Cigarette Smoking
Its Relationship to Coronary Heart Disease and Related Risk Factors in the Western Collaborative Group Study

By C. David Jenkins, Ph.D., Ray H. Rosenman, M.D., and Stephen J. Zyzanski, Ph.D.

SUMMARY
The association of the incidence of coronary heart disease (CHD) with smoking habits was studied for 4½ years in over 3,000 healthy, employed men, aged 39 to 59 years, at intake into a prospective, epidemiological investigation. The risk of CHD was significantly associated with current and former cigarette usage. More specifically, this association was found to prevail in men suffering symptomatic and fatal myocardial infarction but not in men sustaining silent myocardial infarction or angina pectoris only and was much stronger in younger than in older age groups. Altered risk of CHD was not found in pipe or cigar smokers.

Cigarette habits at intake were associated with differences in serum lipids and other risk variables, but when the latter were controlled statistically, the smoking-CHD associations remained.

The cigarette-CHD relationship was studied further in men with and without the coronary-prone behavior pattern (type A). In the younger age decade the increased risk of CHD associated with moderate and heavy cigarette smoking occurred primarily in men with the type A behavior pattern.

Additional Indexing Words:
Myocardial infarction Blood pressure Serum lipids Tobacco
Coronary-prone behavior pattern Epidemiology

A LARGE NUMBER of clinical and epidemiological studies have established a relationship between smoking and coronary heart disease (CHD). Nevertheless, as recently emphasized, further studies have revealed a complex and less than consistent picture of this relationship. Moreover, although a statistical association between certain smoking habits and excess morbidity from CHD generally has been found, such studies have failed to clarify the mechanisms by which smoking might causally relate to the incidence of clinical CHD.

The need for further studies to define possible causal relationships seems clear. The occurrence of clinical CHD during 4½ years of follow-up in the Western Collaborative Group Study (WCGS), a prospective study of 3,182 employed men, provided the opportunity of determining longitudinally the association of past and current smoking history with the incidence of CHD and also of determining cross-sectionally the association of smoking habits with the levels of an

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array of other factors capable of influencing the risk of CHD.

Methods

The methodology of this study has previously been published in detail. Comprehensive data were obtained at intake (1960-1961) and at annual follow-up examinations. The population consisted of 3,296 male employees of 11 California corporations, aged 39 to 59 years at intake in the study, of whom 3,182 were judged to be free of clinical coronary heart disease (CHD) at intake. Nearly 3,000 men were still under surveillance at the end of 1965, the cutoff point for data analyzed in this report. Data gathered at intake and at annual follow-up included medical history of parents and self, education, occupation, income, dietary habits, exercise, and smoking, measures of blood pressure, blood lipids, body habitus, electrocardiograms, determinations of “the coronary-prone behavior pattern,” and other variables. The fasting triglycerides were initially determined in 1962. Changes in smoking habits were minor in this population over this 1 to 2-year interval. An additional description of procedures is found in a later report by the same team.

These 39 to 59-year-old men were free of clinical CHD at intake and were in sufficiently sound general health to be pursuing full-time employment. The diagnosis of myocardial infarction or angina pectoris was made solely by the independent medical referee of the study. The CHD incidence data are based on the 133 cases certified by the medical referee for the mean 4½-year period of follow-up from intake into the study (1960-1961) through the 1965 examinations. The categories of the smoking variable were developed from the participants' reports at intake. Due to the complexity of the data, it was not feasible further to subdivide former smokers by the recency of stopping smoking or the number of cigarettes smoked prior to stopping. Similarly, although data are available on year by year changes in smoking habits, these fluctuations will not be considered in the present paper. In a further effort to retain adequate sample sizes in each subgroup, only four smoking categories were established for each age decade for the analyses of CHD incidence.

For the cross-sectional analysis of the relationship of smoking to other possible CHD risk factors, all subjects were classified by their cigarette usage into the following six groups: (1) men who had never smoked, (2) men who had smoked cigarettes but had stopped prior to entry into the WCGS (former cigarette smokers), (3) men who at entry into WCGS were current or former smokers of only pipes or cigars or both, (4) men who at entry smoked 1 to 15 cigarettes per day, (5) men who at entry smoked 16 to 25 cigarettes per day, and (6) men who at entry smoked 26 or more cigarettes per day. Means and variances of rank-ordered and continuously measured risk factors to CHD were computed for each of these six smoking groups. Using a multivariate analysis of covariance developed as part of a series for the Biometric Laboratory of the University of Miami, a one-way multivariate analysis of covariance was computed, categorizing subjects by smoking history, covarying out the effects of age on the dependable variables, using each of 10 CHD risk factors as dependent variables. The multivariate test statistics, the F-ratios, and their corresponding levels of significance reported in the tables were thus adjusted for the known strong influence of age on serum lipids, blood pressures, income level, and each of the other factors considered. For each factor, age-adjusted means are listed. In the tables each age-adjusted mean, for example that for serum cholesterol level, is the mean that each smoking group would have shown had the age-composition of each smoking group been identical with that of the total study population dealt with in that table. Statistical procedures utilized in later portions of the analysis will be described subsequently. The population was divided into two age decades for purposes of analysis: men aged 39 to 49 years and men aged 50 to 59 years at intake into the WCGS.

Results

Association of Smoking with Incidence of CHD

The incidence of new clinical coronary heart disease (CHD) was strongly associated with smoking history and with the number of cigarettes smoked in the sample of men, aged 39 to 49 years (table 1). The association of CHD and smoking in men, aged 50 to 59, was in the same general direction but not sufficiently strong to reach statistical significance by use of the two-tailed chi square test (table 2).

Among the younger men, current and former cigarette smokers exhibited similar annual CHD incidence rates (8.9 and 9.3 per 1,000), and these were considerably higher than those observed in pipe or cigar smokers (1.6) or in men who had never smoked (2.9) (table 1). CHD rates in current cigarette smokers increased progressively with increasing quantity of cigarettes smoked daily. The CHD rate observed in younger heavy
Table 1

Association of Smoking Habits with Incidence of CHD in Men Aged 39 to 49 Years at Intake

<table>
<thead>
<tr>
<th>Smoking history</th>
<th>Total subjects</th>
<th>Never smoked</th>
<th>Pipe &amp; cigar only</th>
<th>Former cigarette</th>
<th>Current cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>Rate*</td>
<td>N</td>
<td>Rate</td>
<td>N</td>
</tr>
<tr>
<td>Total no. at risk</td>
<td>2258</td>
<td>540</td>
<td>405</td>
<td>239</td>
<td>1074</td>
</tr>
<tr>
<td>Total no. CHD cases†</td>
<td>63</td>
<td>6.2</td>
<td>7</td>
<td>2.9†</td>
<td>3</td>
</tr>
<tr>
<td>All myocardial infarction</td>
<td>52</td>
<td>5.1</td>
<td>4</td>
<td>1.7</td>
<td>3</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>38</td>
<td>3.7</td>
<td>1</td>
<td>0.4</td>
<td>2</td>
</tr>
<tr>
<td>Unrecognized</td>
<td>14</td>
<td>1.4</td>
<td>3</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>Fatal</td>
<td>9</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Angina pectoris only</td>
<td>11</td>
<td>1.1</td>
<td>3</td>
<td>1.2</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current cigarette smoking by no. per day</th>
<th>None Rate*</th>
<th>1-15 Rate</th>
<th>16-25 Rate</th>
<th>26 or over Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1191</td>
<td>211</td>
<td>434</td>
<td>422</td>
</tr>
<tr>
<td>Rate</td>
<td>20</td>
<td>3.7†</td>
<td>5</td>
<td>5.3</td>
</tr>
<tr>
<td>17</td>
<td>3.1</td>
<td>4</td>
<td>4.2</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>2.0</td>
<td>4</td>
<td>4.2</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>0.6</td>
<td>1</td>
<td>1.0</td>
<td>5</td>
</tr>
</tbody>
</table>

*Annual rate per 1,000 men at risk.
†Indicated number of cases accumulated in 4% years.
‡These distributions of cases for various smoking categories are significantly different from chance at P = 0.001.
§Difference in CHD frequency between this group and those who never smoked cigarettes (Col. 1 & 2 combined) is significant at P = 0.01 by chi square test corrected for continuity.
**Difference in CHD frequency between this group and current noncigarette smokers is significant at P = 0.01.

Table 2

Association of Smoking Habits with Incidence of CHD in Men, Aged 50-59 Years at Intake

<table>
<thead>
<tr>
<th>Smoking history</th>
<th>Total subjects</th>
<th>Never smoked</th>
<th>Pipe &amp; cigar only</th>
<th>Former cigarette</th>
<th>Current cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>Rate*</td>
<td>N</td>
<td>Rate</td>
<td>N</td>
</tr>
<tr>
<td>Total no. at risk</td>
<td>924</td>
<td>182</td>
<td>161</td>
<td>137</td>
<td>444</td>
</tr>
<tr>
<td>Total no. CHD cases†</td>
<td>70</td>
<td>16.8</td>
<td>9</td>
<td>11.0††</td>
<td>11</td>
</tr>
<tr>
<td>All myocardial infarction</td>
<td>52</td>
<td>12.5</td>
<td>6</td>
<td>7.3</td>
<td>8</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>35</td>
<td>8.4</td>
<td>4</td>
<td>4.9</td>
<td>4</td>
</tr>
<tr>
<td>Unrecognized</td>
<td>17</td>
<td>4.1</td>
<td>2</td>
<td>2.4</td>
<td>4</td>
</tr>
<tr>
<td>Fatal</td>
<td>14</td>
<td>3.4</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Angina pectoris only</td>
<td>18</td>
<td>4.3</td>
<td>3</td>
<td>3.7</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current cigarette smoking by no. per day</th>
<th>None Rate*</th>
<th>1-15 Rate</th>
<th>16-25 Rate</th>
<th>26 or over Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>483</td>
<td>109</td>
<td>167</td>
<td>165</td>
</tr>
<tr>
<td>Rate</td>
<td>29</td>
<td>13.3††</td>
<td>6</td>
<td>12.2</td>
</tr>
<tr>
<td>19</td>
<td>8.7</td>
<td>5</td>
<td>10.2</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>5.5</td>
<td>4</td>
<td>8.2</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>3.2</td>
<td>1</td>
<td>2.0</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>2.8</td>
<td>2</td>
<td>4.1</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>4.6</td>
<td>1</td>
<td>2.0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Annual rate per 1,000 men at risk.
†Indicated number of cases accumulated in 4% years.
‡These distributions of cases for various smoking categories could occur 0.10 of the time by chance hence are not significant at P = 0.05.
§Difference in CHD frequency between this group and current noncigarette smokers is significant at P = 0.01.
smokers (10.5) was nearly three times the rate for all men not presently smoking cigarettes (3.7 per 1,000).

A higher CHD rate also was observed in the older-age decade in current moderate (21.3) and heavier (25.6) cigarette smokers but not in lighter smokers (12.2) (table 2), when compared to current noncigarette smokers (13.3). The older smokers of 26 or more cigarettes a day had about twice the CHD risk found in men of equivalent ages who had never smoked, and this difference was statistically significant. However, the overall differences among all four groups of the older subjects whether categorized by smoking history or by current smoking habits were statistically significant at $P = 0.05$ only by the “one-tailed” chi test. The latter may be utilized when the direction of difference is predicted in advance, a prediction which is legitimate in this instance in view of the previous findings of other investigators.

The irregularities in the observed associations of CHD incidence with smoking history and with number of cigarettes smoked daily could be due in part to the small samples but could not be ascribed to differences in the mean ages of various subgroups, since these were closely similar.

In view of the above findings, it was believed important to determine whether the association of smoking habits to the incidence of CHD prevailed for all types of initially manifested CHD. For this purpose the incidence rates were examined by smoking history in subjects whose clinical CHD initially was manifested by angina pectoris alone or by myocardial infarction. Subjects who incurred myocardial infarction also were subdivided on the basis of whether the infarction was symptomatic or clinically unrecognized (silent) or fatal. In the younger age decade (table 1) the association of CHD incidence with former or current cigarette smoking and with moderate to heavy current cigarette smoking habits was found to prevail most strikingly for subjects whose clinical disease was initially manifested by symptomatic myocardial infarction or by initially fatal infarction. Only a slight, insignificant relationship was observed with the incidence of either of clinically unrecognized (silent) infarction or with angina pectoris. In the older age decade (table 2) the same relationships generally were found but were less striking. In this group, pipe and cigar smokers had consistently higher CHD rates than those who never smoked. The dose-response relationship between number of cigarettes smoked and rate of various subtypes of CHD contained many inconsistencies.

In view of the small number of subjects in certain of these clinical subgroups, the standard statistical tests could not be performed. The two age decades were, therefore, combined to permit evaluation of the association of smoking with clinical subtypes of CHD. The incidence of myocardial infarction was significantly higher in former cigarette smokers (8.9 per 1,000 per year) and current cigarette smokers (10.0) compared to rates in men who had never smoked cigarettes (3.6). Myocardial infarction occurred significantly more often in moderate and heavy cigarette smokers (11.0) than in light cigarette smokers (5.0). Only small nonsignificant differences between smoking groups were observed for incidence of angina pectoris. Among the subjects whose CHD was manifested by myocardial infarction, the incidence of symptomatic infarction was significantly higher in former (7.1) and current (7.3) cigarette smokers than in men who had never smoked cigarettes (1.9) and again was significantly higher in moderate to heavy cigarette smokers (7.9) than in nonsmokers and light cigarette smokers (3.5). The difference in incidence rates for men incurring clinically unrecognized (silent) infarction was not significant. Current cigarette smokers exhibited a significantly higher rate of fatal myocardial infarction (2.3) than did men who had never smoked cigarettes (0.5), and moderate to heavy cigarette smokers exhibited a significantly higher rate of fatal infarction (2.6) than occurred in light cigarette smokers (1.0) (table 3).
Table 3

Association of Smoking Habits with Incidence of Type of CHD: All Ages Combined*

<table>
<thead>
<tr>
<th>Total no. at risk</th>
<th>Smoking history†</th>
<th>Current no. cigarettes/day†</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Rate%</td>
<td>N</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Total no. CHD cases</td>
<td>3182</td>
<td>1228</td>
</tr>
<tr>
<td>All myocardial infarction</td>
<td>133</td>
<td>9.3</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>104</td>
<td>7.3</td>
</tr>
<tr>
<td>Unrecognized</td>
<td>73</td>
<td>5.1</td>
</tr>
<tr>
<td>Fatal</td>
<td>31</td>
<td>2.2</td>
</tr>
<tr>
<td>Angina pectoris only</td>
<td>22</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*All tests of significance in this table are derived from the one-sample chi square test with one degree of freedom, computing expected cases on the basis of the distribution of total number at risk. This is then corrected for continuity.
†All comparisons in the Smoking History section are with the “Never Cigarettes” group. Comparison in the Current Cigarettes section are between the two levels listed.
‡Includes men who never smoked or who currently or formerly smoked only pipe and cigars.
§Annual rate per 1,000 men at risk.
**P = 0.05.
††P = 0.001.
‡‡P = 0.01.

Association of Smoking with CHD Risk Factors

The question was then raised whether the men in different smoking categories might also differ from each other with regard to other characteristics associated with altered risks of developing CHD. If, for example, the smoking groups differed in age, serum lipid levels, blood pressures, or other risk factors, the interpretation of the relationship of smoking to CHD would be complicated. Such differences, if found, might result from selection; that is, men of different biological risk may selectively develop certain smoking patterns. Such risk factor differences could also develop after the smoking habit was established either by a direct causal mechanism or by the triggering by smoking of a predisposition to physiological or biochemical alteration.

Intake data on smoking habits and selected CHD risk factors were analyzed for these possibilities. The cross-sectional nature of the data preclude determination of the time sequence of relationships, but analysis of the pattern of differences among the different groups allows some inferences to be offered regarding the hypothesis of selection. Some methodological issues raised by the repeated use of the same sample to test hypotheses about a large number of variables must first be considered.

When a given sample is studied in terms of a large number of dependent variables, particularly if some of the variables are intercorrelated, the resulting statistics lack independence. This can lead to risk of reporting “significant” findings occasionally merely as a result of making many computations. To guard against this risk in the present study, a multivariate test statistic was computed to provide an overall probability statement to give assurance of the validity of the subsequent detailed inferences.*

The highly significant value of the multivariate test statistic indicates that some combination of CHD risk factors sharply discriminates the smoking groups. This supports the validity of evaluating relative sizes of the differences of smoking group means for

*In this analysis, the test of the multivariate hypothesis makes use of Rao’s F approximation for Wilk’s lambda criterion. The smoking effect in both decades (tables 4 and 5) yields probabilities of less than 0.001 on the null hypothesis. Hence, the null hypothesis that smoking groups were equally affected with respect to each of the 10 measures implicated in CHD incidence was rejected.
Table 4

Multivariate Test Statistic and Age-Adjusted Means of Selected CHD Risk Factors and Personal Characteristics for Six Smoking Groups for Men Aged 39 to 49 Years Only (N = 2,258)

<table>
<thead>
<tr>
<th>Effect</th>
<th>d.f.*</th>
<th>F-Approx</th>
<th>d.f.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking groups</td>
<td>5</td>
<td>4.89</td>
<td>50/9017</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Serum cholesterol†            | 217.24| 224.31   | 218.35| 224.14| 231.52| 231.83| 0.001|
| Beta/alpha lipoprotein ratio  | 1.90  | 2.01     | 1.93  | 1.89  | 2.08  | 2.13  | 0.003|
| Lipalbumin                    | 21.11 | 20.97    | 20.60 | 21.01 | 19.40 | 19.43 | 0.001|
| Systolic BP                   | 126.30| 127.49   | 128.01| 126.33| 126.23| 129.89| 0.001|
| Diastolic BP                  | 82.04 | 82.36    | 81.94 | 80.65 | 79.87 | 81.33 | 0.002|
| Ponderal index                | 12.62 | 12.57    | 12.55 | 12.71 | 12.72 | 12.68 | 0.001|
| Physical activity on job      | 1.95  | 1.89     | 1.92  | 1.98  | 2.00  | 1.95  | 0.298|
| Amount of exercise            | 2.18  | 2.16     | 2.16  | 2.19  | 2.07  | 2.05  | 0.002|
| Income                        | 2.75  | 2.76     | 2.78  | 2.56  | 2.51  | 2.75  | 0.001|
| Triglycerides                 | 135.07| 144.04   | 147.18| 142.62| 153.95| 156.49| 0.002|

*Degrees of freedom for hypothesis.
†Throughout this paper the units of measurement of the several risk factors are as follows: Cholesterol, milligrams per 100 ml; Lipalbumin, mean percent of total lipoproteins; Triglycerides, milligrams per 100 ml; Blood pressures, casual, sitting, in millimeters of mercury; Ponderal index, height in inches divided by cube root of weight in pounds; Physical activity on job, 1 = sedentary, 2 = light, 3 = moderate to heavy; Amount of exercise, 1 = none, 2 = occasional, 3 = regular; Income, 1 = under $5,000, 2 = $5,000-$10,000, 3 = $10,000-$15,000, 4 = $15,000-$25,000, 5 = over $25,000.

Each of the dependent variables by considering the univariate F-statistics and age-adjusted means.

Smoking history and current cigarette usage in the younger age group (table 4) were associated at high levels of statistical significance with differences in serum cholesterol, lipalbumin, ratios of beta to alpha lipoprotein, fasting serum triglycerides, and reported amount of voluntary exercise, but not with reported physical activity on the job. The heavier cigarette smokers exhibited mean values of cholesterol, ratios of beta to alpha lipoprotein, and triglycerides which were higher than, and mean lipalbumin levels which were lower than, those found in men who had never smoked, with intermediate values being found in the former cigarette smokers and the former and current pipe and cigar smokers.

The associations of smoking behavior with differences in ponderal index and diastolic blood pressure were also significant. In these instances the current cigarette smokers tended to be leaner and to exhibit slightly lower mean diastolic pressures than nonsmokers.

Mean systolic blood pressures and income level also showed statistically significant differences among groups but revealed no consistent trends by amount of cigarettes consumed. It is interesting to note that average pulse pressure increased slightly as smoking increased. Means of reported voluntary physical activity (rated on a 1 to 3 scale) were irregular in trend, with heavier cigarette smokers tending to exhibit the least regular exercise habits.

The multivariate analysis of covariance for men aged 50 to 59 years (table 5) also showed clear differences in these risk factors among the six smoking groups. It was found, however, that the previous substantial quantitative trends were much less marked in the older age group. Thus the older subjects did not show statistically significant differences between smoking categories for any of the
Table 5
Multivariate Test Statistic and Age-Adjusted Means of Selected CHD Risk Factors and Personal Characteristics for Six Smoking Groups for Men Aged 50 to 59 Years Only (N = 924)

<table>
<thead>
<tr>
<th>Effect</th>
<th>d.f.*</th>
<th>F-Approx</th>
<th>d.f.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking groups</td>
<td>5</td>
<td>1.96</td>
<td>50/3967</td>
<td>0.001</td>
</tr>
<tr>
<td>Never smoked</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pipe &amp; cigar only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 or over</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol†</td>
<td>229.86</td>
<td>232.67</td>
<td>229.48</td>
<td>233.19</td>
</tr>
<tr>
<td>Beta/alpha lipo-protein ratio</td>
<td>2.17</td>
<td>2.13</td>
<td>2.18</td>
<td>2.04</td>
</tr>
<tr>
<td>Lipalbumin</td>
<td>19.70</td>
<td>19.62</td>
<td>20.25</td>
<td>20.65</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>130.86</td>
<td>134.88</td>
<td>132.80</td>
<td>129.13</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>84.05</td>
<td>85.48</td>
<td>85.13</td>
<td>82.31</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>12.55</td>
<td>12.50</td>
<td>12.51</td>
<td>12.66</td>
</tr>
<tr>
<td>Physical activity on job</td>
<td>1.97</td>
<td>1.91</td>
<td>1.97</td>
<td>2.02</td>
</tr>
<tr>
<td>Amount of exercise</td>
<td>2.17</td>
<td>2.19</td>
<td>2.20</td>
<td>2.22</td>
</tr>
<tr>
<td>Income</td>
<td>2.84</td>
<td>3.02</td>
<td>2.98</td>
<td>2.71</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>149.65</td>
<td>150.80</td>
<td>145.03</td>
<td>150.14</td>
</tr>
</tbody>
</table>

*Degrees of freedom for hypothesis.
†For description of units of measurement for all variables, see footnote to table 4.

Table 6
Rate of New Coronary Heart Disease by Smoking Habits Adjusted for Age and Seriatim for Specified Other Risk Factors (Rates Are Annual Incidence Adjusted for Two Covariates per 1,000 Men Aged 39 to 49 Years at Entry into Study)

<table>
<thead>
<tr>
<th>Second covariate</th>
<th>Never smoked</th>
<th>Former cigarette smokers</th>
<th>Pipe &amp; cigar only</th>
<th>Cigarettes 1-15</th>
<th>Cigarettes 16-25</th>
<th>Cigarettes 26 or over</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>33</td>
<td>93</td>
<td>22</td>
<td>49</td>
<td>89</td>
<td>100</td>
<td>0.005</td>
</tr>
<tr>
<td>Beta/alpha ratio</td>
<td>31</td>
<td>91</td>
<td>18</td>
<td>49</td>
<td>91</td>
<td>102</td>
<td>0.001</td>
</tr>
<tr>
<td>Lipalbumin</td>
<td>31</td>
<td>95</td>
<td>18</td>
<td>51</td>
<td>89</td>
<td>102</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>31</td>
<td>91</td>
<td>18</td>
<td>49</td>
<td>95</td>
<td>100</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>29</td>
<td>89</td>
<td>16</td>
<td>49</td>
<td>95</td>
<td>104</td>
<td>0.001</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>29</td>
<td>91</td>
<td>16</td>
<td>49</td>
<td>95</td>
<td>107</td>
<td>0.001</td>
</tr>
<tr>
<td>Physical activity</td>
<td>29</td>
<td>93</td>
<td>18</td>
<td>47</td>
<td>93</td>
<td>104</td>
<td>0.001</td>
</tr>
<tr>
<td>Amount of exercise</td>
<td>29</td>
<td>91</td>
<td>18</td>
<td>49</td>
<td>93</td>
<td>104</td>
<td>0.001</td>
</tr>
<tr>
<td>Income level</td>
<td>29</td>
<td>91</td>
<td>18</td>
<td>49</td>
<td>93</td>
<td>104</td>
<td>0.001</td>
</tr>
<tr>
<td>All of the above</td>
<td>36</td>
<td>93</td>
<td>20</td>
<td>51</td>
<td>89</td>
<td>98</td>
<td>0.007</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>31</td>
<td>88</td>
<td>20</td>
<td>40</td>
<td>80</td>
<td>104</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Level of significance of F-ratio for analysis of covariance.

lipid measures or the systolic blood pressure. In the older group, however, several measures did show systematic differences by smoking category (table 5). Cigarette smokers of this age decade again exhibited lower mean diastolic blood pressures than did non-smokers and again tended to be leaner. Smokers of 16 or more cigarettes per day again reported significantly less physical exercise off the job. There was also differentiation in the smoking history of older men in terms of income level, but the trends were irregular.

Association of Smoking with Incidence of CHD, Controlling for Influence of Other Major Risk Factors

In view of the association of smoking history with other factors related to the prospective risk of CHD, notably blood lipids in the younger age decade, it was believed important to ask the question: What is the...
relation between smoking behavior and the incidence of new coronary heart disease when the confounding influences of related risk factors (such as age and cholesterol) are held constant by statistical means?

One approach to answering this question is to stratify individuals by levels of a risk factor such as cholesterol, and then ascertain whether smoking is still related to CHD incidence at each stratum of the “control variable.” This approach has weaknesses, however.*

A more advantageous approach involves retaining continuous measures, such as those available for cholesterol and many other risk factors, and utilizing a covariance procedure.† Therefore, a one-way univariate analysis of covariance was performed for each age decade, separately treating each one of nine listed risk factors and age as simultaneous covariates and rate of CHD as the dependent variable. In tables 6 and 7, the row labeled “All of the above” reports the significance level of the association between smoking category and CHD incidence and the estimated annual incidence of CHD where both are adjusted to eliminate the combined influence of all these risk factors.

Triglycerides are considered as an individual covariate at the foot of tables 6 and 7, but this variable is omitted from the multiple covariance computations (see tenth row in each of these tables). This was done because this determination was performed 1 year after the other measures, and by that time some loss of persons from the sample had occurred, including dropout due to disabling and fatal

---

*When individuals are cross-classified both by smoking history and a broad stratification of another risk factor like cholesterol, which has just been shown to be correlated with smoking, the control of the second factor (in this case cholesterol) becomes more presumed than real. It would be most probable, for example, that nonsmokers within a cholesterol stratum of 200 to 239 mg/100 ml would exhibit a lower mean cholesterol than heavy smokers similarly stratified, even though both means of necessity would lie somewhere between 200 and 239 mg/100 ml. The size of this difference between means could be reduced by narrowing the range of the intervals used in stratifying by cholesterol. This, in turn, would lead to smaller numbers of subjects and CHD cases in each cell in the table and thereby make a statistical analysis increasingly difficult and of reduced power.

†There is some question about possible violation of the requisite statistical assumptions when one does covariance analyses on proportions with such extreme values as 0.02 or 0.05, as is done here. The very large sample sizes, the adequate number of cases of CHD making up the proportion in each cell, and the robust nature of the statistic itself, seem to overcome this possible objection.8

---

Table 7
Rate of New Coronary Heart Disease by Smoking Habits Adjusted for Age and Seriatim for Specified Other Risk Factors (Rates Are Annual Incidence Adjusted for Two Covariates per 1,000 Men Aged 50 to 59 Years at Entry into Study)

<table>
<thead>
<tr>
<th>Second covariate</th>
<th>Never smoked</th>
<th>Former cigarette smokers</th>
<th>Pipe &amp; cigar only</th>
<th>Cigarettes</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>115</td>
<td>142</td>
<td>153</td>
<td>115</td>
<td>211</td>
<td>264</td>
<td>0.154</td>
</tr>
<tr>
<td>Beta/alpha ratio</td>
<td>107</td>
<td>142</td>
<td>144</td>
<td>120</td>
<td>213</td>
<td>262</td>
<td>0.127</td>
</tr>
<tr>
<td>Lipalbumin</td>
<td>109</td>
<td>140</td>
<td>151</td>
<td>122</td>
<td>218</td>
<td>262</td>
<td>0.135</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>118</td>
<td>127</td>
<td>144</td>
<td>129</td>
<td>211</td>
<td>266</td>
<td>0.136</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>109</td>
<td>127</td>
<td>135</td>
<td>127</td>
<td>220</td>
<td>273</td>
<td>0.066</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>107</td>
<td>131</td>
<td>140</td>
<td>122</td>
<td>222</td>
<td>269</td>
<td>0.084</td>
</tr>
<tr>
<td>Physical activity</td>
<td>113</td>
<td>142</td>
<td>149</td>
<td>115</td>
<td>213</td>
<td>249</td>
<td>0.216</td>
</tr>
<tr>
<td>Amount of exercise</td>
<td>113</td>
<td>144</td>
<td>151</td>
<td>118</td>
<td>211</td>
<td>255</td>
<td>0.203</td>
</tr>
<tr>
<td>Income level</td>
<td>113</td>
<td>138</td>
<td>147</td>
<td>120</td>
<td>220</td>
<td>258</td>
<td>0.156</td>
</tr>
<tr>
<td>All of the above</td>
<td>113</td>
<td>118</td>
<td>138</td>
<td>140</td>
<td>213</td>
<td>258</td>
<td>0.158</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>113</td>
<td>147</td>
<td>144</td>
<td>80</td>
<td>195</td>
<td>260</td>
<td>0.121</td>
</tr>
</tbody>
</table>

*Level of significance of F-ratio for analysis of covariance.
CHD. In the younger decade (table 6) triglyceride data are based on 117 fewer men, including five fewer with CHD, as compared to the variables gathered at intake. In the older group (table 7) triglycerides are unavailable for 35 men, among them six with CHD. Ten of these 11 persons with new CHD who dropped from the study before the 1962 triglyceride determinations were cigarette smokers.

The relative strength of each risk factor, in "explaining away" the observed association between smoking category and CHD rates may be inferred from the separate analyses of covariance. These separate analyses provide for an individual evaluation of the influence of each risk factor and an opportunity to inspect the overall pattern exhibited by these adjusted CHD rates. Tables 6 and 7 show the significance of the association between smoking and CHD incidence under each of the 10 "controlled" circumstances and also display the estimated annual CHD incidence adjusted to eliminate the slight age differences and not so slight differences in each of these other risk factors among the six smoking habit categories. Heeding the implications that smoking has a different relative influence on cardiovascular variables at different ages (tables 4 and 5), the population was divided into separate age decades for these analyses.

Table 6 reports the association of smoking behavior with rate of CHD-controlled for age and other risk factors among men aged 39 to 49 years at entry into the study. Smok- ing behavior retains a significant association with incidence of CHD even when the influence of age and any one of the 10 other risk factors is statistically removed. The surprising constancy of the figures in each column (for example, for those who "never smoked" the 10 adjusted rates are all between 29 and 36) suggests that in general the adjustments for the two covariates in each computation caused very little practical alteration of the rates. When the combined contribution of nine risk factors, plus age, are taken into account, the differences in CHD rates between smoking categories remain statistically significant ($P = 0.04$) and retain approximately the same quantitative relationship, including a 2.7 to 1.0 relative risk for heavy smokers compared to men who never smoked. For all analyses of this younger age group, the pipe or cigar smokers had the lowest CHD incidence and the smokers of over 25 cigarettes per day had the highest rate.

Among the men aged 50 to 59, smoking category was not associated at a statistically significant level with incidence of CHD when each risk factor was considered separately, nor when all risk factors were considered simultaneously (table 7). The differences observed among CHD rates could occur by chance on the average of about 12 times in a hundred such sets of six (smoking) samples. Significance was nearly attained when diastolic blood pressure was a covariate ($P = 0.066$) as compared with the usual standard for acceptance of $P = 0.050$. In eight of the analyses the "never smoked" group showed the lowest rate. In one instance and one tie the lowest rate was among the smokers of 1 to 15 cigarettes per day. For all analyses for both age groups, however, the smokers of over 25 cigarettes per day had by far the highest CHD rates.

Epidemiologists have observed that many factors associated with elevated risk of CHD exhibit higher relative risk ratios among younger persons than the same risk factor quantified in the same way exhibits in an older cohort. This situation is repeated here with regard to the association of smoking and CHD. These data do not negate a possible influence of cigarette smoking in the older group, but rather suggest that exposure to all atherogenic factors over a longer time interval increases the CHD risk of all subjects regardless of smoking history. Thus, an increase of the denominator (the CHD rate of the "low risk group" on any one factor) may be a major reason for the reduction of relative risk ratios (rate of high risk group divided by rate of low risk group) among older subjects.
SMOKING AND CORONARY HEART DISEASE

Table 8

<table>
<thead>
<tr>
<th>Behavior pattern</th>
<th>Never smoked</th>
<th>Former smokers</th>
<th>Pipe &amp; cigar only</th>
<th>Cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41.3</td>
<td>46.4</td>
<td>46.7</td>
<td>44.5</td>
</tr>
<tr>
<td>Type A</td>
<td></td>
<td></td>
<td></td>
<td>48.6</td>
</tr>
<tr>
<td>Type B</td>
<td>58.7</td>
<td>53.6</td>
<td>53.3</td>
<td>55.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51.4</td>
</tr>
<tr>
<td>Test of difference of distributions:</td>
<td>$\chi^2 = 23.62$</td>
<td>d.f. = 5</td>
<td>$P = 0.001$</td>
<td></td>
</tr>
</tbody>
</table>

Ages: 39-49 years

<table>
<thead>
<tr>
<th>Behavior pattern</th>
<th>Never smoked</th>
<th>Former smokers</th>
<th>Pipe &amp; cigar only</th>
<th>Cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51.1</td>
<td>67.9</td>
<td>49.1</td>
<td>58.7</td>
</tr>
<tr>
<td>Type A</td>
<td></td>
<td></td>
<td></td>
<td>56.3</td>
</tr>
<tr>
<td>Type B</td>
<td>48.9</td>
<td>32.1</td>
<td>50.9</td>
<td>41.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43.7</td>
</tr>
<tr>
<td>Test of difference of distribution:</td>
<td>$\chi^2 = 16.46$</td>
<td>d.f. = 5</td>
<td>$P = 0.01$</td>
<td></td>
</tr>
</tbody>
</table>

Ages: 50-59 years

Association of Smoking with Overt Behavior Pattern

Earlier reports of this research group implicated a specific overt behavior pattern (type A) in the pathogenesis of coronary heart disease.4, 9-11 The presence of this behavior pattern can be determined reliably by means of a structured interview administered by trained personnel.3, 12 The prospective epidemiological data of the Western Collaborative Group Study had confirmed that this behavior pattern is associated with accelerated coronary atherosclerosis13 and with the risk of CHD to a highly significant degree.4, 11

The association between smoking habits and the behavior pattern is shown in table 8. Men who were judged to exhibit pattern A (high risk) at intake are significantly more likely to smoke 26 or more cigarettes per day and are less likely to be in the "never smoked" category. This association of smoking history with behavior type holds for both age decades and is highly significant statistically in both. Whether these variables are related to CHD risk independently or by some dependent or interactive process was then considered.

The coronary-prone behavior pattern is at present rated as a dichotomous variable

Table 9

<table>
<thead>
<tr>
<th>Behavior type</th>
<th>Never smoked</th>
<th>Former cigarette smokers</th>
<th>Current &amp; former pipe &amp; cigar only</th>
<th>Cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-15</td>
</tr>
<tr>
<td>A</td>
<td>5.3* (5)†</td>
<td>13.8 (7)</td>
<td>1.3 (1)</td>
<td>16 (1)</td>
</tr>
<tr>
<td>B</td>
<td>1.3 (2)</td>
<td>5.1 (3)</td>
<td>2.2 (2)</td>
<td>7.3 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>2.9 (7)</td>
<td>9.1 (10)</td>
<td>1.8 (3)</td>
<td>4.9 (5)</td>
</tr>
</tbody>
</table>

Analysis of variance table

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of squares</th>
<th>d.f.</th>
<th>Mean square</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within cells</td>
<td>59.471</td>
<td>2245</td>
<td>0.026</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression on age</td>
<td>0.458</td>
<td>1</td>
<td>0.458</td>
<td>17.296</td>
<td>0.001</td>
</tr>
<tr>
<td>Between smoking groups‡</td>
<td>0.504</td>
<td>5</td>
<td>0.101</td>
<td>3.81</td>
<td>0.002</td>
</tr>
<tr>
<td>Between behavior types‡</td>
<td>0.329</td>
<td>1</td>
<td>0.329</td>
<td>12.43</td>
<td>0.001</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.396</td>
<td>5</td>
<td>0.079</td>
<td>2.99</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Rates are age-adjusted annual incidence per 1,000 men.
†Numbers in parentheses are number of CHD cases in each subgroup.
‡Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

Circulation, Volume XXXVIII, December 1968
Table 10
Incidence of New Coronary Heart Disease by Smoking Category and Behavior Type for Men, Aged 50-59 Years

<table>
<thead>
<tr>
<th>Behavior type</th>
<th>Never smoked</th>
<th>Former cigarette smokers</th>
<th>Current &amp; former pipe &amp; cigar only</th>
<th>Cigarettes</th>
<th>Smoking group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-15</td>
<td>16-25</td>
</tr>
<tr>
<td>A</td>
<td>12.4* (5)†</td>
<td>18.6 (8)</td>
<td>21.8 (8)</td>
<td>16.4 (5)</td>
<td>21.5 (9)</td>
</tr>
<tr>
<td>B</td>
<td>10.0 (4)</td>
<td>5.1 (1)</td>
<td>8.4 (3)</td>
<td>4.7 (1)</td>
<td>21.1 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>11.1 (9)</td>
<td>14.2 (9)</td>
<td>14.9 (11)</td>
<td>11.5 (6)</td>
<td>21.3 (16)</td>
</tr>
</tbody>
</table>

* Rates are age-adjusted annual incidence per 1,000 men.
† Numbers in parentheses are number of CHD cases in each subgroup.
‡ Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

(type A = high risk, type B = low risk). Smoking behavior in this study is also treated as a categorical variable. CHD status, while basically dichotomous, is treated as continuous inasmuch as group rates are under study. These conditions suggested the use of a two-way analysis of variance design in considering the simultaneous influence of smoking and behavior patterns on CHD incidence rates.

The analysis of covariance involves two-way classification with disproportionate cell sizes. To avoid the confounding of significant main effects in this nonorthogonal design and to permit direct interpretation of results, the analysis has been computed twice with order of effects permuted. Tables 9 and 10 summarize the findings of these procedures.

The findings in the younger age decade are shown in table 9. CHD occurred in only three pipe or cigar smokers and in only five light cigarette smokers (1 to 15 per day), precluding meaningful comparison in these categories between men of different behavior patterns. The CHD rates in the remaining smoking categories were from 2.7 to 5.1 times greater in the type A subjects than in their respective type B counterparts. The overall difference in CHD rates in type A and type B men was highly significant (P = 0.001). The contrast between the strong association between CHD and moderate, heavy, and former cigarette usage in type A men as compared with the relatively low rates among type B men of all smoking categories can be accepted as a genuine difference in pattern, the F-ratio for interaction being highly significant (P = 0.01). This suggests that the impact of smoking on CHD rates is strongly modified by behavior type. The incidence of CHD was observed to be substantially higher in moderate and heavy cigarette smokers only if they also exhibited the type A behavior pattern. Indeed, as also shown in table 9, the CHD rates in the heavy type B cigarette smokers was less than that observed in type A men who had never smoked and was less than half that observed in type A men who had stopped smoking prior to intake into the study.

The CHD rates were greater for the older type A than type B men in all categories, although in one category this difference was small (table 10). The differences were generally of lesser degree than those observed in the younger age decade, yet overall they
were statistically significant \( (P = 0.04) \). Again, type B men who were moderate or heavy cigarette smokers exhibited CHD rates similar to those observed in type A former cigarette smokers and in type A pipe and cigar smokers. The analysis of variance does not support significant differences in CHD rates among the six smoking groups for this older decade, however. While one cannot reject the null hypothesis that smoking history makes no difference in this older sample \( (P = 0.19) \), neither can one accept the null hypothesis with any contentment in view of findings by previous investigators studying this age cohort with larger samples. Inconclusiveness is also in order in view of the lack of significance of the regression of CHD rate on age in table 10 \( (P = 0.11) \), age being a variable of undoubted relation to CHD. Following the trend of all other risk factors here analyzed for their relation to CHD, the relative risk ratio and statistical significance of behavior type as a risk factor was stronger in the younger age decade than in the older \( (P = 0.001 \) versus \( P = 0.040) \).

Discussion

A host of both retrospective and prospective field studies and mortality data have confirmed an association between smoking habits and clinical coronary heart disease (CHD).\(^1\),\(^2\),\(^4\),\(^14\),\(^15\) An increased rate of CHD generally has been found in men currently smoking cigarettes but not in pipe or cigar smokers.\(^1\),\(^2\),\(^4\),\(^14\),\(^15\) The increased risk of CHD in prospective studies has been relatively more significant in younger subjects, the relative risk ratio progressively decreasing after age 50 years.\(^1\),\(^14\),\(^15\) A number of studies also have found a CHD incidence gradient according to the number of cigarettes smoked by daily habit\(^1\),\(^14\),\(^15\) and by amount of smoke reported to be inhaled.\(^15\) The elevated risk ratio for cigarette smokers versus nonsmokers generally has been limited to victims of myocardial infarction and has not shown significant differences for men whose CHD is manifested solely by angina pectoris.\(^13\),\(^16\),\(^17\) The present findings of an increased incidence rate of CHD in current cigarette smokers compared to men who never smoked or who smoke only pipe or cigars, with a greater rate differential in younger subjects and in heavier smokers, is in good agreement with those earlier findings of other investigators. It should be recalled, however, that such associations have not been universally found. Certain investigations have failed to find a significantly increased prevalence of atherosclerosis at autopsy in heavy smokers compared to nonsmokers,\(^18\) or an increased overall incidence or mortality rate from CHD among cigarette smokers,\(^19\) or a significant relationship of CHD smokers,\(^19\) or a significant relationship of CHD mortality rate to the amount smoked.\(^20\) Moreover, as recently pointed out,\(^2\) although the highest CHD incidence rates in the current large-scale epidemiological studies are found in the heaviest cigarette smokers, the gradient is not always consistent between light and moderate smokers or between smokers and nonsmokers, an observation confirmed here.

The present findings confirm the general failure\(^14\),\(^16\),\(^17\) to find a significantly increased risk ratio between smokers and nonsmokers for angina pectoris, although a trend is present. Moreover, as we previously noted,\(^21\) the association of incidence of myocardial infarction with cigarette smoking was found to prevail for men suffering symptomatic, and fatal myocardial infarction, but was not significant for men whose myocardial infarction was "silent" or clinically unrecognized. In the population studied here, the CHD rate for men who stopped cigarette smoking prior to intake into the study was as high as for those currently smoking at entry among the younger subjects and intermediate between current smokers and men who never smoked among the older subjects. Previous prospective studies have generally found men who stopped cigarette smoking to have a CHD incidence rate intermediate between that of active smokers and that of the group who had never smoked.\(^20\),\(^22\) One study found men who stopped smoking to have similar CHD rates to those observed in men who never smoked.\(^13\) The inconsistent and sometimes contradictory findings in this regard have
been pointed out,\textsuperscript{2} and the need for more definitive study has been emphasized.\textsuperscript{1}

The demonstration of statistical association does not indicate a causal relationship,\textsuperscript{1, 2} or define the physiological or biochemical mechanisms by which smoking might engender an increased risk of myocardial infarction or enhanced mortality rate from acute infarction. One such mechanism might be acceleration of the severity of coronary atherosclerosis per se. Although this has been suggested by a few studies,\textsuperscript{23} proof of a causal relationship between smoking and coronary atherogenesis has been lacking despite a substantial number of investigations.\textsuperscript{24} Such a primary mechanism is seemingly negated (1) by the generally observed absence of association between duration of smoking and risk of myocardial infarction, (2) by the evidence that smoking is acutely associated with CHD rather than having a cumulative effect, (3) by the absence of an association of incidence of angina pectoris with smoking, and (4) by the generally observed decreased CHD incidence in former smokers.\textsuperscript{1, 13, 25}

As presently observed, younger cigarette smokers exhibit significantly higher mean levels of serum cholesterol, triglycerides, and beta lipoproteins compared to nonsmokers,\textsuperscript{16, 26-29} and as generally observed by other investigators,\textsuperscript{26-28} our smokers showed a tendency to be leaner in body habitus and to exhibit lower diastolic blood pressures than nonsmokers.\textsuperscript{1, 26, 28, 30} In general, the association of smoking and CHD has not been found to be ascribable to differences in body build, weight, or habitual diet.\textsuperscript{1, 26, 28, 30}

However, a distinction between statistical and clinical significance should be emphasized. Differences which are not statistically significant cannot be accepted as having clinical significance because of their known probability of arising solely by random variability among samples. Moreover, statistical significance can occur particularly when sample sizes are large, even though absolute differences are so small as probably to be unimportant in terms of pathogenesis. Although the lipid variables exhibited their "least healthy" levels among our heaviest cigarette smokers, the statistical analysis specifically controlling for differences in these variables indicates that the effect of smoking is not mediated by serum lipids or other commonly studied risk variables.\textsuperscript{1-30} Moreover, covariance analyses reveal that the smoking-CHD relationship is influenced only to a minor degree by correlations of smoking with most other risk factors (even when 11 covariates are considered simultaneously). Thus, the present data indicate that smoking has an independent relationship to CHD when most other risk variables are statistically controlled, implying that its primary pathogenetic mechanism functions apart from the usual risk factors.

The association of cigarette smoking with CHD risk is most strongly related to the risk of acute symptomatic myocardial infarction and subsequent death. It has been suggested that this may be engendered by "the triggering of a lethal arrhythmia or thrombosis in subjects predisposed by an already compromised coronary circulation."\textsuperscript{31} Although smoking may enhance platelet adhesiveness, critical analysis of available studies has failed to confirm that smoking causes any significant changes in blood coagulability.\textsuperscript{32} The stimulation of the sympathetic nervous system and the augmented liberation of catecholamines induced by smoking\textsuperscript{33} with associated hemoodynamic effects,\textsuperscript{26, 34} are believed to be due to absorption of inhaled nicotine, and it is possible that these may somehow trigger the mechanism underlying acute occlusion\textsuperscript{35} or enhance the danger of a lethal arrhythmia once acute thrombotic occlusion has occurred. However, the acute cardiovascular hemoodynamic effects of smoking a cigarette are relatively short-lived, and we are not aware of any study that has shown a proximate relationship of smoking to the onset of the acute occlusive episode. Another problem is indicated by the fact that although the incidence of CHD is unrelated to cigar smoking, the latter is associated with slightly higher absorption of nicotine than occurs with inhalation of cigarette smoke,\textsuperscript{33} and the
nicotine absorbed from smoking four cigars equals that from inhalation during smoking of 20 cigarettes.\textsuperscript{2, 15} The present studies throw no light on these considerations, nor do they examine carefully other differences between cigarette smoking and pipe and cigar smoking, such as the temperature of the smoke entering the mouth and the trace elements and compounds found in these hot gases.

A final set of hypotheses has questioned whether the increased CHD rate of cigarette smokers may be ascribed to other characteristics of smokers that may be responsible for their enhanced coronary-proneness. One such specific hypothesis concerns exercise habits. Thus, the incidence of CHD and especially of fatal myocardial infarction is increased in men who are habitually physically inactive.\textsuperscript{19} Another approach to this issue resides in the observations by many investigators of personality and behavioral differences between cigarette smokers and nonsmokers or pipe and cigar smokers. Thus cigarette smokers have been found to exhibit enhanced anger and hostility under stress,\textsuperscript{36, 37} to be more extroverted, less rigid,\textsuperscript{38} and more energetic and restless\textsuperscript{39} than nonsmokers. Although a well-defined smoker's personality has not emerged from these reports,\textsuperscript{2} the differences appear sufficient to support the association of a difference of psychological makeup\textsuperscript{2} and to lead to the suspicion that the association of cigarette smoking and CHD incidence may in part be complicated by personality and behavioral differences of cigarette smokers\textsuperscript{40} and by differences in their exposure and response to stressful socioeconomic and other pressures. The higher rate of CHD found in men with certain stressful occupations has remained high even among those who have stopped smoking.\textsuperscript{22, 41}

The present study revealed interesting findings in this regard. Men with the type A behavior pattern, previously found to be associated with increased prevalence\textsuperscript{9, 10} and incidence\textsuperscript{31, 4, 11} of CHD, were here found to include a higher proportion of heavy smokers than men with the converse type B behavior pattern. Statistical analysis revealed that in the younger decade smoking habit and behavior type interact to produce a "joint effect" on CHD risk. A significant elevation of CHD rates was observed in former cigarette smokers and current moderate and heavy smokers of cigarettes. This trend, however, was due almost entirely to the sharp gradient among type A men. Type B men showed only an irregular association between smoking and CHD rates. This mutually potentiating relationship of smoking habits and behavior type is highly significant statistically. In general, men of behavior type A incurred 2.7 to 5 times more CHD than men of behavior type B. Two reversals of this trend were noted, however, among the two smallest subgroups (pipe and cigar smokers and smokers of 15 or fewer cigarettes per day).

It is important to observe that type A men of the younger decade who had never smoked exhibited a CHD incidence slightly greater than type B men who were currently moderate to heavy smokers of cigarettes. While the independent association of smoking and of behavior type with CHD are both highly significant, the clear-cut interaction described above underscores the complexity of these relationships.

The parallel analysis for the older decade shows no such complexity of interaction among these variables. Moderate to heavy smokers had two to three times the CHD rates of men who never smoked among both type A and type B men. However, behavior type also shows a strong, direct association with CHD in this age decade with type A men having higher rates than their type B counterparts in all six smoking categories. In any event, the present findings lend considerable support to the belief of some observers\textsuperscript{38-42} that the effects of cigarette smoking on the incidence of CHD are in part related to behavioral characteristics which enhance coronary proneness\textsuperscript{3, 4, 9-11} although such relationships are observed more significantly in younger age groups.

What might account for the different dynamic relationships of these variables in the different age decades? Our data do not
speak to these issues, but certain categories of explanation might be raised as hypotheses. CHD seems to become a less “well focused” disease with advancing age. Traditional risk factors tend to lose individual sensitivity in older decades, as the process of aging and prolonged exposure to all atherogenic factors make it impossible to ascribe a given case of CHD to a distinct anomaly in one or two specific risk factors. A second category of explanation would involve the possibility that different kinds of men developed into heavy cigarette smokers (or pipe smokers, or others) in the life histories of the two decades of men in this sample (“cohort effect”).

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**References**


A Quotation for Interpretation

? Diet and Health (Ancient Greek)

An instinct, perhaps inherited, prompts me to introduce my subject with a text. A Greek author, centuries ago, left these words behind, but not his name: "You ask of the gods health and a beautiful old age; but your tables are opposed to it; they fetter the hands of Zeus."—E. W. Emerson, M.D.: Henry Thoreau: As Remembered by a Young Friend. Thoreau Foundation, Concord, Massachusetts, 1968.