Health Consequences of Using Smokeless Tobacco: Summary of the Advisory Committee's Report to the Surgeon General

JOSEPH W. CULLEN, PhD
WILLIAM BLOT, PhD
JACK HENNINGFIELD, PhD
GAYLE BOYD, PhD
ROBERT MECKLENBURG, DDS, MPH
MARILYN M. MASSEY, MPH

Dr. Cullen is Deputy Director, and Dr. Boyd is Research Psychologist, Division of Cancer Prevention and Control, National Cancer Institute. Dr. Blot is Chief, Biostatistics Branch, Division of Cancer Etiology, National Cancer Institute. Dr. Henningfield is Chief, Biology of Dependence and Abuse Potential Assessment Laboratory, Addiction Research Center, National Institute on Drug Abuse. Dr. Mecklenburg is Assistant Surgeon General and Chief Dental Officer of the Public Health Service. Ms. Massey is Senior Associate, Prospect Associates.

Other important contributors researched the literature and wrote sections of the Surgeon General's report. They included Charles Darby, MA, Staff Coordinator for Addiction and Dependence, Prospect Associates, "Trends in Smokeless Tobacco Use"; Dietrich Hoffmann, PhD, Associate Director for Chemistry and Biochemistry, American Health Foundation, "Carcinogenesis"; Stephen B. Corbin, DDS, MPH, Chief, Dental Disease Prevention, Centers for Disease Control, Dushanka Kleinman, DDS, MScD, Special Assistant to the Associate Director for Program Coordination, Epidemiology and Oral Disease Prevention, National Institute of Dental Research, and Lireka P. Joseph, DrPH, Medical Radiation Specialist, Food and Drug Administration "Non-Cancerous and Precancerous Oral Health Effects"; Neal Benowitz, MD, Associate Professor of Medicine, Chief of Clinical Pharmacology and Experimental Therapeutics, University of California at San Francisco, and Margaret Mattson, PhD, Special Assistant for Science, Office of the Director, Division of Cancer Prevention and Control, National Cancer Institute, "Addiction and Other Physiologic Effects."

Tearsheet requests to Joseph Cullen, PhD, National Cancer Institute, Rm 4A 46, Bldg. 31, National Institutes of Health, Bethesda, MD 20894.

Synopsis

On March 25, 1986, the Surgeon General of the Public Health Service released a report that detailed the results of the first comprehensive, indepth review of the relationship between smokeless tobacco use and health. This review, prepared under the auspices of the Surgeon General's Advisory Committee on the Health Consequences of Using Smokeless Tobacco, is summarized in this article.

In the United States, smokeless tobacco is used predominantly in the forms of chewing tobacco and snuff. During the past 20 years, the production and consumption of these products have risen significantly in marked contrast to the decline in smokeless tobacco use during the first half of the century. National estimates indicate that more than 12 million persons age 12 and older in the United States used some form of smokeless tobacco in 1985, and half of these were regular users. The highest rates of smokeless tobacco use occurred among adolescent and young adult males.

Examination of the relevant epidemiologic, experimental, and clinical data revealed that oral use of smokeless tobacco is a significant health risk. This behavior can cause cancer in humans, and the evidence is strongest for cancer of the oral cavity, particularly at the site of tobacco placement. Smokeless tobacco use can also lead to the development of noncancerous oral conditions, particularly, oral leukoplakias and gingival recession. Further, the levels of nicotine in the body resulting from smokeless tobacco can lead to nicotine addiction and dependence.

IRONICALLY, WHILE CIGARETTE smoking has declined during the past 20 years, the production and apparent consumption of smokeless tobacco products have risen significantly. These increases are in marked contrast to the decline in smokeless tobacco use in the United States during the first half of this century. Smokeless tobacco products, particularly chewing tobacco and snuff, have recently emerged as popular products for the first time since the turn of the century.

The increased use and appeal of these products have raised serious questions about the health effects of this behavior. Almost 30 years after the Public Health Service's (PHS) first statement on the health effects of cigarette smoking, it is now possible to issue the first comprehensive, indepth review of the relationship between smokeless tobacco use and health. On March 25, 1986, the Surgeon General of the Public Health Service released a report on the health consequences of

Table 1. General principles in evaluating carcinogenic risk of chemicals or complex mixtures—International Agency for Research on Cancer

- Evidence for carcinogenicity in experimental animals
  Qualitative aspects:
  a. Experimental parameters under which chemical was tested.
  b. Consistency with which chemical is shown to be carcinogenic.
  c. Spectrum of neoplastic response.
  d. Stage of tumor formation in which chemical involved.
  e. Role of modifying factors.
  Hormonal carcinogenesis.
  Complex mixtures.
  Quantitative aspects; increasing incidence of neoplasms with increasing exposure.
- Evidence for activity in short-term tests:
  Use of valid test system.
  Sufficiently wide dose range and duration of exposure to the agent and appropriate metabolic system employed in test.
  Use of appropriate controls.
  Specification of the purity of the compound, and in the case of complex mixtures, source and representativeness of sample tested.
- Evidence of carcinogenicity in humans
  For studies showing positive association:
  a. Existence of no identifiable positive bias.
  b. Possibility of positive confounding considered.
  c. Association unlikely to be due to chance alone.
  d. Association is strong.
  e. Existence of dose-response relationship.
  For studies showing no association:
  a. Existence of no identifiable negative bias.
  b. Possibility of negative confounding considered.
  c. Possible effects of misclassification of exposure or outcome have been weighed.

using smokeless tobacco. This report was the work of numerous experts within the Department of Health and Human Services and in the non-Federal scientific community, prepared under the direction of the Surgeon General's Advisory Committee on the Health Consequences of Using Smokeless Tobacco. It is scheduled for final publication in mid-June 1986.

This article is a summary of that report. It reviews the background, methods, findings, and conclusions of the Advisory Committee's efforts in completing the PHS's examination of the role of smokeless tobacco in cancer, noncancerous and precancerous oral diseases or conditions, addiction, and other adverse effects.

Historical Perspective

The use of smokeless tobacco is a worldwide practice with numerous variations in the nature of the product used as well as in the customs associated with its use. In the United States, smokeless tobacco is used predominantly in the form of chewing tobacco and snuff. Chewing tobacco is chewed or held in the mouth between lip and gum. Three primary types of chewing tobacco are marketed: looseleaf, plug, and twist. Snuff has a much finer consistency than chewing tobacco and is held in place in the mouth without chewing. It is marketed in both dry and moist forms. The predominant mode of use of these nonsmoked tobaccos is oral, although dry snuff may be placed or inhaled into the nasal cavity. However, tobacco sniffing has been and remains a rare practice in the United States.

Smokeless tobacco was used in the American colonies in the early 1600s after snuff made its way from the Jamestown Colony in Virginia in 1611 through the efforts of John Rolfe (*1*). Tobacco chewing, however, was not reported until a century later in 1704 (*2*).

Scientific observations concerning the health effects of smokeless tobacco use were first noted in 1761 by John Hill, a London physician and botanist who reported five cases of polypuses, a "swelling in the nostril that was hard, black and adherent with the symptoms of an open cancer" (*3*). He concluded that nasal cancer could develop as a consequence of tobacco snuff use (sniffing).

Evidence that suggested a possible association between smokeless tobacco use and oral conditions in North Americans and Europeans was not reported until 1915 when Abbe identified several tobacco chewers among a series of oral cancer patients and commented that smokeless tobacco use might be a risk factor for this cancer (*4*). In the late 1930s in Sweden, Ahblom observed that more patients with buccal, gingival, and "mandibular" cancers than with other cancers reported the use of snuff or chewing tobacco (*5*). In the United States, case reports of oral cancer among users of snuff or chewing tobacco appeared in the early 1940s (*6*). The first epidemiologic study of smokeless tobacco was not conducted until the early 1950s (*7*). Since that time, several scientists have described a pattern of increased risk of oral cancer among smokeless tobacco users.

Investigations of other possible health effects of smokeless tobacco use (for example, noncancerous and precancerous oral effects, addiction, and other physiologic consequences) are more recent subjects of scientific inquiry. Such research has been undertaken primarily in the past two decades.

A brief review of the health consequences of smokeless tobacco was presented in the 1979 Surgeon General's report on smoking and health (*8a*). Since that review, the results of additional

studies addressing the health consequences of smokeless tobacco uses have become available, and they provide the basis for this comprehensive review.

Review Methods

For the purpose of evaluating the scientific evidence to be included in the review, the Advisory Committee employed the following criteria to determine causality. The same criteria have been used in a number of Surgeon General's reports on smoking during the past two decades:

- consistency of the association—similar observations by a number of independent investigators, at different times, and using different methods of study.
- strength of the association—high ratio of disease rate for the population exposed to the suspected risk factor compared to the population not exposed to the risk factor.
- specificity of the association—the precision with which one component of an associated pair predicts the occurrence of the other.
- temporal relationship of the association—exposure to the suspected etiologic factor preceding the disease.
- coherence of the association—observations consonant with all else that is known about the disease.

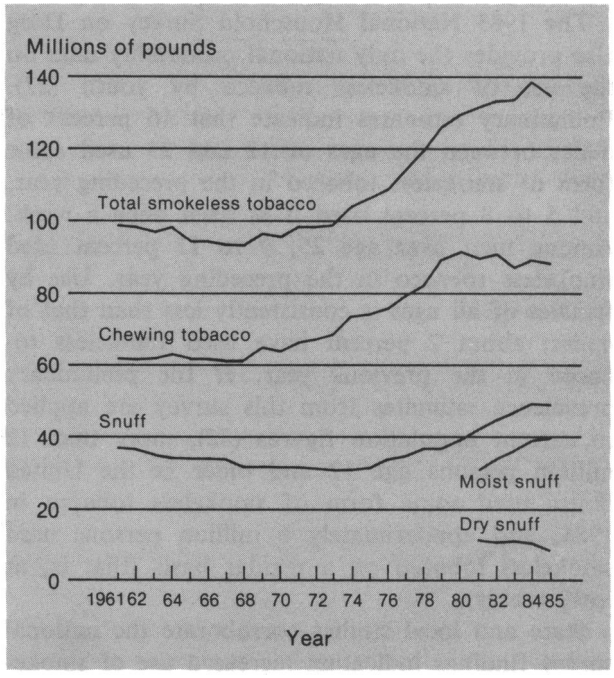
In addition to these criteria, the general principles employed by the International Agency for Research on Cancer (IARC) in evaluating the carcinogenic risk of chemicals or complex mixtures (table 1) were used as needed to supplement the criteria for primary causation (*9*).

Trends in Smokeless Tobacco Use

The use of smokeless tobacco products in the United States was widespread until the end of the 19th century. With the advent of antispitting laws, loss of social acceptability, and increased popularity of cigarette smoking, its use declined rapidly during much of this century. However, recent data indicate a resurgence in smokeless tobacco habits, particularly among teenage and young adult males.

Trends in production and sales. United States Department of Agriculture (USDA) records on the annual production and sales of smokeless tobacco serve as indicators of the population's consumption patterns. Because sales figures closely resemble those for production, only production data are reported. Between 1944 and 1968, total smokeless tobacco production declined 38.4 percent from 150.2 to 92.5 million pounds (*10*). Subsequently, production climbed to 135.6 million pounds in 1985, an increase of 42 percent since 1968 (*10–16*). Figure 1 depicts temporal trends in the quantities of smokeless tobacco (by type) that were manufactured in the United States from 1961 to 1985.

Figure 1. Manufacturing trends: quantities of smokeless tobacco manufactured in the United States, 1961-85



Trends in self-reported use: survey data. Surveys indicate that the highest rates of smokeless tobacco use occur among adolescent and young adult males. National data from 1964 to 1985 are available from eight different probability surveys and a survey of college students (*8b, 17–21*).

Between 1964 and 1985, the prevalence of smokeless tobacco use among adults remained fairly stable (*17–19*). However, a marked change in the age distribution of users took place during this period. In 1970, use of smokeless tobacco was most common among older men (unpublished data of the National Center for Health Statistics, National Health Interview Survey). In 1985, the highest rates of use were observed in the younger age groups (*19, 21*). Similar findings resulted from a smoking supplement to the 1985 Current Popula-

tion Survey of the U.S. census (unpublished data of the Office on Smoking and Health, PHS).

The 1985 National Household Survey on Drug Use provides the only national probability data on the use of smokeless tobacco by youth (*21*). Preliminary estimates indicate that 16 percent of males between the ages of 12 and 25 used some form of smokeless tobacco in the preceding year, and 5 to 8 percent used it at least once a week. Among men over age 25, 9 to 11 percent used smokeless tobacco in the preceding year. Use by females of all ages is consistently less than that of males; about 2 percent have used smokeless tobacco in the previous year. If the preliminary prevalence estimates from this survey are applied to current population figures (*22*), more than 12 million persons age 12 and older in the United States used some form of smokeless tobacco in 1985, and approximately 6 million persons used smokeless tobacco on a regular basis (that is, at least weekly).

State and local studies corroborate the national survey findings indicating increased use of smokeless tobacco products by young males. Although prevalence varies widely by region, use is not limited to a single region. In several parts of the country, as many as 25 to 35 percent of adolescent males have indicated current use of smokeless tobacco. Other findings of these studies include the following:

- Use of smokeless tobacco by youth is generally higher in rural than urban areas, in small communities, and in areas where there is a tradition of smokeless tobacco use (*23–25*).
- Information on smokeless tobacco use by ethnic and racial background indicates that rates for youth are comparable among Hispanic and non-Hispanic whites. Native American rates were consistently higher than those for whites and, in most locales, use was less common among Asians and blacks (*25*).
- Among youth, the likelihood of using smokeless tobacco appears to increase with age as well as over time (*23–25, 27–30*).
- Peers and family members are found consistently to be important influences on smokeless tobacco use by children and adolescents (*23,26,28, 29,31–35*).

Carcinogenesis

The Surgeon General's Advisory Committee performed a systematic review of the world's medical literature describing experimental and human evidence pertinent to the evaluation of smokeless tobacco as a potential cause of cancer. Five categories of research relevant to assessing the role of smokeless tobacco in cancer causation were addressed:

- epidemiologic studies and case reports of oral cancer in relation to smokeless tobacco use.
- epidemiologic studies of other cancers in relation to smokeless tobacco use.
- chemical constituents of smokeless tobacco.
- metabolism of constituents of smokeless tobacco.
- experimental studies involving exposing laboratory animals to smokeless tobacco or its constituents.

Because smokeless tobacco products used in different regions of the world vary considerably in composition and usage patterns, North American and European data are considered separately from Asian data. Citations to the literature from India and other Asian countries where quids containing tobacco and other ingredients are commonly used orally focus on research that attempts to distinguish tobacco from other ingredients in the quids as possible determinants of cancer risk.

Epidemiologic studies and case reports of oral cancer in relation to smokeless tobacco use. The association between smokeless tobacco use and cancer is strongest for cancers of the oral cavity. The current age-adjusted incidence rate for cancers of the buccal cavity and pharynx in the United States is approximately 11 cases per 100,000 population per year, with these tumors accounting for about 3 percent of all cancer deaths (*36*).

Numerous clinical and pathological reports published during the past four decades in the United States and elsewhere have commented on the use of smokeless tobacco by oral cancer patients, and some authors have described the entity known as snuff-dipper's carcinoma (*37–39*). These findings have provided the basis for the hypothesis that the prolonged use of snuff or chewing tobacco is associated with an increased risk of low-grade, verrucal or squamous cell carcinoma of the buccal mucosa and gingivobuccal sulcus.

The number of epidemiologic investigations in North America and Europe evaluating the relation between smokeless tobacco and oral cancer is not large, and several studies have methodologic limitations. The major concern for validity in the epidemiologic studies of smokeless tobacco and

oral cancer is uncontrolled confounding. The two primary confounding factors of concern are alcohol consumption and smoking, both strong risk factors for oral cancer (*40*). It is not clear on a priori grounds, however, to what extent alcohol consumption would be correlated with smokeless tobacco use, and the relation between smoking and smokeless tobacco use may be complex. Users of smokeless tobacco may be more likely to have been smokers at some time. On the other hand, heavy users of smokeless tobacco typically cannot be heavy users of cigarettes, so that smoking is presumably negatively correlated with smokeless tobacco use. Failure to control confounding by smoking would therefore lead to underestimates of the effect of smokeless tobacco.

Most of the epidemiologic evidence comes from several case-control studies of oral cancer (*7,41–53*). The low prevalence of smokeless tobacco use in most North American populations contributes to a low statistical efficiency in most of these studies. Good information has been obtained, however, from studies that were either very large, were conducted in an area where there was a high prevalence of smokeless tobacco use, or were analyzed according to site within the oral cavity (since the effects of snuff use appear to be highly localized).

One such study was drawn from a female population in North Carolina where exposure rates are high and potentially confounding variables could be taken into account (*41, 54–57*). This investigation revealed that oral cancer occurs several times more frequently among snuff dippers than among nontobacco users and that the excess risk of cancers of the cheek and gum may reach nearly fiftyfold among long-term snuff users. The study showed that nearly all of the tumors of the cheek and gum were due to snuff use and that it is the use of snuff that accounts for the high rates of oral cancer mortality among southern women. The pattern of increased oral cancer risk among smokeless tobacco users also has been found in case-control studies conducted elsewhere in the South and in other parts of North America (*19,20,22–26,28*), with excess risks tending to be greatest for those anatomic sites where tobacco exposures are greatest.

The increased risk of oral cancer among smokeless tobacco users is most clearly demonstrable for users of snuff. Some investigations suggest that the use of chewing tobacco may also increase the risk of oral cancer (*7,42,44,46,48*), but evidence is not as strong and risks have yet to be quantified.

Evidence from parts of Asia, where the prevalence of smokeless tobacco use is high and oral cancer is the most common tumor, indicates a strong association between the chewing of quids that contain tobacco and other substances and oral cancer. Users of quids that contain tobacco have much higher oral cancer rates than users of quids that do not; the association is not confounded by cigarette smoking, raising the possibility that smokeless tobacco per se contributes to the elevated oral cancer risk in this part of the world (*3,58–63*).

Epidemiologic studies of other cancers in relation to smokeless tobacco use. The epidemiologic studies showing an association between the use of snuff and oral cancers indicate that topical exposure of tissues to smokeless tobacco can cause cancers at the site of the exposure. Case reports of neoplasms developing in the ear (*64*) and nose (*3,65*) of persons who used snuff at these sites raise the possibility that direct exposure may increase the risk in tissues outside the oral cavity; however, insufficient epidemiologic data exist to evaluate this possibility. Other tissues that come in contact with constituents of smokeless tobacco in more dilute concentrations include the linings of the esophagus, larynx (supraglottic portion), and stomach. Results of studies of cancers of these three sites in relation to smokeless tobacco are inconclusive; however, many studies had limited power to detect small increases in risk and did not control for relevant, potentially confounding variables. However, some studies of these three cancer sites do show an increase in risk in relation to the use of smokeless tobacco (*48,52,66–73*).

Constituents of smokeless tobacco can enter the bloodstream, and some are excreted in the urine. The kidney and bladder are thus potentially exposed to these products and their metabolites but presumably in lower concentrations than are tissues of the upper aerodigestive tract. Evidence suggests that the risk of bladder cancer is not altered to any large extent in persons who use smokeless tobacco products (*49,52,73–81*), but the results from studies of kidney cancer are inconsistent (*82–84*).

In summary, evidence for an association between smokeless tobacco use and cancers outside of the oral cavity in humans is sparse. While some investigations suggest that smokeless tobacco users may face increased risks of tumors of the upper aerodigestive tract, results are currently inconclusive.

Table 2. N-nitrosamines in smokeless tobacco

1. Volatile nitrosamines
   NDMA Nitrosodimethylamine
   NDEA Nitrosodiethylamine
   NMOR Nitrosomorpholine
   NPIP Nitrosopiperidine
   NPYR Nitrosopyrrolidine
2. Nonvolatile nitrosamines
   NDELA Nitrosodiethanolamine
   NMBA Nitrosomethylbutyric acid
   NMPA Nitrosomethylpropionic acid
   NPIC Nitrosopipecolic acid
   NPIPAC Nitrosopiperidine-acetic acid
   NPRO Nitrosoproline
   NPYRAC Nitrosopyrrolidine-acetic acid
3. Tobacco-specific nitrosamines
   NAB N'-Nitrosoanabasine
   NAT N'-Nitrosoanatabine
   NNAL 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol
   NNK 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
   NNN N'-Nitrosonornicotine
   NNO 4-(Methylnitrosamino)-1-(3-pyridyl)butene-1
   Red NNA 4-(Methylnitrosamino)-4-(3-pyridyl)-1-butanol

Table 3. Permissible limits for individual N-nitrosamines in consumer products

Product	Permissible limit ppb (μg per kg)	Agency
Bacon (meat)	5	USDA[1]
Beer	5	FDA[2]
Rubber nipples of baby bottles	10	FDA[3]

[1] No "confirmable levels of nitrosamines" (reference *111*).
[2] Regulation set for N-nitrosodimethylamine (reference *112*).
[3] Regulation set for any individual volatile N-nitrosamine (reference *113*).

Chemical constituents of smokeless tobacco. In processed tobacco, more than 2,500 chemical compounds have been identified (*85*). Among these are three classes of carcinogens that are known to occur in smokeless tobacco products: N-nitrosamines (*86–102*), polynuclear aromatic hydrocarbons (*103–108*), and polonium-210 (*108–110*).

Tobacco leaves contain an abundance of amines in the form of proteins and alkaloids. Tobacco also contains up to 5 percent nitrates and traces of nitrite. Thus there is the potential for the formation of N-nitrosamines from the nitrate, nitrite, and amines during the processing of smokeless tobacco products. In tobacco, we distinguish between volatile nitrosamines, nonvolatile nitrosamines, and tobacco-specific nitrosamines (table 2). With the exception of some N-nitrosamino acids, the nitrosamines in tobacco are animal carcinogens that are formed after harvesting of the tobacco during curing, fermentation, or aging.

The most prevalent organic carcinogens are the tobacco-specific N-nitrosamines that are formed from the *Nicotiana* alkaloids during the processing of tobacco leaves. The tobacco-specific nitrosamines NNN and NNK are powerful carcinogens in rats, mice, and hamsters (*9*) and often have been detected in smokeless tobacco at levels 100 or more times higher than the regulated levels of other nitrosamines found in bacon, beer, and other consumer products (tables 3 and 4). NAB and NNAL are moderately carcinogenic, and NAT is inactive in rats in doses up to 9 millimols per kilogram (*9*). The carcinogenicity of NNO and Red NNA has not been tested.

A number of polynuclear aromatic hydrocarbons have been identified in processed tobacco. Analyses of British snuff in 1957 showed levels of 260 ppb of pyrene, 335 ppb of fluoranthene, and 72 ppb of benzo(a)pyrene (*107*). In the five most popular snuff brands in the United States that were analyzed in 1985, benzo(a)pyrene ranged from less than 0.1 to 63 ppb (*108*).

Polonium-210 has long been incriminated as a human carcinogen (*109*). In recent studies of the five leading U.S. snuff brands, polonium-210 ranged from 0.16 to 1.22 pCi per g (*108*).

Metabolism of constituents of smokeless tobacco. The tobacco-specific nitrosamines NNK and NNN are quantitatively the major known carcinogens that are present in snuff and other types of smokeless tobacco. Molecular changes that are induced in the genetic material of tobacco chewers are most likely to arise from the metabolism of these two nitrosamines. Review of the literature provides persuasive evidence that the carcinogenic nitrosamines NNN and NNK are metabolized by target tissues of experimental animals (*114–131*) and by human tissues (*132,133*) to intermediates that can modify the genetic material of the cell.

Exposure of laboratory animals to smokeless tobacco or its constituents. Chewing tobacco and extracts from various chewing tobaccos have been tested by oral administration in mice (*134*), by topical application to the oral mucosa of mice, rats, and hamsters (*135–140*), and by subcutaneous administration (*141*) and skin application to mice (*9,141–148*). These investigations failed to demonstrate significantly increased tumor production. Short application times and low-dose exposures,

however, limit the evaluation of the carcinogenicity of chewing tobacco or its extracts. Bioassays of snuff have likewise generally shown no excess cancer (*139,149–155*), although some experiments suggest that it may cause oral tumors in rats and hamsters that are infected with herpes simplex virus (*150, 152, 153*). The latter finding raises some concern in as much as 20 to 40 percent of the U.S. population have periodic occurrences of labial herpes (*156*).

Among the chemical components of snuff, the tobacco-specific nitrosamines NNN and NNK are powerful animal carcinogens. The doses of NNN and NNK that produce tumors in experimental animals are close to the doses estimated from lifetime exposure among human snuff dippers (*157,158*).

Noncancerous and Precancerous Effects

The health effects of smokeless tobacco use on the oral tissues were addressed through a systematic review of the relevant scientific literature on animal and human studies. The major areas reviewed were the effects of smokeless tobacco use on the oral soft tissues, the periodontium, and the teeth. The potential for oral tissues altered by smokeless tobacco use to transform to dysplasia and malignancy was also assessed.

Oral leukoplakia. Smokeless tobacco use is responsible for the development of a portion of oral leukoplakias (white patches or plaques of the oral mucosa) in both teenage and adult users. Studies from both the United States and Scandinavia demonstrate this association (*7,159–165*). In two studies, a higher prevalence of oral leukoplakia was found in users compared with nonusers of smokeless tobacco—22.7 percent compared with 4.7 percent (*163*) and 34.0 percent compared with 7.4 percent (*159*). In all of these studies, between 8 and 59 percent of smokeless tobacco or snuff users were found to have oral leukoplakia.

Dose-response effects have been noted by a number of investigators. The duration of use (in years) and daily exposure (in hours or minutes) to smokeless tobacco appear to be critical in the development and severity of oral leukoplakia. Three studies using similar approaches to the definition of oral leukoplakia and to the measurement of exposure noted this effect (*161,162,165*). In addition, in several studies of persons who had stopped smokeless tobacco use, the oral leukoplakia disappeared (*7,160,166,167*).

Table 4. Range of individual nitrosamines present in snuff tobaccos

Nitrosamine	Nitrosamine level ppb (μg per kg)
NNN	[1]5,800– 64,000
NNK	[1]100– 3,100
NAT	[1]3,300–215,000
NAB	[1]200– 6,700
NDELA	[2]160– 6,800

[1] Range in the leading 5 U.S. brands (1984–85).
[2] Range in 13 U.S. brands (1980–85).
SOURCES: references *88, 90, 91*.

It appears that the oral leukoplakia noted in smokeless tobacco users is found commonly at the habitual site of tobacco placement. Using a similar grading classification for snuff-induced lesions (*161,168*), all of the mucosal pathology that was noted in several studies was at the site of habitual tobacco placement (*161,162,164,165*). Similarly, the majority of the oral leukoplakia that was described in the case reports (*166,167,169–173*) was found where the tobacco was usually placed.

Transformation of oral soft tissues. Smokeless tobacco-associated lesions that have been traditionally classified as leukoplakias (white lesions) reflect varying degrees of clinical differentiation and may persist or progress with continued smokeless tobacco use. In fact, 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 have been found to develop into carcinomas of either a verrucous or squamous cell variety.

In characterizing the role of smokeless tobacco use in the clinical and histologic course of oral lesions, oral leukoplakia should be considered a dynamic changing lesion of the oral mucosa (*174*). To achieve comparability of results among investigators, a standard system for gauging epithelial dysplasia is needed. Because ethical considerations do not allow lesions to be monitored continuously from benign states to moderate and severe dysplasias and to carcinoma in situ, the next best alternative is to provide estimates of risk for malignant transformation based on empirical and clinical observations or at least to quantify descriptively the association that smokeless tobacco-induced lesions have with other lesions or other potential etiologic factors.

The body of literature on smokeless tobacco-induced lesions in the oral mucosa and their potential for malignant transformation allows for the development of a conceptual model of the natural history of smokeless tobacco-induced lesions (fig. 2). This model is a composite of various prospective, retrospective, cross-sectional, and case studies that relate to smokeless tobacco-induced lesions. It reflects progressive changes that may occur in some persons who are habitual users of smokeless tobacco and potential outcomes that could include death or disfigurement for some who use smokeless tobacco for several decades.

The data are clear that habitual smokeless tobacco use can produce mucosal lesions. It is also clear that where groups of patients with smokeless tobacco-induced leukoplakias have been followed for several years, cases of cancer have been identified (*175–177*). Finally, among studies of oral cancers in habitual smokeless tobacco users, there appears to be a consistent finding of leukoplakias either having been previously excised in the area of habitual tobacco placement (*167,176,178*) or being found concurrently and in proximity to oral cancers (*7,46,179–182*).

Gingiva, periodontal tissue, and salivary glands. The relationship of smokeless tobacco use and the health of gingival and periodontal tissue has received minimal study. Available studies of the effects of smokeless tobacco use on gingival and periodontal tissues have resulted in equivocal findings. Furthermore, variations in study designs and diagnostic criteria make comparisons between available studies inappropriate. Thus the effects of smokeless tobacco use on these tissues are not clearly understood.

While gingival recession is a common outcome from smokeless tobacco use (*161,163,171*), gingivitis may or may not occur (*163,183*). Because longitudinal data are not available, the role of smokeless tobacco in the development and progression of gingivitis or periodontitis has not been confirmed.

Evidence concerning the effects of smokeless tobacco use on the salivary glands is similarly inconclusive. Limited evidence suggests a possible relationship between the use of snuff and damage to the salivary glands (*165,177,184,185*). 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.

Teeth. Negative health effects on the teeth from smokeless tobacco use are suspected but unconfirmed (*186,187*). Present evidence, albeit sparse, does suggest that the combination of smokeless tobacco use in persons with existing gingivitis may increase the prevalence of dental caries compared with nonusers without concomitant gingivitis (*163*).

Plaque, calculus, and staining are extrinsic factors that may be associated with smokeless tobacco use (*35,171,188,189*). 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.

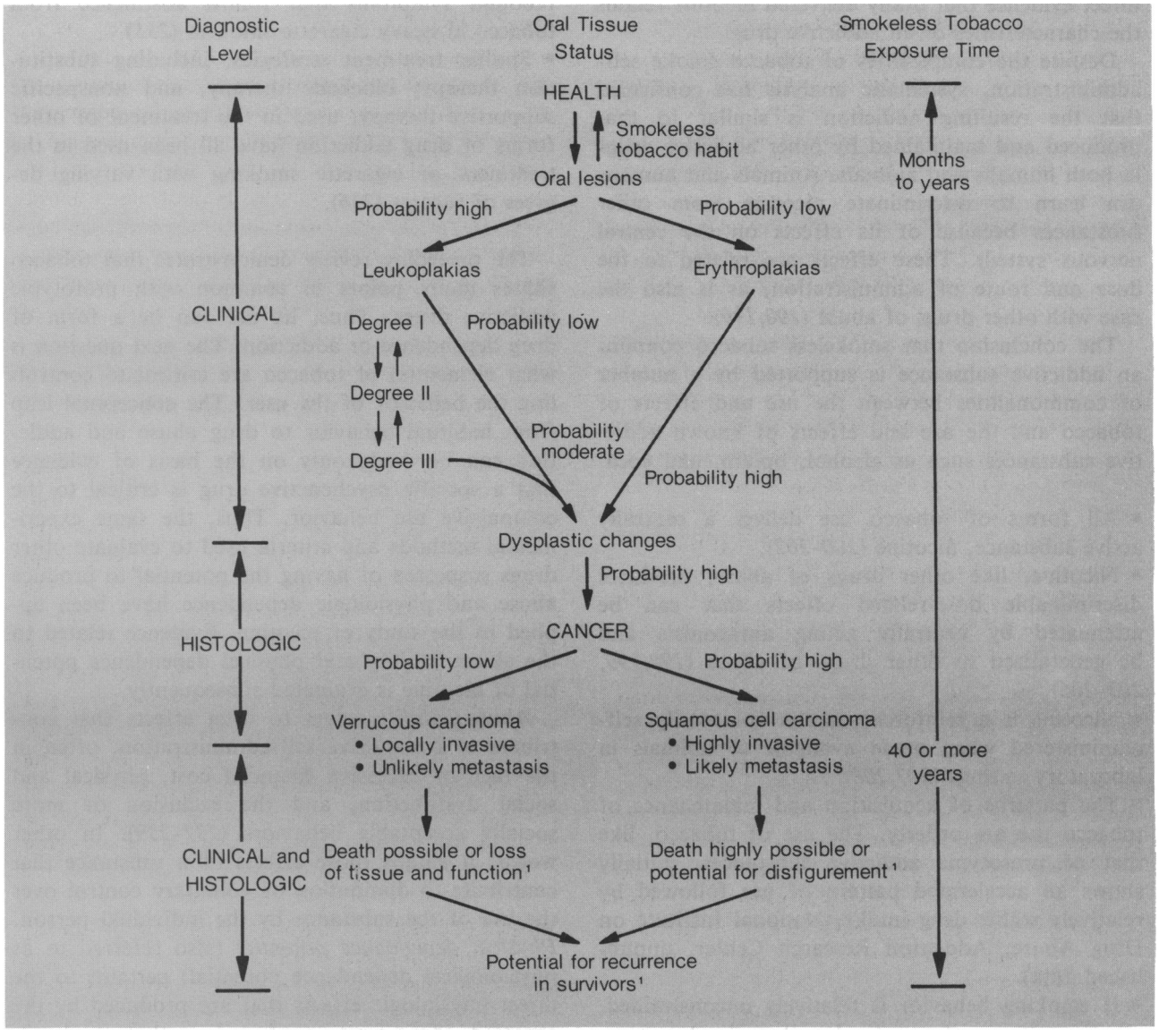
Addiction and Other Physiologic Effects

The consequences of exposure to nicotine from smokeless tobacco are examined in this section. This review 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. Three areas of research are addressed. The first describes the pharmacokinetics of nicotine, including absorption, distribution, and elimination. The second reviews the established evidence that nicotine is an addictive and dependence-producing substance. The third 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. An examination of the pharmacokinetics of nicotine (that is, nicotine absorption, distribution, and elimination) resulting from smoking and smokeless tobacco use indicates that the magnitude of nicotine exposure is similar for both. Assuming a daily consumption of 10 grams of smokeless tobacco, the habitual user can be exposed to roughly 130 to 250 milligrams (mg) nicotine per day. Within a similar range, a person who smokes a pack of cigarettes daily (*190*) would be exposed to 180 mg nicotine per day (assuming 9 mg nicotine per cigarette).

Although exposure to nicotine may be similar, the absorption and distribution characteristics of nicotine via oral smokeless tobacco use versus cigarette smoking differ. Smokeless tobacco products are buffered to an alkaline pH that facilitates absorption; more nicotine is absorbed from the use of smokeless tobacco products than from cigarette smoking. The rate of absorption of nicotine from oral snuff (and presumably chewing tobacco),

Figure 2. Conceptual natural history of oral mucosal changes associated with the use of smokeless tobacco



[1] These factors depend upon stage of diagnosis, form of treatment and continuation of habit(s).

however, is more gradual than after cigarette smoking (*191*). The direct absorption of nicotine from smoking into the pulmonary circulation, rather than through the portal or systemic venous circulation, results in a very short lag time between smoking and the appearance of nicotine in the brain. Thus, central nervous system concentrations of nicotine from smokeless tobacco are likely to be lower than from cigarette smoking (*192*).

In contrast to the absorption and distribution differences, intake of nicotine and nicotine levels in habitual users of smokeless tobacco are similar to those that are observed in habitual cigarette smokers (*193–196*). Furthermore, nicotine accumulates over 6 to 8 hours of regular smoking, and nicotine levels persist overnight (*197*). The same accumulation is probable with repeated smokeless tobacco use.

Nicotine addiction. 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. The evidence that smokeless tobacco is addicting includes the pharmacologic role of the nicotine dose in regulating tobacco intake, the commonalities between nicotine and other prototypic dependence-producing substances, the abuse liabil-

ity and dependence potential of nicotine, and the direct evidence that orally delivered nicotine retains the characteristics of an addictive drug.

Despite the complexities of tobacco smoke self-administration, systematic analysis has confirmed that the resulting addiction is similar to that produced and maintained by other addictive drugs in both humans and animals. Animals and humans can learn to discriminate nicotine from other substances because of its effects on the central nervous system. These effects are related to the dose and route of administration, as is also the case with other drugs of abuse (*198,199*).

The conclusion that smokeless tobacco contains an addictive substance is supported by a number of commonalities between the use and effects of tobacco and the use and effects of known addictive substances such as alcohol, opium, and coca.

- All forms of tobacco use deliver a centrally active substance, nicotine (*200–202*).
- Nicotine, like other drugs of abuse, produces discriminable dose-related effects that can be attenuated by centrally acting antagonists and be generalized to other drugs of abuse (*198,199, 203–206*).
- Nicotine is a reinforcer that is voluntarily self-administered when made available to animals in laboratory settings (*207,208*).
- The patterns of acquisition and maintenance of tobacco use are orderly. The use of tobacco, like that of prototypic addictive substances, initially shows an accelerated pattern of use followed by relatively stable drug intake (National Institute on Drug Abuse, Addiction Research Center, unpublished data).
- If smoking behavior is relatively unconstrained, regular patterns of use develop that closely resemble those of psychomotor stimulant self-administration in animals (*209*) and in humans (*210–213*).
- Self-administration of tobacco varies as a function of nicotine dose manipulated by changing the quantity (unit dose) (*210,214*), by pretreating the individual (animal or human) with either an agonist or antagonist (*215–218*), or by altering the rate of nicotine elimination (*219*).
- Tolerance of nicotine develops with repeated use (neuroadaptation). A variety of mechanisms account for tolerance to many of nicotine's effects, including those of a metabolic (*220*), behavioral (*221–223*), and physiologic (*224–226*) nature.
- Nicotine produces therapeutic effects, including enhanced performance on a variety of cognitive tasks (*227–229*), mood regulation (*230*), and appetite suppression (*231–234*). Nicotine gum alleviates rebound symptoms that follow abstinence from tobacco in heavy cigarette smokers (*235*).
- Similar treatment strategies, including substitution therapy, blockade therapy, and nonspecific supportive therapy, used in the treatment of other forms of drug addiction have all been used in the treatment of cigarette smoking with varying degrees of success (*236*).

The preceding review demonstrates that tobacco shares many points in common with prototypic addictive drugs. Thus, its use can be a form of drug dependence or addiction. The next question is what element(s) of tobacco are critical to controlling the behavior of the user. The conceptual leap from habitual behavior to drug abuse and addiction can be made only on the basis of evidence that a specific psychoactive drug is critical to the compulsive use behavior. Thus, the same experimental methods and criteria used to evaluate other drugs suspected of having the potential to produce abuse and physiologic dependence have been applied to the study of nicotine. Evidence related to the abuse liability and physical dependence potential of nicotine is evaluated subsequently.

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 (*237–239*). In other words, it entails those effects of a substance that contribute to diminution of voluntary control over the use of the substance by the individual person. *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 (*201,237*). 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.

It has been confirmed that nicotine can function in all of the capacities that characterize a drug with a liability to widespread abuse. Specifically, nicotine is psychoactive (*199*), producing transient dose-related changes in mood and feeling. It is a euphoriant that produces dose-related increases in scores on standard measures of euphoria (*199,238*). It is a reinforcer (or reward) in both human and animal intravenous self-administration paradigms, functioning as do other drugs of abuse (*207,240,241*). Additionally, it has been demon-

strated that nicotine via smoking not only produces these effects but causes neuroadaptation leading to tolerance and physiologic dependence (*242–247*). Taken together, these results confirm the hypothesis that the role of nicotine in the compulsive use of tobacco is the same as the role of morphine in the compulsive use of opium derivatives or of cocaine in the compulsive use of coca derivatives.

All commonly marketed and consumed smokeless tobacco products contain substantial quantities of nicotine (*193,248–250*). The nicotine is delivered to the central nervous system in addicting quantities when used in the fashion that each form is commonly used (or as recommended in smokeless tobacco marketing campaigns). The delivery of nicotine in the form of smokeless tobacco is not believed to alter the addictive properties of nicotine. There is now direct evidence that orally delivered nicotine retains the characteristics of an addictive drug (*251–253*).

Several other characteristics of tobacco products in general, including smokeless tobacco, may function to increase further the number of persons who are subject to nicotine dependence: nicotine-delivering products are widely available and relatively inexpensive; and the self-administration of such products is legal, relatively well tolerated by society, and produces minimal disruption to cognitive and behavioral performance. Nicotine produces a variety of individual-specific therapeutic actions such as mood and performance enhancement; the brief effects of nicotine ensure that conditioning occurs, because the behavior is associated with numerous concomitant environmental stimuli.

Physiologic and pathogenic effects. The exposure to nicotine from smokeless tobacco is similar in magnitude to nicotine exposure from cigarette smoking. It is, therefore, likely that those health consequences of smoking caused by nicotine also would be associated with smokeless tobacco use. Areas of particular concern in which nicotine may play a contributory or supportive role in the pathogenesis of disease include coronary artery and peripheral vascular disease (*254–258*), hypertension (*259,260*), peptic ulcer disease (*261–263*), and fetal mortality and morbidity (*264–269*).

Conclusions

After a careful examination of the relevant epidemiologic, experimental, and clinical data, the Advisory Committee concluded that the oral use of smokeless tobacco represents a significant health risk. It is not a safe substitute for smoking cigarettes. It can cause cancer and a number of noncancerous oral conditions and can lead to nicotine addiction and dependence. The major conclusions of the review follow:

'Although exposure to nicotine may be similar, the absorption and distribution characteristics of nicotine via oral smokeless tobacco use versus cigarette smoking differ. Smokeless tobacco products are buffered to an alkaline pH that facilitates absorption; more nicotine is absorbed from the use of smokeless tobacco products than from cigarette smoking.'

1. It is estimated that smokeless tobacco was used by at least 12 million people in the United States in 1985 and that half of these were regular users. The use of smokeless tobacco, particularly moist snuff, is increasing, especially among male adolescents and young male adults.

2. The scientific evidence is strong that the use of snuff can cause cancer in humans. The evidence for causality is strongest for cancer of the oral cavity, wherein cancer may occur several times more frequently in snuff dippers compared with nontobacco users. The excess risk of cancer of the cheek and gum may be nearly fiftyfold among long-term snuff users.

3. Some investigations suggest that the use of chewing tobacco may also increase the risk of oral cancer, but the evidence is not as strong and the risks have yet to be quantified.

4. Experimental investigations reveal potent carcinogens in smokeless tobacco. These include nitrosamines, polycyclic aromatic hydrocarbons, and radiation-emitting polonium. The tobacco-specific nitrosamines often have been detected at levels 100 or more times higher than U.S. Government-regulated levels of other nitrosamines permitted in foods eaten by Americans.

5. Smokeless tobacco use can lead to the development of oral leukoplakias (white patches or plaques of the oral mucosa), particularly at the site of tobacco placement. Based on evidence from several studies, a portion of leukoplakias can

undergo transformation to dysplasia and further to cancer.

6. Gingival recession is a commonly reported outcome of smokeless tobacco use.

7. A number of studies have shown that nicotine exposure from smoking cigarettes can cause addiction in humans. In this regard, nicotine is similar to other addictive drugs such as morphine and cocaine. Since nicotine levels in the body resulting from smokeless tobacco use are similar in magnitude to nicotine levels from cigarette smoking, it is concluded that smokeless tobacco use also can be addictive. Besides, recent studies have shown that nicotine administered orally has the potential to produce a physiologic dependence.

8. Some evidence suggests that nicotine may play a contributory or supportive role in the pathogenesis of coronary artery and peripheral vascular disease, hypertension, peptic ulcers, and fetal mortality and morbidity.

These conclusions are substantially in agreement with those published following a recent National Institutes of Health Consensus Development Conference on the Health Implications of Smokeless Tobacco Use (*270*). The strength of the association between the conditions just cited and smokeless tobacco use, combined with the upward trend in this behavior, should instill vigilance among public health officials and others responsible for guiding the health of our nation. It is critical that our society be made aware of the new knowledge about the health consequences of smokeless tobacco use so that informed decisions can be made regarding its use.

References

1. Christen, A. G., Swanson, B. Z., Glover, E. D., and Henderson, A. H.: Smokeless tobacco: The folklore and social history of snuffing, sneezing, dipping, and chewing. J Am Dent Assoc 105: 821–829 (1982).
2. Gottsegen, J. J.: Tobacco: a study of its consumption in the United States. Pitman, New York, 1940, p. 3.
3. Redmond, D. E.: Tobacco and cancer: the first clinical report, 1761. N Engl J Med 282: 18–23, Jan. 1, 1970.
4. Abbe, R.: Cancer of the mouth. NY Med J 102: 1–2 (1915).
5. Ahblom, H. E.: Predisposing factors for epitheliomas of the oral cavity, larynx, pharynx, and esophagus. Acta Radiol 18: 163–185 (1937). In Swedish.
6. Friedell, H. L., and Rosenthal, L. M.: The etiologic role of chewing tobacco in cancer of the mouth. JAMA 116: 2130–2135, May 10, 1941.
7. Moore, G. E., Bissinger, L. L., and Proehl, E. C.: Tobacco and intraoral cancer. Surg Forum 3: 685–688 (1952).
8. U.S. Public Health Service: Smoking and health. A report of the Surgeon General. DHEW Publication No. (PHS) 79–50066. U.S. Government Printing Office, Washington, DC, 1979; (*a*) pp. 13–10, 13–38 to 41; (*b*) pp. A:8 to A:29.
9. International Agency for Research on Cancer: Tobacco habits other than smoking: betel-quid and areca-nut chewing and some related nitrosamines. IARC Monogr Eval Carcinog Risk Chem Hum No. 37, Lyon, France, 1985, p. 291.
10. U.S. Department of Agriculture, Agricultural Marketing Service: Annual report on tobacco statistics, 1973. Statistical Bull No. 528, Washington, DC, 1974.
11. U.S. Department of Agriculture, Economic Research Service: Tobacco: outlook and situation report. Washington, DC, 1985.
12. U.S. Department of Agriculture, Agricultural Marketing Service: Annual report on tobacco statistics, 1976. Statistical Bull No. 570, Washington, DC, 1977.
13. U.S. Department of Agriculture, Agricultural Marketing Service: Annual report on tobacco statistics, 1981. Statistical Bull No. 685, Washington, DC, 1982.
14. U.S. Department of Agriculture, Agricultural Marketing Service: Tobacco stocks, as of January 1, 1983. Washington, DC, 1983.
15. U.S. Department of Agriculture, Agricultural Marketing Service: Tobacco stocks, as of January 1, 1984. Washington, DC, 1984.
16. U.S. Department of Agriculture, Agricultural Marketing Service: Tobacco stocks, as of January 1, 1986. Washington, DC, 1986.
17. National Clearinghouse for Smoking and Health: Use of tobacco: practices, attitudes, knowledge, and beliefs. Atlanta, GA, fall 1964, spring 1966, and July 1967.
18. National Clearinghouse for Smoking and Health: Adult use of tobacco, 1975. U.S. Department of Health, Education, and Welfare, Public Health Service, 1976. Atlanta, GA, 1976.
19. Simmons Market Research Bureau, Inc.: Study of media and markets, 1980-1985. New York, 1985.
20. Simmons Market Research Bureau, Inc.: Simmons national college study, 1983 and 1985, New York, 1983, 1985.
21. Rouse, B. A.: National prevalence of smokeless tobacco use. Paper presented at the NIH Consensus Development Conference on the Health Implications of Smokeless Tobacco Use, Bethesda, MD, Jan. 13–15, 1986.
22. U.S. Bureau of the Census: Current population projections of the population of the United States 1982 to 2050. CP Series P25, No. 922 (1982).
23. Bonaguro, J. A., Pugy, M., and Bonaguro, E. W.: Multivariate analysis of smokeless tobacco use by adolescents in grades four through twelve. Health Educ Q. In press.
24. Jones, R. B.: Smokeless tobacco: a challenge for the 80's. Wisconsin Dent Assoc 10: 717–721 (1985).
25. Boyd, G. M., et al.: Use of smokeless tobacco among children and adolescents in the United States. Prev Med. In press.
26. Chassin, L., et al.: Psychosocial correlates of adolescent smokeless tobacco use. Addict Behav. In press.
27. Marty, P. J., McDermott, R. J., and Williams, T.: Patterns of smokeless tobacco use in a population of high school students. Am J Public Health 76: 190–192 (1986).
28. Newman, I. M., and Duryea, E. J.: Adolescent cigarette

smoking and tobacco chewing in Nebraska. Nebr Med J 243-244 (1981).
29. Lichtenstein, E., Severson, H. H., Friedman, L. S., and Ary, D. V.: Chewing tobacco use by adolescents: prevalence and relation to cigarette smoking. Addict Behav. In press.
30. Hunter, S. M., et al.: Longitudinal patterns of cigarette smoking and smokeless tobacco use in youth. Am J Public Health 76: 193-195 (1986).
31. Marty, P. J., McDermott, R. J., Young, M., and Guyton, R.: Prevalence and psychosocial correlates of dipping and chewing in a group of rural high school students. Health Educ Q. In press.
32. Severson, H., Lichtenstein, E., and Gallison, C.: A pinch or a pouch instead of a puff? Implications of chewing tobacco for addictive processes. Bulletin of Psychologists in Addictive Behaviors 4: 85-92 (1985).
33. Schaefer, S. D., Henderson, A. H., Glover, E. D., and Christen, A. G.: Patterns of use and incidence of smokeless tobacco consumption in school-age children. Arch Otolaryngol. In press.
34. Young, M., and Williamson, D.: Correlates of use and expected use of smokeless tobacco among kindergarten children. Psychol Rep 56: 63-66 (1985).
35. Office of the Inspector General: Youth use of smokeless tobacco: More than a pinch of trouble. Control No. P-06-86-0058. U.S. Department of Health and Human Services, Washington, DC, January 1986.
36. Young, J. L., Percy, C. L., and Asire, A. J.: Surveillance, epidemiology, and end results: Incidence and mortality data, 1973-77. Natl Cancer Inst Monogr 57, National Cancer Institute, Bethesda, MD, 1981.
37. Rosenfeld, L., and Callaway, J.: Snuff dipper's cancer. Am J Surg 106: 840-844 (1963).
38. Wilkins, S. A., and Vogler, W. R.: Cancer of the gingiva. Surg Gynecol Obstet 105: 145-152 (1957).
39. Hartselle, M. L.: Oral carcinoma as related to the use of tobacco. Ala J Med Sci 14: 188-194 (1977).
40. Rothman, K., and Keller, E.: The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J Chron Dis 25: 711-716 (1972).
41. Winn, D. M., et al.: Snuff dipping and oral cancer among women in the southern United States. N Engl J Med 304: 745-749, Mar. 26, 1981.
42. Moore, G. E., Bissinger, L. L., and Proehl, E. C.: Intraoral cancer and the use of chewing tobacco. J Am Geriatr Soc 1: 497-506 (1953).
43. Wynder, E. L., Hultberg, S., Jacobsen, F., and Bruss, I. J.: Environmental factors in cancer of the upper alimentary tract. Cancer 10: 470-487 (1957).
44. Wynder, E. L., Bross, I. J., and Feldman, R. M.: A study of the etiological factors in cancer of the mouth. Cancer 10: 1300-1323 (1957).
45. Peacock, E. E., Greenberg, B. G., and Brawley, B. W.: The effect of snuff and tobacco on the production of oral carcinoma. Am Surg 151: 542-550 (1960).
46. Vogler, W. R., Lloyd, J. W., and Milmore, B. K.: A retrospective study of etiological factors in cancer of the mouth, pharynx, and larynx. Cancer 15: 246-258, March-April 1982.
47. Vincent, R. G., and Marchetta, F.: The relationship of the use of tobacco and alcohol to cancer of the oral cavity, pharynx, or larynx. Am J Surg 106: 501-505 (1963).
48. Martínez, I.: Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. JNCI 42: 1069-1094 (1969).
49. Williams, R. R., and Horm, J. W.: Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. JNCI 58: 525-547 (1977).
50. Browne, R. M., Camsey, M. C., Waterhouse, J. A. H., and Manning, G. L.: Etiological factors in oral squamous cell carcinoma. Community Dent Oral Epidemiol 5: 301-306 (1977).
51. Westbrook, K. C., Sven, J. Y., Hawkins, J. M., and McKinney, D. C.: Snuff dipper's carcinoma: fact or fiction? *In* Prevention and detection of cancer, H. E. Nieburg, editor. Marcel Dekker, New York, 1980, pp. 1367-1371.
52. Wynder, E. L., and Stellman, S. D.: Comparative epidemiology of tobacco-related cancers. Cancer Res 37: 4608-4622 (1977).
53. Wynder, E. L., Kabat, G., Rosenberg, G., and Levenstein, M.: Oral cancer and mouthwash use. JNCI 70: 255-260 (1983).
54. Winn D. M., Blot, W. J., and Fraumeni, J. F.: Snuff dipping and oral cancer. N Engl J Med 305: 230-231, July 23, 1981.
55. Winn, D. M., et al.: Diet in the etiology of oral and pharyngeal cancers among women from the southern United States. Cancer Res 44: 1216-1222 (1984).
56. Blot, W. J., Winn, D. M., and Fraumeni, J. F.: Oral cancer and mouthwash. JNCI 70: 251-253 (1983).
57. Winn, D. M.: Smokeless tobacco and oral-pharynx cancer: the role of cofactors. Banbury Report. In press.
58. Wahi, P. N.: The epidemiology of oral and oropharyngeal cancer. Bull WHO 38: 495-521 (1968).
59. Chandra, A.: Different habits and this relation with cheek cancer. Bull Cancer Hosp Natl Cancer Res Center 1: 33 (1962).
60. Shanta, V., and Krishnamurthi, S.: A study of aetiological factors in oral squamous cell carcinoma. Br J Cancer 13: 381 (1959).
61. Jafarey, N. A., and Zaidi, S. H.: Carcinoma of the oral cavity in Karachi, Pakistan: an appraisal. Trop Doct 6: 63-67 (1976).
62. Jussawalla, D. J., and Deshpande, V. A.: Evaluation of cancer risk in tobacco chewers and smokers: an epidemiologic assessment. Cancer 28: 244-252 (1971).
63. Gupta, P. C., Pindborg, J. J:, and Mehta, F. S.: Comparison of carcinogenicity of betel quid with and without tobacco. An epidemiological review. Ecol Dis 1: 213-219 (1982).
64. Root, H. D., Aust, J. B., and Sullivan, A.: Snuff and cancer of the ear. N. Engl J Med 262: 819-820, Apr. 21, 1960.
65. Higginson, J., and Oettle, A. G.: Cancer incidence in the Bantu and Cape colored races of South Africa: report of a cancer survey in the Transvaal. JNCI 24: 589-671 (1960).
66. Wynder, E. L., and Bross, I. J.: A study of etiological factors in cancer of the esophagus. Cancer 14: 389-413 (1961).
67. Winn, D., Walrath, J., Blot, W., and Rogot, E.: Chewing tobacco and snuff in relation to cause of death in a large prospective cohort [Abstract]. Am J Epidemiol 116: 567 (1982).
68. Bjelke, E., and Schuman, L. M.: Chewing tobacco and use of snuff: Relationships to cancer of the pancreas and

other sites in two prospective studies. *In* Proceedings of the 13th International Congress on Cancer, International Union Against Cancer, Geneva, 1982, p. 207.
69. International Agency for Research on Cancer: Tobacco habits other than smoking: betel-quid and areca-nut chewing and some related nitrosamines. IARC Monogr Eval Carcinog Risk Chem Hum No. 37, Lyon, France, 1985, pp. 103-104.
70. Stephen, S. J., and Uragoda, C. G.: Some observations on oesophageal carcinoma in Ceylon, including its relationship to betel chewing. Br J Cancer 24: 11-15 (1970).
71. Waterhouse, J., Muir, C., Shanmugaratnam, and Powell, J.: Cancer incidence in five continents, vol. IV. International Agency for Research on Cancer, Lyon, France, 1982.
72. Shanta, V., and Krishnamurthi, S.: Further study in aetiology of carcinomas of the upper alimentary tract. Br J Cancer 17: 8-23 (1963).
73. Sarma, S. N.: A study into the incidence and etiology of cancer of the larynx and adjacent parts in Assam. Indian J Med Res 46: 525-533 (1958).
74. Wynder, E. L., Onderdonk, J., and Mantel, N.: An epidemiological investigation of cancer of the bladder. Cancer 11: 1388-1406 (1963).
75. Dunham, L. J., et al.: Rates, interview and pathology study of cancer of the urinary bladder in New Orleans, Louisiana. JNCI 41: 683-709 (1968).
76. Cole, P., Monson, R. R., Haning, H., and Friedell, G. H.: Smoking and cancer of lower urinary tract. N Engl J Med 284: 129-134, Jan. 21, 1971.
77. Kabat, G. C., Dieck, G. S., and Wynder, E. L.: Bladder cancer in non-smokers. Cancer 57: 362-367 (1986).
78. Howe, G. R., et al.: Tobacco use, occupation, coffee, various nutrients, and bladder cancer. JNCI 64: 701-713 (1980).
79. Hartge, P., Hoover, R., and Kantor, A.: Bladder cancer risk and pipes, cigars, and smokeless tobacco. Cancer 55: 901-906 (1985).
80. Mommsen, S., Aagaard, J., and Sell, A.: An epidemiologic study of bladder cancer in a predominantly rural district. Scand J Urol Nephrol 17: 307-312 (1983).
81. Mommsen, S., and Aagaard, J.: Tobacco as a risk factor for bladder cancer. Carcinogenesis 4: 335-338 (1983).
82. Bennington, J. L., Campbell, P. B., and Ferguson B. R.: Epidemiologic studies of carcinoma of the kidney, II. Association of renal adenocarcinoma with smoking. Cancer 22: 821-823 (1968).
83. Armstrong, B., Garrod A., and Doll R.: A retrospective study of renal cancer with special reference to coffee and animal protein consumption. Br J Cancer 33: 127-136 (1976).
84. McLaughlin J. K., et al.: Population-based case-control study of renal cell carcinoma. JNCI 72: 275-284 (1984).
85. Dube, M. F., and Green, C. R.: Methods of collection of smoke for analytical purposes. Recent Advances in Tobacco Science 8: 42-102 (1982).
86. Baumslag, N., Keen, P., and Petering, H. G.: Carcinoma of the maxillary antrum and its relationship to trace and metal content in snuff. Arch Environ Health 23: 1-5 (1971).
87. Brunnemann, K. D., Scott, J. C., and Hoffmann, D.: N-nitrosomorpholine and other volatile N-nitrosamines in snuff tobacco. Carcinogenesis 3: 693-696 (1982).
88. Brunnemann, K. D., Genoble, L., and Hoffmann, D.: N-nitrosamines in chewing tobacco: An international comparison. J Agric Food Chem 33: 1178-1181 (1985).
89. Brunnemann, K. D., and Hoffmann, D.: Assessment of the carcinogenic N-nitrosodiethanolamine in tobacco products and tobacco smoke. Carcinogenesis 2: 1123-1127 (1981).
90. Hoffmann, D., and Adams, J. D.: Carcinogenic tobacco-specific N-nitrosamines in snuff and in the saliva of snuff dippers. Cancer Res 41: 4305-4308 (1981).
91. Osterdahl, B. G., and Slorach S.: N-nitrosamines in snuff and chewing tobacco on the Swedish market in 1983. Food Additiv Contamin 1: 299-305 (1984).
92. Nair, J., et al.: Tobacco-specific and betel nut-specific N-nitroso compounds. Occurrence in saliva and urine of betel quid chewers and formation *in vitro* by nitrosation of betel quid. Carcinogenesis 6: 295-303 (1985).
93. Brunnemann, K. D., Scott, J. C., and Hoffmann, D.: N-nitrosoproline, an indicator for N-nitrosation of amines in processed tobacco. J Agric Food Chem 31: 905-909 (1983).
94. Palladino, G., et al.: Snuff-dipping in college students: a clinical profile. Milit Med. In press.
95. Oesterdahl, B. G., and Slorach, S. A.: Volatile N-nitrosamines in snuff and chewing tobacco on the Swedish market. Food Chem Toxicol 21: 759-762 (1983).
96. Brunnemann, K. D., Yu, L., and Hoffmann, D.: Assessment of carcinogenic volatile N-nitrosamines in tobacco and in mainstream and sidestream smoke from cigarettes. Cancer Res 37: 3218-3222 (1977).
97. Nair, J., et al.: N-nitroso compounds (NOC) in saliva and urine of betel quid chewers: Studies on occurrence and formation. Carcinogenesis 6: 295-303 (1985).
98. Ohshima, H.: Identification and occurrence of new N-nitrosamino acids in human urine and environmental samples. Paper presented at the Conference on Organic and Biological Chemistry of Carcinogenic and Carcinostatic Agents Containing Nitrogen-Nitrogen Bonds, Harpers Ferry, WV, May 17-21, 1985, sponsored by the Division of Cancer Etiology, National Cancer Institute.
99. Ohshima, H., et al.: Identification and occurrence of two new N-nitrosamino acids in tobacco products: 3-(N-nitroso-N-methylamino) propionic acid and 4-(N-nitroso-N-methylamino) butyric acid. Cancer Lett 26: 153-162 (1985).
100. Hoffmann, D., et al.: Nitrosonornicotine: presence in tobacco, formation and carcinogenicity. IARC Sci Publ 14: 307-320 (1976).
101. Munson, J. W., and Abdine, H.: Determination of N-nitrosonornicotine in tobacco by gas chromatography/mass spectroscopy. Anal Lett 10: 777-786 (1977).
102. Adams, J. D., Brunnemann, K. D., and Hoffmann, D.: Rapid method for the analysis of tobacco-specific N-nitrosamines by gas-liquid chromatography with a thermal energy analyzer. J Chromatogr 256: 347-351 (1983).
103. Schmeltz, I., Tosk, J., and Hoffmann, D.: Formation and determination of naphthalenes in cigarette smoke. Anal Chem 48: 645-650 (1976).
104. Nicolaus, G., and Elmenhorst, H.: Nachweis und quantitative Bestimmung von Alkylnaphthalinen in Latakia-Tabak. Beitr Tabakforsch 11: 133-140 (1982).
105. Campbell, J. M., and Lindsey, A. J.: Polycyclic hydrocarbons extracted from tobacco: The effect upon total quantities found in smoke. Br J Cancer 10: 649-652 (1956).
106. Onishi, I., Nagasawa, M., Tomita, H., and Fukuzumi, T.: Studies on the essential oil of tobacco leaves, pt. XVI. Neutral fraction (3). Polycyclic aromatic hydrocarbons of

Burley tobacco leaf. Bull Agric Chem Soc Japan 22: 17–20 (1958).
107. Campbell, J. M., and Lindsey, A. J.: Polycyclic aromatic hydrocarbons in snuff. Chemistry and Industry London, 951 (1957).
108. Hoffmann, D., et al.: Carcinogenic agents in snuff. JNCI. In press.
109. Lundin, F. E., Jr., Wagoner, J. K., and Archer, V. E.: Radon daughter exposure and respiratory cancer. Quantitative and temporal aspects. Joint NIOSH/NIEHS Monogr 1. U.S. Public Health Service, Washington, DC, 1971.
110. Harley, N. H., Cohen, B. S., and Tso, T. C.: Polonium-210: a questionable risk factor in smoking-related carcinogenesis. Banbury Rep 3: 93–104 (1980).
111. U.S. Department of Agriculture, Food Safety and Quality Service: Nitrates, nitrites and ascorbates (or isoascorbates) in bacon. Federal Register 43: 20992–20995, May 16, 1978.
112. U.S. Food and Drug Administration: Dimethyl nitrosamine in malt beverages; availability of guide. Federal Register 45: 39341–39342, 1980.
113. U.S. Food and Drug Administration: Action levels of total volatile N-nitrosamines in rubber baby bottle nipples; availability of revised compliance policy guide. Federal Register 49: 50789–50790, Dec. 31, 1984.
114. Singer, B., and Grunberger, D.: Molecular biology of mutagens and carcinogens. Plenum Publishing Corp., New York, 1983, pp. 45–96.
115. Sukumar, S., Nofario, V., Martin-Zanca, D., and Barbacid, M.: Induction of mammary carcinomas in rats by nitrosomethylurea involves malignant activation of H-ras-1 locus by single point mutations. Nature 306: 658–662 (1983).
116. Singer, B.: Alkylation of the 06 of guanine is only one of many chemical events that may initiate carcinogenesis. Cancer Invest 2: 233–238 (1984).
117. Castonguay, A., Tharp, R., and Hecht, S. S.: Kinetics of DNA methylation by the tobacco specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in the F344 rat. *In* N-nitroso compounds: occurrence, biological effects and relevance to human cancer, I. K. O'Neill, et al. editors. IARC Sci Publ 57: 805–810 (1984).
118. Chung, F-L., Wang, M., and Hecht, S. S.: Effects of dietary indoles and isothiocyanates on N-nitrosodimethylamine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone alpha-hydroxylation and DNA methylation in rat liver. Carcinogenesis 6: 539–543 (1985).
119. Foiles, P., Trushin, N., and Castonguay, A.: Measurement of 0 6 -methylde-oxyguanosine in DNA methylated by the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone using a biotin-avidin enzyme-linked immunosorbent assay. Carcinogenesis 6: 989–993 (1985).
120. Hecht, S. S., Trushin, N., Castonguay, A., and Rivenson, A.: Comparative tumorigenicity and DNA methylation in F344 rats by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N-nitrosodimethylamine. Cancer Res 46: 498–502 (1986).
121. Belinsky, S. A., et al.: Accumulation of DNA adducts in hepatic and respiratory tissue following multiple administrations of the tobacco-specific carcinogen 4-(N-methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Proc Am Assoc Cancer Res 26: 100 (1985).
122. Konstantinidus, A., Smulow, J. B., and Sonnenschein, C.: Tumorigenesis at a predetermined oral site after one intraperitoneal injection of N-nitroso-N-methylurea. Science 216: 1235–1237, June 11, 1982.
123. Hecht, S. S., Lin, D., and Castonguay, A.: Effects of alpha-deuterium substitution on the mutagenicity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Carcinogenesis 4: 305–310 (1983).
124. Hecht, S. S., Lin, D., Chuang, J., and Castonguay, A.: Reactions with deoxyguanosine of 4-(carbethoxynitrosamino)-1-(3-pyridyl)-1-butanone, a model compound for alpha-hydroxylation of tobacco specific nitrosamines. J Am Chem Soc. In press.
125. Hecht, S. S., Young, R., and Maeura, Y.: Comparative carcinogenicity in F344 rats and Syrian golden hamsters of N'-nitrosonornicotine and N'-nitrosonornicotine-1-N-oxide. Cancer Lett 20: 333–340 (1983).
126. Hecht, S. S., et al.: Alpha-hydroxylation of N-nitrosopyrrolidine and N'-nitrosonornicotine by human liver microsomes. Cancer Lett 8: 35–41 (1979).
127. Hecht, S. S., and Lin, D.: Comparative mutagenicity of 4-(carbethoxynitrosamino)-4-(3-pyridyl)-butanol and 4-(carbethoxynitrosamino)-1-(3-pyridyl)-1-butanone, model compounds for alpha-hydroxylation of N'-nitrosonornicotine. Carcinogenesis. In press.
128. Hecht, S. S., et al.: Tobacco-specific nitrosamines: carcinogenicity, metabolism, and possible role in human cancer. J Environ Sci Health 1: 1–54 (1983).
129. Linjinsky, W., Taylor, H. W., and Keefer, L. K.: Reduction of rat liver carcinogenicity of 4-nitrosomorpholine by alpha-deuterium substitution. JNCI 57: 1311–1313 (1976).
130. Chung, F-L., Palladino, G., and Hecht, S. S.: Reactions of N-nitrosomorpholine metabolites with deoxyguanosine and DNA. Proc Am Assoc Cancer Res 26: 89 (1985).
131. Chung, F-L., and Hecht, S. S.: Formation of the cyclic 1,N2-glyoxaldeoxyguanosine adduct upon reaction of N-nitroso-2-hydroxymorpholine with deoxyguanosine. Carcinogenesis 6: 1671–1673 (1985).
132. Castonguay, A., Stoner, G. D., Schut, H. A. J., and Hecht, S. S.: Metabolism of tobacco-specific N-nitrosamines by cultured human tissues. Proc Natl Acad Sci USA 80: 6694–6697 (1983).
133. Bartsch, H., Camus, A., and Malaveille, C.: Comparative mutagenicity of N-nitrosamines in a semi-solid and in a liquid incubation system in the presence of rat liver tissue fractions. Mutat Res 37: 149–162 (1976).
134. Shah, A. S., Sarode, A. V., and Bhide, S. V.: Experimental studies on mutagenic and carcinogenic effects of tobacco chewing. J Cancer Res Clin Oncol 109: 203–207 (1985).
135. Mody, J. K., and Ranadive, J. K.: Biological study of tobacco in relation to oral cancer. Indian J Med Sci 13: 1023–1037 (1959).
136. Gothoskar, S. V., Sant, S. M., and Ranadive, K. J.: Effect of tobacco and lime on oral mucosa of rats fed on vitamin B deficient diet. Int J Cancer 12: 424–429 (1975).
137. Suri, K., Goldman, H. M., and Wells, H.: Carcinogenic effect of a dimethylsulphoxide extract of betel nut on the mucosa of the hamster buccal pouch. Nature 230: 383–384 (1971).
138. Ranadive, K. J., and Gothoskar, S. V.: Betel quid chewing and oral cancer: Experimental studies. *In* Prevention and detection of cancer, edited by H. E. Nieburgs. Pt. I, vol. 2. Marcel Dekker, New York, 1976, pp. 1745–1766.
139. Rao, A. R.: Modifying influences of betel quid ingredients on B(a)P-induced carcinogenesis in the buccal pouch of

hamster. Int J Cancer 33: 581–586 (1984).
140. Peacock, E. E., Jr., and Brawley, B. W.: An evaluation of snuff and tobacco in the production of mouth cancer. Plast Reconstr Surg 23: 628–635 (1959).
141. Ranadive, K. J., Gothoskar, S. V., and Khanolka, V. R.: Experimental studies on the etiology of cancer types specific to India. A. Oral cancer, B. Kangri cancer. Acta Unio Internatl Contra Cancrum 19: 634–639 (1963).
142. Wynder, E. L., and Hoffmann, D.: Tobacco and tobacco smoke. Studies in experimental carcinogenesis. Academic Press, New York, 1967, pp. 198–202.
143. Hoffmann, D., Hecht, S. S., Ornaf, R. M., and Wynder, E. L.: Nitrosonornicotine: Presence in tobacco, formation and carcinogenicity. IARC Sci Publ 14: 307–320 (1976).
144. Wynder, E. L., and Hoffmann, D.: A study of tobacco carcinogenesis, X. Tumor promoting activity. Cancer 24: 289–301 (1969).
145. Wynder, E. L., and Wright, G. A.: A study of tobacco carcinogenesis. I. The primary fractions. Cancer 10: 255–271 (1957).
146. Bock, F. G., Moore, G. E., and Crouch, S. K.: Tumor promoting activity of extracts of unburned tobacco. Science 145: 831–833, Aug. 21, 1964.
147. Bock, F. G., Shamberger, R. J., and Meyer, H. K.: Tumor promoting agents in unburned cigarette tobacco. Nature 208: 584–585 (1965).
148. Van Duuren, B. L., et al.: The tumor-promoting agents of tobacco leaf and tobacco smoke condensate. JNCI 37: 519–526 (1966).
149. Homburger, F., et al.: Absence of carcinogenic effects of chronic feeding of snuff in inbred Syrian hamsters. Toxicol Pharmacol 35: 515–521 (1976).
150. Park, N. H., Herbosa, E. G., Ninkian, K., and Shklar, G.: Combined effect of herpes simplex virus and tobacco on the histopathologic changes in lips of mice. Oral Surg 59:154–158 (1985).
151. Hirsch, J. M., and Johansson, S. L.: Effect of long-term application of snuff on the oral mucosa: an experimental study in the rat. J Oral Pathol 12:187–198 (1983).
152. Hirsch, J. M., Johansson, S. L., and Vahlne, A.: Effect of snuff and herpes simplex virus-1 on rat oral mucosa: possible associations with the development of squamous cell carcinoma. J Oral Pathol 13:52–62 (1984).
153. Park, N. H., Herbosa, E. G., and Sapp, J. P.: Oral cancer induced in hamsters with herpes simplex infection combined with simulated snuff-dipping [Abstract 10]. *In* Proceedings of International Herpes Virus Workshop, Ann Arbor, MI, Aug. 11–16, 1985, p. 297.
154. Schmahl, D.: Prufung von Kautabakextract auf cancerogene Wirkung bei Ratten. Arzneimittelforsch 15: 704–705 (1965).
155. Druckrey, H., Schmahl, D., Beuthner, H., and Muth, F.: Vergleichende Prufung von Tabakrauch-Kondensaten, Benzopyren und Tabakextract auf carcinogene Wirkung bei Ratten. Naturwissenschaften 47: 605–606 (1960).
156. Barker, R., Burke, J., and Zieve, P., editors: Principles of ambulatory medicine. Williams and Wilkins, Baltimore, 1983, p. 1074.
157. Hecht, S. S., Adams, J. D., Numoto, S., and Hoffmann, D.: Induction of respiratory tract tumors in Syrian golden hamsters by a single dose of 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and the effect of smoke inhalation. Carcinogenesis 4: 1287–1290 (1983).
158. Hoffmann, D., Rivenson, A., Amins, S., and Hecht, S. S.: Dose-response study of the carcinogenicity of tobacco-specific N-nitrosamines in F344 rats. J Cancer Res Clin Oncol 108:81–86 (1984).
159. Peacock, E. E., Jr., et al.: The effect of snuff and tobacco on the production of oral carcinoma: an experimental and epidemiological study. Ann Surg 151:542–549 (1960).
160. Smith, J. F., Mincer, H. A., Hopkins, K. P., and Bell, J.: Snuff-dipper's lesion. A cytological and pathological study in a large population. Arch Otolaryngol 92:450–456 (1970).
161. Greer, R. O., Jr., and Poulson, T. C.: Oral tissue alterations associated with the use of smokeless tobacco by teen-agers. Oral Surg 56:275–284 (1983).
162. Poulson, T. C., et al.: A comparison of the use of smokeless tobacco in rural and urban teenagers. CA 34:248–261 (1984).
163. Offenbacher, S., and Weathers, D. R.: Effects of smokeless tobacco on the periodontal, mucosal and caries status of adolescent males. J Oral Pathol 14:169–181 (1985).
164. Axell, T.: A prevalence study of oral mucosal lesions in an adult Swedish population. Odontol Rev (supp. 36), 27:1–103 (1976).
165. Hirsch, J. M., Heyden, G., and Thilander, H.: A clinical, histomorphological and histochemical study on snuff-induced lesions of varying severity. J Oral Pathol 11:387–398 (1982).
166. Hoge, H. W., and Kirkham, D. B.: Clinical management and soft tissue reconstruction of periodontal damage resulting from habitual use of snuff. J Am Dent Assoc 107:744–745 (1983).
167. Pindborg, J. J., and Renstrup, G.: Studies in oral leukoplakias, II. Effect of snuff on oral epithelium. Acta Derm Venereol 43:271–276 (1963).
168. Axell, T., Mornstad, H., and Sundstrom, B.: The relation of the clinical picture to the histopathology of snuff dipper's lesions in a Swedish population. J Oral Pathol 5:229–236 (1976).
169. Christen, A. G., et al.: Intraoral leukoplakia, abrasion, periodontal breakdown, and tooth loss in a snuff dipper. J Am Dent Assoc 98:584–586 (1979).
170. Christen, A. G., et al.: Snuff dipping and tobacco chewing in a group of Texas college athletes. Tex Dent J 97:6–10 (1979).
171. Zitterbart, P. A., et al.: Dental and oral effects observed in a long-term tobacco chewer: case report. J Indian Dent Assoc 62:17–18 (1983).
172. Pindborg, J. J., and Poulsen, H. E.: Studies in oral leukoplakias, I. The influence of snuff upon the connective tissue of the oral mucosa. Preliminary report. Acta Pathol Microbiol Immunol Scand 55:412–414 (1962).
173. Frithiof, L., et al.: The snuff-induced lesion. Acta Odontol Scand 1:53–64 (1983).
174. Banoczy, J., and Sugar, L.: Progressive and regressive changes in Hungarian oral leukoplakias in the course of longitudinal studies. Community Dent Oral Epidemiol 3:194–197 (1975).
175. Mehta, F. S., Gupta, P. C., and Pindborg, J. J.: Chewing and smoking habits in relation to precancer and oral cancer. J Cancer Res Clin Oncol 99:35–39 (1981).
176. Tyldesley, W. R.: Tobacco chewing in English coalminers (2). Malignant transformation in a tobacco-induced leukoplakia. Br J Oral Surg 14:93–94 (1976).
177. Roed-Petersen, B., and Pindborg, J. J.: A study of Danish snuff-induced oral leukoplakia. J Oral Pathol 2:301–313 (1973).

178. Jungell, P., and Malmstrom, M.: Snuff-induced lesions in Finnish recruits. Scand J Dent Res 93:442–447 (1985).
179. McGuirt, W. F.: Snuff dipper's carcinoma. Arch Otolaryngol 109:757–760 (1983).
180. Sundstrom, B., Mornstad, H., and Axell, T.: Oral carcinomas associated with snuff dipping. Some clinical and histological characteristics of 23 tumours in Swedish males. J Oral Pathol 11:245–251 (1982).
181. Rosenfeld, L., and Callaway, J.: Snuff dipper's cancer. Am J Surg 106:840–844 (1963).
182. Landy, J. J., and White, H. J.: Buccogingival carcinoma of snuff dippers. Am Surg 27:442–447 (1961).
183. Modeer, T., et al.: Relation between tobacco consumption and oral health in Swedish schoolchildren. Acta Odontol Scand 38:223–227 (1980).
184. Greer, R. O., et al.: Smokeless tobacco associated oral changes in the juvenile, adult, and geriatric patients: clinical and histomorphologic features including light microscopic, immunocytochemical and ultrastructural findings. Gerodontics 2:3 (1986).
185. Hecht, S. S., et al.: Tobacco-specific nitrosamines: formation from nicotine *in vitro* and during tobacco curing and carcinogenicity in strain A mice. JNCI 60:819–824 (1978).
186. Sitzes, L.: On chewing tobacco. ADA News 8:2 (1981).
187. Croft, L.: Smokeless tobacco: a case report. Tex Dent J 99:15–16 (1981).
188. Van Wyk, C. W.: The oral lesion caused by snuff. A clinico-pathological study. J Dent Assoc S Afr 21:109–116 (1966).
189. Christen, A. G.: The case against smokeless tobacco: Five facts for the health professional to consider. J Am Dent Assoc 101:464–469 (1980).
190. Benowitz, N. L., et al.: Smokers of low-yield cigarettes do not consume less nicotine. N Engl J Med 309:139–142, July 21, 1983.
191. Russell, M. A. H., Jarvis, M. J., West, R. J., and Feyerabend, C.: Buccal absorption of nicotine from smokeless tobacco sachets. Lancet No. 8468:1370, Dec. 14, 1985.
192. Jenner, P., Gorrod, J. W., and Beckett, A. H.: The absorption of nicotine-l'-N-oxide and its reduction in the gastrointestinal tract in man. Xenobiotica 3:341–349 (1973).
193. Hoffmann, D., et al.: Carcinogenic agents in snuff. JNCI 76:435–437 (1986).
194. Russell, M. A. H., Jarvis, M. J., Devitt, G., and Feyerabend, C.: Nicotine intake by snuff users. Br Med J No. 6295:814–817 (1981).
195. Armitage, A. K., et al.: Absorption and metabolism of nicotine from cigarettes. Br Med J No 5992:313–316 (1975).
196. Herning, R. I., Jones, R. T., Benowitz, N. L., and Mines, A. H.: How a cigarette is smoked determines nicotine blood levels. Clin Pharmacol Ther 33:84–91 (1983).
197. Benowitz, N. L., Kuyt, F., and Jacob, P., III.: Circadian blood nicotine concentration during cigarette smoking. Clin Pharmacol Ther 32:758–764 (1982).
198. Rosecrans, J. A., and Meltzer, L. T.: Central sites and mechanisms of action of nicotine. Neurosci Biobehav Rev 5: 497–501 (1981).
199. Henningfield, J. E., Miyasato, K., and Jasinski, D. R.: Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. J Pharmacol Exp Ther 234:1–12 (1985).
200. Schmiterlaw, C. G., et al.: Distribution of nicotine in the central nervous system. Ann NY Acad Sci 143:2–14 (1967).
201. Jaffe, J. H.: Drug addiction and drug abuse. *In* Goodman and Gilman's pharamacological basis of therapeutics, edited by A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad. Macmillan, New York, 1985, pp. 532–581.
202. Russell, M. A. H.: Tobacco smoking and nicotine dependence. *In* Research advances in alcohol and drug problems, edited by R. J. Gibbons, et al. John Wiley and Sons, Inc. New York, 1976, pp. 1–46.
203. Stolerman, I. P., et al.: Nicotine cue in rats analyzed with drugs acting on cholinergic and 5-hydroxtryptamine mechanisms. Neuropharmacology 22:1029–1033 (1983).
204. Rosecrans, J. A.: Nicotine as a discriminative stimulus to behavior: its characterization and relevance to smoking behavior. *In* Cigarette smoking as a dependence process, edited by N. A. Krasnegor. DHEW Publication No. (ADM) 82-800, NIDA Research Monogr 23. U.S. Government Printing Office, Washington, DC, 1979, pp. 58–69.
205. Stolerman, I. P.: Discriminative stimulus properties in nicotine: Correlations with nicotine binding. *In* Proceedings of the International Symposium on Tobacco Smoking and Health: a neurobiologic approach. University of Kentucky Tobacco-Health Research Institute, Lexington. In press.
206. Henningfield, J. E., Miyasato, K., Johnson, R. E., and Jansinski, D. R.: Rapid physiologic effects of nicotine in humans and selective blockade of behavioral effects by mecamylamine. *In* Problems of drug dependence, 1982, edited by L. S. Harris. NIDA Research Monogr. 43. GPO Stock No. 017-024-01162-2, U.S. Government Printing Office, Washington, DC, 1983, pp. 259–265.
207. Henningfield, J. E., and Goldberg, S. R.: Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol Biochem Behav 19:989–992 (1983).
208. Goldberg, S. R.: Nicotine as a reinforcer in animals. *In* Nicotine and appetite, edited by M. E. Jarvik. Proceedings of the International Symposium on Tobacco Smoking and Health: a neurobiological approach. In press.
209. Griffiths, R. R., Bigelow, G. E., and Henningfield, J. E.: Similarities in animal and human drug taking behavior. *In* Advances in substance abuse: behavioral and biological research, edited by N. K. Mello. JAI Press, Greenwich, CT, 1980, pp. 1–90.
210. Griffiths, R. R., and Henningfield, J. E.: Pharmacology of cigarette smoking behavior. Trends in Pharmaceutical Science 3:260–263 (1982).
211. Chait, L. D., and Griffiths, R. R.: Smoking behavior and tobacco smoke intake: response of smokers to shortened cigarettes. Clin Pharmacol Ther 32:90–97 (1982).
212. Nemeth-Coslett, R., and Griffiths, R. R.: Determinants of puff duration in cigarette smokers I. Pharmacol Biochem Behav 20: 965–971 (1984).
213. Nemeth-Coslett, R., and Griffiths, R. R.: Determinants of puff duration in cigarette smokers II. Pharmacol Biochem Behav 21:903–912 (1984).
214. Gritz, E. R.: Smoking behavior and tobacco abuse. *In* Advances in substance abuse: behavioral and biological research, edited by N. K. Mello JAI Press, Greenwich, CT, 1980, pp. 91–158.
215. Grabowski, J., and Hall, S. M.: Pharmacological adjuncts in smoking cessation. DHHS Publication No. (ADM) 85-1333. NIDA Research Monogr 53. U.S. Government Printing Office, Washington, DC, 1985.
216. Rose, J. E., Herskovic, J. E., Trilling, Y., and Jarvik,

M. E.: Transdermal nicotine reduces cigarette craving and nicotine preference. Clin Pharmacol Ther 38: 450–456 (1985).
217. Stolerman, I. P., Goldfarb, T., Fink, R., and Jarvik, M. E.: Influencing cigarette smoking with nicotine antagonists. Psychopharmacologia 28: 247–259 (1973).
218. Nemeth-Coslett, R., Henningfield, J. E., O'Keeffe, M. K., and Griffiths, R. R.: Effects of mecamylamine on cigarette smoking and subjective effects. Psychopharmacology 88: 420–425 (1986).
219. Benowitz, N. L., and Jacob, P., III.: Nicotine renal excretion rate influences nicotine intake during cigarette smoking. J Pharmacol Exp Ther 234: 153–155 (1985).
220. Beckett, A. H., and Triggs, E. J.: Enzyme induction in man caused by smoking. Nature 216: 587 (1967).
221. Clarke, P. B. S., and Kumar, R.: The effects of nicotine on locomotor activity in non-tolerant and tolerant rats. Br J Pharmacol 78: 329–337 (1983).
222. Stitzer, M., Morrison, J., and Domino, E. F.: Effects of nicotine on fixed-interval behavior and their modification by cholinergic antagonists. J Pharmacol Exp Ther 171: 166–177 (1970).
223. Stolerman, I. P., Bunker, P., and Jarvik, M. E.: Nicotine tolerance in rats: Role of dose and dose interval. Psychopharmacology 34: 317–324 (1974).
224. Faulkerborn, Y., Larsson, C., and Nordberg, A.: Chronic nicotine exposure in rats: A behavioral and biochemical study of tolerance. Drug Alcohol Depend 8: 51–60 (1981).
225. Domino, E. F.: Behavioral, electrophysiological, endocrine and skeletal muscle actions of nicotine and tobacco smoking. *In* Electrophysiological effects of nicotine, edited by A. Remond and C. Izard. Elsevier, Amsterdam, 1979, pp. 133–146.
226. Fagerstrom, K. O., and Gotestam, K. G.: Increase in muscle tonus after tobacco smoking. Addict Behav 2: 203–206 (1977).
227. Wesnes, K., and Warburton, D. M.: Smoking, nicotine and human performance. Pharmacol Ther 21: 189–208 (1983).
228. Wesnes, K., and Warburton, D. M.: The effects of cigarettes of varying yield on rapid information processing performance. Psychopharmacology 82: 338–342 (1984).
229. Williams, G. D.: Effect of cigarette smoking on immediate memory and performance in different kinds of smokers. Br J Psychol 71: 83–90 (1980).
230. Pomerleau, O. F., and Pomerleau, C. S.: Neuroregulators and the reinforcement of smoking: towards biobehavioral explanation. Neurosci Biobehav Rev 8:503–513 (1984).
231. Garvey, A. J., Bosse, R., and Seltzer, C. C.: Smoking, weight change, and age. A longitudinal analysis. Arch Environ Health 28: 327–329 (1974).
232. Heyden, S.: The workingman's diet. Nutrition and Metabolism 20: 381–386 (1976).
233. Grunbers, N. E.: The effects of nicotine and cigarette smoking on food consumption and taste preferences. Addict Behav 7:317–331 (1982).
234. Jarvik, M. E.: Nicotine and apetite. *In* Proceedings of the International Symposium on Tobacco Smoking and Health: a neurobiological approach. University of Kentucky Tobacco-Health Research Institute, Lexington. In press.
235. Hughes, J. R., et al.: Effect of nicotine on the tobacco withdrawal syndrome. Psychopharmacology 83: 82–87 (1984).
236. Henningfield, J. E.: Pharmacologic basis and treatment of cigarette smoking. J Clin Psychiatry 45: 24–34 (1984).
237. The Committee on Problems of Drug Dependence, Inc.: Testing drugs for physical dependence potential and abuse liability, edited by J. V. Brady and S. E. Lukas. NIDA Research Monogr 52. U.S. Government Printing Office, Washington, DC, 1984.
238. Jasinski, D. R., Johnson, R. E., and Henningfield, J. E.: Abuse liability assessment in human subjects. Trends in Pharmacological Sciences 5: 196–200 (1984).
239. Jasinski, D. R.: Assessment of the abuse potentiality of morphine-like drugs (methods used in man). *In* Handbook of experimental pharmacology, edited by W. R. Martin, vol, 45. Drug Addiction I. Springer-Verlag, Berlin, Federal Republic of Germany, 1977, pp. 197–258.
240. Henningfield, J. E., Miyasato, K., and Jasinski, D. R.: Cigarette smokers self-administer intravenous nicotine. Pharmacol Biochem Behav 19: 887–890 (1983).
241. Henningfield, J. E., and Goldberg, S. R.: Control of behavior by intravenous nicotine injections in human subjects. Pharmacol Biochem Behav 19: 1021–1026 (1983).
242. Ulett, J. A., and Itil, T. M.: Quantitative electroencephalogram in smoking and smoking deprivation. Science 164: 969–970, May 23, 1969.
243. Knott, V. J., and Venables, P. H.: EEG alpha correlates of nonsmokers, smoking, and smoking deprivation. Psychophysiology 14: 150–156 (1977).
244. Shiffman, S. M., and Jarvik, M. E.: Withdrawal symptoms: first week is the hardest. World Smoking Health 5: 15–21 (1980).
245. Hatsukami, D. K., Hughes, J. R., Pickens, R. W., and Svikis, D.: Tobacco withdrawal symptoms: an experimental analysis. Psychopharmacology 84: 231–236 (1984).
246. Hughes, J. R., and Hatsukami, D.: Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry. In press.
247. Hatsukami, D. K., Hughes, J. R., and Pickens, R. W.: Characteristics of tobacco abstinence: Physiological and subjective effects. *In* Pharmacological adjuncts in smoking cessation, edited by J. Grabowski and S. M. Hall. DHHS Publication No. (ADM) 85–1333. NIDA Research Monogr 53. U.S. Government Printing Office, Washington, DC, 1985.
248. Hoffmann, D., et al.: Chemical studies on tobacco smoke. XLII. Nitrosonornicotine: Presence in tobacco, formation and carcinogenicity. *In* Environmental N-nitroso compounds, analysis and formation, edited by E. A. Walker, P. Bogovski, and L. Griciute. IARC Sci Publ No. 14. Lyon, France, 1976, pp. 307–320.
249. Gritz, E. R., et al.: Plasma nicotine and cotinine concentrations in habitual smokeless tobacco users. Clin Pharmacol Ther 30: 201–209 (1981).
250. Russell, M. A. H., Jarvis, M., West, R. J., and Feyerabend, C.: Buccal absorption of nicotine from smokeless tobacco sachets. Lancet No. 8468: 1370, Dec. 14, 1985.
251. Hughes, J. R., Pickens, R. W., Spring, W., and Keenan, R. M.: Instructions control whether nicotine will serve as a reinforcer. J Pharmacal Exp Ther 235: 106–112 (1986).
252. Hughes, J. R., Hatsukami, D., and Skoog, K. P.: Physical dependence on nicotine gum: a placebo substitution trial. Paper presented at Committee on Problems of Drug Dependence Meeting, Baltimore, MD, 1984.
253. West, R. J., and Russell, M. A.: Effects of withdrawal from long-term nicotine gum use. Psychol Med 15: 891–893 (1985).
254. Billimoria, J. D., et al.: Effect of cigarette smoking on

lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. Atherosclerosis 21: 61–76 (1975).
255. Mustard, J. F., and Murphy, E. A.: Effect of smoking on blood coagulation and platelet survival in man. Br Med J No. 5334: 846–849 (1963).
256. Renaud, S., et al.: Platelet function after cigarette smoking in relation to nicotine and carbon monoxide. Clin Pharmacol Ther 36: 389–395 (1984).
257. Maouad, J., et al.: Diffuse or segmental narrowing (spasm) of the coronary arteries during smoking demonstrated on angiography. Am J Cardiol 53: 354–355 (1984).
258. Bellet, S., et al.: The effect of inhalation of cigarette smoke on ventricular fibrillation theshold in normal dogs and dogs with acute myocardial infarction. Am Heart J 83: 67–76 (1976).
259. Schroeder, K. L., and Chen, M. S.: Smokeless tobacco and blood pressure. N Engl J Med 312: 919, Apr. 4, 1985.
260. McPhaul, M., et al.: Snuff-induced hypertension in pheochromocytoma. JAMA 252: 2860–2862, Nov. 23–30, 1984.
261. Korman, M. G., et al.: Influence of smoking on healing rate of duodenal ulcer in response to cimetidine or high-dose antacid. Gastroenterology 80: 1451–1453 (1981).
262. Murthy, S. N. S., Dinoso, V. P., Clearfield, H. R., and Chey, W. Y.: Simultaneous measurement of basal pancreatic, gastric acid secretion, plasma gastrin, and secretin during smoking. Gastroenterology 73: 758–761 (1977).
263. Konturek, S. J., Dale, J., Jacobson, E. D., and Johnson, L. R.: Mechanisms of nicotine-induced inhibition of pancreatic secretion of bicarbonate in the dog. Gastroenterology 62: 425–429 (1972).
264. Abel, E. L.: Smoking during pregnancy: A review of effects on growth and development of offspring. Hum Biol 52: 593–625 (1980).
265. Longo, L. D.: The biological effects of carbon monoxide on the pregnant woman, fetus and newborn infant. Am J Obstet Gynecol 129: 69–103 (1977).
266. Bureau, M. A., et al.: A study of P50,2,3-diphosphoglycerate, total hemoglobin, hematocrit and type F hemoglobin in fetal blood. Pediatrics 72: 22–26 (1984).
267. Ayromlooi, J., Desiderio, D., and Tobias, M.: Effect of nicotine sulfate on the hemodynamics and acid base balance of chronically instrumented pregnant sheep. Dev Pharmacol Ther 3: 205–213 (1981).
268. Resnik, R., Brink, G. W., and Wilkes, M.: Catecholamine-mediated reduction in uterine blood flow after nicotine infusion in the pregnant ewe. J Clin Invest 63: 1133–1136 (1979).
269. Hibberd, A. R., O'Connor, V., and Gorrod, J. W.: Detection of nicotine, nicotine-1'-N-oxide and cotinine in maternal and fetal body fluids. *In* Biological oxidation of nitrogen, edited by J. W. Gorrod. Elsevier, Amsterdam, 1978, pp. 353–361.
270. National Institutes of Health: Health implications of smokeless tobacco use. Consensus Development Conference Statement. Vol. 6, No. 1, Bethesda, MD, 1986.

Smoking and Smokeless Tobacco Use Among Adolescents: Trends and Intervention Results

STEVEN PAUL SCHINKE, PhD
LEWAYNE D. GILCHRIST, PhD
ROBERT F. SCHILLING, II, PhD
VIRGINIA A. SENECHAL, BA

Dr. Schinke is Professor and Dr. Schilling is Assistant Professor, School of Social Work, Columbia University, New York, NY. Dr. Gilchrist is Research Scientist and Ms. Senechal is Research Associate, School of Social Work, University of Washington, Seattle.

Funding was provided by grant No. CA29640, Division of Cancer Prevention and Control, National Cancer Institute.

Tearsheet requests to Dr. Schinke, School of Social Work, Columbia University, 622 West 113th St., New York, NY 10025.

Synopsis

Data from a 2-year study describe tobacco use trends, perceptions, and prevention effects for 1,281 5th and 6th graders enrolled in 12 randomly selected Washington State elementary schools. Youths were pretested, then randomly divided by school into skills, discussion, and control groups. Preventive intervention curriculums for the skills and discussion groups included age-relevant information on smoked and smokeless tobacco use, peer testimonials, debates, games, and homework. Youths in the skills group also learned communication and problem-solving methods for handling difficult situations around tobacco use. Following intervention, youths were posttested, then retested semiannually for 2 years.

During the 2-year study, three-quarters of all smokers and nonusers and half of all smokeless tobacco users maintained their statuses. Only 10 percent of all smokers and 3 percent of all smokeless users quit their habits. One in six reported new tobacco use, one-third of smokers began using smokeless tobacco, and two-thirds of all smokeless users began smoking during the study. Most youths at final measurement perceived smokeless tobacco as less of a health risk than smoking. Nearly one in two of all smokeless users intended to smoke, and two-thirds were actually smoking at 24-month followup. Both smoked and smokeless tobacco use rates increased in all groups, and youths in the skills intervention group consistently showed the lowest rates relative to the other groups. These findings demonstrate the potential of skills intervention methods for lowering tobacco use rates among adolescents.