Autopsy Studies in Atherosclerosis

I. Distribution and Severity of Atherosclerosis in Patients Dying without Morphologic Evidence of Atherosclerotic Catastrophe

By James C. Roberts, Jr., M.D., Campbell Moses, M.D., and Robert H. Wilkins, B.S.

Gross lesions of atherosclerosis in many arterial sites were graded in 500 consecutive autopsies in a general hospital. The grading system used took into account both the total area of intimal involvement and the severity of individual lesions. The first report analyzes the distribution and severity of atherosclerosis in the 347 men and women of the study group who died without morphologic evidence of atherosclerotic catastrophe in the heart, aorta, or brain. The second report describes the atherosclerotic lesions in patients who died with evidence of atherosclerotic catastrophe. The third report carries out a similar investigation in those subjects who presented evidence of obesity, hypertension, nephrosclerosis, and rheumatic heart disease.

This study was initiated to determine the distribution and severity of atherosclerosis in the major arteries of 500 consecutive adults dying in a general hospital. The present report describes the severity and distribution of atherosclerosis in 347 patients from this group who died without morphologic evidence of atherosclerotic catastrophe in the heart, aorta, or brain. The 2 succeeding papers deal with the atherosclerosis found in patients in the study group who died with evidence of atherosclerotic catastrophe, and the distribution of atherosclerosis in patients with obesity, hypertension, nephrosclerosis, and rheumatic heart disease.

Methods and Procedures

The 3 hospitals from which the patients came are combined in 1 physical plant with common laboratory facilities. No obstetric patients are admitted to these hospitals and no pediatric patients came to autopsy. During the period of this study (September 1955 through August 1957) 16,962 patients were admitted, of whom approximately 47 per cent were male and 93 per cent were white. The hospital death rate was 4.4 per cent (732 patients), and 510 of these came to autopsy (70 per cent). Ten autopsies were excluded from the study because incomplete autopsy examinations were authorized. Brain examinations (75 per cent of the autopsied cases) were routinely performed unless specifically excluded by the family. Primary causes of death for the entire study group are listed in Table 1. Distribution of the autopsied cases by age and sex are listed in Tables 2 and 3. A total of 261 white men, 35 Negro men, 173 white women, and 31 Negro women (i.e., 59 per cent male patients, and 87 per cent white patients) were studied.

Thoracic and abdominal organs, including the arteries, were stored in Jores preservative; tissue blocks and the brain including cerebral arteries were fixed in 10 per cent formalin. After examination of tissue sections from the organs of each case, all final morphologic diagnoses were reviewed by one or more of 3 staff pathologists.*

When brain examinations were not performed, an average of 27 of 29 sites from 20 arteries were studied grossly and graded. When brains were examined, an average of 38 of 41 sites from 32 arteries was included. All arteries were opened longitudinally with the exception of occasional occluded, stenotic, or calcified small arteries. These were examined by transverse cross-sections every 2 to 3 mm. The cerebral arteries were dissected from the brain and at least 5-cm. segments of anterior, middle, and posterior cerebral arteries were

*Dr.s. T. J. Moran and R. S. Totten participated in this aspect of the study and gave important advice and assistance throughout.

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TABLE 1.—Primary Cause of Death

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<th>Male</th>
<th>Female</th>
<th>Total</th>
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<tr>
<td>Cancer</td>
<td>131</td>
<td>66</td>
<td>197</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>64</td>
<td>20</td>
<td>84</td>
</tr>
<tr>
<td>Renal disease</td>
<td>16</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Gastrointestinal and liver diseases (other than above)</td>
<td>14</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>18</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>Hypertension (other than above)</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Syphilis and tuberculosis</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Trauma</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>29</td>
<td>56</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>296</td>
<td>204</td>
<td>500</td>
</tr>
</tbody>
</table>

removed. The length of the vertebral artery segments varied, but they usually measured over 1 cm.

The grading system used combined both an estimate of area of total intimal involvement in a given site and the severity of the worst individual plaque at the site. Lipid stains were not used. If no atherosclerosis was observed (fig. 1A), the letter “O” was recorded. If less than 25 per cent of the area of the intimal surface was involved with any grossly visible lesions (fig. 1B), the degree of involvement was recorded as “A”; if 25 to 75 per cent of the intima was involved (fig. 1C), it was recorded as “B”; and if over 75 per cent was involved (fig. 1D), the site was recorded as “C.”

The worst lesion at each site was then studied (no distinction was made between lipid and fibrous plaques). If the worst lesion was not ulcerated or thrombosed and its largest diameter was less than one fifth the inner circumference of the site (fig. 1E), a numerical value of 1 was added to the letter grade; if the plaque was larger than one fifth the inner circumference of the site, but without ulcer or thrombus, (fig. 1F), 2 was added to the letter grade; if an ulcer, but no thrombus, was present on any-sized lesion (fig. 1G), 3 was added to the letter grade; and if a thrombus (occlusive or nonocclusive) was present on any-sized lesion (fig. 1H), 4 was added to the letter grade. The grading was done by the authors in about one half the cases and in one half by residents who were instructed in the grading system.

For visualization of the atherosclerosis of the sites studied, “atherosclerosis profiles” were constructed by assigning to the letter grade O, A, B, or C the value 1, 2, 3, or 4, and adding this to the number of plus signs recorded at each site. These 2 values were then averaged (table 4). The average obtained were grouped for the various sex, race, and disease categories and charted as group atherosclerosis profiles.

Statistical analyses of the results observed in 8 areas were performed according to the Mann-Whitney U test, a nonparametric test. These were the right main coronary artery, the anterior descending coronary artery, the descending thoracic aorta, the middle of the abdominal aorta, the right internal iliac artery, the right renal artery, the right middle cerebral artery, and the basilar artery. A nonparametric test was necessary for analysis of our data because this type of statistical test does not make assumptions about the normal population distribution, and avoids the use of arithmetic processes on scores derived from a scale that does not have an absolute zero or equal units. Although in our grading system uninvolved areas were scored zero, the values assigned to involved areas were arbitrary and not necessarily separated by equal units.

In addition, the age, race, and disease distribution of patients was evaluated by means of the $x^2$, and Fisher exact probability tests, both of which compare the proportions of cases falling into various categories in one group with the proportions of cases falling into the same categories in another group. The $x^2$ test was applied to those groups which contained more than 40 patients, and the Fisher test was employed when smaller groups were involved. The probability level of significance for all of these statistical tests was arbitrarily set at $p = 0.01$.

Atherosclerotic catastrophes are defined in this study as recent or old myocardial infarcts; aneurysms of the aorta not due to cystic medial necrosis or syphilis; thrombotic occlusion of the abdominal aorta; and recent or old cerebral infarcts. The 317 patients who died without evidence of these catastrophes are the subjects of this report.

Figures 2 to 7 are the group atherosclerosis profiles of the various patients without atherosclerotic catastrophes; below each atherosclerosis profile are recorded the 8 sites that were studied statistically. The arteries are listed across the tops of the atherosclerosis profiles in the following order: right and left pulmonary; right and left main coronary; left circumflex coronary; anterior and posterior descending coronary; ascending, arch, and descending portions of the thoracic aorta; 3 segments of the abdominal aorta; 3 segments of right common iliae; 3 segments of left common iliae; right and

*Joseph F. Sunder, M.S., gave important advice and assistance in this phase of the study.
Fig. 1. A, area involved, grade 0; B, area involved, grade A; C, area involved, grade B; D, area involved, grade C; E, severity grade 1 plus; F, severity grade 2 plus; G, severity grade 3 plus; H, severity grade 4 plus.
Fig. 2 Top. Ages 16-30. Statistical analyses. Right pulmonary, 0.160; right main coronary, 0.319; anterior descending coronary, 0.367; descending thoracic aorta, 0.087; middle abdominal aorta, 0.198; right internal iliac, 0.298; right renal, 0.460; right middle cerebral, 0.174; basilar, 0.174.

Fig. 3 Bottom. Ages 30-39. Statistical analyses. Right main coronary, 0.00003*; anterior descending coronary, 0.004*; descending thoracic aorta, 0.017; middle abdominal aorta, 0.040; right upper common iliac, 0.006*; right internal iliac, 0.097; right external iliac, 0.009*; right renal, 0.010*; right middle cerebral, 0.195; basilar, 0.053 (*Significant at 0.01 or less.)
Fig. 4 Top. Ages 40-49. Statistical analyses. Right main coronary, 0.045; anterior descending coronary, 0.394; descending thoracic aorta, 0.323; middle abdominal aorta, 0.271; right internal iliac, 0.203; right renal, 0.230; right middle cerebral, 0.209; basilar, 0.206.

Fig. 5 Bottom. Ages 50-59. Statistical analyses. Right main coronary, 0.409; anterior descending coronary, 0.156; descending thoracic aorta, 0.037; middle abdominal aorta, 0.048; right internal iliac, 0.334; right renal, 0.145; right middle cerebral, 0.359; basilar, 0.365.
left internal iliac; right and left external iliac; splenic; celiac; superior and inferior mesenteric; right and left renal; right and left anterior cerebral; anterior communicating cerebral; right and left middle cerebral; right and left posterior communicating cerebral; right and left posterior cerebral; basilar; and right and left vertebral arteries.

RESULTS AND DISCUSSION

The distribution of atherosclerosis in the body at autopsy has long been the subject of morphologic studies. Most of these studies, however, have been either retrospective, selective as to patients, selective and incomplete as to the arteries studied, or based on grading systems which considered primarily either the worst area involved or the total intimal involvement. This study has been prospective and has included all patients autopsied in a general medical and surgical hospital. It has included as many cerebral, thoracic, and abdominal arteries as was feasible, and has been based on a grading system that takes into account both the area of most severe involvement and the total extent of intimal involvement.

The atherosclerosis profiles of these subjects dying without vascular catastrophes support the generally accepted views that atherosclerosis increases with age and involves primarily the larger arteries. Statistical analysis of these profiles demonstrates a significant sex difference in the distribution and severity of atherosclerosis only in the fourth decade and only in the coronary, iliac, and renal arteries. These data are in conflict with those of others who report prominent sex differences until the seventh decade. Although our data support the generally recognized view that males have more vascular catastrophes than females (table 2), the finding of similarly widespread and severe atherosclerosis in “non-catastrophic” males and females, suggests that the occurrence of catastrophes may be sex related, but that the extent and severity of atherosclerosis are not necessarily so influenced.

Pulmonary Arteries. The pulmonary arteries showed relatively few lesions of atherosclerosis at any age, no discernible differences between the sexes, and no differences between the right and left artery.

Coronary Arteries. In the men and women in this study, as in other reports, the right main coronary artery and the anterior descending coronary artery generally contained the most severe coronary atherosclerosis.

In young men under 30 no artery had more than slight disease. Enos et al. found what they considered moderate to severe lesions in many men under 30 dying in Korea. However, their grading was based on the severity of single lesions rather than on both the extent and severity of involvement, and their subjects were healthy men, killed in action, rather than men with terminal disease.

Aorta. The abdominal aorta in all decades and in both sexes contained by far the most severe atherosclerosis, and the lower two thirds (below the orifice of the celiac artery) contained more than the first third. The arch of the aorta was the most severely involved portion of the thoracic aorta. The lack of atherosclerosis in the ascending aorta of our subjects was striking, and is at variance with older studies quoted by Allbutt. The explanation may lie in the decrease in syphilis over the years, since the few syphilitic cases we studied demonstrated severe lesions in the ascending aorta. Our data are in essential agreement with those of Gore and of Holman et al.

Iliac Arteries. The common iliac arteries were similar to the arch and descending thoracic aorta throughout the decades and demonstrated sex differences only in the fourth decade. The internal iliac arteries had little atherosclerosis in either sex until the fifth decade, when significant disease in both sexes was readily demonstrable. The external iliac arteries of males of the fourth decade had an increased degree of atherosclerosis when compared with females, but no other sex difference was observed. Past the age of 50, the internal iliac arteries appeared to contain more atherosclerosis than did the external iliacs.
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**Fig. 6 Top.** Ages 60-69. Statistical analyses. Right main coronary, 0.363; anterior descending coronary, 0.436; descending thoracic aorta, 0.484; middle abdominal aorta, 0.334; right internal iliac, 0.104; right renal, 0.014; right middle cerebral, 0.429; basilar, 0.268.

**Fig. 7 Bottom.** Ages 70-97. Statistical analyses. Right main coronary, 0.251; anterior descending coronary, 0.027; descending thoracic aorta, 0.245; middle abdominal aorta, 0.251; right internal iliac, 0.076; right renal, 0.417; right middle cerebral, 0.071; basilar, 0.444.
TABLE 2.—Age by Decades

<table>
<thead>
<tr>
<th>Decade</th>
<th>Nonecatastrophic Male</th>
<th>Nonecatastrophic Female</th>
<th>Catastrophic Male</th>
<th>Catastrophic Female</th>
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<tr>
<td>16-29</td>
<td>16</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>30-39</td>
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<td>40-49</td>
<td>24</td>
<td>37</td>
<td>9</td>
<td>4</td>
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<tr>
<td>50-59</td>
<td>42</td>
<td>37</td>
<td>26</td>
<td>12</td>
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<tr>
<td>60-69</td>
<td>58</td>
<td>27</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>70-79</td>
<td>32</td>
<td>23</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>155</td>
<td>104*</td>
<td>49*</td>
</tr>
</tbody>
</table>

*The proportion of men with catastrophes is significantly larger than the proportion of women with catastrophes ($p = 0.01$).

TABLE 3.—Sex Distribution

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Total studied</td>
<td>296</td>
<td>204</td>
<td>500</td>
</tr>
<tr>
<td>Nonecatastrophic</td>
<td>192</td>
<td>155</td>
<td>347</td>
</tr>
<tr>
<td>Catastrophic*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heart</td>
<td>78</td>
<td>28</td>
<td>106</td>
</tr>
<tr>
<td>Brain</td>
<td>20</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Aorta</td>
<td>26</td>
<td>10</td>
<td>36</td>
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</tbody>
</table>

*Several had multiple catastrophes.

TABLE 4.—Weighing the Extent and Severity of Atherosclerosis

<table>
<thead>
<tr>
<th>Severity of worst lesion</th>
<th>Extent of intimal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
</tr>
<tr>
<td>+</td>
<td>1.0</td>
</tr>
<tr>
<td>++</td>
<td>2.0</td>
</tr>
<tr>
<td>+++</td>
<td>3.0</td>
</tr>
<tr>
<td>++++</td>
<td>4.0</td>
</tr>
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</table>

_Splenic and Celiac Arteries._ These vessels rarely had much atherosclerosis until the patients were beyond the age of 70, and no sex difference occurred. At any age they had less disease than almost any other vessels studied. This is again at variance with the older works quoted by Allbutt, wherein these vessels were listed high in the order of liability. These observers may have equated tortuosity and medial calcification with intimal lesions.

_Mesenteric and Renal Arteries._ The superior mesenteric artery and the renal arteries were similar to the splenic and celiac arteries at any age. There were no sex differences noted except in the renal arteries in the fourth decade. The inferior mesenteric artery was almost uniformly without lesions, a finding also stressed by Allbutt.4

_Cerebral Arteries._ These arteries demonstrated no consistent pattern and were extremely variable. The thoracic and abdominal arteries tended to be moderately homogeneous in their distribution of lesions, but the cerebral arteries showed no such homogeneity, and about 30 per cent (males 7/23; females 4/12) of the patients over 70 showed no gross atherosclerotic lesions in the 12 vessels examined. The anterior cerebral and communicating arteries had few lesions at any age and generally less than the other visceral and cerebral vessels. The posterior cerebral and vertebral arteries had somewhat more atherosclerosis than the anterior cerebral and communicating vessels. The middle cerebral and basilar arteries had the most atherosclerosis. Unfortunately, the internal carotid arteries were not included in the study. If a "parallelism" between the atherosclerosis of cerebral and visceral arteries exists, it is not clearly evident in our material. In this series, cerebral atherosclerosis started later and remained less severe than that in visceral arteries of the same size. This is in agreement with the findings of Winter et al.17 but at variance with other reports.20 The inclusion of cerebral examination in 75 per cent of the routine autopsies (without regard to antemortem cerebral findings) may explain the discrepancy of these data with reports20 describing the presence of more and severe cerebral atherosclerosis in later years of life.

**Summary**

The distribution and severity of gross atherosclerosis at autopsy in 347 patients dying without morphologic evidence of atherosclerotic catastrophes in the heart, aorta or brain have been graphically outlined. This study used a grading system for atherosclerosis that included consideration of both the extent and severity of intimal involvement. The observations included (a) the similarity of the severity and distribution of atherosclerosis in both sexes after the age of 40, (b) the lack of atherosclerosis in the cerebral...
vessels of patients in the later decades, and (c) the minimal atherosclerosis in the pulmonary and abdominal visceral arteries.

ACKNOWLEDGMENT
The authors thank Mr. Allen Ellis for his loyal help in the study. The photography was performed by Mr. Albert Levin, F.B.P.A.

SUMMARIO IN INTERLINGUA
Es delineate graphicamente le distribution e le severitate de atherosclerosis grossier notate in 347 necropsias de patients morte sin evidentia morphologic de catastrophes atherosclerotic in corde, aorta, a cervebro. Le present studio utilisa un systema de notas evaluatori pro le varie casos de atherosclerosis que prende in consideration tanto le extension como etiam le severitate del affection intimal. Le observationes include (a) le similitude del severitate e del distribution de atherosclerosis in le due sexos post le etate de 40 annos, (b) le absentia de atherosclerosis in le vasos cerebral de patients de etates plus avianti, e (c) le presentia de atherosclerosis minimal in le arterias visceral pulmonar e abdominal.

REFERENCES
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