A Comparative Study of Cerebral Atherosclerosis in Males and Females

By George C. Flora, M.D., A. B. Baker, M.D., Ruth B. Loewenson, Ph.D., and Arthur C. Klassen, M.D.

SUMMARY
An evaluation of the influence of sex upon cerebral atherosclerosis was carried out in 5,033 consecutive autopsies studied by a special well-standardized coding technique. A sex difference in frequency of cerebral atherosclerosis appears from the fourth to the sixth decade. During this period the percentage of female cases with no atherosclerosis lags behind the percentage of male cases by a 15-year period. After the sixth decade, the frequency of cerebral atherosclerosis increases more rapidly in females, so that beyond the age of 65 years the frequency of cerebral atherosclerosis is equal in the two sexes. Furthermore, younger males show a higher degree of cerebral atherosclerosis than females of the same age and a reverse trend appears in the oldest age groups. Diabetic females have more cerebral atherosclerosis than nondiabetic males, and beyond the fourth decade they have at least as much involvement as the diabetic males.

Additional Indexing Words:
Diabetes Estrogens Lipid changes

ONE of the challenging problems concerning atherosclerosis is the influence of sex upon its incidence, progress, and complications. Extensive documentation suggests that clinical coronary disease occurs from five to ten times as often in men as in women.1-6 In contrast to the evidence that clinical coronary disease is more common in males, the literature is much less convincing regarding the status of pathologically documented coronary atherosclerosis in the two sexes. A number of statistical studies of the frequency of coronary atherosclerosis carried out in North America and Europe indicate that atherosclerosis occurs at an earlier age and is more extensive in males than in females.7-13 During the third through the fifth decades of life, the severity of atherosclerosis in men has been established to be twice that of women.9,11,12,14-16 The frequency of coronary atherosclerosis in the sexes apparently becomes equal in the older age groups, varying in different reports from age 5014,16,17 to age 70.7,8

It is apparent, from a review of the literature, that in the North American population there appears to be a definite difference in the frequency and severity of coronary atherosclerosis in the sexes, with the males being more severely implicated. However, this situation does not necessarily hold true for atherosclerosis in all vessel groups. In most reports, the aorta does not seem to follow the same pattern as the coronary arteries.16,18,19 Since there appears to be a difference in the atherosclerotic process in each of the artery groups within the body, one cannot form any definite conclusions regarding atherosclerosis of the cerebral arteries from reports now available on other artery groups. It was, therefore, felt of value to undertake a comprehensive study of atherosclerosis in the cerebral arteries in a large series of autopsied cases. A review of the available literature on atherosclerosis of the cerebral arteries offered little conclusive information, since no carefully controlled large
series of cases has been reported. In most of the reports, no differences in the degree or the severity of cerebral atherosclerosis have been found in the two sexes.\textsuperscript{15, 20, 21}

**Methods**

The present report consists of an evaluation of the influence of sex upon cerebral atherosclerosis in a study of 5,033 consecutive autopsies. The study material was obtained from routine autopsies performed at the University of Minnesota Hospitals (UMH) and at Hennepin County General Hospital (HCGH) during the period between 1961 and 1965. The University of Minnesota Hospitals serves the metropolitan area of Minneapolis and St. Paul, as well as the whole State of Minnesota, as a referral center. The Hennepin County General Hospital serves primarily the population of Hennepin County, which includes Minneapolis and most of its suburban area.

The number of autopsies and the number of circles of Willis obtained for the study in the year 1965 are listed by sex in Table I. In the same table, the autopsy rates are given; in addition, the table includes the cases entered into the study as a percentage of hospital deaths and of autopsies performed. The ratio of male to female deaths is much higher at Hennepin County General Hospital (HCGH) than at the University of Minnesota Hospitals (UMH). The sex ratio for deaths for both hospitals together is 1.5; in 1965 the same ratio for Hennepin County was 1.3 and for the State of Minnesota it was 1.4. The autopsy rate for UMH is slightly higher for males than for females, while at HCGH the rates are the same for both sexes. A higher autopsy rate for males than for females was also found by Beadenkopf and associates\textsuperscript{22} and by McMahan.\textsuperscript{23} These authors also pointed out that younger individuals more frequently come to autopsy than older ones; a similar difference was found between the age distributions of our autopsied cases and all deaths in Minnesota for the year 1965.\textsuperscript{24} The proportion of autopsied cases in which the circle of Willis was studied is higher for males than for females at UMH, but this is reversed at HCGH; for the total in 1965, the two proportions are almost equal.

In each of these autopsied cases the arteries of the circle of Willis were carefully coded for the atherosclerotic process, using the coding system of Baker and his associates.\textsuperscript{25, 26} The coding technique divides atherosclerosis into four fairly clear-cut groups (fig. 1): grade 1+, opacity involving only a small part of the vessel circumference with no narrowing of the lumen; grade 2+, (A) diffuse thin plaque that does not involve the entire vessel circumference with minimal luminal narrowing; (B) a small thick plaque that produces less than 25% luminal narrowing; grade 3+, (A) a diffuse thin plaque involving the entire vessel circumference with mild luminal narrowing; (B) a localized thick plaque producing 25 to 50% luminal narrowing; and grade 4+, (A) a thick plaque involving the entire vessel circumference with moderate or marked luminal narrowing; (B) a localized thick plaque resulting in over 50% luminal narrowing.

In order to determine the extent of the total atherosclerotic process, 22 well-defined areas along the circle of Willis were studied and graded as to the degree of atherosclerosis, according to the above-named coding system (fig. 2). Each of these 22 areas was graded from 0 to 4+. The total numerical value for the degree of the atherosclerotic process could then be obtained.

<table>
<thead>
<tr>
<th></th>
<th>UMH</th>
<th>HCGH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>M/F</td>
</tr>
<tr>
<td>Deaths</td>
<td>434</td>
<td>376</td>
<td>1.2</td>
</tr>
<tr>
<td>Autopsies</td>
<td>376</td>
<td>282</td>
<td>1.3</td>
</tr>
<tr>
<td>Circles of Willis</td>
<td>306</td>
<td>213</td>
<td>1.4</td>
</tr>
<tr>
<td>(% of deaths)</td>
<td>86.6</td>
<td>80.3</td>
<td></td>
</tr>
<tr>
<td>Circles of Willis</td>
<td>81.4</td>
<td>75.5</td>
<td></td>
</tr>
<tr>
<td>(% of autopsies)</td>
<td>70.5</td>
<td>60.7</td>
<td></td>
</tr>
</tbody>
</table>

*Admissions by sex are not available at these institutions.

Total admissions: UMH = 15,558; HCGH = 12,433. Note: "Admissions" do not coincide with "patients" because of multiple admissions.
by adding the totals of all the graded areas. Thus, since 22 areas were coded and the most severe change was 4+, using this technique, the greatest degree of atherosclerosis was 22x4, or 88. Few cases showed as much as 40 points of atherosclerosis, since many of the smaller vessels studied rarely showed any gross involvement.

We felt that this coding technique definitely offered certain advantages over a number of previously published coding procedures for the following reasons: (1) The different grades of involvement were so well-defined that the coding could be readily duplicated with a high degree of accuracy by different investigators. (2) The coding technique was simple enough so that it could be completed within minutes without interfering with the general autopsy studies; thus it enabled a large series of cases to be studied in a relatively short time. (3) The areas of the circle of Willis to be coded were clearly defined so that identical areas were coded in each case. (4) The coding system indicated involvement of both the vessel wall and the vessel lumen. (5) Enough areas were coded to give an adequate indication of both the degree and extent of the entire atherosclerotic involvement of the circle of Willis.

Reliability studies on the scoring method were conducted between the two investigators who had scored nearly the entire series of circles of Willis. In a first study, 24 circles of Willis, unidentified as to the age and the sex of the patients, were scored twice by coders using the routine procedure. The scoring was performed independently and "blind." The 95% confidence interval for the difference in mean scores was 0.3 ± 1.6. The standard deviation for repeated readings for a given coder was ±3.9. The variability in repeated scorings was largely due to the fact that, after several cuttings of the arteries at the scoring sites, pieces of the vessel were lost between codings. In a second study the same number of specimens were cut at various scoring sites by a pathologist not involved in the scoring, and the two coders scored only the precut vessels. The results of the second study were as follows: the 95% confidence interval for the difference in mean scores was 0.8 ± 1.1 and the standard deviation for repeated scorings was ±2.1.24

**Observations**

Since our material consisted chiefly of hospitalized patients, the question can be raised as to whether this study would adequately...
Figure 2
Twenty-two areas of the circle of Willis which are graded according to the degree of atherosclerosis.

Figure 3
The frequency of atherosclerosis in hospitalized and accidental injury cases by age. Note the marked similarity of the findings.

Figure 4
Median vessel score in cases of accidental deaths as compared with those in all cases. The scores for the two groups are similar until the seventh decade of life.

Figure 5
Distribution of total vessel scores by sex. Values are presented in percentiles at a given age. Note that males have a higher atherosclerotic score than females in all age groups, up to the eighth decade.

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CEREBRAL ATHEROSCLEROSIS

Table 2

Number Of Cases By Age and Sex

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>442</td>
<td>310</td>
<td>752</td>
</tr>
<tr>
<td>10-19</td>
<td>120</td>
<td>77</td>
<td>197</td>
</tr>
<tr>
<td>20-29</td>
<td>164</td>
<td>86</td>
<td>250</td>
</tr>
<tr>
<td>30-39</td>
<td>184</td>
<td>148</td>
<td>332</td>
</tr>
<tr>
<td>40-49</td>
<td>336</td>
<td>282</td>
<td>618</td>
</tr>
<tr>
<td>50-59</td>
<td>527</td>
<td>334</td>
<td>861</td>
</tr>
<tr>
<td>60-69</td>
<td>560</td>
<td>337</td>
<td>897</td>
</tr>
<tr>
<td>70-79</td>
<td>536</td>
<td>278</td>
<td>814</td>
</tr>
<tr>
<td>80+</td>
<td>198</td>
<td>114</td>
<td>312</td>
</tr>
<tr>
<td>Total</td>
<td>3,067</td>
<td>1,966</td>
<td>5,033</td>
</tr>
</tbody>
</table>

The distributions of total vessel scores by sex is presented in figure 5. The fifth, twenty-fifth, fiftieth (median), seventy-fifth, and ninety-fifth percentiles were determined for each 10-year age group. These percentile points were plotted at the midpoints of each 10-year age interval, and the lines connecting equal percentile points represent curves for all ages. The number of cases by 10-year age groups and sex are given in table 2.

The comparison between percentile curves for males and females shows that males have higher cerebral atherosclerosis scores than females for a given age until the eighth decade, when all female percentile curves cross those for males; in the oldest age group the percentile scores for females are consistently higher than those for males. The largest sex difference is found in the ninety-fifth percentiles in the fourth and fifth decades, indicating that the males have a considerably higher degree of cerebral atherosclerosis than the females in these age groups. The largest differences between median scores occur in the sixth decade and in the age group 80 years and older. In the sixth decade the median value for males is 6 and that for females is 2. The median curve for males has a value of 2 a decade earlier, indicating that, on the average, males show a given degree of cerebral atherosclerosis 10 years earlier than females during the fifth and sixth decades. A reversed sex difference of 7 points is found between the median scores in the oldest age group.

Not only the severity but also the frequency of any detectable cerebral atherosclerotic lesions is greater in the males than in the females in all but the oldest age group; all percentile curves except that for the fifth percentile rise above a zero score one decade earlier in the males than in the females. This sex difference in the frequency of detectable atherosclerosis in the circle of Willis is further illustrated in figure 6, where the percentage of zero scores in each age group is shown for both sexes.

Cerebral atherosclerosis first becomes apparent in both sexes in the first decade of life. Our youngest female patient was a premature infant 2 days old who had seven fairly extensive and grossly visible plaques of sclerosis in the circle of Willis involving both middle cerebral arteries, both posterior cerebral arteries, and the basilar artery. Our youngest male was a 7-year-old boy with congenital heart disease. He had five distinct plaques in various branches of the circle. Cerebral atherosclerosis remains relatively infrequent but somewhat equal in the sexes through the first three decades of life (fig. 6). It then increases fairly rapidly in both sexes, but more so in the male, so that from the fourth through the sixth decades of life approximately 20% more of the male population reveal

Figure 6

The frequency of zero scores for cerebral atherosclerosis by decades in the two sexes, as observed in 5,033 consecutive autopsies in a Minnesota population.
atherosclerotic changes than the female group. During this period the percentage of 0-scores for females lags behind the males by a 15-year period. After the sixth decade, the frequency of cerebral atherosclerosis increases more rapidly in the female population so that beyond the age of 65 years the frequency of cerebral atherosclerosis is equal in the two sexes (fig. 6).

Since there is some question as to the comparability of the patterns of atherosclerosis in different vessel groups, it might be of interest to compare our findings in the cerebral arteries with those reported for the coronary arteries. Generally, one is impressed by the similarity of the pathological involvement of these two vessel groups. Neth and Schwarting,12 in a study of coronary atherosclerosis in 10,383 cases, found that the involvement in the two sexes was identical up to the thirtieth year. There was then a sharp increase in frequency in both sexes, but this increase was more pronounced in the males. These observations are identical to our findings in the cerebral arteries. There is considerable difference of opinion concerning how long this sex difference persists in the coronary arteries. Neth and Schwarting12 and Henschen27 felt that the sex difference persisted to the eighth decade of life. On the other hand, many investigators such as Antichkov,28 Zschoch,17 and Groom et al.18 reported an equalization in the frequency of the coronary involvement in the sexes by the end of the fifth decade. Even the degree of difference between the two sexes appears to be very similar in the coronary and the cerebral arteries. Kolb,9 as well as Lober,14 observed that coronary atherosclerosis appears in women 10 to 15 years later than in men, an observation that is identical to our findings in the cerebral arteries in certain age groups. Dormanns and Emminger7 reported severe changes in the coronary arteries which were almost identical to those observed by us for the cerebral vessels. In their cases the frequency of severe changes became equal in the sexes in the seventh decade, which coincides approximately with our observations on the cerebral arteries.

It has been pointed out that the apparent immunity of young white women to coronary

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**Table 3**

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetes</td>
<td>No diabetes</td>
</tr>
<tr>
<td>0-9</td>
<td>2</td>
<td>440</td>
</tr>
<tr>
<td>10-19</td>
<td>1</td>
<td>119</td>
</tr>
<tr>
<td>20-29</td>
<td>2</td>
<td>162</td>
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<td>30-39</td>
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<td>50-59</td>
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<td>60-69</td>
<td>39</td>
<td>521</td>
</tr>
<tr>
<td>70-79</td>
<td>37</td>
<td>499</td>
</tr>
<tr>
<td>80+</td>
<td>9</td>
<td>189</td>
</tr>
</tbody>
</table>

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**Figure 7**

The influence of diabetes in cerebral atherosclerosis. Note that diabetic females have more involvement than normal males. By the fifth decade of life the diabetic females have as much cerebral atherosclerosis as the diabetic male.
atherosclerosis rapidly disappears in the presence of diabetes or hypertension, two conditions that appear to be highly atherogenic. Root and his associates,29 in a study of coronary atherosclerosis in 349 diabetics, found the coronaries to be involved in 45% of the males and in 53% of the females, whereas in the nondiabetics, only 36.7% of the females and 63.3% of the males were implicated. Similar findings were reported by Nathanson.30 Our studies were somewhat limited by the number of diabetics available for coding; the sample sizes by age and sex are given in table 3. However, even in our small series, the trend for the frequency of cerebral atherosclerosis in the sexes was striking (fig. 7). The median vessel scores for diabetic and nondiabetic males and females are shown in figure 8. Cerebral atherosclerosis was greatly increased by the diabetic process in both sexes. The diabetic females had considerably more cerebral atherosclerosis than the normal males. Beyond the fourth decade the frequency of cerebral atherosclerosis in the diabetic female was approximately the same as in the diabetic male, and in the fifth and sixth decades the diabetic females actually showed higher median vessel scores than the diabetic males. It is apparent that any protection offered by the patient's sex is rapidly lost in the presence of such a highly atherogenic condition as diabetes.

Discussion

From an analysis of our cases, it would appear that there is a definite sex influence on cerebral atherosclerosis which is similar to that reported for the coronary arteries. A number of factors have been suggested as playing a role in producing this reduction of the atherosclerotic process in the female population. Differences in the lipid composition of the plasma of men and women have been detected by a number of investigators using various techniques.31-33 All these investigators have observed a sex-linked variation in the lipoprotein composition of the plasma. Young men and young women have an almost equal concentration of cholesterol, but in young women the concentration of phospholipid is higher and the cholesterol-phospholipid ratio tends to be lower than in young men. It has been suggested that the physiological depression, at ovulation, of the plasma total cholesterol and the cholesterol-phospholipid ratio might be due to endogenous estrogen secretion and could account for the sex influence on the blood lipids.34-37 It has now been definitely shown that estrogens administered to humans can effect the distribution of lipids in the plasma, resulting in a reduction of the serum cholesterol and cholesterol-phospholipid ratio; there is also a reduction of the beta lipoproteins, which approaches the patterns and levels found in the normal premenstrual woman.38-40 Ei- lert41,42 reported that oral administration of estrogens to menopausal women results in an average decrease in the serum cholesterol level, together with an increase in the serum phospholipid content.

Estrogens have now been used fairly extensively in males surviving their first myocardial infarct. Invariably the estrogens will produce a favorable change in the serum lipid ratios which can be maintained under such therapy. However, to date there is limited evidence that such therapy reverses the atherosclerotic process in man or improves
the prognosis once myocardial infarction has occurred.\textsuperscript{45-48}

Estrogens have also been used extensively in males who have been castrated as therapy for carcinoma of the prostate.\textsuperscript{49, 50} Rivin and Dimitroff\textsuperscript{49} reported on 153 such cases, in 53 of which estrogen was given for 3 months or more. There was less coronary atherosclerosis in the estrogen-treated group. The aorta and cerebral vessels also showed some decrease but to a lesser degree.

In determining the possible influence of hormonal factors on atherosclerosis, a significant observation from the standpoint of our studies would be the rate at which atherosclerosis develops in the female at different periods of life as compared to the male. If endocrine factors are important, there should be a rapid increase in the frequency and severity of atherosclerosis at the time of menopause when the estrogens are reduced and the serum lipids show a change toward the male level. This did occur in our cases. Until the sixth decade of life, the females showed a consistent reduction in the frequency and severity of the cerebral atherosclerosis. After the sixth decade, the frequency of cerebral atherosclerosis increased more rapidly in the female population, so that beyond age 70, the females showed as much or more cerebral atherosclerosis than the males. Similar observations were reported by Ackerman and his associates\textsuperscript{5} and Novak and Williams,\textsuperscript{51} who found that the degree of coronary atherosclerosis in women rose steadily from the fourth to the eighth decades of life.

The reported studies on the influence of estrogens on atherosclerosis in animals and man present an optimistic picture in relation to this process. There is no question that the observations of Pick,\textsuperscript{52} and Katz and associates\textsuperscript{57} have shown that estrogens will cause a regression of cholesterol-induced coronary atherosclerosis in chicks despite continued presence in the diet of an atherogenic stimulus. In order for estrogens to reduce atheroma in the age group of prostatic carcinoma, one would have to postulate not only protection but also actual reversal of the atherosclerotic process. This has been suggested by a number of investigators.\textsuperscript{49, 50, 53-55} The observations of Baker and his associates\textsuperscript{65} on the frequency of cerebral atherosclerosis in patients with malignancy as compared to a normal population would further suggest that atherosclerosis is a reversible process. In these studies, patients with malignancy had atherosclerosis at a later age than the normal population (1 to 2 decades later). Since the patients with malignancy lived only a year or two after the onset of the illness, one would have to postulate that the marked difference in the atherosclerotic process could only be accounted for by the fact that the cerebral atherosclerosis actually regressed in patients with malignancy.

Some investigators have felt that the sex difference in atherosclerosis is congenital in origin and is apparent in the vascular structures even at the time of birth. Dock\textsuperscript{54} suggested that there is a structural difference in the coronary arteries of males and females even in the newborn. Sixty-one per cent of the females and only 32% of the males had endothelium lying directly on the inner elastic membrane with no thickening of the intima. The male begins life with about three times as much coronary intima as the female. Lober,\textsuperscript{14} in a detailed study of the coronary arteries in 536 hearts, reported that there was a mathematically significant difference in intimal thickness in arteries in specimens from males and females between the ages of 1 to 12 months. He felt that if intimal thickness is used as a criterion, the age at which sex differences appear is very early. Similar studies on vessels other than the coronaries have not been reported. Unless similar findings are available for vessels other than the coronary arteries, the significance of such observations in regard to the influence of sex on atherosclerosis must be reserved.

Conclusions

A review of the literature suggests that coronary atherosclerosis in North America
and Europe is more frequent and more extensive in males than in females between the ages of 30 and 60.

Conclusions from the study of the possible sex influence on atherosclerosis of the cerebral arteries carried in process this autopsies by the in the equal of extensive in males, through the first decade of life in plasma cholesterol-phospholipid difference atherosclerosis in men and women; so that by the ninth decade of life the females have more cerebral atherosclerosis than the males.

4. Diabetes is strongly atherogenic. Diabetic females have considerably more cerebral atherosclerosis than the normal male, and beyond the fourth decade they have as much or more involvement as the diabetic male.

5. A number of factors may play a role in the sex influence upon atherosclerosis: (a) a difference in the lipid composition of plasma of men and women; (b) a physiological depression of plasma total cholesterol and the plasma cholesterol-phospholipid ratio by endogenous estrogens; and (c) a structural difference in the arteries of males and females.

References
22. Beadenkoff, W. G., Polan, A. K., Marks,


100 Years Ago
Diathesis to Thrombosis in Cancer
Armand Trousseau (1801-1867)

Je suppose que le cancer ne soit point accessible à nos moyens d’investigation, comme dans le fait que je viens de vous rappeler, il est un signe précieux de diagnostic que je dois vous indiquer. Ce signe, sur lequel je crois avoir le premier, il y a plus de quinze ans, appelé l’attention des pathologistes, c’est la phlébite oblitérante.

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