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Population Characteristics and Cigarette Yield as Determinants of Smoke Exposure

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BRIDGES, R. B., J. G. COMBS, J. W. HUMBLE, J. A. TURBEK, S. R. REHM AND N. J. HALEY. *Population characteristics and cigarette yield as determinants of smoke exposure.* PHARMACOL BIOCHEM BEHAV **37**(1) 17–28, 1990.—Relationships of population characteristics, smoking history, and cigarette yield with smoke exposure as measured by peripheral blood concentrations of thiocyanate, carboxyhemoglobin, nicotine and cotinine were sought in 170 male smokers. This population of smokers had significant elevations of serum thiocyanate, blood carboxyhemoglobin and plasma nicotine and cotinine concentrations as compared with an equal number of age- and sex-matched nonsmokers and these concentrations correlated significantly with past 24-hour cigarette consumption. Although the nicotine yield of the cigarette correlated significantly with plasma cotinine and marginally with plasma nicotine, the reduction in plasma nicotine and cotinine was not proportionate to the reduced yield of the cigarettes, suggesting that smokers partially compensate for the lower yields of their cigarettes. Blood levels of carboxyhemoglobin, nicotine and cotinine were also significantly associated with the weight of the subjects, presumably due to the relationship between weight and the volume of distribution. Univariate and multiple regression analyses provided evidence that coffee and alcohol consumption and years smoked also may be important determinants of smoke exposure.

Thiocyanate Carboxyhemoglobin Plasma nicotine Plasma cotinine Cigarette yield Body weight Coffee Alcohol Smoking history

CIGARETTE smoking is associated with an increased incidence of both respiratory and cardiovascular disease as well as cancer (49–51); however, many life-long smokers suffer no such impairment of health. It is likely that both the dose of smoke constituents and the individual response of smokers to these constituents account for the variable susceptibility of smokers to these diseases. In an attempt to reduce the intake of tar and nicotine, commercial cigarettes have been developed which produce lower yields of these components under standardized smoking conditions (48).

Although lower yield cigarettes are associated with lower plasma nicotine concentrations (19,45), no consistent relationship has been observed between the nicotine yield of the cigarette and plasma cotinine concentrations (4). This lack of a relationship suggests that the smokers of low yield cigarettes may compensate

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in their puffing behavior to derive a greater nicotine delivery than that obtained under machine smoking conditions. Increases in puff volume, puff duration and puff number have all been associated with decreased nicotine yield of the cigarette smoked (2, 15, 37). These compensatory changes in puffing behavior may obliterate any health benefits which might accrue from smoking low tar and nicotine cigarettes. Nicotine has been suggested to be the primary pharmacologic reinforcer controlling puffing behavior (39).

Previous studies have demonstrated that blood concentrations of smoke constituents and their metabolites are highly variable among smokers. In the context of a larger study to determine the relationship between cigarette smoking and the development of obstructive pulmonary disease, we sought the major determinants of smoke exposure and absorption as measured by blood levels of thiocyanate, carboxyhemoglobin, nicotine and cotinine in 170 smokers. The purpose of the present study was to determine how population characteristics, smoking history (cigarettes per day, years smoked, and pack-years), and nicotine yield of the cigarette related to smoke exposure and absorption as determined by blood levels of these smoke constituents and their metabolites.

METHOD

Male smoking and nonsmoking volunteers for this study consisted of faculty, staff and students of the University of Kentucky as well as individuals recruited by advertising in the local newspaper. All subjects gave written informed consent for this study, which was approved by the Human Investigations Committee of the University. Subjects were excluded from this study if they were taking medications or had diseases known to affect inflammatory mediators or if they had a history of bronchospasm or asthma. Male smokers were recruited without regard to their age, the brand of cigarette smoked, the number of cigarettes smoked per day or the pack-years smoking history. The 170 smokers were compared with a group of 170 age-, sex- and race-matched nonsmokers who had never smoked on a regular basis. The subjects for this study completed a detailed questionnaire concerning medical, pulmonary, smoking (both active and passive) and drug usage histories. In addition, these subjects recorded their alcohol and coffee consumption, exposure to environmental pollutants, and demographics.

Smokers provided data on the smoking history questionnaire concerning the cigarette brand and number of cigarettes smoked per day for each five-year interval of their smoking history. The subjects also completed a questionnaire indicating cigarette consumption in the previous 24 hours. Smokers and nonsmokers who used tobacco in any other form (i.e., pipe, cigars or smokeless tobacco) were excluded from the data analyses. The smokers in this study consumed their own brand of cigarette. The nicotine yield of the cigarette was derived from the Federal Trade Commission using standard machine smoking conditions (21).

Subjects for this study also provided data on beverage (alcohol, coffee, and tea) consumption for each five-year interval of their drinking history. For each of these five-year periods, the subjects indicated the weekly alcohol consumption as number of 12 ounce bottles or cans of beer, the number of 5 ounce glasses or 25.4 ounce bottles of wine, and the number of 2 ounce shots, 16 ounce pints, or 25.4 ounce fifths of distilled spirits. Alcohol consumption was converted to pure ounces of alcohol assuming a 3.8% alcohol content for beer, 10% for wine and 45% for distilled spirits. The total cumulative and daily alcohol consumption were calculated from these data and expressed as total ounces of pure ethanol consumed during a lifetime or on a daily basis, respectively. Coffee and tea consumption were expressed as number of cups consumed daily.

TABLE 1

POPULATION CHARACTERISTICS*

	Nonsmokers	Smokers	*p*
Age (years)	37.1 ± 0.8	37.8 ± 0.8	0.52
Height (m)	1.792 ± 0.006	1.788 ± 0.006	0.65
Weight (kg)	79.7 ± 1.0	77.6 ± 0.9	0.12
Body Mass Index	24.8 ± 0.3	24.3 ± 0.3	0.19
Tea Consumption (cups/day)	1.01 ± 0.12	0.94 ± 0.15	0.70
Coffee Consumption (cups/day)	1.69 ± 0.18	3.84 ± 0.30	0.0001
Alcohol Consumption† Present (ounces/wk)	2.57 ± 0.29	8.73 ± 1.06	0.0001
Cumulative (ounces)	2249 ± 316	10254 ± 1341	0.0001

*Results are expressed as mean ± S.E.M. for 161 smokers and 168 nonsmokers.

†Alcohol consumption is expressed as equivalent ounces of pure alcohol consumed.

Smokers were requested to smoke ad lib and to smoke a cigarette 5 minutes prior to venipuncture. Venous blood samples were collected at 8 a.m. after an overnight fast. Blood carboxyhemoglobin (expressed as % of saturation) was determined spectrophotometrically using a fresh whole blood sample and a CO-oximeter (Instrument Laboratories, Model 182) (30). Frozen ($-80°C$) blood samples were used to analyze for thiocyanate and plasma nicotine and cotinine. Serum thiocyanate (expressed as μmoles/l) was determined spectrophotometrically as previously described (10). Plasma nicotine and cotinine concentrations were determined by radioimmunoassay; the inter- and intraassay variations are 6% with a sensitivity of 1 ng/ml for nicotine and cotinine (27,29).

Statistical analysis of the data utilized Student's *t*-test for unpaired data and Pearson's correlates for linear regression analysis. Significant differences between groups were determined by analysis of variance (ANOVA) while predictors of blood levels of smoke constituents or their metabolites were determined using multiple regression analyses. These analyses were accomplished using appropriate SAS (Statistical Analysis System, SAS Institute, Inc., Cary, NC) programs and an IBM 3083 computer.

RESULTS

Characteristics of Populations

A comparison of the smoking and nonsmoking populations according to age, height, weight, body mass (Quetelet) index {i.e., weight (kg)/[height (m)]^2} (28), and consumption of tea, coffee and alcohol is given in Table 1. Smokers consumed significantly ($p<0.0001$) more coffee and alcohol (both present and cumulative) than did their nonsmoking counterparts.

Smoking History

The smoking history variables are given in Table 2. As indicated by the range of values, there was considerable variation in smoking history within this population. The normal mean cigarette consumption per day was indicated by the smoker in the questionnaire concerning the five-year blocks of smoking history while the past 24-hour cigarette consumption was indicated by the smoker for the number of cigarettes smoked in the 24-hour time period immediately prior to participation in this study. The number

TABLE 2

SMOKING HISTORY*

	Mean (±S.E.M.)	Range
Normal Cigarette Consumption/Day†	31.8 ± 1.0	8–80
Cigarettes Smoked Past 24 Hours†	24.8 ± 1.0	5–70
Years Smoked	20.3 ± 0.9	3.7–53.7
Pack-Years	24.6 ± 1.0	3.8–60.0
Nicotine Yield of Cigarette‡	0.98 ± 0.02	0.28–1.56

*Results are expressed as means (±S.E.M.) for 161 smokers.

†Normal daily cigarette consumption (i.e., cigarettes per day) was significantly ($p \leq 0.0001$) higher than the number of cigarettes smoked in the past 24 hours.

‡Nicotine yield is expressed as mg nicotine/cigarette as determined by the Federal Trade Commission (21). Since 20 smokers consumed generic cigarettes for which nicotine yield was not available, the mean nicotine yield was calculated for 141 smokers.

of cigarettes smoked in the past 24 hours was significantly ($p<0.001$) less than the normal mean number of cigarettes smoked per day possibly as a result of some of the smokers attempting to reduce their consumption. The mean nicotine yield of the cigarettes smoked was 0.98 mg per cigarette, ranging from ultra-low yield cigarettes (0.28 mg per cigarette) to nonfiltered cigarettes (1.40 to 1.56 mg per cigarette).

Relationships Between Population Characteristics and Smoking History

The relationships between population characteristics and smoking history are given in Table 3. Age was significantly related to parameters of cumulative smoking history (i.e., pack-years and years smoked) and nicotine yield of the cigarette, but not daily cigarette consumption. Weight, body mass index and tea consumption were not associated with any of the indices of smoking history. Increased coffee and alcohol consumption were associated with increased normal daily cigarette consumption, cigarettes smoked in the past 24 hours, years smoked and pack-years smoking history. In addition, increased age in smokers (but not nonsmokers) was significantly ($p<0.0008$) associated with coffee consumption ($r=.312$) and cumulative (but not present) alcohol consumption ($r=.263$).

TABLE 4

BLOOD CONCENTRATIONS OF SMOKE CONSTITUENTS*

	Nonsmokers	Smokers†
Serum Thiocyanate (μmoles/l)	98.3 ± 2.6 (0–223.9)	161.2 ± 3.7 (46.9–390.4)
Carboxyhemoglobin (%)	2.2 ± 0.1 (0–5.2)	7.4 ± 0.2 (2.8–15.0)
Plasma Nicotine (ng/ml)	2.3 ± 0.3 (0–21.1)	31.1 ± 1.3 (2.9–94.4)
Plasma Cotinine (ng/ml)	2.9 ± 0.4 (0–39)	384.0 ± 12.5 (35–717)

*Results are expressed as means (±S.E.M.) for 161 smokers and 168 nonsmokers. The range of concentrations is indicated in the parentheses.

†Concentrations of all smoke constituents were significantly ($p \leq 0.0001$) higher in smokers.

Blood Concentrations of Smoke Constituents and Their Interrelationships

As shown in Table 4, the smokers had significantly ($p<0.0001$) higher blood levels of thiocyanate, carboxyhemoglobin, nicotine and cotinine than the nonsmokers. There was considerable variation in these concentrations with overlapping values being observed within the smoking and nonsmoking populations. Fourteen nonsmokers had a carboxyhemoglobin level greater than 3%, whereas only 1 smoker had a carboxyhemoglobin level less than 3% (data not shown).

Plasma nicotine and cotinine concentrations were more useful in differentiating smokers from nonsmokers. Only 4% (7 of 161) of the nonsmokers had a plasma nicotine which exceeded 10 ng/ml in contrast to 97% (155 of 161) of the smokers. This relatively high plasma nicotine concentration in a few nonsmokers was possibly due to environmental contamination, since these values were not paralleled by comparable increases in cotinine concentrations. Only 2 of 168 nonsmokers had a plasma cotinine which

TABLE 3

CORRELATES—POPULATION CHARACTERISTICS AND SMOKING HISTORY*

	Normal Daily Cigarette Consumption	Cigarettes Past 24 Hours	Years Smoked	Pack-Years	Nicotine Yield
Age	.047	.016	.922¶	.516¶	.167†
Weight	.064	−.057	−.030	.037	.014
Body Mass Index	.094	−.014	−.035	.037	.062
Tea Consumption	−.073	.037	−.019	−.043	.071
Coffee Consumption	.300¶	.134	.392¶	.427¶	.218†
Alcohol Consumption					
Present	.287§	.233‡	.122	.217†	.103
Cumulative	.344¶	.213†	.350¶	.458¶	.208†

*Pearson's correlates for 161 smokers, except for nicotine yield (n = 141).

†$p \leq 0.05$; ‡$p \leq 0.01$; §$p \leq 0.001$; ¶$p \leq 0.0001$.

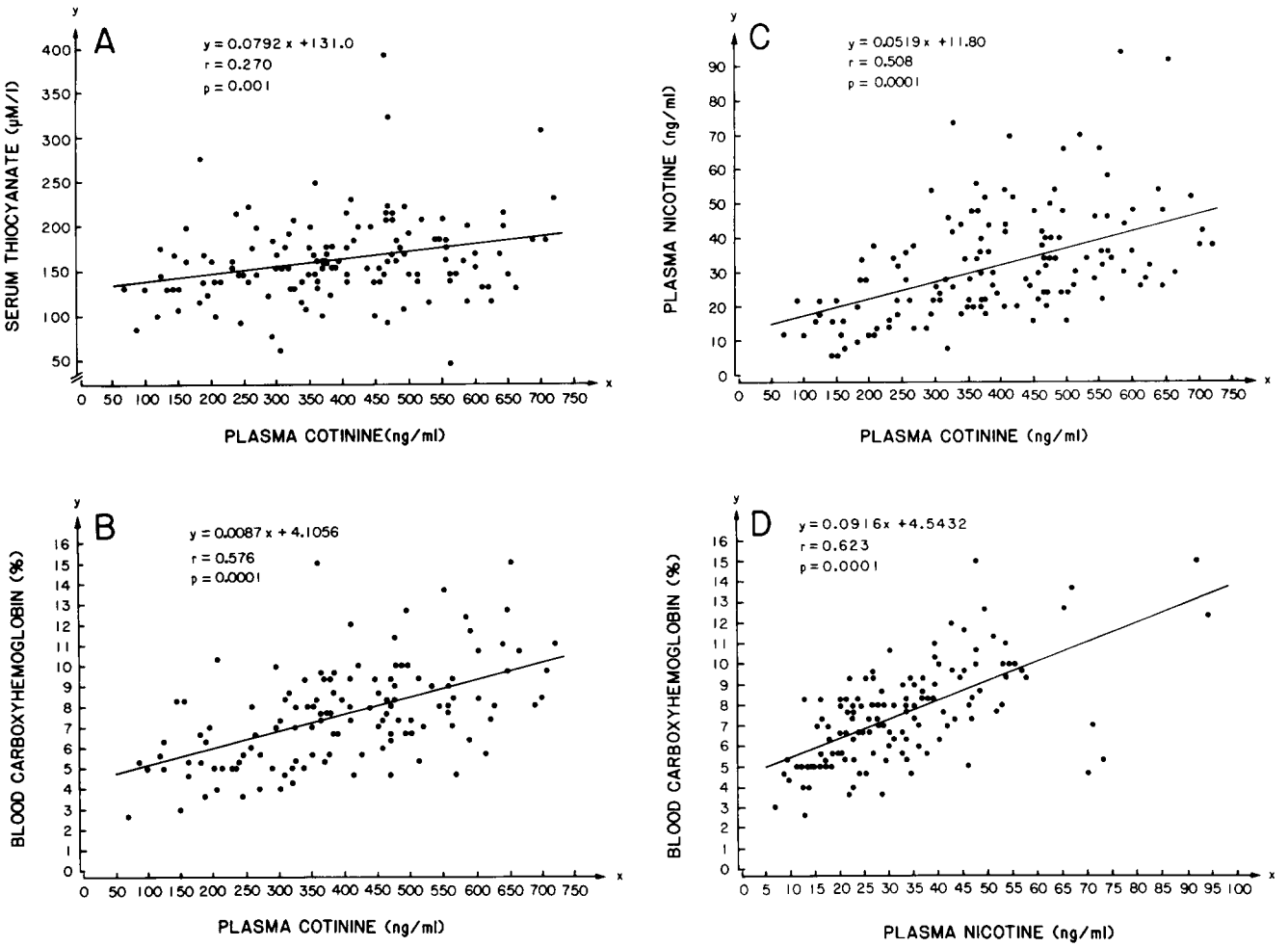

FIG. 1. Linear relationships among the blood concentrations of cigarette smoke constituents. The graphical representation for each of these relationships includes the equation for the inserted least-squares best fit line; the correlation coefficient (r); and the level of significance for the correlation. The data are given for the total population (n = 161) smoking all brands of cigarettes.

exceeded 20 ng/ml, while only 5 of 161 smokers had a plasma cotinine concentration of less than 100 ng/ml. The possibility cannot be precluded that some nonsmokers were "closet smokers." No relationship was observed between these plasma concentrations of nicotine or cotinine in nonsmokers and their self-assessment of passive smoke exposure (data not shown).

Nicotine, cotinine and carboxyhemoglobin correlated with one another in a highly significant manner ($r > .508$, $p < 0.0001$) as shown in Fig. 1B, C and D. Serum thiocyanate concentration also correlated significantly with plasma cotinine (Fig. 1A), but not with carboxyhemoglobin ($r = .111$, $p = 0.14$) or plasma nicotine ($r = .113$, $p = 0.16$).

Relationships of Blood Concentrations of Smoke Constituents or Their Metabolites to Population Characteristics

The relationships between population characteristics and blood concentrations of smoke constituents are given in Table 5. Significant negative correlations were observed between weight and the concentrations of carboxyhemoglobin, nicotine and cotinine. Also, significant or marginally significant relationships were observed between the body mass index and thiocyanate, nicotine and cotinine concentrations. Coffee and cumulative alcohol consumption were also significantly associated with plasma nicotine concentrations.

TABLE 5

CORRELATES—POPULATION CHARACTERISTICS AND BLOOD CONCENTRATIONS OF SMOKE CONSTITUENTS*

	Thiocyanate	Carboxy-hemoglobin	Nicotine	Cotinine
Age	.070	.068	.116	.091
Weight	−.139	−.195†	−.190†	−.179†
Body Mass Index	−.154†	−.107	−.153	−.163†
Coffee Consumption	−.031	.066	.212‡	.135
Alcohol Consumption				
Present	.031	.113	.073	.053
Cumulative	.052	.128	.265§	.150

*Pearson's correlates for 161 smokers.
†$p \leq 0.05$; ‡$p \leq 0.01$; §$p \leq 0.001$.

TABLE 6

CORRELATES—SMOKING HISTORY AND BLOOD CONCENTRATIONS OF SMOKE CONSTITUENTS*

	Thiocyanate	Carboxy-hemoglobin	Nicotine	Cotinine
Normal Cigarette Consumption/Day	.119	.254‡	.245‡	.238‡
Cigarettes Smoked Past 24 Hours	.174†	.332§	.259‡	.372§
Years Smoked	.082	.001	.219‡	.121
Pack-Years	.120	.150	.322§	.218‡
Nicotine Yield of Cigarette	−.037	.014	.238‡	.220‡

*Pearson's (linear) correlates for 161 smokers, except for nicotine yield (n = 141).

†$p \leq 0.05$; ‡$p \leq 0.01$; §$p \leq 0.0001$.

Relationships of Blood Concentrations of Smoke Constituents to Smoking History

The relationships between blood concentrations of smoke constituents and indices of smoking history are given in Table 6. Significant correlations between thiocyanate, carboxyhemoglobin, nicotine or cotinine concentrations and past 24-hour cigarette consumption were all observed. Although significant correlates were also observed between these concentrations and the normal daily cigarette consumption, the past 24-hour cigarette consumption was always the better predictor. Also, the logarithmic transformation was shown in each case to increase the prediction of the blood concentrations of these smoke constituents (rather than the linear plot) (Fig. 2). The log of the past 24-hour cigarettes consumption was the best predictor of plasma cotinine concentration (accounting for 13.9% of its variation), followed in order by carboxyhemoglobin (10.1%), nicotine (5.8%) and thiocyanate (3.2%). Increased plasma nicotine and cotinine concentrations were both significantly associated with pack-years smoking history and the nicotine yield of the cigarette, whereas only increased plasma nicotine concentrations were significantly associated with years smoked.

Nicotine Yield

The significant association between nicotine yield of the cigarette and age, years smoked or pack-years smoking history suggested that the smokers consuming different yield cigarettes might also differ in population characteristics or indices of smoking history. The smoking population was, therefore, arbitrarily divided into six groups according to relatively narrow ranges of nicotine yield of their cigarette (Table 7). Comparing the characteristics of these groups, smokers consuming nonfilter

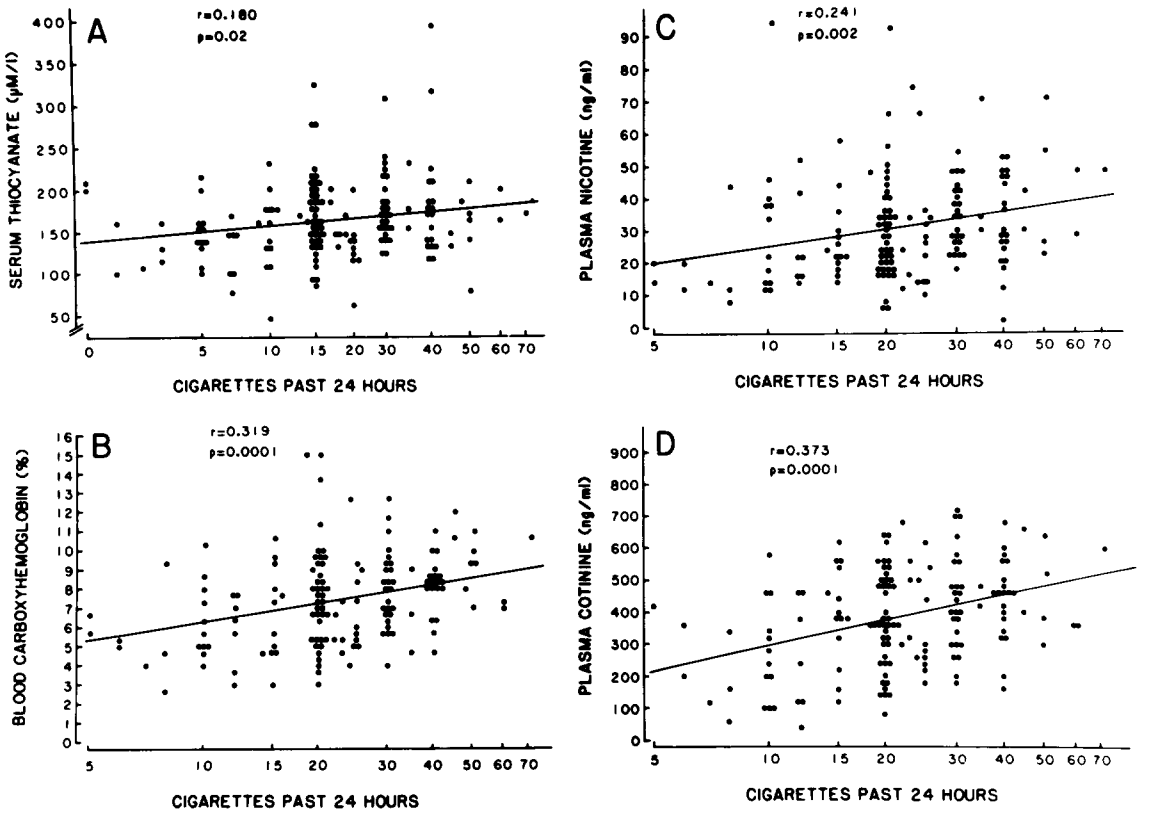

FIG. 2. Relationships between blood concentrations of smoke constituents with cigarette consumption in the past 24 hours. The log-linear (cigarettes past 24 hours − concentration of smoke constituent) graphical representation in each case provided a more highly significant correlation and least-squares best fit than did the linear relationship. The correlation coefficient (r) and the level of significance are given for each of these relationships. The data given are for the total population (n = 161) smoking all brands of cigarettes.

TABLE 7

CHARACTERISTICS OF SMOKERS ACCORDING TO NICOTINE YIELD OF THEIR CIGARETTE*

Group	Range of Nicotine Yield	N	Age (years)	Cigarettes Past 24 Hours	Years Smoked	Pack-Years
1	0.28–0.43	5	36.1 ± 2.5	19.4 ± 5.4	16.8 ± 3.0	23.8 ± 7.2
2	0.50–0.70	16	35.2 ± 2.2	23.1 ± 2.6	15.9 ± 1.7	20.2 ± 2.6
3	0.71–0.90	22	40.0 ± 2.8	24.7 ± 6.6	20.5 ± 2.9	23.5 ± 6.7
4	1.05–1.10	65	36.1 ± 1.2	25.6 ± 1.6	19.1 ± 1.2	24.1 ± 1.5
5	1.11–1.20	17	30.6 ± 1.4†	24.2 ± 2.6	13.5 ± 1.5†	16.4 ± 2.2†
6	1.40–1.60	14	48.4 ± 2.1†	24.1 ± 3.0	33.9 ± 2.6†	37.9 ± 3.2†

*Data are expressed as mean (± S.E.M.) for the indicated number of subjects in each group.

†Groups 5 and 6 differed significantly ($p \leq 0.05$) from the other 4 groups in mean age, years smoked, and pack-years smoking history. Group 6 also differed from the remaining five groups in having a higher consumption of both coffee and alcohol (data not shown).

cigarettes (Group 6) had significantly higher mean age, years smoked, and cumulative smoking history (pack-years), while smokers in Group 5 had significantly lower mean age, years smoked and pack-years smoking history. In addition, smokers in Group 6 had a significantly higher coffee and alcohol consumption than did the other 5 groups (data not shown). The first 4 groups did not differ significantly in population characteristics or smoking history characteristics (normal cigarette consumption, cigarettes past 24 hours, pack-years smoking history or years smoked). These differences in the 6 smoking groups were consistent with the significant correlation observed between nicotine yield and pack-years smoking history ($r = .196$, $p = 0.02$) or years smoked ($r = .256$, $p = 0.002$), while nicotine yield did not correlate significantly with either of these parameters in the first 4 smoking groups. In order to avoid the complicating effects of the observed differences in population characteristics of Groups 5 and 6 vs. 1–4, further regression analyses were limited to Groups 1–4.

The blood concentrations of smoke constituents in each of the six groups were also determined (Table 8). Smokers consuming the lowest nicotine yielding cigarettes also had the lowest blood concentrations of thiocyanate, carboxyhemoglobin, nicotine and cotinine. This effect was especially pronounced for smokers in Group 1. Although the serum thiocyanate and blood carboxyhemoglobin concentrations were not significantly different in the first four groups, plasma nicotine and cotinine concentrations appeared to increase progressively with increasing nicotine yield of the cigarette.

These decreases in plasma nicotine and cotinine observed with decreasing nicotine yield of the cigarette were supported by the linear relationships between plasma nicotine or cotinine concentrations and the cigarette yield in smokers consuming filter cigarettes (Groups 1–4) (Fig. 3). The nicotine yield of the cigarette smoked contributed marginally ($p = 0.08$) to the prediction of plasma nicotine (2.8%) and significantly ($p = 0.008$) to the prediction of plasma cotinine (6.6%). However, the nicotine yield of the cigarette did not correlate significantly with either serum thiocyanate concentration ($r = .082$, $p = 0.40$) or blood carboxyhemoglobin level ($r = .105$, $p = 0.28$). Carbon monoxide yield of the cigarette also did not correlate significantly with carboxyhemoglobin level ($r = .112$, $p = 0.20$).

Although smokers of low yield cigarettes had lower plasma nicotine and cotinine concentrations than did smokers of higher

TABLE 8

BLOOD CONCENTRATIONS OF SMOKE CONSTITUENTS IN GROUPS OF SMOKERS ACCORDING TO NICOTINE YIELD OF THEIR CIGARETTE*

Group	Mean Nicotine Yield (mg/cigarette)	Thiocyanate (μmoles/l)	Carboxy-hemoglobin (%)	Plasma Nicotine (ng/ml)	Plasma Cotinine (ng/ml)
1	0.34	132.2 ± 17.5	5.7 ± 1.0	18.0 ± 1.4	256 ± 92
2	0.56	160.7 ± 9.1	7.4 ± 0.6	29.7 ± 5.3	330 ± 37
3	0.76	175.9 ± 11.3	7.6 ± 0.5	28.4 ± 3.1	351 ± 28
4	1.06	163.6 ± 6.0	7.6 ± 0.3	32.5 ± 1.7	409 ± 19
5	1.16	143.8 ± 8.9	7.9 ± 0.7	29.8 ± 3.6	382 ± 45
6	1.48	162.3 ± 10.2	7.4 ± 0.7	44.4 ± 5.7	459 ± 42
% Change†	−77%	−18.5%	−23.0%	−59.4%	−44.2%

*Data are expressed as mean ± S.E.M. with the number of subjects in each group given in Table 7.

†The percentage change in the means comparing Groups 6 and 1.

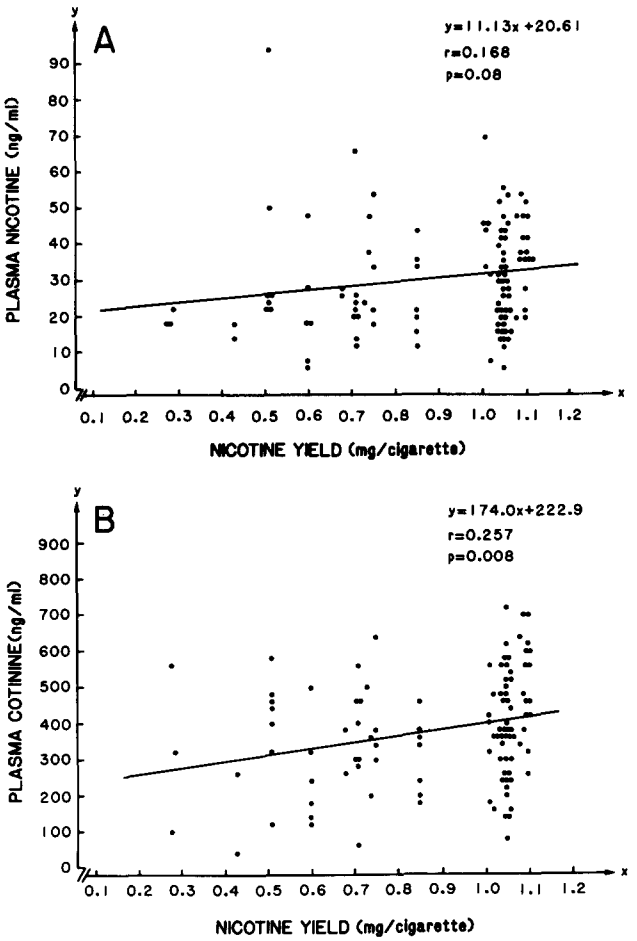

FIG. 3. Relationships between plasma concentrations of nicotine or cotinine and nicotine yield of the cigarette. The graphical representation of these relationships includes the equation for the inserted least-squares best fit line; the correlation coefficient; and the level of significance for the correlation. The data are given for smokers smoking filter cigarettes with nicotine yields of 0.28 to 1.10 mg/cigarette (n = 108).

yield cigarettes, these decreased concentrations were not proportionate to the decrease in yield of the cigarette smoked. For example, comparing smokers in Groups 6 and 1, there was a 77% decrease in the mean nicotine yield of the cigarettes with a corresponding 59.4% and 44.2% decrease in mean plasma nicotine and cotinine concentrations, respectively. Similar results are obtained by comparing other groups (e.g., Groups 4 and 1).

This apparent compensation for low yield cigarettes was not achieved by an increase in the number of cigarettes smoked per day. No significant difference in number of cigarettes smoked in the past 24 hours was observed in any of the six groups. Further, there were no significant linear correlations between nicotine yield and normal daily cigarette consumption ($r = .069$, $p = 0.48$) or cigarettes smoked in the past 24 hours ($r = .110$, $p = 0.26$).

Relationships of Blood Concentrations of Smoke Constituents to Cumulative Smoking History

The relationships of blood concentrations of smoke constituents with pack-years smoking history was also determined in the first 4 groups of smokers (Fig. 4). Increased cumulative smoking history was significantly associated with increased blood concentrations of carboxyhemoglobin, nicotine and cotinine. These significant correlates were probably due in part to the significant

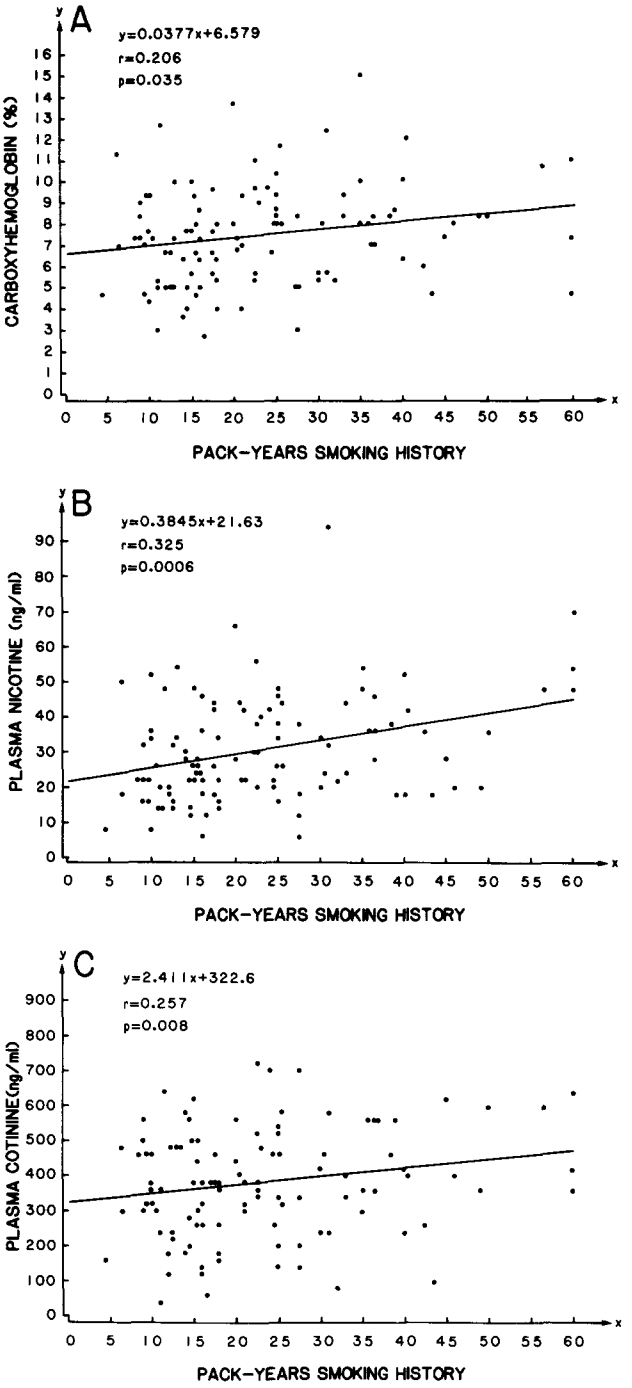

FIG. 4. Relationship between pack-years smoking history and blood levels of carboxyhemoglobin, nicotine or cotinine. The graphical representation of these relationships includes: the equation for the inserted least-squares best fit line; the correlation coefficient (r); and the level of significance for the correlation. The data are given for smokers smoking filter cigarettes with nicotine yields of 0.28 to 1.10 mg/cigarette (n = 108).

TABLE 9

PREDICTORS OF SERUM THIOCYANATE AND BLOOD CARBOXYHEMOGLOBIN IN SMOKERS BY MULTIPLE REGRESSION ANALYSES*

	Thiocyanate†			Carboxyhemoglobin‡		
	Coefficient	Standard Error	*p*	Coefficient	Standard Error	*p*
Intercept	2.68767			1.47285		
Independent Variables:						
A. Cigarettes Past 24 Hours	—			.5119	0.1044	0.0001
B. Years Smoked	—			—		
C. Nicotine Yield	—			.1248	0.1237	0.32
D. Coffee Consumption	.0640	0.0624	0.31	.0067	0.0092	0.47
E. Alcohol—Present	.0255	0.0180	0.16	—		
F. —Cumulative	—			.000026	0.000014	0.07
G. Body Weight	−.0118	0.0044	0.009	−.0158	0.0036	0.0001
Interaction Terms:						
A*B	—			−.0111	0.0041	0.008
A*C	—			—		
A*D	−.0144	0.0177	0.42	—		
A*E	−.0081	0.0055	0.14	—		
A*F	—			−.000008	0.000004	0.06
A*G	.0030	0.0011	0.01	—		
B*C	.0053	0.0039	0.18	—		
B*D	−.0012	0.0008	0.14	—		
B*E	—			—		
B*F	—			—		
B*G	—			.00046	0.00016	0.004

*Multiple regression analysis performed on the homogeneous smoking population with nicotine yield of 0.28 to 1.10 mg/cigarette (Groups 1–4, n = 108). Serum thiocyanate,blood carboxyhemoglobin, and cigarettes past 24 hours were all entered as their logarithmic transformations.

†Total R^2 for thiocyanate was .1164 ($p = 0.12$) for the eight variable model including interaction terms.

‡Total R^2 for carboxyhemoglobin was .2996 ($p \leq 0.0001$) for the eight variable model including interaction terms.

relationship between pack-years smoking history and normal cigarette consumption per day (r = .704, $p = 0.0001$) or the number of cigarettes smoked in the last 24 hours (r = .503, $p = 0.0001$). Unlike pack-years, the number of years smoked did not correlate significantly with cigarette consumption per day (r = .134, $p = 0.17$) or in the past 24 hours (r = .098, $p = 0.31$). However, the number of years smoked still correlated significantly with plasma nicotine (r = .268, $p = 0.005$), marginally with carboxyhemoglobin (r = .176, $p = 0.07$), but not with cotinine (r = .106, $p = 0.28$).

Multiple Linear Regression Analysis

Multiple linear regression analyses were done to determine the most important variables contributing to the prediction of the blood concentrations of smoke constituents (Tables 9 and 10). A better prediction was obtained if the blood concentrations were expressed as a logarithmic vs. linear transformation and if the population utilized was the more homogeneous population (Groups 1–4) according to nicotine yield vs. the total population. Although the independent variables adding significantly to the prediction were generally not different in the total vs. homogeneous populations, alcohol consumption (or its interaction with the other independent variables) was always more significant in the total vs. homogeneous populations. Interaction terms also improved the prediction over models not containing these interaction terms. Finally, the inclusion of body mass index did not appreciably affect the model as compared to those models excluding this independent variable.

The model not including interaction terms demonstrated that cigarettes smoked in the past 24 hours was the only significant ($p = 0.083$) predictor accounting for 6.28% of the variation in serum thiocyanate concentration (data not shown). In the model including interaction terms (Table 9), body weight and the product of cigarettes past 24 hours and body weight were significant predictors accounting for 11.64% of the variation in serum thiocyanate; however, the overall regression was still not significant ($p = 0.12$).

Noninteractive regression analysis with carboxyhemoglobin concentration as the dependent variable revealed that cigarettes past 24 hours and body weight were significant predictors accounting for 17.70% of the variation (data not shown). Although cigarettes past 24 hours and body weight still remained as significant predictors in the interactive model (Table 9), the products of cigarettes past 24 hours and years smoked, and years smoked and weight also contributed significantly to the prediction. Also it should be noted that cumulative alcohol and the product of cigarettes past 24 hours and cumulative alcohol were marginally significant predictors of carboxyhemoglobin levels. Thus, the regression analysis including the independent variables and their interactions accounted totally for 29.96% of the variation in carboxyhemoglobin levels.

The three regressors which were found to be significant predictors of plasma nicotine concentrations in the noninteractive

TABLE 10

PREDICTORS OF PLASMA NICOTINE AND COTININE IN SMOKERS BY MULTIPLE REGRESSION ANALYSES*

	Nicotine†			Cotinine‡		
	Coefficient	Standard Error	p	Coefficient	Standard Error	p
Intercept	4.06701			6.40525		
Independent Variables:						
A. Cigarettes Past 24 Hours	—			—		
B. Years Smoked	—			—		
C. Nicotine Yield	−1.5555	0.4747	0.001	1.0179	0.5474	0.07
D. Coffee Consumption	—			−.3134	0.1262	0.01
E. Alcohol—Present	−.1017	0.0396	0.01	−.1150	0.0489	0.02
F. —Cumulative	.000054	0.000028	0.06	.00011	0.00004	0.006
G. Body Weight	—			−.0344	0.0106	0.002
Interaction Terms:						
A*B	—			—		
A*C	.5941	0.1438	0.0001	—		
A*D	—			.0948	0.0393	0.02
A*E	.0226	0.0108	0.04	.0327	0.0146	0.03
A*F	−.00001	0.000008	0.10	−.00004	0.00001	0.002
A*G	−.0040	0.0011	0.0004	.0055	0.0023	0.02
B*C	—			−.0373	0.0277	0.18
B*D	—			—		
B*E	.0008	0.0003	0.009	—		
B*F	—			.0000005	0.0000005	0.26
B*G	—			.00046	0.00034	0.18

*Multiple regression analysis performed on the homogeneous smoking population with nicotine yield of 0.28 to 1.10 mg/cigarette (Groups 1–4, n = 108). Plasma nicotine and cotinine concentrations and cigarettes past 24 hours were all entered as their logarithmic transformations.

†Total R^2 for plasma nicotine was .3417 ($p \leq 0.0001$) for the eight variable model including interaction terms.

‡Total R^2 for plasma cotinine was .3981 ($p \leq 0.0001$) for the twelve variable model including interaction terms.

model included cigarettes past 24 hours, years smoked and body weight accounting for 26.05% of the variation (data not shown). Multiple regression analysis using interaction terms produced a markedly different model increasing the total prediction to 34.17% and included significant contributions to the prediction by nicotine yield, present alcohol consumption, cigarettes past 24 hours, body weight, and years smoked either as independent variables or within interaction terms (or both). The positive and highly significant coefficient of cigarettes past 24 hours times nicotine yield suggests that the product of these parameters is an important predictor of plasma nicotine. The product of these parameters is greater in magnitude than nicotine yield itself which may account for the negative but significant coefficient for nicotine yield as a significant independent variable. Present alcohol consumption and body weight as products with cigarettes past 24 hours and present alcohol consumption as an independent variable were also significant predictors. The negative coefficient for the product of cigarettes past 24 hours and body weight is likely due to the negative relationship between body weight and plasma nicotine concentration. The product of years smoked and present alcohol consumption was also a significant predictor. Thus, plasma nicotine concentrations are not only dependent upon cigarettes past 24 hours, body weight and years smoked, but also nicotine yield and present alcohol consumption.

Noninteractive, multiple regression analysis with plasma cotinine as the dependent variable demonstrated that cigarettes past 24 hours was a highly significant ($p<0.0001$) predictor with marginally significant contributions to the prediction by nicotine yield ($p=0.12$) and body weight ($p=0.06$) with these variables accounting for 29.28% of the variation in plasma cotinine (data not shown). The prediction of plasma cotinine concentrations was markedly improved by regression analysis including the interactive terms (39.81%) (Table 10). In this interactive model, cigarettes past 24 hours itself was no longer a significant predictor; however, the products of cigarettes past 24 hours and coffee consumption, present or cumulative alcohol consumption, and body weight were significant predictors and replaced cigarettes past 24 hours as an independent variable in the model. With the inclusion of these interactive terms, coffee consumption, present and cumulative alcohol consumption were individually added to the model. Using the interactive model, body weight became a significant ($p=0.002$) predictor while nicotine yield remained as a marginally significant predictor ($p=0.07$).

DISCUSSION

Blood concentrations of thiocyanate, carboxyhemoglobin, nicotine and cotinine have been used as measures of cigarette smoke intake and absorption, which are dependent upon the number of cigarettes smoked per day, the yield of the cigarette, individual smoking behavior, inhalation behavior, and the uptake of smoke constituents (16). Other factors contributing to the variation in the blood concentrations of these smoke constituents include their rates of absorption, metabolism and excretion, body weight, and their availability from other environmental sources. The purpose of this study was to determine the relationship, if any, between

blood concentrations of these smoke constituents and population characteristics or smoking history.

The subjects in this study were relatively young and the asymptomatic smokers had a relatively brief smoking history. Variations in population characteristics were intimately associated with the smoking history variables (e.g., age was significantly related to years smoked, pack-years smoking history, and the nicotine yield). Differences were observed in subgroups of the smoking population according to the nicotine yield of their cigarette necessitating the examination of relationships between parameters by regression analyses in the more homogeneous population smoking filtered cigarettes (Groups 1–4, nicotine yield 0.28–1.10 mg). Thus, the biases introduced by the observed differences in population characteristics or smoking history in the total smoking population were minimized.

The smokers had significantly higher blood concentrations of thiocyanate, carboxyhemoglobin, nicotine and cotinine than age-matched nonsmokers. Consistent with previous reports (14, 18, 31, 52, 53, 55), considerable overlap of values for thiocyanate and carboxyhemoglobin levels were observed in the smoking and nonsmoking populations. In contrast, plasma nicotine and cotinine, being more specific for tobacco consumption, allowed for the differentiation between smokers and nonsmokers. Linear correlations among serum thiocyanate, blood carboxyhemoglobin, and plasma nicotine and cotinine in smokers were consistent with their relative half-lives and specificity for tobacco smoke exposure. Further, although passive smoking has been suggested to elevate blood levels of nicotine (40,42), cotinine (20,35), and carboxyhemoglobin (41), we could not demonstrate elevations of blood concentrations of any of these smoke constituents associated with passive smoking or recent marijuana smoking in either smokers or nonsmokers.

The log of the cigarette consumption in the past 24 hours was the best predictor of plasma cotinine, followed in order by blood carboxyhemoglobin, plasma nicotine and thiocyanate. The better correlation of cigarette consumption in the past 24 hours with cotinine concentrations is likely due to its specificity for tobacco smoke exposure, its half-life of 19 hours (9), and the fact that its concentration varies less throughout the smoking day than does nicotine and carboxyhemoglobin (8,9). The lesser prediction of nicotine and carboxyhemoglobin concentrations were likely due to their shorter terminal half-lives (100–120 minutes and 2–4 hours, respectively) (6,44), their variation during the smoking day (8), and the lack of specificity of carboxyhemoglobin for smoking (12,23). Further, individual differences in elimination of nicotine and cotinine due to urinary pH (3, 5, 9) and carboxyhemoglobin by physical activity (54) have been observed and might have confounded their relationship to 24-hour cigarette consumption. The relatively long half-life of thiocyanate (i.e., 10–14 days) (18,36) and its poor specificity for tobacco consumption (17, 18, 56) are probably the most important factors contributing to its poor correlation with 24-hour cigarette consumption.

In agreement with a previous study (9), while 24-hour cigarette consumption is the best predictor of plasma cotinine, it still accounted for only 13.9% of its variation, suggesting that the number of cigarettes smoked per day is inadequate to explain daily nicotine intake. Although individual differences in rates of metabolism or excretion may partially account for the variability in plasma cotinine, evidence is presented here that yet other factors such as nicotine yield of the cigarette, cumulative smoking history, body weight and alcohol or coffee consumption might also contribute to this variation.

In the present study, several observations support the conclusions that nicotine yield is an important determinant of smoke exposure and that smokers of low yield cigarettes partially compensate for these low yields by a mechanism other than increasing daily cigarette consumption. First, although the mean concentrations of nicotine and cotinine were not significantly different in groups of smokers according to the nicotine yield of their cigarette, a decrease in plasma nicotine and cotinine concentrations was observed with decreasing nicotine yield. However, the decrease in plasma nicotine or cotinine concentrations was not comparable to the decrease in nicotine yield of the cigarette. Secondly, a significant linear correlation was observed between nicotine yield and plasma cotinine, while only a marginally significant linear correlation was observed between nicotine yield and plasma nicotine. Finally, multiple regression analyses revealed that nicotine yield was a significant predictor of plasma nicotine and a marginally significant predictor of plasma cotinine.

Although some investigators (19, 22, 43, 46) have reported that compensation is achieved by increased daily cigarette consumption, we, like others (47), did not find this to be the case. The smokers in groups according to nicotine yield smoked approximately the same number of cigarettes daily with no significant linear correlates between nicotine yield and daily cigarette consumption. Thus, compensation by smokers of low yield cigarettes was likely a result of differences in puffing or inhalation behavior, or both.

Although lower mean blood levels of thiocyanate and carboxyhemoglobin were most notable in the group of smokers smoking the lowest yield cigarettes, these differences were not statistically significant. Further, nicotine yield did not significantly contribute to the prediction of either thiocyanate or carboxyhemoglobin in multiple regression analyses. These data suggest that smokers of low nicotine yield cigarettes, while possibly reducing their intake of particulate matter (i.e., tar and nicotine), do not significantly reduce the intake of the gas phase components of cigarette smoke.

Significant correlations were observed between indices of cumulative smoking history (i.e., pack-years and years smoked) and blood concentrations of smoke constituents. Correlations with pack-years was likely due in part to the relationship between pack-years and daily cigarette consumption. However, years smoked did not correlate significantly with daily cigarette consumption but correlated significantly with plasma nicotine and marginally with carboxyhemoglobin concentrations. Further, years smoked as an interactive term was a significant predictor of carboxyhemoglobin and plasma nicotine in multiple regression analyses. The relationship between years smoked and blood levels of nicotine and carboxyhemoglobin may have been due to a greater cigarette consumption immediately prior to venipuncture (not measured in this study) by smokers with a longer cumulative smoking history or alternatively, the development of a nicotine tolerance with cumulative smoking history (13,26).

Correlations between blood concentrations of smoke constituents and population characteristics revealed that decreased levels of carboxyhemoglobin, nicotine and cotinine were associated with increased body weight and (less significantly) body mass index. This observation was supported by the fact that body weight (either itself or as an interaction with daily cigarette consumption or years smoked) was a significant predictor of carboxyhemoglobin, nicotine and cotinine by multiple regression analyses. Decreased concentration of these blood levels of smoke constituents with increased weight is likely due to the association of volume of distribution with body weight.

Significant correlations were also observed between daily cigarette consumption and consumption of alcoholic and caffeine-containing beverages in this, as well as previous studies (1,34). Although an enhanced rate of cigarette smoking was associated with ethanol consumption by alcoholics (25), the effects of coffee consumption on the rate of cigarette consumption is equivocal (32–34). In the present study, coffee and alcohol consumption were also significantly correlated with plasma nicotine and coti-

nine concentrations. These latter relationships may have been due in part to the relationships between daily cigarette consumption and plasma nicotine or cotinine concentrations; however, in multiple regression analyses taking into account differences in daily cigarette consumption, alcohol consumption (either present or cumulative or both) was a significant predictor of plasma nicotine and cotinine and a marginally significant predictor of carboxyhemoglobin. Further, coffee consumption both independently and as an interaction with cigarettes past 24 hours was a significant predictor of plasma cotinine concentrations. These data provide further evidence to support the suggestion that coffee and alcohol consumption may not be just habits associated with smoking but may interact with smoking parameters to affect blood levels of smoke constituents.

Although two studies have reported no relationship between caffeine intake and puffing behavior (11,38), a significant correlation ($r = .159$, $p = 0.046$) was observed between coffee consumption and total puff volume per cigarette in this population (unpublished observations). Thus, relationships between coffee or alcohol consumption and puffing behavior or intake of smoke constituents seem plausible.

Mechanisms whereby coffee or alcohol consumption could affect smoking behavior or dose remain to be determined. Coffee (or caffeine) consumption could conceivably increase nicotine clearance by the kidney due to its diuretic action, alter the rate of nicotine metabolism, or increase puff volumes due to its bronchodilator effects (24). That alcohol consumption may affect smoke dose is supported by the finding that ethanol ingestion increases the renal clearance of nicotine (7).

In summary, the results of this study suggest that present and cumulative smoking history, nicotine yield of the cigarette smoked, body weight, and alcohol or coffee consumption may be important determinants of smoke exposure as measured by blood concentrations of smoke constituents or their metabolites. Further, this study has demonstrated that smokers of low yield cigarettes partially compensate for this lower yield by a mechanism other than increasing daily cigarette consumption. Yet to be determined is the mechanism whereby cumulative smoking history, or alcohol or coffee consumption affect smoke exposure. The results of this study emphasize the importance of consideration of population and smoking history characteristics in any study of smoke exposure.

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