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SNUFF—AN ALTERNATIVE NICOTINE DELIVERY SYSTEM

by Lars M. Ramström, PhD

Snuff Use

Snuff is a form of smokeless tobacco containing finely ground or cut tobacco leaves. It can be either dry (water content < 10%) or moist (water content 40%-60%). Snuff can be administered in the nose or in the oral cavity. Nasal use means "sniffing" dry snuff into the nose. Oral use is putting a portion ("pinch") of dry or moist snuff between the upper or lower lip or cheek and the gum. Snuff is not chewed like plug and twist (chewing tobacco) and it is therefore unsuitable to talk about "chewing" snuff, as is sometimes done. The pinch of snuff may be subjected to some squeezing but basically is held in position for about half an hour, letting the saliva extract various compounds. Then the remainder is taken out and discarded. This type of oral use is most often referred to as "snuff dipping," although this expression originally referred to a special procedure whereby snuff was administered to the gums by means of wooden sticks that had been "dipped" in snuff (1).

In the western world, snuff is mainly used in Sweden and North America. Moist snuff is the dominant type, while dry snuff is a small and shrinking part of the whole market (2). This paper focuses on moist snuff.

Manufacturing Procedures

Overview

Moist snuff is usually made from a mixture of several kinds of tobacco leaves, such as dark, nicotine-rich, fire-cured, and air-cured leaves. The proportion of different kinds of leaves in this mixture determines to a large extent the taste and other properties of the final product. Individual brands thereby have their own specific characteristics.

The manufacturing procedures may differ between producers. Most important is the distinction between procedures that include fermentation and those that do not. The fermentation method is the traditional one still prevalent among American producers. In Sweden, the only producer (Swedish Match, Snuff

Division—formerly Swedish Tobacco) switched in 1981 to a strictly nonfermentation method using a heat-treatment process (3). In both cases, the leaves are mechanically ground or cut to small particles or thin strips (exact size differing between brands), small amounts of flavoring agents and other additives are provided, and the humidity of the end product is controlled to reach values around 50%. The snuff is packed in pocket-size tins or boxes typically containing 50 g. The boxes may contain either "loose" snuff or tea-bag-like "sachets" with 1.0 g of snuff. In Sweden, "mini-pinches" of 0.5 g are also available.

American Snuff

The main feature of the usual American manufacturing procedure is a microbiological fermentation of the tobacco, resulting in major changes in its physical and chemical characteristics. One feature is the formation of nitrite, thereby allowing for nitrosation of tobacco alkaloids, that is, formation of tobacco-specific nitrosamines (TSNAs). Another important feature is that the bacteria involved in the fermentation consume much of the acids originally present in the tobacco, thereby increasing the pH to make the snuff alkaline, which accelerates oral uptake of nicotine. The fermentation takes place at a temperature of 25-30°C. At the end of this process, the tobacco is cooled down and no further reactions are meant to occur. However, since bacteria are still there, continued formation of TSNAs may occur, especially if the snuff packages are stored for an appreciable time unrefrigerated before being sold and consumed (1, 2).

Swedish Snuff

The main feature of the Swedish manufacturing procedure is a heating process. After grinding and sieving of the tobacco leaves, the dry "tobacco meal" undergoes a 24-36-hour processing program with different temperature phases in which it is treated with water vapor under continuous stirring. Various flavoring and other agents are added. In the absence of fermentation, there is no formation of nitrite and consequently no continued formation of TSNAs. The appropriate pH is achieved by adding sodium carbonate. The originally present bacteria are killed by the heat, and the end product is virtually sterile. Therefore, the risk for formation of TSNAs during storage is greatly reduced. As a further measure to prevent formation of TSNAs during storage, Swedish snuff comes to the retailer with a message printed on the wrapper of each package of 10 boxes recommending refrigeration until it is picked up by the consumer.

The heating process also eliminates most of the volatile nitrosamines present in the raw tobacco through evaporation (3).

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Composition of Moist Snuff

Main Ingredients

The Swedish manufacturers have listed the following proportions of main ingredients of their nonfermented moist snuff (3):

Tobacco	40 - 45%
Water	45 - 60%
Sodium chloride (for preservation purposes)	1.5 - 3.5%
Humectants	1.5 - 3.5%
Sodium carbonate	1.2 - 2.5%
Flavor	< 1%

On this general level, the corresponding data for fermented moist snuff are probably similar.

The tobacco in snuff contains most of the substances present in green tobacco leaves plus substances that have been formed during curing and processing. At least 2500 compounds have been identified in processed tobacco (2).

Alkaloids

Alkaloids constitute 0.5-5.0% of the leaf, depending on the strain, variety, and agricultural practices that are employed during the tobacco cultivation. Nicotine makes up between 85% and 95% of total alkaloids. Other major alkaloids are nornicotine, anatabine, and anabasine. Different kinds of snuff contain from 0.5% to 1.3% nicotine.

N-Nitrosamines

Certain volatile nitrosamines are present in cured tobacco leaves and are still present in fermented snuff. In the Swedish nonfermentation manufacturing procedure, the heating forces most of the volatile nitrosamines to evaporate so that the snuff is virtually free of these compounds. This is illustrated by measurements made at the laboratory of the Swedish Food Administration. In 1979, when the old process was still used in Sweden, concentrations of 107 ppb were commonly measured. In the years 1982 and 1983, when the new heating process was introduced, new measurements found concentrations of 8.2 ppb and 5.9 ppb, respectively (4). The large reduction came with the introduction of the new manufacturing process, and further progress was made by refinement of the process and sharpening of the quality requirements for the raw tobacco being used. Analysis of American moist snuff in 1985/1986 showed concentrations of volatile nitrosamines in different brands ranging from 35 ppb to 166 ppb (5).

With regard to potential carcinogenic effects of snuff dipping, the greatest attention has been given to the TSNAs. The background conditions for formation of TSNAs are established already in the tobacco fields when nitrate-containing fertilizers are used and taken up in the tobacco plant. During curing and fermentation, bacteria-induced reactions reduce nitrate to nitrite so that there is a nitrosation of tobacco alkaloids, resulting in formation of TSNAs. Different alkaloids will give rise to different TSNAs (2).

Nornicotine + Nitrite ===> NNN (N-nitrosonornicotine)
Anabasine + Nitrite ===> NAB (N-nitrosoanabasine)
Anatabine + Nitrite ===> NAT (N-nitrosoanatabine)
Nicotine + Nitrite ===> NNN + NNK (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone)

Table 1 gives examples of concentrations (ppm dry weight) of TSNAs found in studies in the United States and Sweden.

Table 1
Examples of TSNA Concentration in Moist Snuff

	USA		Sweden	
	1985/86*	1994†	1986‡	1992§
NNN	14.0 - 64.0 ppm	3.0 - 8.7 ppm	4.3 ppm	1.9 ppm
NAT/NAB	3.7 - 220.0 ppm	1.7 - 6.6 ppm	2.9 ppm	1.9 ppm
NNK	0.1 - 3.1 ppm	0.5 - 1.9 ppm	0.75 ppm	0.64 ppm

NNN = N-nitrosonornicotine
NAT/NAB = N-nitrosoanatabine / N-nitrosoanabasine)
NNK = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone
* Range covered by 5 leading brands (5)
† Range covered by 5 leading brands (6)
‡ Mean of 34 sample from 18 brands (4)
§ Mean of 20 samples from 20 brands (4)

In both the United States and Sweden, TSNA levels have been decreasing. One way this may have been achieved is through a sharpening of the quality requirements for the raw tobacco used. Adjustments of the manufacturing procedures would also have contributed. In the United States, modifications of the fermentation process have been especially important in this respect. However, the Swedish nonfermentation process seems able to yield clearly lower TSNA levels than the fermentation process.

Polynuclear Aromatic Hydrocarbons

Snuff contains some polynuclear aromatic hydrocarbons (PAHs) such as benzo(a)pyrene (B(a)P). These compounds mainly originate from the fire-cured tobacco that has traditionally been part of the raw material for manufacturing snuff in both the United States and Sweden. By using air-cured instead of fire-cured tobacco, it has been possible to reduce the amounts of B(a)P. Measurements in Sweden indicate that snuff containing some fire-cured tobacco may contain B(a)P concentrations of 48-51 ppb, while snuff without fire-cured tobacco has concentrations around 10 ppb (3).

Polonium-210

The third class of carcinogens known to occur in snuff is the radioactive isotope polonium-210. This is not a tobacco-specific substance but occurs in most crops and originates mainly from fertilizers. The radiation activity found in snuff has been assessed at 11-60 Bq/kg. A Swedish risk assessment indicated that regular snuff dipping would correspond to a radiation exposure of about 1/50 of background radiation (7). This risk is so small that no special measures would be needed.

Antimutagens and Antioxidants

Like many other plant products, tobacco contains substances that can be anticarcinogenic. In snuff we find some such substances; for example, ubiquinone alpha-tocopherol, and certain fatty acids as well as flavonoids and isoprenoids. It is, however, uncertain if the concentrations of these substances in tobacco are high enough to act as real protection (8).

Nicotine Delivery From Snuff

Availability

The nicotine concentrations in different brands of snuff can vary, mainly depending on the kind of tobacco used. Most commonly, we find concentrations between 9 mg/g and 12 mg/g, while some "low-nicotine" brands can contain 4-5 mg/g.

However, all of the nicotine is not taken up by the user. Some nicotine is never extracted from the pinch but left in the remainder that is thrown away at the end of the usage period. Some is lost with saliva that is spit out during use. Some is swallowed and goes to the gastrointestinal system, where the bioavailability is quite low—around 30% (2, 9).

The conditions for nicotine uptake differ depending on the kind of snuff that is used, loose or portion-packed. This has been shown in a Swedish study of habitual snuff users who were using their ordinary brand ad libitum (Table 2) (10).

Table 2
Nicotine Delivery From Different Kinds of Snuff (10)

Type of snuff	Daily consumption of snuff (g)	Nicotine (mg/g)	Degree of nicotine extraction (%)
Portion-packed	14.4 ± 7.1	9.0 – 10.3	37.4 ± 17.6
Loose	20.8 ± 15.5	8.6 – 9.1	49.1 ± 17.2

	Extracted nicotine (mg/24 hrs)	Saliva cotinine (ng/ml)	Systemic dose nicotine equiv. (mg/24 hrs)
Portion-packed	47.6 ± 31.4	343 ± 181	34.5 ± 23.1
Loose	94.7 ± 67.9	327 ± 136	35.6 ± 18.6

Users of loose snuff had a higher daily consumption level than users of portion-packed snuff. This, combined with the higher degree of extraction, gave users of loose snuff about twice as much extracted nicotine as users of portion-packed snuff. In spite of this large difference, the saliva cotinine levels and the systemic dose per 24 hours were the same in both groups. This discrepancy between the amount of extracted nicotine and the actual uptake of nicotine may be due to the fact that users of loose snuff have a higher salivary secretion rate and therefore spit or swallow much more saliva (with dissolved nicotine) than users of portion-packed snuff.

The oral mucous membrane will most rapidly absorb nicotine present in unprotonated form. The proportion of unprotonated nicotine is strictly related to the pH, which can vary substantially between brands, depending on the amount of sodium carbonate (or equivalent substance) that is added and, for fermented snuff, the exact design of the fermentation process. Thus the amount of nicotine that is available for uptake can differ very much between brands. As soon as some unprotonated nicotine is absorbed, part of the remaining protonated nicotine will change to unprotonated form to keep the proportion constant (as long as the pH stays constant). Most of the extracted nicotine will therefore eventually be available for uptake. The more nicotine that is unprotonated at start of use, the faster the maximum blood concentration is reached. Consequently, the pH influences the rate of uptake of nicotine, while the total amount of nicotine absorbed over time will not be affected as much (see Table 3 for examples) (11).

For each brand, means and ranges of measurements from a number of samples bought at different locations are shown. Variations between brands are certainly intentional and meant to create specific brand characteristics. However, variations between different samples of the same brand are surprisingly large. Different batches in the production may differ to some extent, but the larger part of this variation is probably the result of differences between outlets in storage conditions and length of storage. As pointed out above, continued fermentation may occur during storage whereby there is an increase of the pH and an increase in the proportion of unprotonated nicotine. This explanation is supported by the observation that the range is relatively much larger for the proportion of unprotonated nicotine, which is affected by a continued fermentation, than for the amount of total nicotine.

Swedish snuff is not fermented at all during manufacturing and is virtually free from bacteria that could induce any fermentation. Therefore, changes during storage could not easily occur and are further prevented by the Swedish practice of refrigerating snuff at the outlet until sale.

Pharmacokinetics

Most of the nicotine in snuff is absorbed through the oral cavity. The blood levels of nicotine increase gradually during the 30 minutes or so that the snuff is typically kept in the mouth, the average increment being around 15 ng/ml. With repeated administration, the average blood levels accumulate to higher levels. US studies have found levels around 35 ng/ml, with very large variation between individuals (2, 9). A Swedish study found levels around 23 ng/ml, again with very large variation between individuals (12).

These blood levels of nicotine are quite similar to the levels reached by cigarette smokers, but the speed of absorption differs. During smoking, the overall nicotine

Table 3
Examples of Nicotine and pH Levels in American Moist Snuff (Derived from 11)

Brand	pH of snuff suspension	Total nicotine at start of use (mg/g)
	Mean & range	Mean & range
Copenhagen	8.0	12.0
	(7.7 – 8.4)	(11.4 – 13.3)
Skoal, Fine Cut, Wintergreen	7.5	11.9
	(7.3 – 7.7)	(10.0 – 12.6)
Skoal Bandits, Straight	5.4	10.1
	(5.2 – 5.5)	(9.2 – 11.3)
Kodiak Wintergreen	8.2	10.9
	(8.0 – 8.3)	(10.1 – 12.0)
	Percentage of unprotonated nicotine (%)	**Unprotonated nicotine at start of use (mg/g)**
	Mean & range	Mean & range
Copenhagen	49.0	5.9
	(28.0 – 69.0)	(3.3 – 8.9)
Skoal, Fine Cut, Wintergreen	22.0	2.6
	(15.0 – 26.0)	(1.7 – 3.5)
Skoal Bandits, Straight	0.23	0.023
	(0.13 – 0.29)	(0.015 – 0.027)
Kodiak Wintergreen	60.0	6.5
	(48.0 – 66.0)	(5.6 – 7.9)

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level in the blood reaches its peak three to four times more rapidly than during use of oral moist snuff with "normal" pH (nasal use of dry snuff is more similar to cigarette smoking in this respect). The pharmacokinetic differences between cigarette smoking and oral snuff are actually even greater. In the case of cigarette smoking, the pulmonary rather than oral absorption means that the limited blood volume involved in the interchange of substances in the lung alveoli during the few seconds of a single puff on the cigarette will achieve a nicotine concentration much higher than any standard measurement that represents overall values from blood where the nicotine has been diluted in a larger volume. In the case of cigarette smoking, these high but short-lived peaks can be described as superimposed on the "overall curve," which is already rising at a high rate. In the case of snuff dipping, there is no such "bolus" effect. These differences are important since the rate of exposure to psychotropic drugs is a major determinant of their effects in producing dependence.

A Swedish study has further shown that nicotine yield does differ between brands of portion-packed snuff with different nicotine content but similar pH. Under controlled conditions, snuff users who switched from their usual brand to a brand with about half the nicotine concentration were observed for several weeks before and after the switch. There was a 15% increase in the amount of snuff used, indicating some compensatory behavior, but the exposure measured as saliva content of cotinine decreased to about half the original value (from 336 ng/ml to 153 ng/ml) (13).

Toxicology/Epidemiology

Nicotine has many effects on the human body, ranging from acute intoxication to involvement in certain diseases. Considering the well-established connection between smoking and cardiovascular diseases, the most important question here would be to what extent is nicotine exposure from snuff related to cardiovascular morbidity and mortality. Experts from the Institute of Environmental Medicine (IMM) at the Karolinska Institute, University of Stockholm, have recently prepared a report entitled "Health Hazards of Moist Snuff" commissioned and published by the Swedish National Board of Health and Welfare (8). The authors note that several studies have looked for relations between long-term snuff use and various known risk factors for cardiovascular disease (CVD). In summary, they conclude that long-term use of snuff does not have any marked effects on the major risk factors for cardiovascular disease. Only two studies have investigated direct relations between snuff use and CVD. One of these found an increase in cardiovascular mortality for snuff users compared to "never tobacco users" (relative risk 1.4 with 95% confidence interval [CI] 1.2-1.6). The other found a reduced cardiovascular morbidity for snuff users (relative risk 0.89 with 95% CI 0.62-1.29) (8). These contradictory results suggest the need for further research.

Delivery of Substances Other Than Nicotine

Availability

Besides nicotine, the main interest has been in the TSNAs in snuff. Concentrations of TSNAs can differ significantly between types and brands of snuff. Here, just as with nicotine, loose snuff differs from portion-packed snuff. A study performed at the Swedish Food Administration examined TSNA levels in the saliva of users of loose snuff and portion-packed snuff (Table 4) (14).

Table 4
Mean TSNA Levels (ng/g) in Saliva 10 Minutes After Intake of Snuff (14)

	Loose Snuff	Portion-packed Snuff
NNN	109	21
NAT	60	10
NNK	12	2

NNN = N-nitrosonornicotine
NAT = N-nitrosoanatabine
NNK = 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone

Toxicology

The IMM report cites several studies of toxicological effects of snuff (8). The authors conclude that there is a low probability that Swedish snuff is carcinogenic due to genotoxic mechanisms, possibly because of the presence of antimutagenic substances. Animal experiments seem to indicate carcinogenic properties of snuff, at least when applied in a test channel created by special surgery. Combined exposure to snuff and herpes simplex virus seems to yield more tumors than exposure to one of the agents alone. Snuff use does entail characteristic lesions in the mucous membrane of the oral cavity, but the probability is small that these lesions will develop into cancers.

Epidemiology

The International Agency for Research on Cancer monograph on smokeless tobacco published in 1985 concluded that the epidemiological and other studies avail-

able at that time supported the view that snuff was carcinogenic to humans. However, many of those epidemiological studies suffered from serious methodological weaknesses, and none of them dealt with the kind of snuff and/or snuff use that is now most common in North America or Sweden. The IMM experts therefore attach most weight to two large recent Swedish studies on oral cancer (15, 16). For active snuff users, these studies find relative risk values (compared to never users of tobacco) of 0.7 (95% CI 0.4-1.1) and 1.0 (95% CI 0.7-1.6), respectively. In its summary, the IMM report states that these studies do not support the conclusion that snuff use increases the risk for cancer. At the same time, there is insufficient evidence for excluding such a risk.

This report made the National Board of Health and Welfare (NBHW) feel uneasy in its role as signatory of the legally prescribed warning label on snuff packages: "Causes cancer." So the NBHW sent a letter to the Ministry of Health, drawing attention to the manifested lack of scientific basis for this warning label.

The conclusion that snuff use has not contributed to a clinically noticeable number of oral cancers in Sweden is further supported by international comparisons. Sweden has long had and still has a unique position among developed countries as a leader in snuff consumption. Estimated per capita consumption of snuff in six countries in 1966 was: (1, 2)

Canada . . . . . .27 g
Denmark . . . . . .10 g
France . . . . . .7 g
Ireland . . . . . not available
Sweden . . . . . .400 g
U.S.A. . . . . .70 g

In 1997, the Swedish per capita consumption of snuff had risen to 740 g. If snuff dipping had been a major contributor to oral cancer, Sweden's high levels of snuff dipping in the late 1960s and later should have been reflected in high death rates for oral cancer about 1990 compared with other countries. Instead, Sweden has lower rates for male oral cancer than all of the above countries. If we look at all developed countries, we find age-standardized annual death rates/100,000 for mouth and pharynx cancer in males, all ages, ranging from 2.1 to 22.1. The mean rate is 7.9 and the Swedish rate is 3.8, well below the average (17). This low rate seems not to be attributable to low alcohol consumption, since, as far as strong liquor is concerned, the per capita consumption in Sweden is slightly above the average for Northern and Western Europe.

Consumer Aspects

While few people start smoking after the age of 21, many people, at least in Sweden, start using snuff at an older age. Virtually all of these are cigarette smokers. Some of them want to stop smoking and use snuff either permanently as an alternative nicotine delivery system or temporarily as a smoking cessation aid. Others continue smoking but use snuff either as a means of reducing cigarette consumption in general or as a means of continued supply of nicotine when they are unable to smoke because of restrictions. In all cases, there is a background of nicotine dependence, and the role of snuff is predominantly as a source of nicotine. These snuff users would not accept snuff with too small a nicotine yield; "taste" factors play only a secondary role.

Others are "primary" snuff users, that is, those whose first tobacco use was snuff. These are most often adolescents. Without a previously acquired nicotine dependence, they may prefer brands with less nicotine and may also appreciate flavoring that adds to the taste. In Sweden there is little demand for nontobacco flavors, while in North America, certain brands appear to be formulated as "starter" products and marketed accordingly.

The large price difference between cigarettes and snuff may have influenced consumer preferences in Sweden. In 1996, the average smoker's daily consumption (15 cigarettes) cost about USD 3.00, while the average snuff user's daily consumption (20 g) cost about USD 0.80. This means that cigarette smoking was almost four times as expensive as snuff use. As a result of two price increases in 1997, cigarettes became 45% and snuff 40% more expensive in Sweden. This resulted in such a heavy increase in the smuggling of cigarettes (but not snuff) that in August 1998, cigarette prices were lowered to just about 11% above the 1996 level. Consequently, cigarette smoking was about three times as expensive as snuff use as of September 1998. This may still encourage consumers to prefer snuff to cigarettes.

There are data suggesting that the widespread use of snuff in Sweden helps keep smoking rates low rather than promoting smoking. In surveys of randomized samples of the Swedish population in 1987 and 1988, respondents who had ever used tobacco were specifically asked whether their primary tobacco use was smoking or snuff dipping (18, 19).

Among young adult men 18-34 years of age, 43% were ever daily smokers; of these, 21.5% were ex-smokers and 21.5% were current daily smokers. Fifty-one percent of women of the same age were ever daily smokers: 18.5% ex-smokers and 32.5% current daily smokers.

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From these figures, it can be concluded that the lower prevalence of current smoking among men compared with women results from a combination of lower onset rate (43% instead of 51%) and higher overall quit ratio (50% instead of 36%). Since one major difference between men and women in Sweden is the widespread use of snuff among men and virtually no snuff use among women, it seems probable that male snuff use has both kept down onset of smoking and increased smoking cessation. These matters are further elucidated by more detailed data on male "careers" of tobacco use.

Among primary dippers (25% of all), just two in seven later started smoking. This is far below the average onset rate (43%), and half of them later quit smoking. Among primary smokers with a history of dipping (15% of all), the quit smoking ratio is 0.67. Among primary smokers without a history of dipping (21% of all), the quit smoking ratio is much lower at 0.38.

If there had been no snuff available, all primary smokers (36% of all) would probably have had the 0.38 quit ratio, contributing 22% ([1 – 0.38] × 36%) to the total prevalence of current daily smokers instead of the 18% of (all) current daily smokers that come from this category. It is further reasonable to assume that, in the absence of the snuff alternative, a larger proportion of those who are now primary dippers would have started smoking. Then the total male prevalence of current daily smoking would have been a bit more than 25.5% instead of 21.5%. This assumption is further supported by the above comparison between men and women, since male smoking rates are usually higher than female ones.

In conclusion, these data suggest that the availability of snuff in Sweden has kept smoking rates low, both by reducing initiation and by increasing cessation.

Summary Assessment

An unambiguous ranking of properties of snuff on a scale from 0 to 3 (lowest to highest) is almost impossible because of the wide variation in characteristics of different types and brands. Therefore, the rankings indicated below should be taken as very tentative ones that would apply to some of the most common varieties of snuff.

Toxicity to user 1
Toxicity to others 0
Addictiveness 2
Consumer acceptability 2

While snuff use may entail some health risks, there is good evidence that these are substantially lower than those associated with smoking. Switching from smoking to snuff use would therefore represent a reduction in health risks.

Finally, it should be pointed out that the characteristics of the consumer product can largely be controlled by the choice of raw material and processing procedures. Consequently, it would be feasible to design regulatory standards to minimize undesirable effects of use, which would make it easier for consumers to make a rational choice among alternative products.

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Discussion

Greg Connolly: The data are clear, based on studies reviewed by the World Health Organization and the Surgeon General, that snuff is a cause of mouth cancer among humans. I think we have to relate the discussion to the regulation of alternative nicotine delivery devices. Lars presented a very good case for snuff as an alternative nicotine delivery device. The question is, how do we regulate those devices? The nitrosamine levels in Swedish snuff are about 1,000 times greater than would be allowed by the US Food and Drug Administration in Nicorette gum, or about 1,000 times greater than those allowed by the US Department of Agriculture. So, on that scale, the levels are still enormously high.

In about 1982, a snuff brand called Skoal Bandits was brought in, with advertising emphasizing it was easy to use, anywhere, any place, any time. There were instructions for the new user. How long should I keep the pouch in my mouth? The instructions from the company said, if you haven't used Skoal Bandits before, we recommend that you keep one in your mouth about a minute, then remove it. The next time you try another one, leave it in for a bit longer, just like your first beer.

There was an industry document in a court case that talked about a "graduation strategy," in which highly flavored cherry products with very low nicotine levels were promoted as starter products, including free samples. As the user progressed, the marketing technique brought them to products with a higher pH, until finally it brought them up to the Copenhagen brand. For Copenhagen, which is the highest nicotine brand, with a very high pH, there are no free samples. All the ads for it do is show the product, with the slogan, "sooner or later it's Copenhagen." And at the bottom of the ad, it says "it satisfies."

Before the marketing campaign in the United States, the lowest use of snuff was among 17-to-19-year-olds—about 0.3% of the population. The highest users were males over 55, about 2.5%. After the marketing campaign, we saw an increase among the 17-to-19-year-olds—up to about 7.6%. And there was no diminution in smoking rates in that same cohort. So snuff did not replace smoking among the cohort; in fact, a couple small studies suggest that snuff users may later switch to cigarette smoking.

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What this speaks to is the issue of regulation. Do we rely on the tobacco industry to solve our problems and let Swedish tobacco fight it out with Philip Morris over snuff or cigarettes? I think the US experience would say no. You have got to look at a very high regulatory standard for any alternative nicotine delivery product, or the industry would just capture the youth market—the nonusing youth market—because that's the easiest market to catch.

Nigel Gray: There are many countries in the world where snuff products don't exist. When Skoal Bandits was launched in the United States, aimed at kids, it would have been possible to ban its use. Australia is one of those countries that did ban use, and there are quite a few countries where snuff products are illegal. They're not available for sale at all.

John Ferguson: If there is a competitive advantage to using a healthier way to prepare the product, then we would expect a healthy market to adopt the better use. So I want to ask Dr. Ramström a question. Based on the figures in your paper, the Swedish Tobacco method of treating its snuff has some significant benefits in reducing the health consequences. That method of preparing snuff is also probably less expensive than the fermentation process, and it's certainly more easily controlled, so it's something that you would expect a manufacture to want to do. Why don't US Tobacco and the other snuff manufacturers switch to that system?

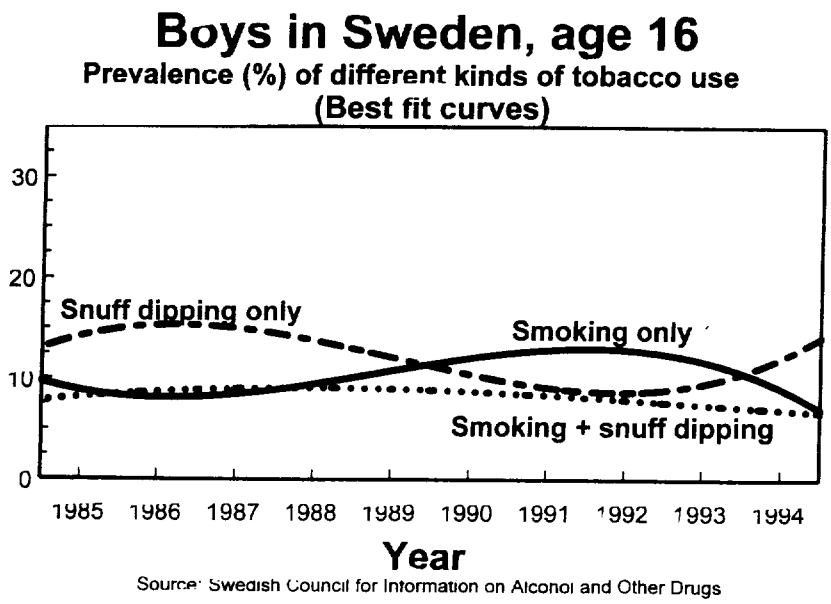
Lars Ramström: I'm not competent to give a good answer; my guess is that it is a combination of concerns: expensive investments in new machinery associated with changing manufacturing processes, and complications on the market side. Since there are slight differences in taste, consumers used to one taste might not immediately accept a sudden switch. I suppose it would be good to encourage this kind of switch by appropriate regulatory distinctions.

John Hughes: I want to comment on the low-tar, low-nicotine history. The main thing I take home from that is how embarrassed I am for us as scientists for not having studied low-tar/low-nicotine cigarettes. This is the biggest policy change that we've had. And we have not had a single prospective study of whether changing to these cigarettes had any health benefit, or whether it increased or decreased cessation. One of the main things that we should conclude at this conference is, no matter how logical something sounds, it has to be studied. My big fear is that Eclipse gets on the market because it appears safest and because people say we can't wait for studies to see if it really is safer. So my major concern is that we don't repeat the errors of the past, that is, that 20 years from now we're not looking back and seeing we made the same errors.

Jack Henningfield: I have a brief comment on the cigar data. Cigars obviously have a high potential to cause dependence, given their nicotine content and availability. But they also illustrate very nicely a point that Dr. Kalant was making, and that is that you have to consider the kinetics and the formulation in the nature of the nicotine delivery. Cigarettes require you to inhale into the lungs to obtain nicotine, where the effects are quite pronounced. Cigars allow you to not inhale, thus attenuating the potential effects of nicotine. This would be consistent with the observation that it appears that a lower percentage of cigar smokers are addicted compared with cigarette smokers. Of course, numerous other factors contribute to the apparently lower rates of addiction in past cohorts of cigar smokers (eg, declining social acceptability, adult onset of use).

Lars Ramström: Let me show you the data from annual studies of 16-year-old Swedish boys, from 1985 to 1994 (Figure 1) (1). The data suggest that snuff replaced some of the tobacco smoking for Swedish boys.

Figure 1. Trends in different kinds of tobacco use by adolescent boys in Sweden. The pattern suggests that increased snuff use may be linked to decreased smoking.



Source: Swedish Council for Information on Alcohol and Other Drugs

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Question from the floor: I'm interested to know the use by women of snuff in Sweden.

Lars Ramström: It's virtually nonexistent.

Question from the floor: What's their smoking rate?

Lars Ramström: A good deal higher for girls than for boys.

Neal Benowitz: There's an unfortunate situation in the United States, Lars, which is quite the opposite. The data from Oregon suggest that boys start using snuff in junior high school (2). They use it on a regular basis until they start dating and becoming more social (3), and in that context, because the girls don't like to kiss people with a mouth full of snuff, they end up switching to smoking cigarettes. So actually in the Oregon population, probably the biggest harm from snuff is not any direct oral cancer but the fact that it leads them to become cigarette smokers.

Lars Ramström: I made a study a few years ago asking people what did you start first, snuff use or smoking? so I could map the development. The results implied that more people stop smoking with the help of snuff use than take up smoking after starting on snuff.

Lynn Kozlowski: In his talk, Bill Rickert cited a paper in the *British Medical Journal* by Tang et al. (4), referring to a 23% reduction in mortality related to a 15-mg shift in tar yield. I think it really needs to be emphasized that in that study, the 15-mg shift in tar yield was a shift from 30 to 15 mg. But the tar yield in North America has been at 15 mg for a while, and we should be very cautious in extrapolating from the shift from 30 to 15 to what might happen if we go down from 15 mg.

Bill Rickert: Lynn, I went on to say that therein lies the problem. Most of today's cigarettes are close to 15 mg, and there's absolutely no guarantee that when we move down from 15 that history is going to repeat itself. I believe that this is a serious issue.

Jed Rose: Can I ask a question on that very point? If we know it goes down as we move from 30 down to 15, and we know that at 0, it's much lower, it's certainly a plausible guess that it will turn out that there are going to be reductions as you go down from 15 to 0.

Don Shopland: If I'm not mistaken, we're down to around 12.5 or 13 mg on Federal Trade Commission–measured tar right now. We've been stuck at that level

now for a period of 10 or 15 years—we have not been able to effectively get it down below 12.5 milligrams of tar. So we might be reaching a threshold below which the consumer is not going to accept it, because as you reduce the tar you reduce the nicotine as well.

Greg Connolly: The whole thing with tar is that tar is a euphemism for junk. With cigarette design changes, today's cigarettes may be more toxic than the tar we were talking about 20 years ago. As we've shifted to higher nicotine leaf yields, we get more nitrates, and as we burn it we get more nitrosamines. We may get fewer hydrocarbons because of higher burn rates, but we may have more toxic tar. We really don't know. I think we should be very cautious about using the term *tar* and communicating information to public about the term *tar*. Maybe we should be talking about the 10 leading bad constituents—like the listing on your cereal box.

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Introduction

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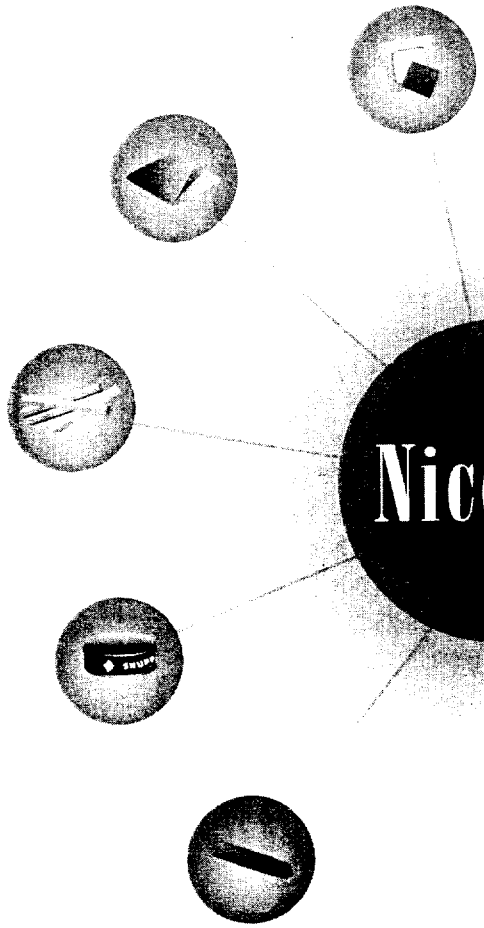

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edited by:

Roberta Ferrence, PhD
John Slade, MD
Robin Room, PhD
Marilyn Pope, BSc

APHA
AMERICAN PUBLIC HEALTH ASSOCIATION
800 I ST NW
WASHINGTON DC 20001-3710

American Public Health Association
800 I Street, NW
Washington, DC 20001-3710

Mohammad N. Akhter, MD, MPH
Executive Vice President

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