Autopsy Studies in Atherosclerosis

III. Distribution and Severity of Atherosclerosis in the Presence of Obesity, Hypertension, Nephrosclerosis, and Rheumatic Heart Disease

By ROBERT H. WILKINS, B.S., JAMES C. ROBERTS, JR., M.D., and CAMPBELL MOSES, M.D.

The preceding reports from this study have dealt with the atherosclerosis in patients dying with and without morphologic evidence of atherosclerotic catastrophe. In this report we present an analysis of the distribution and severity of atherosclerosis in the subjects of this study who presented evidence of obesity, hypertension, nephrosclerosis, or rheumatic heart disease.

Methods and Procedures

With use of a grading system discussed previously, which takes into account both the total area of intimal involvement and the severity of individual gross lesions, up to 41 sites in 32 different arteries were graded in 500 consecutive autopsies at the Presbyterian, Eye and Ear, and Woman's Hospitals in Pittsburgh from October 1955 to September 1957. Description of the subjects included in this study and the methods employed in collecting and analyzing the data are partially discussed in the first paper of this series. In table 1 is summarized the decade distribution of the various groups studied.

The weight and height of each patient were measured at autopsy and the weight-height index of Quetelet-Bouchard (i.e., weight in kilograms divided by height in centimeters) was calculated for each. With the assumption that a liter of serous fluid weighs approximately a kilogram, the weights of patients with measured ascites and pleural effusion were appropriately adjusted. After this adjustment the patients were arranged in serial order by their indices, and 4 standard deviations around the mean weight-height index were omitted. The remaining 47 heavy males and 30 heavy females and their light counterparts were grouped for further study.

Translated into more familiar terms, the median indices of obese and thin patients can be expressed as the weight in pounds corresponding to any chosen height in inches. A height of 5 feet, 6 inches was found to correspond to 180 pounds in obese women and 98 pounds in thin women. Similar calculations for obese and thin men at a height of 5 feet, 10 inches were 191 pounds and 108 pounds, respectively.

Criteria for hypertension in this study were cardiac weights of over 500 Gm. for men and 400 Gm. for women, in the absence of significant valvular or pulmonary lesions which could have accounted for the cardiomegaly. Of the 47 obese men (40 white, 7 Negro) studied, 13 (28 per cent) were hypertensive (11 white, 2 Negro), and of the 30 obese women (24 white, 6 Negro), 13 (43 per cent) were hypertensive (9 white, 4 Negro). None of the 47 thin males (41 white, 6 Negro) and only 2 of the 30 thin females (25 white, 5 Negro) were hypertensive. In the entire autopsy series there were 38 men (32 white, 6 Negro) and 32 women (23 white, 9 Negro) with hypertensive cardiomegaly. Nonhypertensive patients (i.e., heart weights of less than 500 Gm. in males and 400 Gm. in females) are tabulated as normotensive in the present report.

The autopsy protocols were reviewed and the severity of benign nephrosclerosis, when it was present, was graded arbitrarily as 1, 2, and 3, on the basis of kidney weights and the degree of microscopic arteriolar hyalinization and necrosis. Among the 500 autopsied patients, there were 50 men (41 white, 9 Negro) and 42 women (32 white, 10 Negro) with nephrosclerosis of 2 or 3 severity.

There were, in addition, 22 men (21 white, 1 Negro) and 23 women (20 white, 3 Negro) who died because of rheumatic cardiac valvular involvement, of whom 8 men and 12 women had mitral stenosis.

Mainland pointed out that hospital populations, and especially autopsy populations, are not representative of the general population of sick persons, and that this can considerably bias the apparent relationships of diseases to one another. In our

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TABLE 1.—Age Distribution of Patients

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Under 40</td>
<td>40-49</td>
</tr>
<tr>
<td>Caucasians</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Negroes</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Obese, hypertensive</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Obese, normotensive</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Thin, hypertensive</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thin, normotensive</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Normotensive</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Age-matched controls</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Rheumatic carditis</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Age-matched controls</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>

TABLE 2.—χ² and Fisher Tests

<table>
<thead>
<tr>
<th></th>
<th>Total number of patients</th>
<th>Total number of patients autopsied</th>
<th>p-value</th>
<th>Number of cerebral embolus</th>
<th>p-value</th>
<th>Number of aneurysm embolus</th>
<th>p-value</th>
<th>Number of cardiac embolus</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive men</td>
<td>38</td>
<td>27</td>
<td>&lt;0.001*</td>
<td>&gt;0.200</td>
<td>&gt;0.900</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhypertensive men</td>
<td>190</td>
<td>56</td>
<td>13</td>
<td>18</td>
<td>10</td>
<td>4</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive women</td>
<td>32</td>
<td>17</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhypertensive women</td>
<td>128</td>
<td>21</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&gt;0.500</td>
<td>&lt;0.010*</td>
<td>&lt;0.010*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese, nonhypertensive men</td>
<td>34</td>
<td>15</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thin, nonhypertensive men</td>
<td>47</td>
<td>6</td>
<td>&lt;0.010*</td>
<td>&gt;0.020</td>
<td>&gt;0.300</td>
<td>&lt;0.010*</td>
<td>&lt;0.010*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese, nonhypertensive women</td>
<td>17</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thin, nonhypertensive women</td>
<td>28</td>
<td>3</td>
<td>&gt;0.050</td>
<td>&gt;0.990</td>
<td>&gt;0.500</td>
<td>&gt;0.200</td>
<td>&gt;0.200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Probability 0.01 or less.

In this study, community incidence and fatality rates of the diseases studied could not be determined, and so these areas remain undefined and possible sources of error. The race and sex distributions of the patients admitted to the hospital and of those autopsied were similar, however, and this adds support to the validity of our data.

Control groups, unless otherwise denoted, were selected in every instance from patients of the same sex from this same autopsy series. The controls were decade-matched, but otherwise randomly selected (table 1). Atherosclerosis, obesity, and hypertension all become more severe with increasing age, but since the selection of control patients in this study involved decade-matching, distortion of results from unequal age distributions was minimized. In addition, in all of the study and control groups the patients were all of the same sex, thus eliminating bias due to differences in sex distributions. Although differences in atherosclerosis in white and Negro patients have been reported, the racial distributions of the pa-
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Table 3.—χ² and Fisher Test

<table>
<thead>
<tr>
<th></th>
<th>Total men with catastrophes</th>
<th>Control men</th>
<th>p-value</th>
<th>Total women with catastrophes</th>
<th>Control women</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with hypertension</td>
<td>27</td>
<td>11</td>
<td>&lt;0.001*</td>
<td>15</td>
<td>11</td>
<td>&lt;0.010*</td>
</tr>
<tr>
<td>Patients without hypertension</td>
<td>83</td>
<td>145</td>
<td></td>
<td>15</td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>

Higher incidence of hypertension, when compared with female control patients. On further analysis, it was found that the incidence differences in men were significant only in those men who had experienced cardiac catastrophes, whereas there were no significant increases in the occurrence of hypertension or obesity in men with aortic or cerebral catastrophes. In contrast, women with either cardiac or cerebral catastrophes had a significantly greater incidence of hypertension than their controls.

Conversely, as demonstrated in Table 3, both men and women with hypertension had a significantly greater number of atherosclerotic catastrophes, and especially of cardiac catastrophes, than did nonhypertensive patients. This was also true of obese, nonhypertensive men, but in contrast, the incidence of catastrophes was no higher among obese, nonhypertensive women than among their thin counterparts.

There was a significantly greater incidence of hypertension among obese patients of both sexes than among thin patients, and hypertensive patients were more often obese than were their nonhypertensive colleagues.

Patients of either sex with nephrosclerosis were hypertensive more often than patients without this disease, and likewise, hypertensive patients had nephrosclerosis a significantly greater number of times than did normotensive patients.

Atherosclerosis Profiles

In the obese men studied, according to Figure 1, the coronary arteries appear to be the only sites where atherosclerosis was more severe than in control patients. Furthermore, the presence of hypertension in these obese men demonstrates no additive effect on the degree of atherosclerosis in the various arteries. When the entire group of hypertensive men were examined with their control group (fig. 2), however, hypertension in males was found to be associated with an increase in the incidence and severity of atherosclerosis in both the coronary and cerebral arteries.

In women (fig. 3) obesity was not associ-
Fig. 1 Top. Mann-Whitney U Test: Probability (p) Values. Statistical analyses. Right main coronary, 0.002*; anterior descending coronary, 0.010*; descending thoracic aorta, 0.016; middle abdominal aorta, 0.460; right internal iliac, 0.027; right renal, 0.052; right middle cerebral, 0.00005*; basilar, 0.003.* (*Significance at 0.01 or less.)
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ated with increased atherosclerosis in any of the arteries studied, but hypertension, on the other hand, was associated with a striking increase in several areas. When all of the females with hypertension were studied (fig. 4), this increase was found to be even more marked and to include almost all of the vessels studied.

Although no illustrative figures are included in this report, there was no difference noted between the atherosclerosis of thin men and thin women. Likewise, the atherosclerosis profiles of obese, normotensive males and females, and of all the obese males and females resembled each other. Obese, hypertensive females, however, had more severe and widespread atherosclerosis than their male counterparts in their iliac and cerebral arteries. On the other hand, no quantitative differences were noted between the atherosclerosis of the entire group of hypertensive men and age-matched hypertensive women.

The amount of atherosclerosis in patients with nephrosclerosis, with few exceptions, resembled that occurring in patients with hypertension.

Although the pulmonary arteries in the men and women with rheumatic carditis appeared on the profiles to contain more widespread and more severe atherosclerosis than the pulmonary arteries of control patients, this was not statistically significant (figs. 5 and 6). There were no significant differences in any of the other arteries studied in these 4 groups. Men and women with mitral stenosis also appeared to have more severe and widespread atherosclerosis in their pulmonary arteries than did their controls, but these groups did not contain enough patients for adequate analysis. No quantitative differences were noted between the atherosclerosis of men and age-matched women with rheumatic heart disease.

DISCUSSION

Obesity and Atherosclerosis

Most observers have failed to find a direct relationship between atherosclerosis and obesity.9-11 There does seem to be a correlation, however, with physique, and atherosclerosis in men is thought to be earliest in onset and most severe in those with mesomorphic build.12, 13 Wilens5, 14 has pointed out that, since any change in nutrition that occurs with fatal disease is usually in one direction (i.e., well nourished to poorly nourished), any terminal thin group will include some persons who were formerly normal or obese. Therefore, he concluded that terminal loss of weight would tend to reduce rather than to exaggerate any true differences in the amount of atherosclerosis, if these were present, between obese and thin patients.

Various studies have shown that there is an increased incidence of both hypertension and diabetes in obese people,15-17 and patients with either hypertension or diabetes are more prone than patients without these diseases to develop severe atherosclerosis and to experience atherosclerotic catastrophes.16-20 Unfortunately, the number of patients with diabetes in this study was too small for statistical evaluation, but the presence of obesity in our nonhypertensive patients was not associated with an obviously increased incidence of diabetes. There was, however, a significantly greater occurrence of hypertension among obese patients of both sexes.

In our patients, obesity that was uncomplicated by hypertension appeared to influence significantly the severity and distribution of atherosclerosis only in the coronary arteries, and only in men. In obese, nonhypertensive men, compared with thin, nonhypertensive men, there was not only more widespread and severe coronary atherosclerosis, but also a greater number of cardiac atherosclerotic catastrophes.

Hypertension and Atherosclerosis

Agreeing with Goldenberg et al.21 that autopsy heart weight is the most reliable pathologic criterion of hypertension, in this study we used a weight of 400 Gm. for female hearts and 500 Gm. for male hearts as the top normal weights. These normal standards were set at slightly heavier weights than those used by previous authors,22 28 since it was considered that this would give sharper differentiation between hypertensive and normo-
<table>
<thead>
<tr>
<th></th>
<th>Obese, Hypertensive vs. thin</th>
<th>Obese, normotensive vs. thin</th>
<th>Obese vs. thin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right main coronary</td>
<td>0.012</td>
<td>0.302</td>
<td>0.057</td>
</tr>
<tr>
<td>Anterior descending</td>
<td>0.011</td>
<td>0.152</td>
<td>0.022</td>
</tr>
<tr>
<td>descending coronary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descending thoracic aorta</td>
<td>0.345</td>
<td>0.305</td>
<td>0.326</td>
</tr>
<tr>
<td>Middle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>0.008*</td>
<td>0.134</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*Significance at 0.01 or less.

**Fig. 3 Top.** Mann-Whitney U Test: Probability (p) Values.

**Fig. 4 Bottom.** Mann-Whitney U Test: Probability (p) Values. Right main coronary, 0.00003*; anterior descending coronary, 0.0003*; descending thoracic aorta, 0.0003*; middle abdominal aorta, 0.0005*; right internal iliac, 0.00003*; right renal, 0.0005*; right middle cerebral, 0.00003*; basilar, 0.00003.* (*Significance at 0.01 or less.)
tensive patients, especially in light of the reported ability of uncomplicated coronary artery disease to cause cardiac hypertrophy.\textsuperscript{24}

Obesity is reported to be more common among hypertensive than normotensive patients,\textsuperscript{10,16} and this was the case with our patients. Since obesity in our study group, however, was found in general to exert only a minor influence on the degree of atherosclerosis, our hypertensive patients were not cate-
dorized as to the presence or absence of obesity. Diabetes has also been reported to be more common among hypertensive patients, but this was not demonstrable in our patients with hypertension.

Although hypertension has usually been associated with increased atherosclerosis in both sexes, this has been especially true in women. Hypertension in the men in our study was associated with an increased degree of atherosclerosis in their coronary and cerebral vessels, and with a greater occurrence of cardiac catastrophes. This association was even more marked, and involved more arteries, among women with hypertension. These women had more severe atherosclerosis than normotensive women in most of the arteries studied, and in addition had a significantly higher number of cardiac catastrophes. Even though the presence of obesity or hypertension alone was associated with no quantitative difference between the atherosclerosis of men and of women, the presence of both of these diseases in the same patients was associated with a greater increase in atherosclerosis in women than in men.

Other Disease Relationships

The atherosclerosis of patients in our series who had nephrosclerosis was quantitatively similar to that in the patients who had hypertension. Furthermore, as stated above, patients of either sex with nephrosclerosis were significantly more often hypertensive than patients without this disease; and likewise, hypertensive patients had nephrosclerosis a significantly greater number of times than did normotensive patients.

It has been suggested that rheumatic arteritis increases the distribution and severity of coronary atherosclerosis, although other studies have indicated that persons dying of rheumatic carditis have less atherosclerosis than controls. The patients in our study group who had rheumatic carditis, however, had neither more nor less severe and widespread atherosclerosis than their control patients.

Summary

The incidences of obesity, hypertension, nephrosclerosis, and rheumatic carditis in 500 adult patients were noted at autopsy, and were correlated with the distribution and severity of concomitant atherosclerosis.

In men, obesity uncomplicated by hypertension was associated with a significant increase in the severity of coronary atherosclerosis and the occurrence of cardiac catastrophes. Uncomplicated obesity in women appeared to have no effect upon concomitant atherosclerosis.

Hypertension in men was associated with significantly increased coronary and cerebral atherosclerosis, and with a greater occurrence of myocardial infarction. Hypertensive women had significantly more severe atherosclerosis than normotensive women in most of the arteries studied, and also had significantly more myocardial infarcts.

The atherosclerosis of patients who had nephrosclerosis was similar in distribution and severity to that of patients who had hypertension.

The presence of rheumatic carditis appeared not to influence the extent or severity of concomitant atherosclerosis.

Acknowledgment


Summary in Interlingua

Le incidentia de obesitate, hypertension, nephrosclerosis, e carditis rheumatic esseva notate in 500 necropsias de patientes adulte, e le resultatos esseva correlacionate con le distribution e grados de severitate de atherosclerosis concomitante.

In masculos, obesitate non complicate per hypertension esseva associate con un augmento significative in le severitate de atherosclerosis coronari e le occurruntia de catastrophes cardiac. Obesitate sin complication in femininas parece haber nulle effecto super le atherosclerosis concomitante.
Hypertension in masculos esseva associate con augmentos significative de atherosclerosis coronari e cerebral e con un plus alte incidência de infarimento myocardial. Femiñas con hypertension havéba grados significativevamente plus sever de atherosclerosis que femininas normotensive in le majoritate del arterias studiase, e illas etiam havéba un significativevamente plus alte incidência de infarimentos myocardial.

Le atherosclerosis de patientes con nephro-sclerosis esseva simile in distribution e grado de severitate a illo del patientes con hypertension.

Le presentia de carditis rheumatic non pareva influentar le extension o le severitate de atherosclerosis concomitante.

REFERENCES
WILKINS, ROBERTS, MOSES


It has taken long ages of toilsome and often fruitless labour to enable man to look steadily at the shifting scenes of the phantasmagoria of Nature, to notice what is fixed among her fluctuations, and what is regular among her apparent irregularities; and it is only comparatively lately, within the last few centuries, that the conception of a universal order and of definite course of things, which we term the course of Nature, has emerged.

But, once originated, the conception of the constancy of the order of Nature has become the dominant idea of modern thought. To any person who is familiar with the facts upon which that conception is based and is competent to estimate their significance, it has ceased to be conceivable that chance should have any place in the universe, or that events should depend upon any but the natural sequence of cause and effect. We have come to look upon the present as the child of the past and as the parent of the future; and, as we have excluded chance from a place in the universe, so we ignore, even as a possibility, the notion of any interference with the order of Nature. Whatever may be men's speculative doctrines, it is quite certain that every intelligent person guides his life and risks his fortune upon the belief that the order of Nature is constant, and that the chain of natural causation is never broken.—Thomas H. Huxley. American Addresses with a Lecture on the Study of Biology. London, MacMillan and Co., 1877, p. 2.
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