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The Relationship of Cigarette Smoking to Coronary Heart Disease

The Second Report of the Combined Experience
of the Albany, NY, and Framingham, Mass, Studies

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The relationship of smoking habit to total mortality and to the incidence of new manifestations of coronary heart disease (CHD) has been examined in 2,282 middle-aged men under medical surveillance for ten years in Framingham, Mass, and 1,838 middle-aged men followed for eight years in Albany, NY. It was found that in men who report habitual consumption of 20 or more cigarettes per day the risk of myocardial infarction was about three times greater than in nonsmokers, former cigarette smokers, or pipe and cigar smokers. No relationship was shown between smoking habit and angina pectoris when this symptom was the sole manifestation of CHD. The association between heavy cigarette smoking and increased morbidity and mortality from CHD was unexplained, although it appeared to be relatively immediate. It is inferred that stopping cigarette smoking lessens the risk of CHD.

Three years ago two large prospective studies of cardiovascular disease indicated that men who habitually smoke 20 or more cigarettes daily experience a risk of myocardial infarction or of death from all causes three times greater than nonsmokers or smokers of pipes and cigars.¹ On the other hand, cigarette smoking bore no apparent relationship to the incidence of angina pectoris, considered as an isolated manifestation of coronary heart disease (CHD), an observation similar to that made in an earlier clinical study by White and Sharber.² These findings, taken with the massive documentation of a positive relationship between cigarette smoking and CHD accruing in the large scale studies of the role of smoking in lung cancer,^{3,4} recently

led the surgeon general's committee to conclude that:

... a significant relationship has been established between cigarette smoking and the incidence of myocardial infarction and sudden death in males, especially in middle life, in population groups whose members appear so far to be similar for smoking habits."

The present report confirms and extends the observations presented earlier.

Methods

The data presented in both this and in the first report are derived from two prospective studies of degenerative cardiovascular disease, the Framingham study established in 1949 by the US Public Health Service and the Albany study established in 1952 by the New York State Department of Health.

In Framingham, Mass, 4,469 men and women, initially between 30 and 62 years of age (69% of a randomly selected sample), agreed to participate in a longitudinal study of heart disease. To these have been added 734 volunteer subjects. A detailed appraisal of each individual including a history, physical examination, an x-ray of the chest, an electrocardiogram, and other laboratory tests have been done. A total of 2,282 men originally free of coronary heart disease and followed for ten years constitute the population at risk considered in this report.

In Albany, NY, 1,913 male civil servants, 39 to 55 years of age (89% of those eligible), volunteered for a similar investigation of the incidence of degenerative cardiovascular disease. A somewhat more detailed examination is done than in Framingham and an electrocardiographic stress test is done. Those individuals evincing an abnormal electrocardiographic response to exercise as the sole manifestation of CHD are not included as cases in this

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Table 1.—Average Annual Incidence of Selected Events in Men Age 40-49 and Free of Disease at Entry Into Study According to Smoking Category*

	Population At Risk	Myocardial infarction Including CHD Deaths		Angina Pectoris		All Deaths		CHD Deaths	
		Total Events	Rate†	Total Events	Rate†	Total Events	Rate†	Total Events	Rate†
Non-cigarette smokers									
Total	812	17	2.6	12	1.8	13	2.0	4	0.6
Albany	553	14	3.1	9	2.0	10	2.2	3	0.7
Framingham	259	3	1.4	3	1.4	3	1.4	1	0.5
Cigarette smokers									
Total	1,272	92	9.0	21	2.1	64	6.3	26	2.6
Albany	766	58	9.5	10	1.6	34	5.5	16	2.6
Framingham	506	34	8.4	11	2.7	30	7.4	10	2.5

*Eight-year period of observation.
†Per 1,000 per year.

report. A total of 1,838 men originally free of coronary heart disease and followed for eight years are included in this report.

Both populations are homogeneous in terms of sex, age, race, occupation, and diet. Fewer than 1% of either population has been lost to follow-up. Further, it is known that the occurrence of CHD in these persons in both groups is similar to that in the participants.

At the first examination in Framingham and in Albany, a detailed smoking history was taken from each participant. This information has been correlated with the incidence of CHD for over ten years in Framingham and eight years in Albany irrespective of subsequent change in smoking habit.

The following manifestations of CHD have been correlated with initially reported smoking habit: myocardial infarction, angina pectoris, sudden death, and death attributed to arteriosclerotic heart disease. Individuals suffering from both angina pectoris and myocardial infarction are listed under the latter category. The criteria for these diagnostic categories have been rigorously defined collaboratively by the Framingham and the Albany investigators and correspond closely to the definitions propounded at the Beaconsfield and Princeton conferences and later by WHO expert committee.^{7,9}

Results

Of particular importance is the occurrence of

death and disability in men in the prime of life. Table 1 sets forth the total mortality experience of nearly 2,100 men in the combined Albany-Framingham group, originally between 40 and 49 years of age, according to cigarette habit.

Although the remainder of the presentation applies to the entire groups under observation in each study, Table 1 considers only the largest directly comparable age group in each study. New events of CHD are expressed in conventional incidence rates. The data for each study cover equivalent lengths of time, ie, eight years for each group, and thereby the rates in each study represent comparable periods of exposure to risk for men of the same age.

It is obvious that cigarette smokers die at a rate much higher than noncigarette smokers with much of the excess rate attributable to myocardial infarction. There is no apparent relationship, however, between cigarette habit and angina pectoris when it is the sole manifestation of CHD. The death rate from causes other than CHD in Framingham is higher than in Albany, but the number of deaths is too few to identify any particular pattern.

Tables 2 through 7 use morbidity or mortality ratios, rather than the incidence rates of Table 1, as indicators of risk, so that the entire age-time experience in the two groups can be utilized. These ratios relate the observed to the expected incidence of coronary heart disease in each subgroup. The

Table 2.—Occurrence of New Coronary Heart Disease or Death in Men Free of Disease at Entry Into Study According to Initial Smoking Habit

Smoking Habit	All Deaths			CHD Deaths			Myocardial Infarction (Including CHD Death)			Angina Pectoris															
	Ratio Observed to Expected†			Ratio Observed to Expected†			Ratio Observed to Expected†			Ratio Observed to Expected†															
	Observed, No.	A*	F*	Total	Observed, No.	A	F	Total	Observed, No.	A	F	Total	Observed, No.	A	F	Total									
Non-cigarette smokers																									
Total	18	41	59	53‡	64‡	60‡	6	14	20	43§	62	55‡	22	30	52	51‡	58‡	55‡	14	16	30	108	86	95	
Never smoked	7	18	25	48§	77	66§	3	8	11	79	9	14	23	49§	74	61§	6	7	13	6	7	13	108	108	
Former cigarette smoker	4	4	8	32‡	42‡	1	2	3	7	6	13	73	60	65	4	1	5	4	1	5	4	1	5	111	
Cigar or pipe on'y	7	19	26	56	68	65§	2	4	6	41§	6	10	16	40§	45‡	43‡	4	8	12	4	8	12	96	96	
Cigarette smokers total	64	126	190	136§	124§	128‡	27	46	73	143	124	131§	82	109	191	136‡	126§	130‡	16	35	51	91	111	104	
<20 per day	12	31	43	98	102	101	3	14	17	130	108	15	29	44	97	116	109	4	11	15	4	11	15	111	
20 per day	22	44	66	129	107	113	9	11	20	74	92	24	40	64	111	114	113	8	10	18	8	10	18	78	
>20 per day	30	51	81	171§	169‡	170‡	15	21	36	208§	187§	195‡	43	40	83	187‡	150§	167‡	4	14	18	4	14	18	109

*A = Albany; F = Framingham.
†Expected number of events based on local age-specific rates for total population without regard to smoking habit.
‡Significantly different from 100 at P = 0.01 level.
§Significantly different from 100 at P = 0.05 level.
¶Ratio not shown if fewer than 10 cases expected.

expected number of events is computed on the null hypothesis which holds that if the factor under consideration is unrelated to the disease (for example, cigarette smoking to coronary heart disease), observed differences in incidence rates are only chance variations. The best estimate of the true or expected incidence of the disease is then derived by using the rate for the entire population irrespective of the factor under investigation. Since age itself may increase susceptibility to a given disease independently of other factors an appropriate adjustment is made by computation of the expected incidence in each age interval. The sum of these is the age-adjusted expected incidence of disease. Under the null hypothesis in each of the various smoking categories the value of the ratio of the observed to the expected number of events would be 100. This method of analysis permits combining the results without concern about minor differences between the two studies in population characteristics and interpretation of clinical findings which might exist.

Table 2 shows deaths from all causes according to six smoking categories and the ratio of observed to expected deaths for the entire group of 4,120 men ranging in age from 30 to 62 years at entry into the respective studies. An increasing gradient of mortality with increasing cigarette smoking is noted. The heaviest cigarette smokers (>20 per day) experience a hazard three times that of nonsmokers. Former cigarette and pipe and cigar smokers are at about the same risk as nonsmokers. The same trends are evident when smoking habit is related to fatal and nonfatal myocardial infarction. On the other hand, there is no significant difference in the incidence of angina pectoris as the sole manifestation of CHD and tobacco habit. If cases in which angina pectoris was the initial manifestation of CHD are tabulated in the same way, there is still no correlation with smoking practice.

Mortality ratios presented in Table 2 are based on age-specific rates for the total populations rather than on age-specific rates for nonsmokers, since ratios based on the small populations of nonsmokers are likely to exhibit erratic fluctuations. The total age-specific rates show differences in risk for a variety of smoking categories compared with the total population, and also the similarity between Albany and Framingham. Furthermore, these morbidity ratios for the combined populations can be used to calculate risks for each smoking category relative to nonsmokers. These relative risks and their 0.95 confidence limits are shown in Table 3. These confidence limits define an interval which will include the true value 95% of the time. The assumptions under which these limits are derived and a complete description of their calculation are published elsewhere.¹⁰

Table 4 relates the duration of heavy smoking, defined as the consumption of 20 or more cigarettes daily, to the risk of myocardial infarction. No differences in the incidence of this manifestation

are evident among the four groups with varying degrees of exposure to risk.

Tables 5, 6, and 7 relate the incidence of death and of CHD to smoking habit when an attempt is made to take into account the generally accepted risk factors of arterial blood pressure level and serum total cholesterol concentration.

Comparisons are made between smokers and nonsmokers after subdividing each group on the basis of systolic blood pressure (above and below the population median) and serum total cholesterol (above and below the population median). Thus, there are four smoking pairs in which to compare risk.

These tables show that the increased risk of death or of fatal or nonfatal myocardial infarction associated with smoking persists when an attempt is made to standardize for these factors. For example, risk of death from all causes (Table 5), death from CHD (Table 6), and development of myocardial infarction (Table 7), is consistently higher in cigarette smokers than in non-cigarette smokers regardless of whether the subjects are above or below the median for blood pressure and/or cholesterol level.

In general, the risk for smokers is always greater, and in almost every instance at least twice as great as that for nonsmokers. The differences in risk between smokers and nonsmokers are highly significant where the serum total cholesterol is elevated. On the other hand, the incidence of disease is low in the groups with a serum total cholesterol concentration below the median and the difference is statistically far less striking. Although these smaller differences could be genuine, they may be statistical artifacts due to small numbers. Since the potential implications of this observation are so important, the association between cigarette smoking, cholesterol concentration, and incidence of CHD demands continued close scrutiny.

Comment

The relationship between tobacco habit and the incidence of CHD over an eight- to ten-year period in two large groups of middle-aged men is strikingly consistent and is virtually identical with the findings reported previously after a six- and an eight-year follow-up.

The manner in which cigarette smoking impairs longevity remains unexplained. The excess mortality in heavy cigarette smokers is due not to a disproportionate increase in the frequency of any particular disease save lung cancer, but to a general increase in the rate of dying from all causes, of which CHD is much the most common.¹¹ This would point to a nonspecific lethal effect, presumably operating through a respiratory portal of entry in the case of cigarette smokers, inasmuch as noninhaling cigar and pipe smokers are relatively immune to the ill-effects of tobacco.

The acute circulatory responses to smoking are greatest in cigarette smokers and are attributed to

Table 3.—Ratio of Relative Risks: Combined Albany-Framingham Data

Comparison	Myocardial Infarction Including CHD Deaths		
	All Deaths	CHD Deaths	CHD Deaths
All cigarette smokers relative to non-cigarette smokers Relative risk	2.1	2.4	2.4
0.95 confidence limits on relative risk	1.6-2.9	1.4-4.1	1.7-3.2
<20 per day smokers relative to non-cigarette smokers Relative risk	1.7	2.0	2.0
0.95 confidence limits on relative risk	1.1-2.5	1.0-4.0	1.3-3.0
20 per day smokers relative to non-cigarette smokers Relative risk	1.9	1.7	2.1
0.95 confidence limits on relative risk	1.3-2.7	0.9-3.3	1.4-3.0
>20 per day smokers relative to non-cigarette smokers Relative risk	2.8	3.5	3.0
0.95 confidence limits on relative risk	2.0-4.0	2.0-6.5	2.1-4.2
Former cigarette smokers relative to never cigarette smokers Relative risk	0.6	1.1
0.95 confidence limits on relative risk	0.2-1.4	0.5-2.2

the rapid absorption of nicotine from the bronchopulmonary mucosa, a slower and less complete process from the lining of the mouth. No component of tobacco smoke other than nicotine exerts a measurable acute circulatory effect. Chronic hemodynamic or morphologic vascular changes attributable to tobacco usage or to nicotine, with the possible and controversial exception of thromboangiitis obliterans, have never been demonstrated.¹²

That the smoking effect may be acute is suggested by the reversion of risk to virtually that of the nonsmokers after cessation of cigarette smoking, among heavy smokers, a lack of gradient for CHD risk in relation to years of exposure, and the absence of a relationship between cigarette smoking and the incidence of angina pectoris. The risk of CHD or death for ex-cigarette smokers in these two populations was nearly equal to the risk for those who never smoked, in contrast with the observations in the prospective studies of Hammond and Horn⁴ and of Doll and Hill³ which show rates for ex-smokers intermediate between present smokers and those who never smoked. The cause of these differences is unexplained but may be related to methodology and to selection of populations. Investigation of prior smoking habits in those who

Table 4.—Incidence of Myocardial Infarction (Including CHD Death) in Men Smoking 20 Cigarettes or More per Day According to Duration of Cigarette Smoking

Duration of Smoking, Years	Observed, No.			Ratio Observed to Expected*		
	Albany	Framingham	Total	Albany	Framingham	Total
	Less than 10	6	0	6
10-19	9	13	22	80	97	88
20-29	36	30	66	109	110	110
30 or more	16	34	50	92	96	95

* Expected number of events based on local age-specific rates for smokers of 20 cigarettes or more per day without regard to duration of smoking.

† Ratios not shown when the expected number of events is less than 10. (....)

Table 5.—Deaths From All Causes in Men Free of Disease at Entry Into Study by Smoking, Blood Pressure and Cholesterol Levels*

In Relation to Local Median†		Cigarette Smoking Habit	Observed in Combined Population, No.	Ratio Observed to Expected‡	Significance Level For Difference Between Smoking Categories
Systolic Blood Pressure	Cholesterol				
—	—	No	7	37	P>0.05
—	—	Yes	21	70	
—	+	No	3	18	P<0.01
—	+	Yes	25	97	
+	—	No	24	84	P<0.05
+	—	Yes	53	156	
+	+	No	30	89	P<0.05
+	+	Yes	71	152	

* Combined Albany-Framingham data.

† Classification in each study:

	Framingham	Albany	—	+
Systolic blood pressure, mm Hg	<130	<130	130 and over	130 and over
Cholesterol, mm/100 cc	<220	<226	220 and over	226 and over

‡ Expected values based on local age-specific rates without regard to smoking status.

stopped smoking indicates no important differences from those who continue to smoke. These observations may be construed as evidence that atherogenesis is not related to the use of tobacco. The morphologic observations of Wilens and Plair support this conclusion.¹³ On the other hand, the acute occlusive complications of atherosclerosis are, apparently, aggravated by tobacco smoking. The mechanism of this effect is unknown. Coronary arteriospasm, often proposed as a possible reaction to tobacco smoke, has never been proved. The even more plausible possibility that tobacco smoke may accelerate thrombus formation has not been convincingly substantiated. The explanation of the ill-effects of tobacco must almost certainly take into account the fact that inhaled smoke comes into repeated and intimate contact with the entire circulating blood volume. Toxic substances could thus be rapidly conveyed throughout the body and precipitate an occlusive episode.

Since it appears that it is only the immediate and not any cumulative effect of inhaling cigarette smoke which precipitates myocardial infarction and death from CHD, the implications for prevention for the general public and especially for the patient

Table 6.—Deaths From Coronary Heart Disease in Men Free of Disease at Entry Into Study by Smoking, Blood Pressure and Cholesterol Levels*

In Relation to Local Median†		Cigarette Smoking Habit	Observed in Population, No.	Ratio Observed to Expected‡	Significance Level For Difference Between Smoking Categories
Systolic Blood Pressure	Cholesterol				
—	—	No	2	27	P>0.05
—	—	Yes	6	51	
—	+	No	0	0	P<0.01
—	+	Yes	14	138	
+	—	No	9	84	P>0.05
+	—	Yes	15	114	
+	+	No	11	88	P<0.05
+	+	Yes	33	186	

† Classification in each study:

* Combined Albany-Framingham data.

	Framingham	Albany	—	+
Systolic blood pressure, mm Hg	<130	<130	130 and over	130 and over
Cholesterol, mg/100 cc	<220	<226	220 and over	226 and over

‡ Expected values based on local age-specific rates without regard to smoking status.

Table 7.—Incidence of Myocardial Infarction (Including CHD Death) in Men Free of Disease at Entry Into Study by Smoking, Blood Pressure and Cholesterol Levels*

In Relation to Local Mediant		Cigarette Smoking Habit	Observed in Combined Population, No.	Ratio Observed to Expected†	Significance Level For Difference Between Smoking Categories
Systolic Blood Pressure	Cholesterol				
—	—	No	6	27	P>0.05
—	—	Yes	19	44	
—	+	No	10	54	P<0.01
—	+	Yes	45	153	
+	—	No	13	47	P>0.05
+	—	Yes	34	103	
+	+	No	28	91	P<0.05
+	+	Yes	83	187	

* Combined Albany-Framingham data.

† Classification in each study:

Systolic blood pressure, mm Hg	Framingham	<130	130 and over
	Albany	<130	130 and over
Cholesterol, mg/100 cc	Framingham	<220	220 and over
	Albany	<226	226 and over

‡ Expected values based on local age-specific rates without regard to smoking status.

with clinically overt CHD seem evident. While it is recognized that those who gave up smoking were not randomly selected and induced to give it up, the fact that those who had given up smoking developed no more disease than those who had never smoked suggests strongly that a substantial reduction in CHD mortality and morbidity by the reduction in the consumption of cigarettes by the general public may be achieved.

Summary and Conclusions

The total mortality and the incidence of new

manifestations of coronary heart disease (CHD) in 2,282 men, originally 30 to 62 years of age, has been reported for a ten-year period in Framingham, Mass, and in 1,838 men, originally 39 to 55 years of age, for an eight-year period in Albany, NY. These observations have been related to smoking habit reported at the time of admission to the respective studies. Men reporting the habitual consumption of 20 or more cigarettes daily experienced a death rate from all causes about three times greater than of nonsmokers, former cigarette smokers, or pipe and cigar smokers. Heavy cigarette smokers experience a similar increase in risk of myocardial infarction compared with non-cigarette smokers. Increased risk of myocardial infarction or death was associated with cigarette smoking in all combinations of high and low systolic blood pressure and cholesterol levels.

The risk of angina pectoris as the sole or initial manifestation of CHD appears to be unrelated to the tobacco habit. The explanation of the association between heavy cigarette smoking and the increased risk of death from all causes and of death or disability from CHD in particular remains speculative, but the effect appears to be relatively immediate. No cumulative effect on the development of the underlying atherosclerosis appears evident. The inference that stopping cigarette smoking has a beneficial effect in preventing or delaying the onset of the lethal manifestations of CHD appears warranted.

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CONTROL OF ATHEROSCLEROTIC HYPERLIPEMIA.—Since atherosclerotic hyperlipemia is characterized by elevations in serum cholesterol, phospholipids, glycerides, and the low density lipoproteins, therapeutic approaches have been aimed at lowering serum lipids. Although the exact relationship between abnormal lipid and lipoprotein patterns remains obscure, attempts to lower lipid constituents of serum seem to hold the most promise in the control of atherosclerotic hyperlipemia. Evidence is not yet available that any specific lipid depressant will reduce the incidence of atherosclerosis or improve the prognosis after the disease is clinically evident. However, continued attempts to find effective means for reducing grossly elevated serum lipids appear more than justified on an empirical basis alone. . . .—Searcy, R. L., and Berquist, L. M.: *Lipoprotein Chemistry in Health and Disease*, Springfield, Ill.: Charles C Thomas. 1962, p 168.