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METABOLISM OF NICOTINE IN SMOKERS AND NONSMOKERS*

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ABSTRACT

While a number of secondary reinforcers may exert some influence on cigarette smoking behavior, the major factor responsible for tobacco habituation is believed to be nicotine. Two studies on the metabolism of the N-oxidative metabolites have revealed substantial in vivo reduction of these compounds to nicotine after their chronic and subchronic administration to rats. Nicotine-N,N'-dioxide was also shown to be back-reduced to the parent alkaloid as evidenced by high levels of nicotine and cotinine in the plasma and urine of treated rats. In another study, the rate of elimination of cotinine in smokers and passively exposed nonsmokers was measured. Ten smokers quit smoking and the elimination of cotinine in plasma and urine was measured for eight days after cessation. Four nonsmokers were exposed to a sidestream smoke-polluted environment and the rate of cotinine disappearance was assessed. Cotinine elimination in the plasma of the passively exposed nonsmokers took at least twice as long as that of chronic cigarette smokers. The rate of elimination from the urine was also significantly slower in nonsmokers when compared with smokers. A new nicotine delivery method, a nicotine aerosol rod, was examined under standard FTC machine smoking conditions. In a pilot study, the uptake of nicotine from this nicotine aerosol rod was also measured in smokers and nonsmokers. The results indicated that per puff deliveries of nicotine were too small to be assessed by radioimmunoassay and that this method of nicotine delivery did not result in smoker satisfaction. More work is necessary if alternate methods of nicotine delivery are to be accepted by the population which continues to smoke.

INTRODUCTION

Exposure to tobacco smoke constituents can occur through the active intake of mainstream smoke, the passive intake of sidestream smoke, or the transfer of tobacco smoke constituents by the maternal bloodstream to the developing fetus (1,2,3). Exposure can be evaluated by physiological or

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biochemical means as well as by self-reported daily consumption of tobacco products in active smokers (4). However, the actual uptake and body burden of tobacco components can be quantitated only by direct measures of the constituents or their metabolites.

The measurement of nicotine is specific for tobacco but, for in vivo measurements, is limited by a short biological half-life. Assessment of its terminal metabolite cotinine has proven more useful in appraising active and passive uptake of tobacco smoke compounds (5,6,7).

In this article, we present a series of investigations on nicotine uptake, absorption, and metabolism, beginning with two studies on the less prominent N-oxidative metabolites of nicotine and then proceeding to several studies on the metabolism of nicotine in active smokers as well as passively exposed adults and neonates. Finally, some data are presented on a nicotine aerosol delivery method that is currently being marketed in the U.S. for use by smokers and others who desire nicotine.

Studies on the N-oxidative Metabolites of Nicotine in Rats

It is well established that the major pathway of nicotine metabolism to cotinine is by α-hydroxylation (8,9). However, substantial quantities of nicotine are metabolized to nicotine-N'-oxides by N-oxidation (10,11). While less than 1/3 of absorbed nicotine is biotransformed by this pathway, it is nonetheless important for two reasons. First, the fact that nicotine-N'-oxides are rapidly back-converted to nicotine both in vivo and in vitro (12,13) means that these metabolites represent a nicotine reserve that is involved in reinforcing nicotine habituation. Secondly, these compounds are easily nitrosated to form the powerful tobacco specific carcinogens N'-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK). Klemish and Stadler in 1979 demonstrated that the in vitro formation of NNN is 3 times higher from nicotine-N'-oxides than from nicotine itself (14).

In a recent study that we conducted on the chronic effects of the metabolites of nicotine, male Fischer rats were divided into one control and 3 experimental groups (15). Each treatment group received either

TABLE 1. Nicotine and Cotinine Concentrations in Rats Administered Cotinine and Nicotine-N-Oxides

	Serum Levels		Urine Levels	
	Nicotine ng/ml	Cotinine ng/ml	Nicotine ng/per mg creatinine	Cotinine µg/per mg creatinine
Cotinine (N = 29)	ND*	23206 ±1300	76. ±5.	>650
Nicotine-N-Oxide (100% trans) (N = 33)	119 ±12	995 ±125	6150 ±880	18.7 ±2.0
Nicotine-N-Oxide (64% trans-36% cis) (N = 32)	123 ±17	605 ±144	3300 ±269	14.3 ±1.9

*ND = Not detected
From Sepkovic, et al. (15)

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0.02% pure trans nicotine-N'-oxide, 0.02% of a diastereomeric N'-oxide mixture, or 0.1% cotinine in drinking water for 78 weeks. Plasma and urinary nicotine and cotinine levels were measured in the various treatment groups (Table 1). Substantial concentrations of plasma and urinary cotinine were observed in both N'-oxide treatment groups which were checked to be the result of back-conversion of these metabolites to nicotine and subsequent α-hydroxylation of nicotine to cotinine via 5'-hydroxycotinine. Pure trans-N'-oxide readily back-converts to nicotine while the diastereomeric mixture is less readily reduced in vivo. Body weights of the animals were significantly reduced in both of the N'-oxide treatment groups (Fig. 1). These findings prompted us to conduct a short-term study administering purified preparations of trans- or cis-nicotine-N'-oxide or nicotine-N,N'-dioxide in rats for three weeks and then measuring the back-conversion of these metabolites to nicotine (16). The metabolites were given in drinking water in the same concentrations as in the previous chronic study. Blood samples were obtained weekly for three weeks. After seven days of metabolite administration, nicotine levels in the plasma of the trans-nicotine-N-'-oxide group rose to approximately twice the concentrations observed in the other groups (Fig. 2). After two weeks, plasma nicotine levels declined for both nicotine-N'-oxide diasteromers and were approximately equal. Nicotine concentrations in these groups remained similar and continued to decline in week three. Plasma nicotine concentrations above 200 ng/ml were observed during week one of the study in nicotine-N,N'-dioxide-treated animals. Mean plasma nicotine concentrations decreased to approximately 100 ng/ml by week two and continued to decrease during week three. Plasma cotinine concentrations were similar for both cis-and trans-nicotine-N'-oxides during week one (Fig. 3). However, cotinine levels were increased in the trans-N'-oxide group relative to cis-N'-oxide-treated rats in week two. At week three, both groups began to exhibit decreases in plasma cotinine concentrations. Plasma cotinine concentrations in nicotine dioxide-treated rats rose less dramatically when compared with the N'-oxide groups, but significant amounts of cotinine were present in the serum of these animals. The results of this short-term study confirm that both isomers of nicotine-N'-oxide are readily back-converted in vivo from the nicotine-N'-oxide to its nicotine congener. Nicotine-N,N'-dioxide was also shown to be reduced to nicotine. This seldom-studied compound comprises approximately 5% of the N-oxidation products of nicotine metabolism and its back-conversion has not been previously reported. These findings and those of other workers suggest the involvement of the liver and/or other tissues in the reduction of N-oxidative metabolic products of nicotine (12,13). Increases of cotinine in the urine of all three treatment groups reflect decreases in the blood as well as concomitant induction of α-hydroxylation hepatic microsomal enzymes.

These findings have relevance to smoking and health issues since nicotine has the chemical potential to act as a precursor for the formation of the tobacco specific nitrosamines (17,18). This is especially important since age-related shifts in nicotine metabolism from cotinine to nicotine-N'-oxides have been reported (19). The increased availability of nicotine from the in vivo reduction of nicotine-N'-oxides and from nicotine-N,N'-dioxides provides the substrate for increased nitrosation. Also, the capacity of the nicotine-N'-oxides to be directly nitrosated to form NNN (14) emphasizes the possibility that individuals who undergo shifts in nicotine metabolism, either caused by aging or by metabolic alteration, might be at increased risk for tobacco-related diseases.

Cotinine Elimination in Smokers and Nonsmokers

A number of epidemiological studies have indicated an association of environmental smoke exposure with tobacco-related diseases (20-23).

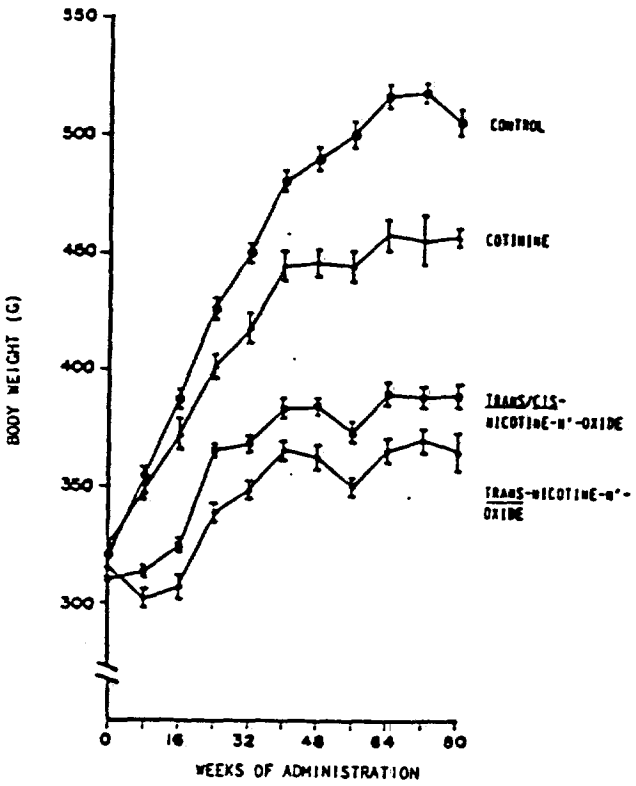

Fig. 1. Body weights from rats administered nicotine metabolites for 78 weeks. Each point equals the mean ± SEM. From Sepkovic, et al. (15).

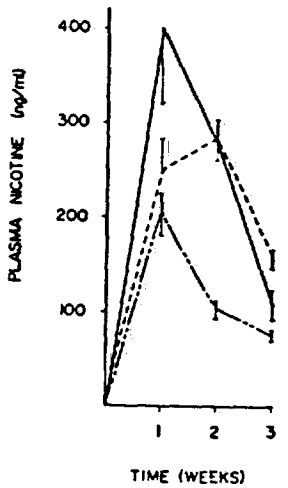

Fig. 2. Plasma nicotine concentrations in rats receiving trans-nicotine-N'-oxide (——), cis-nicotine-N'-oxide (– – –) or nicotine-N,N'-oxide (— – — –) for 3 weeks. Each point equals the mean ± the SEM of 20 animals. From Sepkovic, et al. (16).

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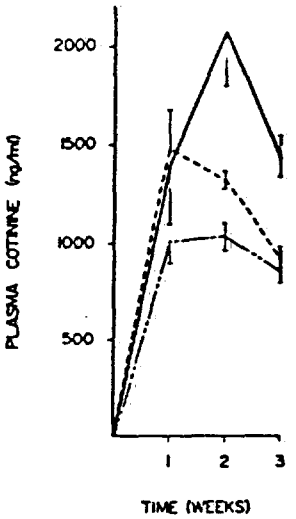

Fig. 3. Plasma cotinine concentrations in rats receiving trans-nicotine-N'-oxide (——), cis-nicotine-N'-oxide (——) or nicotine-N, N'-dioxide (— — —) for 3 weeks. Each point equals the mean ± the SEM of 20 animals. From Sepkovic, et al. (16).

Environmental tobacco smoke pollutants are primarily those products of tobacco combustion that emit as sidestream smoke from the smoldering product in between puff-drawing (Table 2). The composition of tobacco sidestream smoke differs significantly from that of mainstream smoke in that, before dilution with air, the former is actually enriched in some toxic gas phase components including carbon monoxide, formaldehyde, nitrogen oxides, and acetone (Table 3). N-nitroso compounds, benzo(a)pyrene, and heavy metals are also more abundant in sidestream than in mainstream smoke before dilution (24) (Table 4). Elevated concentrations of such harmful chemical compounds in heavily polluted environments may constitute a health risk to passively exposed individuals. In comparison with tobacco smokers, nonsmokers thus exposed may actually be subjected to a disproportionate increase in body burden of toxic substances since the hepatic microsomal enzyme systems that detoxify tobacco compounds in smokers may not be fully induced. By measuring cotinine in plasma and in urine, we have estimated the rate of elimination

TABLE 2. Comparisons of Mainstream and Sidestream Smoke of Cigarettes

Parameters	MS	SS/MS
Peak Temperature During Formation (°C)	900	600
Particle Sizes (μm)	0.1 - 1.0	0.01 - 0.1
Median Diameter	0.4	
Smoke Dilution (Vol. %) (10 mm from burning cone)		
Carbon Monoxide	3 - 5	1
Carbon Dioxide	8 - 11	2
Oxygen	12 - 16	16 - 20
Hydrogen	15 - 3	0.5

From Hoffmann, et al. (24)

TABLE 3. Distribution of Compounds in the Gas Phase in Cigarette Mainstream Smoke (MS) and Sidestream Smoke (SS) - Nonfilter Cigarettes

Gas Phase	MS	SS/MS
Carbon Monoxide	10 - 23 mg	2.5 - 4.7
Carbon Dioxide	20 - 60 mg	8 - 11
Formaldehyde	70 - 100 µg	0.1 - -50(?)
Acrolein	60 - 100 µg	8 - 15
Acetone	100 - 250 µg	2 - 5
Pyridine	20 - 40 µg	10 - 20
3-Vinylpyridine	15 - 30 µg	20 - 40
Hydrogen Cyanide	400 - 500 µg	0.1 - 0.25
Nitrogen Oxides	100 - 600 µg	4 - 10
Ammonia	50 - 130 µg	40 - 130
N-Nitrosodimethylamine	10 - 40 µg	20 - 100
N-Nitrosopyrrolidine	6 - 30 µg	6 - 30

From Hoffmann, et al. (24)

of this end product of nicotine metabolism in both smokers and in passively exposed nonsmokers (25). Ten volunteer smokers selected for the study smoked their customary cigarettes ad libitum for 5 days and reported to the clinic each day at 9:30 a.m. for blood and saliva sampling. At 12:00 midnight, on day 5, the subjects quit smoking. Sampling on the following two days provided two blood samples and four saliva samples per day. Blood and saliva samples were taken once daily from day 8 through day 12 when the study was terminated. Total urine voids were collected daily throughout the study period.

TABLE 4. Distribution of Compounds in the Particulate Phase in Cigarette Mainstream Smoke (MS) and Sidestream Smoke (SS) Nonfilter Cigarettes

Particulate Phase	MS	SS/MS
Particulate Matter	15 - 40 mg	1.3 - 1.9
Nicotine	0 - 2.3 mg	2.6 - 3.3
Phenol	60 - 120 µg	2.0 - 3.0
Catechol	100 - 280 µg	0.6 - 0.9
Aniline	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine	1.7 ng	30
Benz(a)anthracene	20 - 700 ng	2 - 4
Benzo(a)pyrene	20 - 40 ng	2.5 - 3.5
N'-Nitrosonornicotine	200 - 3,000 ng	0.5 - 3
NNK	100 - 1,000 ng	1 - 4
N-Nitrosodiethanolamine	20 - 70 ng	1.2
Nickel	20 - 80 ng	13 - 30
Polonium-210	0.03 - 0.5 pCi	

From Hoffmann, et al. (24)

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In this same study, four nonsmokers, 25-35 years of age, were exposed to the sidestream smoke-polluted environment generated by four Kentucky 1R1 Reference cigarettes twice daily for 80 minutes each time in a test laboratory. This exposure schedule was maintained for four consecutive days. The laboratory consisted of a bare room of 16 m^3 with 6 air changes per hour (26). An indwelling catheter was inserted before exposure permitting continuous blood sampling. Saliva and urine samples were also taken from each subject after each exposure period at a different location which was free of smoke pollutants. Monitoring continued for 7 days. Cotinine elimination in the plasma of the passively exposed nonsmokers took at least twice as long as that of the chronic cigarette smokers (Fig. 4). The rate of cotinine disappearance from the urine had also significantly slowed down in the nonsmokers compared with smokers (Fig. 5).

These findings have significance in several ways. First, the slower clearance in nonsmokers of a terminal nicotine metabolite commonly used to measure exposure to tobacco smoke could result in a misinterpretation of "cigarette equivalents" which some researchers use to calculate passive exposure (27). The prolonged elimination of cotinine shown by passive smokers precludes an extrapolation to "cigarette equivalents of smoke uptake" from a single measurement of urinary cotinine.

Secondly, the prolonged elimination and likely slower metabolism of nicotine in nonsmokers would suggest that passively exposed individuals also carry a body burden of other toxic tobacco components for longer periods than do long-term cigarette smokers. The extended residence time of nicotine (and possibly of other tobacco alkaloids) increases also the probability of the endogenous formation of carcinogenic tobacco-specific N-nitrosamines (28). Thus, this phenomenon of prolonged elimination should not be disregarded in the analysis of relative risk for tobacco-related cancers.

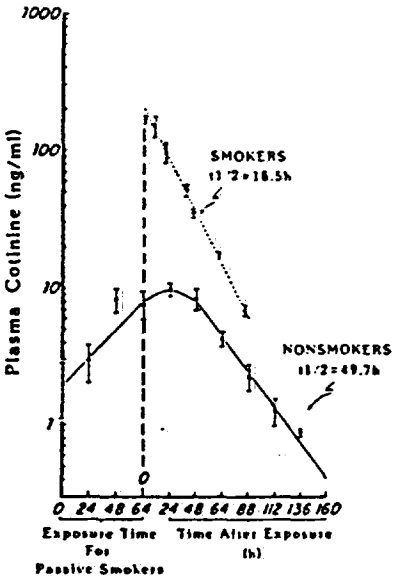

Fig. 4. Plasma cotinine elimination in smokers and passively exposed nonsmokers. The computer program used for pharmacokinetic analysis was provided by Johnston and Wollard (33). From Sepkovic et al. (25).

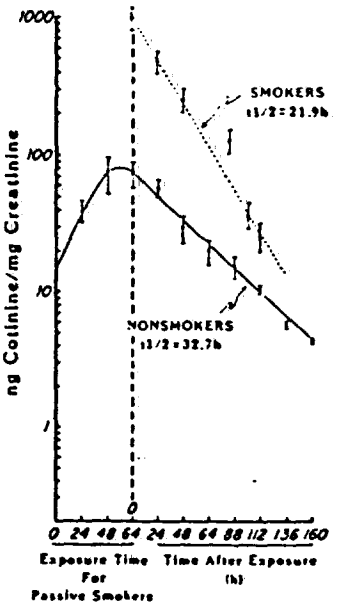

Fig. 5. Urinary cotinine elimination in smokers and in passively exposed nonsmokers. Urinary cotinine concentrations are normalized by creatinine. The computer program for pharmacokinetic analysis was provided by Johnston and Wollard (33). From Sepkovic et al. (25).

Cotinine Concentrations in Passively Exposed Neonates

An important field study was conducted to measure passive exposure to environmental tobacco smoke in infants from mothers who smoke. The study was conducted with the collaboration of Drs. Robert Greenberg, Ruth Etzel,and Frank Loda, from the University of North Carolina at Chapel Hill (29). Urine and saliva was collected from infants one to three months of age who were not breast fed. Based on self-report of the primary caretaker, infants were classified as exposed or nonexposed. Cotinine measures clearly differentiated these groups (Fig. 6). There was a dose-response relationship between the daily number of cigarettes smoked by the mother and infant excretion of cotinine (Fig. 7). While the levels of cotinine observed in adult and child passive smokers are very low, the study indicates that infants, including neonates who are cared for in households that include smokers, absorb tobacco smoke constituents and excrete nicotine in addition to metabolizing nicotine to form cotinine. These results conform to those of other workers (30).

Upon determining that neonates were able to take up and metabolize nicotine from an environment that was tobacco smoke polluted, it then became important to explore whether the fetus of a smoking mother is exposed to nicotine. In collaboration with the Chapel Hill group we selected 11 neonates of smoking mothers and 12 neonates of nonsmoking mothers who were delivered at North Carolina Memorial Hospital (3). To be eligible for the study, infants had to be isolated from exposure to all sources of tobacco smoke products after birth, including breast feeding. On the day after delivery, all the mothers of the eligible babies were asked whether they had smoked in the 24 hours just before delivery. Urine was collected from each group and analyzed for cotinine (Fig. 8). Significant concentrations of urinary cotinine were observed in the

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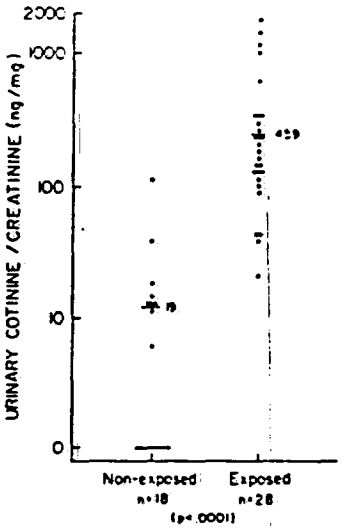

Fig. 6. Urinary cotinine concentrations in infants exposed and not exposed to tobacco smoke. Cotinine concentrations were normalized over urinary creatinine. From Greenberg, et al. (29).

neonates of smoking mothers when compared with the neonates of nonsmoking mothers. Interestingly, the half-elimination time of cotinine in newborns was discovered to be two to three times longer than in adults (68 hours).

Commercial Aerosol Rods as Nicotine Supplements

The acquisition of nicotine represents the primary motivation for cigarette smoking. During the act of smoking, a wide variety of toxic substances are inhaled along with nicotine. These vapor phase and particulate phase compounds have been implicated in a number of pulmonary disease states. The Surgeon General reports that cigarette smoking is the major cause of chronic obstructive lung disease in the United States for both men and women. The mortality ratios for chronic obstructive lung

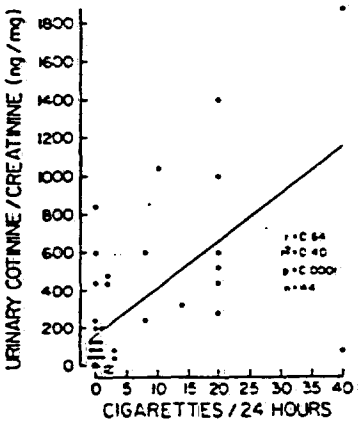

Fig. 7. Maternal cigarette smoking versus infant urinary cotinine excretion from Greenberg, et al. (29).

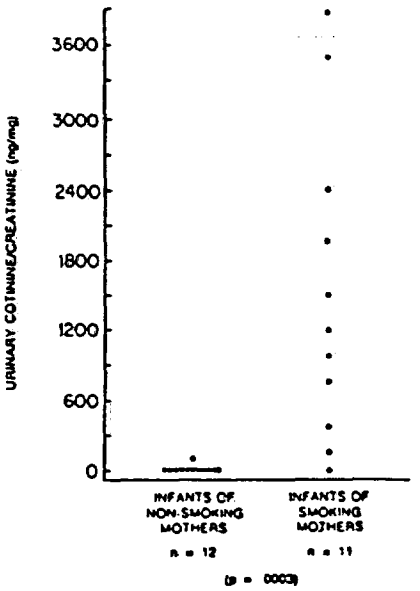

Fig. 8. Urinary concentrations of cotinine during the first day of life in neonates of smoking and nonsmoking mothers. From Etzel, et al. (3).

disease in smokers are as large as or larger than for lung cancer, the disease most people associate with cigarette smoking (31).

The elimination of such toxic tobacco smoke compounds would significantly decrease the health risk associated with cigarette smoking. The possibility exists that nicotine supplementation by inhalation of nicotine as an aerosol could alter smoking behavior patterns and reduce the uptake of more hazardous tobacco smoke compounds. For this reason, we

TABLE 5. Nicotine Yield of Nicotine Aerosol Rod Under Standard Machine Smoked Conditions*

Puffs	Average Nicotine/Puff (µg)	Total Nicotine (µg)
1 - 10	0.3	3
11 - 20	1.8	18
21 - 30	3.5	35
31 - 40	4.4	44
41 - 50	5.8	58
51 - 60	6.4	64
	Total	222

*Smoked on a Hamburg Heiner Borgwaldt single port piston smoking machine (1 puff/min, 35 ml volume of 2 sec duration). Nicotine was trapped on a Cambridge filter pad and determined by gas chromatography. From Sepkovic et al. (32).

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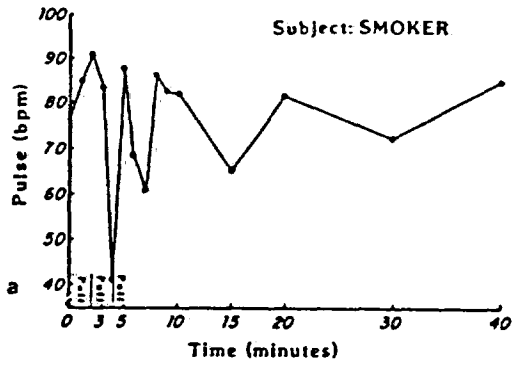

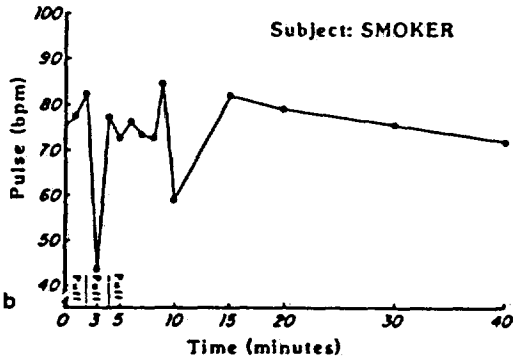

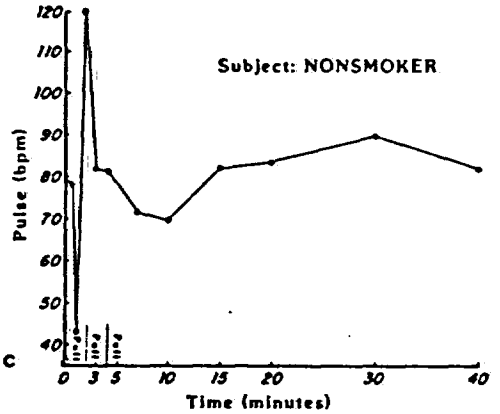

Fig. 9a. Pulse rate in a moderate cigarette smoker (plasma cotinine 223 ng/ml) upon using a nicotine aerosol rod.

b. Pulse rate of a light cigarette smoker (plasma cotinine 116 ng/ml) after using a nicotine aerosol rod.

c. Pulse rate of a nonsmoker after using a nicotine aerosol rod.

became interested in the commercial nicotine aerosol rod as a substitute source of nicotine for cigarette smokers.

The nicotine aerosol rod is currently being test-marketed in Texas. The per puff delivery approximates nicotine concentrations delivered by conventional cigarettes according to the manufacturer.

The aerosol rods were first examined under standard machine smoking conditions with the following results (Table 5) (32). The average nicotine per puff increased with the number of puffs taken from 0.3 µg/puff at 10 puffs to 6.4 µg/puff after 50 puffs.

In order to measure the uptake of nicotine in users of the aerosol rod, we designed the following study. Four smokers and three nonsmokers were asked to abstain for at least 12 hours prior to reporting to each session. After they were comfortably seated, an indwelling catheter was inserted into the antecubital vein of the right forearm and an automatic blood pressure cuff was placed on the left arm. Baseline measurements of blood pressure and pulse were also taken and physiological measurements were continued throughout each session. Puffs of the aerosols were inhaled every 2 minutes for 6 minutes.

In two of the four smokers, an immediate drop in pulse was noted after the second puff (Figs. 9a and b). In one nonsmoker, heart rate decreased after the first puff and then immediately showed a dramatic increase (Fig. 9c). In the other subjects, no change in heart rate was observed. The plasma obtained from smoking and nonsmoking users was analyzed for nicotine and cotinine with the following results (Table 6). No nicotine was observed in the plasma or urine of smokers or nonsmokers after using the aerosol rod.

The amount of nicotine delivered per puff was the equivalent of a hypothetical 0.01-mg nicotine content cigarette, which would provide per puff deliveries too small for nicotine absorbed to be assessed in the plasma. Only after a total of 60 puffs would this rod approximate the nicotine delivery of a 0.2-mg nicotine content cigarette. Furthermore, the rate of absorption of nicotine in aerosol form may not be rate-equivalent to tobacco smoke absorption.

Product satisfaction was also assessed in this pilot study. All subjects commented on a burning sensation following each puff and the nonsmokers complained of sore throats. The physiological effects elicited by the nicotine aerosol rod are somewhat more serious in nature. The heart rate depression in two of our four smokers and the depression followed by the compensatory increase in heart rate in one of three nonsmokers suggests that a more in-depth study with a larger volunteer population is necessary to identify the causative agent responsible for the fluctuations in heart rate.

TABLE 6. Nicotine and Cotinine in the Plasma of Smoking and Nonsmoking (Nicotine Aerosol Rod) Users

	Plasma Nicotine	Plasma Cotinine (ng/ml)	Urinary Cotinine
Smokers	ND	197 ± 174 S.D.	---
Nonsmokers	ND	ND	ND

ND = Not detected

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These investigations into the metabolism of nicotine and the disposition of its metabolites were conducted with the overall goal of more closely identifying the health risk associated with cigarette smoking. Since the acquisition of nicotine is a dependence process and represents the primary motivation for cigarette smoking, any attempt to reduce the hazardous ancillary compounds absorbed along with nicotine would be beneficial to all habituated smokers. The ultimate goal of tobacco-related research should be the elimination of smoking behavior in existing smokers and the prevention of inception of the habit by nonsmokers. However, the health of 52 million people in the United States who continue to smoke cannot be ignored.

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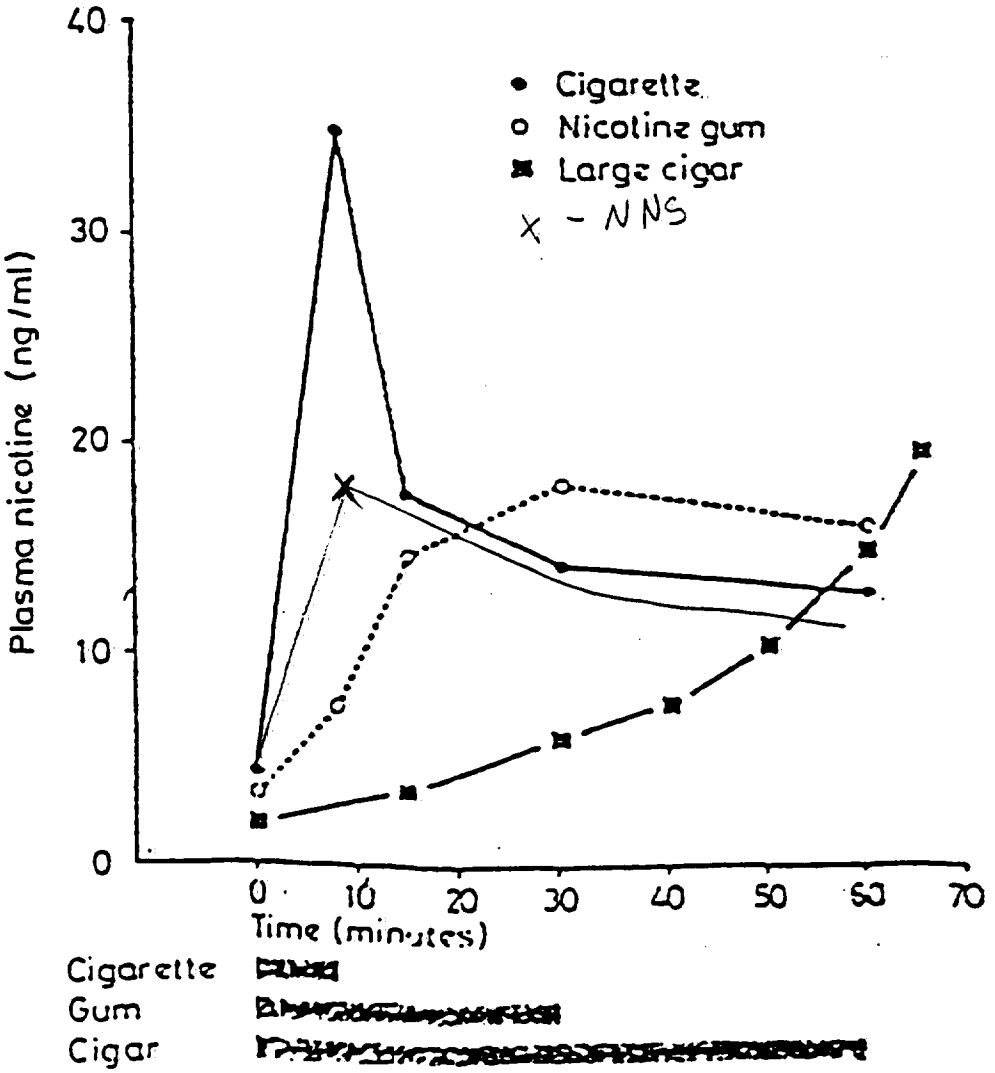

Fig 1—Blood nicotine concentrations after chewing one piece of 4-mg gum compared with smoking a cigarette (1·2 mg nicotine) and a large Havana cigar. At least 12 hours' abstinence before testing.

TABLE 1

PLASMA NICOTINE LEVELS VERSUS TIME AFTER INHALATION OF NICOTINE AEROSOL

Subject No.	Nicotine Levels (*ng/ml**)					
	0 min	2.5 min	5.0 min	7.5 min	10.0 min	12.5 min
1	6 ± 1	6 ± 0	8 ± 1	9 ± 1	10 ± 1	9 ± 0
2	12 ± 1	15 ± 2	21 ± 3	26 ± 3	29 ± 4	26 ± 3
3	21 ± 3	35 ± 13	39 ± 13	45 ± 18	34 ± 8	28 ± 4
4	9 ± 0	21 ± 1	44 ± 1	56 ± 1	55 ± 2	46 ± 2
5	14 ± 2	33 ± 6	55 ± 3	58 ± 1	50 ± 1	41 ± 4
6	10 ± 0	10 ± 0	13 ± 2	17 ± 2	17 ± 3	15 ± 3
7	20 ± 1	23 ± 1	39 ± 3	37 ± 2	30 ± 4	31 ± 3
8	22 ± 2	23 ± 1	26 ± 1	29 ± 2	29 ± 1	28 ± 0
$\bar{x}$	12 ± 2	18 ± 4	28 ± 7	32 ± 7	29 ± 7	25 ± 6

* Values are mean ± SEM for the 8 subjects who completed 3 trials each.

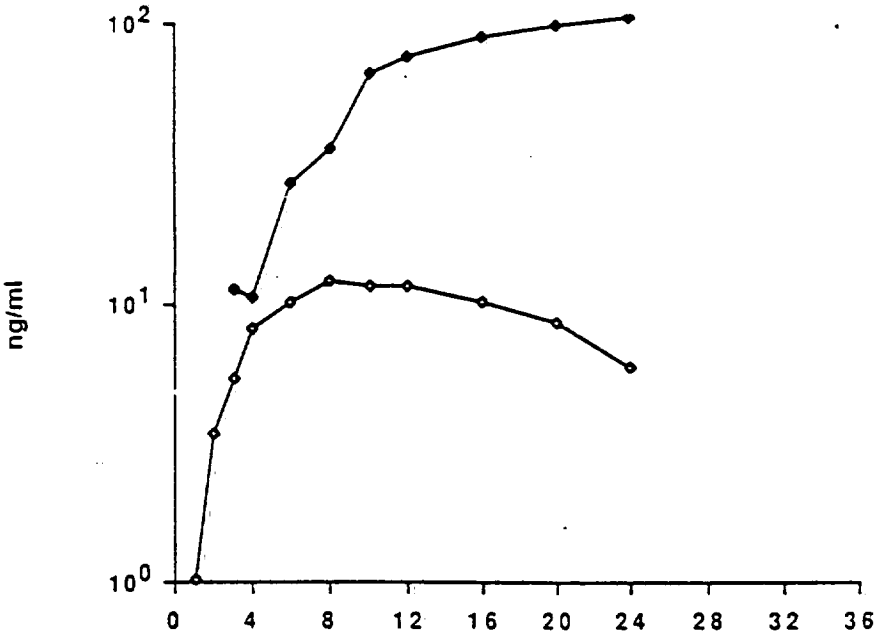

Fig. 1. Mean plasma concentrations of nicotine *(open symbols)* and cotinine *(closed symbols)* at day 1.

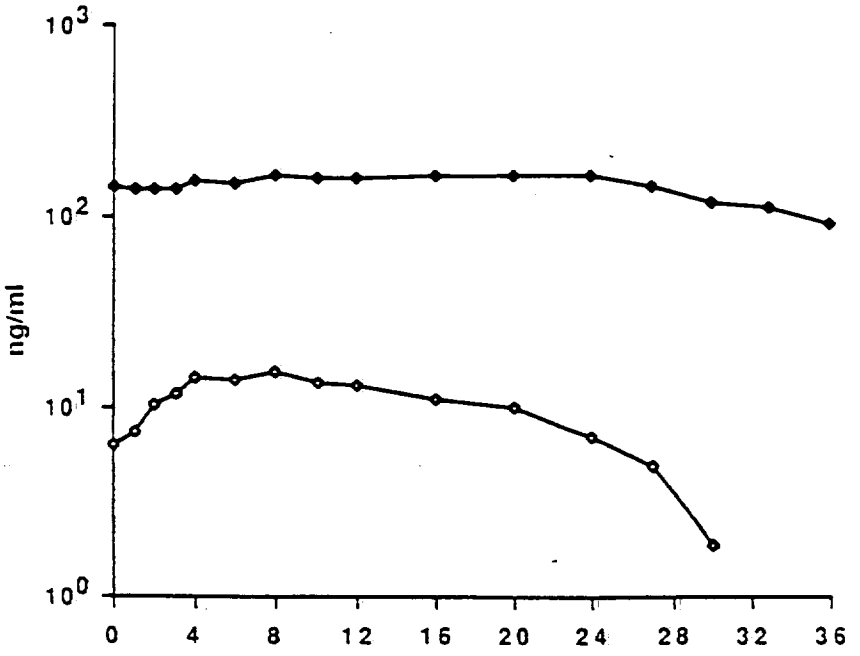

Fig. 2. Mean plasma concentrations of nicotine *(open symbols)* and cotinine *(closed symbols)* at day 7.