CHEMICAL COMPOSITION AND CARCINOGENICITY OF SMOKELESS TOBACCO

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Abstract—In the United States, smokeless tobacco (ST) is marketed as chewing tobacco and as oral snuff. During the past 15 years, consumption of chewing tobacco has declined by 30.6%, whereas snuff use has significantly increased, namely, by 51.8%. This increase is primarily due to the growing popularity of oral snuff use among teenage and young adolescent males. Chewing of tobacco is associated with an increased risk for oral cancer. Snuff dipping is causally and specifically associated with cancer of the cheek, gum, and pharynx. In laboratory animals, snuff induces cancer of the mouth. Several carcinogens have been identified in ST, the tobacco-specific *N*-nitrosamine (TSNA), *N'*-nitrosonornicotine (NNN), and 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) being the most important. NNN and NNK are formed from nicotine during curing, aging, and especially during fermentation of tobacco. Oral swabbing of a low concentration of a mixture of NNN plus NNK in water induces oral tumors in rats. The concentration of the strongly carcinogenic TSNA is higher in snuff than in other ST products. According to our analytical studies, the three leading snuff brands in the US (92% of the market) contain far higher concentrations of nicotine, unprotonated nicotine, and TSNA than the less popular brands. Thus, the leading US snuff brands are the strongest inducers of nicotine dependence and also have the highest carcinogenic potential.

Key words: Bioassay, carcinogenicity, oral neoplasms, smokeless tobacco, snuff, tobacco-specific *N*-nitrosamines.

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In the United States, there are four primary types of smokeless tobacco. These include three kinds of chewing tobacco (loose-leaf [or scrap leaf], plug, and twist tobacco), as well as snuff. Loose-leaf tobacco, accounting for 91.6% of the chewing tobacco sold in 1995 (US Department of Agriculture, 1995), consists mainly of air-cured tobacco. In most cases, loose-leaf tobacco is heavily treated with licorice and sugar. Plug tobacco (6.6% of chewing tobacco sales in 1995) is produced from heavier grades of leaves that are harvested from the top of the plant and separated from stems. It is then immersed into a mixture of licorice and sugar, pressed into a plug, covered with a wrapper leaf, and re-shaped. The chewer keeps plug tobacco between cheek and gum and chews bits of it. Twist tobacco (1.7% of chewing tobacco sales in 1995) is made with air- and fire-cured burley and is flavored and twisted to resemble a decorative rope or pigtail. The dry form of oral snuff is less popular than moist snuff. Dry snuff is produced chiefly from Kentucky and Tennessee fire-cured tobaccos. After the initial curing process, which takes several weeks, the leaves undergo a fermentation process. They are then powdered and often enriched with flavor additives, including spices. US dry snuff, which is taken orally, is somewhat similar to European nasal snuff. Moist snuff, on the other hand, is manufactured from air- and fire-cured tobacco laminae and stems which are shredded. Moist snuff contains from 20 to 60% moisture and is often flavored with wintergreen, raspberry, cinnamon, cherry, or mint. The oral use of snuff was introduced in the US in the middle of the 19th century by Scandinavian lumberjacks working in the northern United States. "Snuff dipping" of loose snuff, or of tobacco placed into sachets, is practiced by placing the product between cheek (or lips) and gums or beneath the tongue. The snuff is then continuously extracted with saliva.

Around the turn of the century, about 120 million pounds of chewing tobacco were consumed in the United States. In the following decades, consumption declined gradually to a low of about 60 million pounds in the mid-'60s (US Department of Agriculture, 1955; Creek *et al.*, 1994). After the first Surgeon General's Report on Smoking and Health that warned about the health hazards of smoking (1964), chewing tobacco became increasingly popular, so that consumption reached a new high of 90 million pounds between 1980 and 1985. Since then, consumption decreased as a consequence of the Surgeon General's 1986 Report on the Health Consequences of Using Smokeless Tobacco. However, the use of snuff, especially moist snuff, has increased from a 1975 low of 31 million pounds to nearly 60 million pounds in 1995; it is predicted to grow further in the coming years and will most likely surpass the consumption of chewing tobacco (Fig. 1). A major reason for the increased use of moist snuff lies in the growing prevalence of snuff

TABLE 1

CONSUMPTION OF ORAL SNUFF, CHEWING TOBACCO, AND CIGARETTES IN THE USA (1950, 1980, and 1995)

Year	Oral Snuff[1]		Chewing Tobacco		Cigarettes		US Adult Population[2]	
	10^6 lbs.	Change %	10^6 lbs.	Change %	10^9	Change %	10^6	Change %
1950	42.7		84.8		375.8		121.97	
1980	40.0		91.2		631.5		182.48	
		- 6.8		+ 7.5		+68.0		+49.6
1995	60.7		63.3		487.0		211.65	
		+51.8		-30.6		-22.9		+16.0

[1] Snuff plus fine-cut tobacco.

[2] Adult = ≥ 15 years of age.

Sources: US Dept. of Agriculture, 1995; Creek *et al.*, 1994.

dipping among male adolescents aged 12 to 18 years and young adults aged 19 years and older (Table 1; Orlandi and Boyd, 1989; Tomar *et al.*, 1995). Banning smoking in public buildings, restaurants, conveyances, and many offices and workplaces also contributed to snuff use as an alternative tobacco habit.

BIOASSAYS FOR CARCINOGENICITY

Until 1981, bioassays had failed to elicit tumors of the oral cavity in laboratory animals treated with smokeless tobacco or extracts thereof (Hoffmann *et al.*, 1992). The major reason for this failure was our inability to reproduce in animals the human habits of tobacco chewing or snuff dipping. Animals were simply not willing to keep smokeless tobacco in their mouths. It was a Swedish dentist who finally tricked rats by creating a surgical canal in the lower lips of the animals into which small amounts of snuff were inserted twice daily, eventually inducing lesions in the oral mucosa. The saliva of the animals served to extract nicotine and the major snuff carcinogens from the snuff in the lip canal (Fig. 2; Hirsch and Thilander, 1981). Upon refining this method, our group (Hecht *et al.*, 1986) and Johansson *et al.* (1989) succeeded in inducing benign and malignant tumors in the mouths of rats. In another bioassay, Park *et al.* (1986) demonstrated that infections with herpes simplex virus type 1 (HSV-1) and HSV-2 promote the carcinogenic effect of snuff in the buccal pouches of hamsters (Table 2).

TABLE 2

TUMORS IN THE ORAL CAVITY INDUCED WITH SNUFF

Authors	Animals	#	Material	Method	Tumors		
					Oral Cavity	Lung	Others
Hecht *et al.*, 1986	Rats	32	Snuff	Lip canal	3[a]	2	13
	Rats	10		Lip canal	0	1	6
Johansson *et al.*, 1989	Rats	29	Snuff	Lip canal	6[b]		
Park *et al.*, 1986	Hamsters	15	Snuff	Buccal pouch	0		
		20	Snuff +HSV-1	Buccal pouch	10[c]		
		20	Snuff +HSV-2	Buccal pouch	11[c]		
		20	HSV-1	Buccal pouch	0		
		20	HSV-2	Buccal pouch	0		

[a] One rat had a papilloma of the gingiva, 1 rat a squamous cell carcinoma (SCC) of the gingiva, 1 rat a tumor of the hard palate, and 3 rats tumors in the lip canal.

[b] One rat had a SCC of the lip, 2 rats SCC of the hard palate, 1 rat SCC *in situ* on the hard palate, 1 rat papilloma of the lip, and 1 rat papilloma of the hard palate.

[c] All tumors were invasive SCC of the buccal pouches.

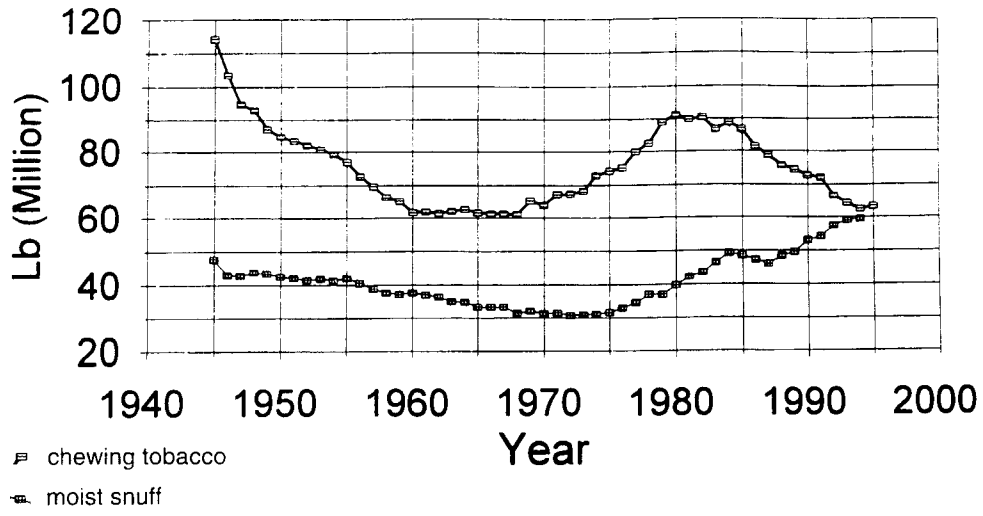

Fig. 1—Smokeless tobacco production in the US, 1945-1994. Sources: USDA, 1995; Creek et al., *1995.*

Fig. 2—Rat with surgically induced lip canal. Source: Hecht et al., *1986.*

The epidemiological data by Winn *et al.* (1981) and by Spitz *et al.*, (1988) and the clinical observations by Wray and McGuirt (1993) had demonstrated a strong association between snuff dipping and cancer of the oral cavity and larynx. These data were now supported by the successful induction of tumors in the mouths of laboratory animals. The increasing use of snuff by teenagers and adolescents and by a high percentage of schoolchildren among some Indian tribes (Bruerd, 1990) and young Eskimos (Peterson *et al.*, 1990) motivated us to continue our research program on smokeless tobacco and oral snuff.

CARCINOGENS IN SMOKELESS TOBACCO

About 30 carcinogens have been identified in chewing tobacco and snuff (Table 3; Brunnemann and Hoffmann, 1992). Among these, the major contributors to the carcinogenic activity of these types of tobacco are the tobacco-specific *N*-nitrosamines (TSNA). These agents are formed exclusively from nicotine and from the minor tobacco alkaloids, primarily during the processing, fermentation, and aging of tobacco (Fig. 3; Hoffmann *et al.*, 1994). The TSNA are organ-specific carcinogens, *i.e.*, independent of the route of their application, they induce mainly tumors in specific host tissues and organs. For example, *N'*-nitrosonornicotine, which is formed by *N'*-nitrosation of nicotine and nornicotine, induces tumors of the esophagus, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) elicits adenoma and adenocarcinoma of the lung in mice, rats, and hamsters (Hoffmann *et al.*, 1994). The significance of the TSNA in oral carcinogenesis is supported by the fact that swabbing of the rats' oral surfaces with a solution of the two nicotine-derived *N*-nitrosamines, NNN and NNK, induced tumors of the cheek, palate, and tongue. Because of the organ-specificity of NNK, we also observed adenocarcinoma of the lung in these rats (Table 4; Hecht *et al.*, 1986). The concentrations of NNN and NNK in the swabbing solution applied in these assays were rather high, namely, 55 ppm and 11 ppm, respectively, by comparison with the concentrations of these agents in the saliva of snuff dippers, which are up to 0.23 ppm and 0.2 ppm (Hoffmann and Adams, 1981; Palladino *et al.*, 1986). Then again, a snuff dipper takes, on the average, 10 dips of snuff *per* day. The rats in our bioassay were ultimately exposed to between 5 and 10 times higher levels of NNN and NNK than the snuff dipper. Also, treating the oral cavity with a cotton swab is less irritating than the abrasion caused by snuff dipping. The latter is believed to enhance absorption of the carcinogens from snuff (Andersson and Axéll, 1989). It is important to bear in mind that the oral surfaces of the snuff dippers are also exposed to carcinogenic *N*-nitrosamino acids, volatile *N*-nitrosamines, formaldehyde, and acetaldehyde, and to traces of carcinogenic hydrocarbons and polonium-210 (Table 3).

BIOCHEMISTRY

Fig. 4 delineates the metabolism of the two major carcinogenic TSNAs, NNN and NNK. Their metabolic activation

TABLE 3

CARCINOGENIC AGENTS IN TOBACCO

	Tobacco Type[b]	Concentration (ng/g)[c]	IARC Evaluation of Evidence of Carcinogenicity[a] In Laboratory Animals	IARC Evaluation of Evidence of Carcinogenicity[a] In Humans
Benzo[*a*]pyrene	NT, S	> 0.1-90.0	Sufficient	Probable
α-Angelica lactone	NT	Present		
β-Angelica lactone	NT	Present		
Coumarin	NT	600	Limited	
Ethyl carbamate	CT	310-375	Sufficient	
Volatile Aldehydes				
Formaldehyde	NT, S	1600- 7400	Sufficient	Probable
Acetaldehyde	NT, S	1400-27,400	Sufficient	
Crotonaldehyde	S	200- 2400		
Nitrosamines				
Nitrosodimethylamine	CT, S	ND- 270	Sufficient	Probable
Nitrosopyrrolidine	CT, S	ND- 760	Sufficient	
Nitrosopiperidine	CT, S	ND- 110	Sufficient	
Nitrosomorpholine	CT, S	ND- 690	Sufficient	
Nitrosodiethanolamine	CT, S	40-6800	Sufficient	
Nitrosamino Acids				
Nitrososarcosine	S	ND-2500	Sufficient	
3-(methylnitrosamino)-propionic acid	CT, S	200-65,700		
4-(methylnitrosamino)-butyric acid	CT, S	ND-9100		
Nitrosoazetadine-2-carboxylic acid	CT	4-140		
Tobacco-specific Nitrosamines				
N'-nitrosonornicotine	CT, S	400-147,000	Sufficient	
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	CT, S	ND-18,000	Sufficient	
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	S	Present		
N'-nitrosoanabasine	SM, S	Present-560	Limited	
Inorganic Compounds				
Hydrazine	SM	14-51	Sufficient	Inadequate
Arsenic	NT	500-900	Inadequate	Sufficient
Nickel	SM, S	180-2700	Sufficient	Sufficient
Cadmium	SM	700-790	Sufficient	Sufficient
		pCi/g		
Polonium-210	NT, S	0.16-1.22	Sufficient	Sufficient
Uranium-235 and -238	S	2.4, 1.91		

[a] Absence of a designation indicates that IARC was not evaluated.

[b] NT, natural tobacco; SM, smoking tobacco; S, snuff; CT, chewing tobacco.

[c] ND = not determined.

occurs by α-hydroxylation. The α-hydroxynitrosamines decompose to alkylating agents that can react with DNA, RNA, or protein. The α-hydroxylation of the methylene group of NNK and decomposition of this hydroxynitrosamine lead, *via* methyl diazohydroxide, to a methyl-radical. The free radical causes the formation of 7-methylguanine and of the mutagenic O^6-methylguanine, as well as of *N*-4-thymidine in DNA. The α-hydroxylation of the methyl group of NNK and

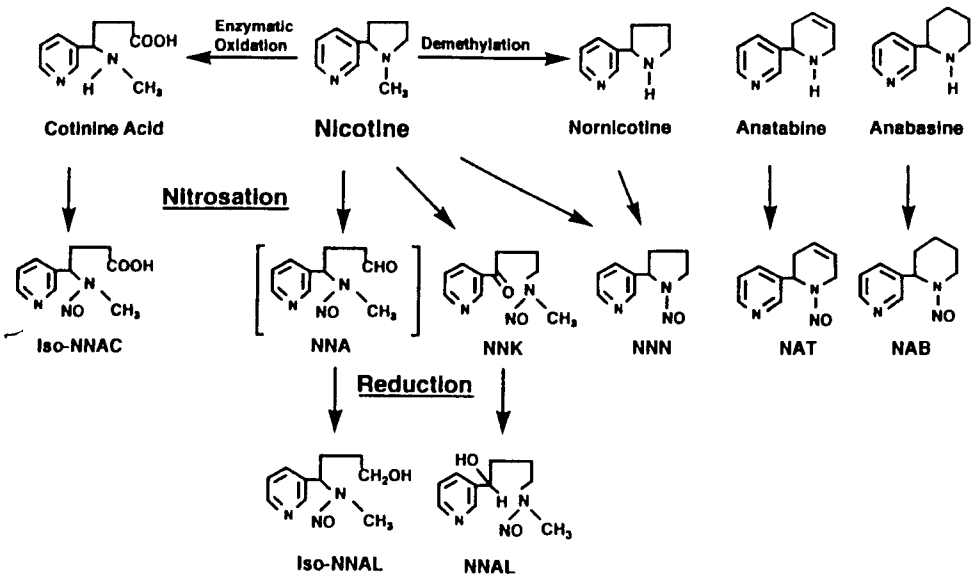

Fig. 3—Formation of tobacco-specific N-*nitrosamines. Source: Hoffmann* et al., *1994.*

serve as a biomarker to indicate exposure to NNN and NNK (Fig. 5; Carmella *et al.*, 1990). In addition, the exposure to NNK is indicated by the reduction product of NNK 4-(3-methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), which can be determined in urine as free NNAL and as a glucuronide (Murphy *et al.*, 1994). Thus, we are now able to assay exposure and uptake of nicotine and TSNA by determining their metabolites in the urine of tobacco chewers and snuff dippers.

NICOTINE DEPENDENCE AND CARCINOGENICITY OF SNUFF BRANDS

NNN at the C-2' position leads *via* 4-(3-pyridyl)-4-oxobutyl diazohydroxide to the corresponding radical which binds to DNA or other proteins. Upon hydrolysis of such adducts, 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB) is released (Carmella *et al.*, 1990; Hecht *et al.*, 1991). Hydrolysis of the hemoglobin adducts of snuff dippers leads to HPB, which can

It is well-known that tobacco habits—including chewing, dipping, and smoking—are fostered by the user's dependence on nicotine (US Surgeon General, 1988). The absorption of nicotine through the oral mucosa of chewers and dippers is enhanced when the pH levels go above 6.0-6.2 (Armitage and Turner, 1970). At acidic pH, nicotine is present in smokeless

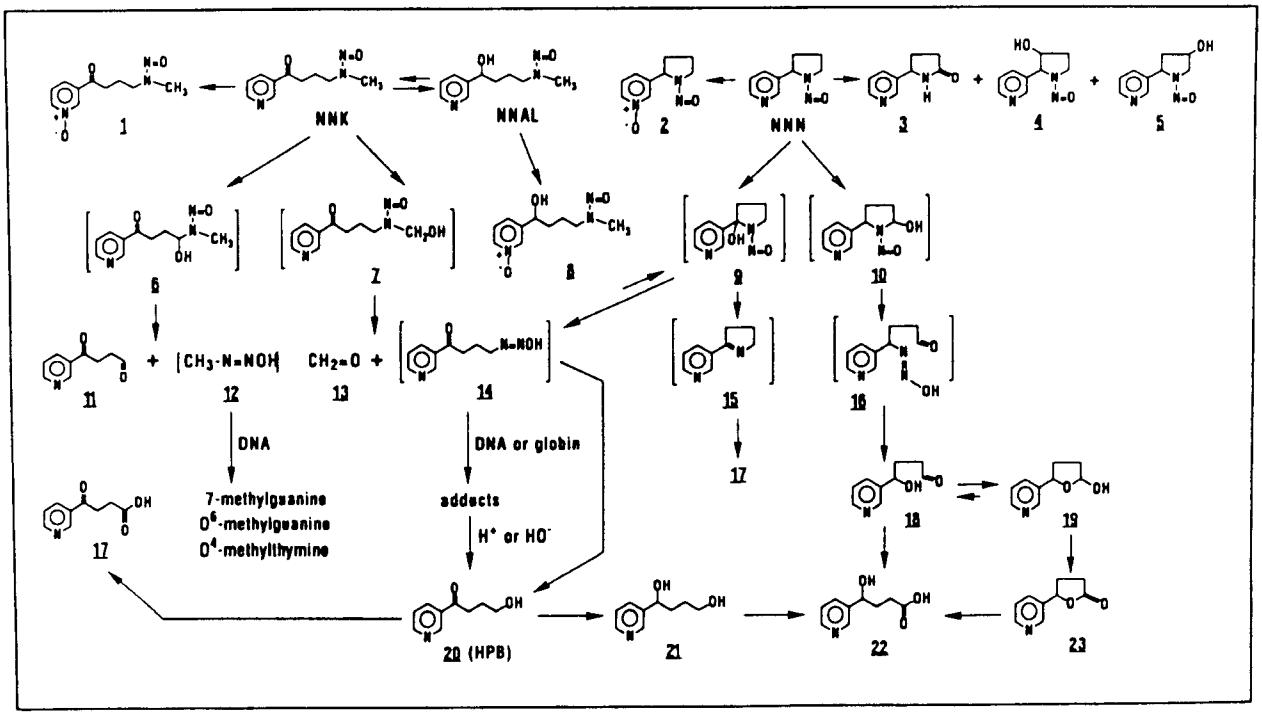

Fig. 4—Metabolic pathways of NNK and NNN. Source: Hecht et al., *1992.*

TABLE 4

SWABBING OF THE ORAL CAVITY OF RATS WITH SOLUTION CONTAINING NNN AND NNK[a]

Group	No. of Rats	No. of Rats with Tumors		
		Oral Cavity	Lungs	Other
NNN + NNK	30	8[b]	5[c]	27
H_2O Control	21	0	1[d]	23

[a] Swabbing of the oral cavity with 0.5 mL of water solution containing 55 ppm NNN and 11 ppm NNK.
[b] Tumors: 6 cheek, 1 hard palate, 2 tongue.
[c] One adenoma, 4 adenocarcinoma.
[d] One adenoma.
Source: Hecht *et al.*, 1986.

tobacco in protonated form as a salt with organic acids (Brunnemann and Hoffmann, 1974). However, 9% of the nicotine at pH 7.0 and 50% of the nicotine at pH 8 are present in chewing tobacco or snuff in unprotonated form as a free base. Free nicotine is absorbed more rapidly and thus reaches the central nervous system (CNS) more quickly, whereby it enhances a sense of well-being, produces first arousal, then relaxation, helps maintain vigilance, and reduces anxiety (Benowitz *et al.*, 1989).

Recent studies by Henningfield *et al.* (1995) and by our group (Djordjevic *et al.*, 1995) have determined that the leading US snuff brands (Copenhagen, Skoal, and Kodiak) have 22% to 60% of the nicotine present in unprotonated form. These three brands account for 92% of the sales in the US snuff market; whereas Hawken and Skoal Bandit, accounting for only 3% of the market, have less than 1% of the nicotine present in unprotonated form. These data on unprotonated nicotine and the sales figures support the concept of Connolly (1995) that the formulation of the leading snuff brands may be aimed at creating and maintaining nicotine dependence. We have to be reminded that, according to Benowitz (1991), the greatest concern for nicotine-related effects is the acceleration or aggravation of cardiovascular disease.

However, we have focused our research on the carcinogenicity of snuff. In a recent monitoring effort, we analyzed the five leading US snuff brands for their concentrations of the highly carcinogenic NNN and NNK. The leading three brands with the highest pH value, highest nicotine levels, and highest percentage of unprotonated nicotine were also found to be the richest in nitrite and, therefore, in the carcinogenic *N*-nitrosamines (Table 5; Hoffmann *et al.*, 1995). The essential factor for the formation of the TSNA is the microbial reduction of nitrate to nitrite, which is the *N*-nitrosating agent for the alkaloids. The differences in the concentrations of unprotonated nicotine, NNN, and NNK between the three leading snuff brands (92% of the market) and the fourth and fifth leading snuff brands (3% of the market) were statistically highly significant. Unfortunately, it is not expected that the high levels of unprotonated nicotine and carcinogenic *N*-nitrosamines in the leading US snuff brands will be voluntarily changed in the near future by the industry.

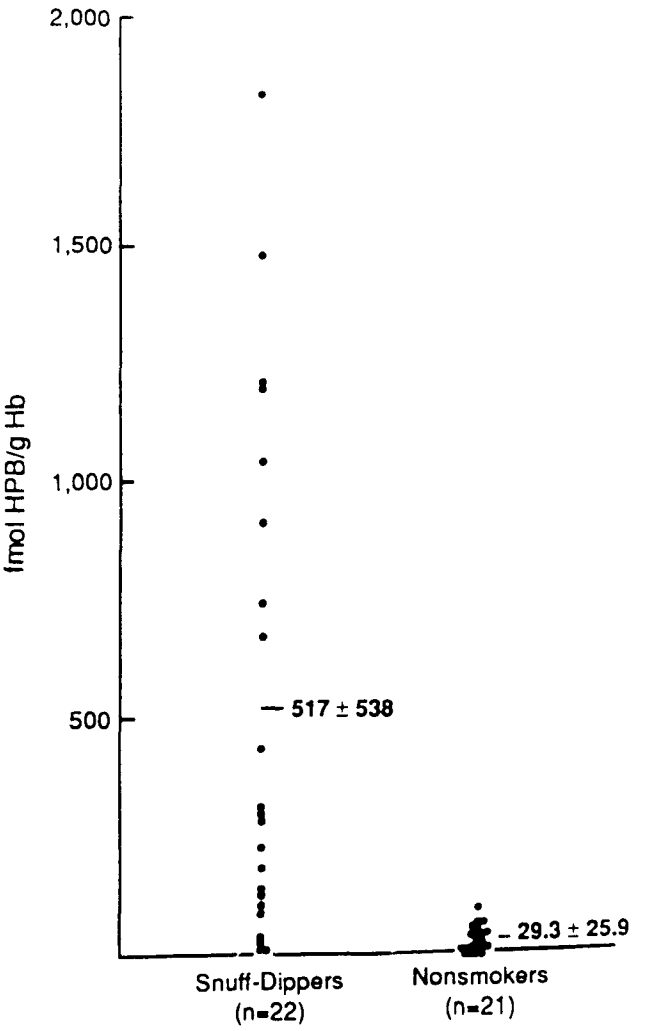

Fig. 5—Levels of HPB released from hemoglobin of snuff dippers and non-smokers. Source: Carmella et al., *1990.*

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REFERENCES

Andersson G, Axéll T (1989). Clinical appearance of lesions associated with the use of loose and portion-bag packed Swedish moist snuff. A comparative study. *J Oral Pathol Med* 18:2-7.

TABLE 5

FIVE LEADING US SNUFF BRANDS[a]

Brand Name	Nicotine mg/g	pH of Suspension	Unprotonated Nicotine, %	Nitrite-N µg/g	NNN µg/g	NNK µg/g
Copenhagen (42)[b]	12.0 ± 0.7	8.00 ± 0.31	49.0 ± 16.7	67.2 ± 297	8.73 ± 1.44	1.89 ± 0.62
Skoal, Fine-cut (39)	11.9 ± 1.3	7.46 ± 0.14	22.0 ± 5.73	64.5 ± 41.9	8.18 ± 1.33	1.25 ± 0.13
Kodiak (11)	10.9 ± 0.8	8.19 ± 0.11	59.7 ± 6.01	2.77 ± 1.13	6.30 ± 1.06	0.55 ± 0.15
Hawken (1)	3.2 ± 0.2	5.71 ± 0.10	0.5 ± 0.11	1.4 ± .8	3.07 ± 0.30	0.23 ± 0.04
Skoal Bandits (2)	10.1 ± 0.8	5.37 ± 0.12	0.23 ± 0.05	1.3 ± 0.4	5.09 ± 1.03	0.92 ± 0.26

[a] Average values from the analysis of 2 samples each from each brand collected on the open market in July, 1994, in 6 US locations (Westchester, NY; Boston, MA; Lexington, KY; Denver, CO; Alameda, CA; Lansing, MI).

[b] Number in parentheses = market share.

Source: Djordjevic *et al.*, 1995; Hoffmann *et al.*, 1995.

Armitage AK, Turner DM (1970). Absorption of nicotine in cigarette and cigar smoke through the oral mucosa. *Nature* 226:1231-1232.

Benowitz NL (1991). Nicotine and coronary heart disease. *Trends Cardiovasc Med* 1:315-321.

Benowitz NL, Jacob P III, Yu L (1989). Daily use of smokeless tobacco: systemic effects. *Ann Intern Med* 111:112-116.

Bruerd B (1990). Smokeless tobacco use among native American school children. *Publ Hlth Rep* 105:196-201.

Brunnemann KD, Hoffmann D (1974). The pH of tobacco smoke. *Food Cosmet Toxicol* 12:115-124.

Brunnemann KD, Hoffmann D (1992). Chemical composition of smokeless tobacco products. Smoking and Tobacco Control Monogr. Vol. 2. National Cancer Institute, pp. 96-108.

Carmella SG, Kagan SS, Kagan M, Foiles PG, Palladino G, Quart E, *et al.* (1990). Mass spectrometric analysis of tobacco-specific nitrosamine hemoglobin adducts in snuff dippers, smokers, and nonsmokers. *Cancer Res* 50:5438-5445.

Connolly GN (1995). The marketing of nicotine addiction by one oral snuff manufacturer. *Tobacco Control* 4:73-79.

Creek L, Capehart T, Grise V (1994). Tobacco statistics 1935-1992. US Dept. of Agriculture. *Stat Bull* 869:299.

Djordjevic MV, Hoffmann D, Glynn T, Connolly GN (1995). US commercial brands of moist snuff, 1994. I. Assessment of nicotine, moisture, and pH. *Tobacco Control* 4:62-66.

Hecht SS, Rivenson A, Braley J, DiBello J, Adams JD, Hoffmann D (1986). Induction of oral cavity tumors in F344 rats by tobacco-specific *N*-nitrosamines and snuff. *Cancer Res* 46:4162-4166.

Hecht SS, Haley NJ, Hoffmann D (1991). Monitoring exposure to tobacco products by measurement of nicotine metabolites and derived carcinogens. In: Molecular dosimetry and human cancer: analytical, epidemio-logical, and social considerations. Groopmann JD, Skipper PL, editors. Boca Raton, FL: CRC Press, pp. 325-361.

Henningfield JE, Radzins A, Cone EJ (1995). Estimation of available nicotine content of six smokeless tobacco products. *Tobacco Control* 4:57-61.

Hirsch J-M, Thilander H (1981). Snuff-induced lesions of the oral mucosa: an experimental model in the rat. *J Oral Pathol* 10:342-353.

Hoffmann D, Adams JD (1981). A study of tobacco carcinogenesis. XXIII. Carcinogenic tobacco-specific *N*-nitrosamines in snuff and in the saliva of snuff dippers. *Cancer Res* 41:4305-4308.

Hoffmann D, Rivenson A, Hecht SS (1992). Carcinogenesis of smokeless tobacco. In: Smokeless tobacco or health: An international perspective. National Cancer Institute, Smoking & Tobacco Control Monogr. 2. NIH Publ. No. 92-3461, Sept., pp. 109-118.

Hoffmann D, Brunnemann KD, Prokopczyk B, Djordjevic MV (1994). Tobacco-specific *N*-nitrosamines and *areca*-derived *N*-nitrosamines: chemistry, biochemistry, carcinogenicity, and relevance to humans. *J Toxicol Environ Hlth* 41:1-52.

Hoffmann D, Djordjevic MV, Fan J, Zang E, Glynn T, Connolly GN (1995). Five leading US commercial brands of moist snuff in 1994: assessment of carcinogenic *N*-nitrosamines. *J Natl Cancer Inst* 87:1862-1869.

Johansson SL, Hirsch JM, Larsson PA, Saidi J, Oesterdahl BG (1989). Snuff-induced carcinogenesis: effect of snuff in rats initiated with 4-nitroquinoline-*N*-oxide. *Cancer Res* 49:3063-3069.

Murphy SE, Carmella SG, Idris AM, Hoffmann D (1994). Uptake and metabolism of carcinogenic levels of tobacco-specific nitrosamines by Sudanese snuff dippers. *Cancer Epidemiol Biomarkers Prev* 3:423-428.

Orlandi MA, Boyd G (1989). Smokeless tobacco use among adolescents; a theoretical overview. *Natl Cancer Inst Monogr* 8:5-12.

Palladino G, Adams JD, Brunnemann KD, Haley NJ, Hoffmann D (1986). Snuff dipping in college students: a clinical profile. *Military Med* 151:342-346.

Park N-H, Sapp JP, Herbosa EG (1986). Oral cancer induced in hamsters with *herpes simplex* infection and simulated snuff dipping. *Oral Surg Oral Med Oral Pathol* 62:164-168.

Peterson JS, Barreto LA, Brunnemann KD (1990). Smokeless tobacco: a product of the new generation of tobacco users. Dipping and chewing in the Northwest Territories, Canada, and its global relevance. *Arctic Med Res* 2(Suppl 49):32-38.

Spitz MR, Fueger JJ, Goepfert H, Hong WK, Newell GR (1988). Squamous cell carcinoma of the upper aerodigestive tract. A case comparison analysis. *Cancer* 61:203-208.

Tomar SC, Giovino GA, Eriksen MP (1995). Smokeless tobacco brand preference and brand switching among US adolescents and young adults. *Tobacco Control* 4:67-72.

US Department of Agriculture (1995). Statistical summary. *Tobacco Sit Ser* 233:13-16.

US Surgeon General (1964). Smoking and health. US Department of Health, Education and Welfare. PHS Publ. No. 1103, p. 387.

US Surgeon General (1986). The health consequences of using smokeless tobacco. US Department of Health and Human Services. NIH Publ. No. 86-2874, p. 195.

US Surgeon General (1988). The health consequences of smoking. Nicotine addiction. US Department of Health and Human Services. DHHS Publ. No. (CDC) 88-8406, p. 639.

Winn DM, Blot WJ, Shy CM, Pickle LW, Toledo A, Fraumeni JF (1981). Snuff dipping and oral cancer among women in the southern United States. *New Engl J Med* 304:745-749.

Wray A, McGuirt WF (1993). Smokeless tobacco usage associated with oral carcinoma. Incidence, treatment, outcome. *Arch Otolaryngol Head Neck Surg* 119:929-933.