The Thoracic Duct

Significance of Age-Related Changes and of Lipid in the Wall

By Adolph J. Rabinovitz, M.D., and Otto Saphir, M.D.†

THE so-called infiltration reaction theory of atherogenesis followed naturally as a consequence of the observation of lipids in the walls of arteries in the absence of atheroma. According to this theory, advocated by Virchow,1 Aschoff2 and Anitschkow,3 lipids enter the wall of the artery from the circulating blood through the endothelium and accumulate in the intima, eventually damaging and distorting the wall. Virchow also postulated an earlier preparatory mechanical loosening of the intimal layer. It was suggested that subsequent reaction to the lipid, with phagocytosis and fibrosis, contributed to the formation of plaques and the ultimately characteristic atherosclerotic lesion.

The thoracic duct receives most of the lymphatic channels from below the diaphragm, including those from intestine and liver containing fluid of high lipid concentration. The gross anatomic characteristics of the duct and the numerous variations in number of channels, course and site of its junction with the venous system have been well documented.4–8 The duct is lined by ovoid endothelial cells, separated from the fibroelastic elements surrounding the smooth muscle of the media by a sharply defined elastic lamella. Histologically, the structure closely resembles that of a vein, differing only in that it contains less muscle and that the individual layers of its wall are less sharply defined. Kausel and co-workers4 have described histologic details of the variations in different segments of the duct.

The thoracic duct lymph normally has a high lipid content. Hawk, Oser, and Summerson9 indicated that 5 to 15 per cent of this fluid consists of emulsified fat, while Shafiroff and Kau,10 on analysis of postabsorptive human thoracic duct lymph obtained by cannulation, found 0.8 to 4.6 Gm. per cent fat, 65 to 220 mg. per cent cholesterol, and 25 to 182 mg. per cent cholesterol esters. Higher concentrations of varying degree may occur in the postprandial lipid content of the fluid. Hellman et al.,11 using C14-labeled cholesterol, found that most of the orally administered cholesterol that was absorbed (4 to 27 per cent of the total) could be recovered in the thoracic duct lymph.

Although the wall of the thoracic duct differs markedly in structure from that of an artery, it is entirely possible that infiltration of lipid into its wall could occur as a consequence of the high lipid content of the thoracic duct fluid, despite the low intraluminal pressure. If the infiltration reaction theory of atherogenesis is valid, subsequent phagocytosis and reactive fibrosis might conceivably result in formation of atheromata in some older individuals. Thus, the study of a large number of thoracic ducts from individuals of varying ages could contribute to an understanding of the role of lipids in the development of atherosclerosis. If intimal fibrosis were found without relation to lipid infiltration, this could indicate that such fibrosis in vascular channels is not necessarily a reaction to lipids and that reaction to free extraluminal lipid need not be anticipated in all body tissues under all circumstances.

Material and Methods

Segments of thoracic duct varying in length from 3 cm. (premature infant of 7 1/2 months gestation) to 39 cm. (mature adult) were removed from 119 bodies at autopsy. The ages of the subjects varied from newborn (6%)
months gestation) to 91 years (table 1). Clinical and autopsy records were carefully scrutinized for the presence and extent of atherosclerosis and diseases known to be associated therewith.

In each case, after the sternum was removed, the right lung was reflected anteromedially and the mediastinal pleura was incised longitudinally between the azygos vein and the aorta. The subjacent loose fibro-fatty tissue was dissected parallel to the incision with blunt instruments to reveal the duct without disruption. It appeared as a vessel 2 to 4 mm. in diameter, continuous with the cisterna chyli and showing no gross connections with adjacent arteries or veins. The lumen was usually empty or contained a scant quantity of clear or occasionally whitish fluid, very rarely blood-tinged. Several segments of mesenteric artery and vein were used as histologic controls. The final identification of all structures was based upon histologic study.

The segments of duct thus obtained were fixed in 10 per cent formalin and sectioned transversely into numerous small pieces, each averaging somewhat less than 1 cm. in length. Multiple segments were embedded in paraffin from each case. In 84 instances, segments were retained for frozen section and fat stain. Three to 44 pieces of thoracic duct per case were embedded in 1 to 5 blocks. Hematoxylin and eosin, van Gieson, orcein, and periodic-acid-Schiff stains were performed on each block. Four to 26 frozen sections on each of the 84 different ducts were stained for fat with Sudan IV.

In addition, 21 to 89 step serial sections were made from blocks of the 12 cases that appeared possibly to manifest atheroma formation in sections studied by the methods described above. In five of the 12, there were neoplastic cells, usually in clots, within the lumen of the duct. Sections from these were searched for possible occlusion of the thoracic duct, with the thought that the increased pressure related to obstruction might result in more lipid infiltration of the wall. In all but one of the 12 cases one half of the

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**Table 1**

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of cases</th>
<th>Density of wall</th>
<th>Intimal fibrosis</th>
<th>Increased depth of elastic plate</th>
<th>Duplication of elastic plate</th>
<th>Presence of intimal polyoid plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>14</td>
<td>±</td>
<td>—</td>
<td>—</td>
<td>±</td>
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<tr>
<td>11-20</td>
<td>2</td>
<td>±</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>21-40</td>
<td>14</td>
<td>±</td>
<td>±</td>
<td>—</td>
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<td>41-60</td>
<td>34</td>
<td>±</td>
<td>—</td>
<td>+</td>
<td>±</td>
<td>—</td>
</tr>
<tr>
<td>61-80</td>
<td>45</td>
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<td>+</td>
<td>±</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>81-100</td>
<td>10</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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**Figure 1**

Wall of thoracic duct of a 43-year-old man. Note single subendothelial elastic lamella and smooth muscle cells evenly distributed throughout entire thickness of wall. Orcein; × 235.

**Figure 2**

Wall of thoracic duct of an 87-year-old man. Muscle cells largely confined to inner half of wall; wall appears compact due to broad collagen fibers closely opposed to one another. Hematoxylin and eosin; × 150.
step sections were stained with hematoxylin and eosin, one quarter were stained with orcein, and one quarter with van Gieson's connective-tissue stain; the slides of the remaining one were stained only with hematoxylin and eosin.

Results

Histologic evidence of atheroma was considered to be represented by the following: intimal fibrosis with foamy macrophages, cholesterol slits, calcification, intimal ulceration, hemorrhage, and necrosis. Although some intimal fibrosis was apparent in many cases, especially in older individuals, in none of these could the histologic features be interpreted as a true atheroma. We did, however, find changes in the wall that enabled us to differentiate thoracic ducts of the young (0 to 20 years) from middle aged (20 to 60 years) and older (above 60 years) persons. The duct from younger individuals was composed of smooth muscle cells arranged in bundles evenly dispersed in a collagenous stroma throughout the wall. Occasionally, the muscular elements were noted to predominate in the inner half of the wall. There was a single uniform elastic lamella situated immedi-

Figure 3

Thoracic duct of a 60-year-old woman (special case no. 6). Generalized intimal fibrosis, increased depth and duplication of subendothelial elastic plate. Note fibroelastic plaque limited by subendothelial elastic lamella and without evidence of atherosclerosis. (One of the thoracic ducts with intimal fibrosis studied in serial section for signs of atherosclerosis.) Orcein; \( \times 30 \).

Figure 4

Wall of thoracic duct of an 85-year-old woman. Note small fibrous polypoid projections on intimal surface and increased thickness, depth and duplication of elastic plate. Orcein; \( \times 235 \).

ately beneath the endothelial cells. This plate was extremely regular, slightly wavy and only occasionally interrupted (fig. 1). In older individuals, the wall appeared denser, with individual muscle and collagen fibers more closely apposed to one another. The collagen fibers appeared broader and often homogeneous, while the muscle fibers tended to be confined to the inner half or two thirds of the wall (fig. 2). The subendothelial elastic plate was often duplicated, of increased thickness, and separated from the endothelium by a thin layer of collagen (fig. 3). Occasionally, microscopic polypoid masses of collagen projected into the lumen (fig. 4).

We attempted to quantitate the degree of alteration of many of the morphologic details of each duct, utilizing a scale of \(-\), \(\pm\), +, and ++. The summary of these findings (table 1) discloses a distinct difference in the ducts of the young compared to the old, with the intermediate age groups showing gradual transitions.

Fat stains were considered positive when obvious sudanophilic globules were noted. Lipid was demonstrated with ease in 83 of the 84 ducts so stained. In the majority of these ducts, fat was found in more than half the sections stained. Figure 5 illustrates the appearance of a frozen section staining posi-
Differences in atherosclerosis in patients with malignant neoplastic disease, we compared the histologic appearance of the ducts from such patients with those of the remaining patients of the same age group. Thirty-eight of the 119 patients had cancer or other malignant disease. These ducts manifested somewhat more intimal fibrosis, a slight increase in density of the wall and a greater degree of duplication of the internal elastic lamella than those from individuals without cancer.

The histologic data on the ducts of 21 patients with various diseases (systemic atherosclerosis, myocardial infarction, and diabetes mellitus) in which one might expect an increased degree of arterial atherosclerosis were compared with those of the remaining 98. Differences between the two groups were insignificant.

Finally, considering the increased flow rate of thoracic duct lymph in cirrhosis of the liver, we compared the ducts of the three cases of cirrhosis in the series with those of the other patients of the same age group. In the cases of cirrhosis, the elastic plate was slightly deeper, it was more frequently duplicated, and the wall was slightly denser than usual.

No histologic evidence of atherosclerosis was found in any of the 12 cases studied with serial step sections. There was severe intimal fibrosis in the five cases with malignant cells in the lumen, but these were associated with little or no lipid infiltration. Of the seven, five showed more pronounced intimal fibrosis than others of the same age group (one of these had areas of virtually occlusive intimal fibrosis), one had focal infiltration of the wall with lymphocytes and eosinophils, and one had a microscopic rupture of the duct wall surrounded by a chronic inflammatory reaction. The microscopic defect in the duct wall in the last was surrounded by congested granulation tissue covered by endothelium, arranged in an angiomatoid pattern between the lumen of the duct and the adjacent adipose tissue (fig. 6). The granulation tissue was infiltrated with lymphocytes, plasma cells, hemosiderin-laden macrophages, and a few neutrophils. Rare foamy macrophages were noted about foci of hyalinized connective tissue in the stroma usually immediately beneath the endotheli-
um. Cholesterol slits were not seen. The unaffected segment of the duct wall showed no alterations inconsistent with the age of the patient. Serial sections through the area of defect disclosed a lumen lined as described above, with its longitudinal axis paralleling the duct and communicating with it through a narrow channel. Unfortunately, no fat stains were made in this area.

**Discussion**

Studies of anatomic changes in the human thoracic duct associated with age are meager and no references dealing directly with the topic are available. Only two references to atherosclerosis in the thoracic duct were found in the older literature. In one, the description and the illustrations do not permit definitive morphologic diagnosis. In the other, Kelbing described a thoracic duct with multiple aneurysms. The intimal fibrosis and lipid deposition were thought to be secondary to severe inflammation. Baum and Kihara described age-related changes in the dog and suggested that the elastic fibers of intima, media, and adventitia, and the connective tissue fibers in the media became thickened with aging. Recently, Lansing reviewed his studies of the thoracic duct in 40 cadavers and described “atheroma,” although the presence of lipid was not mentioned, nor were there detailed descriptions of the histologic findings. Since the generally accepted concept of atheroma requires the presence of lipid, use of the term appears erroneous.

On noting the paucity of lipids and lack of relation between intimal fibrosis and lipids in venous walls, McCluskey and Wilens concluded that phlebosclerosis is a process unlike atherosclerosis in arteries. The changes we noted in the density of the wall are probably similar to those generally reported in connective tissue with increasing age; the alterations in the internal elastic plate could well be related to the intimal fibrosis, but neither appeared to be related to the intramural lipid. We suggest that the lesion be designated “lymphatic sclerosis.”

The histologic alterations in the ducts of patients with diseases predisposing to atherosclerosis, and in those with cirrhosis, may have questionable significance in view of the relatively few cases studied and the crudeness of the semiquantitative histologic estimation. However, the observation that lymphatic sclerosis is not increased in individuals with presumed predilectivity for atherosclerosis suggests that the process of arterial atherogenesis is unrelated to the thoracic duct lesions.

Several observations seem to indicate that the intramural lipid we observed is in transit from the lumen through the wall. First, occasional subendothelial droplets were noted. Additionally, since the lipid was often found between collagen fibers or finely dispersed in the wall, in situ production seems unlikely. Finally, the possibility that the intramural lipid is filtered from vasa vasorum appears unlikely in view of the paucity of lipid transudation from capillary channels in veins.

Comparison of processes in different vascular systems requires cautious evaluation. The arterial system carries blood under high intraluminal pressure in thick-walled pulsatile tubes with regular medial coats of densely packed smooth muscle and elastic tissue. Lipid in the intimal layer and reaction to its presence are common occurrences. In contrast, the venous system, with a thinner, less regularly arranged coat of smooth muscle but with abundant elastic tissue, carries blood under much lower pressure, without pulsation. Phlebosclerosis is largely a collagenous process, and unrelated to lipid infiltration, which is rarely ever seen in veins. The thoracic duct contrasts with both of the above in carrying fluid with far fewer blood cells, with less protein and with more lipid (including cholesterol), especially postprandially. Its intraluminal pressure normally does not exceed that in the venous system. Lipid appears commonly to traverse the wall without exciting a reaction. Our observations indicate that something more than mere entrance of lipid into the wall of a vascular
channel is required to induce atheroma formation.

Summary

In a search for atheromata, multiple sections of thoracic ducts from 119 autopsied individuals, varying in age from newborns to 91 years, were studied histologically with various stains, including fat stains on frozen sections of 84 different ducts.

No atheromata were found. Changes in the wall of the duct apparently related to aging included increasing density, minimal intimal fibrosis, degenerative changes in the internal elastic plate, and the appearance of occasional microscopic fibrous polypoid projections into the lumen.

Although fat was demonstrated with ease in the wall of the duct and did not appear to be related to the intimal fibrosis, it appeared to be passing through the wall of the vessel without exciting either inflammatory reaction or fibrosis.

The findings in the thoracic duct were evaluated with respect to the conventionally accepted definitions of atherosclerosis and phlebosclerosis. It was concluded that the sclerotic changes found in the thoracic duct are more like phlebosclerosis and unlike atherosclerosis in that they bear no relationship to lipid infiltration and reaction thereto. The term "lymphatic sclerosis" was suggested for the condition.

The common presence of lipid in the wall of the thoracic duct without reaction and without true atheroma formation indicates that factors beyond mere lipid infiltration of vascular walls must play an important role in the pathogenesis of atherosclerosis.

References

1. Virchow, quoted by Aschoff.

Circulation, Volume XXXI, June 1965

The Essential Qualities of Scientific Pursuit

I value in a scientific mind, most of all, that love of truth, that care in its pursuit, and that humility of mind which makes the possibility of error always present more than any other quality. This is the mind which has built up modern science to its present perfection, which has laid one stone upon the other with such care that it today offers to the world the most complete monument to human reason. This is the mind which is destined to govern the world in the future, and to solve the problems pertaining to politics and humanity as well as to inanimate nature. It is the only mind which appreciates the imperfections of the human reason, and is thus careful to guard against them. It is the only mind that values truth as it should be valued and ignores all personal feeling in its pursuit.—H. A. Rowland.
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