

# Nicotine intake by snuff users

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## Abstract

Blood nicotine and cotinine concentrations were measured in 27 volunteers before and after taking snuff. Within 10 minutes after snuffing blood nicotine concentrations were comparable to those obtained after the 10 minutes or so that it takes to smoke a cigarette. Nicotine intake from snuffing was related to the experience of the snuffer. In daily and occasional snuffers increases in plasma nicotine concentrations averaged 77.7 and 12.3 nmol/l (12.6 and 2.0 ng/ml) respectively, while the novices showed no appreciable increase. The increase shown by the daily snuffers was comparable to the average increase of 62.3 nmol/l (10.1 ng/ml) obtained from a single cigarette by a group of heavy smokers. The peak nicotine concentrations in the daily snuffers were also similar to the peak values in 136 heavy smokers—222.6 and 226.3 nmol/l (36.1 and 36.7 ng/ml), respectively. Unusual multiple-dose snuffing produced massive increases in plasma nicotine to concentrations that have never been recorded in smokers.

The similarity of the concentrations produced by regular daily snuffing and regular daily smoking suggests that the plasma nicotine concentration has some controlling influence over the self-regulation of these two quite different forms of tobacco use. The rapid absorption of nicotine from snuff confirms its potential as an acceptable and relatively harmless substitute for smoking.

## Introduction

In a preliminary study<sup>1</sup> we showed that the absorption of nicotine from a single pinch of snuff taken by an experienced snuffer was extremely rapid and produced plasma nicotine concentrations comparable to those obtained from cigarette smoking. This suggested that snuff might be an acceptable and relatively harmless substitute for smokers who have difficulty giving up cigarettes. The preliminary study was based on the plasma nicotine concentrations of a single snuffer. We now present the results from a sample of snuff users. We are aware of only one other study of nicotine intake from nasal snuff, and this was limited to measurements of nicotine and its metabolites in urine.<sup>2</sup>

## Subjects and methods

Although there are reportedly about 500 000 regular snuff users in Britain,<sup>3</sup> only three have attended our clinic over the past 10 years. On 24 July 1980 we attended a local meeting of snuff users in Wellington, Somerset, where there is a colony of keen snuff users. Their activities include snuff-taking competitions. The current British snuff-

taking champion was present for our visit and volunteered for the study.

Twenty-seven volunteers took part in the study. Four had never used snuff before ("virgin" snuffers), 12 were occasional snuffers, and 11 took snuff daily. Table I gives their smoking habits and end-expired air carbon monoxide concentrations, which reflected their recent smoking and inhalation.<sup>4</sup> They had been smoking and snuffing as usual up to the time of the study (6 pm to 10 pm).

Venous blood samples were taken one to two minutes before a pinch of snuff and then repeated between six and 17 minutes after taking the snuff (mean 10.1 ± SD 2.4 minutes). Five subjects took multiple doses of snuff, two of them according to championship rules (see figs 2 and 3). In these two subjects serial blood samples were taken using a butterfly cannula. Blood samples were kept in a refrigerator for one to three hours before centrifuging. The plasma was then frozen until analysed for nicotine<sup>5</sup> and cotinine.<sup>6</sup> The plasma nicotine and cotinine concentrations were compared with those of heavy cigarette smokers attending the smokers' clinic at the Maudsley Hospital.

## Results

Table I and figure 1 give the results. The declared smoking habits were well validated by the end-expired carbon monoxide values.

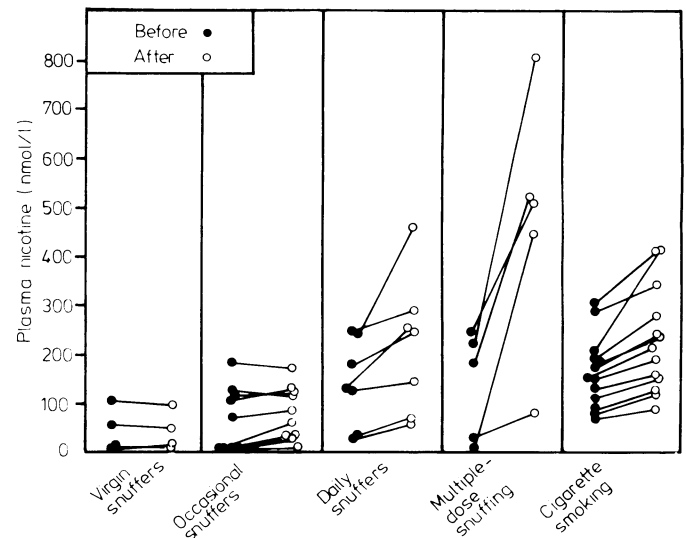


FIG 1—Plasma nicotine concentrations before and after a single pinch of snuff, multiple-dose snuffing, and smoking a cigarette. (Initial values in some snuffers partly attributable to smoking habits (see table I); value before snuffing was missing for one daily snuffer.)

Conversion: SI to traditional units—Nicotine: 1 nmol/l  $\approx$  0.16 ng/ml.

Initial plasma nicotine and cotinine concentrations correlated well with each other ( $r=0.84$ ;  $p<0.001$ ) and with the smoking habits and amount of snuff use. The increase in plasma nicotine concentration produced by a single pinch of snuff was related to the usual frequency of snuff use. The average increase in occasional snuffers was  $12.3 \pm$  SD  $20.3$  nmol/l ( $2.0 \pm 3.3$  ng/ml) compared with  $77.7 \pm 70.3$  nmol/l ( $12.6 \pm 11.4$  ng/ml) for the daily snuffers ( $t=2.8$ ;  $df=15$ ;  $p<0.02$ ). The virgin snuffers showed no evidence of nicotine absorption and registered a mean decrease of  $3.1$  nmol/l ( $0.5$  ng/ml). The increase in plasma nicotine shown by the daily snuffers was similar to that produced by a single cigarette in a group of heavy cigarette smokers (mean  $62.3 \pm 48.1$  nmol/l;  $10.1 \pm 7.8$  ng/ml; fig 1). Multiple doses of snuff produced massive increases in plasma nicotine concentrations,

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TABLE I—Usual smoking and snuff-taking habits of 27 subjects together with plasma nicotine and cotinine concentrations before and after snuffing

Subject	Age and sex	Smoking habits	Snuff use	Time interval between blood samples (min)	ECO (ppm)	Blood nicotine concentration (nmol/l)		Blood cotinine concentration (nmol/l)	
						Before	After	Before	After
<i>Virgin snufflers</i>									
1	23 M	Cigarettes 20 day	Never	11	34	102.3	91.2	493.7	—
2	19 F	Cigarettes 10 day	Never	11	13	51.2	45.0	667.0	576.4
3	16 F	Never smoked	Never	10	4	6.2	6.2	8.6	12.0
4	16 F	Never smoked	Never	10	3	3.7	9.2	20.5	20.0
<i>Occasional snuffer</i>									
5	35 M	Cigars 25 week	1 month	9	20	69.1	84.5	529.1	570.7
6	28 M	Pipe 1 oz (28 g) week	1 month	9	4	3.1	18.5	64.4	58.7
7	25 M	Cigarettes 30 day	1 month	9	25	125.2	108.5	2098.0	2245.0
8	27 M	Cigars 2 week	2 month	9	5	1.8	19.7	37.1	43.3
9	55 M	Pipe 1 oz (28 g) week	2 month	14	3	1.2	21.0	138.0	138.5
10	26 M	Never smoked	1 month	10	4	0.6	4.9	14.8	13.1
11	65 M	Cigar 1 month	1 month	11	4	0	54.5	23.9	29.1
12	71 M	Pipe 1 oz (28 g) week	1 month	8	12	106.7	128.2	2596.0	2552.0
13	28 M	Cigarettes 20 day	1 week	9	30	180.0	165.8	3941.0	3857.0
14	65 M	Cigarettes 90 day	2 week	17	20	111.0	117.1	2629.0	2499.0
<i>Daily snuffer</i>									
15	59 M	Pipe 1 oz (28 g) day	15 day	9	26	123.9	140.0	2449.0	2319.0
16	65 M	Pipe 1 oz (28 g) day	10 day	8	6	174.5	242.3	2796.0	3014.0
17	29 M	Ex-smoker	5 hour	9	7	238.6	281.7	2891.0	2941.0
18	49 M	Cigar 1 week	12 day	11	3	22.2	57.3	84.4	100.9
19	61 M	Ex-smoker	4 hour	10	4	—	290.4	3476.0	3421.0
20	36 M	Never smoked	20 day	10	7	27.7	66.0	66.7	82.1
21	58 M	Never smoked	10 day	10	6	125.2	252.2	1006.0	1027.0
22	53 M	Ex-smoker	3 hour	7 <sub>1</sub>	7	234.3	448.8	1163.0	1157.0
<i>Multiple doses</i>									
23	44 M	Ex-smoker	2 week	7 <sub>2</sub>	5	27.1	78.9	33.1	58.7
24	50 M	Ex-smoker	2 week	6	4	0	437.7	5.1	29.1
25	65 M	Ex-smoker	10 hour	12 <sub>1</sub>	4	213.3	797.2	4884.0	5319.0
26	59 F	Ex-smoker	5 hour	11	4	241.7	498.8	5227.0	4894.0
27	59 M	Cigarettes 20 day	20 day	15	15	177.6	510.5	1713.0	—

ECO = End-expired air carbon monoxide.

Non-smokers usually have end-expired air carbon monoxide values below 10 ppm. Values above 10 ppm usually indicate that the subject has been smoking, but values up to 15 ppm may occur in non-smokers who have been exposed to passive smoking or other causes of raised ambient air carbon monoxide values. Mean age of the subjects was 43.9; SD 18.0 years.

Conversion: SI to traditional units—Nicotine: 1 nmol/l  $\approx$  0.16 ng/ml. Cotinine: 1 nmol/l  $\approx$  0.175 ng/ml.

TABLE II—Comparison of plasma nicotine and cotinine concentrations from cigarette smoking and snuff use. Values are means  $\pm$  SD (ranges in parentheses)

	Plasma nicotine concentration (nmol/l)	Plasma cotinine concentration (nmol/l)
Cigarette smokers (n = 136)	226.3 $\pm$ 85.1 (37.0–474.7)	1913.3 $\pm$ 834.7 (135.7–4310.1)
Daily snufflers (n = 11)	222.6 $\pm$ 130.7 (57.3–448.8)	2353.5 $\pm$ 1744.0 (82.1–5226.9)
Rapid smoking (n = 15)	296.5 $\pm$ 96.8 (66.6–431.6)	—
Multiple-dose snuffing (n = 5)	464.9 $\pm$ 256.5 (78.9–797.2)	—

Plasma nicotine values were peak concentrations 2 min after finishing cigarette and 6–15 min after snuffing. Cotinine values were measured in same specimens as for nicotine. The three daily snufflers who had multiple doses of snuff were not included for mean plasma nicotine concentrations of daily snufflers, and their cotinine values before rather than after multiple dosing were used for mean plasma cotinine concentrations of daily snufflers. The 136 cigarette smokers (37 men, 99 women) were consecutive attenders at Maudsley Hospital smokers' clinic for whom measurements of both nicotine and cotinine were available. Their cigarette consumption averaged 30.5 daily. Rapid smoking is an aversive method of treatment entailing smoking at rate of one puff every 6 s until no further smoking can be tolerated. Average tolerance level was reached after 1.7 cigarettes (43 puffs). Further details of sample (5 men, 10 women) recorded elsewhere.<sup>6</sup>

Conversion: SI to traditional units—Nicotine: 1 nmol/l  $\approx$  0.16 ng/ml. Cotinine: 1 nmol/l  $\approx$  0.175 ng/ml.

which averaged  $332.9 \pm 199.1$  nmol/l ( $54.0 \pm 32.3$  ng/ml) (figs 1 to 3). Plasma nicotine and cotinine concentrations of the daily snufflers were similar to those of a sample of 136 heavy smokers attending our clinic (table II). The unusual multiple-dose snuffing produced plasma nicotine concentrations that were much higher than those produced by an unusual form of rapid smoking that has been used as an aversive method of treatment (table II).<sup>7</sup>

## Discussion

These results confirm the main finding of our single-case study<sup>1</sup> and show that nicotine may be absorbed very rapidly through the nasal mucosa when snuff is taken. Within 10 minutes after taking snuff, blood nicotine concentrations are comparable to those obtained after the 10 minutes or so it takes to smoke a cigarette. As with cigarette smoking, the blood nicotine concentrations after snuffing varied widely. The variation probably depends on several factors, such as the strength of the snuff, the size of the pinch, and the way it is sniffed. We did not measure those variables. There was, however, a clear indication that the nicotine intake from snuff was related to the experience of the snuffer. The novices absorbed little nicotine, probably due to their initiation with small doses of a very mild snuff. The

organisers of the meeting were great proselytisers and well knew how to avoid an unpleasant initiation. The occasional snufflers, most of whom used it less than once a week, also absorbed little nicotine. The daily snufflers, on the other hand, obtained blood nicotine concentrations closely similar to those found in regular smokers, but like cigarette smokers there were one or two (subjects 15, 18, and 20) who absorbed little nicotine despite regular daily use.

Cotinine is one of the main metabolites of nicotine, the other being nicotine-N-oxide. The plasma cotinine concentrations corroborated the findings based on plasma nicotine values, with which they correlated highly. Plasma cotinine concentrations of daily snufflers, however, were on average 23% higher than those of heavy smokers, while the average plasma nicotine concentration was similar. Hence snuffing is slightly less efficient than inhaling cigarette smoke as a means of delivering nicotine to the brain in that a larger dose of nicotine is needed to produce a similar blood (and hence brain) nicotine concentration.

Multiple-dose snuffing produced exceptionally high blood nicotine concentrations, and these were substantially higher than those found after usual smoking in heavy smokers and after unusual smoking, as in the aversive-treatment method of rapid smoking.<sup>7</sup> To our knowledge a concentration as high as 797.2

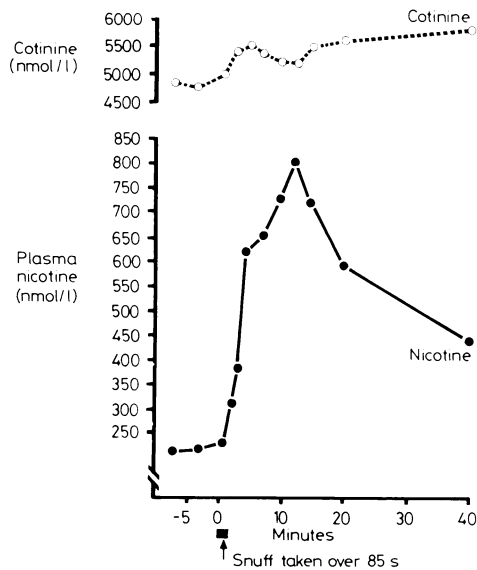


FIG 2—Plasma nicotine and cotinine concentrations in current champion snuffer of Britain (subject 25) before, during, and after multiple-dose snuffing conducted according to world championship rules. (These entail taking 50 spoons of various snuffs as quickly as possible. The "spoon" is about half the size of a mustard spoon. In this experiment 50 spoons of Wilson's Sharrow Mill Best Snuff were taken in about 85 s, but the champion had been known to take 50 spoons of snuff in 46 s. A single sneeze in competitions leads to disqualification.)

Conversion: SI to traditional units—Nicotine: 1 nmol/l  $\approx$  0.16 ng/ml. Cotinine: 1 nmol/l  $\approx$  0.175 ng/ml.

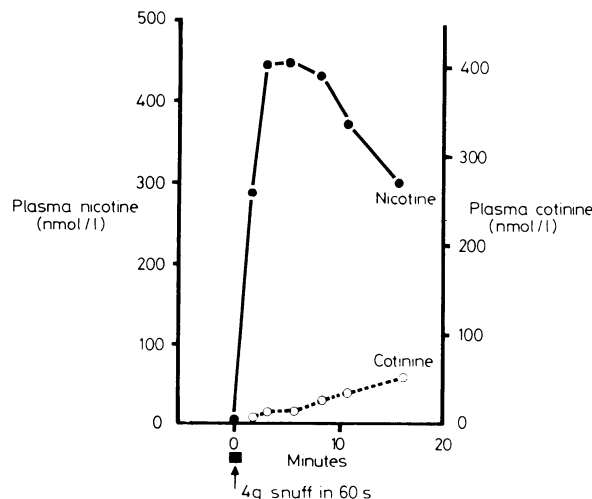


FIG 3—Plasma nicotine and cotinine concentrations in subject 24 before, during, and after multiple-dose snuffing conducted as now discontinued in snuff-taking competitions. Method entails attempting 5 g snuff in 60 s. Subject managed about 4 g Fribourg and Treyer Prince's Special Snuff.

Conversion: SI to traditional units—Nicotine: 1 nmol/l  $\approx$  0.16 ng/ml. Cotinine: 1 nmol/l  $\approx$  0.175 ng/ml.

nmol/l (129.3 ng/ml) plasma, as was shown in the British champion snuffer, has never been recorded before in man. His maximum plasma cotinine concentration (5863.0 nmol/l; 1028.3 ng/ml) was also a record. The highest concentrations found in over 400 heavy smokers attending our clinic were 474.7 nmol/l (77.0 ng/ml) and 4310.0 nmol/l (756.0 ng/ml) for nicotine and cotinine, respectively.

The similarity of the plasma nicotine concentrations in regular smokers and daily snuffers might be merely coincidental. On the other hand, possibly the concentration of nicotine has a controlling influence on the rate and amount of self-dosage of

these two very different forms of tobacco use. To find one group of people who sniff powdered tobacco into their noses have similar blood nicotine concentrations to those of another group who burn it to inhale its smoke suggests that the concentration of nicotine has some controlling influence. It would be a remarkable coincidence if factors such as flavour, strength of tobacco, social influences, and so on just happened to produce similar blood nicotine concentrations resulting from two such different behaviours. The most plausible explanation is that the rituals of snuffing and smoking are determined by the nicotine concentrations that they produce. Whether the use is regulated to obtain the rewards of a given concentration of nicotine or to avoid the unpleasant effects of excessive nicotine intake is another equally important question that remains to be answered.<sup>8</sup>

From our results snuff use may clearly be an efficient method of nicotine intake. This suggests that it might prove sufficiently acceptable to smokers, not only as a temporary substitute to help those who are trying to give up smoking but as a long-term alternative to continued cigarette smoking. It is important, therefore, to consider the health implications of switching from cigarette smoking to long-term snuff use.

Unlike tobacco smoke, snuff is free of tar and harmful gases such as carbon monoxide and nitrogen oxides. Since it cannot be inhaled into the lungs, there is no risk of lung cancer, bronchitis, and emphysema. Indeed, the US Surgeon General's report of 1979 stated that "snuff and chewing tobacco have not been found to increase mortality (either overall or cause-specific) in the United States."<sup>9</sup> This view is probably oversanguine. These forms of tobacco use produce oral leucoplakia,<sup>10</sup> and snuff dipping may cause oral cancer.<sup>11 12</sup> Snuff dipping is the predominant form of snuff use in the USA and Scandinavian countries. It consists in the placement and retention of finely ground tobacco ("wet snuff") in the oral vestibule between the gums and lower lip. This contrasts with snuff use in Britain, which consists in sniffing powdered tobacco ("dry snuff") into the nose. Wet snuff contains nitrosonornicotine, which is carcinogenic in rats.<sup>13 14</sup> There is no reason to expect that nitrosonornicotine is not also present in the dry snuff used in Britain. Though we are not aware of any direct evidence, prolonged heavy use of dry snuff might well carry a slight risk of nasopharyngeal cancer.

The position with coronary heart disease is not clear. It is not known whether nicotine or carbon monoxide is the major culprit responsible for cigarette-induced coronary heart disease. If it is carbon monoxide a switch to snuff would reduce the risk substantially, but even if nicotine plays a part our results show that the intake from snuff is no greater than from smoking.

In conclusion, the rapid absorption of nicotine from snuff confirms its potential as an acceptable substitute for smoking. Switching from cigarettes to snuff would substantially reduce the risk of lung cancer, bronchitis, emphysema, and possibly coronary heart disease as well, at the cost of a slight increase in the risk of cancer of the nasopharynx (or oral cavity in the case of wet snuff). Another advantage of snuff is that it does not contaminate the atmosphere for non-users.

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## Sister chromatid exchange induced by anti-herpes drugs

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### Abstract

The rate of sister chromatid exchange induced by several anti-herpes agents was measured to assess their potential mutagenicity. The agents—5-iodo-deoxyuridine (IDU), 5-trifluoromethyl-deoxyuridine (TFT), and [E]-5-(2-bromovinyl)-deoxyuridine (BVDU)—were incubated at various concentrations with human lymphocytes and fibroblasts, and the rate of sister chromatid exchanges was measured. In lymphocytes and fibroblasts BVDU and IDU did not induce exchange except at concentrations of 50 mg/l, while TFT increased the rate of exchange at a concentration of 0.5 mg/l.

The rate of sister chromatid exchange is a sensitive index of chromosomal damage, and these findings provide information on the safety of some of the anti-herpes agents tested. TFT increased the rate of exchange at a concentration that coincides with its minimal antiviral concentration, but BVDU did not induce exchange at therapeutic concentrations.

### Introduction

Various 5-substituted 2'-deoxyuridines, such as 5-iodo-deoxyuridine (IDU), 5-trifluoromethyl-deoxyuridine (TFT), and [E]-5-(2-bromovinyl)-deoxyuridine (BVDU), are being used or considered for use in the chemotherapy of herpes simplex and

zoster virus infections. There are also several other 5-substituted deoxyuridine derivatives, such as 5-vinyl-deoxyuridine (VDU), which show significant anti-herpes activity, but these compounds do not appear to be sufficiently selective in their antiviral action. From comparative studies of the potency and cytotoxicity of these compounds in cell culture, BVDU has emerged as the most potent and most selective anti-herpes agent.<sup>1</sup>

Since IDU, TFT, and BVDU are all thymidine analogues, they might act as mutagens and hence induce permanent changes in the cellular genome. Sister chromatid exchange is a sensitive indicator of mutagenesis.<sup>2</sup> We therefore examined IDU, TFT, and BVDU for their capacity to induce sister chromatid exchange in human lymphocytes and fibroblasts.

### Methods

Sister chromatid exchange was scored as described previously.<sup>3</sup> IDU was from Ludeco (Brussels) and TFT from Sigma Chemical Co, and BVDU was synthesised as described.<sup>1</sup> VDU, 5-vinyluridine, and 5-vinyluracil were included as reference materials.<sup>1</sup>

The nucleoside analogues were incubated for 48 hours with human (peripheral blood) lymphocytes and 72 hours with human (fetal lung) fibroblasts at concentrations ranging from 0.05 to 50 mg/l in the presence of 3 mg/l bromo-deoxyuridine. Ethylmethane sulphonate (Sigma Chemical Co) served as a positive control: it was added at 60 mg/l, a concentration known to induce a significant increase in the number of sister chromatid exchanges.<sup>3</sup>

### Results

In lymphocytes BVDU and IDU did not increase the number of sister chromatid exchanges until the concentration was raised to 50 mg/l (see table). TFT, however, caused a significant increase in the exchange rate at a concentration of 0.5 mg/l; and at 5 µg/ml it proved even more effective in inducing exchange than the standard mutagen ethylmethane sulphonate.

While not very effective in lymphocytes, VDU turned out to be an exquisitely potent inducer of exchange in fibroblasts, where it caused a significant increase in exchange frequency at concentrations of 0.5 and 5 mg/l, while BVDU and IDU failed to do so. BVDU and IDU increased the frequency of exchange in fibroblasts only at a concentration of 50 mg/l.

The level of significance was assessed by Student's *t* test, and, since the individual values were not distributed normally, significance was also monitored by the Poisson distribution.

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