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Aorto-Coronary By-Pass with Autogenous Saphenous Vein Grafts: Histopathological Aspects

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Summary. The histological modifications in 8 cases of autologous aorto-coronary saphenous vein grafts were studied. In the early stages, these showed intimal thickening and medial hypertrophy, particularly affecting the middle circular layer. The intimal thickening progressed, and the media later became largely replaced by dense fibrous tissue. No aneurysmal dilatations were observed, but in 3 cases the grafts were thrombosed. The pathogenesis of these changes is discussed.

Introduction

The rapid progress and encouraging results obtained with surgical treatment of stenosis in the peripheral vascular system have led to the use of such techniques in the treatment of occlusive coronary artery disease. Endarterectomy of coronary vessels as performed by Bailey *et al.* (1957) and Longmire *et al.* (1958) was superseded by the use of venous patch graft reconstruction (Senning, 1961; Effler *et al.*, 1967). As a result of experimental studies in dogs (Sauvage *et al.*, 1963), the above techniques were replaced by the use of venous grafts, either by interposing short venous segments to replace obstructed sections of coronary arteries (Favolaro, 1968), or by simply by-passing the diseased segment through a bridge directly from the aorta (Favolaro, 1969; Hahn *et al.*, 1970).

The histological changes undergone by such grafts in peripheral positions are well documented, but little has been published about the modifications taking place in the aorto-coronary by-pass.

Materials and Methods

Aorto-coronary by-passes have been performed in more than 100 patients since 1968 at the Surgical Department, Cantonal Hospital, Geneva. Eight have died and these 8 cases form the basis of the present study.

The patients' ages ranged between 41 and 69 years and the post-operative survival varied between a few hours and 10 months. Six of them had proven myocardial infarctions prior to surgery; the remaining 2 had suffered from severe angina.

Complete necropsy was performed on all cases, except No. 7, in which the brain was not examined. Post-mortem coronary angiograms were done in 7 cases, the exception being case No. 5. Coronary angiography was performed either by direct perfusion of the ostia or by using the technique of Baroldi and Scomazzoni (1967). A mixture of barium and gelatin heated to 45° C was perfused at a pressure not exceeding the *in vivo* values.

The grafts were sectioned transversely and longitudinally at different levels. The material was fixed in neutral 10 % formalin, embedded in paraffin, sectioned at 5 μ and stained with hematoxylin-eosin, van Gieson, Goldner-Verhoeff, eosin-Verhoeff, Gomori, PTAH and

Table. *Case records*

Case No.	Sex	Age (years)	Operation performed	Survival after operation (days)	Cause of death	Weight of heart (g)	Pathological findings in heart	State of by-pass	State of coronary arteries
1	♂	56	A-RC by-pass RC endarterectomy LC endarterectomy	2/24	Myocardial infarction (acute)	350	Antero-septal infarction (old). Postero-lateral infarction (recent)	Patent	AIVB atherosclerosis, CB obliterated by atheromatous plaque
2	♂	41	A-LC by-pass A-CB by-pass RC endarterectomy	3/24	Cardiac insufficiency	460	Postero-lateral infarction (old and extensive)	Thrombosed (both grafts)	RC thrombosis (organized)
3	♂	47	A-RC by-pass	10	Pneumothorax, Bronchopneumonia, Lung abscesses	410	Focal necrosis	Patent	RC atherosclerosis (segmental stenosing)
4	♂	56	A-RC by-pass	12	Collapse of left lung, "Hyaline membrane disease", Gastric erosions	640	Posterior infarction (old and extensive, with aneurysm formation), Acute dilatation, Aortic insufficiency	Patent	RC stenosis
5	♂	69	A-RC by-pass A-M implant	15	Acute gastric ulcerations (with hemorrhage)	460	Dilatation	Patent (Implant thrombosed)	Diffuse stenosing atherosclerosis of all coronary arteries
6	♂	43	A-RC by-pass RC endarterectomy	34	Cardiac insufficiency	570	Antero-lateral infarction (old), Postero-septal infarction (recent and extensive)	Thrombosed	RC thrombosis (organized), LC atherosclerosis (stenosing)
7	♂	46	A-RC by-pass	42	Bronchopneumonia, Lung abscesses, Perforated duodenal ulcer, Peritonitis	420	Sub-endocardial scarring	Patent	RC stenosis AIVB thrombosis (fresh)
8	♂	44	A-RC by-pass Apical patch Correction of mitral insufficiency	300	Acute cardiac insufficiency	720	Postero-septal infarction (old), Apical patch	Thrombosed	RC thrombosis (organized) LC atherosclerosis (stenosing)

♂ = male; A-RC = aorto-right coronary; A-LC = aorto-left coronary; A-CB = aorto-circumflex branch; RC = right coronary artery; LC = left coronary artery; AIVB = anterior interventricular branch; CB = circumflex branch; A-M implant = vein graft connected at one end to aorta and other end implanted directly into myocardium of left ventricle.

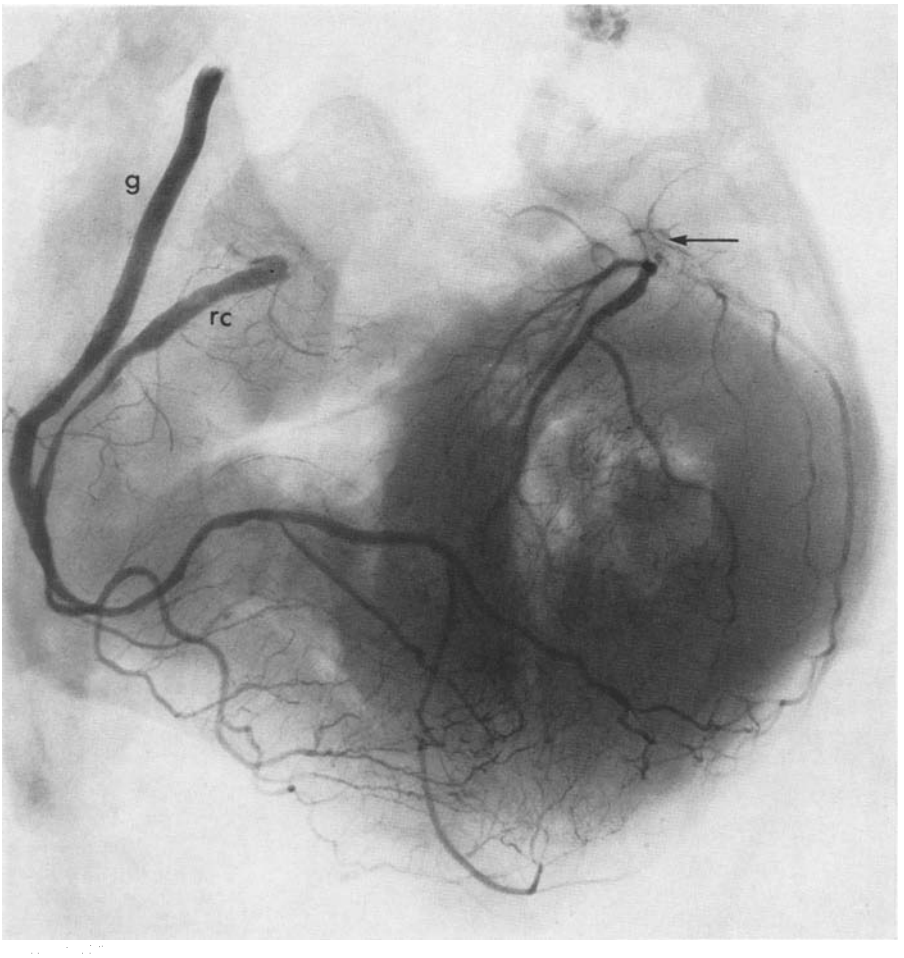


Fig. 1. Post-mortem coronary angiogram of the right coronary (*rc*) and of the graft (*g*) showing the patency of the graft. Note filling of the left coronary artery through anastomoses. The left interventricular branch is blocked (arrow). Case No. 7 (42 days)

Masson. Frozen sections were stained with Oil-red-O. Saphenous vein controls were obtained in some of the cases or from other subjects; they were injected with barium-gelatin (as above) and were examined in the same way.

Results

The relevant clinical information and the main pathological features are summarized in the Table.

In 4 cases (No. 1, 2, 6 and 8), death was of cardiac origin (infarcts or acute cardiac failure), while in two others (No. 3 and 4) it was due to respiratory complications, and in the remaining two (No. 5 and 7) to digestive causes (acute gastric ulcers: one hemorrhagic and the other perforated with peritonitis).

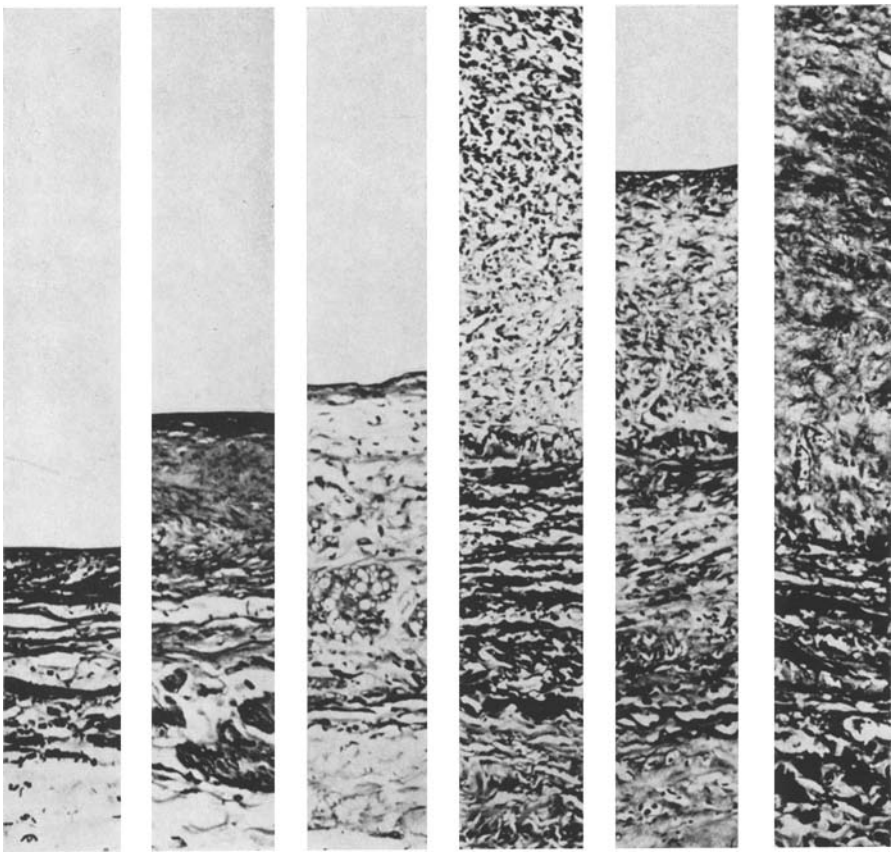


Fig. 2. Modifications of saphenous veins in aorto-coronary by-pass. Figures refer to days after grafting. The sections have been taken from (in order): control, cases No. 1, 4, 6, 7 and 8. Eosin-Verhoeff. 35 ×

Coronary angiography (performed in 7 cases) showed that the grafts in 4 cases (No. 1, 3, 4 and 7) were patent (Fig. 1). The grafts in 3 cases were blocked, either partially (No. 6) or completely (No. 2 and 8). It should be noted that case No. 2 had 2 grafts (Table): both were completely obliterated. In case No. 5, in which coronary angiography was not performed, no thrombi were found macroscopically or histologically.

Histological studies showed the following:

a) Normal Saphenous Vein

The wall of the normal saphenous vein is composed of 3 layers (Figs. 2 and 8b). The *intima* consists of an endothelium and a thin sub-endothelial collagenous layer. This is separated from the second layer by fine elastic fibrils of lamellae oriented longitudinally. The *media* forms the greater part of the thickness of the

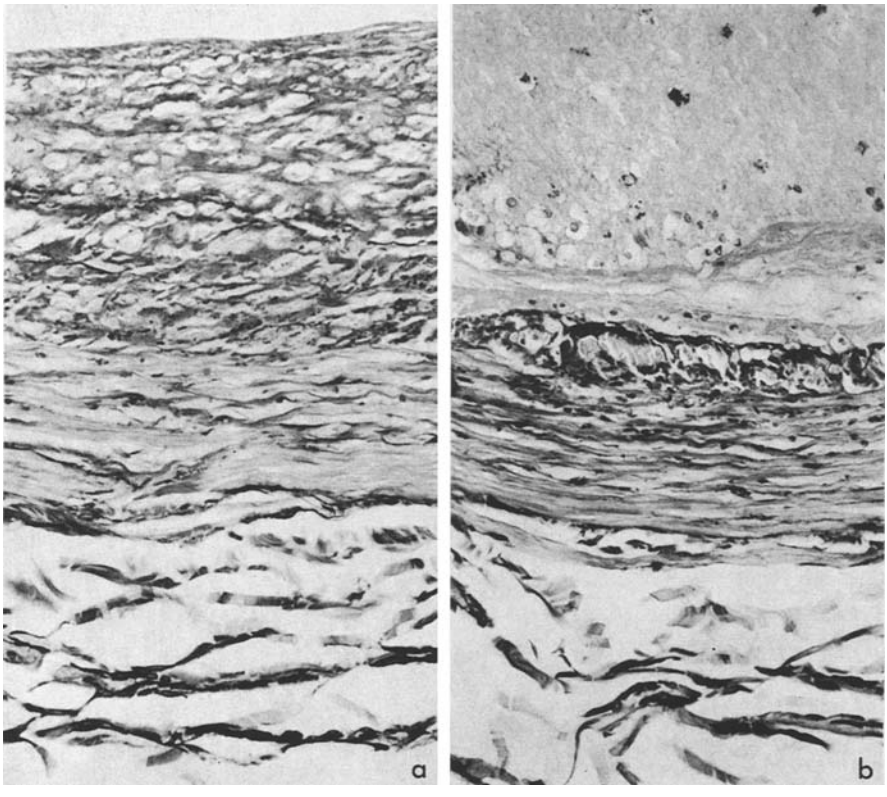


Fig. 3. a Pre-existing phlebosclerosis. b Normal area of same vein. Case No. 2. Van Gieson. 225 ×

wall. It is composed of 3 smooth muscle coats: the inner and outer are longitudinal, and are separated by the middle circular layer. Only the latter appears to be continuous. The internal and middle layers are much thicker than the external, and contain numerous short elastic fibers. The external layer on the other hand contains large thick elastic fibers. The *adventitia* consists of a loose connective tissue containing vasa vasorum, which may in some instances reach the middle circular layer.

b) Grafts (Fig. 2)

Few Hours. The by-pass saphenous vein grafts which had functioned only for a few hours (cases No. 1 and 2) showed various degrees of phlebosclerosis, which was interpreted as a pre-existing lesion (Fig. 3). The sclerosis observed in case No. 2 was less marked than in case No. 1. Both grafts in case No. 2 contained recent thrombi, not only on the thickened intima but also on the venous valves of one of the veins (Fig. 4) located near the distal anastomosis.

10–15 Days. Cases No. 3, 4 and 5 which were in place for 10, 12 and 15 days respectively showed various degrees of thickening of the wall. This was quite noticeable in the intima which was not only thickened but somewhat sclerosed,

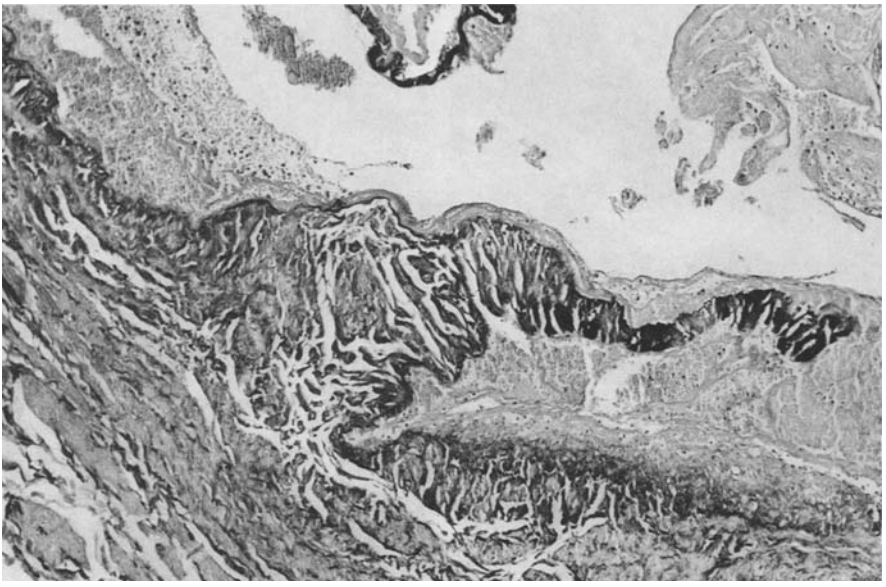


Fig. 4. Thrombosis on a venous valve, a few hours after operation. Case No. 2. Van Gieson. 90 ×

basophilic and alcian-blue positive. The van Gieson-stained precollagenous fibers seemed to separate the fibroblasts within the sub-intimal layer and the smooth muscle cells within the longitudinal internal layer. None of these grafts contained thrombi.

The circular middle layer was also thickened and showed an increase in the number of smooth muscle cells. Here there were fewer collagen fibers than in either the internal or external layer. In the external longitudinal layer, the smooth muscle cells were vacuolated and separated by a marked sclerosis (Fig. 5). The elastic fibers bordering the external longitudinal layer were thickened and appeared to form a continuous ring.

34 Days. The graft in case No. 6 was thrombosed. The thrombosis was partially organized and extended to the distal coronary-venous junction (Fig. 6). It was recanalized in places. The lesions in the wall of the graft were far more advanced in this case than in the previous ones. The intima was quite thickened, sclerosed and contained numerous fine elastic fibrils and some smooth muscle cells. This was clearly noticeable in the proximal portion of the graft near the aorto-venous suture line (Fig. 7) where there were no thrombi. The internal limit of the intima was difficult to define in the remainder of the graft because of the thrombosis. In the internal longitudinal layer, the smooth muscle was for the most part replaced by dense, thick collagen fibers. In the external longitudinal muscular layer, the elastic fibers formed several continuous bands. The few remaining smooth muscle cells were separated by thick collagenous fibers which appeared to continue into the adventitia. The vasa vasorum were numerous and penetrated deep into the thickness of the venous wall, almost to the thickened intima.

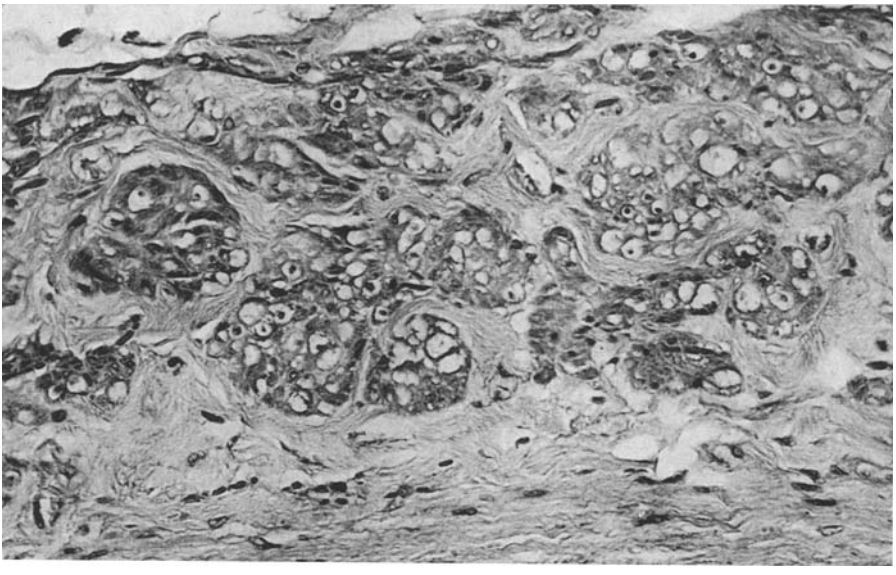


Fig. 5. Vacuolization of smooth muscle cells in the densely fibrous external longitudinal layer after 12 days. Case No. 4. Hematoxylin-eosin. 225 ×

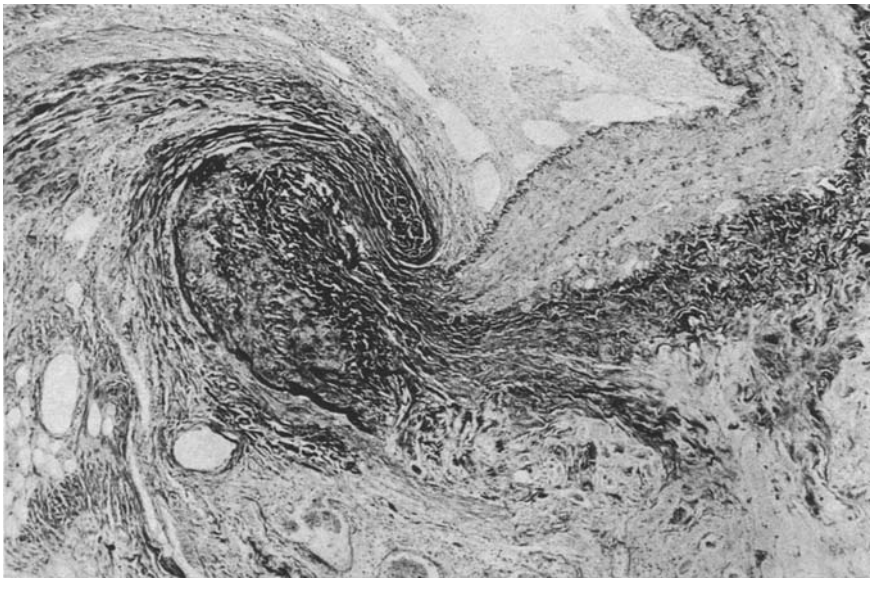


Fig. 6. Thrombosis (top left) on the distal coronary-venous junction after 34 days. Case No. 6. Van Gieson. 90 ×

42 Days. In case No. 7, similar changes were observed as those described in the previous case, but with some particular features. The intimal thickening (Fig. 8) as well as the staining qualities were similar but there were no elastic

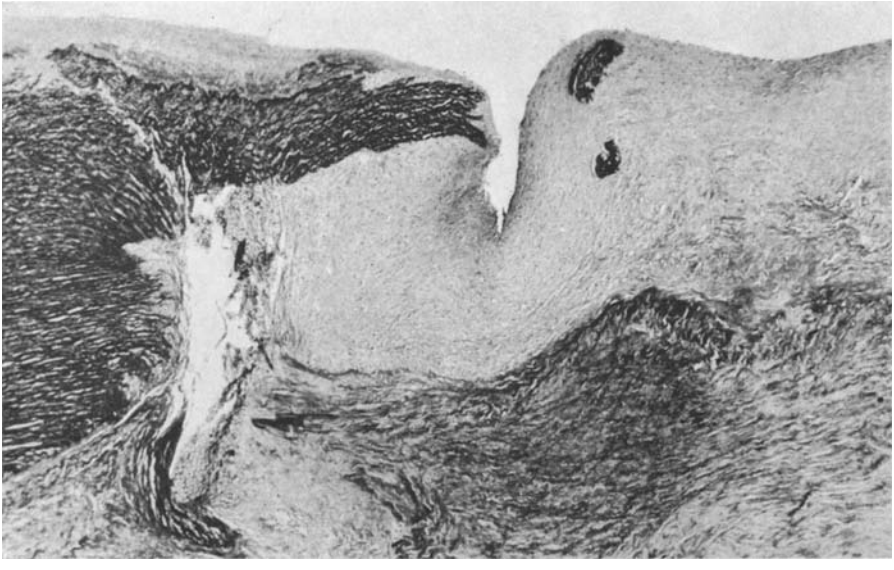
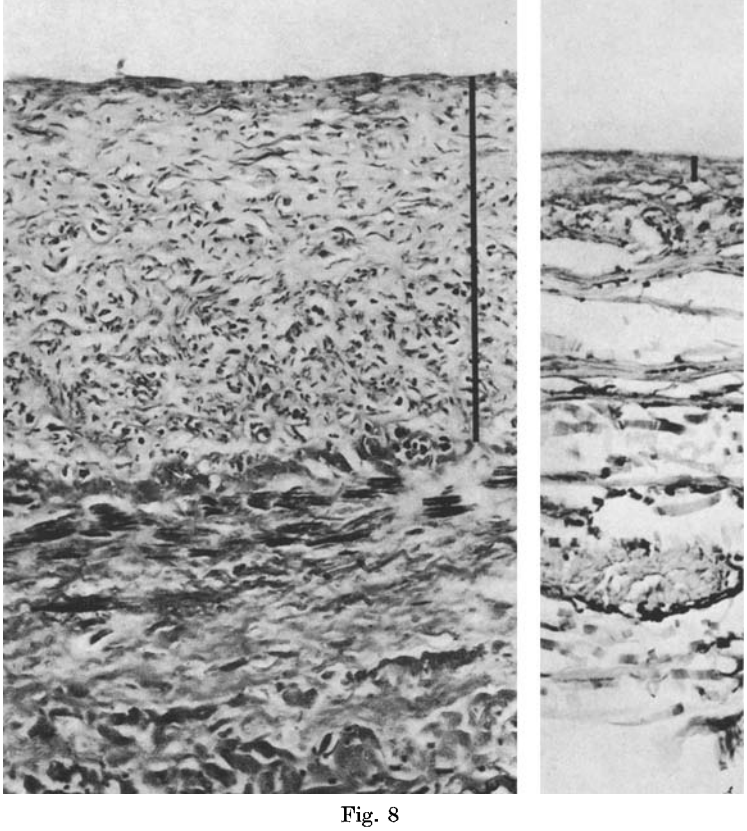
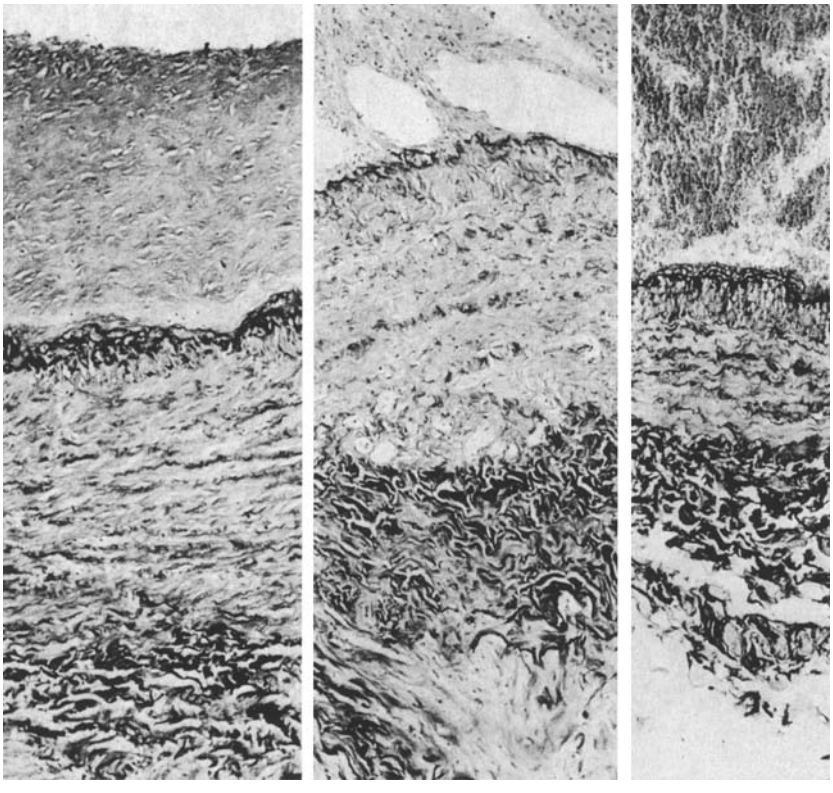


Fig. 7. The aorto-venous suture zone after 34 days. Intimal hyperplasia in the venous graft (on the right). Case No. 6. Van Gieson. 35 ×



a b

Fig. 8



a b c

Fig. 9 a–c. Hypertrophy of the wall and intimal hyperplasia, more prominent near the aorto-venous junction (a) than towards the distal coronary-venous junction (b). Compared with contralateral saphenous vein control (c). Case No. 7 (42 days). Van Gieson. 90 ×

fibers. The internal longitudinal layer, even though quite sclerosed, contained a few smooth muscle cells. Its thickness was less than that of the preceding case and the elastic fibers appeared grouped together. The smooth muscle of the middle circular and external longitudinal layers was completely replaced by a sheet of fibrous tissue, continuous with the adventitia, and interrupted only by groups of elastic fibers. All these changes were less prominent at the distal coronary-venous junction (Fig. 9).

10 Months. In case No. 8, the modifications noted above were accentuated. There was a marked hyperplasia of the intima which was rich in collagen. This zone was basophilic, alcian-blue positive and practically devoid of elastic fibers. In parts, the vessel lumen contained organized thrombus, and in these areas

Fig. 8. a Intimal thickening in graft after 42 days. b Saphenous vein control. The thickness of the intima is indicated, in each case, by the length of the black line. Case No. 7. PTAH. 225 ×

the inner limit of the thickened intima was ill-defined. In addition, recent thrombus was found occluding the distal end of the graft. The internal longitudinal layer was reduced to a sclerosed band containing a few thick elastic fibers. The middle circular layer appeared atrophied and sclerosed, but contained a few smooth muscle cells. The same was true for the external longitudinal layer which contained rather thick collagen bands with isolated muscle cells.

Discussion

Venous grafts acting as aorto-coronary by-passes for long periods show histological changes which can be summarized as follows:

1. Thickening of the entire wall due principally to an intimal hyperplasia.
2. Transient muscular hypertrophy of the media followed by atrophy and progressive replacement by fibrous tissue with thick collagen bands.
3. Formation of thick elastic fibers towards the external region of the wall, preceded by grouping of fine isolated fibrils.

These modifications are similar to those observed in human saphenous venous grafts in peripheral arterial reconstruction and also to those obtained in animal experiments (Deterling, 1959).

Oudot (1951) observed intimal thickening of venous grafts in the aortic position for 3 to 4 weeks, whereas Kautzki and Brussatis (1956) only found this change after 9 weeks when the venous grafts were placed in the peripheral position. Curcio (1911) placed venous grafts in the aorta and noted intimal changes after 23 days. In our material, cases No. 3 and 4 showed considerable intimal proliferation after 10 and 12 days respectively. This seemed to be the result of a continuous process of proliferation of fibroblasts and smooth muscle cells. The longer the vessels remained patent the more striking these overall changes became. Similar modifications were observed both by Stein *et al.* (1966) and by McNamara *et al.* (1967).

The pathogenesis of this intimal thickening is not clear, but could be related to turbulence of flow induced by irregularities at the suture points or by the difference between the diameters of the venous graft and the coronary artery. There were no atheromatous plaques, nor lipids, nor cholesterol as described by various authors (Ejrup *et al.*, 1961; Rivkin *et al.*, 1963). However, case No. 8 presented changes in the hyperplastic intima which were suggestive of an early atheromatosis.

The sclerosis of the internal and external longitudinal muscular layers was already present after 10 days and in some areas was advanced. The middle circular layer appeared to respond to the new hemodynamic conditions by hyperplasia of its muscle cells and only later became sclerosed. The vacuolization of the muscle cells which was observed at about the tenth day (cases No. 3 and 4) may be due to anoxia and could be the cause of the sclerosis observed at later stages. The internal longitudinal and middle circular layers of the thrombosed venous grafts (cases No. 2, 6 and 8) were considerably modified, possibly as a consequence of nutritional disturbances and poor diffusion across the wall.

The material examined showed no aneurysmal dilatations. These, however, were frequently observed when venous grafts were placed in the aortic position

in animals (Coleman *et al.*, 1951; Sako, 1951), or in the peripheral position in man (Dye *et al.*, 1956; Steenaert *et al.*, 1970). The absence of aneurysmal dilatations in our cases agrees with the results of Favolaro (1969) who did not observe dilatation of aorto-coronary vein grafts in coronary angiograms performed up to 1 year after operation. However, it is possible that such dilatations may occur at later stages, as found by Steenaert *et al.* (1970) in peripherally placed grafts up to 4 years after operation.

Various factors must be taken into consideration when evaluating the pathogenesis of thrombosis in the venous grafts. Apart from such conditions as hypercoagulability of blood, increased stickiness of the platelets (case No. 2), intimal changes and turbulent flow, a poorly developed vascular bed in the myocardium may result in a decreased blood flow with consequent stasis in the grafts instead of the increased rate that would be expected.

In addition, thrombus formation may be favored by the presence of venous valves (Barner *et al.*, 1969; Breslau *et al.*, 1965) and possibly also by phlebosclerosis in the grafted veins.

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