Arteriosclerotic Vascular Disease and Testicular Fibrosis

By Frederic G. Dalldorff, M.D.

The purpose of this paper is to report an interesting inverse relationship between arteriosclerotic vascular disease and advanced testicular fibrosis. In recent years increasing attention has been paid to the possible role of gonadal hormones in the pathogenesis of arteriosclerosis.\(^1\)\(^2\) It has long been suspected that high estrogen levels protect premenopausal women from the development of arteriosclerosis.\(^3\)\(^4\) More recently, evidence has been presented that suggests these hormones may play a similar role in men.\(^5\) Progressive testicular fibrosis is a condition thought to occur more frequently in older men. Occasionally it is associated with a known cause (i.e., cirrhosis of the liver, long-term estrogen therapy), but in most cases its etiology remains obscure.\(^6\)\(^8\)

Materials and Methods

The records of the Department of Pathology at the University of North Carolina School of Medicine contain completed protocols of 442 autopsies performed on men older than 35 years from January 1, 1955 through December 31, 1959. In order to study a more meaningful sample it was decided to exclude from this study all cases with known predisposing factors for or causes of either testicular fibrosis or vascular disease. The clinical summaries and autopsy protocols were reviewed and 185 cases were excluded at the start of the study for the following reasons: 112 patients had antemortem clinical diagnosis of hypertension; 24 patients had diabetes mellitus; 28 patients had cirrhosis of the liver; one patient had Marfan's syndrome; one patient had disseminated lupus erythematosus; one patient had tuberculosis of the testes; two patients had tumor tissue infiltrating the testes; one patient had had mumps orchitis; one patient had hemochromatosis involving the testes; two patients had received stilbestrol therapy for carcinoma of the prostate; one patient had previously undergone bilateral orchietomy; in 10 cases the autopsies were limited; and the age of one patient was unknown.

The protocols of the remaining 257 cases were reviewed with special attention to the cause of death and the degree of arteriosclerosis in the coronary, cerebral, and systemic arteries and the aorta. All cases were classified into five groups according to the severity of arteriosclerotic vascular disease described. Group 1 consisted of those patients showing minimal atherosclerosis with only smooth yellow plaques in their elastic aortas and minimal or no intimal thickening of the cerebral and coronary arteries. Group 2 consisted of those patients showing moderate arteriosclerosis. Their aortas usually contained some calcified as well as yellow intimal plaques. Elasticity of the aorta was often still preserved to some degree and the coronary or cerebral arteries, or both, were only moderately narrowed. Group 3 consisted of those patients with severe arteriosclerotic disease of the aorta or cerebral or coronary arteries. Their aortas had poor elasticity and usually showed many gritty and roughened intimal plaques. The coronary and cerebral arteries were markedly narrowed and with many, often gritty, intimal plaques. Group 4 contained those patients who not only had severe arteriosclerosis of the aorta or coronary or cerebral arteries but who also showed definite lesions caused by this disease (i.e., myocardial or cerebral infarcts, peripheral arterial insufficiency with gangrene, arteriosclerotic aneurysms). Group 5 comprised those patients who died of arteriosclerotic vascular disease as a result of vascular insufficiency or hemorrhage from an arteriosclerotic vessel. All decisions regarding suitability of cases and degree of arteriosclerosis were made without knowledge of the testicular findings. The ages of the patients were recorded and the cases arranged in 5-year age groups (table 1).

The routine hematoxylin and eosin sections of the testes were obtained from the autopsy files. In the majority of cases a section of only one testis had been submitted. The testicular material was inadequate in 58 cases. The final sample was 199 patients.

Results

Histologic Findings

Many of the sections of testes in all age groups were essentially normal. The seminiferous tubules were large and lined by
Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Patients with normal or minimally fibrotic testes (155 Cases)</th>
<th>Patients with advanced testicular fibrosis (44 Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96-100</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>91-95</td>
<td>1</td>
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</tr>
<tr>
<td>86-90</td>
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<tr>
<td>81-85</td>
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<tr>
<td>76-80</td>
<td>5 4 3 3 3 3 3 2 2 2</td>
<td>3 3 2 2</td>
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<tr>
<td>71-75</td>
<td>5 5 5 5 5 5 5 5 4 4 4 3 3 3 3 2 2 2 2 2</td>
<td>5 4 4 1</td>
</tr>
<tr>
<td>66-70</td>
<td>5 5 5 5 4 4 3 3 3 3 3 3 3 3 3 2 2 2 2 2 2 2 2</td>
<td>3 3 2 1 1 1 1</td>
</tr>
<tr>
<td>61-65</td>
<td>5 5 5 5 5 5 5 5 5 4 4 4 3 3 3 3 3 2 2 2 2 2 2 2 2 2 2 2 2 2</td>
<td>3 2 1</td>
</tr>
<tr>
<td>56-60</td>
<td>5 5 5 4 3 3 3 3 3 3 3 3 3 3 3 3 3 3 2 2 2 2 2 2 2 2 2 2 2 2</td>
<td>3 3 3 2 1 1 1 1 1 1 1 1</td>
</tr>
<tr>
<td>51-55</td>
<td>5 5 5 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2</td>
<td>3 2 2 2 1 1</td>
</tr>
<tr>
<td>46-50</td>
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</tr>
<tr>
<td>41-45</td>
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<td>2 2 1 1</td>
</tr>
<tr>
<td>36-40</td>
<td>5 5 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</td>
<td>1 1 1 1</td>
</tr>
</tbody>
</table>

Group 1, minimal atherosclerosis; 2, moderate arteriosclerosis; 3, marked arteriosclerosis; 4, marked arteriosclerosis with lesions due to vascular disease; 5, death due to arteriosclerotic vascular disease. Each group number represents one case.

Other sections had changes that were interpreted as representing early atrophy and fibrosis. In some cases there was only diffuse fibrosis. In a few instances Leydig cells were increased in number. In others there was diffuse atrophy of the germinal epithelium which was often increased in number. The Leydig cells were hyalinized or had only slight thickening of the peritubular fibrous membranes. In a few instances Leydig cells were increased in number. In an otherwise normal testis, Leydig cells scattered small clumps of a few mature epithelium. Their lumina contained mature sperm. The peritubular fibrous membranes were not involved. In others Leydig cells scattered small clumps of a few
fibrosis varied from one to the other (8 cases) the testis that was least involved was used for the final histologic classification.

**Correlation between Severity of Arteriosclerotic Vascular Disease and Advanced Testicular Fibrosis**

The results are presented in table 1. Of the 155 patients with normal or minimally fibrotic testes, 47 (30.3 per cent) had complications of arteriosclerotic vascular disease (groups 4 and 5), and 36 (23.2 per cent) died of those complications. Of the 44 patients with advanced testicular fibrosis, four (9.1 per cent) showed complications of arteriosclerotic vascular disease (groups 4 and 5) and only one (2.3 per cent) died of this disease. The incidence of complications of arteriosclerotic vascular disease (groups 4 and 5) among patients free of testicular fibrosis is significantly higher than the incidence of complications of arteriosclerotic vascular disease (groups 4 and 5) among those patients with advanced testicular fibrosis.

<table>
<thead>
<tr>
<th></th>
<th>groups 4 and 5</th>
<th>groups 1-2</th>
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</thead>
<tbody>
<tr>
<td>Normal testes</td>
<td>47</td>
<td>108</td>
</tr>
<tr>
<td>Fibrotic testes</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>148</td>
</tr>
</tbody>
</table>

\[
\chi^2 = 7.04; \quad 0.01 > p > 0.005.\]  

Since the only individuals in this study who are known to have had progressive arteriosclerotic vascular disease at the time of death are those who died of the disease (group 5), it is of interest that all but one of these 37 men (97 per cent) had little or no testicular fibrosis.

**Discussion**

The data presented here show a striking inverse relationship between arteriosclerotic vascular disease and idiopathic testicular fibrosis, but they do not explain the reason for this correlation. There are at least three possible explanations.

I. One possibility is that these conditions are related, as cause and effect. Perhaps older individuals with atrophic testes produce less androgenic hormones and these hormones in some way influence the development of arteriosclerosis. This does not seem likely. There is often an apparent increase in the number of Leydig cells associated with testicular fibrosis. The influence of androgens on the development of atherosclerosis has not been clearly demonstrated.\(^5\)\(^,\)\(^10\) Indeed, there is some evidence that they play no role at all.\(^11\)

II. Another possible explanation is that the inverse relationship between testicular fibrosis and arteriosclerotic vascular disease is due to the patient’s general state of nutrition. As can be seen in table 1, the individuals with advanced testicular fibrosis have a higher incidence of poor nutrition or cachexia, as described at autopsy, than do the individuals with minimal or no testicular fibrosis. It is also apparent that there are fewer obese patients, as described at autopsy, in the group with testicular fibrosis. If the general state of nutrition was the controlling factor in both conditions, then by studying a limited sample composed of patients who were described as being “well nourished” but not “obese,” the observed correlation should no longer exist. These restrictions would bring the total sample to 124 cases, 20 with testicular fibrosis and 104 without. Of the 104 patients with normal or minimally fibrotic testes, 34 (32.7 per cent) had complications of arteriosclerotic disease (groups 4 and 5). Of the 20 patients with fibrotic testes, two (10 per cent) showed complications of arteriosclerotic disease (groups 4 and 5). Thus, the relative incidence of complications of arteriosclerotic vascular disease remains the same in both groups, even when the variable of general nutritional status is removed.

III. The last, and most attractive, hypothesis is that testicular fibrosis and the decreased incidence of arteriosclerotic vascular disease are separate manifestations of long-standing high levels of circulating estrogenic hormones. Many investigators believe that high levels of estrogenic hormones protect individuals from the development of arteriosclerosis. This was first observed in women\(^3\)\(^,\)\(^4\) and has more recently been demonstrated in men.\(^5\) Men and women who are free of symptomatic arteriosclerotic vascular disease excrete greater amounts of biologically active estrogenic hor-
mones in their urine than do those individuals suffering from myocardial infarction. When large doses of estrogens are given to individuals suffering from arteriosclerotic vascular disease, the levels of blood cholesterol decrease and the levels of phospholipids rise. Some investigators consider, however, that physiologic doses of these hormones have no influence on cholesterol or phospholipid blood levels.\(^{13}\)

The association of testicular atrophy and advanced cirrhosis of the liver has long been recognized and is believed to be the result of prolonged exposure to high levels of circulating estrogens.\(^{14}\) Patients who have been given long-term estrogen or stilbestrol therapy for carcinoma of the prostate or arteriosclerotic vascular disease develop progressive peritubular fibrosis and atrophy of the testes,\(^{12, 15, 16}\)

These observations of others suggest that the phenomenon observed here is merely the result of the presence of a spontaneous high level of circulating estrogenic hormones. When an abnormal high level of estrogenic hormones persists for a long period of time, it may well arrest the development or progression of arteriosclerosis and at the same time produce progressive testicular fibrosis. It should be emphasized that not all cases of testicular fibrosis can be attributed to high levels of circulating estrogenic hormones. Patients who have testicular fibrosis and sterility associated with Klinefelter’s syndrome evidently do not excrete excessive amounts of estrogenic hormones.\(^{17, 18}\) Further direct studies are indicated before any conclusions can be reached.

Summary

The autopsy protocols and sections of the testes were examined in a group of 199 men over the age of 35 years who were free of known causes of either vascular disease or testicular fibrosis. In 44 (22 per cent) of the cases, testicular sections showed marked fibrosis of the peritubular membranes or complete hyalinization. Testes of the remaining men showed minimal or no signs of testicular fibrosis. Of these 155 patients with normal or minimally fibrotic testes, 47 (30.7 per cent) had complications of arteriosclerotic vascular disease (i.e., myocardial or cerebral infarcts, arteriosclerotic aneurysms, etc.) and in 36 cases (23.5 per cent) those complications were considered to be the cause of death. Of the 44 cases with advanced testicular fibrosis, four (9.1 per cent) had complications of arteriosclerotic vascular disease and only one patient (2.2 per cent) died of the disease. An interpretation of these findings is presented.

Acknowledgment

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References

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Nature, Science and Understanding

I believe most simply in the nobility of this great effort to understand nature, and (understand) what we can of ourselves, that is science. I hope, less simply, that it may be a brave and worthy chapter of man’s history to cope, with a full awareness of the frailty of his institutions, of his society, and of himself, with the new problems and new choices that this knowledge has opened. For, if we do not treasure the great inheritance on which all our work and life are based, and understand the radical novelty and the gravity of the situation in which we find ourselves, there will be few of our children to ask again of the need for new knowledge.—Dr. Robert Oppenheimer. The American Scientist, Vol. 47, p. 213A, September 1959.
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