SERIAL ARTERIOGRAPHY
IN ATHEROSCLEROSIS*

G. C. WELLIS, M.D.,†
A. W. LIGHT, M.D.,‡ and
W. S. GOW, M.D.,§ Montreal

The present day concepts of the pathogenesis of atherosclerosis have been built upon autopsy studies in man and experimental animals. The drawback of this reliable approach to the problem is that the atherosclerotic process can be visualized only at one point in time in a given case. Nevertheless, by integrating all the facts from a large autopsy series, some idea has been gained as to the nature of early and late lesions. However, the fate of an individual plaque has never been followed during life, and there is thus little accurate knowledge as to the rate of progression of the disease, nor is it known definitely whether spontaneous regression ever occurs. This failure to visualize the atheromatous plaque from time to time during life has placed the assessment of aggravating or ameliorating factors largely upon subjective or, at best, non-specific grounds.

Perhaps the closest approach to a feasible periodic study of the vascular tree has been by ophthalmoscopy. This method has been extensively reviewed and although it permits direct visualization of the fundal vessels, certain objections have been raised.† The type of vessel observed in the retina is of arteriolar rather than arterial calibre, and only the external aspect is seen. Furthermore, in the great majority of cases of atherosclerosis there are no visible atheromatous plaques in the retinal vessels. Ophthalmoscopy is considerably more valuable in studying hypertensive vascular disease than it is in the assessment of atherosclerosis.

Other criteria used to assess atherosclerosis have in actual fact been only observations of secondary phenomena. Changes in symptoms, skin temperature, digital blood flow and electrocardiogram are all influenced by many factors other than atherosclerosis; they therefore fall short as accurate criteria of the disease. The relationship of biochemical studies to atherosclerosis is even more uncertain.

To overcome these difficulties it was decided to study the femoral and popliteal arteries by serial arteriography. In this way, using a standard x-ray technique, it is possible to observe the natural history of atherosclerotic plaques. The effect of influencing factors upon the disease can likewise be evaluated. In a pathological study of the femoral and popliteal arteries previously reported,§ it was noted that atherosclerosis in these arteries was uniformly associated with atherosclerosis elsewhere. Thus of the 152 cases studied at autopsy, 27 had had a myocardial infarction at some time, and none of these 27 was free of atherosclerosis in the thigh vessels. Aortic atherosclerosis likewise tended to parallel the atherosclerosis of these lower limb vessels in degree. Dow* in his detailed examination of all the main arteries in the body, noted that the abdominal aorta, and common iliac, femoral and popliteal arteries were more extensively affected than any other vessel. A large combined x-ray and pathological study made by Lindborn† revealed that thrombosis of the lower limb vessels is considerably more common than coronary thrombosis in the older age group. On these grounds it may be taken that the degree of atherosclerosis in the femoral and popliteal arteries is a reliable indication of the degree of atherosclerosis likely to be present elsewhere.

MATERIAL AND METHODS

The patients studied by arteriography were selected from the Queen Mary Veterans* and St. Anne's Hospitals. All were men, varying in age from 55 to 77, with an average age of 64 years, and were those who had shown many of the clinical manifestations ordinarily considered to be associated with atherosclerosis. Frequently the cases had been clinically diagnosed as “generalized atherosclerosis.”

Unilateral femoral arteriography was performed in all cases. Premedication included Seconal gr. 1/4, atropine gr. 1/150 and morphine gr. 1/6 to 1/4, given half to one hour before the procedure. No local anaesthesia was used, as this was found to make arterial puncture more difficult. In spite of this, there was only slight pain during the insertion of the needle. A preliminary test dose of 35% Diodrast was given to all patients, 0,5 c.c. being injected intravenously 15 to 20 minutes prior to the intraarterial injection. No instance of sensitivity to Diodrast was encountered. The
System. A record was made of these findings, paying attention to the extent of such symptoms as intermittent claudication and angina pectoris. In addition, plasma cholesterol levels were determined in most of the cases at the outset and during the study.

None of the patients, with the exception of diabetics, was given any special diet. The treated group were given 500 mgm. of ascorbic acid daily three times a day but otherwise were the same as the control group.

![Fig. 1](image-url) - A typical bilateral femoral arteriogram. Note the numerous atheromatous plaques.

After various periods of time ranging from 2 to 6 months, arteriography was repeated using the same standard technique. The original arteriograms were then compared with the later ones and any changes noted. In order that judgment on this matter would be unbiased, one of us (A.W.L.) made this decision without knowing to which group a particular case belonged. The estimation of the progression or regression of the disease was based upon changes in the size of the intimal plaques.

Besides observation of the plaques, certain other interesting phenomena were studied, including the development of collateral vessels, occlusion of pre-existing channels, recanalization of thrombi and the occurrence of post-stenotic dilatation distal to a plaque.
### TABLE I

**RESULTS OF SERIAL ANGIOGRAPHY IN CONTROLS**

<table>
<thead>
<tr>
<th>Case age</th>
<th>Diagnosis</th>
<th>Time observed in days</th>
<th>Changes in plaques</th>
<th>Cholesterol before</th>
<th>Cholesterol after</th>
<th>Symptom changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 72</td>
<td>Severe peripheral atherosclerosis</td>
<td>176</td>
<td>2 plaque bigger, 2 unchanged</td>
<td></td>
<td></td>
<td>Impending gangrene</td>
</tr>
<tr>
<td>2 74</td>
<td>Severe peripheral atherosclerosis</td>
<td>70</td>
<td>6 plaque bigger, multiple small plaques unchanged</td>
<td>332</td>
<td>230</td>
<td>No change</td>
</tr>
<tr>
<td>3 63</td>
<td>Diabetes</td>
<td>70</td>
<td>No change</td>
<td>240</td>
<td>278</td>
<td>No change</td>
</tr>
<tr>
<td>4 77</td>
<td>Atherosclerotic heart disease, diabetes</td>
<td>89</td>
<td>No change</td>
<td>218</td>
<td>232</td>
<td>No change</td>
</tr>
<tr>
<td>5 59</td>
<td>Severe periph. atherosclerosis</td>
<td>172</td>
<td>1 plaque bigger</td>
<td></td>
<td></td>
<td>Required amputation</td>
</tr>
<tr>
<td>6 65</td>
<td>Diabetes</td>
<td>192</td>
<td>No change</td>
<td>332</td>
<td>257</td>
<td>No change</td>
</tr>
</tbody>
</table>

### TABLE II

**RESULTS IN GROUP GIVEN ASCORBIC ACID**

<table>
<thead>
<tr>
<th>Case age</th>
<th>Diagnosis</th>
<th>Time observed in days</th>
<th>Changes in plaques</th>
<th>Cholesterol before</th>
<th>Cholesterol after</th>
<th>Symptom changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 69</td>
<td>Severe atherosclerotic heart dis.</td>
<td>62</td>
<td>3 plaques bigger, 2 unchanged</td>
<td>360</td>
<td>262</td>
<td>Died 1 mo. later of pneumonia</td>
</tr>
<tr>
<td>8 59</td>
<td>Severe periph. atherosclerosis Amp. left.</td>
<td>172</td>
<td>2 plaques, smaller</td>
<td>375</td>
<td>360</td>
<td>No change</td>
</tr>
<tr>
<td>9 72</td>
<td>Periph. atherosclerosis Imp. gangrene</td>
<td>136</td>
<td>3 plaques smaller, 3 unchanged</td>
<td></td>
<td></td>
<td>Claudication decreased</td>
</tr>
<tr>
<td>10 58</td>
<td>Old myocardial infarction</td>
<td>125</td>
<td>2 plaques bigger, several unchanged</td>
<td>323</td>
<td>287</td>
<td>No change</td>
</tr>
<tr>
<td>11 56</td>
<td>Diabetes, Xanthomatosus. Ang. pectoris</td>
<td>110</td>
<td>7 plaques smaller, 7 unchanged</td>
<td>312</td>
<td>216</td>
<td>Xanthomata, softer and less painful, but same size</td>
</tr>
<tr>
<td>12 64</td>
<td>Hypercholesterolemia. Old myocardial inf.</td>
<td>105</td>
<td>6 plaques bigger, 2 unchanged</td>
<td>500 to 435</td>
<td>455</td>
<td>No change</td>
</tr>
<tr>
<td>13 85</td>
<td>Old myocardial inf. Cerebral thrombosis</td>
<td>116</td>
<td>5 plaques unchanged</td>
<td>258</td>
<td>255</td>
<td>No change</td>
</tr>
<tr>
<td>14 61</td>
<td>Diabetes. Old myocardial inf.</td>
<td>96</td>
<td>1 plaque smaller, multiple unchanged</td>
<td>285</td>
<td>312</td>
<td>No change</td>
</tr>
<tr>
<td>15 65</td>
<td>Diabetes</td>
<td>100</td>
<td>1 plaque smaller, 6 unchanged</td>
<td>221</td>
<td>248</td>
<td>No change</td>
</tr>
<tr>
<td>16 65</td>
<td>Angina pectoris</td>
<td>255</td>
<td>3 plaques smaller, multiple unchanged</td>
<td>292</td>
<td>390</td>
<td>Angina much less</td>
</tr>
</tbody>
</table>

*These cases in error each had a period up to 3 weeks without therapy. All the others had continuous therapy.*
Results

The appearance of the opacified vessels on different examinations was amazingly similar. The thrombosed portions were always similarly located; the profunda femoris always showed the same relationship to the main vessels and provided an opportunity to compare rotation in subsequent examinations. The atheromatous plaques that were visualized on one examination could always be identified on subsequent examinations. The plaques were most common in the region of Hunter's canal and the upper popliteal artery and varied in length from a few millimetres to 2 to 3 cm. The deeper ones were most easily identified and showed the more dramatic changes while the more shallow ones usually showed little change on different examinations. In areas where the femoral artery was completely thrombosed, the same collateral circulation was demonstrated on later examinations. It is interesting to note that spastic was never encountered during the course of arteriography.
The serialographic films taken over a 7½ second period demonstrated successful filling of the same vessels on repeat examinations. The degree of rotation in subsequent arteriograms matched well with the originals.

Table I shows the results in the control group while the results of ascorbic acid therapy are demonstrated in Table II.

Fig. 2 illustrates the arteriographic evidence of progression of an atheromatous plaque in case 12, while Fig. 3 shows the improvement in case 11.

Cases 1 and 5 were followed up for a time as controls and a second arteriographic study was made. They were then placed on treatment as cases 6 and 8 respectively and a third x-ray study was made after an interval of treatment. Case 15 was always in the treated group but was reviewed by arteriography on three occasions.

It will be seen from the tables that intimal plaques may enlarge or become smaller, change being restricted to only some of the plaques visualized in a given case. Regression and progression of plaques were never found co-existent in the same case. Without treatment none of the 6 cases improved; 3 cases deteriorated while 3 were unchanged. In the treated group, 6 out of 10 cases improved while 3 became worse and 1 was stationary. The development of post-stenotic dilatation distal to a plaque was observed only once (Case 1).

Although old occlusions were observed radiologically several times, recanalization was not a striking feature. The channel was never observed to increase in calibre between examinations. Collateral vessels formed a much more prominent source of blood supply following occlusion. No entirely new plaques were seen to develop during the period of observation.

There was a correlation between the arteriographic changes and the signs and symptoms in only some of the cases. The plasma cholesterol levels failed to fluctuate in relation to the changes in the plaques.

DISCUSSION

Except for a single case reported by Lindbom, this is the first time that the evolution of atheromatous plaques has been observed over a period of time. Not only have the plaques been demonstrated, but they have been followed up and any changes noted in them. It is true that, in the projection employed, the plaques situated along the medial and lateral walls of the arteries were best visualized and those along the anterior and posterior walls were indistinct. However, by standardizing the method, on all subsequent examinations the same plaques were demonstrated. The period of observation so far has been short, but it is believed that it has been possible to visualize the same atheromatous plaques in the same patient on different occasions even though slight rotation of the limb was sometimes unavoidable and the relationship of the vessel to the femoral shaft changed a little. The fact remains that on some of the patients it has been possible to take three different arteriograms at various time intervals, and some of the plaques have remained perfectly constant in outline while other plaques along the same vessel showed a change.

From these serial arteriograms it may be appreciated that atherosclerosis is not always a slow and inevitably progressive disease. Plaques may enlarge or become smaller with surprising rapidity. The fact that only some of the plaques in a given case are seen to progress in the interval of observation is evidence in favour of the importance of local rather than systemic etiological factors. This local factor is most likely partly mechanical in nature, as outlined in a previous paper. Intimal hemorrhage is very common and plays an important part in enlarging the plaque in which it occurs. Although there is no proof, it would seem likely that in the present series some of the instances of enlargement of plaques are attributable to intimal hemorrhage.

Of major importance is the observation of regression of plaques. Regression of plaques in cholesterol-fed herbivorous animals is said to be very slow when cholesterol feeding is discontinued. This is probably due to the prolonged persistence of the etiological factor, namely hypercholesterolemia. In the dog, on the other hand, hypercholesterolemia passes off in less than a week from the cessation of cholesterol feeding and regression of lesions is rapid. The report of regression of atherosclerotic lesions in human subjects dying of wasting diseases is speculative, as the arteries were seen only at one point in time. Furthermore advanced atherosclerotic plaques are a striking feature of the arteries of victims of malnutrition.
In the six control cases in this present study, spontaneous regression was not observed. The number of cases is obviously too small to warrant the conclusion that such regression never occurs.

**Therapy in Atherosclerosis**

Several forms of therapy have proved effective in inhibiting the development of atherosclerosis in animals subjected to cholesterol feeding. Cessation of cholesterol feeding is followed by some regression of lesions as previously mentioned. Desiccated thyroid has been shown to inhibit atherosclerosis in cholesterol-fed rabbits. Cortisone, alloxan, and heparin all have the same beneficial effect. Estrogen therapy, while promoting atherosclerosis in the chick aorta, exerts a sparing effect on the coronary arteries of the same animal. Finally certain wetting agents have been shown to protect the artery from hypercholesterolemia.

Recently it has been shown that ascorbic acid deficiency in guinea-pigs is followed rapidly by atherosclerosis without cholesterol feeding. Parenteral ascorbic acid has a protective effect against atherosclerosis in the cholesterol-fed guinea-pig.

In searching for a feasible form of therapy for atherosclerosis in man, the results in experimental animals have naturally been the guide. Many of the forms of therapy described can be discarded at once because of undesirable side effects. Low cholesterol diets are at present very popular. The rationale for their use is based upon the fact that cholesterol feeding with subsequent hypercholesterolemia results in atherosclerosis in some animals. However the hypercholesterolemia and reticulo-endothelial lipid deposits have no counterpart in the usual case of atherosclerosis in man. An objective assessment of the efficacy of the low cholesterol diet in human atherosclerosis has not yet been reported.

Heparin has been tried in atherosclerosis, again because of its value in the cholesterol-fed animal. It does not produce regression of lesions in the rabbit but does inhibit their development. This treatment is not without its side effects and studies in man based upon symptomatic relief in angina pectoris have shown no improvement.

Ascorbic acid therapy has been combined with rutin in an uncontrolled study of atherosclerosis in man and the results based on symptomatic grounds were favourable.

The rationale for ascorbic acid therapy is based upon studies of the pathogenesis of atherosclerosis. Gross depletion of ascorbic acid has been demonstrated to be frequent in human arteries at autopsy. Ascorbic acid deficiency in guinea-pigs is accompanied by rapid deposit of lipid in the intima of arteries morphologically identical to human atherosclerosis. These lesions occur at normal plasma cholesterol levels and are not accompanied by lipid deposits in the reticulo-endothelial system. The concept of atherosclerosis as a lesion of the intimal ground substance localized at points of mechanical stress, as suggested by Virchow and Aschoff, is incorporated in the atherosclerosis of ascorbic acid deficiency. Finally the lipid accumulation in the arteries would seem to be related to the increased rate of incorporation of C14 acetate into cholesterol which occurs in ascorbic acid deficiency.

**Aute-mortem ascorbic acid therapy is capable of making good the ascorbic acid deficiency observed in the arteries at routine hospital autopsies.** Although parenteral ascorbic acid therapy is considerably more potent in inhibiting the atherosclerosis of cholesterol-fed guinea-pigs, it has certain practical drawbacks. For this reason oral therapy for long term studies was employed. No toxic effects have been reported from the use of oral ascorbic acid, nor were any observed in this study. The dose chosen was based upon the studies of ascorbic acid absorption and saturation as described by Faulkner et al. and Todhunter et al. The aim was to ensure continuous saturation of tissues with ascorbic acid.

The results in this present study of ascorbic acid therapy in human atherosclerosis as followed by serial arteriography are encouraging. Once again it must be pointed out that the series is small and that final conclusions must await studies carried out for a longer time with more cases added. This is being done, and the present review is to be considered as a preliminary report.
Fig. 4.—The results of ascorbic acid therapy in the case of xanthoma tuberosum described in the text. The pictures were taken (A) before and (B) after 3 months of therapy.

Fig. 4 illustrates the results of ascorbic acid therapy in a male of 30 suffering from xanthoma tuberosum and a myocardial infarction. No study was made of this patient's arteries because of technical difficulties. Successful therapy of xanthomatosis has been reported in a case of myxocemia after administration of thyroid and a low cholesterol diet and is said to follow heparin therapy. 19

SUMMARY AND CONCLUSIONS

1. The problem and the importance of studying atherosclerosis objectively during life are outlined and serial arteriography is suggested as a method of study.

2. Evidence is set forth to indicate that femoral and popliteal arteriography is a useful means of estimating the degree of atherosclerosis likely to be present throughout the body.

3. The method of serial arteriography is described.

4. The development of thrombosis, collateral vessels, reanastomosis of thrombi and post-stenotic dilation distal to a plaque is discussed.

5. Both progression and regression of plaques are observed to occur over relatively short periods of time. Progression and regression did not co-exist in the same cases during one period of observation.

6. Various forms of therapy in atherosclerosis are mentioned and some of them discussed. Serial arteriography is suggested as a means of assessing therapy.

7. The rationale for ascorbic acid therapy is briefly outlined as based upon previous studies of the pathogenesis of atherosclerosis.

8. Preliminary results of ascorbic acid therapy in human atherosclerosis are encouraging.

REFERENCES


Queen Mary Veterans' Hospital, Montreal.