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SERIAL ARTERIOGRAPHY IN ATHEROSCLEROSIS*

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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.[1] 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 atherosclerotic 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,[2] 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[3] 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 Lindbom[4] 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."

Bilateral femoral arteriography was performed in all cases. Premedication included Seconal gr. 1½, atropine gr. 1/150 and morphine gr. 1/6 to ¼, given half to one hour before the procedure. No local anæsthesia 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

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patient was supine with the feet strapped to an inverted T shaped splint. The heels and toes were held snugly against the upright, thus ensuring the same projection on repeat arteriograms.

The technique of injection was modified from that of Lindbom.[4] After preparation of the skin with iodine, the point of maximum pulsation of the femoral artery was located at the inguinal ligament and fixed between two fingers. An 18-gauge 2½-inch (6.25 cm.) needle with stilette was inserted, bevel up, in a retrograde direction, entering the skin about ½ inch below the inguinal ligament and penetrating to a point where the arterial pulsation was transmitted to the needle. In most cases a distinct give was felt when the artery had been pierced and this was accompanied by slight pain. A definite arterial spurt after withdrawing the stilette confirmed the insertion. The needle was then rotated through 180° so that the bevel was parallel to the posterior arterial wall, and then threaded up 1 to 2 cm. to avoid extravascular injection. With both needles securely in place, 20 c.c. of 35% Diodrast was injected simultaneously into both arteries from 50 c.c. syringes equipped with stopcocks, polyethylene tubing and Luer locks. The injection lasted about 7 seconds and was accompanied by fairly severe but transient pain followed by a burning sensation passing down into the legs and feet and lasting 20 to 30 seconds. This was followed by visible flushing of the skin of the legs in some cases. Meanwhile 5 to 7 x-ray films 14" x 17" (35 x 42.5 cm.) were exposed with a cassette changer at 1½ second intervals, starting when about 10 c.c. of the dye had been injected. The needles were then immediately withdrawn and firm pressure was applied to the site of injection for 2 to 3 minutes. The only complications encountered were occasional small hæmatomas at the injection site which absorbed without sequelæ. At the outset of the study, several extravascular injections were made without any complications. Fig. 1 is a typical bilateral arteriogram.

Those cases in which there was arteriographic evidence of intimal plaques were then divided into two groups. One was followed up with a view to studying the spontaneous changes occurring in arteries, while the other group was used for the assessment of therapy. All the cases in the two groups were reviewed clinically in detail, with particular reference to the vascular 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 orally three times a day but otherwise were the same as the control group.

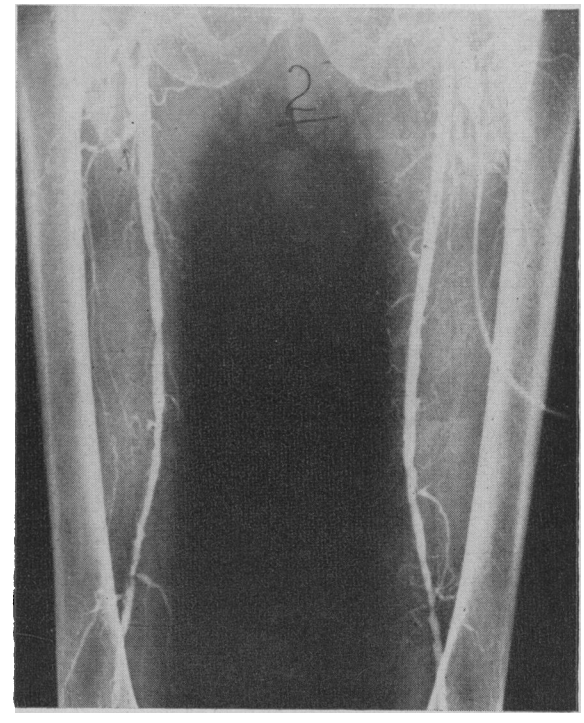

Fig. 1.—A typical bilateral femoral arteriogram. Note the numerous atheromatous plaques.

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 judgement 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 ARTERIOGRAPHY IN CONTROLS

Case age	Diagnosis	Time observed in days	Changes in plaques	Cholesterol Mgm. % before	Cholesterol Mgm. % after	Symptom changes
1 72	Severe peripheral atherosclerosis	176	2 plaques bigger 2 unchanged			Impending gangrene
2 74	Severe peripheral atherosclerosis	70	4 plaques bigger; multiple small plaques unchanged	332	290	No change
3 63	Diabetes	70	No change	240	278	No change
4 77	Atherosclerotic heart disease, diabetes	82	No change	216	232	No change
5 59	Severe periph. atherosclerosis	172	1 plaque bigger			Required amputation
6 62	Diabetes	192	No change	332	287	No change

TABLE II.

RESULTS IN GROUP GIVEN ASCORBIC ACID

Case age	Diagnosis	Time observed in days	Changes plaques	Cholesterol Mgm. % before	Cholesterol Mgm. % after	Symptom changes
7 69	Severe atherosclerotic heart dis.	62	3 plaques bigger 2 unchanged	350	262	Died 1 mo. later of pneumonia
8* 59	Severe periph. atherosclerosis Amp. left.	172	2 plaques smaller	375	360	No change
9 72	Periph. atherosclerosis. Imp. gangrene	136	3 plaques smaller, 3 unchanged			Claudication decreased
10* 58	Old myocardial infarction	125	2 plaques bigger several unchanged	323	287	No change
11 56	Diabetes. Xanthomatosis. Ang. pectoris	110	7 plaques smaller 7 unchanged	312	216 240 340	Xanthomata softer and less painful, but same size
12* 64	Hypercholesterolæmia. Old myocardial inf.	105	6 plaques bigger 2 unchanged	560 to 435	485	No change
13 65	Old myocardial inf. Cerebral thrombosis	116	5 plaques unchanged	258	255	No change
14 61	Diabetes. Old myocardial inf.	96	1 plaque smaller multiple unchanged	255	312	No change
15* 55	Diabetes	100	1 plaque smaller 6 unchanged	221	248	No change
16 63	Angina pectoris	155	3 plaques smaller multiple unchanged	292	390	Angina much less

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

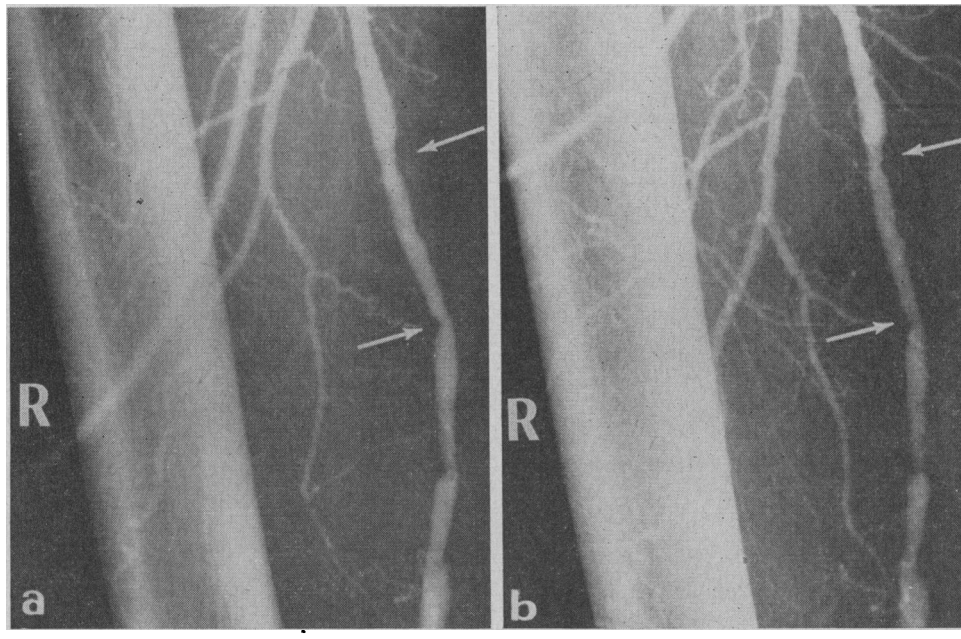

Fig. 2.—The arteriographic evidence of enlargement of intimal plaques in case 12. Arteriogram (a) is the initial one while (b) is the repeat arteriogram 105 days later.

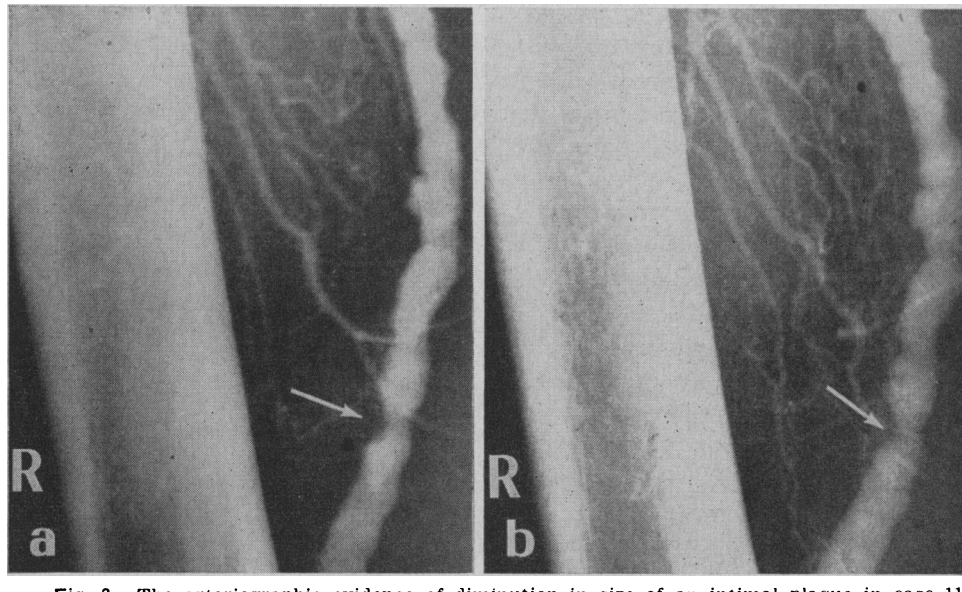

Fig. 3.—The arteriographic evidence of diminution in size of an intimal plaque in case 11. Arteriogram (a) is the initial one while (b) is the repeat arteriogram 110 days later.

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 spasm 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 9 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,[4] 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.[5] Intimal hæmorrhage is very common[6] and plays an important part in enlarging the plaque in which it occurs.[6] 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 hæmorrhage.

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.[7] This is probably due to the prolonged persistence of the etiological factor, namely hypercholesterolæmia. In the dog, on the other hand, hypercholesterolæmia passes off in less than a week from the cessation of cholesterol feeding and regression of lesions is rapid.[8] The report of regression of atherosclerotic lesions in human subjects dying of wasting diseases[9] 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.[10]

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.[11] Cortisone,[12] alloxan,[13] and heparin[14] all have the same beneficial effect. Œstrogen therapy, while promoting atherosclerosis in the chick aorta, exerts a sparing effect on the coronary arteries of the same animal.[15] Finally certain wetting agents have been shown to protect the artery from hypercholesterolæmia.[16]

Recently it has been shown that ascorbic acid deficiency in guinea-pigs is followed rapidly by atherosclerosis without cholesterol feeding.[17] Parenteral ascorbic acid has a protective effect against atherosclerosis in the cholesterol-fed guinea-pig.[17]

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 hypercholesterolæmia results in atherosclerosis in some animals. However the hypercholesterolæmia and reticulo-endothelial lipid deposits have no counterpart in the usual case of atherosclerosis in man.[18] 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[7] but does inhibit their development.[14] This treatment is not without its side effects[19] and studies in man based upon symptomatic relief in angina pectoris have shown no improvement.[19]

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.[20]

The rationale for ascorbic acid therapy is based upon studies of the pathogenesis of atherosclerosis.[21, 22] Gross depletion of ascorbic acid has been demonstrated to be frequent in human arteries at autopsy.[22] Ascorbic acid deficiency in guinea-pigs is accompanied by rapid deposit of lipid in the intima of arteries morphologically identical to human atherosclerosis.[17] 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,[23] is incorporated in the atherosclerosis of ascorbic acid deficiency.[22] Finally the lipid accumulation in the arteries would seem to be related to the increased rate of incorporation of C^{14} acetate into cholesterol which occurs in ascorbic acid deficiency.[24]

Ante-mortem ascorbic acid therapy is capable of making good the ascorbic acid deficiency observed in the arteries at routine hospital autopsies.[22] Although parenteral ascorbic acid therapy is considerably more potent in inhibiting the atherosclerosis of cholesterol-fed guinea-pigs,[17] 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.*[25] and Todhunter *et al.*[26] 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.

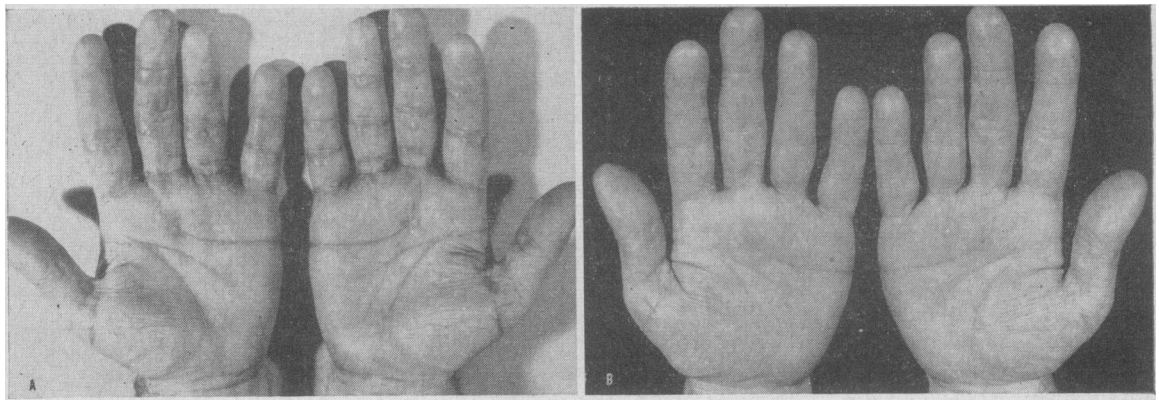

Fig. 4.—The results of ascorbic acid therapy in the case of xanthoma tuberosum described in the text. The pictures were taken (A) before and (B) after 5 months of therapy.

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 myxœdema after administration of thyroid and a low cholesterol diet[27] and is said to follow heparin therapy.[28]

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, recanalization of thrombi and post-stenotic dilatation 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.

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