Chapter 4

Nicotine Effects and Addiction

CONTENTS

Pharmacology of Smokeless Tobacco Use: Nicotine Addiction and Nicotine–Related Health Consequences[1]

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ABSTRACT Nicotine is easily absorbed from smokeless tobacco and could contribute to adverse health consequences of ST use. Because nicotine is the cause of addiction to cigarettes, ST use may have a similar addiction liability. Cessation of ST use is difficult for many people. The nicotine withdrawal syndrome that follows the cessation of regular ST use supports the idea that some users are addicted to ST. Experimental data in support of this proposition indicate that ST users adjust their tobacco-consuming behavior to regulate levels of nicotine in the body. ST use results in cardiovascular effects that are similar to those of cigarette smoking. Chronic systemic exposure to nicotine from cigarette smoking may contribute to accelerated coronary and peripheral vascular disease, acute cardiac ischemic events, delayed wound healing, reproductive disturbances, peptic ulcer disease, and esophageal reflux. Insofar as nicotine contributes to the adverse health effects of cigarette smoking, the nicotine in ST would be expected to present similar hazards. Illness caused by systemic absorption of nicotine and other toxins from ST should be considered a potential sequel to long-term tobacco use.

INTRODUCTION In addition to causing oral pathology, there is concern that habitual, long-term smokeless tobacco use produces systemic effects that might adversely affect health. Of particular concern is exposure to nicotine, which is present in large amounts in smokeless tobacco (Table 1). This paper reviews the pharmacology of nicotine as related to the use and potential health hazards of smokeless tobacco.

PHARMACOLOGY OF NICOTINE Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. Nicotine binds to acetylcholine receptors at ganglia and neuromuscular junctions and in the brain (Benowitz, 1988). In its non-ionized form, nicotine freely permeates membranes, including the buccal mucosa and the blood-brain barrier. As a weak base, nicotine is less ionized and penetrates membranes more easily in alkaline solutions. Chewing tobacco and snuff, as well as nicotine gum, are buffered to an alkaline pH to facilitate absorption of nicotine.

Nicotine is absorbed more slowly from ST than from tobacco smoke, but peak venous levels are similar (Figure 1). Whereas blood levels of nicotine fall rapidly after smoking, the concentrations plateau during and after ST use, consistent with continued absorption even after the tobacco is removed from the mouth (Benowitz et al., 1988). Possibly, continued absorption of nicotine is attributable to release of nicotine from mucous membranes and/or absorption of nicotine that has been swallowed. The systemic absorption of nicotine per dose is greater with the use of chewing tobacco (average 4.5 mg nicotine from an average dose of 7.9 g chewed for

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Table 1
Nicotine content of cigarettes and smokeless tobacco

	Concentration of Nicotine (mg/g)	Typical Single Dose (g Tobacco)	Nicotine in Single Dose (mg)	Nicotine in Dose Typically Consumed in 1 Day
Cigarettes (15)[a]	15.7 (13.3-26.9)[b]	0.54	8.4	168 mg per 20 cigarettes
Moist Snuff (8)[a]	10.5 (6.1-16.6)[b]	1.4	14.5	157 mg per 15 g
Chewing Tobacco (2)[a]	16.8 (8.1-24.5)[b]	7.9	133.0	1,176 mg per 70 g

[a] *Number of brands tested.*
[b] *Range.*
Source: Adapted from Benowitz et al., 1990.

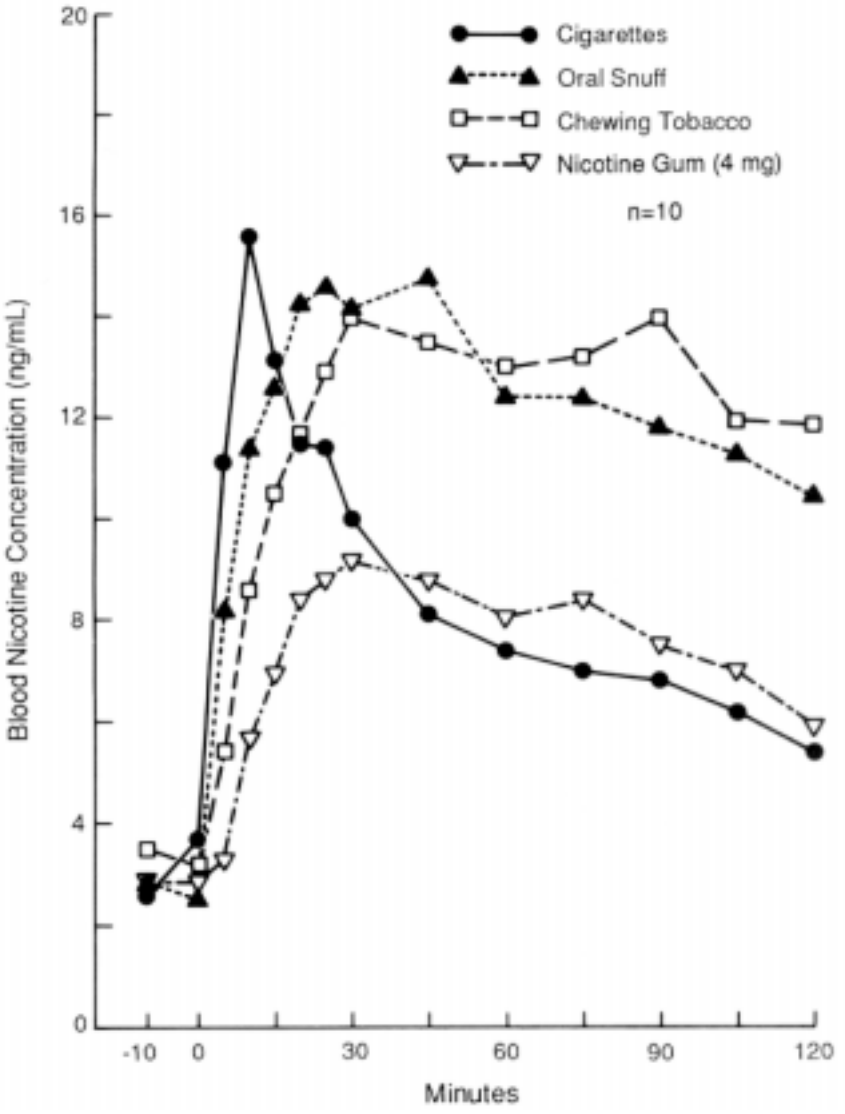
30 min) or snuff (average 3.6 mg nicotine from 2.5 g moist snuff kept in the mouth for 30 min) compared with that from smoking cigarettes (average 1.0 mg nicotine per cigarette). Individuals vary considerably in the amount of nicotine reaching the systemic circulation, even when they use a fixed dose of smokeless tobacco. For example, we found an eightfold range in peak plasma nicotine concentration (range 4 to 33 ng/mL) among 10 subjects who placed 2.5 g snuff in the mouth for 30 min. The average systemic bioavailability of nicotine from cigarettes and smokeless tobacco can be estimated from the average systemic doses of nicotine absorbed, as described above, and the data on the amount of nicotine in tobacco, as shown in Table 1. Systemic bioavailability is estimated to be 12.0 percent, 14.0 percent, and 3.4 percent for cigarette smoke, oral snuff, and chewing tobacco, respectively.

Nicotine is extensively metabolized by the liver (Benowitz, 1988). The major metabolite is cotinine, which has been used as a marker for nicotine intake. The half-life of nicotine averages 2 to 3 h. Consistent with this half-life, nicotine accumulates for 6 to 8 h throughout the day with regular ST use, and the levels of nicotine persist overnight, even while the user sleeps (Figure 2) (Benowitz et al., 1989).

NICOTINE AND COTININE LEVELS IN BLOOD

As Figure 1 shows, peak levels of nicotine after cigarette smoking or single doses of oral snuff or chewing tobacco are similar. Likewise, nicotine levels after the use of ST in sachets (Skoal Bandits) and after nasal insufflation of fine, ground nasal snuff are similar, although in the latter case absorption is very rapid, resembling absorption from cigarette smoke (Russell et al., 1981 and 1985).

Figure 1
Nicotine absorption rates from tobacco smoke and smokeless tobacco

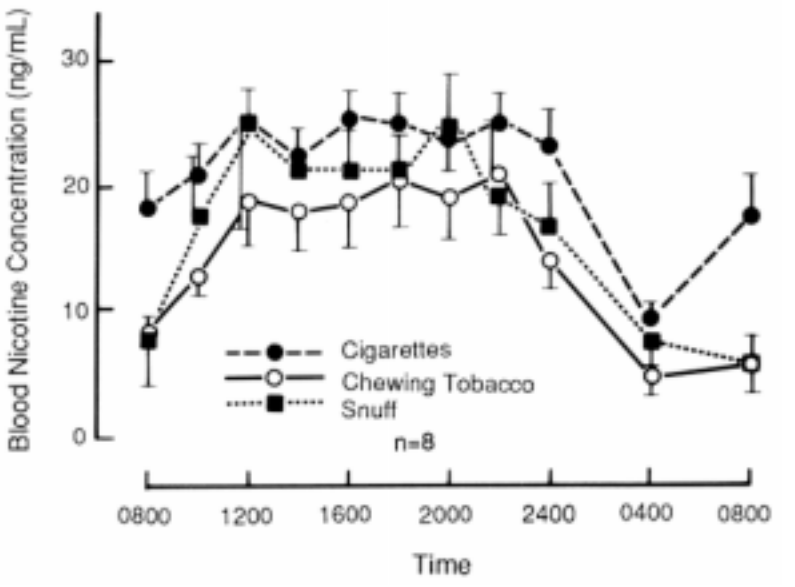


Average blood nicotine levels in 10 men who smoked for 9 min (1.3 cigarettes), placed 2.5 g moist oral snuff in the mouth for 30 min, chewed an average of 7.9 g (range of 0.9 g to 17.8 g) chewing tobacco for 30 min, and chewed 4 mg nicotine gum (two 2-mg pieces of Nicorette) for 30 min. Studies were performed in the morning after overnight abstinence from tobacco.

Source: Adapted from Benowitz et al., 1988.

With regular daily cigarette smoking, blood or plasma levels of nicotine sampled in the afternoon when those levels are at or near steady state generally range from 10 to 50 ng/mL. In a research ward study of eight

Figure 2
Circadian blood nicotine concentration with cigarette smoking, chewing tobacco, and oral snuff



Blood nicotine concentrations in subjects who smoked cigarettes (closed circles), used chewing tobacco (open circles), or used oral snuff (closed squares). Data are shown as mean ± S.E. for eight subjects.

Source: Adapted from Benowitz et al., 1989; used with permission.

men, the levels of nicotine during ad libitum use of oral snuff (averaging 15.6±5.9 g/d) or chewing tobacco (averaging 72.9±21.6 g/d) were similar to those observed with cigarette smokers (average 15.6±5.9 cigarettes/d) (Figure 2) (Benowitz et al., 1989).

Using plasma cotinine as an indicator of daily nicotine consumption from ST, one can compare consumption in different populations (Table 2). Cotinine levels in our research volunteers were somewhat higher than those measured in other groups. The college students and young men studied by Gritz et al. (1981) and Biglan et al. (in press) had cotinine levels averaging 55 to 60 percent of those seen in our research subjects, the latter of whom were, on average, much older. Professional baseball players had, in general, much lower cotinine values, particularly among the chewing tobacco users (Siegel et al., 1992). The lower level of cotinine in the baseball players reflects intermittent use, often in conjunction with playing baseball.

NICOTINE AND ST ADDICTION

People smoke cigarettes for the psychoactive effects of nicotine, and it is presumed that smokeless tobacco is consumed for the same reason. Nicotine may enhance the sense of well-being, produce arousal or relaxation, help maintain vigilance, and reduce anxiety (Benowitz, 1988).

Table 2
Serum cotinine in different populations of ST users

Source	ST Type	Users (n)	Plasma Cotinine (ng/mL)	
			Mean	Range
Gritz, 1981	Snuff	11	197[a]	14–556
Benowitz, 1989	Snuff	8	356[b]	182–868
Benowitz, 1989	Chew	8	354[b]	100–836
Siegel, 1992	Snuff	182	144[c]	–
Siegel, 1992	Chew	48	82[c]	–
Biglan, 1992	Snuff	20	217[d]	–

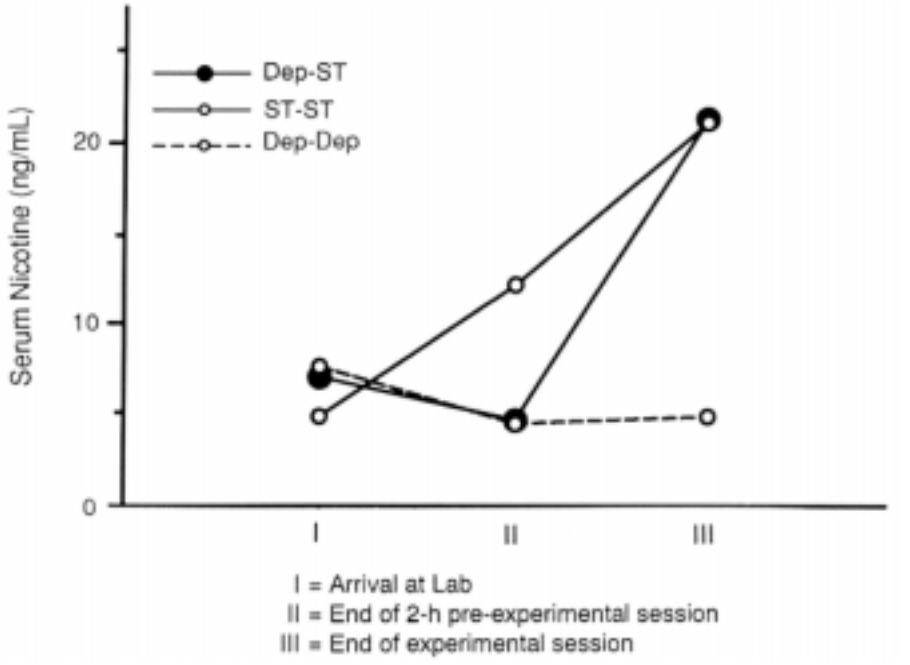
[a] *Afternoon measurement.*
[b] *Mean values throughout 24 h.*
[c] *Different times of day.*
[d] *Morning measurement.*

Whether enhancement of performance and mood is the result of an intrinsic enhancing effect of nicotine, or of relief of symptoms of abstinence in habitual users, is unclear. ST use is especially common among male athletes, some of whom believe that it enhances their athletic performance. Studies of the effects of ST on reaction time in athletes, however, have not confirmed any improvement in performance (Edwards and Glover, 1986).

Addiction to or dependence on smokeless tobacco can be defined as compulsive use despite awareness of substantial reasons not to use it. Formal criteria for establishing drug dependence have been developed in the Surgeon General's Report, *The Health Consequences of Smoking: Nicotine Addiction* (US DHHS, 1988). The primary criteria include highly controlled or compulsive use, psychoactive effects, and drug-reinforced behavior. Additional criteria include physical dependency, among several others. The compulsive use of smokeless tobacco has been reported and is described elsewhere in this volume. Nicotine from ST clearly has psychoactivity, and nicotine withdrawal symptoms develop after sudden cessation of ST use (Hatsukami et al., 1987).

That nicotine reinforces ST use has been shown recently in studies by Biglan and coworkers (in press). In a laboratory setting, depriving young men who regularly use smokeless tobacco from their tobacco for a period of time resulted in a greater consumption of ST than in a condition under which smokeless tobacco was given as a loading condition (Figure 3). The level of ST consumption was such that, whether or not subjects were preloaded with smokeless tobacco, after a period of ad libitum consumption, serum nicotine levels were similar in all conditions. In a second study of young men who regularly used snuff and smoked cigarettes, Biglan and coworkers found that when ST use was restricted, subjects smoked more cigarettes, and when cigarette use was restricted, subjects consumed more smokeless tobacco, compared to when both forms of tobacco were available

Figure 3
Serum nicotine concentration after deprivation then ad libitum oral snuff use in regular users



Condition I was on arrival at the laboratory after overnight tobacco abstinence. Condition II was at the end of a 2-h pre-experimental session when subjects were either deprived of (Dep) or preloaded with smokeless tobacco (ST). Condition III was at the end of the experimental session during which subjects were either deprived or had ad libitum access to smokeless tobacco.

Source: Adapted from Biglan et al., in press.

(Biglan et al., in press). These studies indicate that habitual ST users are titrating a level of nicotine in the body, as has been well described for cigarette smokers, supporting the dependence criterion of drug-reinforced behavior. That habitual ST use increases the likelihood of cigarette smoking when smokeless tobacco is unavailable or undesirable because of social constraints is supported by population survey data (Glover et al., 1989).

Thus, the criteria for addiction to nicotine are met for at least some ST users. The 1986 Surgeon General's Report on smokeless tobacco concluded that ST is an addicting substance (US DHHS, 1986). It is unclear what proportion of all ST users are addicted. Professional baseball players who use smokeless tobacco intermittently, often only in association with playing their game, for the most part do not seem to be addicted to ST.

HEALTH CONSEQUENCES OF NICOTINE EXPOSURE

Nicotine has many actions on the human body (Benowitz, 1988) (Table 3). The role of nicotine in producing these effects has been established by studies of direct administration. In general, the responses are consistent with activation of the sympathetic nervous system. Cardiovascular effects include heart rate acceleration (10 to 20 beats/min) and increased blood pressure (5 to 10 mmHg), similar to the effects of cigarette smoking. Nicotine also increases the circulating levels of catecholamines and free fatty acids, which may contribute to the increased level of total cholesterol and decreased levels of high-density lipoprotein cholesterol that are found in habitual cigarette smokers. Inhibition of prostacyclin synthesis and other effects on platelets may enhance coagulation.

The potential adverse health consequences of nicotine may be summarized as follows:

- Nicotine intoxication;
- Accelerated coronary and peripheral vascular disease;
- Stroke;
- Hypertension (complications);
- Delayed wound healing;
- Reproductive or perinatal disorders (low birth weight, prematurity, spontaneous abortion);
- Peptic ulcer disease; and
- Esophageal reflux.

For more details, see Benowitz (1988, 1991a, and 1991b) and US DHHS (1986 and 1988).

The greatest concern for nicotine–related effects is acceleration or aggravation of cardiovascular disease (Benowitz, 1991a). In a study of the cardiovascular effects of daily ST use, we found that the most prominent effects of nicotine—heart rate acceleration and increased urinary catecholamine excretion—were similar throughout the day in people smoking cigarettes and those using smokeless tobacco (Benowitz et al., 1989). In addition, urine sodium excretion was greater during use of smokeless tobacco than during smoking, probably because of the absorption of sodium, which, in smokeless tobacco, acts as an alkaline buffer to facilitate nicotine absorption. Insofar as nicotine contributes to adverse health effects of cigarette smoking, nicotine in smokeless tobacco would be expected to present similar hazards.

Nicotine could promote atherosclerotic vascular disease by contributing to hyperlipidemia, endothelial injury, or both (Benowitz, 1991a). Although cigarette smoking is not associated with an increased risk of hypertension, complications of hypertension are more severe in people who also smoke cigarettes (Isles et al., 1979). Nicotine may aggravate hypertension by causing vasoconstriction. Case histories of patients with hypertension aggravated by the use of smokeless tobacco have been reported (McPhaul et al., 1984; Wells and Rustick, 1986), and one survey of college students indicated that ST users had elevated blood pressure (Schroeder and Chen,

Table 3
Actions of nicotine in humans

Affected Systems	Effects
CNS	Arousal or relaxation Enhanced concentration, vigilance Appetite suppression Electroencephalographic changes
Cardiovascular	Increased heart rate, cardiac contractility, blood pressure Cutaneous vasoconstriction Systemic venoconstriction Increased muscle blood flow Catecholamine release
Metabolic	Lipolysis with fatty acid release Increased energy expenditure
Endocrine	Increased growth hormone Adrenocorticotrophic hormone/cortisol Vasopressin Beta endorphins Inhibition of prostacyclin synthesis

1985). However, a more recent study of ST use among baseball players revealed no relationship between smokeless tobacco and blood pressure (Ernster et al., 1990).

There is considerable evidence that nicotine may contribute to acute cardiac ischemia, such as aggravating angina pectoris, precipitating unstable angina or acute myocardial infarction, and even sudden death (Benowitz, 1991a). The possible mechanisms of nicotine effect include its systemic hemodynamic effects (which increase myocardial work), enhancement of thrombosis, induction of coronary vasoconstriction, and/or arrhythmogenesis.

Whether habitual use of smokeless tobacco is associated with hyperlipidemia, increased incidence of complications from hypertension, accelerated atherosclerotic vascular disease, and/or increased risk of acute cardiac ischemic events remains to be established in studies of large populations of users. Of interest in this regard is a recent study of users of smokeless tobacco that indicated they had a higher prevalence of hypercholesterolemia (when normalized for age and education) than did nonusers of tobacco (Tucker, 1989). Considering that the levels of nicotine in the blood are similar in smokers and users of smokeless tobacco, it seems likely that people with coronary artery disease are at increased risk from ST use.

Other suspected adverse health effects of nicotine, particularly reproductive disorders and peptic ulcer disease, must also be considered as potential complications of habitual ST use.

CONCLUSIONS The following may be concluded about nicotine and ST use: Systemic absorption and blood levels of nicotine are substantial and are often comparable in ST users and cigarette smokers. Data from a few studies performed to date indicate that ST use has the potential to produce dependency similar to that seen in cigarette smokers. However, it appears that in some populations, such as baseball players who use smokeless tobacco only intermittently, many ST users are not dependent. Smokeless tobacco use by young people does pose a concern for later development of dependence on cigarettes.

The health hazards known to be caused by cigarette smoking, and suspected to be related to acute or chronic nicotine exposure, are expected to be a hazard of habitual ST use as well. The major concerns are acceleration or aggravation of coronary artery disease and reproductive disorders.

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Recent Advances in Understanding The Actions of Nicotine in the Central Nervous System

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ABSTRACT There is now a consensus that nicotine is the key factor in habitual tobacco use and that it is the drug's actions on the central nervous system that are particularly important. Knowledge of sites and mechanisms of nicotine's CNS actions is advancing rapidly. Precisely which actions of the drug contribute to its reinforcing properties remain to be identified, but the participation of the mesolimbic dopamine pathway of the brain seems likely. Current pharmacological approaches to cessation of tobacco use have focused on nicotine replacement and have not met with great success. The high relapse rates encountered with this treatment approach (and with other current tobacco cessation techniques) may reflect the persistence of learned associations acquired during tobacco use. These associations could be extinguished (unlearned) through use of a drug that blocks the central actions of nicotine. Nicotine blockade therapy thus represents an attractive but largely untried treatment approach.

INTRODUCTION

Tobacco use is a major cause of preventable cancer. This review is intended primarily for health workers involved in the prevention and treatment of cancer. Its purpose is to provide an overview of recent advances in the understanding of nicotine's actions in the central nervous system and to highlight areas of uncertainty. This survey is selective and does not cover certain fields that may prove extremely important, such as the pharmacogenetic aspects of nicotine (Collins et al., 1990), the effects of nicotine on development (Navarro et al., 1989), and the interactions of nicotine with other drugs.

Two key questions serve as a framework for this review: (1) What does nicotine do in the CNS to account for its central role in tobacco use? and (2) Can pharmacologists help the tobacco user who wishes to quit?

NICOTINE'S ACTION IN THE CNS

There is widespread agreement among scientists and clinicians that most habitual smokers continue to smoke because they are dependent on nicotine. Nicotine dependence is thought to underlie the use of smokeless tobacco as well. The evidence, which has been reviewed at length elsewhere (Jaffe, 1990; US DHHS, 1988), can be summarized as follows:

As the Primary Reinforcer

- Nicotine is consumed not only via tobacco smoke but also via smokeless tobacco, thus avoiding the many pyrolysis products contained in smoke;
- Nicotine-free cigarettes generally are not smoked;

[1] The author receives research funding from Fonds de la Recherche en Santé de Québec and the Medical Research Council of Canada.

- Cigarette smokers regulate their levels of nicotine in response to pharmacological manipulations such as preloading with nicotine or receptor antagonism;
- Nicotine is self-administered intravenously by humans and animals in the laboratory;
- Self-administered doses of nicotine are psychoactive; and
- Habitual smokers experience withdrawal symptoms that can be alleviated by administration of nicotine.

Central vs. Peripheral Effects

Virtually all the known actions of nicotine appear to be mediated by nicotinic receptors (Clarke, 1987; US DHHS, 1988). There are receptors for nicotine in the CNS and in the periphery. Precisely which pharmacological actions of nicotine are important to tobacco smokers is unclear; however, it appears that the primary reinforcing actions of nicotine occur within the CNS.

Most of the evidence for this claim comes from work in animals. Almost all the behavioral effects of nicotine that have been investigated in animals appear to be attributable to direct CNS actions (Clarke, 1987), and recent evidence suggests that nicotine's reinforcing properties are no exception. Several species of laboratory animals have been shown to self-administer intravenous infusions of nicotine voluntarily. Rates of nicotine self-administration in rats were found to be markedly reduced after central administration of the nicotinic receptor blocker chlorisondamine in a low dose that was unlikely to act peripherally (Corrigall et al., 1992). Moreover, as described in a later section of this paper, lesion studies in rats have focused attention on a particular nerve pathway in the brain that seems to be intimately connected with nicotine's rewarding effects.

Central actions of nicotine also appear to be important in regulating cigarette smoking by humans. In one study, acute administration of mecamylamine, a centrally active nicotinic antagonist, altered smoking behavior, whereas the nicotinic antagonist pentolinium, which does not readily pass into the CNS, did not (Stolerman et al., 1973). In this short-term experiment, mecamylamine actually *increased* indices of smoke intake, and it seems likely that subjects smoked more in an attempt to overcome a blockade of nicotine's effects. In contrast, a preliminary report suggests that chronic treatment with mecamylamine can dramatically *reduce* smoking behavior and even permit highly dependent smokers to quit (Tennant et al., 1984). There appear to be no reports of the effects of nicotinic antagonists on consumption of smokeless tobacco.

Actions of nicotine in the peripheral nervous system may also contribute to the maintenance of tobacco use. If the evidence just reviewed suggests that the primary reinforcing effects of nicotine are likely attributable to central actions of the drug, its peripheral actions may act as secondary reinforcers. At doses obtained from cigarette smoke, nicotine appears to exert significant actions at the autonomic ganglia and at certain sensory nerve endings (but not on skeletal muscle). Jarvik and Assil (1988) have

reported that the nicotinic receptor antagonist mecamylamine attenuates the sensation produced by direct application of a nicotine solution to the tongue. This ability of nicotine to stimulate sensory nerve endings is of special interest, since sensory cues that occur in temporal proximity to smoking behavior would most readily tend to acquire the properties of secondary reinforcers. Consistent with this notion, Rose and colleagues (1985) have demonstrated that sensory stimuli produced in the airways by smoke inhalation can affect the immediate satisfaction derived from cigarettes. Although these findings are suggestive, nicotine is but one constituent of tobacco smoke, and the extent to which it contributes to secondary reinforcement remains to be determined.

Subtypes of CNS Nicotinic Receptors

On pharmacological grounds, nicotinic receptors in the periphery have long been subdivided into those occurring at the neuromuscular junction and those found in the autonomic ganglia and adrenal glands. With the advent of powerful immunological and molecular genetic techniques, an extended family of nicotinic receptors has recently been revealed. (See Deneris et al., 1991, for a review.) All known nicotinic receptors comprise a number of subunits. Generally speaking, each subunit is encoded by a different gene. An ever-growing number of such genes have been identified. For example, in the rat, more than a dozen putative subunits have been found; each receptor subtype is made up of a unique permutation of subunits, and the potential for diversity is staggering.

One factor that may limit this diversity is incompatibility between subunits. By injecting species of nicotinic receptor messenger RNA into frog oocytes, it is possible to produce and test the electrophysiological properties of "artificial" nicotinic receptors. The results of such studies show that certain combinations of subunits do not work as nicotinic receptors (Deneris et al., 1991).

In addition, receptor subunits (and, by implication, receptor subtypes) are differentially regulated. Thus, receptor subunits tend to show characteristic anatomical patterns of expression. For example, receptor subunits expressed in muscle are different from those expressed in the brain. The richest diversity of nicotinic receptors probably occurs in the CNS, where overlapping but unique distributions have been elegantly revealed by the technique of in situ hybridization histochemistry (Wada et al., 1989). Not only are the nicotinic receptor subtypes found in different places, but also at different times; receptor subunits manifest characteristic patterns of expression during development, some disappearing before adulthood.

At present, we simply do not know how many receptor subtypes exist. Considerable diversity is suggested not only by the several subunit-encoding mRNA species detected in the brain (Deneris et al., 1991; Wada et al., 1989), but also by findings at the protein level (Clarke et al., 1985; Schulz et al., 1991).

Nicotine's Complex Agonist Actions at the Receptor Level

On a molecular level, the best studied nicotinic receptors are those found in the electric organ of the electric ray and in mammalian muscle. Each of these receptors comprises five subunits, which together form the walls of an ion channel that transverses the cell membrane. Agonists such as nicotine and the neurotransmitter acetylcholine bind to certain of the subunits. Binding of an agonist induces the receptor macromolecule to undergo a conformational change (i.e., a change in shape), which in turn allows the channel to open and results in a net flow of positively charged ions (cations) into the nerve cell. The entry of these cations (primarily Na^+) tends to depolarize the neuron, making firing of the cell more likely. Calcium ions also may enter the cell in significant numbers. Calcium plays an important role in intracellular signaling pathways, and the consequences of calcium entry can be complex. Most nicotinic receptors are believed to control the passage of positively charged ions into the cell, thereby producing excitation. However, two reports in the last 5 yr suggest that some nicotinic receptors in the brain may be inhibitory (de la Garza et al., 1987; Wong and Gallagher, 1989).

Within the receptor macromolecule, certain receptor subunits bind nicotine (and other agonists). Other subunits, sometimes referred to as "structural subunits," do not, but their presence can indirectly influence agonist binding (Deneris et al., 1991). Antagonists can act in several different ways: some tend to compete for the agonist recognition site, others block the ion channel once it is opened, and yet others target additional sites on the molecule (Changeux et al., 1984). The precise mode of action depends on the drug and even on the type of nicotinic receptor in question. The receptor macromolecule also presents a target for endogenous substances, notably certain peptides, exerting a modulatory role (Boksa and Livett, 1984).

It is clear that the diversity of nicotinic receptors and our present state of ignorance about them make generalization difficult. In some respects each nicotinic receptor subtype is unique. In certain other respects there are considerable characteristics in common. Furthermore, the extended family of nicotinic receptors form part of a yet wider *superfamily* of ligand-gated ion channels, and certain common organizing principles are beginning to emerge. Studies of non-nicotinic members of this receptor superfamily suggest that nicotinic receptors may well be modulated by a variety of endogenous and pharmacological factors acting at a number of distinct sites on the macromolecule.

Desensitization Of Receptors

Activation of receptors by nicotine may lead to receptor desensitization. This is seen macroscopically as tachyphylaxis, in which the tissue becomes refractory to further applications of the drug. First described in the periphery, tachyphylaxis also occurs in central actions of nicotine. Central-occurring tachyphylaxis is well established in animals (Clarke, 1987) and also occurs in humans, although there are fewer human data available (US DHHS, 1988).

Neuronal nicotinic receptors (e.g., those located in autonomic ganglia or in the brain) are more sensitive than muscle nicotinic receptors to the

activating and desensitizing actions of nicotine (Paton and Savini, 1968). (Were this not so, tobacco use would be acutely harmful to one's health.) There appear to be considerable differences between putative subtypes of CNS nicotinic receptors in their sensitivity to nicotine-induced activation and desensitization (Couturier et al., 1990; Luetje and Patrick, 1991).

The implication is that doses of nicotine relevant to smoking and ST consumption may selectively activate certain subtypes of CNS receptors, leaving others unactivated and perhaps still other receptor subtypes in a more or less permanent state of desensitization. Evidence for this is discussed below, in the context of central sites of action.

Nicotine's ability to induce desensitization may underlie certain aspects of tobacco use. Habitual cigarette smokers inhale intermittently and space their cigarettes over time. This pattern of intermittent dosing may optimize the tradeoff between receptor activation and desensitization. Habitual smokers report that the first cigarette of the day is generally the most satisfying (US DHHS, 1988); the period of abstinence imposed by sleep may allow a large proportion of receptors to return from a desensitized to an activatable state. In addition, the greater difficulty people have in quitting cigarette smoking compared to giving up other forms of tobacco consumption may be due in part to the pharmacodynamic peculiarities of this form of nicotine administration (Benowitz et al., 1990).

Locating Central Sites of Action

Nicotinic receptors have been visualized most directly by autoradiography. Sections of brain tissue are mounted on microscope slides and incubated with radioactive probes that selectively label nicotinic receptors. The sections are then exposed to film, and the resulting images reveal the neuroanatomical location of the receptors. In this way, nicotinic receptors have been mapped in rat brain (Clarke et al., 1985; Schulz et al., 1991; Swanson et al., 1987), and to some extent in human brain (Adem et al., 1988). Nicotinic receptors are concentrated in a number of brain regions and nuclei, the precise distribution depending on the receptor subtype in question.

In animals, a variety of other approaches have been used to locate central sites of nicotine action. Several of the brain areas that feature prominently in nicotinic receptor autoradiographs have been studied electrophysiologically, and many neurons in these areas respond to the local application of nicotine. (For a review, see Clarke, 1990a.) Through recording the responses of neurons in brain tissue slices maintained in vitro, it has been possible to show that many cells are directly acted upon by nicotine, via receptors located on the cell body, on dendrites, or on both. By contrast, studies of transmitter release, again in vitro, have shown that nicotine can also exert direct effects on nerve terminals (Chesselet, 1984).

It must be stressed that nicotine does not occur naturally in the body. The endogenous agonist for nicotinic receptors is acetylcholine. Thus, nicotine is often employed because it is a convenient cholinergic agonist. In many cases, high doses of the drug are used which are of doubtful relevance to tobacco use. Furthermore, a recent electrophysiological report suggests that there is a prevalent subtype of nicotinic receptor in the brain that has

so far eluded detection because it desensitizes extremely rapidly in the presence of even low concentrations of nicotine (Couturier et al., 1990). This receptor subtype, although physiologically important, may play no role in nicotine dependence.

One way to study the pharmacological effects of "smoking doses" of nicotine would be to expose animals to tobacco smoke. This has rarely been attempted, partly because of practical difficulties, but also because such an approach introduces unwanted chemicals and may be highly stressful. Nevertheless, similar effects of smoke exposure and nicotine have been reported (Fuxe et al., 1986).

Typically, nicotine is administered to conscious animals in single doses which provide steady-state plasma levels similar to those measured in habitual smokers. This sort of approach has been used to measure the effects of nicotine on neuronal activity in the rat brain, as indicated by uptake of radiolabeled 2-deoxyglucose (Grunwald et al., 1988; London et al., 1988). By this index, nicotine activates a number of brain structures, and the most affected structures are, with few exceptions, those that possess the highest density of nicotinic receptors, as measured by autoradiography using radiolabeled nicotine. These functional and receptor mapping studies only roughly approximate actual smoking with the transient peaks that may be attained through individual puffs. Taken together, however, they strongly suggest that only certain nicotinic subtypes are significantly activated by doses of nicotine relevant to tobacco consumption.

Reinforcement Through Mesolimbic Dopaminergic Neurons

The reinforcing effects of nicotine in animals are of central origin (see above). Nicotine activates a large number of brain regions, many of which could conceivably participate in the drug's reinforcing effects. However, one neuronal system calls for particular attention—the mesolimbic dopaminergic pathway. This nerve pathway is one of several in the brain that secrete dopamine. Its cell bodies are located in the ventral tegmental area (VTA) of the midbrain, and it projects to the forebrain, where its major area of termination is the nucleus accumbens. Animals will work hard to increase the release of dopamine from this latter structure. This can be achieved either through electrical stimulation via indwelling electrodes, or through the self-administration of certain drugs, of which amphetamine is a good example (Wise and Rompre, 1989). Crudely, then, this system can be looked upon as a "reward pathway," and the meager evidence available suggests this system serves a similar function in humans.

The neurons that constitute the mesolimbic dopaminergic pathway represent targets for nicotine (reviewed in Clarke 1990b and 1990c). Thus, autoradiography has revealed nicotinic receptors both at the cell body/dendrite level and on terminals in the nucleus accumbens. Electrophysiological experiments have shown that nicotine, applied directly, can increase the firing rate of these neurons, and biochemical studies have shown that nicotine can act directly on terminals to promote the release of dopamine. In conscious rats, nicotine-induced dopamine release has been documented in the nucleus accumbens. Furthermore, near-total destruction

of the mesolimbic dopaminergic system markedly suppresses the rate of nicotine self-administration. The latter observation suggests that nicotine, like amphetamine, exerts its reinforcing effects to a large extent by activating the mesolimbic dopaminergic system.

All these findings are subject to an important caveat. The above studies have firmly established that nicotine, given acutely, can stimulate the release of mesolimbic dopamine. It remains an open question whether nicotine would have the same effect, were it to be administered chronically in such a way as to mimic the pharmacodynamic patterns of cigarette smoking or tobacco chewing.

PHARMACOLOGICAL HELP FOR QUITTING TOBACCO USE

Quitting the tobacco habit is notoriously difficult, and even the best strategies are rather ineffective (US DHHS, 1988). The most effective current methods for quitting are behavior-based, and they place considerable demands on the time of health personnel. For these reasons, it is worthwhile to seek a pharmacological aid for tobacco use cessation.

Limits of Current Pharmacotherapies

The only drug treatment readily available for those who wish to quit using tobacco is nicotine replacement therapy. This approach follows, logically enough, from the widely held view that habitual tobacco use is a form of nicotine dependence. Although considerable success was reported in early studies from cessation clinics using nicotine polacrilex (nicotine gum), the cumulative results are less than dramatic. Lam and coworkers (1987), in reviewing more than a dozen randomized, controlled trials, concluded that nicotine gum was marginally more effective than placebo gum, but in both cases, only a small minority of subjects remained abstinent in the long run (23 percent and 13 percent, respectively, at 12 mo). Beside its modest efficacy, nicotine chewing gum is associated with several undesirable side effects (Hughes, 1988).

As a form of drug delivery, the transdermal patch offers some distinct advantages over nicotine gum. Nevertheless, the problem of efficacy remains. In a double-blind study, Abelin and colleagues (1989) reported a statistically significant but small advantage to using nicotine patches; at the end of 3 mo of treatment, 36 percent of subjects were abstinent or nearly so, compared to 23 percent of controls receiving placebo. Rose and coworkers (1990) reported higher rates of recidivism, with only 18 percent of subjects remaining abstinent after 3 wk (compared to 6 percent of placebo controls). In another recent study (Hurt et al., 1990), high rates of abstinence at 6 wk were followed by substantial relapse, leading the authors to recommend adjunctive behavioral intervention and training to address this problem.

Clearly, results to date with nicotine chewing gum and transdermal patches have been disappointing. In the absence of other cessation strategies, they help only a minority of tobacco smokers achieve lasting abstinence. Can one hope that these treatments will be of more help for those wishing to quit smokeless tobacco products? Nicotine polacrilex and the transdermal patch release nicotine in a gradual manner that fails to mimic the puff-by-puff exposure to nicotine that cigarette smoking affords

(Benowitz et al., 1990). It has been hypothesized that, among many cigarette smokers, those transient boli of nicotine may play an important role in the dependence process (Russell and Feyerabend, 1978). Blood nicotine levels resulting from the use of ST (oral snuff, chewing tobacco), though, are less transient in nature, and thus can be more closely modeled by gum or by transcutaneous delivery (Benowitz et al., 1990). Nicotine gum and skin patches offer complementary features. The former does not fully replace blood nicotine levels, but offers the possibility of obtaining a boost of nicotine when it is wanted; transdermal patches can deliver adequate total amounts of nicotine, but administration is continuous.

Conditioning And Effective Pharmacotherapy

Many people give up the use of tobacco products for a few days or weeks with little difficulty. Some even manage to remain abstinent for a considerable time. Eventually, however, most attempts to quit fail. The addiction can reassert itself by even a minor relapse after years of abstinence. This "priming" effect is not unique to nicotine, but has been reported also, for example, in cocaine abusers (Jaffe et al., 1989).

Why does the abstinent individual remain susceptible to relapse? One reason may be that ex-smokers remain partially tolerant to the nauseating effects of nicotine and hence have less of a barrier to overcome than novice smokers. The persistence of tolerance cannot, however, explain why after the discomfort of quitting, and after experiencing the healthful, gustatory, and economic advantages of cessation, so many tobacco users relapse. Something is drawing them back.

This powerful force appears to be secondary reinforcement. Over the course of their dependence, tobacco users are likely to associate many stimuli with nicotine delivery. Many of these cues will initially be neutral, but through repeated pairing with the primary reinforcer, some are likely to assume reinforcing properties even in the absence of nicotine. The potency of these secondary reinforcers is borne out by verbal reports of smokers. In addition, laboratory studies have formally demonstrated the establishment of secondary reinforcers in monkeys self-administering nicotine intravenously (Goldberg et al., 1981).

Nicotine Blockade Therapy— A Neglected Approach

In my view, most tobacco users relapse because they retain the well-learned connection between tobacco administration and nicotine delivery. For example, an abstinent smoker knows that he or she has only to start smoking a cigarette to experience rapid reinforcement. This association, encoded in some form in the brain, may underlie the phenomenon of craving. It follows that, to abjure the tobacco habit permanently, one should extinguish these long-established associations. Current smoking cessation methods do not provide for this deprogramming (or, in psychological parlance, "extinction").

The most effective extinction procedure would be one in which individuals intending to quit would be administered a drug that would block the reinforcing effects of nicotine. They would then be encouraged to continue to use tobacco products in their customary way for a limited time, under the influence of the medication. It should be possible to achieve such

a blockade by administering a nicotine receptor blocker that is centrally active (Clarke, 1991; Stolerman, 1986). This approach has been largely untried. Results to date, although preliminary, are encouraging (Tennant et al., 1984). However, before nicotinic blockade therapy can be properly tested in human subjects, there is a clear need for a nicotinic receptor antagonist with a selective CNS action (Clarke, 1991).

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Dependence on Smokeless Tobacco

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ABSTRACT One of the key issues determining the threat to public health from smokeless tobacco is the degree of dependence experienced by users. Data documenting nicotine absorption and dependence on smokeless tobacco products are reviewed. Single case histories of individuals who either chewed cigarette butts or brushed snuff into their gums provide evidence of compulsive behavioral rituals accompanied by substantial uptake of the drug nicotine. Studies of dependent users of moist oral or dry nasal snuff show rapid absorption of nicotine from a single pinch and blood levels from normal use that parallel those seen in cigarette smokers. Among users of Swedish oral snuff, blood nicotine levels and subjective dependence were similar to those of cigarette smokers. These observations, which are derived from relatively few subjects, indicate that nicotine intake exerts a controlling influence over self-administration of smokeless tobacco products and that subjective dependence may be no less than among cigarette smokers. Available data from short-term cessation have been interpreted as showing that smokeless tobacco users experience less severe withdrawal effects than do cigarette smokers. Further studies on cessation of smokeless tobacco are needed.

INTRODUCTION The potential burden to society from the use of smokeless tobacco depends both on the threat it poses to health and on the users' degree of addiction. With cigarette smoking, we see hundreds of thousands of deaths each year in the United States because tobacco smoke is exceptionally damaging to health and because smokers, despite awareness and acceptance of the risks, find it very difficult to overcome their addiction. If addiction to oral and nasal snuff is less tenacious than addiction to cigarettes, smokeless tobacco users will find it easier to quit. But if dependence on smokeless tobacco turns out to be as strong as it is with tobacco smoke, the trends toward increasing prevalence of use, particularly by the young, may create problems in the future.

In considering the addictiveness of smokeless tobacco, the U.S. Surgeon General drew on three lines of evidence (US DHHS, 1986). The first two related to the presence of nicotine in smokeless tobacco and evidence of its absorption. This led to the following conclusion: "Given the nicotine content of smokeless tobacco, its ability to produce high and sustained blood levels of nicotine, and the well-established data implicating nicotine as an addictive substance, one may deduce that smokeless tobacco is capable of producing addiction in users." Direct evidence of addiction to smokeless tobacco, which was the third line of evidence, was at that time rather scanty, and comprised mainly reports of withdrawal symptoms upon cessation of smokeless tobacco (Hatsukami et al., 1987) or nicotine gum use (Hughes et al., 1986; West and Russell, 1985).

This paper follows a similar course, (1) reviewing our laboratory evidence of patterns of nicotine absorption from smokeless tobacco products and (2) presenting some new data that attempt to link nicotine absorption with the crucial issue of feelings of subjective dependence.

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NICOTINE UPTAKE FROM UNUSUAL USE OF TOBACCO

Frequently we are approached for advice about chronic psychiatric patients who do not smoke but who use tobacco in unusual ways and whose behavior puzzles those who care for them. Two such cases are presented briefly here.

A woman of Indian origin, diagnosed as schizophrenic, had the habit of brushing her gums with a toothbrush that had been dipped in dry nasal snuff (Edwards, 1987). She spent up to 9 h/d in this activity, could not explain why she did it, and became tense and irritable if deprived of snuff. On a day when she was permitted to apply 1.4 g of snuff in this way for half an hour in the morning, her blood nicotine rose from a baseline of 7.3 ng/mL to peak some 4 h later at 35.5 ng/mL, a value similar to that seen in heavy cigarette smokers.

More recently, we were contacted about a mentally handicapped resident at a long-stay hospital who regularly collected and consumed the butt-ends from used cigarettes. Apparently the patient swallowed the cigarette butts, and the expressed concern was more about the aesthetics of the behavior and disruption of life on the ward than about potential addiction. A blood specimen was taken at 5 p.m. on a day when he had consumed six filter tips. The blood nicotine concentration was found to be 29.2 ng/mL, and the corresponding cotinine was 622.2 ng/mL. Again, the nicotine level is comparable with that seen in dependent smokers, whereas the cotinine concentration, at about double the average in smokers, reflects extensive first-pass metabolism of swallowed nicotine by the liver, preventing nicotine from reaching the systemic circulation.

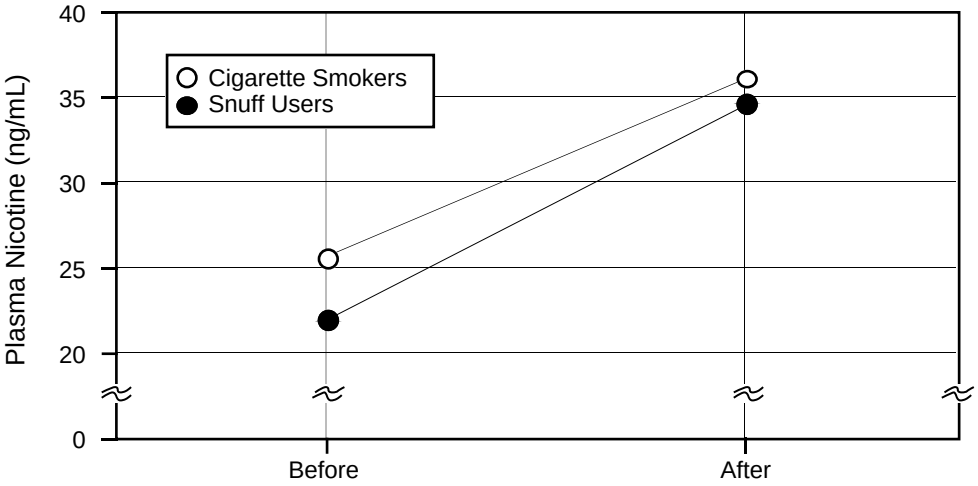
Evidence from single cases such as these has obvious limitations, and explanations couched solely in behavioral terms rather than invoking nicotine dependence cannot be completely ruled out. Nevertheless, that such compulsive rituals should give rise to blood nicotine levels characteristic of cigarette smoking is suggestive.

NICOTINE ABSORPTION FROM DRY NASAL SNUFF

Smokeless tobacco is used in Britain mainly as finely ground tobacco sniffed into the nose. In a habitual user, there was an increase in blood nicotine concentration of 21.1 ng/mL over 5 min from a single pinch (Russell et al., 1980). This evidence of rapid absorption prompted the study of a group of snuff users in the West of England (Russell et al., 1981). Among seven daily users, the average trough blood nicotine was 21.9 ng/mL, rising to 34.5 ng/mL after their taking a pinch of their usual snuff in their usual way. Both the trough and the postdosing peak were close to levels observed in a comparison group of smokers before and after a cigarette (see Figure 1). In interpretation of the results, it was suggested that the similarity was unlikely to be coincidental (Russell et al., 1981):

> To find that one group of people who sniff powdered tobacco into their noses have similar blood nicotine concentrations to those of another group who burn it to inhale its smoke suggests that the concentration of nicotine has some controlling influence. It would be a remarkable coincidence if factors such as flavor, strength of tobacco, social influences, and so on just happened to produce similar blood nicotine

Figure 1.
Average plasma nicotine levels before and after a pinch of snuff (n=7) or a cigarette (n=13). Tobacco use had been normal for both groups up to the time of the test.



Source: Russell et al., 1981; used with permission.

concentrations resulting from two such different behaviors. The most plausible explanation is that the rituals of snuffing and smoking are determined by the nicotine concentrations that they produce.

Several of these snuff users took unusually large multiple doses, as practiced in snuff-taking competitions. The mean increment in plasma nicotine observed was 54 ng/mL. In one subject, who was the current British champion, a boost of 97 ng/mL was obtained over 12.5 min (Russell et al., 1981). This man reported a very high degree of dependence. He said that he "was always on it [snuff]," and even woke several times each night to take a pinch.

NICOTINE INTAKE AND DEPENDENCE IN SWEDEN

The above results paint a convincing picture of the use of smokeless tobacco as a drug-taking behavior. However, subjective aspects of dependence were not systematically studied. We have recently examined nicotine absorption and measures of dependence in users of Swedish moist oral snuff (Holm et al., in press). Snuff has a long tradition in Sweden, and its use is currently on the increase, particularly among the young (Nordgren and Ramström, 1990). About 20 percent of adult Swedish males take snuff.

Two studies were conducted. The first examined absorption from a single dose of 2 g kept in the mouth for 30 min. Among 10 subjects, the peak increment in blood nicotine concentration, which averaged 14.6 ng/mL, was observed at 35 min, shortly after the snuff was discarded. The pattern of absorption showed an average increase of 9.9 ng/mL in the

first 10 min, with a slower rise thereafter, and a relatively flat plateau maintained up to 1 h. The two individuals with the most rapid absorption had increments of 12.8 ng/mL and 16.2 ng/mL in the first 5 min of dosing.

These results, which are similar to findings from the United States (Benowitz et al., 1988; Gritz et al., 1981), showed substantial absorption of nicotine and indicated that a blood specimen taken between 5 and 15 min after the snuff is discarded should adequately capture the peak blood nicotine level. Thus, these results were used to inform the design of the second study, which combined measures of nicotine uptake and subjective dependence in regular snuff takers (n=27) and cigarette smokers (n=35).

On a day of normal snuff use or smoking, blood specimens were taken from snuff users 5 to 15 min after they discarded a pinch of the subjects' usual snuff taken in the usual way, and from cigarette smokers 1 min after their smoking a cigarette of their regular brand. A questionnaire assessed various aspects of dependence. The postdosing nicotine concentrations were similar in the snuff users and smokers (36.6 ng/mL and 36.7 ng/mL, respectively) and were also similar to the earlier findings with British dry snuff users (Russell et al., 1981). On questionnaire measures of dependence, there were no significant differences between the snuff users and smokers in self-assessed addiction, craving for tobacco, or difficulty in giving up. The majority in each case rated themselves as fairly or extremely addicted, they frequently or always craved when without their snuff or cigarettes, and they anticipated that giving up would be very difficult. However, the snuff users found their habit much more enjoyable (16 of 27 rated it as "extremely enjoyable," compared with 3 of 35 smokers, $p < 0.0001$) and rated enforced abstinence for an hour or two as more unpleasant. For their part, the smokers were significantly more likely to have their first cigarette of the day before tea or coffee than were the snuff users ($p < 0.01$).

The picture that emerges from these results is of regular snuff users and cigarette smokers as being remarkably similar in both nicotine intake and dependence. Latency to first tobacco use of the day, which is perhaps the best indicator of dependence among cigarette smokers (Heatherton et al., 1989), was shorter in the smokers, but it seems likely that this disparity reflects the incompatibility between taking snuff and ingesting food or drink rather than any difference in dependence. Of more interest is the apparently greater enjoyment of snuff use than of smoking. Rather than resulting from intrinsic differences in the rewarding qualities of the two habits, it may be that cigarette smokers now carry with them a permanent awareness of the health risk and the increasingly unfavorable climate of social opinion. If snuff users, as seems likely, view their habit as safer than smoking, they are that much freer to indulge without worry or guilt.

Limitations on the generalizability of these findings stem from the small sample size and the possibility that both the snuff users and cigarette smokers might not have been representative of the wider population of users. Nevertheless, there is a strong indication that among groups of snuff users and smokers matched for nicotine levels, subjective dependence is also likely to be similar.

CESSATION OF SMOKELESS TOBACCO USE

The data reviewed so far lead to the conclusion that nicotine exerts a controlling influence on the maintenance of smokeless tobacco use and that regular users experience levels of dependence similar to those of tobacco smokers. But it does not necessarily follow that cessation of smokeless tobacco use will be equally difficult. It could be the same, more difficult, or less difficult. One factor that might contribute to making cessation more difficult is the perception that risks to health from smokeless tobacco are lower. Motivation to quit and level of dependence are not entirely independent in their effects on probability of cessation. At a given level of dependence, a lower level of concern about potential damage to health will reduce the discomfort the person is prepared to tolerate to achieve cessation. On the other hand, it has been suggested that the lack of bolus effects and the lower frequency of reinforcement from smokeless tobacco may make it easier to quit than cigarettes (Hatsukami, 1991; West and Krafona, 1990).

Only limited data are available on acute withdrawal effects from smokeless tobacco. Hatsukami and associates (1987) reported a range of withdrawal symptoms, including craving for tobacco, and raised total scores on self-rated and observer-rated checklists. However, the symptoms were less intense and fewer in number than among a comparison group of cigarette smokers. Decrements in performance measures have also been reported after short-term withdrawal from smokeless tobacco (Keenan et al., 1989). There is an urgent need for further studies in this area.

The scope for successful long-term cessation is even less clear. Among adolescents, 30 percent of smokeless tobacco users believed that quitting their habit would be very difficult, compared with 23 percent of cigarette smokers (Brownson et al., 1990). In the 1986 Adult Use of Tobacco Survey in the United States, 39 percent of current users of smokeless tobacco had attempted to quit, and of these, 47 percent reported experiencing difficulty in doing so (Novotny et al., 1989). The implications of these findings for actual cessation are unclear. Few cessation studies have been undertaken, and those on a small scale (Eakin et al., 1989; Glover, 1986).

FUTURE RESEARCH NEEDS

A number of studies have examined the prevalence of smokeless tobacco use, both in the general population and in subgroups such as male adolescents (US DHHS, 1989). However, dependence, which in conjunction with prevalence of use and health risks will determine the extent of future morbidity and mortality, has received less attention. Available evidence indicates that dependence on smokeless tobacco may be no less tenacious than dependence on cigarettes. This conclusion is based on a limited range of studies on relatively few subjects. A clearer picture will emerge if future surveys include a number of items to assess the degree of subjective dependence. It would also be informative to look not only at whether users of smokeless tobacco see their habit as a threat to health, but also at how hazardous they perceive it to be in comparison with cigarette smoking and the extent to which they see it as a personal risk. These factors have important implications for motivation to quit.

The extent and severity of withdrawal symptoms and ways of facilitating long-term cessation of smokeless tobacco use are important areas for future research. If the analogy with cigarette smoking is valid, the majority of those who wish to quit will do so by themselves, without assistance. This means that motivation derived from public health campaigns will be crucial, and much will depend on epidemiologists' clarifying issues such as the magnitude of the excess mortality attributable to long-term use of smokeless tobacco.

For those who do seek help, there would seem to be a natural affinity between smokeless tobacco use and nicotine replacement methods. Nicotine chewing gum is itself an oral tobacco product, though purified of carcinogens. Nicotine skin patches, which give substantial plateau levels of blood nicotine without rapid absorption and without providing a behavioral ritual, may also have a part to play.

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