

# Mouth Versus Deep Airways Absorption of Nicotine in Cigarette Smokers<sup>1</sup>

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GORI, G. B., N. L. BENOWITZ AND C. J. LYNCH. *Mouth versus deep airways absorption of nicotine in cigarette smokers*. PHARMACOL BIOCHEM BEHAV 25(6) 1181-1184, 1986.—Nicotine from the alkaline smoke of cigars is absorbed through the buccal mucosa, but such absorption from the more acidic smoke of American cigarettes has not been reported. Forty-one male and 52 female smokers were studied under normal ventilation and smoking conditions, and under high ventilation and controlled smoking conditions that restricted intake to the mouth only, with no inhalation. The major finding is that there is virtually no intake of nicotine through the buccal mucosa while smoking American cigarettes. Confirming prior reports, plasma nicotine and expired CO levels showed no correlation with the analytical yields of nicotine and CO of the cigarettes smoked. Fifteen nonsmokers (7 male, 8 female) participated in this study as controls. Data from these subjects provided additional information regarding absorption of nicotine and carbon monoxide during passive smoking. Within the highly ventilated environment, there was no significant change of CO and nicotine levels of nonsmokers. However, within the normally ventilated environment, there was minimal increase in both substances, statistically significant only for nicotine. These results suggest that nicotine may be a better indicator of exposure to second-hand smoke than carbon monoxide.

Nicotine bioavailability    Nicotine intake    Passive smoking    Environmental tobacco smoke

NICOTINE in cigarette smoke is carried by aerosolized particles in association with tar. Nicotine is assumed to be absorbed primarily from the lungs. The extent of absorption of nicotine from cigarette smoke via the mouth in humans has not been reported.

Nicotine is a weak base (pKa=7.9). The degree of ionization differs according to whether its environment is alkaline or acidic. Based on studies of blood pressure response to smoke in the mouth in cats, nicotine is known to be absorbed through the buccal mucosa from the alkaline smoke of cigars [2], but there appears to be less absorption from acidic smoke [1]. We specifically studied the intake of nicotine from the buccal mucosa in smokers of American Cigarettes, which have a relatively acidic smoke.

## METHOD

### Subjects

Forty-one male and 52 female smokers at least 21 years of age were recruited by direct interviews in shopping malls and through public notices in the metropolitan Atlanta, GA region. Criteria for acceptance into the study included smoking at least 20 cigarettes per day for at least one year and engaging in no other form of tobacco smoking or other smoking-related practices (cigars, snuff, pipes, chewing tobacco and

nontobacco smoking products). All individuals were in good health and were taking no medications. Subjects with a history of alcohol abuse, abnormal body weight ( $\pm 20\%$  of ideal) and pregnant women were excluded. Cigarette brands smoked by subjects covered virtually the entire range of Federal Trade Commission (FTC) nicotine yields present in the United States cigarette market in 1983. Forty-four different brands of cigarettes were smoked by the volunteers, ranging from the lowest-yield Carlton Light (0.5 mg tar, 0.05 mg nicotine, 0.5 mg CO), to the highest-yield Marlboro 100 (16.9 mg tar, 1.12 mg nicotine, 16.4 mg CO). Mean yields of the 44 brands were:  $9.54 \pm 0.83$  mg tar,  $0.71 \pm 0.051$  mg nicotine, and  $10.36 \pm 0.82$  mg CO. Twenty-five of the brands were smoked by the men (mean yields:  $9.44 \pm 1.15$  mg tar,  $0.69 \pm 0.072$  mg nicotine, and  $10.11 \pm 1.15$  mg CO). Thirty-three of the brands were smoked by the women (mean yields:  $9.37 \pm 0.95$  mg tar,  $0.70 \pm 0.058$  mg nicotine, and  $10.43 \pm 0.98$  mg CO).

In order to examine passive absorption of nicotine and carbon monoxide, 15 nonsmokers (7 male, 8 female) were recruited. Each subject received nominal monetary compensation. Summary characteristics of the smokers and controls are given in Table 1.

### Procedures

All subjects reported to the test center for two sessions,

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TABLE 1  
CHARACTERISTICS OF SMOKERS AND CONTROLS

	Male Smokers N=41	Male Controls N=7	Female Smokers N=52	Female Controls N=8
Age (years)				
Mean	38.0 ± 1.58*	34.6 ± 5.45	35.8 ± 1.50	41.0 ± 3.84
Range	21-60	23-59	22-62	23-56
Height (inches)				
Mean	70.2 ± 0.50	70.9 ± 1.24	64.3 ± 0.44	61.6 ± 1.45
Range	61-77	65-75	51-72	52-65
Weight (kg)				
Mean	81.2 ± 2.10	79.9 ± 4.91	60.8 ± 1.16	61.4 ± 0.66
Range	52-118	59-102	45-89	50-80
Cigarettes smoked per day				
Mean	35.7 ± 1.62		34.2 ± 1.34	
Range	20-60		20-60	
Years as a smoker				
Mean	15.3 ± 1.78		14.8 ± 1.42	
Range	1-40		1-40	

\*Mean values ± SEM.

held on consecutive days. For the first session, subjects (smokers and nonsmokers) reported to the center at 7:00 a.m., without having been previously exposed to smoke that morning. They were randomly divided into groups of approximately 20 subjects each and assigned to separate conference rooms, each measuring 41×18×8 feet. To minimize the extent of passive inhalation of cigarette smoke, stringent unidirectional air ventilation from the back of the subjects was maintained (7 air volume changes per hour). As measured in the center of the test room, ambient air CO averaged 2.6 ppm during this session, and never exceeded 4 ppm.

Baseline plasma samples and exhaled air CO measurements were obtained from all subjects prior to smoking. Smokers were then instructed to smoke, at approximately 30 min intervals, 10 of their own brand of cigarettes. On the first day they were instructed to take one puff each minute, drawing the smoke into the mouth only, and discharging it. During the session they were permitted to drink water only. Nonsmokers were seated alongside smokers. At the end of the smoking period, approximately noontime, all subjects (smokers and nonsmokers) provided additional plasma and expired air samples and were dismissed until the following day.

On the second day, smokers were instructed to inhale smoke in their usual fashion while smoking 10 cigarettes of their own brand. Other procedures were similar to the first day except that normal conference room air ventilation levels were maintained, rather than the unidirectional ventilation system of the previous day. Ambient air CO averaged 4.1 ppm, and never exceeded 8 ppm.

#### Analytical Methods

Concentrations of nicotine in plasma were determined using gas chromatography according to the method of Jacob *et al.* [7]. Tests for standardization and quality control for this assay have been previously reported [5].

Expired air samples were obtained by trained technicians. Subjects were instructed to loosen tight fitting clothing, assume a standing position, take a full deep breath, hold it for 5 sec, and exhale all but an amount of air sufficient to fill a 1 liter sample bag, which was collected. The CO concentration was measured using a carbon monoxide analyzer (Ecolyzer, Energetics Sciences, Inc.), with a full scale sensitivity of ± 1 ppm.

Comparisons between the before-and-after dependent observations were made using the paired *t*-test. These were all one-sided tests since it was the change in tobacco smoke biological markers from no-inhalation to full-inhalation that was being tested. The Analysis-of-Variance (Completely Randomized Designed, Fixed Effects Model) was used for analyzing differences in response as a function of the FTC nicotine yield of the cigarettes smoked. All tests were carried out at the 5% level of significance. The Spjøtvoll-Stoline modification of Tukey's Honestly Significant Differences technique was used to preserve the level of significance [8].

#### RESULTS

Results for male subjects, female subjects, and all subjects combined are summarized in Tables 2, 3, and 4.

For the smokers, beginning (baseline) expired air CO and plasma nicotine concentrations for Session 2 (full inhalation) were not significantly different from the corresponding baseline values for Session 1 (mouth exposure only), for men and women separately or combined (all *p*-values >0.05). However, these values were significantly higher at the end of Session 2 than at the end of Session 1, for men and women separately and also combined (0.01 < *p* < 0.05).

For Session 1, there were no significant differences in expired air CO or plasma nicotine concentrations between the beginning and ending values, for men and women separately or combined (all *p*-values >0.05).

TABLE 2  
EXPIRED CARBON MONOXIDE AND PLASMA NICOTINE LEVELS AFTER MOUTH ONLY AND FULL INHALATION  
SMOKING—MALE SUBJECTS\*

	N	Carbon Monoxide in Expired Air (ppm)				Plasma Nicotine (ng/ml)			
		Mouth Only		Inhalation		Mouth Only		Inhalation	
		Begin	End	Begin	End	Begin	End	Begin	End
Nonsmokers	6	5.1 ± 0.6	5.3 ± 0.3	5.2 ± 0.5	5.5 ± 0.6	1.8 ± 0.1	2.1 ± 0.4	1.2 ± 0.2	2.1 ± 0.2
All smokers	41	15.7 ± 0.9	10.6 ± 0.5	14.0 ± 0.8	33.1 ± 2.1	3.3 ± 0.3	3.4 ± 0.3	3.4 ± 0.3	23.6 ± 1.5
FTC nicotine yield of cigarettes smoked (mg/cigarette)									
-0.20	8	15.6 ± 1.4	10.5 ± 1.1	13.5 ± 1.2	30.9 ± 2.5	3.4 ± 0.5	3.1 ± 0.8	2.9 ± 0.5	26.7 ± 3.2
0.21-0.40	4	9.8 ± 2.6	7.8 ± 1.2	11.3 ± 3.4	23.3 ± 10.0	2.8 ± 0.4	3.3 ± 0.9	2.6 ± 0.2	17.1 ± 4.1
0.41-0.60	6	21.0 ± 2.7	12.7 ± 1.4	16.7 ± 1.7	36.3 ± 4.5	3.7 ± 0.5	2.8 ± 0.6	2.5 ± 0.8	17.9 ± 2.3
0.61-0.80	10	16.9 ± 2.0	11.4 ± 1.0	16.3 ± 2.2	40.2 ± 5.2	3.0 ± 0.5	3.0 ± 0.4	4.1 ± 0.5	22.9 ± 3.3
0.81-1.00	4	13.5 ± 2.8	9.0 ± 0.8	12.5 ± 1.7	29.3 ± 8.6	3.9 ± 1.0	3.6 ± 1.2	3.3 ± 0.9	23.0 ± 5.3
1.01-	9	14.6 ± 1.6	10.4 ± 1.5	12.1 ± 1.5	31.1 ± 2.0	3.4 ± 0.8	4.2 ± 1.2	4.0 ± 1.0	28.7 ± 3.8

\*Mean values ± SEM.

TABLE 3  
EXPIRED CARBON MONOXIDE AND PLASMA NICOTINE LEVELS AFTER MOUTH ONLY AND FULL INHALATION  
SMOKING—FEMALE SUBJECTS\*

	N	Carbon Monoxide in Expired Air (ppm)				Plasma Nicotine (ng/ml)			
		Mouth Only		Inhalation		Mouth Only		Inhalation	
		Begin	End	Begin	End	Begin	End	Begin	End
Nonsmokers	8	4.6 ± 0.5	4.6 ± 0.4	4.8 ± 0.5	5.3 ± 0.4	3.0 ± 0.9	3.1 ± 0.7	1.9 ± 0.3	2.7 ± 0.4
All smokers	52	14.7 ± 0.6	9.9 ± 0.4	14.0 ± 0.6	36.7 ± 1.7	3.1 ± 0.3	3.1 ± 0.3	3.1 ± 0.4	27.8 ± 1.8
FTC nicotine yield of cigarettes smoked (mg/cigarette)									
-0.20	5	18.2 ± 2.2	12.2 ± 1.5	14.6 ± 2.0	32.2 ± 3.7	4.7 ± 1.3	5.7 ± 2.2	4.4 ± 1.1	26.6 ± 5.1
0.21-0.40	9	11.9 ± 0.9	8.9 ± 0.6	12.3 ± 0.7	35.3 ± 3.3	2.8 ± 0.6	2.4 ± 0.4	2.7 ± 0.4	26.1 ± 4.1
0.41-0.60	6	14.2 ± 2.0	9.7 ± 1.3	12.2 ± 1.3	31.0 ± 2.9	2.1 ± 0.5	2.0 ± 0.3	1.9 ± 0.4	29.6 ± 7.8
0.61-0.80	9	18.6 ± 1.7	11.4 ± 1.0	16.8 ± 2.0	44.2 ± 5.6	3.4 ± 0.6	4.3 ± 0.6	3.5 ± 0.5	28.3 ± 5.4
0.81-1.00	9	13.2 ± 1.1	8.4 ± 0.8	14.0 ± 1.6	33.4 ± 3.5	2.9 ± 0.5	2.0 ± 0.4	2.1 ± 1.8	21.4 ± 1.8
1.01-	14	13.9 ± 1.0	9.8 ± 0.9	13.8 ± 0.9	38.9 ± 3.7	3.2 ± 0.6	3.2 ± 0.5	3.9 ± 1.1	32.2 ± 3.2

\*Mean values ± SEM.

For Session 2, expired air CO and plasma nicotine concentrations were significantly higher at the end of the session than at the beginning, for men and women separately and also combined ( $0.01 < p < 0.05$ ).

For the nonsmokers (controls), there was a statistically significant increase in plasma nicotine concentration during Session 2 ( $p = 0.015$ ) for the combined data, although the difference was quantitatively small, and could be due to baseline nicotine values that were lower in Session 2 than in Session 1. There were no other significant differences in expired air CO or plasma nicotine concentration for the nonsmokers within or between sessions, for men and women separately or combined (all  $p$ -values  $> 0.05$ ).

FTC nicotine yields of the brands smoked were only marginally associated with expired air CO and plasma

nicotine concentrations (lower portions of Tables 2, 3, 4), the yields accounting for less than 3% of the variation in these latter variables, all correlation coefficients being less than 0.16.

#### DISCUSSION

The major finding of this study is that there is virtually no intake of nicotine through the buccal mucosa while smoking American cigarettes. These findings are consistent with the data of Armitage and Turner [1] in experimental animals demonstrating little buccal absorption of nicotine from acidic cigarette smoke. Popular American cigarettes tend to produce smoke with an acidic pH (around 5.5), resulting in

TABLE 4  
EXPIRED CARBON MONOXIDE AND PLASMA NICOTINE LEVELS AFTER MOUTH ONLY AND FULL INHALATION  
SMOKING—MALE AND FEMALE SUBJECTS\*

	N	Carbon Monoxide in Expired Air (ppm)				Plasma Nicotine (ng/ml)			
		Mouth Only		Inhalation		Mouth Only		Inhalation	
		Begin	End	Begin	End	Begin	End	Begin	End
Nonsmokers	14	4.9 ± 0.4	4.9 ± 0.2	4.9 ± 0.3	5.4 ± 0.3	2.5 ± 0.5	2.7 ± 0.5	1.6 ± 0.2	2.5 ± 0.3
All smokers	93	15.1 ± 0.5	10.2 ± 0.3	14.0 ± 0.5	35.1 ± 1.3	3.2 ± 0.2	3.2 ± 0.2	3.2 ± 0.2	25.9 ± 1.2
FTC nicotine yield of cigarettes smoked (mg/cigarette)									
-0.20	13	16.6 ± 1.2	11.2 ± 0.9	13.9 ± 1.1	31.4 ± 2.0	3.9 ± 0.6	4.1 ± 1.0	3.5 ± 0.5	26.7 ± 2.6
0.21-0.40	13	11.2 ± 1.0	8.5 ± 0.5	12.0 ± 1.0	31.6 ± 3.9	2.8 ± 0.4	2.6 ± 0.4	2.6 ± 0.3	23.3 ± 3.2
0.41-0.60	12	17.6 ± 1.9	11.2 ± 1.0	14.4 ± 1.2	33.7 ± 2.7	2.9 ± 0.4	2.4 ± 0.3	2.2 ± 0.4	23.7 ± 4.2
0.61-0.80	19	17.7 ± 1.3	11.4 ± 0.7	16.5 ± 1.4	42.1 ± 3.8	3.2 ± 0.4	3.6 ± 0.4	3.8 ± 0.3	25.5 ± 3.0
0.81-1.00	13	13.3 ± 1.1	8.6 ± 0.6	13.5 ± 1.2	32.2 ± 3.4	3.2 ± 0.5	2.4 ± 0.5	2.5 ± 0.4	21.9 ± 1.9
1.01-	23	14.1 ± 0.9	10.0 ± 0.8	13.1 ± 0.8	35.9 ± 2.5	3.3 ± 0.5	3.6 ± 0.5	3.9 ± 0.8	30.9 ± 2.4

\*Mean values ± SEM.

nicotine absorption exclusively through the airways below the oropharynx. However, other cigarettes, cigars and pipes that generate more alkaline smoke may be associated with buccal absorption of nicotine [9].

Our data also provide information about the extent of absorption of nicotine and carbon monoxide during passive smoking. In circumstances of high ventilation, there was no demonstrable change in the levels of these substances. However, in the normally ventilated circumstance, there was a statistically significant but very small increase in nicotine consistent with other studies of passive smoke exposure.

Expired CO changes were equally small and not statistically significant. These results suggest that plasma nicotine may be a more sensitive indicator of exposure to second-hand smoke than carbon monoxide.

The increments of nicotine or carbon monoxide after smoking 10 cigarettes showed no correlation to the widely varying FTC yields of the cigarettes smoked. This finding is consistent with those of previous reports indicating that smokers tend to self-select a nicotine intake level independent of analytical machine yield of the brand smoked [3,6].

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