Section of Epidemiology and Preventive Medicine

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Symposium on Arteriosclerosis

untoward effects. Debate still goes on as to the quantitative relationship between atherosclerotic disease and the occurrence of thrombotic episodes.

Just as pathology can be studied both by macroscopic and microscopic methods, each contributing its share, epidemiology can be similarly divided into macroscopic and microscopic studies. In general, just as in pathology, observations made from macroscopic studies lead to a more detailed study with the field of vision limited to a small segment of the population.

Observations of the macroscopic type which have been carried out for many years, by comparing rates of arteriosclerotic heart disease in different countries or widely divergent populations, have suggested that factors such as sex, dietary habits, physical activity, &c., may be related to its development. It is unfortunate that these observations could not have been carried out more precisely. Due to inadequacy of death certification, lack of uniformity in definitions of disease entities, inability to recognize certain clinical syndromes, differences in pathological techniques and classifications, we are still left with some doubts about the existence of real differences in the occurrence of atherosclerotic disease and its manifestations in the many populations studied. In spite of the inadequacies of such gross observations, apparent differences in widely divergent population groups have served to whet the appetite of epidemiologists and to encourage more detailed study under conditions which can be better controlled. Ever since the abortive efforts of Sir James MacKenzie (1926) to study heart disease in a human population, the concept has been current that a detailed study of the natural history of atherosclerotic cardiovascular disease and an attempt to relate its development to certain environmental factors would prove to be of great value in future attempts to prevent or control the disease.

In 1950 the National Heart Institute of the United States Public Health Service undertook

The Epidemiology of Coronary Heart Disease—The Framingham Enquiry

by Thomas R Dawber MD, William B Kannel MD, Nicholas Revotskie MD and Abraham Kagan MD (Framingham, Mass.)

Epidemiology earned its rightful place as one of the branches of medical science by its contributions in the field of infectious disease. It has upheld its position in certain non-infectious diseases in which the ‘incubation period’ has been relatively short. Although it seems reasonable to believe that the application of the same epidemiological principles to the major non-infectious diseases, e.g. cancer and atherosclerotic cardiovascular disease, now of primary concern to those populations in which the infections have been largely controlled, will yield valuable information which may lead to the prevention and control of these diseases, this belief is still unsubstantiated.

The major differences between infectious disease epidemiology and the epidemiological study of these chronic diseases are: (1) The onset of the chronic disease process is often difficult to date with any degree of precision. (2) The period of observation of factors suspected to be associated with the development of the disease must be long and is ill defined, i.e. no definite ‘incubation period’ is known. (3) In chronic diseases it appears less likely that single causative agents will be demonstrated.

In atherosclerotic cardiovascular disease the problem is further complicated by the fact that we are probably dealing with two independent yet closely related pathological mechanisms: (1) The underlying atherosclerotic disease of the arterial wall. (2) The superimposed thrombotic episodes. Although the second cannot occur without the first, the first can be present for a normal life span and produce no apparent

the epidemiological investigation of arteriosclerotic heart disease and hypertension (Dawber et al. 1951). For this purpose a field study was set up in the town of Framingham, Massachusetts, in the United States. This town was reasonably typical of many towns in New England. Its population at that time was about 30,000. It was believed, on the basis of assurances received, that such a study would be acceptable to the townspeople and that the response would be adequate to yield an adult population for study. The selection of this town was therefore governed primarily by the belief that such a study could be carried on there successfully rather than by the possibility of forming general conclusions about the entire United States population. Due to the size of the United States with its varying racial distribution, &c., it would be manifestly impossible to select any locality from the study of which unqualified generalizations could be made.

Because of the inability to recognize the presence and extent of atherosclerosis anywhere in the body except by post-mortem study it has not been possible to study the epidemiology of atherosclerosis per se, coronary or otherwise. Since for epidemiological purposes it is necessary to define and detect the disease under consideration in an acceptable and yet practicable manner, the first task of this study was to decide what could be studied and how this was to be carried out.

The term ‘arteriosclerotic heart disease’ has been in general use and is a specific item in the international list. The use of this term in the United States, however, is not as specific as is implied. It was therefore decided to use the term coronary heart disease (CHD) by which was meant those clinical syndromes due to heart disease secondary to impaired blood flow in the coronary arteries. CHD is thus synonymous with ‘ischaemic heart disease’, a label which has been popular in the United Kingdom.

For epidemiological studies definitions must be in terms of morbid states recognizable clinically or in terms of causes of death which are acceptable as due to the disease in question. CHD is manifested in the living as: (1) Angina pectoris. (2) Myocardial infarction.

(1) Angina pectoris: The syndrome of chest discomfort is well recognized in an advanced state but often difficult to diagnose with certainty in population surveys. With few exceptions angina pectoris is due to coronary atherosclerosis with or without previous myocardial infarction. In the absence of diagnasable myocardial infarction some may consider angina pectoris a better indicator of coronary atherosclerosis than are other manifestations of CHD.

(2) Myocardial infarction represents necrosis of the heart muscle with healing by scar formation and results almost always from coronary occlusion, complete or partial, due to coronary atherosclerosis with or without coronary thrombosis. Myocardial infarction can be defined objectively. In the Framingham study it was required that there be evidence of muscle necrosis as demonstrated by characteristic electrocardiographic changes or rise in enzyme levels during the acute episode. Myocardial infarction is considered the most clearcut manifestation of CHD but it is recognized that it is usually the resultant of two factors, i.e. coronary atherosclerosis and superimposed coronary thrombosis and cannot per se be taken as a direct measure of coronary atherosclerosis.

Death may be due to CHD and may occur in persons in whom it has not been possible to make a clinical diagnosis. Two categories of death have been accepted as indicative of CHD: (1) Sudden death, documented to have occurred within a matter of minutes and unexpected, from some other illness. It is believed there is sufficient evidence that sudden unexpected death in adults in the United States is due almost always to coronary artery disease. This group has therefore been included in the category of CHD (Spain et al. 1960). (2) Death, not sudden, in persons who have clinical manifestations of CHD but who do not present sufficient evidence for a clinical diagnosis, e.g. those who do not live long enough to develop typical electrocardiographic changes.

The population at risk in Framingham has been observed in our clinic at two-year intervals since initial examination in 1950. In addition, we have attempted to obtain as much information as possible on the state of health, intercurrent illnesses and factors associated with the death of everyone in the population sample. On the basis of this information the entire population of the Framingham study has been classified in terms of the presence of the above manifestations of CHD.

Results
This report presents the findings of the Framingham enquiry after eight years of observation of the population at risk. Associations of various factors with the development of CHD are presented in terms of morbidity ratios, i.e. the ratios of observed to expected cases multiplied by 100.

The composition of the population at risk, i.e. initially free of CHD, is presented in Table 1. From the population selected by a random sampling technique it was possible to bring in 4,469 persons (68·8%) for initial examination. An additional 740 volunteers were added and, since their overall experience has not differed
Table 1
Derivation of Framingham study group

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sample</td>
<td>6,507</td>
<td>3,074</td>
<td>3,433</td>
</tr>
<tr>
<td>Respondents</td>
<td>4,469</td>
<td>2,024</td>
<td>2,445</td>
</tr>
<tr>
<td>Volunteers</td>
<td>740</td>
<td>312</td>
<td>428</td>
</tr>
<tr>
<td>Respondents free of CHD</td>
<td>4,394</td>
<td>1,975</td>
<td>2,419</td>
</tr>
<tr>
<td>Volunteers free of CHD</td>
<td>734</td>
<td>307</td>
<td>427</td>
</tr>
<tr>
<td>Total free of CHD:</td>
<td>5,128</td>
<td>2,282</td>
<td>2,846</td>
</tr>
</tbody>
</table>

from the sample group, they have been included in the study population. When those persons with evidence of CHD at initial examination were excluded, the remaining 5,128 persons free of CHD constituted the population at risk of developing CHD subsequently. These persons were all aged 30–59 at the time of entry into the study.

This group has been studied for eight years. During that time 245 subjects developed CHD as determined by our own clinical examination and from review of all pertinent medical data. Fig 1 shows the eight-year incidence rates of CHD by age and sex. It will be observed that, in accordance with the experience of others, CHD is predominantly a male disease. The increasing rate with age holds for both sexes. It will be seen that for total CHD, women behave similarly to men ten years their juniors.

The basic objective of the Framingham enquiry was to describe the characteristics of persons who were destined to develop CHD during the period of observation and to see in what particulars they differed from the remainder of the population. This can best be done by dividing the population at risk at the time the study began into distinct subgroups, according to the various characteristics to be investigated. The experiences of the different subgroups during the ensuing period of observation can then be compared. This procedure has been followed as regards a number of quantitative variables and it will be seen that certain characteristics are closely related to the risk of developing CHD.

(1) Serum cholesterol level: One of the foremost hypotheses under study was that elevation of serum cholesterol level was associated with an increased risk of development of CHD. The relative risk of developing CHD during the eight years' observation period for the several subgroups of men 30–49 at entry based on serum cholesterol level is presented in Fig 2. It is seen that those men with cholesterol levels above 260 mg% had over twice the risk of developing CHD as compared to the total group, and that those with levels below 220 mg% had less than half the standard risk. The risk increased more than fivefold from low to high levels of serum cholesterol. Fig 3 presents similar observations for men 50–59 at entry. Although the gradient is not as steep, the relationship is similar to that for younger men.

In the female population the effect of serum cholesterol level is evident for the younger group

![Fig 2](image1.png)  
Fig 2 Risk of developing CHD in eight years according to initial serum cholesterol level. Men 30–49 at entry

![Fig 3](image2.png)  
Fig 3 Risk of developing CHD in eight years according to initial serum cholesterol level. Men 50–59 at entry

![Fig 1](image3.png)  
Fig 1 Eight-year incidence of CHD by age and sex: Framingham study group
aged 40–49, but past the age of 50 no risk appeared to be attached to the elevation of serum cholesterol (Fig 4).

It appears therefore that serum cholesterol level is an important factor in estimating the risk of the subsequent development of CHD, and that the higher the level the greater the risk.

(2) Blood pressure level: A second hypothesis which has been advanced is that elevation of blood pressure level increases the risk of subsequent development of CHD. When the population at risk is subdivided according to systolic blood pressure level, it is apparent that both for males and females there is a striking increase in risk of CHD with increasing levels of blood pressure (Figs 5 and 6). A similar but less striking effect is seen if diastolic pressure is used since in the Framingham population there is a high correlation between systolic and diastolic blood pressure. Because there is a wider range in systolic blood pressure and because it is easier to measure it with certainty, the determination of blood pressure subgroups can be more readily accomplished by using systolic rather than diastolic pressures. As with serum cholesterol level it is also evident that blood pressure is of great importance in determining risk of subsequent CHD. No critical level is seen. The higher the blood pressure the greater the risk.

(3) Overweight: Life insurance experience has indicated that excess weight is accompanied by increased mortality from cardiovascular disease. It has been possible to observe the effect of excess weight on the morbidity of CHD in the Framingham population. The population was subdivided according to the relative weight of individuals compared with the median for all subjects of the same height. Figs 7 and 8 show the apparent effects of increased relative weight on the development of CHD. It would seem that only those at the upper end of the relative weight scale have an added risk. When the effect of increased blood pressure and elevated serum cholesterol are eliminated, the effect of excess weight becomes relatively small. It is still possible that persons with marked obesity may be at greater risk, but there were too few such persons in the study to permit any conclusions to be drawn.

(4) Cigarette smoking: The effect of cigarette smoking on the subsequent development of CHD has also been under investigation. The relatively small number of non-smokers of cigarettes in the male population has made it difficult to study this effect until the present analysis. For this purpose the population was subdivided on the basis of their smoking habits as follows: (1) Those who never smoked tobacco in any form. (2) Those who smoked cigars or pipes but not cigarettes. (3) Those who smoked cigarettes but had stopped smoking at entry into the study. (4) Those who smoked cigarettes.
It was observed that there was little difference in the incidence of CHD in the first three of these groups who either had never smoked cigarettes or had already stopped using them. The rates for all three were about half that expected for the standard population. The cigarette smokers, on the other hand, had a greater than standard expectancy of developing CHD. As would be expected from the fact that 67% of the entire population of men smoked cigarettes, the difference between smokers and the entire population was not great. Since it was possible that the different categories of CHD might behave in different ways, these were examined independently. It is seen from Fig 9 that the risk of developing myocardial infarction or of dying suddenly is quite different in the non-smokers of cigarettes, compared with smokers, with more than a twofold increase of risk in the smoking group. Differences in risk of developing angina pectoris between the two groups is not significant.

Interpretation of these data must still be speculative. However, they do suggest that the hazards of cigarette smoking are basically related to the development of myocardial infarction and sudden death. These two aspects of CHD result primarily from the development of thrombotic episodes or the onset of ventricular fibrillation.

Since those cigarette smokers who gave up smoking have the same low rate of development of disease as those who never smoked, it would appear that there is little cumulative effect. The effect of cigarette smoking can be best explained as a relatively immediate one, on persons who already have coronary atherosclerosis of a sufficient degree. Such a concept in turn suggests the wisdom of discontinuing cigarette smoking by persons who have any manifestations of CHD.

(5) Electrocardiographic abnormalities: An appreciable number of persons in the adult population present abnormalities in the ECG not diagnostic of CHD. Possibly the most important of these is the pattern of left ventricular hypertrophy (LVH). When persons with this abnormality are studied, it is observed that they develop CHD much more frequently than those without it. Fig 10 indicates the added risk of CHD development in both males and females with the finding of LVH by ECG. Since LVH is also associated with hypertension, it was necessary to look at this finding in persons with different blood pressure levels. When this was done, the
added risk of LVH for any blood pressure group was evident (Fig 11).

(6) Vital capacity: Although observations of the vital capacity of subjects in the study were made originally in the belief that changes in vital capacity might reflect early evidence of congestive heart failure, when this characteristic was used as a predictor of CHD, an interesting relationship was observed. When the population of males is subdivided according to vital capacity determinations it is seen that those men with vital capacity levels below 3 litres had about twice the risk of developing CHD as those with vital capacity measurements of 4 litres or above (Fig 12). An explanation of the relationship between vital capacity and development of CHD has not as yet been clarified.

Combination of Risk Factors
When more than one of these factors is present, the risk of developing CHD increases still further. By selecting groups of individuals with certain combinations of high risk characteristics, it is possible to describe a small segment of the population which is at excessively high risk of developing CHD. An example of the effect of the combination of several risk factors is presented in Fig 13 which compares the relative risk of men 30–59 in terms of their cholesterol levels, blood pressure, and cigarette smoking habits. It is clear that men with low serum cholesterol levels and low blood pressure, who do not smoke cigarettes, have less than a third the standard risk. When all three factors are present the risk goes up over tenfold. In this way it is possible to determine the relative susceptibility to CHD of various subgroups of the population based on the presence of one or more of the high risk characteristics.

Discussion
It is believed that the Framingham enquiry and other similar investigations have demonstrated beyond question that certain characteristics are associated with the development of coronary heart disease (Kannel et al. 1961, Doyle et al. 1957, Keys et al. 1962, Chapman et al. 1957).

With the exception of the suggested benefit of the cessation of cigarette smoking no evidence is presented which directly bears on the effects of changing any of the characteristics mentioned. It seems reasonable to believe that influencing blood pressure, blood cholesterol level, obesity, and smoking habits in a favourable direction by whatever means possible may be beneficial. If the influence can be exerted when the subject is still young, it would seem even more reasonable to expect a beneficial effect on the development of atherosclerotic vascular disease. If the factors mentioned affect the development of thrombotic complications their change at any age may still be of value.

The need for further applied epidemiologic research to determine the effects of change in any

1 For purposes of this analysis "low" refers to the group in the lowest quartile of the distributive curve
of the above-mentioned factors is obvious. Meanwhile, since the procedures advocated are not considered hazardous, it seems reasonable to recommend that persons with high risk characteristics should attempt to change them in a favourable direction.

Summary and Conclusions
(1) Evidence has been presented demonstrating that elevated serum cholesterol level, elevated blood pressure, obesity, cigarette smoking, and low vital capacity are associated with an increased risk of developing coronary heart disease.

(2) Combinations of risk factors further augment susceptibility making it possible to select subgroups of the population at particularly high risk of developing coronary heart disease. Estimates of the magnitude of risk are presented.

(3) Although evidence is still lacking that favourable change in these factors is necessarily beneficial, it is suggested that such an assumption is reasonable.

REFERENCES

Arteriosclerosis: Clinical Surveys in Finland
by M J Karvonen MD PhD (Helsinki, Finland)

Existing Epidemiological Information
The most important sources of epidemiological information have been and still are the mortality statistics. According to these, atherosclerotic diseases, particularly coronary heart disease (CHD), are common among all nations belonging to Western civilization. The coronary mortality of a nation generally is roughly related to the national wealth or to several indicators of it.

Finland shares with the Anglo-Saxon countries the top places on the list, with an incidence of coronary deaths (International List, Sixth Revision, Nos. 420–422 Chron. World Hlth Org. (1958)) which seems even to exceed that in the United States. This appears somewhat puzzling, since Finland is by no means one of the leading countries in the economic sphere. It is noteworthy that the Scandinavian neighbours of Finland – Sweden, Norway and Denmark – show considerably smaller coronary mortality than Finland, particularly among middle-aged men, although these countries have been ahead of Finland in their general economic development.

A regional analysis of mortality within Finland has brought out interesting differences (Kannisto 1947): the coronary mortality is highest in the east and lowest in the south-west. The latter is a relatively rich agricultural area, while forestry is the main source of income in the east; there the majority of men are rather poor smallholders who do farming in the summer and woodcutting in the winter. While international comparisons of mortality statistics suffer from many sources of error, a comparison within a country may be more reliable. An analysis of death certificates according to several factors which might be responsible for ‘artificial’ regional differences in coronary mortality has not yielded any obvious explanation (Teir & Kankaanpää 1961, personal communication).

A similar difference in the prevalence of cardiovascular disease is also shown by the existing morbidity statistics. The State Pension Office pays pensions to those disabled by cardiovascular disease considerably more often in the east than in the south-west of Finland. In other major diagnostic entities, regional differences, if any, are much less marked (Kansaneläkelaitos 1956).

Clinical surveys
Even if there is no reason to suspect a systematic bias in the existing mortality and morbidity statistics, the basic sources of information are often unreliable. To obtain more accurate data, special surveys are needed. Two such studies have been carried out in Finland, the first in 1956 and the second in 1959. Both were planned as a part of an international co-operative study, directed by Professor Ancel Keys of the University of Minnesota. The aims were (1) to compare within Finland two regions of widely different mortality records, and (2) to obtain data which may be used for international comparisons. The first survey was a study of 869 ostensibly healthy men, aged 20 to 59, and its primary purpose was to characterize the ‘normal’ population as regards several parameters (Rautaharju et al. 1961). The second was a ‘total population’ study of all men from 40 to 59 years old, living in selected regions. A total of 1,677 men was examined in two regions. This was 97–98% of the total male population in this age range living in the areas chosen. A thorough clinical examination was made and the results were recorded on standardized forms. Four clinicians shared this work, two of them working in both areas. The number of