

# Relationship of Various Factors to the Degree of Coronary Atherosclerosis in Women

By ROBERT F. ACKERMAN, M.D., THOMAS J. DRY, M.B., AND JESSE E. EDWARDS, M.D.

The degree of coronary artery atherosclerosis present in 600 hearts obtained from women, 100 in each of the decades from 30 through 89 years, was determined by one observer. Coronary atherosclerosis increased with age until the eighth decade when the atherosclerosis tended to level off. Cardiac hypertrophy and diabetes were associated with increased degrees of atherosclerosis. Hearts from the undernourished exhibited less atherosclerosis than did hearts from average weight or overweight individuals. A comparison with data compiled on 600 hearts from men by White and associates has been included.

MOST of the reported pathologic data on the relation of degree of atherosclerosis to various factors have been derived exclusively from necropsy protocols.<sup>1-3</sup> Information available from such study indicates that the degree of coronary atherosclerosis progresses steadily with age; that men suffering from disease of the coronary arteries far outnumber women; and that among other factors hypertension, diabetes and the state of nutrition influence the formation of atheromatous lesions. There has been a tendency to emphasize the part played by age to the exclusion of other factors. Any one report on the relationship of age to the degree of coronary atherosclerosis often includes the observations of many individuals who wrote the protocols used in the particular analysis. A more reliable analysis would obviously be one in which the same observer studied all of the hearts reported on. This would yield a more standard evaluation of the degree of disease.

White personally examined the entire coronary tree in each of 600 consecutive hearts.<sup>4</sup> He found that the degree of coronary atherosclerosis reached a peak in the sixth decade of life. In later decades there was less severe atherosclerosis. His study was confined to male subjects and was reported by White, Edwards and Dry.<sup>5</sup> The present report deals with female subjects.

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## METHODS AND MATERIALS

Hearts from women in the age group 30 through 89 years were chosen for this study. One hundred consecutive hearts in each of the six decades were examined. The material parallels the study of White and associates<sup>5</sup> from the Mayo Clinic on hearts of men. The specimens used in the current study had been saved at the time of necropsy as a routine procedure. Hearts from patients dying from disease of the coronary arteries or from any other disease were not excluded.

Both left and right coronary arteries were studied in each heart by one of us (Ackerman). The left coronary artery consists of its main trunk and its anterior descending and circumflex branches. The right coronary artery consists of its main trunk and its marginal and posterior descending branches. Each of these six divisions was arbitrarily subdivided into proximal, middle and distal portions, except for the main left coronary artery which is usually less than 2.5 cm. in length and was considered too short for subdivision (fig. 1). The sixteen subdivisions of the coronary arteries so obtained were evaluated individually for the maximal degree of atherosclerosis present.

To establish the degree of atherosclerosis, cross sections of the arteries were made with a sharp knife at 3 mm. intervals. Actual grading was on a basis of 1 to 4, with 1 representing minimal sclerosis and 4 complete atherosclerotic closure of the lumen. The photomicrographs presented (fig. 2) are representative of the various grades of sclerosis and are reproduced through the courtesy of White and associates. It is important to stress that the maximal rather than the average degree of atherosclerosis was recorded for each of the sixteen subdivisions. This is defined as the *grade of sclerosis*. Grading was simplified by using in-between points such as 2.5 when the degree of sclerosis fell midway between 2 and 3. The grading is identical with that used in the study by White and associates. Grade 1 is used

to designate less than 25 per cent reduction in the diameter of the lumen, grade 2 represents 25 per cent closure of the luminal diameter, grade 3 represents 50 per cent closure and grade 4 represents 100 per cent closure of the lumen. When the vessel was occluded by a clot, only the underlying sclerosis was used as the basis for grading; the clot was not considered.

The cardiac weight, the principal and contributing causes of death and any sign or symptom leading to a clinical suspicion of coronary disease were recorded from data in necropsy protocols and abstracts of the

anterior descending) in every decade. The one exception was a higher grade of sclerosis in the middle part of the main right coronary artery than was present in the proximal part in the seventh decade. The grade of sclerosis was least in the distal part of all five divisions in every decade. Since the trunk of the left coronary is less than 2.5 cm. in length, it was not divided into parts as were the other five divisions.

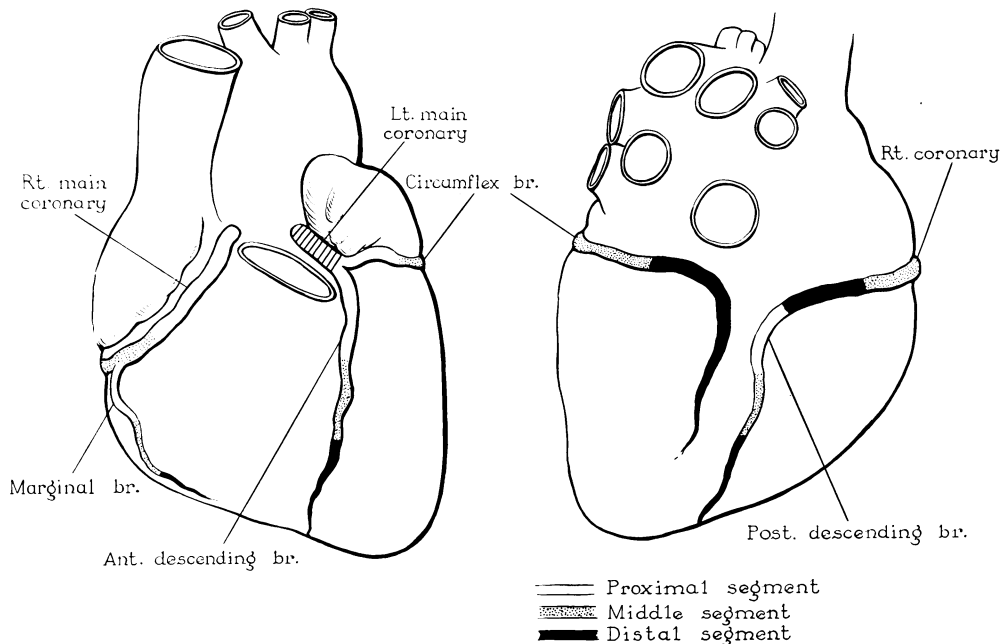


FIG. 1.—The sixteen segments of the coronary arteries in which the degree of atherosclerosis was determined.

clinical records. To determine the effect of emaciation and obesity on atheromatous deposits the state of nutrition as noted in each necropsy protocol was recorded. The presence of diabetes was also noted.

## RESULTS

### *Correlation of the Degree of Coronary Atherosclerosis With Age*

In the study made by White, Edwards and Dry<sup>5</sup> an analysis was made to determine the degree of atherosclerosis in each of the sixteen portions of the coronary arterial tree. With one exception these authors found a higher grade of sclerosis in the proximal part in five of the six major divisions (anterior descending, left circumflex, right main, right marginal and pos-

In this study a similar analysis was made. With but two exceptions the proximal part in five of the six major divisions had a higher grade of sclerosis than did the middle or distal parts in each decade. One exception occurred in the left circumflex artery where the grade of sclerosis in the middle part was greater than that in the proximal part in the eighth and ninth decades. The other exception occurred in the main right coronary artery; a higher grade of sclerosis was present in the middle part than was present in the proximal part in the eighth decade. The grade of sclerosis was least in the distal part of all five divisions in every decade.

### *Average Grade of Sclerosis in the Six Main*



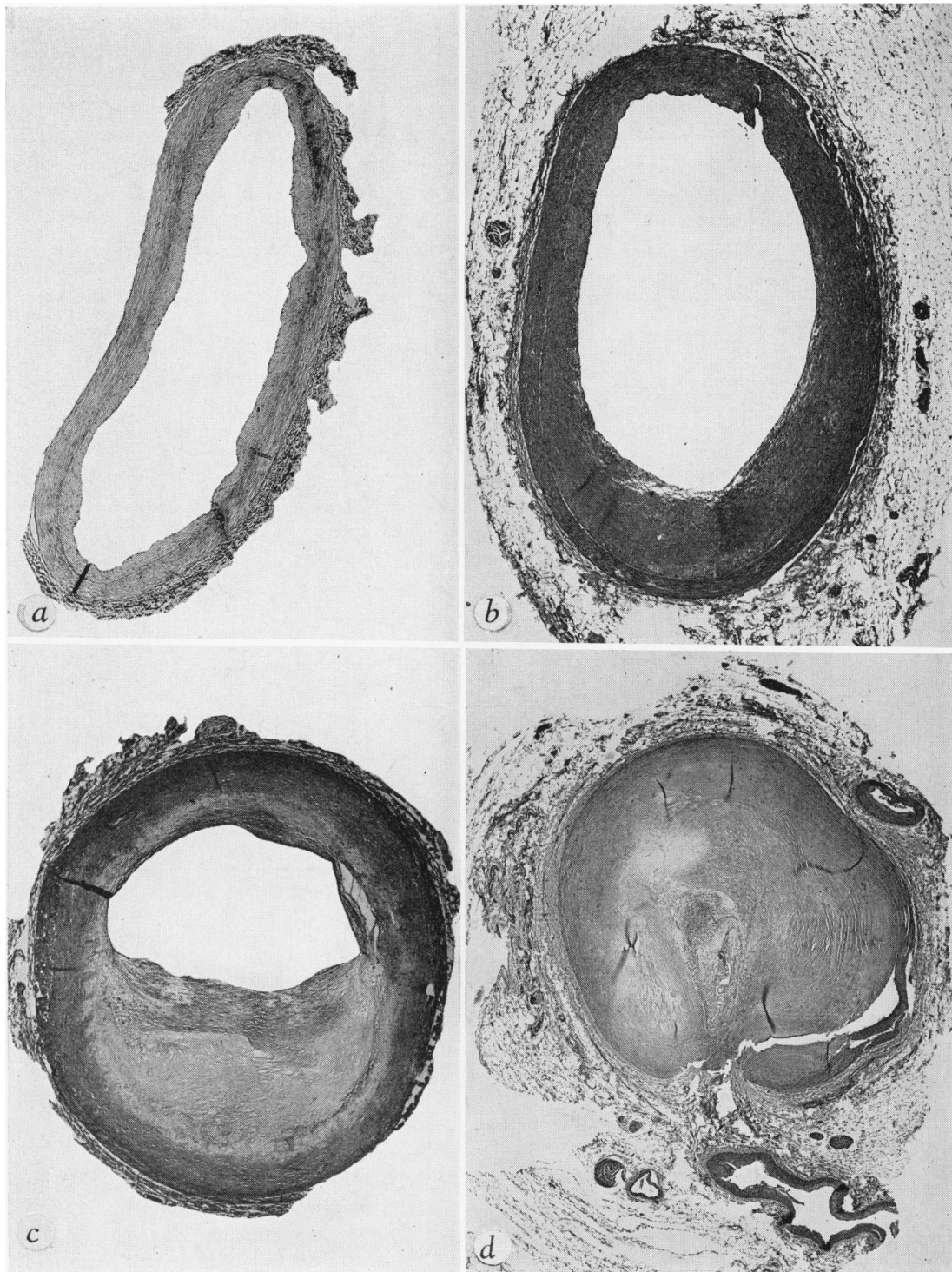


FIG. 2.—Examples of the four grades of sclerosis in coronary arteries. Sections stained with hematoxylin and eosin. *a*, grade 1 ( $\times 30$ ); *b*, grade 2 ( $\times 22$ ); *c*, grade 3 ( $\times 15$ ); and *d*, grade 4 ( $\times 15$ ).

*Divisions.* The highest grade of sclerosis was determined in each of the sixteen parts of the

coronary arterial tree as described in a previous paragraph. To determine the highest grade of

sclerosis in each of the six main divisions (left main, anterior descending, left circumflex, right main, right marginal and posterior descending), one value, the highest grade of sclerosis occurring in the proximal, middle or distal part of that vessel, was used.

Atheromatous deposits involved the six main divisions in the following descending order of severity: anterior descending, right main, left

fourth decade through the eighth decade in all divisions of the coronary arterial tree. In the ninth decade there was a tendency to level off. In three divisions in the ninth decade the grade of sclerosis was equal to or less than that in the eighth decade. In three other divisions there was a rise from the eighth to the ninth decade which, however, was less marked than between earlier decades.

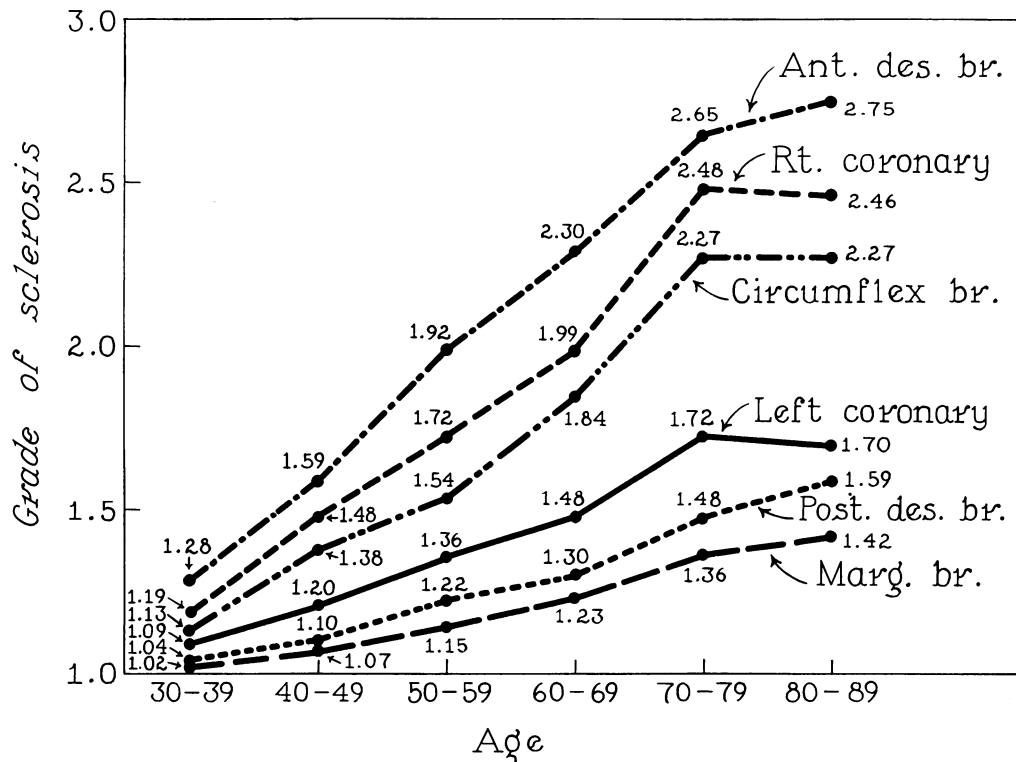


FIG. 3.—The average of the maximal degrees of atherosclerosis for each of the six major divisions of the coronary arteries by decades. The value for the greatest degree of coronary sclerosis present in either the proximal, middle, or distal part of a major division was taken as the grade of sclerosis for that division. The one hundred values thus obtained in each decade were then added and the sum divided by 100 (the number of hearts in each decade) to obtain the average grade of sclerosis for a major division.

circumflex, left main, posterior descending and marginal (fig. 3). In the anterior descending branch the grade of sclerosis increased from 1.28 in the fourth decade to 2.75 in the ninth decade. The grade of sclerosis in the main right coronary artery increased from 1.19 in the fourth decade to 2.48 in the eighth decade; it was 2.46 in the ninth decade. The general trend was a steady consistent rise from the

#### *Percentage of Hearts With Severe Sclerosis.*

Five per cent of hearts in the fourth decade had a severe degree of atherosclerosis (grade 3 or higher) at some point in the coronary arterial system (fig. 4). After the fourth decade the rise in the curve is accentuated with the passing of each ten-year period up to the eighth decade. By the eighth decade 60 per cent of the hearts showed a severe degree of involvement. Like-

wise, 60 per cent of hearts were so involved in the ninth decade, suggesting a leveling off after the eighth decade.

*Comparison of Right and Left Coronary Arteries.* A greater number of hearts had severe sclerosis in the left coronary artery than in the right (fig. 4). This discrepancy was most

represent a composite of those of figure 3. The data are presented in this fashion because in all subsequent calculations which have been made to evaluate the influence of factors other than age on coronary atherosclerosis, the average grade of sclerosis has been used for comparison. Hereinafter the term "average grade of scler-

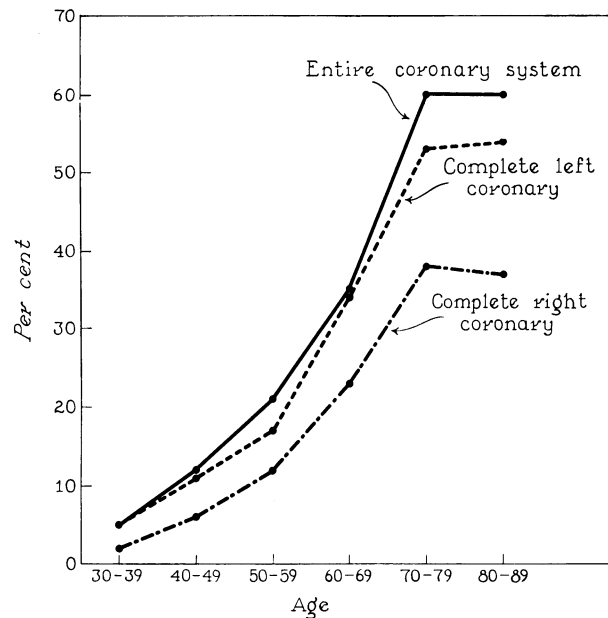


FIG. 4.—The percentage of hearts showing at some point in the coronary arterial system a degree of sclerosis of grade 3.0 or greater. Comparison is made between the complete left coronary, the complete right coronary, and the entire coronary artery system, the last-mentioned representing all hearts with grade 3 or greater sclerosis in the complete left coronary plus those hearts with less than grade 3 in the complete left coronary but with grade 3 or more somewhere in the complete right coronary artery.

marked in later decades. In the eighth decade 52 per cent of the left coronary arteries and only 36 per cent of the right coronary arteries were involved by a severe degree of atherosclerosis (grade 3 or greater).

*The "Average" Grade of Coronary Atherosclerosis.* The average grade of sclerosis for each heart was determined by adding the values for grade of sclerosis in each of the six main divisions of the coronary arterial tree and dividing by six. The figures thus obtained for all the hearts in a given decade were added together and divided by 100 (the number of hearts in each decade). The result was an "average" of the grade of sclerosis for the hearts in that decade (fig. 5). In essence the values obtained

rosis" will refer to figures obtained in the manner used to construct figure 5.

#### *Relation of Cardiac Weight to Coronary Atherosclerosis*

The data were analyzed to determine if cardiac weight had any relation to the grade of sclerosis. According to Smith,<sup>6</sup> more than 75 per cent of the hearts from women with hypertension weigh more than 350 Gm; in the female sex nearly all normal hearts weigh less than 350 Gm.<sup>7</sup>

The data were studied to see whether there was any correlation between cardiac weight and the average grade of coronary atherosclerosis (tables 1 and 2). Inspection of these tables



leaves little doubt that the heavier hearts had a greater degree of atherosclerosis than did lighter ones. As shown in table 1 the heavier hearts had a 15 to 43 per cent higher average

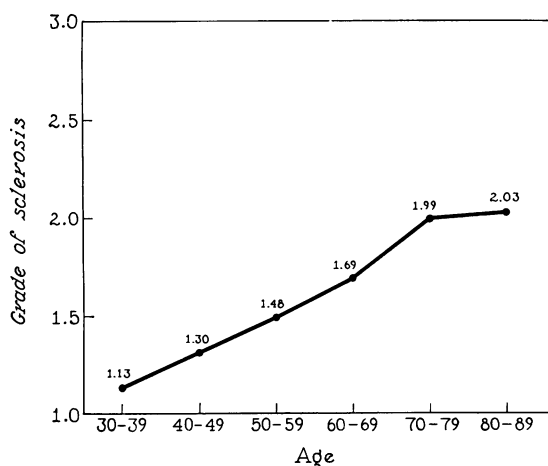


FIG. 5.—The average grade of coronary atherosclerosis by decades. For each heart the greatest sclerosis in each of the six major divisions was determined, and an average of the six values thus derived was obtained. For each decade these averages were totaled and divided by 100 to yield the average grade of sclerosis for that decade.

TABLE 1.—Relation of Cardiac Weight to Coronary Sclerosis (All Hearts)

Age, years	Hearts weighing 100-349 Gm.		Hearts weighing 350 Gm. or more		Per cent difference*
	Number	Sclerosis, grade	Number	Sclerosis, grade	
30-39	73	1.06	27	1.52	+43.4
40-49	75	1.22	25	1.54	+26.2
50-59	63	1.37	37	1.67	+21.9
60-69	49	1.57	51	1.81	+15.3
70-79	44	1.76	56	2.18	+23.9
80-89	46	1.83	54	2.20	+20.2
Totals.....	350		250		

\* The percentage by which the average grade of sclerosis of the large hearts exceeded that of the small hearts.

grade of sclerosis than did the lighter ones. In table 2 it is shown that the heavier hearts had a 15 to 35 per cent higher average grade of sclerosis than did the lighter ones. In general, heavier hearts had significantly higher grades

of coronary atherosclerosis than did lighter hearts.

#### *Incidence of Clinical Coronary Disease*

The 600 abstracted histories in the protocols were searched for a history of angina pectoris or evidence of myocardial infarction (table 3). The incidence of clinical diagnoses of coronary

TABLE 2.—Relation of Cardiac Weight to Coronary Sclerosis (All Diseased Hearts Except Those Associated With Hypertension Were Excluded If the Heart Weighed More Than 300 Gm.)

Age, years	Hearts weighing 100-349 Gm.		Hearts weighing 350 Gm. or more		Per cent difference*
	Number	Sclerosis, grade	Number	Sclerosis, grade	
30-39	73	1.06	21	1.35	+27.4
40-49	74	1.22	20	1.65	+35.2
50-59	63	1.37	31	1.68	+22.6
60-69	49	1.57	50	1.81	+15.3
70-79	44	1.76	53	2.21	+25.6
80-89	45	1.85	54	2.20	+18.9
Totals.....	348		229		

\* The percentage by which the average grade of sclerosis of the large hearts exceeded that of the small hearts.

TABLE 3.—Age Distribution of Clinical Coronary Disease

Age, years	Cases
30-39	1
40-49	3
50-59	3
60-69	14
70-79	20
80-89	18
Total.....	59 (9.8%)

insufficiency paralleled to a remarkable degree the number of hearts with a severe degree of sclerosis. The 59 cases in which there was a clinical diagnosis of coronary disease represented 9.8 per cent of the total number of cases.

#### *Diabetes Mellitus and Coronary Atherosclerosis*

The 600 protocols were reviewed to determine the number of cases of diabetes present

in each decade. Hearts from diabetics were then separated from those of nondiabetics. The average degree of sclerosis for each of the two groups was determined; this was higher in the

TABLE 4.—*Relation of Diabetes Mellitus to Coronary Sclerosis*

Age, years	Nondiabetics		Diabetics		Per cent difference*
	Number	Sclerosis, grade	Number	Sclerosis, grade	
30-39	100	1.13	—	—	—
40-49	98	1.11	2	1.50	+35.1
50-59	94	1.26	6	1.83	+45.2
60-69	95	1.45	5	1.84	+26.9
70-79	91	1.97	9	2.22	+12.7
80-89	97	2.03	3	1.93	-4.9

\* The percentage by which the average grade of sclerosis of diabetics exceeded that of nondiabetics.

of death was the criterion used to place each patient into one of the three named categories of the state of nutrition. The average grade of sclerosis in the underweight group was less than that in the average weight and overweight groups in each decade. The average grade of sclerosis in patients of average weight was essentially the same as that in persons who were overweight.

#### COMMENT

The literature indicates that coronary atherosclerosis increases steadily with age. White, Edwards and Dry found the hearts in men to have the highest degree of sclerosis in the sixth decade. The sclerosis decreases slightly in subsequent decades. In part this work has been confirmed by the data presented herein. In figures 3, 4 and 5 the severity of coronary

TABLE 5.—*Relation of State of Nutrition to Coronary Sclerosis*

Age, years	Underweight		Average weight		Overweight	
	Number	Sclerosis, grade	Number	Sclerosis, grade	Number	Sclerosis, grade
30-39	27	1.08	42	1.13	31	1.15
40-49	23	1.15	43	1.36	34	1.34
50-59	10	1.36	37	1.79	53	1.52
60-69	17	1.65	38	1.71	45	1.71
70-79	23	1.69	39	2.14	38	2.03
80-89	34	1.88	34	1.95	32	2.28
Totals	134	1.49	233	1.67	233	1.67

diabetics than in the nondiabetics in every decade except the fourth and the ninth (table 4). In the ninth decade there was a slightly higher grade of sclerosis in the hearts of the nondiabetics; in the fourth decade there were no cases of diabetes to serve as a basis for comparison.

#### *Relation of State of Nutrition at Death to Coronary Sclerosis*

The cases were grouped according to whether the patient was underweight, of average weight or overweight, and the average grade of sclerosis was determined by decades for each of the three groups (table 5). The protocol description of the condition of bodily nutrition at the time

sclerosis in women is shown to increase steadily with age from the fourth to the eighth decade, but there is a leveling off in the ninth decade. Figure 6 compares the manner in which atherosclerosis affected the coronary arteries in men and women; the curve for men is based on data presented by White, Edwards and Dry. The severity of the atherosclerosis was far greater in men than in women; nevertheless, after the seventh decade the average grade of sclerosis in men was only 13 to 17 per cent greater than in women. The curves for the two sexes are similar in that there is a leveling off in later decades. In men this occurs after the sixth decade; in women it occurs after the eighth decade.

What causes the marked difference in the

degree of atherosclerosis that occurs in men and women? Unfortunately, there is no ready explanation in the data presented herein. Some factor seems to have more influence than age. Figure 6 impresses one with the marked increase in atherosclerosis which occurs in the men from the fifth to the sixth decade. In women a comparable rise occurs between the seventh and the eighth decade. Some attempt should be made to determine if early menopause increases the prevalence of atherosclerosis in women.

Few studies have indicated the manner in which atherosclerosis affects the smaller

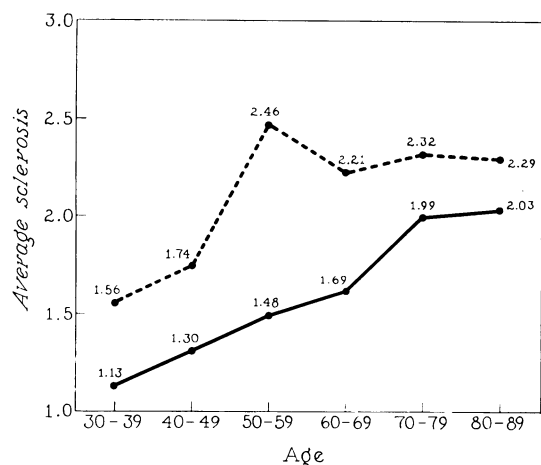


FIG. 6.—Comparison of the average grades of coronary atherosclerosis in men (dotted line) and women (solid line). The curve for men was constructed from data presented by White, Edwards and Dry.

branches of the coronary arteries. It has been held that the anterior descending branch of the left coronary artery is subject to a greater degree of atherosclerosis than are the other branches.<sup>8</sup> In our study the branches of the coronary arteries were involved by atherosclerosis in the following order of decreasing severity: left anterior descending, main right coronary, left circumflex, main left stem, posterior descending branch and marginal branch (figs. 1 and 3). This is in full agreement with the observations made in the parallel study of hearts in males. A severe degree of atherosclerosis (grade 3 or more) was present in the left coronary artery in a consistently greater

number of hearts in each decade than in the right coronary. This tendency was more pronounced after the sixth decade. A severe degree of atherosclerosis was present in the right coronary artery in 3.2 per cent of the hearts when there was not a severe degree of atherosclerosis in the left coronary. White, Edwards and Dry found this relation in 11 per cent of hearts of men while Clawson<sup>9</sup> found such a relationship in less than 1 per cent of his series of 928 hearts from both men and women. The difference between right and left arteries is consistent. There is no acceptable explanation for this difference.

The 59 cases in which there was clinical evidence of coronary insufficiency in this series represented 9.8 per cent of the total number of subjects. This incidence compares with the estimates given by Master<sup>10</sup> for deaths from coronary disease for the entire population of the United States in 1942. He stated that disease of the coronary arteries accounted for 8.5 per cent of all deaths in this country. White, Edwards and Dry found that 11.5 per cent of the male patients had had clinical evidence of coronary insufficiency. Our series, then, is not unduly weighted with hearts which were known clinically to have disease of the coronary arteries.

The relation between hypertension and coronary atherosclerosis has been pointed out repeatedly.<sup>8, 11, 12</sup> In our series the only indication of hypertension consistently available was the cardiac weight. The fact that the average grade of coronary sclerosis in the heavier hearts was 15 to 43 per cent greater than that in the lighter hearts is in agreement with observations made in men.<sup>5</sup> The difference in men amounted to only 5 to 10 per cent. The clinical significance of a greater degree of sclerosis in hypertrophied hearts is apparent. A greater blood supply is necessary to support any cardiac hypertrophy. If there is impairment of the coronary circulation by atherosclerotic plaques in hypertrophied hearts the tendency will be to reduce blood flow and render such hearts more susceptible to failure. This obviously does not take the development of collateral circulation into consideration. Prinzmetal and Simkin<sup>13</sup> and others demonstrated that collateral circu-



lation is established by the coronary arteries in response to a decreased blood flow. It is difficult to know the functional effect of severe degrees of atherosclerosis on the myocardium when only morphologic data are at hand.

Since hypertrophied hearts do exhibit greater degrees of atherosclerosis in the coronary arteries than do hearts of normal size, the question is prompted: Is the hypertrophy due to hypertension or to the coronary insufficiency itself? Clawson<sup>8</sup> indicated that coronary atherosclerosis does not cause cardiac hypertrophy. This view is generally accepted. However, the cardiac hypertrophy which occurs when the left coronary artery has an anomalous origin from the pulmonary trunk<sup>14</sup> is strong evidence that coronary insufficiency can cause cardiac hypertrophy. Davis and Blumgart<sup>15</sup> observed a correlation between the degree of coronary atherosclerosis and cardiac hypertrophy when congestive failure had been present. When no congestive failure had been present there was little if any correlation between cardiac weight and degree of coronary sclerosis. No such comparisons were attempted in this study. Cardiac hypertrophy in a series such as this may indicate the presence of hypertension. It is possible that coronary insufficiency in itself may cause cardiac hypertrophy through the medium of causing myocardial insufficiency.<sup>14</sup> This matter must be kept in mind in evaluating the relation of coronary atherosclerosis to cardiac weight.

Of interest is the relation of coronary atherosclerosis to the state of nutrition. Our study showed that in each decade the underweight groups of subjects had less atherosclerosis than did the average weight or overweight groups. There was no difference between the average weight and the overweight groups, however. Wilens<sup>16</sup> has shown that terminal loss of weight decreases the number of fresh atheromatous deposits present in the aorta. This cannot be confirmed in this study because of lack of consistent knowledge of the state of nutrition for the entire group of patients prior to the terminal illness.

#### SUMMARY

1. Six hundred hearts obtained from consecutive necropsies on women, 100 in each of the decades from 30 through 89 years of age,

have been examined to determine the degree of atherosclerosis present in the coronary arteries.

2. The average degree of sclerosis, based on the maximal amount of sclerosis present in each heart, rose steadily from the fourth decade to the eighth decade and then tended to level off so that in the ninth decade there was approximately the same degree of coronary atherosclerosis as was present in the eighth decade.

3. The number of hearts with a severe degree of atherosclerosis rose steadily from 5 per cent in the fourth decade to 60 per cent in the eighth decade. Sixty per cent of the hearts in the ninth decade also had a severe degree of atherosclerosis.

4. Atherosclerosis was greatest in the anterior descending branch of the left coronary artery and next greatest in the main right coronary. The left circumflex, left main, posterior descending and marginal arteries followed in the order named.

5. Hearts exhibiting hypertrophy had a constantly greater degree of atherosclerosis than did nonhypertrophied hearts. This difference ranged from 15 to 43 per cent in general, and is striking because it appeared in all decades.

6. Coronary atherosclerosis was consistently less severe in the undernourished, but no differences were found in the average degrees of sclerosis for individuals of normal weight as compared to those who were overweight.

7. Diabetics had 12 to 45 per cent greater degrees of coronary atherosclerosis in the fifth to the eighth decades than did nondiabetics. In the ninth decade diabetics had 4.9 per cent less atherosclerosis than did nondiabetics. The total number of diabetics was only 25; it is felt that, in general, diabetics have a greater degree of atherosclerosis than do nondiabetics. The discrepancy in the ninth decade was not accounted for.

8. The pattern of development of atherosclerosis in the right coronary artery was similar to that in the left. There was, however, a greater average degree of atherosclerosis in the left coronary than in the right. In addition the left coronary artery showed a constantly greater degree of involvement by severe degrees of atherosclerosis than did the right coronary.

9. A comparison of our data with those compiled for a series of 600 hearts from men by White and associates is included.

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