, not only as an acceptable form of drug abuse but as a highly desirable one as well. Currently, the rate of expenditure to advertise and market tobacco products approximates $2.5 billion per year in the United States.

One consequence of this lack of understanding of the addictive potential of nicotine is that persons who have wanted to quit smoking have generally been given advice such as "You just need willpower," or "All you have to do is set your mind to it," or it was assumed that all a person really needed was to have the health risks more clearly defined. Whereas some people have undoubtedly been helped by such information, it is plausible that others have been discouraged, thought less well of themselves, and possibly even avoided trying to quit, unaware that there was a physiologic basis to this seemingly voluntary pleasure and their apparent "weakness of will." Tobacco users who find it difficult to quit may now be relieved to know that there really is a physical basis for the difficulty: they may be dependent upon nicotine. This conclusion is shared by many health-related agencies and has also been acknowledged by the US Public Health Service, which observed that use of cigarettes and smokeless forms of tobacco may lead to dependence on or addiction to nicotine. The organic basis of tobacco addiction is now better understood than ever before, and this understanding can lead to hope for those who want to quit. Just as important for those who want to help, there is now a rational biomedical basis for the treatment of tobacco dependence.

Application of principles learned from other organically-based disorders can offer more encouragement than ever before to those who want to quit their tobacco use. The purpose of this article is to present a brief review of the pharmacologic basis of nicotine dependence. The emphasis is on pharmacologic issues that would seem to be relevant in helping the patient understand his disorder and in helping the clinician treat the disorder. It is our belief that the clinician has a potentially effective armamentarium at his or her

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disposal for helping people quit smoking, but critical issues in the addictive process require further elucidation. We hope that this article will provide the clinician with that information.

**Drug Dependence**

**Definitions**

While the conceptualization of tobacco as a dependence-producing substance emerges from its pharmacologic characterization and not from any particular definition, it is useful to begin with some working definitions of common but variably used terms. "Drug dependence" is synonymous with "drug addiction;" however, the term "dependence" is preferred by the World Health Organization and other organizations that are concerned with public health. The term "drug dependence" will be used throughout this paper since it is also somewhat less encumbered by overly general use (eg, the so-called addictions to love, sugar, and video games) and has fewer antiscientific connotations than the term "drug addiction." Drug dependence may be defined as a substance-seeking behavior involving a psychoactive drug that acts in the central nervous system (CNS); tolerance and physiologic withdrawal may or may not be present. Drug dependence does not differ from habitual or compulsive behaviors but, rather, is a subset of habitual or compulsive behaviors in which the role of a specific exogenously administered, centrally active chemical is critical (Fig 1). "Drug abuse" is often used synonymously with "drug dependence;" however, at times this term is used to designate a broader range of inappropriate or nontherapeutic drug use in which level of dependence may be negligible.

Simple exposure to tobacco does not ensure that dependence will develop, nor is everyone who uses tobacco dependent upon nicotine. Additionally, severity of dependence may vary across individuals. However, compared to other dependence-producing substances, it would appear that a substantially greater proportion of those who sample tobacco go on to become regular daily users who are not able to abstain at will. The American Psychiatric Association has further provided objective criteria for the determination that a person who uses nicotine-delivering products is dependent. The Fagerstrom Tolerance Questionnaire may also provide an estimate of the severity of nicotine tolerance and dependence.

**Misconceptions**

The many misconceptions about drug dependence in general obscure the understanding and treatment of tobacco dependence in particular. A few of the more common misconceptions include the following:

**Misconception 1.** Intoxication is evident in persons who are using dependence-producing drugs.

**ALL MOTIVATED BEHAVIOR**

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<thead>
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<th>work</th>
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<td>normal eating</td>
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Control is considered voluntary; social factors may be important; drive may be strong, but behavior may change with changing incentives.

**HABITUAL OR COMPULSIVE**

| TV watching |
| gambling |
| over-eating |

Loss of control; adverse effects may occur; behavior can usually be changed by behavioral strategies.

**DRUG ADDICTION**

| heroin |
| alcohol |
| cocaine |
| nicotine |

Chemical factor in control of behavior; treatment is helped by addressing drug-related factors.

**Figure 1.** Motivated behaviors which become out of control and/or produce adverse effects are classified as habitual or compulsive behaviors. Drug dependence is a subtype of habitual or compulsive behaviors. While motivation, loss of control and adverse consequences are still involved, the new element which has been added is the drug which, by affecting the central nervous system, exerts additional control over behavior.

Whereas high doses of most dependence-producing drugs, including nicotine, can produce marked behavioral disruption, intoxication is often not present in experienced drug users since they develop a considerable degree of tolerance and social adaptation.

**Misconception 2.** Escalation of drug intake occurs indefinitely. Although escalation of drug use may be related to the development of tolerance and certainly does seem to be related to the development of dependence, drug use eventually stabilizes; if not, overdose and death might occur.

**Misconception 3.** Drug-taking individuals are distinguished by bizarre and erratic behavior. Stable supplies can mitigate against erratic behavior that may, in part, reflect cycles of involuntary abstinence and intense drug-seeking behavior. For example, physicians and pharmacists with stable supplies of narcotics and sedatives have been known to escape detection for many years at levels of dependence that were severe and probably would have been associated with a considerable degree of antisocial behavior in persons without such supplies.

**Misconception 4.** The drug is the only relevant factor driving the behavior and the only relevant factor in treatment. Use of all dependence-produc-
ing drugs occurs in the context of a variety of environmental stimuli, and often the drug-taking behavior itself develops a considerable degree of functional autonomy from the drug. One consequence of this is that the desire to use the drug (often termed “craving”) may be elicited by environmental stimuli relatively independent of physiologic state or need. Since availability of the drug, relative cost, social pressures, and so forth may all influence the drug-taking behavior, all of these factors may be of relevance in treatment.  

**Misconception 5.** Abstinence from chronic drug-taking leads to an overt and health-threatening withdrawal syndrome. Among generally abused drugs, this has only been reliably shown to be the case for certain opioids, sedatives, and alcohol, and then only under certain dosing conditions. Abstinence from other opioids and sedatives and other classes of drugs such as cocaine, amphetamine-like stimulants, and nicotine, produce a reliable physiologic withdrawal syndrome, but one which is not marked by such obvious signs and is rarely health-threatening. This does not necessarily mean that the syndrome is of any less functional consequence for the individual who does not show marked signs, only that detection of the withdrawal by an observer is more difficult.  

**Misconception 6.** Drug dependence is largely due to vulnerability factors in certain individuals. Vulnerability factors (including genetic, personality, stress, etc) may alter the probability of an individual abusing a particular drug; however, the wide range of conditions under which certain drugs can control behavior and exert toxic physiologic effects indicates that the presence of specific vulnerability factors are not necessary. The drug, however, is necessary and is sufficient under an extremely broad range of conditions.

**Testing Drugs for Dependence Potential**

The efficacy of a substance to produce drug dependence (ie, its dependence potential) may be assessed in laboratory studies. The overall dependence potential is addressed by tests technically referred to as abuse liability and physical dependence potential.  

Abuse liability studies measure the effects of a drug in an attempt to predict the likelihood that initial use (experimentation or sampling) will result in its continued self-administration, even in the face of harm. Physical dependence potential studies measure physiologic and behavioral sequelae to repeated drug administration: specifically, physical dependence (evidenced by the occurrence of an abstinence-induced withdrawal syndrome) and tolerance (evidenced by decreased responsivity when doses are repeatedly given).

The role of nicotine in the compulsive use of tobacco products is now known to be equivalent to the role of cocaine in cocoa leaf use, ethanol in alcoholic beverage consumption, morphine in opium poppy use and tetrahydrocannabinol in marijuana use, and all commonly-used tobacco products contain varying amounts of nicotine. At first blush, it would seem that tobacco use would lend itself to unambiguous study. However, as will be discussed in greater detail, tobacco use has been remarkably difficult to evaluate in certain respects, particularly in its most common form, cigarette smoking. Yet, in the past few years, advancing technology and procedures have enabled researchers to determine that tobacco use, particularly in the form of cigarette smoking, is an orderly behavior that is lawfully controlled by the same behavioral and pharmacologic variables as are the more commonly studied forms of drug dependence. These common factors suggest that treatment programs for cigarette smoking could be enhanced by incorporation of those strategies proven effective with drug-dependent persons. Before reviewing the factors which link the various forms of drug dependence, it would seem worth taking note of a few of the characteristics of the various forms of nicotine self-administration which have made it deceptively difficult to study and have obscured some of the orderly functional relations between drug and behavior.

![Figure 2. Average plasma nicotine concentration in three men produced by "working" one tobacco sachet for 30 min and in three subjects who smoked one middle tar cigarette (1.4 mg nicotine yield) and chewed one piece of nicotine polacrilex (Nicorette, 2 mg).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21574/)
Nicotine Self-administration

Nicotine is readily absorbed via a variety of routes, with the main exception of note being the gastrointestinal route in which little nicotine escapes hepatic degradation. However, many specific factors determine the actual dose of nicotine delivered to the plasma (and, in turn, to the central nervous system) and the rate at which such delivery occurs. Both total dose and rate of administration are important factors determining the effects of most drugs, and nicotine is no exception. In fact, the rapid onset and offset of some of nicotine's effects, its power (efficacy) in producing certain effects, and its considerable potency provide a situation in which small variations in factors that determine total dose or kinetics may have substantial impact. As shown in Figure 2, the route of nicotine administration is one determinant of the kinetics of nicotine absorption. At one extreme, inhaled tobacco smoke rapidly enters the blood following massive surface area exposure to nicotine in the alveoli of the lungs (Fig 3). By contrast, absorption of nicotine from the polacrilex form (nicotine gum) is much slower, impeded by factors that are described below (Fig 4). Transdermal nicotine absorption would probably occur even more slowly.

Nicotine Administration via Tobacco Smoke Inhalation

Many early studies of tobacco smoking and also some treatment strategies relied on the assumption that the amount of nicotine delivered to the central nervous system was largely a function of the amount of nicotine contained in the cigarette or, more commonly believed, the amount delivered under standard conditions by a smoking machine (ie, Federal Trade Commission estimates). This premise is now known to be false. In fact, across a fairly wide range of cigarette nicotine delivery estimates, there is very little relation between the estimates and the amount of nicotine actually absorbed. There is also a weak relationship between FTC yield and nicotine content. As shown in Figure 3, the difficulty begins with the constituents of tobacco and of the smoke itself. A typical American cigarette contains approximately 10 mg nicotine and delivers approximately 1 mg to a smoking machine under standard test conditions. How the individual smokes varies as a function of several factors, however, and engineering features of cigarettes may obscure the relations even further. For instance, most cigarettes which achieve low estimates of tar and nicotine yield do so because of the ventilation holes which are placed

**Figure 3.** This illustration shows that nicotine delivery from the cigarette smoking process is complex and that the most fundamental variable to study—dose of the ingested substance—is difficult to measure.
near the end of the cigarette, proximal to the mouth; the smoking machine then draws a dilute mixture of air and tobacco smoke with each "puff." Since the holes are near the end of the cigarette filter and are often deliberately concealed, cigarette smokers may inadvertently (or deliberately) block the holes with their lips and thus achieve far higher nicotine yields than the smoking machines.27,28 Another factor receiving more recent attention is the concentration of nicotine and other constituents of sidestream smoke which are inadvertently inhaled.29 Finally, the behavioral interaction of nicotine dose, rate of smoking and various puffing and inhaling parameters produce an enormous source of confusion that is not present with drugs which are taken either orally or parenterally.30-33 The same kinds of factors are operational when cigars or pipes are smoked. However, the higher pH level of the smoke generated by the burning of nonflue-cured pipe and cigar tobacco is fairly well-absorbed buccally so that inhalation factors, while a source of dose confound, are not critical for nicotine absorption per se.

Nicotine Administration via Smokeless Tobacco or Polacrilex

As shown in Figure 4, absorption of nicotine via smokeless tobacco or nicotine polacrilex (nicotine gum) is not appreciably less complex than via smoke inhalation, but some of the factors differ. Unlike many medications designed for buccal or sublingual absorption, nicotine is bound to its vehicle (cut or ground tobacco leaf, or the nontobacco polacrilex). Its rate of release from the vehicle is positively related to amount of oral movement and contact with saliva. Once released into the saliva, absorption is directly related to the pH of the nicotine-saliva solution. Nicotine which is swallowed prior to absorption through the buccal mucosa is not well absorbed and is largely detoxified by its first pass through the gastrointestinal system and liver.33 Problematic for both the establishment of smokeless tobacco use and the therapeutic use of nicotine polacrilex (gum) was the development of a more effective control of dose administered. Tobacco companies have controlled nicotine content and pH level of their products for many years, but achieved a major advancement (as evidenced in product distribution and sales) with the development of the unit dosing tobacco sachet or "pouch." Another advance in the unit dosing system is the recently approved treatment of tobacco dependence with nicotine polacrilex. There are two important differences between these two nicotine delivery systems. The first is related to toxicity; whereas the polacrilex vehicle is comprised of only FDA-approved constituents with minimal toxicity, smokeless tobacco contains a variety of toxins present in quantities that substantially exceed limits set by the FDA on products under its purview.11 A second difference is related to possible abuse of the products; the polacrilex is aversive tasting to many people and requires considerable effort (chewing) to
extract the nicotine, resulting in a substance with attenuated abuse potential. The smokeless tobacco product, on the other hand, is designed to maximize utility by a wide range of potential consumers, including preadult.* These characteristics of nonsmoked nicotine delivery systems are relevant not only to an understanding of the dependence process but also to efforts aimed at treatment of such dependence.

**Nicotine Use as Drug Dependence: Common Factors**

Tobacco use can occur as a form of drug dependence in which nicotine is the dependence-producing drug. As an instance of drug dependence, it may be useful to review some of the characteristics of nicotine and the resulting dependence that may develop to it from the broader perspective of characteristics common to dependence-producing drugs and the resulting dependence syndrome which they can engender. It is this context that provides a conceptual perspective for understanding the dependence process that underlies tobacco use, as well as the precedent for various strategies of treatment. These commonalities, not necessarily any particular definition regarding dependence, require that tobacco be designated a dependence-producing substance, the use of which may lead to a type of drug dependence.

**Drug Use in the Face of Damage**

The simplest and perhaps most fundamental behavorial commonality engendered by dependence-producing drugs is that they tend to be used persistently despite known damage that may result from such use. This is not to say that health warnings are without effect in suppressing drug abuse in society; presumably, under certain conditions, such information does have an effect in promoting more healthful behaviors.34-38 Of course, such campaigns are met head-on by the tobacco industry with attempts to counter health warnings in their advertising campaigns.4,7 However, the repeated observation of individuals who persist in taking drugs that they believe to be damaging results in the concept of “loss of control” associated with drug-seeking. In the case of tobacco, the statistics are overwhelming. It is variously estimated that tobacco-related mortalities currently occur at a rate of 250,000 to 350,000 per year. This is more than those deaths resulting from all other dependence-producing drugs plus automobile accidents in the United States.15 In addition, most cigarette smokers and adult smokeless tobacco users believe that use of tobacco is harmful to their health and would like to quit, and approximately 10 percent of these would-be quitters seek advice and assistance from their physicians.34 In fact, while immediacy of health risk is related to quitting smoking, most smokers who undergo myocardial infarction resume smoking after hospitalization.37 Possibly related to reports of adverse health effects is the recent decline in cigarette smoking by preadults as well as certain well-educated adult populations.38 However, many of those who try tobacco continue to become dependent, and most of these individuals began using tobacco products during their adolescent years. Interestingly, recent data show that many adolescent smokeless tobacco users do not smoke cigarettes and either started to use smokeless tobacco and/or switched to smokeless tobacco from cigarettes in part due to their belief that the smokeless product was safer and more socially acceptable.30

The difficulty in quitting has been known for centuries.34 Since publication of the 1964 Surgeon General's Report, many millions of Americans have quit smoking, and the overall percentage of adult American smokers has declined somewhat. However, it is estimated that more than 50 million people continue to smoke cigarettes and more than 10 million people use smokeless tobacco products, together supporting an approximately $20 billion industry which provides tax revenues in excess of $10 billion to federal and state governments.8 Furthermore, out of 1,000 people who actually attempt to quit smoking, less than two in ten succeed on their first effort; in fact, after seven or more attempts, less than half succeed.5 Taken together, these observations are inconsistent with the theory that tobacco use is a simple, voluntary pleasure.

The persistence of certain forms of drug dependence despite known health risks has led to the postulation of specific vulnerability factors and/or an addictive personality type which are necessary to establish the dependence. Whereas the data bearing on these issues are considerable and diverse, the following conclusion can be reasonably made: while there is some degree of overlap in personality type of individuals who have become dependent to drugs (eg, elevated extroversion, psychopathy and risk-taking scores on various scales), and there is some overlap in situations which are related to drug relapse (eg, stress and anxiety),39 no specific vulnerability factors have been consistently

*This opinion comes from the conclusions of J.E. Henningfield based upon review of company documents produced pursuant to an order of a Federal District Court. Those documents included details of a strategy for establishing smokeless tobacco use by the development of a series of products intended to facilitate acquisition of smokeless tobacco self-administration. The documents further described the strategy by which these products were marketed in order of “graduating” nicotine dose administration levels (in the order of increasing nicotine content and pH). Among the documents were two reports of apparent US Tobacco-funded studies in which the pharmacokinetics of nicotine delivery via cigarettes and smokeless tobacco were compared (See plaintiff’s exhibits nos. 3.27, ‘‘Pharmacokinetics of Nicotine and its Major Metabolites in Naive and Habitudated Snuff Takers,” and 3.28 ‘‘Results of Comparison of Routes of Nicotine Administration [Snuff vs Cigarette Smoking].’’ From: Marsee vs United States Tobacco Company, US District Court of the Western District of Oklahoma, Oklahoma City, No. Civ. -84-2777 R [1986].)
found across drug classes and/or populations which are either necessary or sufficient to produce drug dependence.21

The critical factor is simple—exposure to the drug. Tobacco differs in a quantitative fashion from many other drugs of abuse since it appears that a greater percentage of those who sample tobacco become regular daily users than those who sample other drugs of abuse.18 A variety of factors may contribute to this relationship, including greater social acceptability of tobacco than many other drugs, relatively low cost and ready availability. Another factor which receives less attention is that tobacco use tends to begin at an earlier age than use of most other dependence-producing drugs.40

Are young people more vulnerable to becoming drug dependent? Are they physiologically and/or behaviorally more susceptible to lasting changes induced by chronic psychoactive drug exposure than are adults? Whatever the answers to these questions, some facts have been established. Most smokers begin smoking at an early age, smoke for some period of time, attempt to quit, then relapse. Preliminary evidence shows that users of smokeless tobacco follow a similar course of acquisition and maintenance, but smokeless tobacco use tends to begin at an even earlier age than cigarette use.11,41 This developmental pattern shares a number of similarities with other dependence-producing drugs. For example, both opium and tobacco habits develop rapidly and, in both cases, simple exposure to the substance (experimentation) may lead to chronic use.42 Other factors such as peer pressure, social trends, marketing and politics also contribute to the acquisition and maintenance of such behaviors.

Drug Delivery to the Central Nervous System

If use of a substance does not result in the delivery of a specific chemical to the CNS, issues concerning drug dependence are not applicable. However, typical methods of use of marijuana, opium, coca leaf, and alcoholic beverages all result in the delivery of a specific exogenous drug to the central nervous system. Similarly, it is now known that all common forms of tobacco use result in the delivery of nicotine to the plasma, where it is rapidly carried to the central nervous system. This observation is not incompatible with the finding that certain effects of the drug are mediated by various neurohormonal responses and that similar responses may occur during various activities (eg, jogging and sex) or consumption of food: the intact nervous system has a variety of final common paths which must be followed to effect responses.

Among the earlier quantitative data were those collected by Schmiterlow and colleagues,43 who used radiotracer techniques to characterize the distribution of nicotine accumulation throughout the body and central nervous system. Nicotine was found to be quickly distributed to all highly blood-perfused tissues, including the brain.

More recently, the findings of Schmiberlow and co-workers43 have been verified and extended. For instance, London and co-workers36,51 have shown that nicotine binds to specific receptors in the rat brain, with a distribution that closely parallels the patterns of metabolic stimulation in response to nicotine. Specifically, the density of nicotine binding sites is

![Figure 5](http://journal.publications.chestnet.org/pdffaсess.ashx?url=/data/journals/chest/21574/)

**Figure 5.** Brain slices of animals exposed to low doses of nicotine, high doses of nicotine, or saline solution. The red areas show the foci of increased glucose utilization. Interestingly, some of the same patterns of change in brain energy utilization have been found to occur with drugs like cocaine. Reprinted with permission from London et al (unpublished data).
highest in the interpeduncular nucleus, the medial habenula, and the superior colliculus. London and her coworkers have also used the autoradiographic 2-deoxy-D-[1-14C] glucose (or 2-DG) method to evaluate the possible changes in local cerebral glucose utilization which might be altered as a function of administration of a variety of dependence-producing drugs. As shown in Figure 5, subcutaneous administration of nicotine to rats resulted in specific regional increases in glucose utilization. The greatest increases occurred in the habenulointerpeduncular system and portions of the thalamus. Increases were related to nicotine dose and were blocked by the centrally and peripherally-acting nicotinic antagonist mecamylamine, but not the peripherally-acting antagonist hexamethonium. 

Another recent area of active research has taken the examination of site of action of nicotine a step further. While it has been known for nearly a century that nicotine was a ganglionic agonist in the peripheral cholinergic nervous system, specific receptor sites in the central nervous system have been identified and their functional properties are being explored.44-46 As long as such research continues to parallel advances in earlier studies with opioid receptors which led to the identification of specific receptor subtypes (and, in turn, to the development of better therapeutic compounds), the research on specific neural mechanisms of nicotine's effects also may eventually yield more effective pharmacologic aids for the treatment of tobacco dependence.

Nicotine's actions are also mediated via modulation of various neurohormones. Pomerleau and colleagues47 have been systematically exploring the role of nicotine as a neurohormonal regulator. It is plausible that some of nicotine's benefits are individual-specific, depending upon physiologic needs or environmental pressures. For instance, the possible role of nicotine to enhance learning via cholinergic mechanisms may be more important to individuals for whom such activities are particularly critical. Nicotine's ability to alleviate boredom and stress by its adrenergic effects may be most critical to individuals in boring or stressful situations. Better understanding of these interrelationships may lead to the development of more individual-specific therapeutic aids.

Tobacco Use as a Controlled Behavior

A casual analysis of tobacco use in the usual environment of the cigarette smoker or snuff dipper might suggest that the use of tobacco is a spontaneous, voluntary and capricious behavior. However, after cigarette smoking or smokeless tobacco use has stabilized and remains unrestricted, predictable patterns of self-administration emerge. A close examination of the behavior reveals that tobacco use is an orderly form of drug-taking behavior. Furthermore, tobacco use has now been clearly shown to be controlled by the same kinds of factors that control other forms of drug-taking behavior. It is the interactions of many of these controlling variables that help determine specific patterns of drug intake. Some of the more widely studied factors are summarized below.

Deprivation Increases Drug Seeking

Deprivation of tobacco increases the desire of the smoker to smoke cigarettes and decreases the latency to smoke when the opportunity arises. Commonly observed during the “cigarette break,” “theater intermission,” or when cigarettes had been unavailable for a few hours,† this effect has also been experimentally studied. One study showed that the deprivation effect is directly related to the time since the last cigarette.48 That nicotine plays a specific role in the tobacco deprivation effects has been established by a variety of lines of evidence. For instance, the effect is inversely related to the magnitude of nicotine preloading given either in tobacco smoke49 or when nicotine is given via other routes of administration,50,51 most recently including transdermally-administered nicotine.52 Although the suppression effect is a behavioral component of drug withdrawal in the physiologically-dependent person, measurable effects of deprivation on subsequent drug intake or desire to use the drug may occur in the absence of any other measured signs of withdrawal.

Increased Tobacco Cost Decreases Intake

For tobacco, as for many other substances, increasing the cost in terms of effort or money decreases intake; analogously, specific monetary incentives can be used to limit drug intake.53 In fact, this relation even holds when per capita cigarette consumption is examined as a function of cigarette tax rates across many different countries.53 One experimental treatment approach that has been evaluated with opioids, sedatives and tobacco is the use of monetary incentives to reduce or eliminate target drug intake. The effects of such manipulations were similarly effective for all three drug classes.54-57 It has also been suggested that this economic factor might be used in the form of increased tobacco taxes in an effort to reduce the detrimental public health effects of tobacco.35,36

Paired Stimuli Can Increase Drug Use

The role of environmental stimuli in strengthening the overall control of dependence-producing drugs

†Filmmaker-author Jon Waters has stated that "the real reason to have sex is that cigarettes taste so much better afterwards" (National Public Radio interview, October 8, 1986). This commonly reported deprivation effect may also be enhanced by hormonal variations but has not been systematically studied.

Smoking Cessation
over behavior has been well known, although not widely studied, for decades. The fundamental observation is that the drug can produce discrete and readily identifiable effects. All drugs that are widely abused produce such effects, and these have been measured in animals and human subjects. Given that a drug can function as a stimulus, it follows that its stimulus properties can be extended through other stimuli that are paired with it. Nicotine in its usual vehicle (ie, tobacco and/or tobacco smoke) seems to provide an ideal confluence of drug and paired stimuli.

Pioneering in this area were the observations and work of Wikler and coworkers which showed that the effects of opiates could be elicited by environmental stimuli previously associated with the administration of opiates. It has also been shown that the desire to use alcohol in alcoholic patients is increased by presentation of alcohol-associated stimuli. Recent studies with opioid-dependent persons have found that both the effects of drug administration and drug withdrawal can be elicited by various environmental stimuli. Only preliminary work has been done with respect to tobacco; however, the role of nicotine-paired stimuli would appear to function analogously to the role of such stimuli in other dependence-producing drugs. For instance, Gritz found that amount of smoking decreased as the nicotine-paired stimuli were removed. The subject smoked most in the full presence of the cigarette and smoke, less when a clear screen attenuated the direct smell of smoke in the room, and the least when an opaque screen blocked the sight and smell of the smoke. Using experimental animals, Goldberg and coworkers studied the role of environmental stimuli in the maintenance of behavior ultimately controlled by morphine, cocaine, nicotine and other drugs. They found that the total amount of drug seeking behavior was greatly increased when stimuli which were systematically paired with the drug were then intermittently available. Taken together, the results of these studies suggest that part of the demonstrably strong behavioral controlling properties of tobacco are due to the seemingly ideal combination of a drug that has well-discriminated interoceptive effects along with the equally well-discriminated exteroceptive stimuli which accompany every puff on a cigarette or chew on a tobacco wad; namely, the sight, smell, feel, and taste of the tobacco and/or smoke.

**Tobacco Taking is Controlled by Delivered Nicotine Dose**

Among the most fundamental pharmacologic factors is the absorbed dose of a drug. Demonstration that certain effects are related to the administered dose of the drug shows that the drug was relevant to the response. The role of nicotine dose as a determinant of a wide variety of centrally and peripherally-mediated actions of nicotine has been systematically studied for nearly a century in a wide variety of species and preparations. Physiologic and behavioral responses to nicotine which have been studied as a function of dose include those of the nicotine receptor itself, skeletal muscle responses, effects on cardiovascular function, electroencephalographic responses, appetite control, changes in mood and emotional state, and even changes in the ability to learn and memorize. In general, nicotine has been found to produce orderly, dose-related effects upon its administration to peripheral or central nervous system tissue.

Taken together, the extensive literature on the effects of nicotine dose as a determinant of tobacco self-administration also yield an unequivocal general conclusion: namely, that nicotine dose is also one determinant of this behavior. The most consistent findings may be summarized as follows: increasing the amount of nicotine circulating in the plasma of the smoker (eg, by preloading with other forms of nicotine, decreasing excretion rate, increasing unit delivered dose) results in diminished cigarette smoking behavior. This effect is often termed "downward compensation" and appears to be somewhat a more robust phenomenon than the "upward compensation" which occurs when acute dosing is decreased. However, upward compensation does occur when, for instance, subjects were given preloads of the ganglionic blocker mecamylamine. The quantitative aspects of the nicotine dose-effect relations in studies of cigarette smoking have been widely debated. Much of the debate has centered around the degree to which smokers regulate their intake of nicotine. Some observations regarding these issues and implications for replacement therapy are presented below.

**Control of Cigarette Smoking by Nicotine Dose**

The above description of upward and downward compensation reflects the literature as a whole. Specific data have led to dichotomous interpretations, however. On one hand, cigarette smokers are viewed as titraters who carefully adjust their nicotine intake in order to maintain stable plasma nicotine levels. On the other hand, cigarette smokers have also been viewed as being remarkably insensitive to changes in nicotine dose. The issues concerning the disparate interpretations of dose-response data in human studies are both empirical and theoretic. Review of the empirically-based portion of this literature shows that few studies of the effects of nicotine dose on cigarette smoking provide confirmation that intended manipulations of nicotine dose had actually been affected. As was shown in Figures 2 and 3, many factors can determine the actual dose of nicotine delivered to the plasma. When major factors are not controlled and there is no physiologic means of verifying that the
dose manipulation obtained was intended, then the finding of a relatively monotonic dose-effect function may accurately reflect the fact that plasma levels were not varied as intended.

Another empiric issue is that certain responses may vary in their sensitivity to manipulated dose. For instance, whereas dose-response functions are generally robust with regard to physiologic and many behavioral responses, the effects of nicotine dose on desire to use tobacco are notoriously insensitive. One recent study showed a significant dose-related suppression of cigarette smoking following pretreatment with nicotine gum in the absence of a significant effect on self-reported desire to smoke.71 Unfortunately, although self-reported desire to smoke (craving) is a notoriously insensitive dependent variable in studies of smoking, it is among the most widely used measures.72

Theoretic issues surrounding the role of dose in the control of tobacco use have been as much a cause for debate as the data themselves. It has been widely observed that decreasing plasma nicotine levels are associated with the occurrence of tobacco withdrawal signs and symptoms, including feelings of discomfort; increasing plasma levels produce desirable effects (although tolerance may attenuate these effects) with continued increases eventually producing acute nicotine toxicity and feelings of discomfort. These upper and lower thresholds of nicotine intake at which discomfort occurs have been regarded as boundaries of the ideal level of nicotine in the dependent smoker, and the theory that smokers will change their behavior in such a fashion as to avoid either boundary has been termed the "boundary hypothesis" by Kozlowski and coworkers.72 Dimensions of the boundary vary across individuals and even within a single day of smoking in a single individual as he becomes increasingly tolerant. However, at a descriptive level it appears to be a generally accurate and useful concept. It is also a useful model to consider when nicotine replacement therapy is used to treat tobacco dependence.

The boundary model, however, does not postulate that there is a specific nicotine plasma level that is desired by a smoker, who will carefully adjust his nicotine intake to maintain that level. This is the premise of the "nicotine titration theory" and the source of considerable debate.18 One of the problems with the theory is that nicotine regulation or titration is postulated as a controlling variable in its own right and not simply as a descriptive construct to summarize the averaged data. Moreover, the possibility that individual tobacco users carefully regulate their intake (ie, "titrate") to provide constant plasma nicotine levels within the day has never been convincingly demonstrated.

What does happen to plasma nicotine levels during the course of the day of the usual smoker? Following each dose of nicotine, plasma levels rapidly decline as nicotine is redistributed throughout the body; the rate of decline subsides after about 15 to 30 min to reach a fairly stable half-life of about two hours. The initial redistribution phase has sometimes been confused with nicotine's metabolic half-life.74 Imposed on this pattern of elimination, doses of nicotine obtained by smoking cigarettes or rapid intravenous injection may produce plasma spikes or boli.75,76 Plasma increases from smokeless tobacco use are somewhat attenuated by comparison.77 Within the day of the smoker, these nicotine boli produce an overall accumulation of nicotine in the plasma until the point is reached (usually after about four to six hours of smoking) at which overall rates of nicotine excretion approximate overall rates of intake. Then there is relatively little change from hour to hour, although between and immediately following each cigarette there remains considerable variation in plasma level. When the smoker retires for the night, plasma nicotine levels may fall to less than 15 percent of the previous day's average.78,79 Physiologically, this variable pattern of plasma nicotine probably serves to enhance the effects of nicotine desired by the smoker. Such effects would otherwise be greatly attenuated by the rapid onset of tolerance or tachyphylaxis which accompanies exposure of neural tissue to nicotine. Therefore, even if a steady and constant effect of nicotine was desired by the smokers and perfect titration of plasma nicotine levels were possible, such titration would not likely yield steady nicotinic effects.

In summary, the notion that people carefully regulate their intake of nicotine on a daily basis in accordance with the levels in their blood is not generally supported by the data. Furthermore, there would yet seem to be a physiologic reason for smokers to maintain stable plasma nicotine levels on an hourly basis. It has been rather consistently noted in studies of the role of nicotine dose in tobacco intake that, when there is reason to believe that dose has been varied, total amount of nicotine obtained is directly related to the dose administered. At the same time, the number of doses that were taken is an inverse function of dose.18,50 Furthermore, as Russell has noted,70 the so-called downward compensation in response to increasing nicotine dose is more robust than the upward compensation in response to decreasing nicotine dose. Finally, nicotine intake tends to be remarkably stable from day to day.78

These observations are consistent with those of other studies of drug intake as a function of drug dose in both human subjects and animals.79 In fact, there are few reported observations of a close correspondence between plasma drug level and the behavior of drug taking.90 Work with intravenous nicotine self-
administration by human subjects and animals similarly shows fairly consistent but weak relations between dose administered and change in behavior.\textsuperscript{81} Whereas there is little evidence that nicotine regulation is any more than a theoretic description of some of the data, it is clear that this most fundamental parameter in pharmacology and therapeutics, dose, is one determinant of the response to nicotine and is one parameter by which tobacco-taking behavior is mediated.

When using a nicotine replacement procedure to treat tobacco dependence, it appears useful to consider these observations in developing an appropriate dosing regimen for patients.\textsuperscript{81} It is plausible, however, that in the initial stages of nicotine replacement therapy for tobacco dependence, attempts to replace the pattern of nicotine accumulation are as relevant as is the actual average plasma level.

\textit{Criteria for Potential for Abuse}

In the preceding sections of this paper, we describe tobacco self-administration as an orderly behavior controlled by the same types of variables previously shown to control other kinds of substance abuse behaviors. Whereas the focus of the prior section was on the aspects of the behavior of tobacco use that lead to its characterization as a form of drug dependence, this section focuses on aspects of nicotine pharmacology that lead to its characterization as an addictive or dependence-producing drug with potential for abuse. While not mutually exclusive topics, the strategies of investigation are somewhat different and would seem to justify this conceptional distinction.

Earlier studies of opioids, stimulants, sedatives, and other dependence-producing drugs have shown that they all produce certain effects which distinguish them from drugs that are not generally abused. Prototypic drugs used as the standards to which others are compared are opioids (eg, morphine and heroin) and psychomotor stimulants (eg, amphetamine and cocaine). When given to persons with histories of drug abuse under double-blind, placebo-controlled conditions, such drugs produce characteristic responses on standard tests. The responses are as follows: 1) Subjects can discriminate drug from placebo and the reliability of discriminations is related to the dose of the drug. If these effects are centrally mediated, then the drug is defined as "psychoactive." 2) Scores on the empirically derived morphine-benzodrine-group (MBG) scale of the Addiction Research Center Inventory (ARCI) and drug liking scales are elevated in a dose-related manner. If these effects are also centrally mediated, then they define the drug as a "euphoriant." 3) Presentation of the drug can condition and control behavior in such a way that the person will seek the drug. Demonstration of such potential of a drug to control subsequent behavior in both human subjects and animals shows that the biologic activity of the drug apart from the various aspects of the vehicle (eg, cigarettes) is critical and the drug is said to serve as a "positive reinforcer."

Nicotine was studied as a drug with the suspected potential to produce these three effects at the Addiction Research Center of the National Institute on Drug Abuse.\textsuperscript{82,83} Volunteer subjects with histories of drug abuse were tested during a residential study in the Clinical Research Laboratory. Individuals with such histories are often used as subjects in studies because they can accurately identify drugs with a potential for abuse and can compare the effects to those of other abused drugs. Nicotine was given both intravenously and in the form of tobacco smoke over a range of doses to each of the eight initial subjects tested. A crossover or within-subjects design was used such that each of four dose conditions was given to each subject on four different occasions. Self-reported (subjective), observer-reported (behavioral), and physiologic variables were measured before, during and after drug administration.

\textbf{Nicotine is psychoactive.} Nicotine produced a similar profile of effects across a variety of measures when given by both routes of administration. In brief, nicotine was shown to be psychoactive as evidenced by its reliable discrimination from placebo. Its self-reported effects peaked within one minute after administration.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{euphoriant_bar_graph.png}
\caption{Euphoriants for Compulsive Behaviors}
\end{figure}

\textbf{Figure 6.} Data from a series of abuse liability studies conducted primarily at the Addiction Research Center (ARC). The cocaine data are standardized and reported from a study of Fischman et al.\textsuperscript{84} The glucose data are recently collected and previously unpublished data from the ARC. The findings that Like 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 the representative narcotic (morphine) and a prototypic stimulant (d-amphetamine). These data are also consistent with the negligible abuse liability of zomeperac.
(by either route) and dissipated within a few minutes. Peak and duration of response were directly related to the dose. When other subjects were pretreated with mecamylamine, the effects of nicotine were attenuated in a dose-related fashion.

Nicotine is a euphoriant. As shown in Figure 6, nicotine produced dose-related increases on the drug liking scale. Interestingly, the main difference from other drugs of abuse on this measure is nicotine’s potency. In fact, intravenous nicotine is approximately five to ten times more potent than intravenous cocaine in producing elevated liking scale scores.84

On the morphine-benzedrine-group scale of the ARCI, nicotine elevated scores relative to placebo (Fig 7). Interestingly, this figure includes data from a study of compulsive gamblers. Compulsive gamblers were asked to simulate “winning at gambling” as they answered each test item. The elevated scores on the MBG scale produced by the simulation show that there is some overlap in the subjective response to an addictive drug with a compulsive behavior which is not mediated by the presentation of a centrally acting drug.

Analogous studies have been conducted using animals as research subjects. Animal studies are critical since they permit an objective differentiation of the effects of the drug from any possible influence or bias carried by human research subjects. In the discrimination or psychoactivity tests, the animals were given a range of doses of the test drug and placebo. They were then trained to press one lever when given placebo and to press another lever when given the test drug. When tested in this fashion, nicotine was found to be well discriminated from placebo by the animals.85 Furthermore, the degree of discrimination was dose-related and was blocked by pretreatment of the animals with centrally (but not peripherally) acting nicotinic antagonists. In the animal analog of euphoriant tests, the animals are trained to press one lever when given the standard drug (eg, amphetamine) and another lever when given another drug (eg, sedative) or placebo. When tested in this manner, nicotine has been found to be unique but more similar to stimulants than to sedatives.86 These findings may be considered systematic extensions of research conducted by Johnston87 and Jones and his co-workers.88

Nicotine is a positive-reinforcer. To determine whether or not nicotine can control behavior, animals and human subjects can be given the opportunity to take intravenous injections. Nearly all drugs that are widely abused by humans are voluntarily taken by animals,79 ruling out the possibility that specific personality factors and other unique human traits are necessary for these drugs to control behavior. The drug-taking behavior must be voluntary in that the animal or person is not required or specifically induced to take the drug following initial training and exposure to it. However, once the drug takes control of behavior, the degree to which the behavior is truly voluntary lessens.

In one such study, volunteers were tested during three-hour sessions in which ten presses on a lever resulted in either a nicotine or placebo injection.89 Subjects were not permitted to smoke cigarettes for one hour before or during the session. A variety of safeguards ensured the safety of the subjects. As shown in Figure 8, nicotine was self-administered. Also shown in the figure, the double-blind substitution of saline solution for nicotine resulted in a decrease of the self-injection behavior. Similarly, when subjects were given access to both nicotine and placebo at the same time (by pressing alternate levers) they chose nicotine, confirming that nicotine was functioning as a positive reinforcer.90 When dose was increased, fewer injections were obtained; however, the subjects obtained more nicotine per session.

The results of these studies provide direct evidence that nicotine, in doses comparable to those delivered by cigarette smoking, is an abusable drug. That is,
Tolerance may be one factor in the dose escalation process that occurs in the earlier stages of development of drug dependence. Figure 10 shows the self-reported number of cigarettes or the amount of smokeless tobacco (SLT) used at various time points from the first day of tobacco use to the fourth (SLT) or eighth (cigarettes) year. Despite the compressed time scale, it can be seen that in the case of cigarettes, it takes a few years before a stable level of approximately one to two packs per day is reached. Smokeless tobacco use appears to asymptote more rapidly, but also follows a period of graduated level of use.

**Physical Dependence over the Course of Drug Administration**

Although physical dependence is neither necessary nor sufficient to produce the behavior of damaging drug self-administration, it can strengthen the control of the drug. Physiologic dependence is measured by the demonstration of an abstinence syndrome generally characterized by rebound signs and symptoms when regular drug administration is discontinued. For instance, in the case of opiate withdrawal pupillary constriction is replaced with pupillary dilation, constipation is replaced with diarrhea, and so forth. With nicotine (as with opiates and sedatives), a prominent characteristic is an increased tendency to want to use the drug, sometimes reported as "craving". In a recently completed study, the tobacco abstinence syndrome was experimentally analyzed. Heavy cigarette smokers volunteered for study in which a baseline period of regular cigarette smoking was followed by a ten-day period of tobacco abstinence, then voluntary re-exposure to regular cigarette smoking. In a separate phase of the study, subjects volunteered for three alternating cycles of four days of regular cigarette smoking interspersed with three days of abstinence. During each three-day abstinence period, varying doses of nicotine polacrilex were administered every hour. Ratings of desire to smoke increased to near peak levels within the first 24 hours of deprivation. After this, ratings of desire to smoke began to decline for the remainder of the deprivation period. Changes in heart rate showed a similar time course with decreases averaging about 5 bpm. However, reversal in the trend of falling heart rate did not begin until the sixth day.

In the nicotine replacement phase of the study, the rate of gum administration and the rate of chewing were carefully controlled. From 8:00 AM until 7:00 PM, subjects chewed one piece of gum per hour for 15 minutes at a chew rate of one chew every 3 s. With regard to overall plasma nicotine levels, 12 pieces (4 each mg) of gum chewed under controlled conditions provided adequate replacement for the smoked tobacco. Hourly chewing of 2 mg of gum did not

![Figure 8](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21574/)

**Figure 8.** Pattern of acquisition of nicotine self-administration for a non-drug-abusing cigarette smoker. Note the gradual onset of behavior over several sessions. As shown in the figure, double-blind substitution of saline solution for nicotine resulted in extinction of the self-injection behavior.

nicotine meets the critical criteria of being psychoactive, producing euphoriant effects and serving as a reinforcer.

**Tolerance Over the Course of Drug Administration**

As mentioned earlier, tolerance develops after repeated administration of most drugs, and nicotine is no exception. A classic way in which tolerance is evaluated in the laboratory is to repeatedly administer a drug and measure the effects of each administration. It has been shown that when nicotine is administered every 10 min, rapid decreases in the liking scale scores are seen by the sixth or seventh injection, an effect not differentiated from when placebo is administered (Fig 9).

![Figure 9](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21574/)

**Figure 9.** The development of tolerance to the self-reported positive effects (euphoria) produced by repeated nicotine injections. The subject was given nicotine injections at 10 min intervals until he terminated the test. Prior to one test, the subject was given 10 mg of the ganglionic blocker, mecamylamine HCl. Mecamylamine attenuated peak effects but not the course of development of tolerance.
maintain plasma nicotine levels at the cigarette-smoking level.

As in the first phase of the study, baseline heart rate for the subjects was about 70 bpm; during the non-smoking days when placebo gum was administered, heart rate decreased about five beats per minute to levels approximating those seen during days two and three of the ten-day deprivation phase of the study. Administration of 2 mg gum attenuated the decrease and 4 mg of nicotine completely abolished this withdrawal effect. In all phases of this study, observers rated global tobacco withdrawal signs and ratings were maximal when placebo gum was administered. Two and 4 mg gum attenuated observer ratings of tobacco withdrawal.

As described above, abstinence from tobacco yields an orderly syndrome which is largely attenuated by replacement of the usual intake of nicotine in the form of the chewing gum. There was one important exception, however. That is, there was no significant difference in ratings of desire to smoke during placebo, 2 mg or 4 mg gum administration. This is an important observation for if the outcome measure in clinical treatment or research study is "desire to smoke," it appears that the gum's effects may be inconsequential.

These findings, that nicotine replacement can alleviate various signs and symptoms of withdrawal without appreciably altering desire to smoke, are consistent with the notion that desire to smoke is more closely related to learning factors and environmental stimuli. An analogous finding is that nicotine replacement in the form of intravenous injections or chewing gum can decrease the behavior of cigarette smoking and intake of carbon monoxide, whereas ratings of desire to smoke remain relatively constant. This summary of findings related to physical dependence to nicotine has focused on the short-term or acute withdrawal syndrome. However, certain aspects of withdrawal may persist well beyond the initial week in which changes in certain variables (e.g., desire to smoke and heart rate) are most prominent. Studies of physical dependence to stimulants have shown that a protracted abstinence syndrome may follow the acute abstinence syndrome and includes measurable physiologic changes for six months or longer after the last period of drug administration. Abstinence-related signs and symptoms may also be elicited by environmental cues for months or even years into abstinence. Studies have been conducted examining the role of such factors in opioid dependence and, to a lesser degree, in alcoholism.

Protracted abstinence from tobacco has not been systematically studied. However, a few observations may be relevant to treatment. In the ARC tobacco withdrawal study, ten days of abstinence were not sufficient for performance to totally recover and it is not known how long such decrements persist. Second, relapse situations are frequently related to known withdrawal effects. For instance, nicotine treatment can reduce anxiety, stress and irritability which are prominent symptoms in tobacco withdrawal and frequent situations in which relapse to tobacco abuse occurs. Taken together, the finding that abstinence effects may persist for months and even years, environmental stimuli can elicit effects associated with drug taking, and relapse actually occurs in expected
situations if such protracted abstinence and conditioning occurred with tobacco suggest that treatment approaches for tobacco dependence must be long term with a focus on maintenance of abstinence and avoidance of relapse. The possible utility of nicotine replacement as a maintenance compound to help prevent relapse over a period of years should also be considered viable.

The results of these studies have implications which are worth highlighting with respect to the use of pharmacologic intervention as a treatment for tobacco dependence. 1) Changes in ratings of desire to smoke were not significantly altered even when the nicotine dose was 8 mg (polacrilex); however, there were reliable dose-related decreases in actual smoking behavior in smokers who expressed no intent to alter their rate and/or pattern of cigarette smoking.2) Whereas intravenous nicotine and inhaled nicotine produce orderly dose-related increases in liking scale scores, responses to nicotine polacrilex are just the opposite. High doses of nicotine given via gum actually produce decreases in liking scale scores. This finding suggests that nicotine polacrilex has a relatively low level of abuse potential. Therefore, when using nicotine polacrilex in treatment, it may be taken as a structured and detailed program to ensure adequate levels of self-medication. 3) Despite the fact that most users do not like the higher dose, when asked to rate the equivalence of the gum to cigarettes, the larger the dose the more equivalent the rating. Therefore, in treatment programs it may be necessary to push the dose higher than what the patient would simply voluntarily take to get an effect.

Useful Effects of Drug Administration

Tobacco, like many other abuse substance, produces effects often considered of utility or benefit to the user. In fact, many drugs of widespread abuse (or forms of them) were originally developed as therapeutic agents and continue to be used as such. Furthermore, people who are dependent on drugs often report some desirable and/or useful effect derived from the drug. Nicotine is not unique in this regard. Specifically, nicotine administration to the tobacco-dependent person can alleviate stress and anxiety, facilitate learning and memory performance, and can function to control appetite and weight.47,48 Some of these effects have also been observed in animals, indicating that they may be at least partially due to direct actions of nicotine and not due simply to alleviation of withdrawal.

Effects of nicotine administration on the enhancement of concentration and performance are particularly interesting since these are frequent complaints of the people who have quit tobacco use. Effects are measurable in laboratory settings; they are specific to nicotine since administration of alternate forms of nicotine (eg, nicotine polacrilex) are effective, and there are a variety of electroencephalographic correlates.93 For instance, common complaints among people who have quit smoking are that their concentration is impaired, they are easily distracted and can't work as effectively on certain tasks. Recent laboratory studies at the Addiction Research Center confirm the organic basis of these complaints. Pickworth94 and Herning95 and their co-workers showed altered electroencephalographic responses during nicotine withdrawal including impaired evoked "cognitive potentials" and enhancements of distracting effects of background noise; certain effects were nicotine-specific since nicotine gum could reverse them. Correlated with the EEG changes was an impairment in performance on tests of ability, performance on rapid automatic, logical reasoning tasks, etc; these impairments, too, were nicotine deprivation-specific nicotine gum administration reversed them, as shown in Figure 11.96 Interestingly, performance impairment had not completely subsided after ten days of tobacco abstinence even though certain acute withdrawal effects (eg, severe desire to smoke, decreased heart rate) had

**COGNITIVE PERFORMANCE**

**Logical Reasoning**

**12 Hours Deprivation**

![Figure 11. Data points represent the average change from baseline in each of the treatment groups after 12 h of cigarette abstinence as assessed on one of the measures (Logical Reasoning) of the computerized performance assessment battery. During the baseline sessions, subjects were allowed to smoke normally up to the time of the test. Chewing 2 and 4 mg nicotine polacrilex reversed the effect of abstinence, whereas placebo gum shows the detrimental effects of 12 hours of tobacco deprivation in smokers (unpublished data by Snyder and Henningfield).**
largely subsided. The degree to which these useful effects of nicotine are withdrawal-specific, independent of short-term withdrawal or, possibly, represent an exceedingly long withdrawal syndrome (protracted abstinence) resulting from many years of tobacco use is not clear at this point.

It is worth note that such effects are sometimes termed "therapeutic;" however, such a term may be misleading when the drug is delivered in a vehicle as toxic as tobacco or the smoke of burning tobacco. Additionally, it is not clear to what degree the effects of nicotine which are useful to the tobacco user are only useful because of a long history of use. In other words, to what degree did the development of dependence to nicotine change the person in such a way that the individual will never, or perhaps not for an extended amount of time, function at peak levels and feel normal or comfortable in the absence of nicotine?

Given the power and potency of nicotine as a behaviorally-active drug, it would seem plausible that chronic exposure in adolescence (the age at which most smokers begin) would have lasting behavioral effects. Yet, relatively little developmental behavioral research with nicotine has been undertaken. In this regard, it is of interest and concern if the younger population (preteenage) that is beginning to use smokeless tobacco products will become more dependent on nicotine for its useful effects. Another issue of interest may also be of relevance in the treatment of tobacco dependence: the possibility that the useful effects of nicotine administration (and conversely, the adverse effects of nicotine abstinence) are related to the life circumstances of the individual patient. For instance, are the effects of nicotine in enhancing concentration and logical reasoning of special concern for writers? Or are the anxiolytic effects of nicotine of special concern for people in high stress occupations? These kinds of issues may be worth consideration in the implementation of tobacco treatment. More importantly, however, is the now conclusive finding that nicotine, for whatever reason, does have utility for many individuals. The utility is organically based, nicotine-specific, and treatable. Therefore, the presenting patient should be viewed not as psychosomatic, but rather as symptomatic to a physical factor.

**Additional Implications**

It should be clear that tobacco and its patterns of use share many characteristics with other prototypic dependence-producing drugs. Initial use—usually on a trial basis—soon escalates as a process of dose graduation to a full level of dependence (physical as well as behavioral). The enhancement of performance, mood, and feeling are critical factors in the drug's ability to control behavior, and the availability, cost, and acceptability of the product promote (rather than deter) dependence. When cigarette smoking was regarded as a voluntary pleasure or a simple habit, there was little reason to treat it as anything else and, in fact, there were limited resources available to the smoker who wanted to quit other than his own determination and motivation. Now that tobacco use has been more universally accepted as a form of drug dependence in which nicotine is the critical abuse-producing agent, there is a rational basis for the treatment of cigarette smoking based on experience with other forms of drug dependence. While such a conclusion will discourage some, for most it should come as a relief to discover that their difficulties in quitting and the pleasures they associate with tobacco are not merely psychological, they are physically based. Moreover, they can be treated. In fact, the acknowledgement and acceptance of nicotine dependence is actually reason for encouragement in treating cigarette smoking, for it provides a rational basis for combining pharmacologic intervention with behavioral techniques.

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