Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience

The Framingham Study

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INCREASINGLY RELIABLE ESTIMATES of the prevalence and incidence of coronary heart disease (CHD) emphasize the importance of this disease as a contemporary health hazard. Cardiovascular disease is now the leading cause of death, with coronary heart disease accounting for two-thirds of all heart disease deaths. While advances in the diagnosis and therapeutic management of CHD have been made in the past decade, no important reduction in morbidity and mortality from CHD has occurred. This is apparent in the relatively slight increase in life expectancy at age 40 which has been achieved in the past several decades, while life expectancy at birth has been substantially prolonged.

Because coronary heart disease is often manifested as sudden unexpected death or "silent" infarction and since the immediate mortality in those surviving to enter a hospital is still distressingly high in spite of the best therapeutic efforts, it appears that a preventive program is clearly necessary. Since it has been established that coronary atherosclerosis is present for many years prior to the development of symptomatic CHD, it seems evident that efforts at prevention must begin many years before the appearance of clinical CHD. A knowledge of the epidemiology of the disease is highly desirable if a program of prevention is to be developed. From a study of the characteristics of persons who develop coronary heart disease under observation in comparison with those who remain free of disease it is possible to determine the characteristics of susceptible individuals. This allows the identification of the coronary prone individual many years before the occurrence of clinically recognizable disease.

Multiple interrelated factors have been demonstrated to be associated with increased risk of development of CHD. To date no single essential factor has been identified. However, epidemiologic information has accumulated which now allows the physician to recognize certain characteristics of increased risk in patients he sees in his practice. Some of these characteristics have been convincingly demonstrated, others are still under investigation. More precise identification will undoubtedly be possible in the future.

The present report deals with three characteristics believed to be associated with proneness to the development of CHD: elevated serum cholesterol levels, hypertension, and the electrocardiographic pat-

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tern of left ventricular hypertrophy. These characteristics have been demonstrated to be associated qualitatively with the development of CHD in a previous report (1). No precise estimate of the magnitude of the increased risk could be made at that time. The present report represents two more years of observation and allows more detailed analysis of these factors as they affect both men and women. Sufficient data have now been accumulated to permit quantitative estimation of the increase in risk associated with these characteristics singly and in combination.

Because of the apparent need to obtain more epidemiologic data in coronary heart disease, a study was established in Framingham, Massachusetts, during the period 1948 to 1950. The Framingham Study was designed to investigate the incidence of cardiovascular disease and factors related to its development. Details of the organization and first four-year follow-up experience have been previously reported (1–5).

Methods

A description of the town of Framingham, the method of selection of the study population, and the response of selected persons has been previously reported (1, 5, 6). Of the 6,507 persons selected at random, 4,469 persons aged 30 to 59 came in for examination and comprised the sample population. An additional 740 persons who volunteered to cooperate in the Study have also been included. The rationale for including the group of volunteers has been discussed elsewhere (1, 5). While the sample and volunteer groups differ in a number of minor particulars, none of the recorded differences appears to present any difficulties in analysis (5). The incidence of new coronary heart disease in the two groups is very similar. Accordingly, these two groups have been combined.

All subjects have been examined in a clinic set up for the Study. A detailed history and a physical examination were completed by a physician assigned to the Study and the findings were entered on standard forms. If any possibility of the new development of CHD was considered, the opinion of a second physician was obtained. Laboratory studies included chest X ray, electrocardiogram, vital capacity determination, urinalysis, hemoglobin, hematocrit, blood glucose, uric acid, lipoproteins, cholesterol, phospholipid, and other special studies.

Upon completion of each examination a diagnosis was made using uniformly applied criteria as indicated below. An abstract of the findings was sent to the personal physician indicated by the subject. No medical advice was provided to any participant beyond encouragement to visit his physician if the need was indicated.

Criteria for Coronary Heart Disease

The criteria used for the classification of coronary heart disease in the Framingham Study are based upon those recommended by the New York Heart Association (7).

1. Angina pectoris: Minimal criteria for the diagnosis of angina pectoris consisted of substernal discomfort of brief duration (i.e., two to three minutes), definitely related to exertion or emotional upset, promptly relieved by rest, and seldom if ever occurring during periods of quiet or rest. The diagnosis was made when symptoms were sufficiently clear cut to allow at least two observers to agree readily as to its presence. Because of the subjective nature of this diagnosis, no possible or questionable instances are included in the group designated as having coronary heart disease.

2. Myocardial infarction: This diagnosis was made only in the presence of electrocardiographic changes of infarction.* All

* Recent or acute myocardial infarction was designated when S-T segment elevation was present associated with late inversion of T waves and the occurrence of loss of initial QRS potentials (i.e., development of "pathological" Q waves of four

TABLE 1. Composition of Framingham Study Group

	Total	Men	Women
Random sample	6,507	3,074	3,433
Respondents	4,469	2,024	2,445
Volunteers	740	312	428
Respondents free of CHD*	4,393	1,976	2,417
Volunteers free of CHD	734	307	427
Total free of CHD: Framingham Study Group	5,127	2,283	2,844

* Coronary heart disease.

hospital records and electrocardiograms were reviewed by the Study personnel. In cases that lacked a history, the development of an unequivocal pattern of myocardial infarction since the previous electrocardiographic tracing was obtained, was accepted as evidence of an unrecognized myocardial infarction. In addition, for the purpose of the present analysis, instances of prolonged acute coronary insufficiency with associated electrocardiographic abnormality were included in this category.

3. Sudden death: This was considered to be due to CHD when it was documented to have occurred in a matter of minutes and was attributed to no other cause by the physician who completed the death certificate and when no other cause of death was suggested by prior medical history. All death certificates and information available regarding the death of the patient were reviewed by clinic personnel.

Whenever available, autopsy information was utilized only to confirm the clinical diagnosis of CHD. The autopsy rate was not high enough to use post-mortem findings as a basis for diagnosis.

hundredths of a second duration or greater), followed by serial changes of evolution if available.

An old or remote myocardial infarction was considered to be present when there was a pathological Q wave of four hundredths of a second duration or greater, or loss of initial QRS potential (R-wave) in those leads in which this would not be expected to occur. This electrocardiographic diagnosis was also considered when changes from a previous tracing indicated a loss of R wave potential previously present and not otherwise explained. More weight was given to this finding if T wave abnormality was also associated. In all instances electrocardiograms antedating the event were available for comparison, a factor of considerable assistance in evaluating patterns of old myocardial infarction.

COMPOSITION OF STUDY GROUP

Table 1 shows the composition of the population being observed for the development of coronary heart disease. The population at risk of developing CHD consisted of those persons who were free of this disease at the initial examination. Of the 6,507 persons selected for study, 4,469 responded and were examined. Of these, 4,393 were found to be free of CHD and were suitable for follow-up study. Of the 740 volunteers, 734 were free of disease. Thus, a group of 5,127 persons free of CHD on entry to the study could be periodically re-examined for the subsequent development of disease; they constituted the Framingham Study Group.

FOLLOW-UP

Of the original study group it was possible to re-examine 87% at the clinic on the fourth biennial examination or later (Table 2). Another 2.4% are known to have died before their fourth examination was due. For this group the cause of death has been ascertained and in each instance

TABLE 2. Six-Year Follow-Up: Framingham Study Group

	Number	Per Cent
Framingham Study Group	5,127	100.0
Examined at clinic at Exam IV*	4,478	87.3
Not examined at clinic at Exam IV*	649	12.7
Dead before Exam IV*	122	2.4
Alive at Exam IV*	523	10.2
Unknown whether alive or dead	4	0.1

* Fourth biennial examination.

TABLE 3A. Six-Year Incidence of CHD* by Age and Sex

Age at Entry	Framingham Study Group		Sample Respondents		Volunteers	
	New CHD	Population at Risk	New CHD	Population at Risk	New CHD	Population at Risk
Men	125	2,283	106	1,976	19	307
30–34	5	388	4	333	1	55
35–39	11	438	9	388	2	50
40–44	15	420	13	357	2	63
45–49	15	352	14	308	1	44
50–54	27	353	19	301	8	52
55–59	41	262	36	221	5	41
60–62	11	70	11	68	—	2
Women	61	2,844	52	2,417	9	427
30–34	—	453	—	388	—	65
35–39	—	582	—	489	—	93
40–44	3	508	3	433	—	75
45–49	16	446	13	376	3	70
50–54	14	421	10	357	4	64
55–59	24	371	22	313	2	58
60–62	4	63	4	61	—	2

* Coronary heart disease.

documentation has been sought to determine whether coronary heart disease had developed by the time of death. From observation of the population at subsequent examinations at the clinic, routine surveillance of admissions to the local hospitals, and inquiries made of friends and relatives appearing at the clinic for examination it was possible to reach a conclusion about the state of health with respect to CHD for another 10.2%. In many instances the physicians of the community, knowing of our interest in the problem, have advised us of the development of new disease in our subjects. It is considered to be unlikely that a significant number of new events of CHD have been missed in the six years of follow-up.

RESULTS

INCIDENCE AND CLINICAL MANIFESTATION OF HEART DISEASE IN SIX YEARS OF OBSERVATION

The incidence of coronary heart disease (defined above as myocardial infarction, angina pectoris, and sudden death) is shown in Tables 3 A and B. The population at risk for this observation was composed of all subjects found to be free of CHD at entry into the Study. There were 186 men and women free of definite CHD at the first examination who developed the disease in the subsequent six years of observation. This represents an over-all six-year incidence of 36.3 per thousand in the age groups under study. The six-year incidence of coronary heart disease in the men was 54.8 per thousand as compared with 21.4 per thousand in the women. In the younger age group (30 to 44 years) there was an incidence of 1.9 per thousand in women as compared with 24.9 per thousand in men (a thirteenfold difference). In the older age group (45 to 62 at entry into the Study) this sex ratio becomes attenuated to only a twofold difference with an incidence of 90.6 per thousand in men as compared with 44.6 per thousand in women. As indicated in Table 4, 24 of the 88 men who developed myocardial infarction* died suddenly.

* All sudden deaths are considered to be myocardial infarctions.

TABLE 3B. Six-Year Incidence Rate of New CHD by Age and Sex

Age at Entry	Rate per 1,000 Population		
	Framingham Study Group	Sample Respondents	Volunteers
Men	54.8	53.6	61.9
30–44	24.9	24.1	29.8
45–62	90.6	89.1	100.7
Women	21.4	21.5	21.1
30–44	1.9	2.3	0
45–62	44.6	44.3	46.4

Of these, 15 (62.5%) had no previous evidence of CHD and this constituted the only known manifestation of the disease. Seven of the men who suffered myocardial infarction had no clinical evidence of the event other than the development of characteristic electrocardiographic evidence of infarction, and the disease would have been undetected unless periodic routine electrocardiograms were undertaken in apparently well individuals. Three of 19 women who suffered myocardial infarction manifested the disease as sudden death. All of these occurred as the first reported manifestation of CHD.

There is clearly a difference in the predominant clinical manifestation of coronary heart disease in the sexes (Table 4). The CHD appearing in the women was predominantly angina pectoris without associated myocardial infarction (69%). This is in contrast to the men in whom angina pectoris without associated myocardial infarction constituted only 30% of the coronary heart disease developing in the six years of observation. Among all cases of

TABLE 4. Clinical Manifestations of CHD Developing in Six Years of Follow-Up

Clinical Manifestation	Number		Per Cent	
	Men	Women	Men	Women
Total CHD	125	61	100.0	100.0
Definite myocardial infarction by history and ECG*	57	14	45.6	23.0
With AP†	32	7		
Without AP†	25	7		
Definite myocardial infarction by ECG only	7	2	5.6	3.3
Sudden death	24	3	19.2	4.9
With pre-existing MI‡	3	—		
With pre-existing AP†	6	—		
Without pre-existing CHD	15	3		
Definite angina pectoris	37	42	29.6	68.8

* Electrocardiogram.
† Angina pectoris.
‡ Myocardial infarction.

TABLE 5. Mean Serum Cholesterol at Initial Examination: Comparison New CHD and Population at Risk

Age at Entry	Number		Mean		Standard Deviation of Population
	New CHD	Population at Risk	New CHD	Population at Risk	
Men					
30–34	5	375	257*	219	45
35–39	11	419	267*	222	42
40–44	14	402	259*	229	46
45–49	14	341	250*	231	37
50–54	27	338	245*	227	40
55–59	41	252	248*	229	43
Women					
40–44	3	480	316*	222	39
45–49	14	423	286*	240	48
50–54	13	403	239	250	46
55–59	24	355	260	258	48

* Significantly elevated (at the 5% level) compared with population at risk.

CHD, myocardial infarction with or without associated angina pectoris occurred as the manifestation of CHD approximately twice as frequently in the male coronary subjects as in the female. The incidence of angina pectoris in subjects with myocardial infarction, however, is about the same in the sexes.

SERUM CHOLESTEROL

The data presented here are based on determinations of serum cholesterol which were made in the Framingham Laboratory by the method of Abell, Levy, Brodie, and Kendall (8). During the period when much of the data was being collected, the laboratory standardized its results by exchange

TABLE 6. Six-Year Incidence of CHD According to Initial Serum Cholesterol Level: Ages 40–59

Serum Cholesterol (mg/100 ml)	New CHD	Population at Risk	Incidence Rate per 1,000 Population	
			Observed	Expected*
Men, 40–59	96†	1,333	72.0	70.6
Less than 210	16	454	35.2‡	69.4
210–244	29	455	63.7	70.8
245 or more	51	424	120.3‡	71.8
Women, 40–59	54†	1,661	32.5	32.7
Less than 210	8	445	18.0	25.2
210–244	16	527	30.4	31.3
245 or more	30	689	43.5	38.7

* Expected rate is calculated by applying age-sex-specific incidence rates (five-year age interval) in the Framingham Study Group to the population in the specified category of sex and cholesterol.

† Total number of new cases of CHD and the population at risk varies in different tabulations since it was not possible to obtain blood specimens on every subject.

‡ Significantly different (at the 5% level) from the expected rate.

TABLE 7A. Mean Systolic and Diastolic Blood Pressures at Initial Exam. Comparison of New CHD and Population at Risk

Age and Sex	Number of Persons		Systolic Blood Pressure			Diastolic Blood Pressure		
			Mean		Standard Deviation, Population	Mean		Standard Deviation, Population
	New CHD	Population at Risk	New CHD	Population at Risk		New CHD	Population at Risk	
Men								
30–34	5	388	128	131	16	83	83	11
35–39	11	438	144*	132	17	95*	85	12
40–44	15	420	133	135	18	90	87	12
45–49	15	352	144	138	21	93*	88	12
50–54	27	353	148*	140	22	90	89	13
55–59	41	262	162*	145	27	96*	88	15
Women								
40–44	3	508	125	131	20	81	83	12
45–49	16	446	158*	142	24	97*	87	12
50–54	14	421	171*	150	30	96	90	14
55–59	24	371	178*	154	31	100*	91	15

* Significantly elevated (at the 5% level) compared with population at risk.
Note: Blood pressures are available for everyone in the Study Group. This is not true for other measures.

of serum lipids with the four laboratories participating in the Cooperative Lipoprotein Study (9).

Higher mean cholesterol levels were demonstrated among subjects who developed coronary heart disease than in the population at risk (Table 5). This indicates an association between serum cholesterol levels and the subsequent development of CHD. In men, serum cholesterol levels tended to be higher for those who subsequently developed CHD in the six years of observation than in the population at risk. This elevation was most marked for men in the youngest age group and diminished with age. Beyond age 59 there were too few persons in the Study for analysis.

The risk associated with serum cholesterol level was analyzed in men in the broad age group, 40 to 59 years at entry into the Study (Table 6). Separation of the men in the population at risk into three categories according to increasing levels of serum cholesterol yields groups of similar size when dividing points are made at levels of 210 and 245 mg per 100 ml. Analysis of these groups reveals a gradient of risk of developing CHD with increasing levels of serum cholesterol, such that those with serum cholesterols over 244 mg per 100 ml have more than three times the incidence of CHD as do those with cholesterol levels less than 210 mg per 100 ml (Table 6). This cannot be attributed to aging within the group studied since no significant gradient of serum cholesterol with age can be demonstrated in men (Table 5). In evaluating the risk associated with elevation of serum cholesterol levels it is important to recognize that in the Framingham population the reference base for serum cholesterol (i.e., "normal" cholesterol) may be high when compared with some other populations in which lower rates of CHD have been claimed.

Since no new coronary heart disease developed in women less than 40 years of age at entry into the Study, no analysis of the association of serum cholesterol level with the risk of CHD was possible. A significant elevation of mean serum cholesterol is evident for women 40 to 49 years old who de-

TABLE 7B. Mean Systolic and Diastolic Blood Pressures at Initial Exam: Comparison of New CHD and Population at Risk, Framingham Study Group Without Left Ventricular Hypertrophy by Electrocardiogram

Age and Sex	Number of Persons		Systolic Blood Pressure			Diastolic Blood Pressure		
			Mean		Standard Deviation, Population	Mean		Standard Deviation, Population
	New CHD	Population at Risk	New CHD	Population at Risk		New CHD	Population at Risk	
Men								
30–34	4	382	128	131	15	84	82	10
35–39	11	426	144*	132	16	95*	84	11
40–44	14	407	133	135	17	90	87	12
45–49	14	336	140	137	20	91	87	11
50–54	24	337	145	139	21	90	88	13
55–59	31	238	158*	143	25	92*	87	14
Women								
40–44	3	501	125	130	19	81	83	12
45–49	15	439	157*	141	23	96*	87	12
50–54	13	397	164*	147	26	93	90	13
55–59	21	357	173*	152	29	97*	90	15

* Significantly elevated (at the 5% level) compared with population at risk.
Note: Blood pressures are available for everyone in the Study Group. This is not true for other measures.

veloped coronary heart disease but not for women 50 to 59 years old (Table 5). However, a significant (although not striking) gradient of risk with increasing cholesterol levels could be demonstrated for the entire group of women aged 40 to 59 years (Table 6).

BLOOD PRESSURE AND ASSOCIATED CHARACTERISTICS

It was evident on the basis of the four-year follow-up experience that elevation of blood pressure was associated with an increased risk of the development of CHD among men 45 to 62 years of age (1). The occurrence of additional cases of new CHD during two more years of observation permits the analysis of this factor to be extended to younger men and to women.

In Tables 7A and B are shown the mean blood pressures of the population at risk (those free of coronary heart disease at the initial examination) and of those of the group who developed CHD during the six years of observation. Among both men and women aged 45 to 59 years on entry, blood pressures, either systolic or diastolic, were significantly higher in the group who subsequently developed CHD than in the whole population at risk. Outside of this age range, the association of elevated blood pressure levels with CHD is not consistently significant. As indicated in Table 8 progressive degrees of blood pressure elevation were associated with increased risk of the subsequent development of CHD. Hypertension associated with the electrocardiographic pattern of left ventricular hypertrophy (LVH by ECG) was associated with a higher incidence of coronary heart disease than was hypertension alone.

It was not possible on the basis of the data to assign greater importance to the diastolic than to the systolic blood pressure level as a predictor of subsequent coronary heart disease. This can be explained by the high correlation between systolic and diastolic blood pressure. Two other values of blood pressure measurement, pulse pres-

sure and systolic lability, were also considered. Both of these measures varied with the level of systolic pressure and both were higher in the coronary group than in the population as a whole. Elevation of either measure, however, did not contribute independently to the risk of subsequent CHD. As previously noted, the electrocardiographic finding of left ventricular hypertrophy is associated with an unusually high risk of the subsequent development of CHD among men age 40 to 59 years (Table 8). Within six years one-third of the men 40 to 59 years of age with this finding had developed overt CHD, as had one-fifth of these men with "possible" LVH by electrocardiogram. The relative infrequency of CHD among women and among younger men during the six years of observation precluded the demonstration of a comparable association among them, though the data are suggestive for older women.

Several possible explanations for the high incidence of coronary heart disease associated with left ventricular hypertrophy by ECG are suggested. It is possible that the group with this finding includes a sizable proportion with subclinical CHD at entry. This might happen if electrocardiographic evidence of LVH masked evidence of CHD in the ECG or if the electrocardiographic patterns for the two conditions could be confused. It could also happen if, in fact, the LVH pattern was an indicator of CHD. These possibilities led to a preliminary analysis excluding persons with left ventricular hypertrophy by electrocardiogram from the population at risk. The effect of this on the analysis of blood pressure can be judged by com-

TABLE 8. Six-Year Incidence Rate of CHD by Blood Pressure Category and Electrocardiogram of Left Ventricular Hypertrophy: Ages 40 to 59

Sex, Hypertensive Status, ECG Evidence of LVH*	Number of Persons		Incidence Rate per 1,000 Population	
	New CHD	Population at Risk	Observed	Expected
Men, 40 to 59	98	1,387	70.7	70.7
Normotension	23	556	41.4	68.8
Borderline hypertension	38	532	71.4	68.6
Definite hypertension	37	299	123.7	77.8
Definite hypertension and ECG evidence:				
No LVH	27	265	101.9	75.8
Possible LVH	3	15	200.0	78.4
Definite LVH	7	19	368.4	105.1
Women, 40 to 59	57	1,746	32.6	32.6
Normotension	6	704	8.5	26.5
Borderline hypertension	20	647	30.9	35.0
Definite hypertension	31	395	78.5	39.8
Definite hypertension and ECG evidence:				
No LVH	26	357	72.8	40.0
Possible LVH	1	19	52.6	34.6
Definite LVH	4	19	210.5	42.2

* Left ventricular hypertrophy.

Note: Expected rate is calculated by applying the age-sex-specific incidence rates (in five-year age intervals) of the Framingham Study Group to the population in the specified sex-hypertension LVH category.

TABLE 9. Mean Systolic and Diastolic Blood Pressures According to Presence or Absence of ECG Evidence of LVH at Initial Examination: Men Aged 45 to 62

ECG Evidence of LVH	New CHD	No CHD
	Mean Systolic Pressure	
Total	154	140
Definite or possible LVH	171	162
No LVH	149	139
	Mean Diastolic Pressure	
Total	93	87
Definite or possible LVH	100	98
No LVH	91	87
	Number of Men Aged 45–62	
Total	94	943
Definite or possible LVH	18	45
No LVH	76	898

paring the results displayed in Table 7A with those in Table 7B. There is a very slight reduction in the association between CHD and blood pressure when the group having LVH by ECG is excluded from the analysis. In general, the omission of this group from the analysis of the factors related to the development of coronary heart disease under consideration in this paper had only a minor effect.

Another possibility which may explain the association of left ventricular hypertrophy by electrocardiogram with the development of CHD is a strong inter-relationship between the electrocardiographic pattern and hypertension. The electrocardiographic abnormality may well reflect either long standing or severe degrees of hypertension. Among the men without LVH by ECG, those who developed coronary heart disease had blood pressures which were higher on the average by 10.4 mm systolic and by 3.9 mm diastolic compared with those who did not develop CHD (Table 9). A similar elevation of blood pressure in those who developed CHD is found within the group of men with definite or possible LVH by ECG. This indicates that blood pressure is associated with the risk of developing coronary heart disease independently of the presence or absence of left ventricular hypertrophy by electrocardiogram.

Whether left ventricular hypertrophy by electrocardiogram is associated with the risk of developing coronary heart disease independently of blood pressure levels is not as easily evaluated. Blood pressures are much higher in the small group with LVH by ECG than in those without it, and this in itself should enhance the risk of developing CHD. How much of the excess risk associated with the electrocardiographic finding is accounted for by elevated blood pressure is difficult to judge because of the small number of cases and because of the large sampling variability in incidence rates among men with this electrocardiographic finding. However, reference to Table 10 indicates the effect of left ventricular hypertrophy by electrocardiogram in blood pressure diagnostic categories. It can be seen that at each diagnostic blood pressure category, the presence of LVH by ECG is associated with an excess incidence of coronary heart disease. Left ventricular hypertrophy by ECG appears to make an

TABLE 10. Six-Year Incidence of CHD According to Hypertensive Status and ECG Evidence of LVH at Initial Exam: Men Aged 40 to 59

Hypertension	LVH Present	LVH Absent
	Incidence Rate per 1,000	
None	200.0	38.5
Borderline	120.0	69.0
Definite	294.1	101.9
	New CHD	
None	2	21
Borderline	3	35
Definite	10	27
	Population at Risk	
None	10	546
Borderline	25	507
Definite	34	265

Note: LVH means definite or "possible" left ventricular hypertrophy.

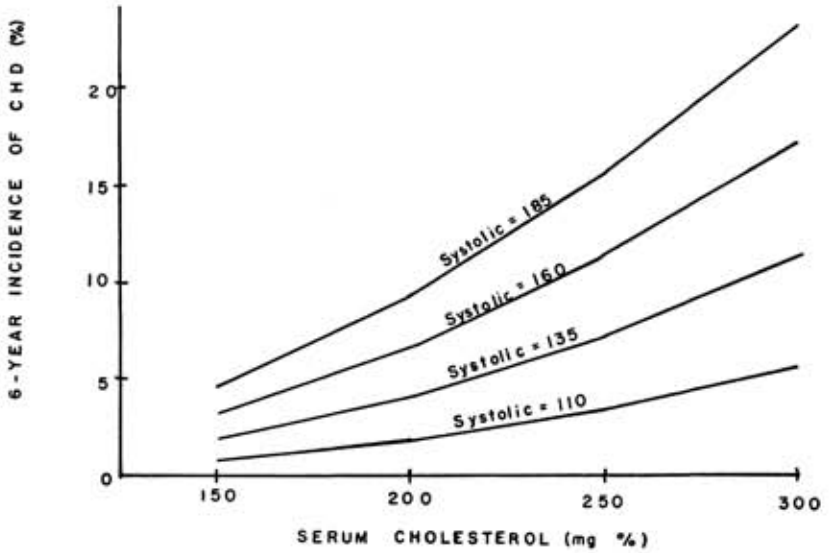

FIGURE 1. Six year incidence of coronary heart disease according to serum cholesterol levels at specified systolic blood pressures (men 45 to 62 years). These curves are based on the following assumptions: (1) The joint distribution of the logarithms of blood pressure value minus 75 and cholesterol value is bi-variate normal within both the coronary heart disease and non-coronary heart disease groups; (2) The variance-covariance matrices in the coronary heart disease and non-coronary heart disease groups are equal (14).

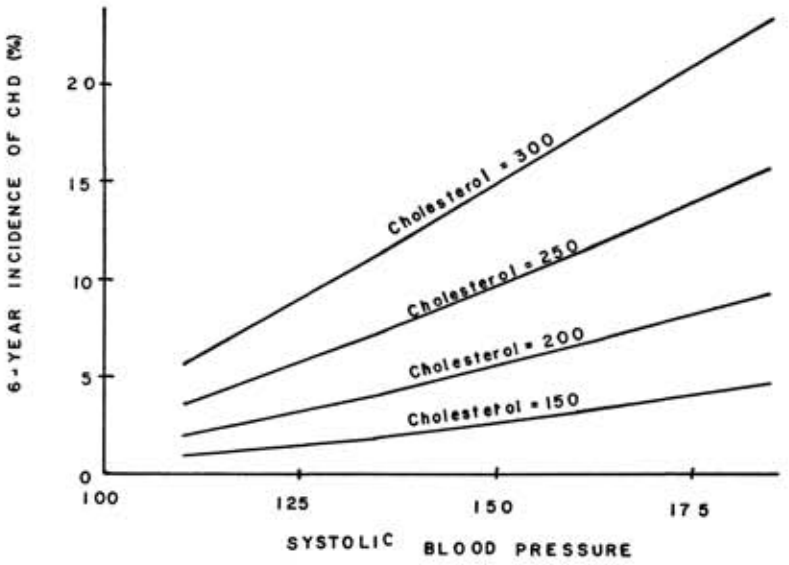

FIGURE 2. Six-year incidence of coronary heart disease according to level of systolic blood pressure at specified serum cholesterol levels (men 45 to 62 years). For explanation, see legends for Figure 1.

TABLE 11. Six-Year Incidence of CHD, According to Combinations of Blood Pressure, Serum Cholesterol, and ECG Evidence of LVH at Initial Exam: Ages 40–59

Sex and Combinations of Blood Pressure, Serum Cholesterol, and ECG Evidence of LVH	Population at Risk		New CHD	Incidence Rate per 1,000 Population	
	Number	Per Cent		Observed	Expected
Men, 40 to 59	1,333	100.0	96	72.0	70.6
Normal* on all three	811	60.8	29	35.8	67.5
Abnormal* on one only	416	31.2	43	103.4	73.6
Blood pressure	186	14.0	17	91.4	76.8
Cholesterol	207	15.5	25	120.8	70.4
LVH	23	1.7	1	43.5	76.4
Abnormal* on two only	98	7.4	20	204.1	81.4
BP and cholesterol	65	4.9	10	153.8	74.1
BP and LVH	25	1.9	6	240.0	87.7
Cholesterol and LVH	8	0.6	4	500.0	121.4
Abnormal* on all three	8	0.6	4	500.0	102.9
Abnormal* on two or three	106	8.0	24	226.4	83.0
Women, 40 to 59	1,661	100.0	54	32.5	32.7
Normal* on all three	888	53.5	15	16.9	27.2
Abnormal* on one only	597	35.9	24	40.2	38.1
Blood pressure	206	12.4	14	68.0	38.0
Cholesterol	382	23.0	10	26.2	38.2
LVH	9	0.5	—	0	37.9
Abnormal* on two only	162	9.8	13	80.2	42.1
BP and cholesterol	134	8.1	10	74.6	43.3
BP and LVH	23	1.4	3	130.4	35.8
Cholesterol and LVH	5	0.3	—	0	39.5
Abnormal* on all three	14	0.8	2	142.9	42.7
Abnormal* on two or three	176	10.6	15	85.2	42.2

* Abnormal blood pressure is defined as definite hypertension, abnormal cholesterol is a serum cholesterol reading of 260 mg/100 ml or higher, and abnormal LVH is a diagnosis of possible or definite LVH on the electrocardiogram. "Normal" means not abnormal; it includes normotension and borderline hypertension, serum cholesterol less than 260 mg/100 ml, no LVH by ECG.

independent contribution to the risk of development of CHD, increasing the risk of development of coronary heart disease two to threefold when blood pressure is held constant. Because of the small numbers it was necessary to examine the broad age group 40 to 59 years in men and hence it is not possible to assess completely the possible effect of age.

INTERACTION OF HYPERTENSION, HYPERCHOLESTEROLEMIA, AND THE ELECTROCARDIOGRAPHIC PATTERN OF LEFT VENTRICULAR HYPERTROPHY

Data already presented indicate that hypertension, hypercholesterolemia, and the electrocardiographic pattern of left ventricular hypertrophy are each associated with an increased risk of the development

of CHD in men 40 to 59 years of age. It has been previously shown (1) that there is almost no correlation between serum cholesterol level and diastolic or systolic blood pressure. Left ventricular hypertrophy by ECG is strongly associated with hypertension, and has been shown to contribute to risk of development of CHD (Tables 8 and 9). At each level of blood pressure in hypertensives the presence of LVH is associated with a two to threefold increase in incidence of CHD (Table 10). Consequently each of these characteristics would be expected to contribute to the risk of development of CHD and combinations of these factors could be expected to augment the risk. From Figures 1 and 2 it can be seen that the incidence of CHD does indeed rise progressively with increasing levels of both blood pressure and serum cholesterol and that a combination of these two factors further augments the risk. In Table 11 the six-year incidence of coronary heart disease in persons having various combinations of these three characteristics is given. Men aged 40 to 59 years, normal in all these characteristics, had a six-year incidence of CHD of only 35.8 per thousand. When abnormal with respect to one of these characteristics the risk almost tripled (103.4 per thousand). If abnormal in two of these characteristics the six-year incidence climbs to 204.1 per thousand, approximately doubling the risk associated with abnormality in one characteristic. Abnormality in all three characteristics probably again doubles the incidence, but because of small numbers available and sampling variability, it is not possible to assess this risk reliably. Abnormality of two or more of these risk characteristics is associated with a six-year incidence of 226.4 per thousand. Approximately the same magnitude of compounding of risk associated with these characteristics (hypertension, hypercholesterolemia, and the ECG pattern of left ventricular hypertrophy) is seen in women 40 to 59 years of age. The incidence rates are generally lower, women normal in all three characteristics having an incidence of 16.9 per thousand, rising to 40.2 per thousand when abnormal in only one characteristic, and doubling to 80.2 per thousand when two abnormal characteristics are present. When two or more factors are abnormal, a six-year incidence of 85.2 per thousand is noted.

These risk characteristics are found with some frequency in the population: 39% of men and 46% of women 40 to 59 years of age have at least one of these abnormal characteristics, while 8% of men and 11% of women have two or more of these abnormal characteristics.

Discussion

The rarity of coronary heart disease in the younger female (two per thousand) is in sharp contrast to the incidence of this disease in the male of the same age (25 per thousand) as indicated in Table 3B. This sex differential is greater than the differences in incidence produced by any other factor thus far investigated in this disease. Clearly, any statement regarding the etiology of CHD will have to explain the sex ratio. This also indicates a fruitful area for research into the pathogenetic mechanism of this disease. The gap between the sexes closes after age 45 so that only a twofold difference exists. This strongly suggests, among other things, an endocrine influence related to the menopause.

Not only the incidence, but the clinical manifestation of CHD appeared to differ markedly in the sexes (Table 4). Coronary heart disease in the female is manifested chiefly as angina pectoris. Seventy per cent of all CHD occurring in females exhibited this manifestation. In the male, on the other hand, the disease is manifested chiefly as myocardial infarction or sudden death with only 30% exhibiting angina pectoris alone. The percentage of sudden death in men (19.2%) greatly exceeded that in women (4.9%). Myocardial infarction was

approximately twice as frequently exhibited by men. It thus appears that the seriousness of the disease developed in the two sexes as well as the incidence differs markedly.

On the basis of clinical studies it is commonly believed that angina pectoris occurs predominantly in males (10). Data presented in Table 4 indicate that if all cases of angina pectoris occurring in a community are considered, rather than only those presenting themselves for medical care, angina pectoris is as common in the female as in the male. In six years of follow-up of persons initially free of CHD 124 cases of angina pectoris developed. In 79 instances this occurred alone, in 39 instances the angina was associated with myocardial infarction, and in six instances it antedated sudden death. Of the 79 instances of angina pectoris unassociated with myocardial infarction 42 occurred in women (53.2%), while of the 39 cases of angina pectoris associated with myocardial infarction only seven were in women (17.9%). Forty per cent of all angina encountered in the study population occurred in women. Angina pectoris in association with myocardial infarction was more common in men.

It is widely accepted that sudden death (occurring within a matter of minutes) is usually the result of coronary heart disease with or without coronary occlusion (11). This is especially likely if other possible causes such as aortic valvular deformity, pulmonary embolism, and aortic dissection or rupture can be excluded. Examination of the Framingham Study subjects prior to the event and careful evaluation of the circumstances under which the sudden death occurred renders it unlikely, although still possible, that these other etiologies were responsible for the deaths. It is recognized that sudden death may be the only manifestation of CHD (11). It has not been possible up until now, however, to determine how often sudden death occurs as the initial manifestation of CHD. In the six years of observation of men in the Framingham Study group, 24 sudden deaths occurred. Nine (37.5%) of these had pre-existing evidence of coronary heart disease (six had angina pectoris and three had myocardial infarction). Thus 62.5% of all sudden deaths attributed to CHD in men occurred as the initial manifestation of the disease.

TABLE 12. Immediate Mortality Following Initial Myocardial Infarction: Men in Framingham Study Group

	Total	Survived*	Died within Three Weeks
Hospitalized	49	43	6
Not hospitalized	39	19	20†
Total	88	62	26

* Known living up to time of report or died of other causes after two-year survival. All survivals in excess of two months.

† All sudden deaths.

It can be seen from Table 12 that there is a high immediate mortality associated with myocardial infarction. For purposes of this discussion sudden death is classified as myocardial infarction. Of 88 cases of myocardial infarction in men occurring in the six years of observation, 26 (29.5%) died within three weeks of the initial infarction. Indeed, 20 of the 26 (77%) deaths wihin three weeks were sudden, occurring in a matter of minutes.

It is also noteworthy that approximately 45% of those with the initial myocardial infarction never got hospitalized. Of these, one-half never had the opportunity to be hospitalized because of the occurrence of sudden death. Approximately 25% of those not hospitalized had unrecognized infarctions discovered only because of routine electrocardiographic studies on biennial examinations. Thus approximately 70% of the initial infarctions not hospitalized in the community never had the opportunity to be hospitalized in order to receive the

benefits of therapeutic medicine. Indeed, the majority of these could not even be seen by a physician prior to their demise. Of the 49 who survived to enter a hospital, six (12.2%) died shortly after admission (only one survived more than ten days). As indicated previously 15 of the 24 (62.5%) sudden deaths which occurred had no prior evidence of coronary heart disease. These data suggest to the authors that in efforts to control CHD, major emphasis must be placed on prevention.

Six years of follow-up experience in the longitudinal prospective study of coronary heart disease in Framingham have confirmed the widely recognized influence of hypertension and hypercholesterolemia on the development of CHD. These factors have been noted in clinical studies to occur in excess in persons with coronary heart disease, and in animal experiments to be associated with the development of atherosclerosis. It is now demonstrated that these factors *precede* the development of overt CHD in humans and are associated with increased risk of the development of CHD. The association of these factors with the subsequent development of coronary heart disease has been independently demonstrated in other longitudinal studies (12, 13). In addition, it is now demonstrated that the electrocardiographic pattern of left ventricular hypertrophy is also associated with increased risk of developing CHD.

It is now possible to assess the magnitude of the increase in risk associated with these characteristics. It can be seen from Table 8, by comparing the ratios of observed to expected incidence rates, that hypertension, as defined, is associated with a 2.6-fold increase in risk of development of CHD in men 40 to 59 years of age and a sixfold increase in women in the same age. This represents a considerable increase in risk. Of interest also is the comparison of risk in the sexes. It is often stated that women tolerate hypertension better than do men. Insofar as the relationship between hypertension and coronary heart disease is concerned, the six-year incidence figures do not support this thesis. If the independent contribution of hypertension to risk is assessed by holding the other factors which contribute to risk constant (i.e., left ventricular hypertrophy by electrocardiogram and elevated serum cholesterol), then, of the three characteristics under consideration, hypertension represents a greater relative increase in risk in women than in men although the absolute incidence of CHD in women never reaches that of men in any category (Table 11). Elevation of serum cholesterol level (i.e., 245 mg per 100 ml or more) is associated with more than a threefold increase in risk in men aged 40 to 59, while in women of the same age a 1.6-fold increase is noted (Table 6). As seen in a comparison of Table 6 and Table 8, and in Table 11, when blood pressure and left ventricular hypertrophy factors are removed from consideration, the independent contribution of cholesterol (at slightly higher levels of 260 mg per 100 ml or greater) to risk in women is further reduced so that cholesterol levels contribute only slightly to the increased risk among women but very significantly among men. Some of the increased risk is undoubtedly attributable to a higher mean age of women with higher cholesterol level, since cholesterol increase with age occurs to a greater extent in women than in men. It thus appears that, in assessing the contribution to risk of developing CHD, of the three factors under consideration, hypertension represents a greater risk factor for women than for men, whereas for serum cholesterol levels the converse is true, cholesterol contributing only slightly to the increased risk among women, but very significantly increasing risk among men.

Combinations of the three risk factors under consideration appear to augment further the risk of subsequent development of coronary heart disease. It has been dem-

onstrated (Figures 1 and 2 and Table 11) that the incidence of coronary heart disease rises progressively as these factors are combined.

There can be no doubt that absence of these characteristics is distinctly advantageous since such persons demonstrate a relatively low risk of developing CHD. Whether or not the correction of these abnormalities once they are discovered will favorably alter the risk of development of disease, while reasonable to contemplate and perhaps attempt, remains to be demonstrated.

As additional longitudinal observations are made, it is hoped that additional risk factors will be determined. This will allow further identification of susceptible individuals and hopefully suggest methods of control.

Summary and Conclusions

A six-year longitudinal study is reported of a stratified random sample of the population of Framingham, Massachusetts, aged 30 to 59 years, covering factors related to the development and clinical manifestations of coronary heart disease. The factors studied include blood pressure, serum cholesterol levels, and certain electrocardiographic abnormalities. Follow-up of the study group free of CHD at the initial examination has been reasonably complete.

One hundred and eighty-six men and women aged 30 to 59 years on entry into the study developed coronary heart disease in the six years of observation, representing an over-all six years' incidence of 36.3 per thousand. In the younger age group, 30 to 44 years, a male to female ratio of 13 to 1 was noted. In the older age group, 45 to 62 years, this sex ratio became attenuated to only a twofold difference.

In addition to incidence, the clinical manifestations of CHD were noted to differ markedly in the sexes. Coronary heart disease in the female was noted to be manifested chiefly as angina pectoris (70%). In the male, the disease was manifested chiefly as myocardial infarction or sudden death, with only 30% exhibiting angina pectoris alone. The incidence rate of sudden death was ten times as common in men (10.5 per 1,000) as in women (1 per 1,000) and the incidence rate of myocardial infarction was five times as high in men. Contrary to general belief, uncomplicated angina pectoris was noted to occur as frequently in women as in men; 53% of all such angina pectoris developing in the population occurred in women. Only angina pectoris in association with myocardial infarction was noted to be more common in men.

It has been noted that 62.5% of all sudden deaths attributed to coronary heart disease in men occurred as the initial manifestation of the disease. A high immediate mortality was noted to be associated with myocardial infarction. Of 88 cases of myocardial infarction in men, 26 (29.5%) died within three weeks of the initial infarction. Of those with initial myocardial infarction 44% were not hospitalized, half of these because of the occurrence of sudden death. Another 23% of those not hospitalized had infarctions that were unrecognized. Thus three of four initial infarctions not hospitalized in the community could not have been hospitalized owing to sudden death or unrecognized infarction. Of those who survived to enter a hospital, 12.2% died shortly after admission.

The well-recognized influence of hypertension and hypercholesterolemia on the development of coronary heart disease is confirmed. It is now demonstrated that these factors precede the development of overt CHD and are associated with increased risk of its development. In addition, it is now demonstrated that the electrocardiographic pattern of left ventricular hypertrophy is also associated with increased risk of developing CHD.

The magnitude of the increase in risk associated with these characteristics has been assessed. Hypertension has been noted

to be associated with a 2.6-fold increase in risk in men 40 to 59 years of age and a six-fold increase in women the same age. With respect to the development of coronary heart disease, hypertension was noted to represent a greater risk factor in women than in men, while elevated serum cholesterol levels contributed only slightly to increased risk among women as compared with men. Elevation of serum cholesterol levels (i.e., 245 mg per 100 ml or more) was associated with more than a threefold increase in risk among men aged 40 to 59 years.

A pattern of left ventricular hypertrophy by electrocardiogram was noted to be associated with a two or three-fold increase in risk of development of CHD at given hypertensive blood pressure levels in men. Combinations of these risk factors (hypertension, elevated serum cholesterol level, and left ventricular hypertrophy by electrocardiogram) were noted to augment further the risk of development of CHD. Men 40 to 59 years of age, lacking these three abnormal characteristics, were noted to have a six-year incidence of coronary heart disease of 35.8 per thousand. When all of these characteristics were present the incidence rose to approximately 500 per thousand. These risk characteristics were shown to occur with sufficient frequency in the population to merit concern, 8% of men and 11% of women having two or more of these abnormal characteristics. At least one abnormal characteristic was present in over 40% of the population aged 30 to 59 years.

Summario in Interlingua

Un specimen de 5.127 subjectos de etates de 30 a 59 annos, le quales initialmente esseva libere de morbo cardiac coronari, esseva observate durante sex annos. In le curso de iste intervallo, 125 masculos e 61 feminas disveloppava manifestationes de morbo cardiac coronari. Inter le 34 casos in le gruppo de etates ab 30 ad 44 annos, le proportion mascule a feminin de incidentia esseva 13 a 1. Inter le 152 casos in le gruppo de etates ab 45 ad 62 annos, le proportion mascule a feminin del incidentia esseva approximativemente 2 a 1. Le incidentia de angina de pectore esseva plus o minus equal pro le duo sexos. Tamen, infarcimento myocardial esseva duo vices plus commun in masculos e morte subite dece vices.

In masculos, un alte mortalitate immediate (30%) esseva associate con infarcimento myocardial initial (incluse mortes subite). Quarantacinque pro cento de 88 masculos suffrente infarcimento myocardial non esseva hospitalisate, primarimente a causa del facto que morte superveniva subitemente o que le infarcimento myocardial non esseva recognoscite como tal.

Factores de risco esseva evalutate in le gruppo de etates inter 40 e 59 annos. Hypertension (160/95 mm de Hg o plus) esseva associate con un quasi triplice augmento del risco in homines e un sextuple augmento in feminas. Elevation del nivello seral de cholesterol (245 mg per 100 ml o plus) esseva associate con un augmento plus que triplice del risco in masculos, durante que illo contribueva pauco (o nihil del toto) al augmento del risco in feminas. Le configuration electrocardiographic de hypertrophia sinistro-ventricular esseva associate con un augmento duplice o triplice del risco de un disveloppamento de morbo cardiac coronari.

Combinationes del tres characteristicas resultava in un augmento progressive in le risco de disveloppar morbo cardiac coronari, durante que subjectos libere de omne le mentionate anormalitates disveloppava le morbo a un prorata de solmente un medietate de illo del population total de iste studio. Le anormalitates occurreva in le population con un frequentia sufficientemente alte pro meritar nostre sollicitude.

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