Cellular Infiltration of the Human Arterial Adventitia Associated with Atheromatous Plaques

By C. J. Schwartz, M.D., and J. R. A. Mitchell, M.B., B.Sc., M.R.C.P.

Cellular INfiltration of the adventitia in atheromatous arteries was noted by Allbutt, Ophüls, and Gerlis, who described the histologic characteristics of cellular aggregates in the adventitia of coronary arteries, and concluded that they were unrelated to the degree of coronary artery disease. He also stated that adventitial cellular infiltration was restricted to the coronary arteries, and did not occur in other arterial sites.

We considered, therefore, that a study of the nature and prevalence of adventitial cellular changes in different segments of the arterial tree would be of interest.

Methods

Aorta, Cervical, and Iliac Arteries

Three hundred and forty-six arterial segments were removed from the aorta, cervical, and iliac arteries of 74 patients on whom a necropsy was performed at the Radcliffe Infirmary, Oxford (38 male and 36 female subjects with ages ranging from 9 to 90 years).

Coronary Arteries

Four hundred and forty-seven arterial blocks were obtained from 56 randomly selected men and 55 randomly selected women aged 35 years and over, upon whom necropsies were performed at the Radcliffe Infirmary, Oxford, and a further 610 blocks were obtained from 56 men and 16 women with histologically confirmed myocardial infarction.

After fixation in 10 per cent formalin, 6μ paraffin sections were prepared and stained with hematoxylin and eosin, orcein elastic, periodic acid-Schiff, Masson's trichrome, Mallory's phosphotungstic acid-hematoxylin, and Azure A stains.

Plaque severity was assessed jointly according to the following arbitrary histologic scale:

1. Free from disease—arteries showing no evidence of disease, or only minor degrees of diffuse intimal thickening.
2. Severely diseased—arteries showing massive confluent plaques with a thickness greater than the original arterial wall. Such plaques would, in smaller vessels, reduce the lumen to less than half its original diameter.
3. Disease present—arteries with lesions less severe than category 2.

We recorded the nature, distribution, and number of cells in the arterial adventitia, three grades of cellularity being recognized:

2. Cellular infiltration slight—several foci of less than 20 cells or a single focus of less than 100 cells.
3. Cellular infiltration marked—many foci of 20 or more cells, or a single focus of 100 cells or more.

Results

In some 70 to 80 per cent of blocks showing disease of a severe degree histologically, adventitial cells were present, as discrete foci showing considerable variation in size, the smallest comprising only some 10 to 20 cells, and the largest many hundreds of cells (fig. 1). These foci were homogeneous in cell type, being composed of small round cells, morphologically identical with small lymphocytes, together with an occasional plasma cell (fig. 2). When a pleomorphic cellular infiltration was seen, there was evidence of syphilis or other disease, and some other distinguishing features could be found, such as the proliferative changes in the vasa vasorum seen in syphilis.

The cellular aggregates were often distributed around the vasa vasorum forming encircling cuffs but they were not restricted to a perivasal distribution, for they also occurred as attenuated bands in the adventitial fibrous tissue or formed perineural cuffs (fig. 3). The aggregates had a focal distribution along the arteries, and contiguous arterial blocks showed differing degrees of adventitial cellular infiltration with the same histologic grade.
of atheroma. In the aorta, carotid, vertebral, iliac, and coronary arteries the cell type and distribution were similar.

**The Prevalence of Adventitial Cellular Infiltration**

In table 1, the degree of cellular infiltration seen on blocks from the aorta, cervical, and iliac arteries is correlated with the histologic grade of arterial plaque severity, and in table 2 the findings in the coronary arteries are shown. Arteries microscopically free from disease were entirely free from adventitial lymphocytes, but with some disease an adventitial infiltration was present in 11 to 25 per cent of the blocks examined, while in arteries with a severe degree of disease, 75 to 81 per cent of the blocks showed an infiltration, of which approximately 20 per cent were of a marked grade. These findings suggest that the extent of adventitial cellular infiltration is related to the presence and severity of the arterial plaques. There is very little difference between the sexes when arteries with severe disease are considered, but with the lesser grade of plaque severity the women consistently showed a lower prevalence of cellular infiltration.

**Effect of Age on Adventitial Cellular Infiltration**

Although the grade of adventitial cellularity showed a strong relationship to arterial plaque severity, this could well have been a false correlation, both phenomena relating to a common factor of age. We have therefore compared the prevalence of cellular infiltration for the three grades of plaque severity in patients under 45, 45 to 64, and 65 years of age and over in blocks from the aorta, cervical, iliac, and coronary arteries, and have not found cellular infiltration in the absence of disease in any of the age groups. Conversely, the prevalence of cellular infiltration in the presence of severe disease did not differ significantly in the three age groups. The cellular infiltration was therefore related to the presence and severity of atheromatous plaques and was not solely an age dependent change.

**Arterial Site and Adventitial Cellularity**

The relationship between severe plaques

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**Figure 1**
Marked cellular infiltration of the adventitia of an atheromatous coronary artery. The cellular homogeneity can be seen, most cells resembling small lymphocytes. Trichrome stain.

**Figure 2**
High-power view of part of adventitial cellular focus, coronary artery, showing homogeneity of cell type. Trichrome stain.

**Figure 3**
Typical perineural lymphocytic infiltration in the adventitia of the common carotid artery. Trichrome stain.
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Table 1
Relationship between Adventitial Cellular Infiltration and Arterial Plaque Severity in Aorta, Cervical, and Iliac Arteries in an Unselected Necropsy Sample

<table>
<thead>
<tr>
<th>Arterial plaque severity</th>
<th>Prevalence of adventitial cellular infiltration (% of blocks examined)</th>
<th>Grade of cellularity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Slight</td>
</tr>
<tr>
<td>Free</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>n* = 48M 46F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>n = 63M 61F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>22</td>
<td>58</td>
</tr>
<tr>
<td>n = 86M 42F</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*n = number of blocks examined.

Table 2
Relationship between Adventitial Cellular Infiltration and Arterial Plaque Severity in the Coronary Arteries from an Unselected Necropsy Sample

<table>
<thead>
<tr>
<th>Coronary arterial plaque severity</th>
<th>Prevalence of adventitial cellular infiltration (% of blocks examined)</th>
<th>Grade of cellularity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Slight</td>
</tr>
<tr>
<td>Free</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>n* = 127M 96F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>77</td>
<td>20</td>
</tr>
<tr>
<td>n = 91M 58F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>25</td>
<td>52</td>
</tr>
<tr>
<td>n = 65M 10F</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*n = number of blocks examined.

and the degree of cellular infiltration in the aorta, cervical, iliac, and coronary arteries is shown in table 3. Although the total prevalence of both grades of adventitial cellularity combined together was similar in the four sites, the cervical arteries showed a lower prevalence of the marked grade of cellular infiltration.

Prevalence of Coronary Adventitial Cellular Infiltration in Patients with Myocardial Infarction

The prevalence and degree of coronary adventitial cellular infiltration in men and women with histologically confirmed myocardial infarction is shown in table 4. Comparison with the random population (table 2) shows that in men the presence of massive myocardial lesions has not appreciably altered the relationship between plaque severity and the grade of cellular infiltration, nor does cellular infiltration occur in these patients in the absence of atheromatous changes. The women cannot be readily compared with the random sample as so few of the latter group of patients showed severe coronary plaques.

The Prevalence of Coronary Adventitial Cellularity in Relation to Thrombosis

Table 5 shows the relationship between plaque severity and the grade of adventitial cellularity in blocks from men with myocardial infarction, according to the presence
and nature of occluding lesions. In artery blocks without thrombus and with recanalizing thrombus, the relationship between plaque severity and the grade of adventitial cellularity was similar to that in the random male population, but in arteries with recent thrombus this relationship was modified considerably, the prevalence of adventitial cellularity being significantly higher than that in the random male sample for both grades of arterial disease. There was therefore some relationship between the presence of recent thrombus in the coronary arteries and the prevalence and degree of the adventitial cellular infiltration.

Discussion

Our results showed that adventitial cellular infiltration was related to atheroma; that the degree of infiltration was similar in the aorta, coronary, and iliac arteries, but was less marked in the cervical arteries, and that although the presence of a myocardial infarction did not increase the adventitial cellularity in the coronary arteries, blocks containing a recent thrombus showed increased cellular infiltration. These results suggested that the conclusions drawn by Gerlis from his excellent descriptive studies were incorrect.

It is perhaps surprising that such prominent cellular accumulations should have received so little attention. Allbutt and Ophüls commented on their presence; Horn and Finkelstein considered that they were especially common in "sclerotic" arteries, while von Hausmann found that they were present in more than 90 per cent of diseased coronary arteries in patients over 40 years of age. There seems little doubt that the striking changes in the intima of diseased arteries have tended to divert attention from the media and adventitia. Nevertheless, since cellular infiltration of the adventitia shows such a constant relationship to the presence and degree of plaque formation, it should not be disregarded.

Two important questions remain unanswered. First, where are the cells? Do the cellular aggregates represent an increased number of lymphocytes within the adventitial lymphatic vessels, or are they collections of cells divorced from the normal lymphatic system? Since the demonstration of lymph vessels on necropsy material by conventional histologic technic is so unsatisfactory, we are undertaking further studies to determine the location of the cellular clumps.

Second, why are these homogeneous lymphocytic aggregates found in relation to atheromatous plaques? Pleomorphic adventitial cellular infiltration is found in syphilis, mycotic arteritis, and idiopathic aortitis, while nonlymphocytic coronary adventitial infiltration occurs in rheumatic heart disease. In none of these conditions do the aggregates resemble those of atheromatous arteries in type or distribution. Lymphocytic infiltration is found in other tissues in so-called "chronic nonspecific inflammatory" conditions; in the thyroid gland, auto-immune disease has been advanced as an explanation for the fibrosis and lymphocyte infiltration found in Hashimoto's thyroiditis. The possibility that an auto-immune process may play a part in arterial lesions should not be discounted and merits further study. On the other hand, the cells may not relate to the genesis of the arterial lesion, but may be secondary to it. This was suggested by Allbutt, who thought that "round cell growth in the adventitia in arte-

Table 3
Percentage Prevalence of Adventitial Cellular Infiltration in Arteries from Different Sites Obtained from an Unselected Necropsy Sample

<table>
<thead>
<tr>
<th>Artery</th>
<th>Prevalence of adventitial cellular infiltration in arteries with severe plaques (% of blocks examined)</th>
<th>Grade of cellularity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td>n = 44</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>Cervical</td>
<td>22</td>
<td>67</td>
</tr>
<tr>
<td>Iliac</td>
<td>21</td>
<td>55</td>
</tr>
<tr>
<td>Coronary</td>
<td>25</td>
<td>52</td>
</tr>
</tbody>
</table>

*n = number of blocks examined.
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Table 4
Percentage Prevalence of Coronary Adventitial Cellular Infiltration in Men and Women with Myocardial Infarction

<table>
<thead>
<tr>
<th>Coronary arterial plaque severity</th>
<th>Males with myocardial infarction</th>
<th>Females with myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free</td>
<td>Prevalence of adventitial cellular infiltration (% of blocks examined)</td>
<td>Grade of cellularity</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>Slight</td>
</tr>
<tr>
<td>Free</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>73</td>
<td>22</td>
</tr>
<tr>
<td>Severe</td>
<td>28</td>
<td>46</td>
</tr>
</tbody>
</table>

*n = number of blocks examined.

Table 5
Relationship between Coronary Adventitial Cellular Infiltration and Arterial Plaque Severity in Males with Myocardial Infarction according to the Presence and Nature of Occluding Thrombus

<table>
<thead>
<tr>
<th>Coronary arterial plaque severity</th>
<th>Blocks without thrombus, n = 248</th>
<th>Blocks with recent thrombus, n = 66</th>
<th>Blocks with recanalizing thrombus, n = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Slight</td>
<td>Marked</td>
</tr>
<tr>
<td>Free</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>77</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Severe</td>
<td>35</td>
<td>41</td>
<td>24</td>
</tr>
</tbody>
</table>

*n = number of blocks examined.

Atherosclerosis is correlated with absorption of depraved matter from the diseased intima"; Morgan also considered that they might be evidence of a "low grade reaction to the atherosclerosis, possibly concerned in the scavenging of degenerate material."

Summary
Homogeneous collections of cells resembling small lymphocytes have been found in the adventitia of atheromatous arteries, and the prevalence and degree of cellular infiltration have been shown to correlate closely with the severity of the plaques. The cells are found in the aorta, coronary, iliac, and carotid arteries; but in the carotid arteries the infiltration is less marked. Arterial blocks containing recent thrombus show more cellular infiltration than blocks without thrombus and with recanalizing thrombus.

The location and significance of the adventitial cellular infiltration is unknown, but it may play a part in the etiology or pathogenesis of arterial plaques.

Acknowledgment
This work was done during the tenure of a C. J. Martin Research Fellowship of the National Health and Medical Research Council of Australia by C.J.S. and of a Clinical Research Fellowship of the Medical Research Council by J.R.A.M.
We are grateful to Professor Sir George Pickering for constant help and encouragement, and to Dr. A. H. T. Robb-Smith and the staff of the Pathology Department, the Radcliffe Infirmary, for access to the necropsy material.

For the photomicrographs we are indebted to Dr. T. M. Parry, and we are grateful to Miss Sheila Briers, Miss Sandra Wheeler, and Mr. P. Manners for technical assistance.

References

Error

As an experienced investigator I have seen not a few instances during my career that have revealed the possibilities of mistakes even after the most careful precautions have been taken. All venturesome scientists are aware of the many chances of going astray as they enter a new field. Michael Faraday, a prince of experimenters, testified “that I may be largely wrong I am free to admit—who can be right altogether in physical science which is essentially progressive and corrective?” If Faraday could feel thus toward experimentation in the realm of physics, how much readier to acknowledge the possibility of error should be an investigator who labors in the more complex and difficult realm of biology.—WALTER B. CANNON, M.D. The Way of An Investigator. New York, W. W. Norton & Company, Inc., 1945, p. 97.
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Circulation. 1962;26:73-78
doi: 10.1161/01.CIR.26.1.73
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

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