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Cigarette Smoking and Arteriosclerosis

Recent reports (*1, 2*) have indicated that heavy smokers of cigarettes are more prone than nonsmokers to have heart attacks due to myocardial infarction. The nature of this relationship has not been fully explored, and a number of different interpretations can be suggested.

Myocardial infarcts may be associated with severer symptoms in heavy smokers than in nonsmokers and thus be detected more readily at the time of onset. Although the clinical and electrocardiographic recognition of such lesions has improved greatly, a high percentage of the infarcts found at necropsy are not diagnosed during life (*3*), presumably because they do not cause pronounced or characteristic symptoms. No positive correlation between the incidence of myocardial infarction at necropsy and cigarette smoking has as yet been reported.

A high incidence of myocardial infarction in heavy smokers could depend to some extent on alterations in blood flow due to various mechanisms, and not entirely on the degree of sclerosis of the coronary arteries. In other words, cigarette smokers may be more vulnerable to ischemic infarction than nonsmokers with an equivalent degree of arterial narrowing. Kagan *et. al.* (*4*) suggested that cigarette smoking does not necessarily produce its effect through the pathogenetic mechanism of atherosclerosis but may operate in an indirect fashion to produce symptoms of coronary insufficiency. There is no proof that sclerosis of coronary arteries develops more rapidly in cigarette smokers than in nonsmokers.

The relation between cigarette smoking and heart attacks could be an indirect or even a fortuitous one. Heavy smokers may have other habits or characteristics that make them vulnerable to myocardial infarcts. For example, in an earlier analysis (*5*) it was found that portal cirrhosis of the liver was more common in heavy smokers of cigarettes than in nonsmokers. Further investigation showed that chronic alcoholism was also more prevalent among heavy smokers than among nonsmokers and that the high incidence of liver disease in the former was obviously attributable to this circumstance. It is therefore necessary to determine whether heavy smokers tend to fall into groups having a high incidence of the so-called atherogenic factors, such as diabetes, hypertension, hypercholesteremia, and obesity.

It is possible that cigarette smoking in some selective fashion promotes the development of sclerotic changes in coronary arteries but not in other vessels. No systematic study of the relation of smoking to the severity of sclerotic changes throughout the arterial system appears to have been made. Furthermore, there is little evidence that heavy smoking of cigarettes is associated with a higher incidence of other lesions that may be related to arteriosclerosis, such as scarring of the kidneys, gangrene of the legs, and cerebral infarcts or hemorrhages.

In an earlier report (*6*) a simple comparative method of evaluating the degree of sclerotic change in the aorta at necropsy was described. A record of the smoking habits of most of the individuals of that study was recorded. It was therefore possible to obtain statistical data concerning the relation of smoking practices to the degree of aortic sclerosis. The purpose of the study reported here is to determine (i) whether the clinical evidence of increased incidence of myocardial infarction in heavy smokers is confirmed by a study of necropsy material; (ii) whether there is a higher incidence of other lesions that can be attributed to arteriosclerosis in heavy smokers than in nonsmokers; (iii) whether the degree of generalized arterial sclerosis is a function of smoking habits; and (iv) whether the groups of men with special attributes that make them particularly susceptible to myocardial infarction tend to be heavy smokers of cigarettes.

The study is based on findings in 989 consecutive necropsies on men, performed at the New York Veterans Administration Hospital between 1958 and 1961. In each case the aorta was given an "arteriosclerotic age" through comparison with a set of previously prepared photographic transparencies of aortas which represented the standard or average degree of sclerotic change observed in each half-decade of adult life. If an aorta was evaluated as showing sclerosis characteristic of an age more than 10 years greater than the age of the patient, it was considered to show above-average sclerosis. If it showed sclerosis characteristic of an age more than 10 years less than the age of the patient, it was judged to show below-average sclerosis. Accordingly it was possible to grade each aorta as to whether or not it showed above-average, average, or below-average sclerotic change, regardless of the age of the patient in question. The details of this method of evaluating the degree of atherosclerosis is described more fully elsewhere (*6*).

Daily smoking of more than one and a half packs of cigarettes for many years was the criterion used to define a heavy smoker of cigarettes. Moderate smokers were those who smoked from one to one and a half packs daily. Those who smoked less than a pack a day were listed as light smokers. No attempt was made to separate the pipe and cigar smokers, or to classify them into "light" or "heavy" categories, because this combined group was a relatively small one. Two tobacco chewers are included in this group. When cigarette smokers also smoked pipes or cigars they were classified only according to their cigarette-smoking habits. "Nonsmokers" included a few persons who had smoked briefly early in life. The "unknown or unclassified" group included those for whom no statement about smoking was available and those whose smoking habits had changed drastically over long periods of their lives. The data on smoking were obtained from the routine clinical records. While free from bias, the information available was often lacking in detail. It is possible that some patients who once smoked heavily had ceased to do so after a heart attack in the past and were listed as nonsmokers. In the Framingham-Albany study (*2*), 15 percent of the group were nonsmokers, and in other statistical analyses a comparable percentage were found to be abstainers.

In the series reported here, only 12 percent were classified as nonsmokers. This indicates that no great number of former smokers were erroneously classified as nonsmokers. Furthermore, carcinoma of the lung was found to be four times as common in this series in heavy smokers of cigarettes as in nonsmokers (*5*). This indicates that the smoking habits of individuals in this series were comparable to smoking habits reported in other analyses.

All the hearts with one or more infarcts, whether recent or healed, are tabulated in Table 1. Areas of necrosis or scarring in the myocardium more than 1 cm in diameter were considered to be infarcts. It may be seen that the incidence in the various categories of smokers and in nonsmokers does not vary significantly. In cigarette smokers the incidence for light smokers is the same as that for heavy smokers; the incidence for nonsmokers is only slightly lower. This finding is in direct contradiction to clinical findings and suggests that myocardial infarcts may be more productive of severe symptoms, and thus more readily recognized, in heavy smokers than in nonsmokers.

All cases of vascular scarring of the kidney, including those involving arterioles and large arteries and those with or without renal insufficiency, are listed in composite form in Table 1. It may be seen that such lesions occur with about equal frequency in all categories of smokers, except that they are slightly more common in pipe and cigar smokers, probably because hypertension is also somewhat more common in this group (see Table 2).

No significant correlation between the incidence of gangrene of the legs, cerebral hemorrhages, or cerebral infarcts and smoking practices was observed (Table 1). It is thus apparent that heavy smokers of cigarettes do not show a striking increase in lesions due to arteriosclerosis at necropsy.

The aortas of about three out of every five men show a degree of sclerosis at necropsy which is commensurate with age, regardless of their smoking habits (Table 3). It should be noted that, among the remaining 40 percent, above-average sclerotic change is more than twice as common in heavy and moderate smokers as in nonsmokers and in pipe and cigar smokers. Similarly, a below-average degree of sclerosis is twice as common in nonsmokers and pipe and cigar smokers as in heavy or moderate smokers of cigarettes. These differences are statistically significant. Findings for light smokers of cigarettes are intermediate in these respects. There is thus evidence that in a minority of men cigarette smoking may be associated with an above-average degree of sclerosis of the aorta.

In Table 2, it may be seen that there is no striking difference in the incidence of hypertension, diabetes, obesity, gallstones, or cortical hyperplasia of adrenals in nonsmokers and in the various categories of smokers. Hypertension, obesity, and gallstones are somewhat more prevalent among the pipe and cigar smokers, a group composed of relatively old men, but the differences are not great. The incidence of these various conditions tends to be slightly

Table 1. Incidence (in percentages) of arteriosclerotic lesions in smokers and nonsmokers.

Lesion	In nonsmokers (N = 161)	In cigarette smokers			In pipe and cigar smokers (N = 70)	In others (smoking habits unknown or unclassified) (N = 119)
		Heavy (N = 199)	Moderate (N = 288)	Light (N = 152)		
Myocardial infarcts	20.5*	25.6*	23.6	25.0	27.1	20.2
Vascular scars of kidneys	19.3†	19.6	15.6	19.1	28.6†	20.2
Cerebral infarcts	9.9	7.5	10.1	14.5	14.3	14.3
Cerebral hemorrhage	1.9	3.0	1.4	2.0		5.0
Gangrene of legs	3.1	2.0	1.4	4.6	2.9	6.7

* $\chi^2 = 1.3$; $P = .028$. † $\chi^2 = 2.5$; $P = .11$.

Table 2. Incidence (in percentages) of conditions associated with increased severity of arteriosclerosis in smokers and nonsmokers.

Condition	In nonsmokers (N = 161)	In cigarette smokers			In pipe and cigar smokers (N = 70)	In others (smoking habits unknown or unclassified) (N = 119)
		Heavy (N = 199)	Moderate (N = 288)	Light (N = 152)		
Hypertension and/or cardiac hypertrophy	50.3*†	38.2*	40.3	45.5	64.3†	44.5
Diabetes	13.7	8.0	4.2	9.2	14.3	10.1
Cortical hyperplasia of adrenals	10.6	11.6	11.1	13.2	11.4	9.2
Obesity	18.6	16.1	10.1	9.9	21.4	21.0
Gallstones	21.7	18.6	18.4	19.7	27.1	18.5

* $\chi^2 = 4.83$; $P = .026$. † $\chi^2 = 3.78$; $P = .053$.

Table 3. Relation of smoking habits to severity of aortic sclerosis at necropsy. All values are percentages.

Severity of aortic sclerosis	In nonsmokers (N = 161)	In cigarette smokers			In pipe and cigar smokers (N = 70)	In others (smoking habits unknown or unclassified) (N = 119)
		Heavy (N = 199)	Moderate (N = 288)	Light (N = 152)		
Above average	9.9*	25.1*	26.4	19.1	10.0	10.9
Average	60.2	61.3	62.5	63.2	60.0	63.0
Below average	29.8†	13.6†	11.1	17.8	30.0	26.1

* $\chi^2 = 13.67$; $P < .001$. † $\chi^2 = 14.34$; $P < .001$.

Table 4. Mean and median blood cholesterol levels in smokers and nonsmokers.

Group	Determinations (N)	Mean (mg/100 ml)	Median (mg/100 ml)
Nonsmokers	60	199.2 ± 9.2	181
Cigarette smokers:			
Heavy	79	223.7 ± 8.9	213
Moderate	130	201.0 ± 6.7	185
Light	63	208.1 ± 10.3	199
Pipe and cigar smokers	37	227.6 ± 15.3	219
Smoking habits unknown or unclassified	43	206.8 ± 11.5	203

lower in light and moderate smokers of cigarettes, a somewhat younger group on the whole, than in the other groups. It is clear that cigarette smoking does not tend to promote development of disorders that may contribute to the development of arteriosclerosis.

The mean and median total-blood cholesterol levels (determined by the Zak method), that were known for the various groups studied are listed in Table 4. These determinations were made for the most part during hospital admissions for various illnesses and therefore do not represent usual blood levels of cholesterol during periods of good health. Cholesterol levels for patients with severe liver disease or biliary obstruction were excluded from the tabulations. It may be seen that there are no striking differences in the mean and median values for any of the groups, although both are higher by about 20 to 30 mg per 100 ml in heavy smokers of cigarettes or of pipes and cigars than in nonsmokers. None of the values is above the accepted upper limits of normal. It is possible, nevertheless, that the higher incidence of severe sclerosis of the aorta and the slightly higher incidence of myocardial infarction in cigarette smokers may be related to these slight differences in blood cholesterol concentrations.

The results of this analysis based on necropsy statistics indicate that if an association exists between smoking practices and the development of arteriosclerosis or lesions resulting therefrom, it is at best tenuous and inconclusive. A sizable minority of heavy smokers of cigarettes seem to develop sclerotic changes in their aortas at a faster rate than nonsmokers and tend to have slightly higher blood cholesterol levels. The incidence of myocardial infarction is only very slightly higher in heavy smokers of cigarettes than in nonsmokers, and there is no consistent rise in the incidence of such lesions with degree of cigarette smoking. The incidence of other types of lesions related to arteriosclerosis is not affected by smoking habits.

The findings do not preclude the possibility that heart attacks due to myocardial infarction may be more severe clinically, and more often fatal during their acute phase, in heavy smokers of cigarettes than in nonsmokers (*7*).

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Synthetic Acrylic Gel: A New Medium for the Study of Immune Precipitates

Abstract. The physicochemical properties of photocatalyzed Cyanogum gel offer practical advantages in the analysis of specific immunological precipitation techniques: use of any buffer at any *p*H; most probable neutrality for stains or reagents; remarkable resolution of the immunological precipitates, visible microscopically; possibility of direct dark-background examination of the precipitates, so that their kinetics can be studied and they can be photographed before dyeing and staining. This gel seems particularly suitable for immunoanalysis of complex and unstable antigenic products, such as tissue homogenates.

The electrophoretic study of hemoglobin by means of a synthetic gel, Cyanogum, was reported in 1959 by Raymond (*1*). Interesting results were also reported (*2*) with the use of Cyanogum gel for the electrophoretic separation of human serum. However, this gel has not yet been utilized for immunological studies. This report describes its use as a medium for the double diffusion of antigen and antibody to form immune precipitates, and includes a description of a method for photopolymerization of the gel which avoids the use of the β-dimethylaminopropionitrile catalyst (*3*).

The uncatalyzed Cyanogum 41 (*4*) is a mixture of two organic monomers: acrylamide and N,N′-methylenebisacrylamide. The catalysis of this mixture results in linear polymers of acrylamide, joined by three-dimensional "methyl" bridges. Two essential physicochemical properties of Cyanogum, "gel" consistency and hydrophilia, result from its "spongy" structure and the exclusive presence of amide groups along the chains (*5*).

A constant thickness of the gel and an adequate horizontal position of the glass plate, which supports it, are easily achieved by allowing the whole to rest on a layer of mercury (Fig. 1). The adhesiveness of Cyanogum gel to the glass plate is usually excellent when the suggested concentrations are used, and if the glass is not strongly scoured. No preliminary coating of the glass plate is needed.

Because of its elasticity, polymerized Cyanogum is cut with difficulty. The troughs and reservoirs needed for immunological studies are formed by means of molds or templates, preferably made of Plexiglas (methacrylate), which are placed in the unpolymerized solution. These molds are easily removed from the gel, especially when they have been coated with a thin layer of siliconated oil (*6*).

The Cyanogum gel concentrations that permit adequate diffusion of proteins are between 3 and 10 percent with an optimal range between 4 and 5 percent for most common procedures. At higher concentrations, the

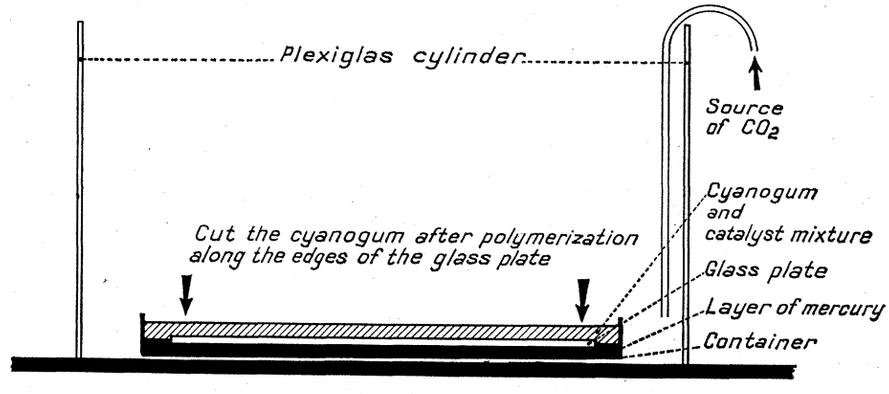

Fig. 1. Vertical section of the apparatus designed for the photopolymerization of regularly thin layers of Cyanogum gel in CO_2 atmosphere.