

Studies in Sweden

Modéer, Lavstedt, and Åhlund studied the oral health effects of smoking and snuff use in 232 Swedish school children ages 13 to 14 years (119 boys and 113 girls) (36). Thirteen (11 percent) of the boys used snuff. The children were interviewed regarding their tobacco and tooth-brushing habits, and examiners (blind to the interview results) clinically assessed the degree of gingival inflammation, oral hygiene, and the presence of calculus (discussed in the next section). Standardized indices were used to assess all oral conditions. Controlling for the presence of dental plaque, gingival inflammation was the only variable that was significantly different between snuff users and nonusers. Snuff use was directly correlated with the degree of gingival inflammation. The gingival inflammation noted was related to the site of smokeless tobacco placement.

Discussion

The relationship of smokeless tobacco use and the health of gingival and periodontal tissue has received minimal study. Because of the variation in study designs and diagnostic criteria, comparisons between available studies are inappropriate. Thus the effects of smokeless tobacco use on these tissues are not clearly understood.

With regard to gingivitis, one cross-sectional study noted no difference between users and nonusers (9). Another study, however, emphasized that there was a significant difference between users and nonusers and that snuff use was directly correlated with the degree of gingival inflammation (36).

Gingival recession is a common finding among users of smokeless tobacco/snuff. In the U.S. cross-sectional studies, gingival recession was found in 25.6 to 60 percent of teenage users (7-9). In the two Colorado studies, all the gingival recession was specific to the site of tobacco placement (25.6 and 26.8 percent) (8). In the Georgia study, only 6.6 percent of the gingival recession was in the area of tobacco placement (9). In addition, several case reports have identified gingival recession at the site of habitual tobacco placement (10-13).

Between 76.6 and 86.6 percent of smokeless tobacco users who had gingival recession also had concomitant mucosal pathology (7,8). These soft tissue changes were found at the site of habitual tobacco placement.

Salivary Glands

Smokeless tobacco or its components may contribute to degenerative changes and severe damage, such as undifferentiated carcinoma, to the salivary glands and excretory ducts of humans and mice (18,20,28,37). In a study that assessed the formation of tobacco-specific nitrosamines from the major tobacco alkaloid nicotine, Hecht et al., reporting from the histologic evaluation, noted two undifferentiated carcinomas of the

salivary glands in two groups of mice that were given injections of nitrosonornicotine (NNN) in saline or trioctanoin (37). Because of the uncommonness of salivary tumors in strain A mice, Hecht et al. concluded that the tumors were probably a result of systemic administration of NNN.

Sialadenitis and degenerative changes in minor salivary glands were found in 16 of 50 habitual snuff dippers with a greater number belonging to the groups that were classified clinically as having the most severe snuff-induced lesions (18) (table 1). The findings from this study included a decrease in oxidative enzyme activities and indications of metabolic atypia that were based on enzyme histochemical tests. The salivary glands appeared to manifest more damage than the oral epithelium from snuff use. Variations in degrees of effect may be attributed to the variations in snuff dipping habits and brands of snuff.

In a recent study by Greer and his colleagues (20) (table 1), 45 smokeless tobacco users ages 13 to 74 years were clinically and histomorphologically assessed for the effects of smokeless tobacco on the oral tissues. Of 45 tissue specimens, 18 included salivary gland tissue. Damage in the form of sialadenitis and other degenerative changes in salivary glands was shown in 4 of the 18 specimens. A consistent pattern for chronic sialadenitis was not found among any of the age groups. The authors did not specify the other degenerative changes. However, four patients, ages 21, 25, 50, and 60 years, demonstrated either a mild, moderate, or severe salivary gland fibrosis. The most severe salivary gland fibrosis was found in the 21-year-old subject who was considered a short-term smokeless tobacco user; a definition for short-term user was not provided. Unlike the findings of Hirsch, Heyden, and Thilander (18), salivary gland fibrosis or changes were not related to the stage (degree) of the clinical lesion. The authors concluded that there is no doubt that salivary gland fibrosis can be shown and that it is likely to be related to the damage from smokeless tobacco. They also commented that "It is likely that the degree of salivary gland fibrosis and degenerative change, along with sialadenitis, may be a factor that is associated with tobacco brand rather than with a generalized reaction caused by all tobacco."

Included among the many questions concerning the effects of smokeless tobacco use on the salivary glands is that of changes on the flow and buffering capacity of saliva. In a sample of 48 Finnish snuff users ages 17 to 21 years (mean 18.9), the resting and stimulated salivary flow was measured (21) (table 1). The subjects refrained from the use of snuff for 1 hour before collection of saliva. The saliva of 10 nonusers was similarly collected. The statistically significant findings demonstrated a higher resting salivary flow of snuff users compared with controls. Although the stimulated salivary flow was also higher among the snuff users than the controls, this difference was not statistically significant. Buffering capacity was the same between the two groups. Although

these findings offer additional information regarding the effects of smokeless tobacco on the salivary glands, the clinical significance of these effects has not been systematically assessed, nor have the outcome differences related to the different products. Replication studies of these findings are needed before firm conclusions can be made.

In contrast to the effects just cited, Archard et al. were unable to identify lesions or dysfunctions associated with smokeless tobacco use (23) (table 2). These investigators carried out histochemical tests on lesions in the oral cavity that were in close proximity to the salivary glands. These tests revealed no evidence of an inflammatory reaction associated with the glands.

Discussion

The interpretation of data within this general area requires caution. Limited evidence suggests a possible relationship between the use of snuff and damage to the salivary glands. Should this be the case, the loss of salivary gland function can result in the decreased production of saliva and the ultimate loss of a protective buffer for the oral epithelium and the teeth against numerous exogenous factors such as infectious agents, including dental caries.

THE EFFECTS OF SMOKELESS TOBACCO USE ON TEETH

Background and Definitions

This section of the chapter addresses the role of various forms of smokeless tobacco in causing or contributing to diseases or conditions of the teeth. Specific effects that are examined include dental caries, abrasion, erosion, plaque and calculus buildup, and staining. For purposes of discussion, definitions are offered for a number of terms that are considered to represent commonly held concepts of diseases and conditions of the teeth as evidenced in the relevant scientific literature.

- Dental caries—Clinically detectable cavitation of the coronal or root surfaces of the tooth that is caused by acid demineralization of colonizing bacteria on tooth surfaces.
- Abrasion—Clinically evident wear of the coronal portion of teeth either generally or focally that appears excessive for a patient of a given age. This is a mechanical effect that is caused by the action of abrasive substances or objects during normal functioning or by oral habits.
- Erosion—Loss of tooth structure that is attributable to a chemical agent.
- Plaque—Bacterial-laden, proteinaceous material that is continually deposited in the oral cavity through the proliferation of bacterial types.

- Calculus—A concretion that forms on the coronal and exposed root surfaces of teeth through the calcification of bacterial plaques.
- Staining—An extrinsic stain deposit that results in discoloration on tooth surfaces.

Dental Caries

Evidence for the effects of smokeless tobacco use on the teeth is available from several cross-sectional studies (table 1), from a limited number of case reports (table 2), and from a limited number of related investigations of the potential for constituents of smokeless tobacco to serve as predisposing or etiologic factors in the development of dental caries.

As previously mentioned, Offenbacher and Weathers reported on the oral soft and hard tissue effects of smokeless tobacco use in a study population that comprised 565 males with a mean age of 13.8 years (9). This population typifies the age group that is commonly described as “the cavity-prone years.” Although caries rates expressed as decayed, missing, or filled teeth (DMFT) were higher for smokeless tobacco users without gingivitis than for nonusers without gingivitis, these differences were not statistically significant. However, when DMFT scores for smokeless tobacco users with gingivitis were compared with scores for nonusers without gingivitis, a significantly higher caries prevalence was found among users. Among students who used both snuff and chewing tobacco, the DMFT score was 6.56 ± 0.71 . This score is significantly elevated compared with scores of nonuser gingivitis-free students and the nonuser group that had gingivitis. There was a 2.4-fold increase in disease experience. In this study, the presence of gingivitis was presented as a cofactor with smokeless tobacco use in the increased prevalence of dental caries. This finding has not been reported elsewhere, and the biologic explanation is unclear.

The differences that were noted in caries rates could not be accounted for based upon differences in oral hygiene or the frequency of dental visits—two factors that could potentially affect DMFT scores. The examiners had no knowledge from the self-reported survey forms of the history of smokeless tobacco use among the group that was examined; thus, a degree of study “blindness” was attained. Absolute blindness in these types of surveys is difficult because it is likely that some evidence of smokeless tobacco use (e.g., tobacco residues, stain, odor, and soft tissue effects) is observable. No quantifiable dose-response effect for smokeless tobacco use and dental caries was reported in this study. Dental caries is highly age dependent, and no age adjustment was made in the statistical analysis.

A cross-sectional study by Greer and Poulson of 1,119 teenage smokeless tobacco users and nonusers from urban Colorado demonstrated neither “tobacco-associated dental caries” nor occlusal or incisal abrasion of the teeth (7). This finding is not surprising because

abrasive effects are cumulative and would likely require a number of years to become evident. The abrasion that has been reported in smokeless tobacco users has been in adults who have used smokeless tobacco products, generally leaf and plug forms of tobacco, for years (10,13). The Greer and Poulson study reported a single case of cervical erosion on the mandibular central incisors.

Some case reports have implied a causative role for smokeless tobacco in the development of dental caries (38,39), while others have postulated a potential protective effect from caries (13,40). The presumed mode of protection would be through a greatly increased salivary flow that may provide a buffering action. Additionally, there is evidence that various forms of smokeless tobacco contain fluoride, from a few tenths to several parts per million, which may offer some cariostatic protection (41). At the same time, various types of smokeless tobacco contain up to five different forms of caries-promoting sugars (42). Two studies reported that constituents in smokeless tobacco products either cause a proliferation of caries-producing bacteria in vitro or, at the least, do not inhibit bacterial growth in vitro (43,44). The fluoride and sugar contents of smokeless tobacco vary by product type (41). This may explain the inconsistent and equivocal results obtained by different investigators. Variations in reported caries rates, if truly reflective of the larger population of smokeless tobacco users, may represent the clinical outcome of a number of antagonistic or synergistic factors that operate while smokeless tobacco is used.

Other Hard Tissue Effects

Plaque, calculus, and staining are extrinsic factors that may be associated with smokeless tobacco use. This is clinically important because dental plaque and calculus that is coated with plaque harbor bacteria that can produce acids and toxins and thus bring about dental caries and diseases of the periodontal structures. The staining of teeth, restorations, and prosthetic appliances have been described as resulting from smokeless tobacco use (13,22,45,46). Van Wyk also reported a constant finding of chronic inflammation of tooth pulps that were extracted from oral snuff users (22). He attributed this as being "probably due to the irritation of the snuff overlying the exposed dentine and cementum." No quantifiable evidence currently documents the risk of smokeless tobacco use compared with nonuse in the development of plaque, calculus, or staining or the relationship of staining to oral disease conditions.

CONCLUSIONS

1. Smokeless tobacco use is responsible for the development of a portion of oral leukoplakias in both teenage and adult users. The degree to which the use of smokeless tobacco affects the oral hard

and soft tissues is variable depending on the site of action, type of smokeless tobacco product used, frequency and duration of use, predisposing factors, cofactors (such as smoking or concomitant gingival disease), and other factors not yet determined.

2. Dose response effects have been noted by a number of investigators. Longer use of smokeless tobacco results in a higher prevalence of leukoplakic lesions. Oral leukoplakias are commonly found at the site of tobacco placement.
3. Some snuff-induced oral leukoplakic lesions have been noted upon continued smokeless tobacco use to undergo transformation to a dysplastic state. A portion of these dysplastic lesions can further develop into carcinomas of either a verrucous or squamous cell variety.
4. Recent studies of the effects of smokeless tobacco use on gingival and periodontal tissues have resulted in equivocal findings. While gingival recession is a common outcome from use, gingivitis may or may not occur. Because longitudinal data are not available, the role of smokeless tobacco in the development and progression of gingivitis or periodontitis has not been confirmed.
5. Evidence concerning the effects of smokeless tobacco use on the salivary glands is inconclusive.
6. Negative health effects on the teeth from smokeless tobacco use are suspected but unconfirmed. Present evidence, albeit sparse, suggests that the combination of smokeless tobacco use in individuals with existing gingivitis may increase the prevalence of dental caries compared with nonusers without concomitant gingivitis. Reports of tooth abrasion or staining have not been substantiated through controlled studies; only case reports are available.

RESEARCH NEEDS

The review of the literature for this component of the report has identified the need for research in each of the areas discussed: the oral soft tissues, the periodontium, the salivary glands, and the teeth. Basically, the effects of the various types and forms of smokeless tobacco in all age groups should be investigated. Controlled studies and comparisons between users and nonusers of smokeless tobacco are needed. Established criteria for assessing tissue changes and disease presence should be applied to permit comparability between studies.

Studies should include the identification and control of variables that also may affect these tissues. Such variables may include alcohol use, diet, oral hygiene practices, microbial flora changes, and salivary flow rate, composition, and pH. In addition to these variables, consideration should be given to the effects of concurrent disease states. For example,

the effects of smokeless tobacco on dental caries in the presence or absence of gingivitis should be investigated.

The natural history of smokeless tobacco-induced lesions resulting from continued, intermittent, and discontinued smokeless tobacco use needs investigation. Histopathologic evaluations and clinical examinations to determine the natural history of oral leukoplakia/mucosal pathology and salivary gland pathology are desirable to understand completely the extent and severity of smokeless tobacco oral effects.

In general, incidence and prevalence studies should be implemented. Prospective study designs should be pursued to assess the temporal relationship between smokeless tobacco use and various health effects. In addition, dose-response studies are needed to assess dose in terms of both duration of use (in months and years) and daily exposure (in minutes and hours).

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Chapter 4.

NICOTINE EXPOSURE: PHARMACOKINETICS, ADDICTION, AND OTHER PHYSIOLOGIC EFFECTS

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INTRODUCTION

This chapter examines the consequences of exposure to nicotine from smokeless tobacco. It draws from the vast literature on the effects of nicotine delivered via smoking and intravenously and includes recent evidence of the effects of orally delivered nicotine.

The first section describes the pharmacokinetics of nicotine, including absorption, distribution, and elimination. The data presented indicate that nicotine is present in smokeless tobacco in significant amounts and that users attain blood levels of nicotine similar to those produced by cigarette smoking.

The second section reviews the established evidence that nicotine is an addictive and dependence-producing substance, having a number of important characteristics in common with prototypic addictive and dependence-producing substances, as well as substantial experimental evidence of its abuse liability and dependence potential. 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. In addition, very recent studies provide direct confirmation that nicotine delivered orally from smokeless tobacco and nicotine chewing gum is addictive, producing abuse liability and dependence potential.

The final section of the chapter reviews the multisystem physiologic effects of nicotine and examines the evidence pertaining to the potential contributory role of nicotine in the causation of several diseases.

PHARMACOKINETICS OF NICOTINE

Levels of Nicotine in Smokeless Tobacco

Tobacco is a plant product, and therefore differences exist in nicotine content among and within different strains of tobacco. Nicotine content among smokeless tobacco products also differs: moist snuff contains 4.56 to 15.1 mg nicotine per gram (1); plug tobacco has been measured to contain 17.2 mg per gram (2). Assuming a daily consumption of 10 grams of smokeless tobacco, the habitual user can be exposed to roughly 130 to 250 mg nicotine per day, of which varying amounts may be absorbed. By comparison, cigarette tobacco averages 15 mg nicotine per gram or 9 mg nicotine per cigarette (3). A person who smokes a pack of cigarettes per day therefore can be exposed to 180 mg nicotine per day.

Absorption of Nicotine

Nicotine is a weak base (pKa 7.9). In its ionized form, as in the acidic environment of most cigarette smoke, nicotine crosses membranes poorly. As a consequence, there is virtually no buccal absorption of nico-

tine from cigarette smoke. In contrast, smokeless tobacco products are buffered to an alkaline pH that facilitates absorption.

The rate of absorption of nicotine from smokeless tobacco depends on the product and the route of administration. With fine-ground nasal snuff, blood levels of nicotine rise almost as fast as those that are observed after cigarette smoking (4). The rate of nicotine absorption with the use of oral snuff (and presumably chewing tobacco) is more gradual (5).

People who use oral smokeless tobacco, particularly those who chew tobacco, generate large amounts of saliva, some of which is expectorated and some of which is swallowed. Due to first pass metabolism in the liver following absorption from the intestines, the bioavailability of swallowed nicotine is approximately 30 percent (6). By changing how much is chewed, how much is held inside the mouth, and how much saliva is expectorated or swallowed, the user of smokeless tobacco has considerable control over the dose of nicotine that is absorbed.

Distribution of Nicotine

Smoking is a unique form of drug administration in that entry into the circulation is through the pulmonary rather than the portal or systemic venous circulations. The lag time between smoking and the appearance of nicotine in the brain is even shorter than after intravenous injection. Nicotine enters the brain quickly, but then brain levels decline rapidly as it is distributed to other body tissues. The rapid brain uptake of nicotine from smoking allows easy puff-to-puff titration of desired nicotine effects and partly may explain the highly addictive nature of cigarette smoking.

In contrast, the concentrations of nicotine that enter the brain from smokeless tobacco use are likely to be lower (6), and the pharmacologic effects may differ. The rate of exposure to psychoactive drugs is an important determinant of their effects. Thus there could be differences in the effects of nicotine that is taken by smoking compared to using smokeless tobacco, even with the same average body concentrations of nicotine.

Nicotine Elimination

Nicotine is rapidly and extensively metabolized primarily in the liver but also to a small extent in the lung and kidney. Renal excretion depends on urinary pH and urine flow and accounts for 2 to 35 percent of total elimination (7,8). The half-life of nicotine averages 2 hours, although there is considerable individual variability that ranges from 1 to 4 hours (9). The major metabolites of nicotine are cotinine and nicotine-N-oxide. Neither metabolite appears to be pharmacologically active (8). Because of its long half-life, cotinine is commonly used as a marker of nicotine intake in survey and cessation studies. It should be recognized, however, that first pass metabolism of swallowed nicotine

may result in cotinine levels that are disproportionately higher than nicotine levels with the use of smokeless tobacco compared to the use of cigarettes.

Nicotine and Cotinine Levels in Users of Smokeless Tobacco

Blood or plasma concentrations of nicotine in cigarette smokers who were sampled in the afternoon generally ranged from 10 to 50 ng/ml (10). The increment in blood nicotine concentration after a single cigarette is smoked ranges from 5 to 30 ng/ml, depending on how the cigarette is smoked (11,12).

In users of moist oral snuff or chewing tobacco, the levels of nicotine increase an average from 2.9 to 21.6 ng/ml during 8 hours of repeated use (1). In habitual users of nasal snuff, blood levels of nicotine increased on average by 12.6 ng/ml after a single dose of snuff, and levels averaged 36 ng/ml after multiple doses (4). Similarly, blood cotinine concentrations averaged 197 ng/ml and 411 ng/ml in groups of oral and nasal tobacco users, respectively, compared to an average cotinine level of 300 ng/ml for cigarette smokers described in many studies (1,4). These comparisons indicate that the intake of nicotine and nicotine levels in habitual users of smokeless tobacco are similar to those that are observed in habitual cigarette smokers.

Time Course of Nicotine Turnover During Daily Tobacco Use

Tobacco use is commonly considered to be a process of intermittent dosing of nicotine, which in turn is rapidly eliminated from the body. Smoking produces considerable variations from highest to lowest blood nicotine levels from one cigarette to the next cigarette. However, consistent with a half-life of 2 hours, nicotine accumulates over 6 to 8 hours of regular smoking, and nicotine levels persist overnight, even as the smoker sleeps (13). The same accumulation is probable with repeated smokeless tobacco use. Thus as with the smoker, the smokeless tobacco user may be exposed to nicotine for 24 hours each day.

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NICOTINE ADDICTION ASSOCIATED WITH SMOKELESS TOBACCO USE

Background and Definitions

Clinical observations and data, historical anecdotes, and sworn testimony all support the conclusion that some users of smokeless tobacco are unable to abstain permanently from smokeless tobacco, even when ill health is apparent (1). Such observations suggest that smokeless tobacco use can become a form of drug addiction or dependence.*

* The terms "addiction and dependence" will be used almost interchangeably throughout this section. While many argue the value of one of these terms over the other, it is important to note that in the context of this chapter they address the question of whether nicotine resulting from smoking or smokeless tobacco use leads an individual to lose voluntary control over his or her use of tobacco products (i.e., does the drug cause either dependence or addiction).

This section of the report will evaluate the scientific evidence that smokeless tobacco is an addictive substance whose use results in drug dependence. *Drug dependence* as used in this review is defined in accordance with the World Health Organization's Expert Committee on Drug Dependence (2) and other recognized sources (3). Drug dependence is substance-seeking behavior that is controlled by the activity of a constituent drug in the central nervous system and displaces other behavior such that drug seeking assumes greater priority. Tolerance and physiologic withdrawal may or may not be present (2,3), and the severity of dependence may vary considerably among individuals.

The scientific standard for classifying a drug as likely to cause addiction or dependence is based on the degree to which "abuse liability" and "physical dependence potential" are present. Both terms are accepted terminology of the Committee on Problems of Drug Dependence and the Addiction Research Center (ARC) of the National Institute on Drug Abuse (4,5)* and are commonly accepted to refer to drugs whose actions are mediated by the central nervous system. *Abuse liability* refers to drug effects that contribute to compulsive self-administration, often in the face of excessive financial cost, physical and social dysfunction, and the exclusion of more socially acceptable behaviors (5,6). *Physical dependence potential* (also referred to as physiological dependence potential) pertains to the direct physiologic effects that are produced by the repeated administration of a drug that results in neuroadaptation (3,4). Neuroadaptation is characterized by demonstrated tolerance to the effects of the drug and the occurrence of physiologic withdrawal signs following the termination of drug administration.

Physiologic or physical dependence, as evidenced by physiologic and behavioral rebound (withdrawal) effects, is neither necessary nor sufficient to define drug dependence (3,5). Nevertheless, the process of drug dependence and abuse entails physical components, including physical interactions between drug and tissue in the central nervous system (specific receptors in the case of some drugs such as nicotine and opioids) that are critical †

Three lines of evidence are important to assess the abuse liability and physical dependence potential of smokeless tobacco use. The first involves inference from the systematic comparison of tobacco use (including smokeless forms) to the use of prototypic dependence-producing drugs (e.g., alcohol, morphine, and cocaine) to determine whether the

* The Committee on Problems of Drug Dependence is an internationally comprised body of researchers who provide advisory information to organizations, including NIDA, the World Health Organization, the Drug Enforcement Administration, and the pharmaceutical industry, regarding the understanding of drug dependence and the identification of dependence-producing drugs. The ARC is the intramural research laboratory of the National Institute on Drug Abuse, which has as a portion of its mandated responsibility the task of assessing the abuse liability and physical dependence potential of substances. For nearly 50 years, the ARC has been the largest research facility in the United States devoted to the problem of drug abuse and addiction.

† A concept that is central to many discussions of drug dependence is that the substance produces damage or debilitation. This aspect of tobacco dependence will not be addressed here because extensive data already exist indicating the actual toxicity of tobacco and there is widespread recognition even by tobacco users that the substance is harmful.

patterns of tobacco use, as well as the behavioral and physiologic effects of such use, are similar to those of the prototypic dependence-producing drugs. This issue is discussed below in the section entitled "Commonalities Between Tobacco Use and Other Dependence-Producing Substances."

The second line of evidence emerges from recent studies in which nicotine was evaluated using the same methods and criteria that have been used to evaluate any substance that is suspected of causing abuse and physical dependence. This deductive approach evaluates whether nicotine meets rigorous experimental criteria as a drug that has substantive liability for abuse and physical dependence potential. This issue is discussed in the section entitled "Experimental Studies of the Abuse Liability and Dependence Potential of Nicotine."

The third line of evidence comes from recently completed studies that involve direct assessments of the abuse liability and dependence potential of orally given nicotine. Examination of these studies provides indications of whether the consumption of nicotine through oral forms of administration delivers pharmacologically active quantities of nicotine to the bloodstream and whether smokeless tobacco itself meets specific criteria for abuse liability and dependence potential. This issue is discussed in the section entitled "Evidence That Orally Delivered Nicotine (Including Smokeless Tobacco) Has a Liability for Abuse and a Potential to Produce Dependence."

Taken together, the first and second lines of evidence support the conclusion that smokeless tobacco contains an addictive substance. The third line of evidence suggests that delivery of the addictive substance (nicotine) in the form of smokeless tobacco does not alter its addictive properties.

Commonalities Between Tobacco Use and Other Addictive Substances

The assertion that tobacco use can occur as a form of drug addiction rests firmly on the observed commonalities between the use and effects of tobacco and the use and effects of addictive substances such as alcohol, opium, and coca. Systematic reviews of these commonalities have been published (7-11), and the major points that tobacco and addictive substances have in common are as follows:

- A centrally (CNS) active substance (drug) is delivered.
- Discriminative (subjective) effects are centrally mediated.
- The substance (drug) is a reinforcer for animals.
- The patterns of acquisition and maintenance of substance ingestion are orderly.
- The patterns of self-administration of the substance are orderly.

- The patterns of self-administration of the substance vary as a function of the dose that is consumed.
- Tolerance to the behavioral and physiologic effects of the substance develops with repeated use (neuroadaptation).
- Therapeutic effects may be produced by the substance.
- The treatment of addiction resulting from the substance (drug) involves similar strategies.

The evidence concerning tobacco and these factors is presented in the following subsections.

Tobacco Use Delivers a Centrally Active Substance—Nicotine

The fundamental commonality between tobacco use and the use of known addictive substances is the delivery of a chemical to the central nervous system. The primary agent in tobacco, nicotine, is delivered to the central nervous system in all commonly used forms of tobacco (12). The fact that cigarette smokers will substitute smokeless tobacco, when cigarettes are not available or when the use of combustibles is restricted, certainly suggests that different forms of tobacco use produce acceptably similar effects for the user (13).

Discriminative Effects of Nicotine Are Centrally Mediated

Nicotine, like other drugs of abuse, produces dose-related effects in animals, which can be attenuated by centrally acting antagonists (14-16). When the animals confuse these effects with other drugs (i.e., effects partially generalize to other drugs of abuse), it is more likely to be a drug like amphetamine rather than a sedative-like drug (17). These findings are also consistent with data derived from studies with humans in which the dose-related effects of intravenously given nicotine were attenuated by mecamylamine pretreatment (18).

Nicotine Is a Reinforcer for Animals

Most drugs that are abused by humans are voluntarily self-administered when they are made available to animals in laboratory studies; in other words, the drug serves as a reinforcer or a reward (19,20). Such findings confirm that the physiologic effects of the drug in the central nervous system are sufficient for the substance to control behavior by virtue of its reinforcing effects. Definitive studies that were undertaken in the early 1980's support this statement. As seen in table 1, nicotine has now been shown to function as a reinforcer for five non-human animal species and under a variety of conditions (21,22). Furthermore, its functional behavioral effects are similar to those engendered when other drugs of abuse (e.g., cocaine) serve as reinforcers.

Patterns of Acquisition and Maintenance of Tobacco Use Are Orderly

The use of tobacco, like that of prototypic addictive substances, is often initiated due to peer influences (23). The contribution of social

TABLE 1.—Summary of Reports in Which Nicotine Was Available Under Intravenous Drug Self-Administration Procedures

Study	Species	Reinforcement Schedule	Main Finding	Comment
Deneau and Inoki (1967)	Rhesus Monkey	Fixed-ratio 1 (FR 1). Several doses of nicotine were tested.	Two monkeys initiated self-administration (S-A); the others required a priming procedure.	Currently accepted criteria to assess reinforcing efficacy were not achieved.
Yanagita, Ando, Oinuma, and Ishida (1974)	Rhesus Monkey	Experiment 1: FR 1. Several doses of nicotine and lefetamine and saline were tested.	Nicotine did not serve as a reinforcer when compared to saline or lefetamine.	—
		Experiment 2: FR 1. Several doses of nicotine were continuously available for at least 4 weeks.	Stable rates of nicotine S-A occurred in most subjects but were not clearly related to dose.	No direct test of reinforcing efficacy was done.
		Experiment 3: Progressive ratio (PR) procedures. Two doses of nicotine and saline and three doses of cocaine were tested.	At 0.2 mg/kg nicotine, response rates slightly exceeded those maintained by saline or the lowest cocaine dose (0.03 mg/kg).	Nicotine was marginally reinforcing when compared to cocaine.
Lang, Latiff, McQueen, and Singer (1977)	Hooded Rat	FR 1. Nicotine and saline were tested in food-sated and food-deprived rats.	In food-deprived (but not food-sated) rats, nicotine was a reinforcer when compared to saline.	—
Singer, Simpson, and Lang (1978)	Hooded Rat	Concurrent [(FR 1: nicotine), (Fixed-time 1 min.: food pellet)] in food-deprived rats. Subsequently, the rats were food-sated.	Food satiation decreased rate of nicotine S-A, however, nicotine was a reinforcer in both conditions.	Results were similar to those obtained when rats were similarly tested with ethanol.

TABLE 1.—Continued

Study	Species	Reinforcement Schedule	Main Finding	Comment
Griffiths, Brady, and Bradford (1979)	Baboon	FR 160 followed by 3-hr. timeout. Several doses of nicotine and saline were substituted for cocaine.	Number of nicotine injections per day did not exceed that of saline.	Caffeine, ephedrine, and a variety of other similarly tested stimulants did serve as reinforcers relative to saline in this paradigm.
Hanson, Ivester, and Moreton (1979)	Albino Rat	FR 1. Several doses of nicotine and saline were tested.	Mecamylamine (centrally acting antagonist) but not pentolinium (peripherally acting antagonist) altered S-A behavior.	Group data suggest that nicotine was a reinforcer; however, there was no clear dose-effect curve.
Latiff, Smith, and Lang (1980)	Hooded Rat	Conc (FR 1: injection) (FT 1 min.: food pellet). Several doses of nicotine and saline were tested.	Nicotine was a reinforcer relative to saline. Urine pH manipulations had mild effects on rate of S-A only during initial exposure to nicotine.	Rate of S-A was inversely related to dose during initial exposure to nicotine but not after nicotine S-A was established.
Smith and Lang (1980)	Hooded Rat	FR 1. One dose of nicotine and saline were tested.	Nicotine was established as a reinforcer both with and without a concurrent food delivery schedule in food-deprived but not food-sated rats.	—
Goldberg, Spealman, and Goldberg (1981)	Squirrel Monkey	Second order schedule FI 1 or 2 min. (FR 10: stimulus) followed by 3-min. timeout. One dose of nicotine and saline was tested.	Nicotine maintained high rates of responding. Rates decreased markedly when (1) saline replaced nicotine, (2) the brief stimuli were omitted, and (3) subjects were pretreated with mecamylamine.	Demonstrated the importance of ancillary environmental stimuli in maintaining high rates of responding.

TABLE 1.—Continued

Study	Species	Reinforcement Schedule	Main Finding	Comment
Ator and Griffiths (1981)	Baboon	FR 2 followed by 15-sec. timeout. Several doses of nicotine and saline and cocaine were tested.	Nicotine was marginally reinforcing compared to saline across a narrow dose range.	Initial dose-response curve was inverted U-shaped, and final dose-response curve was flat (from abstract of study).
Dougherty, Miller, Todd, and Kostenbauder (1981)	Rhesus Monkey	FI 16 and second order FI 1 min. (FR 4: stimulus). Several doses of nicotine and saline were tested.	Nicotine maintained higher rates of S-A than saline under the FI and second order schedules but was only a marginally effective reinforcer when continuously available.	Establishment of nicotine as a reinforcer required several months using procedures that typically require only a few days to establish cocaine or codeine as reinforcers.
Goldberg and Spealman (1982)	Squirrel Monkey	FI 5 min. Several doses of nicotine and cocaine and saline were tested.	Nicotine and cocaine were qualitatively similar reinforcers when compared to saline. Cocaine maintained higher rates of responding in one of two monkeys. Mecamylamine pretreatment reduced rates of nicotine S-A.	This study also showed that nicotine could serve as a punisher similar to electric shock.
Singer, Wallace, and Hall (1982)	Long-Evans Rat	CONC [FR 1: nicotine) (FT 1 min.: food pellet)]. One dose of nicotine was tested.	A group of rats with 6-OHDA lesions in the nucleus accumbens S-A nicotine at lower rates than a sham-lesioned group.	Extended the range of scheduled-induced behaviors that are inhibited by such lesions.