The Incidence and Severity of Atherosclerosis in Estrogen-Treated Males, and in Females with a Hypoestrogenic or a Hyperestrogenic State

By Arthur U. Rivin, M.D. and Sim P. Dimitroff, M.D.

Autopsy records of estrogen-treated men, castrated women, and women with breast carcinoma were analyzed with reference to the degree of atherosclerotic disease. Findings were then compared with those in similar groups of men and women whose estrogen supply was considered normal. Results obtained suggest: (1) that the male treated with estrogen has less atherosclerosis than the normal male; (2) that the oophorectomized female has an incidence of severe atherosclerosis approaching that of the male; and (3) that the hyperestrogenic female with breast carcinoma has less atherosclerosis than the normal female.

The remarkable sex difference in the incidence of atherosclerosis suggests that estrogenic hormones may exert an inhibitory effect on the pathogenesis of this disease. In order to explore this possibility, clinical and autopsy statistics were compiled in groups of patients who demonstrated deviations from their normal estrogen supply. Hyperestrogenism in males was studied in patients with carcinoma of the prostate who were treated with estrogens. Hyperestrogenism in females was considered to be present in women with carcinoma of the breast. The hypoestrogenic state was studied in a group of surgically castrated females. The incidence and severity of atherosclerosis in these patients were then compared with that in similar groups who were apparently normal with reference to their estrogen supply.

Materials and Methods

Autopsy protocols and clinical histories of 153 patients with carcinoma of the prostate were examined. Of these patients 53 were given estrogen therapy for three months or more, 100 received estrogen for less than three months or no hormone at all. The severity of atherosclerosis was compared in the two groups. The selection of three months as the dividing line between the two groups was more or less arbitrary, but was used because it was the minimum length of treatment time at which gynecomastia was noted to appear. Thus it was considered the minimum effective duration of estrogen therapy. The ages of the patients ranged from 46 to 91, with an average age of 69. There was no significant age difference between the treated and untreated groups. The maximum duration of hormonal treatment was seven years, and the average duration 16 months. The average daily dosage of stilbesterol was 75 mg. or more in one group of patients (Wadsworth Hospital). It was 5 mg. or less in another (Los Angeles County Hospital). The two series were tabulated separately, so that any divergence in findings might be observed.

The second portion of the study was devoted to determining the changes in the atherosclerotic process induced by oophorectomy and the hypoestrogenic state. Autopsy and clinical records of oophorectomized women at Los Angeles County Hospital were analyzed. All were patients who had had bilateral oophorectomy before the age of 50, and at least one year before the time of death. Such requirements were stipulated in order to eliminate, in so far as possible, the effect of naturally occurring ovarian atrophy. The maximum interval between oophorectomy and death was 35 years, the minimum one year, and the average five years.

The third phase of this paper represents a study of atherosclerosis in the hyperestrogenic state. The series of cases of breast carcinoma, containing 39 patients, was also studied at the Los Angeles County Hospital.

In these studies note was made of the state of
nutrition at the time of death, the age, associated diseases, areas of metastasis of tumor when present, dosage and duration of administration of estrogen and other methods of treatment, including oophorectomy or orchietomy. In males, evidences of feminization, particularly gynecomastia, were recorded.

The degree of atherosclerosis in three sites, the coronary arteries, aorta, and brain was tabulated. While the autopsy surgeons used the terms none, minimal, moderate, moderately severe, and severe, to describe the degree of arterial narrowing, only two classification categories were used in this study: minimal or none, and moderate or severe.

Diabetics, nephrotics, and patients with other causes for hypercholesterolemia, were eliminated from the series. Hypertensive subjects, however, were included, since it was impossible in arranging the chronology of hypertension and atherosclerosis to decide which of the abnormalities had developed first.

Because it is the commonly held concept that undernutrition reduces the amount of atherosclerosis, all comparisons were first made between the well nourished and the poorly nourished groups. It was found that of the cachectic group, 63 per cent had severe atheromatosis, whereas of the well nourished, 69 per cent were so afflicted. For this reason it was decided to include all cases, regardless of nutrition, in all three sections of the study.

**RESULTS**

The statistical significance of the data presented is estimated by considering the 95 per cent fiducial limits of the observed sample proportions. If the fiducial limit percentages listed in comparing one group with another do not overlap, then it can be concluded that the possibility of chance sampling having produced the apparent difference is less than 1 in 20. On the other hand, if there is overlap in the comparative fiducial limit percentages then the difference is not considered to be statistically significant.

Table 1 summarizes the prostatic carcinoma series in which larger doses of estrogens, 75 mg. of stilbestrol or more, were given daily. It demonstrates that there is less atherosclerosis in the estrogen-treated group. Thus of a total of 30 estrogen-treated cases, 11 had severe coronary atherosclerosis. On a simple percentage basis one could then conclude that 36.6 per cent had severe coronary artery disease. However, using the method of fiducial-limit analysis to determine what the percentage range might be if a much larger series of cases was studied, we find that the figure might range from 22.1 to 53.3 per cent. This computation is made in order to eliminate the possibility that chance alone, and not factual observation, may produce a finding more indicative of luck than of reality.

Similarly, the fiducial limit percentage range for severe coronary artery disease in the untreated group is 73.3 to 90.0. When we compare the boundary figures for the two groups we note that they do not cross and that the percentage ranges are mutually exclusive. Consequently the conclusions are that pure chance cannot be responsible for the differences observed and that the administration of estrogen to one group probably reduced its incidence of severe atherosclerosis in the coronary arteries.

Attention is called to the comparative fiducial limit ranges in the aorta and cerebral artery sites. Here the figures do show overlap and one must conclude that they are not of statistical significance.

While most of these patients were treated with stilbestrol, seven had 0.1 mg. per day of Estinyl or 1.25 mg. per day of Premarin alone or in combination with stilbestrol. All of these latter at postmortem examination showed
minimal atherosclerosis of all sites studied. In the group of 19 men showing minimal or no coronary atherosclerosis, 15 had enough estrogen to produce gynecomastia. All who had gynecomastia due to administered estrogen had minimal coronary atherosclerosis.

Table 2 shows the findings in another series of prostatic carcinoma patients studied at the Los Angeles County Hospital. In this group an average dosage of 5 mg. per day was employed which is much lower than that used in the Wadsworth series. Twenty-three patients were treated with estrogens and 73 were not. Note that all of the estrogen-treated fiducial limit figures range into the fiducial percentages of the untreated column. Therefore none of the comparative data in this table is considered significant.

Convincing evidence of estrogenic protection against atherosclerosis is lacking in the patients studied at the County Hospital. It may be that the 5 mg. daily dosage of stilbestrol was insufficient to produce an antiatherogenic effect. If estrogens are protective, their action may be a function of the dosage administered.

The effect of bilateral oophorectomy performed one year or more prior to death is shown in table 3. These data reveal a remarkably high incidence of atherosclerosis, even below age 60, in women who had been castrated.

Table 4 presents data concerning the incidence of atherosclerosis in the hyperestrogenic state in females as represented by breast carcinoma patients. Atherosclerosis in this group appears to be rare when compared with the incidence in the normoestrogenic female. Figure 1 will illustrate this difference. Table 5 offers a statistical analysis of the differences between the oophorectomized, and the hyperestrogenic group. All the data point in one direction: toward a higher incidence of atherosclerosis in the oophorectomized female. In the case of the coronary arteries in the age groups above 60, the figures establish beyond the realm of chance a real difference between the hyperestrogenic and the hyperestrogenic females.

Figure 1 graphically summarizes the incidence of severe coronary atherosclerosis in the two female groups noted above and compares this form of atherosclerosis in the abnormal endocrine states studied with the incidence of coronary artery disease in 600 women, ages 30 through 89, reported by Ackerman, Dry,
TABLE 4.—The Incidence and Severity of Atherosclerosis in Patients with Carcinoma of the Breast

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Site</th>
<th>Incidence of atherosclerosis graded minimal or none</th>
<th>Incidence of atherosclerosis moderate or severe degree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. pts. %</td>
<td>No. pts. %</td>
<td></td>
</tr>
<tr>
<td>41–50</td>
<td>Coronary arteries</td>
<td>7 100</td>
<td>0 0</td>
</tr>
<tr>
<td></td>
<td>Aorta</td>
<td>7 100</td>
<td>0 0</td>
</tr>
<tr>
<td></td>
<td>Cerebral arteries</td>
<td>7 100</td>
<td>0 0</td>
</tr>
<tr>
<td>51–60</td>
<td>Coronary arteries</td>
<td>10 83</td>
<td>2 17</td>
</tr>
<tr>
<td></td>
<td>Aorta</td>
<td>8 80</td>
<td>2 20</td>
</tr>
<tr>
<td></td>
<td>Cerebral arteries</td>
<td>10 100</td>
<td>0 0</td>
</tr>
<tr>
<td>61–70</td>
<td>Coronary arteries</td>
<td>15 88</td>
<td>2 12</td>
</tr>
<tr>
<td></td>
<td>Aorta</td>
<td>11 65</td>
<td>6 35</td>
</tr>
<tr>
<td></td>
<td>Cerebral arteries</td>
<td>12 86</td>
<td>2 14</td>
</tr>
<tr>
<td>71–100</td>
<td>Coronary arteries</td>
<td>6 83</td>
<td>1 15</td>
</tr>
<tr>
<td></td>
<td>Aorta</td>
<td>3 50</td>
<td>3 50</td>
</tr>
<tr>
<td></td>
<td>Cerebral arteries</td>
<td>5 83</td>
<td>1 17</td>
</tr>
</tbody>
</table>

and Edwards. Comparisons are also made with a group of 500 males of varying age groups reported by White. Patients in both latter groups were studied consecutively as they came to autopsy, without regard to the cause of death. The criteria for grading the severity of atherosclerosis in these series compared with standards used in the present study were substantially the same.

Figure 1 shows that in the age group 30 to 50, the incidence of severe coronary sclerosis in castrated females almost equals that of males, whereas in females with breast carcinoma, it is minimal. In the age group 50 to 60 years, which is predominant for coronary sclerosis in males, the oophorectomized female has a high percentage of severe disease, while the female with breast carcinoma shows the least sclerosis. In age groups 60 to 70, the oophorectomized female again is almost equal to the male in the incidence of severe coronary artery disease.

TABLE 5.—Comparison of Incidence of Severe Atherosclerosis in Hypoestrogenic Oophorectomized Females and Hyperestrogenic Females with Carcinoma of the Breast

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Site</th>
<th>Oophorectomized</th>
<th>Breast Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases with severe involvement</td>
<td>Total no. cases studied</td>
<td>Fiducial limits %</td>
</tr>
<tr>
<td>35–50</td>
<td>Coronary arteries</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Aorta</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Cerebral arteries</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Coronary arteries</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Aorta</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Cerebral arteries</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>61–70</td>
<td>Coronary arteries</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Aorta</td>
<td>28</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Cerebral arteries</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Coronary arteries</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Aorta</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Cerebral arteries</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

* No overlap in range of comparative fiducial limit percentages. Statistically significant.
DISCUSSION

Four groups of patients have been studied with reference to the incidence and severity of atherosclerosis. It was noted that among a group of males treated with high doses of estrogens, there was less intense atherosclerotic disease than in a comparable series of untreated males. An additional finding was the absence of significant coronary artery atherosclerosis in 15 of 19 patients who exhibited gynecomastia as a result of estrogen administration. A group of males who received small estrogen doses demonstrated no change from the untreated group.

In the group of female castrates there appeared to be an increased incidence of advanced atherosclerosis, particularly in the coronary arteries, as compared with the incidence in a normal female population. Similar findings were recently reported in a study from the Mayo Clinic. Among the women with breast carcinoma, representing the hyper-estrogenic state, atherosclerosis was minimal.

What are the implications of these findings? Many theories have been proposed to explain the sex dissimilarities in atherosclerosis. There is substantial experimental evidence to support the concept that the female hormones themselves may be the key factor.

In order for estrogens to reduce atheromatous lesions, in the age group of the prostatic carcinoma patients, one would have to postulate not only protection from, but also actual reversal of well established disease. That this can occur in chickens has been demonstrated by the recent work of Pick and co-workers which showed estrogen-induced reversal of arterial disease to normal even after the development of fibrotic changes in the atheromata. The same investigators have noted estrogen protection of the coronary arteries from atherosclerosis, without protection of the aorta. These findings parallel the results of this study, indicating selective protection of the coronary arteries. In rabbits also, it is possible to prevent cholesterol-induced atherosclerosis by estradiol administration. However (and this is the crucial point), the sex steroids' prophylactic effect was evident only in the female rabbit, and could not be demonstrated after castration.

Since abnormal plasma lipid relationships are implicated in the development of atherosclerosis, the evidence for estrogen influence on the lipid partition is relevant to this discussion. Russ and associates have discovered that the normal female, age 18 to 35, has distinctly more alpha lipoprotein (with a low cholesterol-phospholipid ratio) than males of the same age group. After age 45, no sex differences in lipid content were noted. The Gofman group, utilizing ultracentrifuge analysis, found that it is not until age 50 to 60 that the female reaches the concentration of the S10 molecules most closely correlated with atherosclerosis, that the male had reached at age 30. Such studies suggest that some factor operating at the peak period of sex-hormone activity accounts for the sex differences in lipid fractions. Eilert has noted that the administration of estrogens to menopausal women has altered their serum lipid levels, with a sharp reduction in the cholesterol-phospholipid ratio. Glass and his co-workers have been unable to detect any effect of administered estrogens on lipoproteins.

The biologic mechanisms by which estrogens affect the plasma lipids, and thereby, perhaps, atherosclerosis also, are certainly most obscure. The influences of the steroid hormones on each other, as well as on lipid metabolism and 1 indicating that the estrogen-lipid-atherosclerosis relationship must be a very complex one.

SUMMARY AND CONCLUSIONS

1. Autopsy records have been utilized to draw a statistical comparison between the incidence and severity of atherosclerosis in patients who had deviations from their ordinary estrogen supply, and patients whose estrogen status was normal.

2. Four groups of cases have been studied: 57 patients with prostatic carcinoma, 30 of whom were given an average daily dose of 75 mg. of stilbestrol; 96 patients with prostatic carcinoma, 23 of whom were given an average daily dose of 5 mg. of stilbestrol; 99 female patients who had undergone castration; and
39 women who had carcinoma of the breast with probable accompanying hyperestrogenism.

3. These studies have demonstrated: (a) an apparent diminution of coronary atherosclerosis in males treated with large doses of estrogen; (b) a significant increase in atherosclerosis, especially in the coronary arteries, in women who have had their estrogen supply reduced by castration; (c) an incidence of severe atherosclerosis in the hyperestrogenic female even less than that of the normal female.

4. These findings lend support to the experimental evidence derived from animal studies which suggest that the female has less atherosclerosis than the male because ovarian secretions in some way protect from this disease.

5. Theoretic mechanisms involved in the action of sex hormones on lipid metabolism have been suggested.

ACKNOWLEDGMENTS

We express appreciation to Dr. Frederick J. Moore of the University of Southern California, and to Dr. Alvin E. Lewis of the Atomic Energy Project, University of California at Los Angeles, for their help in the statistical analysis of the data. Dr. Albert A. Kattus of the School of Medicine, University of California at Los Angeles, contributed much time and effort in the organization and preparation of the paper.

SUMARIO ESPAÑOL

1. Los protocolos de autopsia de pacientes con desviaciones de abastecimiento normal de estrógeno y pacientes con abastecimiento normal, han sido utilizados para obtener una comparación estadística entre la incidencia y la severidad de la ateroesclerosis en estos pacientes.

2. Cuatro grupos de pacientes han sido estudiados: 57 pacientes con carcinoma de la prostata, 30 de los cuales se les administró una dosis promedio de 75 mg. de estilbrol; 96 pacientes con carcinoma de la prostata, 23 de los cuales se les administró una dosis diaria de 5 mg. de estilbrol; 99 pacientes hembras que sufrieron castración; y 39 mujeres con carcinoma de la mama con probable hiperestrogenismo.

3. Estos estudios han demostrado: (a) una aparente diminución de ateroesclerosis coronaria en los varones tratados con dosis grandes de estrógeno; (b) un incremento significativo en ateroesclerosis, especialmente en las arterias coronarias, en mujeres que han tenido un abastecimiento de estrógeno reducido por castración; (c) la incidencia de ateroesclerosis severa en la hembra con carcinoma de la mama y hiperestrogenismo fue menor que la de la hembra normal.

4. Estos hallazgos prestan sostén a la evidencia experimental derivada de animales que sugiere que la hembra tiene menos ateroesclerosis que el varón debido a que las secrecciones ováricas de alguna manera protegen de esta enfermedad.

5. Mecanismos teóricos envueltos en la acción de las hormonas sexuales en el metabolismo lipídico han sido sugeridos.

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_Circulation._ 1954;9:533-539
doi: 10.1161/01.CIR.9.4.533

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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