# Biologic Fate of Autogenous Vein Implants as Arterial Substitutes:

## Clinical, Angiographic and Histopathologic Observations in Femoro-Popliteal Operations for Atherosclerosis

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ALTHOUGH autogenous vein grafts, the most nearly ideal arterial substitutes, are widely used and their histologic behavior is undoubtedly an important factor in determining long-range patency, little is known about their biologic fate after implantation in humans. Reports of experimental findings in autogeneic vein grafts are fairly numerous[2,4,15,18,19,21,22,28] (though often conflicting in their conclusions), but only a few isolated cases of clinical post-transplantation observations have been described[1,3,5,6,8,9,10,12,19,20] and no comprehensive study of the subject has been reported. To obtain a better understanding of the natural history of these implants, we have reviewed our experience with lower-limb atherosclerotic occlusive disease in which autogenous saphenous vein bypasses have been used during the period of 1962–1972. We report here our findings in correlating the clinical course of these cases with postoperative angiographic and histopathologic observations.

### *Clinical Material. Method of Study.*

*Case Selection.* Our study is based upon 377 autogenous venous bypasses performed in the lower extremity, of which 316 were femoro-popliteal procedures and 61 were infrapopliteal (Tables 1–4, Fig. 1). In a femoro-popliteal procedures, the vein bypass graft extends from the common or proximal superficial femoral artery to the popliteal artery below the level of the knee joint. In the infrapopliteal operation, the distal anastomosis is formed between the graft and one of the branches of the popliteal artery from the point of its bifurcation to the level of the ankle. All operations were performed to correct the manifestations of atherosclerosis, almost entirely of the occlusive type.

*Method of Follow-up.* The patients were examined by angiographic technics before discharge from the hospital unless the operation was an obvious clinical failure, in which case the angiographic study was omitted. In a few instances, because of complications in postoperative recovery, angiographic examination was delayed for as much as 6 weeks. After discharge, angiographic study was done at 1 year postoperatively and at intervals of 1–3 years thereafter. The technic of translumbar aortography used has been described in a previous report.[24] When the proximal anastomosis was below the level of the common femoral artery, percutaneous femoral arteriography was employed frequently. Of the total number, 289 patients had patent grafts, at hospital discharge, and among these 260 had undergone at least one postoperative angiogram; 214 had undergone femoro-popliteal procedures and 46 were in the infrapopliteal subgroup. Of the combined group involving all regions of the lower extremity, 64.5% of the patients had two or more angiograms and 26.3% had undergone three or more angiographic studies (Table 5). Clinical check-up examinations were carried our at 4 weeks and 6 months postoperatively and once every year thereafter.

As of December 31, 1972, which was the closing date

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TABLE 1. *F-iP Venous Autografts for Occlusive Disease Immediate Results by Severity of Disease*

| Grade | Total No. | Open No. | Open % | Closed No. | Closed % | Amputation No. | Amputation % | Op. Mort. No. | Op. Mort. % |
|---|---|---|---|---|---|---|---|---|---|
| I | 2 | 2 | 100.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| II | 13 | 10 | 76.9 | 1 | 7.7 | 2 | 15.4 | 0 | 0 |
| III | 46 | 36 | 78.3 | 2 | 4.3 | 7 | 15.2 | 1 | 2.2 |
| Total | 61 | 48 | 78.7 | 3 | 4.9 | 9 | 14.8 | 1 | 1.6 |

of the survey, the clinical follow-up was complete in all the patients with or without angiograms, and the angiographic follow-up was complete in all the patients examined angiographically, within 6 months of the closing date of the study. The clinical follow-up periods were considerably longer in the femoro-popliteal group, 72.2% of this group having been followed for 3 years or more and 46.5% for 5 years or more (Table 6). In femoro-infrapopliteal cases only 25% were followed clinically for 3 years or more (Table 7). The extent of angiographic follow-up disclosed similar comparative trends in the two anatomic groups.

*Method of Study.* For the purpose of this study, all angiographic reports prepared by the authors at the time of the original angiographic examination were reviewed. All the angiograms in the description of which some deviation from the normal had been noted were individually studied and details of the deviation were recorded. These details, together with the voluminous clinical data were transferred to punch cards and then to magnetic tape for computer manipulation.

As formerly stated, the primary aim of the study was to detect structural changes in the vein grafts that could be correlated with the clinical course. Since the angiographic information was abundant and adequate in more than 90%, of the patients, the primary factual base of our analysis was angiographic. The ultimate proof of structural changes, however, are the gross and microscopic anatomic findings seen in the grafts themselves. However, since recovered graft material, because of obvious practical exigencies, was relatively scarce, it was necessary to identify, in the first phase of study, the important angiographic changes in the voluminous roentgen material (Table 8) and then find their expression, as the second phase of the study, in recovered specimens by comparing the anatomic findings with the recorded angiographic appearances. A sufficient amount of graft material was obtained to make such a retrospective interpretation highly reliable.

TABLE 2. *F-P Venous Autografts for Occlusive Disease Immediate Results by Severity of Disease*

| Grade | Total No. | Open No. | Open % | Closed No. | Closed % | Amputation No. | Amputation % | Op. Mort. No. | Op. Mort. % |
|---|---|---|---|---|---|---|---|---|---|
| I | 101 | 81 | 80.2 | 20 | 19.8 | 0 | 0 | 0 | 0 |
| II | 78 | 56 | 71.8 | 14 | 17.9 | 6 | 7.7 | 2 | 2.6 |
| III | 137 | 104 | 75.9 | 14 | 10.2 | 13 | 9.5 | 6 | 4.4 |
| Total | 316 | 241 | 76.3 | 48 | 15.2 | 19 | 6.0 | 8 | 2.5 |

TABLE 3. *241 Femoro-popliteal Venous Autografts for Occlusive Disease. Late Cumulative Patency Rates*

| P.O. Length of Observation (Years) | No. of Grafts Total | No. of Grafts Open | % Cumul. Patency | No. of Deaths during Year of Observation | Cumulative no. of Patients Dead |
|---|---|---|---|---|---|
| 1 | 241 | 215 | 89.2 | 18 | 18 |
| 2 | 208 | 177 | 85.1 | 15 | 33 |
| 3 | 177 | 138 | 78.0 | 26 | 59 |
| 4 | 139 | 100 | 71.9 | 8 | 67 |
| 5 | 116 | 74 | 63.8 | 9 | 76 |
| 6 | 95 | 51 | 53.7 | 5 | 81 |
| 7 | 75 | 38 | 50.7 | 6 | 87 |
| 8 | 59 | 28 | 47.5 | 1 | 88 |
| 9 | 45 | 20 | 44.5 | 2 | 90 |
| 10 | 25 | 11 | 44.0 | 2 | 92 |
| 11 | 9 | 2 | 22.2 | 0 | 92 |
| 12 | 5 | 1 | 20.0 | 0 | 92 |

The recovered graft material came from two basically different sources (Table 9). Eight grafts were recovered from patients' extremities who had died of various unrelated causes. In the remaining cases various portions of the graft were recovered at the time of surgical correction of some angiographically recognized abnormality. The recovered graft material was photographed, fixed for histologic studies, and stained with Gomori trichrome technic, hematoxylin-eosin, and orcein.

## Results

### ANGIOGRAPHIC FINDINGS

*Types of Lesions (Table 8, Fig. 2).* Eight types of morphological alterations could be recognized in the analysis of the extensive angiographic material.

The most common change was a wavy narrowing of the lumen, interpreted as intimal thickening (Fig. 3). Generally, this occurred along fairly extensive sections of the graft, occasionally involving the entire graft. The lesion was reminiscent of the fibrin deposition seen

TABLE 4. *48 Femoro-infrapopliteal Venous Autografts for Occlusive Disease Late Cumulative Patency Rates*

| P.O. Length of Observation (Years) | No. of Grafts Total | No. of Grafts Open | % Cumul. Patency | No. of Deaths during Year of Observation | Cumulative no. of Patients Dead |
|---|---|---|---|---|---|
| 1 | 48 | 35 | 72.9 | 6 | 6 |
| 2 | 33 | 19 | 57.6 | 2 | 8 |
| 3 | 13 | 7 | 53.8 | 0 | 8 |
| 4 | 5 | 4 | 80.0 | 1 | 9 |
| 5 | 3 | 2 | 66.7 | 0 | 9 |
| 6 | 2 | 1 | 50.0 | 0 | 9 |
| 7 | 1 | 1 | 100.0 | 0 | 9 |

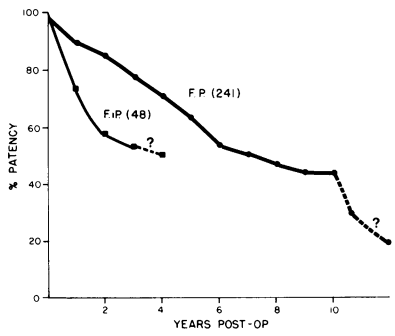



FIG. 1. Cumulative late patency rates of femoro-popliteal and femoro-infrapopliteal venous autografts.

TABLE 5. *Length of Observation and Number of Angiographic Examination. Lower Limb Venous Autografts*

| Length of Observ. (Yrs.) | No. of Angiograms 1 | 2–3 | 4–4 | 6–7 | >7 | Totals |
|---|---|---|---|---|---|---|
| <1 | 83 | 12 | 0 | 0 | 0 | 95 |
| 1–2 | 8 | 54 | 1 | 0 | 0 | 63 |
| 3–4 | 1 | 34 | 8 | 1 | 0 | 44 |
| 5–6 | 0 | 23 | 8 | 1 | 1 | 33 |
| 7–8 | 1 | 7 | 4 | 1 | 0 | 13 |
| >8 | 0 | 5 | 4 | 3 | 0 | 12 |
| Total | 93 | 135 | 25 | 6 | 1 | 260 |

in femoro-popliteal plastic prostheses,[25] but of a lesser degree, and appeared to be slower in development and progression. As will be pointed out presently, the corresponding pathologic change assumed two forms: true subendothelial hypertrophy and intimal clot layering.

Atherosclerosis, the second most common involvement among the structural deteriorations, was seen in 7.7% of the cases (Figs. 4–6 and C 10, C 11). The angiographic appearance consisted of an irregularity of the luminal surface, often associated with local dilatation of mild degree. In more advanced instances the irregular luminal outline assumed the morphological characteristics seen in atherosclerotic arteries: the hunchback contour of a typical atheroma.

Normal venous valve leaflets are often detectable in angiograms of vein grafts in the form of a cone-shaped hairline filling defect; these lead to no loss of lumen. The *fibrotic* valve, on the contrary, is an abnormal structure that does not assume the desired flat position when the vein graft is placed *in situ* and the blood is allowed to flow along the inverted valve leaflets. A sharply defined short-segment narrowing of the lumen is the result, usually in the midshaft of the graft, in which the valves are more closely spaced (Fig. 7).

The so-called *traumatic stenosis* anatomically consists of a fibrotic thickening of the wall which reduces the size of the lumen (Fig. 8). The designation implies trauma as the etiological agent but the evidence for this is not entirely secure. The defect occurs usually in a para-anastomotic position where a holding clamp is usually applied to the graft during placement of the anastomotic suture line. This topographic association between the site of a clamp and the appearance of a fibrotic stenosis strongly suggests that the cause of fibrosis is instrumental trauma to the vein wall.

*Suture stenosis* is perhaps the most obvious of these defects. It is the result of sutures applied too closely during ligation of the tributaries of the saphenous vein. It appears in the angiograms as a sharply localized stenotic ring.

*Aneurysmal dilatation* is a readily recognizable abnormality consisting of an abrupt increase in the diameter of the graft, the dilatation being usually fusiform. More uncommonly, the increase in diameter may be saccular and multiple. In all the cases that we were able to verify by anatomic examination, the dilatation was accompanied by atherosclerotic changes (Fig. 5), but the possibility remains that nonatherosclerotic dilatation may also occur as the result of some intrinsic local structural deficiency.

Two other abnormalities (not illustrated in Fig. 2) can be recognized in angiograms: an excessively long venous

TABLE 6. *Femoro-popliteal Venous Autografts As Arterial Bypasses Distribution of Maximum Periods of Follow-up Observation*

| Length of Follow-up (Yrs.) | Clinical No. of Cases | | | Angiographic No. of Cases | | |
|---|---|---|---|---|---|---|
| 1 | 36 | | | 94 | | |
| 2 | 31 | | | 27 | | |
| 3 | 41 | | | 24 | | |
| 4 | 21 | | | 19 | | |
| 5 | 22 | | | 17 | | |
| 6 | 23 | | | 14 | | |
| 7 | 23 | | 174(72.2%) | 7 | | 99(45.0%) |
| 8 | 10 | 112(46.5%) | | 6 | 56(25.4%) | |
| 9 | 18 | | | 5 | | |
| 10 | 13 | | | 6 | | |
| >10 | 3 | | | 1 | | |
| | 241 | | | 220 | | |

stump at the ligated points of the tributaries, and an anatomical variation in the course of the greater saphenous vein just above the knee, often called "loop formation." These abnormalities do not ordinarily constitute a threat to the patency of the graft.

*Time of Onset.* In determining the time of onset of changes seen in angiograms, one encounters serious difficulties. In clinical material of the type here discussed, it is impossible to present a sequential series of angiograms so spaced as to give the optimum information necessary to determine the onset of a given structural change. Nevertheless, a sufficient number of patients underwent angiographic examinations at appropriate intervals to permit a close approximation of the actual points in time marking the onset of the alterations (Table 8). The time of onset of these changes showed variations that were consistent with the pathologic characteristics of the lesions. Atherosclerosis and aneurysmal dilatation appeared rather late (45 and 20 months postoperatively) as one would expect from the long period of time necessary for the evolution of these structural abnormalities. Suture stenosis, which, of course, has a practically instantaneous onset, was detected the earliest in the entire group. Fibrotic stenosis and intimal thickening occupied intermediate positions on the time scale.

*The Degree of Severity of Lesions.* The degree of severity of the changes must be judged on an arbitrary scale. Since there are no available absolute measuring standards, this does not detract from the value of the classification. Moreover, the degree of severity leaned toward underestimation rather than overestimation of the particular change in question. Whenever a doubtful early change was noted, it was disregarded unless a second angiographic examination confirmed its presence. On this scale, about one-third of all the changes noted were advanced and about two-thirds were early. The degree of involvement had an expected correlation with the type of lesion. Owing to their anatomic characteristics, some of the lesions were easier to recognize early in their evolution. Other lesions progressed slowly and thus recognition was delayed. Atherosclerosis, in particular, had to be moderately to markedly advanced before it could become recognizable in angiograms.

TABLE 7. *Femoro-infrapopliteal Venous Autografts as Arterial Bypasses Distribution of Maximum Periods of Follow-up Observations*

| Length of Follow-up (Yrs.) | Clinical No. of Cases | Angiographic No. of Cases |
|---|---|---|
| 1 | 16 (33.3%) | 23 (57.5%) |
| 2 | 20 (41.7%) | 14 (35.0%) |
| 3 | 7 | 1 |
| 4 | 2 | 0 |
| 5 | 1 | 1 |
| 6 | 2 | 1 |
| | 12(25.0%) | 3(7.5%) |
| | 48 | 40 |

*Progression of the Lesion.* Ideally, the recognition of progression of a morphological change in the graft should be based on inspection of serial angiograms over a relatively protracted time scale. For the reasons already mentioned, in a clinical study including humans, this plan is not practicable. To reconcile the demands of accuracy with the exigencies of clinical practice, the following definition of progression was adopted: (1) Worsening of the lesion in at least two consecutive angiograms; (2) the appearance of a lesion after one or more normal

TABLE 8. *Structural Changes in 220 Femoro-popliteal and 40 Femoro-infrapopliteal Venous Autografts Seen in Postoperative Angiograms*

| Type of Lesion | Total Number | Time of Onset (Mos.) Range | Time of Onset (Mos.) Mean | Degree of Severity +1 | +2 | +3 | Cases Showing Progr* No. % | Cases Showing No Progr No. % | Ultimate Fate of Lesion: Observed Open No. % | Observed Closed No. % | Reoperated Open No. % | Reoperated Closed No. % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Intimal Thickening | 21 | (6–48) | 16.2 | 16 | 5 | 0 | 14(66.6) | 7(33.3) | 15(75.0) | 5(25.0) | 1(All) | 0(—) |
| Atherosclerosis | 20 | (6–70) | 45.2 | 9 | 5 | 6 | 19(95.0) | 1(5.0) | 12(92.3) | 1(7.7) | 7(All ) | 0(—) |
| Fibrotic Valve | 15 | (6–60) | 14.0 | 11 | 1 | 3 | 11(73.3) | 4(26.7) | 4(36.4) | 7(63.6) | 4(All) | 0(—) |
| Fibrotic Stenosis | 11 | (6–60) | 19.1 | 6 | 5 | 0 | 10(90.9) | 1(9.1) | 1(11.1) | 8(88.9) | 2(All) | 0(—) |
| Suture Stenosis | 8 | (6–24) | 9.0 | 7 | 1 | 0 | 6(75.0) | 2(25.0) | 3(37.5) | 5(62.5) | 0(—) | 0(—) |
| Aneurysmal Dilatation | 10 | (6–80) | 28.0 | 7 | 1 | 2 | 5(50.0) | 5(50.0) | 9(90.0) | 1(10.0) | 0(—) | 0(—) |
| Total | 85 | (6–80) | 23.9 | 56 | 18 | 11 | 65(76.5) | 20(23.5) | 44(62.0) | 27(38.0) | 14(100) | 0(—) |

* Progression: (1) At least two consecutive angiograms showing worsening of lesion; (2) The appearance of a lesion after one or more normal angiograms; and (3) Lesion seen in an angiogram followed by closure of graft.

Note: Loop-formation (2 cases) and excessively long stumps of tributaries (2 cases), not being intrinsic, are not included.

TABLE 9. *Femoro-popliteal and Femoro-infra-popliteal Venous Autografts. Graft Material Recovered in Part or in Whole*

| Case | Site | Months of Implantation | Length (cm) | Source of Recovery | Structural Changes | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Athero-sclerosis | Fibrotic Valve | Fibrotic Stenosis | Intimal Thickening | Multiple | "Normal" |
| 1 | F-P | 44 | whole | Autopsy | + | | | | | |
| 2 | F-P | 31 | whole | Autopsy | | | | | | + |
| 3 | F-iP | 13 | whole | Autopsy | | | | + | | |
| 4 | F-P | 58 | whole | Autopsy | + | | | | | |
| 5 | F-P | 63 | whole | Autopsy | | | | | Atherosclerosis with Dilatation | |
| 6 | F-P | 90 | whole | Autopsy | | | + | | | |
| 7 | F-P | 14 | whole | Autopsy | | | | | | + |
| 8 | F-P | 10 | whole | Autopsy | + | | | | | |
| 9 | F-iP | 16 | 30 | Surgical | | | | + | | |
| 10 | F-P | 59 | 25 | Surgical | | | | | Atherosclerosis with Dilatation | |
| 11 | F-P | 78 | 10 | Surgical | | | | | Atherosclerosis with Traumatic stenosis | |
| 12 | F-iP | 6 | 10 | Surgical | | | | + | | |
| 13 | F-iP | 10 | 5 | Surgical | | | | + | | |
| 14 | F-P | 20 | 3 | Surgical | | + | | | | |
| 15 | F-P | 13 | 1 | Surgical | | + | | | | |
| 16 | F-P | 96 | Biopsy | Surgical | + | | | | | |
| 17 | F-F | 7 | Biopsy | Surgical | | | + | | | |
| 18 | F-P | 59 | Biopsy | Surgical | | | | | Atherosclerosis with Fibrotic Valve | |
| 19 | F-P | 19 | Biopsy | Surgical | | + | | | | |
| 20 | F-P | 36 | Biopsy | Surgical | | | + | | | |
| 21 | F-P | 15 | Biopsy | Surgical | | | + | | | |

angiograms; and (3) the appearance of a lesion in an angiogram followed by closure of the graft. The only conjectural part of this definition deals with the establishment of progression after a single angiogram followed by closure of the graft. This part of the definition presumes that no other cause could be detected for eventual loss of patency in the graft. With this qualification the definition has an acceptable degree of clinical accuracy.

In the terms defined, all the angiographic lesions showed progression, albeit with some variations in the rate of progression. Progression was most consistent in atherosclerosis and traumatic fibrous stenosis. Aneurysmal dilation appeared to be the least likely to progress but this may have been partly illusory since the pathologic characteristic of the lesion retards its evolution and it seldom leads to thrombosis even in the late states.

*Ultimate Fate.* The ultimate fate of these alterations was in keeping with the trend observed in their progression. This trend, of course, is seen only in those lesions that were not subject to surgical correction. In this group, closure as an end result was particularly prevalent in all the various forms of stenotic changes. Atherosclerosis, on the contrary, was slow to lead to occlusion. The outcome of the evolution of the lesions was markedly and favorably influenced by reoperation. The results of operation were invariably excellent and no graft, in which a defect had been surgically corrected, occluded during the time of this study. As will be pointed out later, due to their pathologic characteristics some lesions are less suited for surgical repair, whereas others are eminently suitable for correction. Short segment stenotic lesions promise outstandingly good results.

## ANATOMIC FINDINGS

*Source of Material.* The anatomic study of autogenous vein grafts has been very seriously hampered by the difficulties encountered in their recovery after death of the patients. The many practical reasons for this difficulty are obvious. Amputation specimens of grafts that have failed are much easier to come by but, unfortunately, very severe time limitations must be observed in the evaluation of grafts recovered in this manner. Very likely, after 3 or 4 weeks the histologic findings are impossible to interpret with accuracy and even in earlier specimens great caution must be exercised in the analysis of the findings. The operating room is an excellent source of smaller pieces of vein material. This form of acquisition, however, introduces an obvious bias in the study of the natural behavior of these grafts since all the surgically available specimens have been preselected, that is, they have a recognized abnormality for which the surgical procedure is undertaken. When actual resection of an implant is not necessary in course

of a surgical procedure, biopsy also may prove very useful. Nor must one underestimate the value of careful inspection of the graft during surgical exploration, particularly when the inner aspect of the graft is carefully exposed.

We have succeeded in collecting anatomic information on 21 autogenous vein specimens. Seventeen of these specimens came from femoro-popliteal grafts and four from femoro-infrapopliteal grafts. The length of the recovered specimen varied from complete length to shorter segments 1 to 30 cm. in size, and to small biopsy specimens. The average period of implantation was 3 years, ranging from 6 months to 8 years. Eight of the specimens, representing complete grafts, were obtained at autopsy and 13 were recovered at operative interventions.

*Comparative Significance of Anatomic Findings.*—From the point of view of the inherent capability of venous autografts to serve as effective arterial blood conduits (the assessment of which is the principal goal of this study) one must assign different orders of importance to anatomic changes that are due to extrinsic causes and to those that are inherent in the histologic reaction of the graft to its post-implantation environment. With very few exceptions, the lesions of extrinsic etiology are confined to small areas with extensive intervening tissue segments that show no deviation from the normal process of incorporation. In cases of fibrotic stenosis due to trauma, fibrotic valve cusps, or suture stenosis, nearly the whole graft—aside from the site of the lesion—may be free of morbid change. Although, if uncorrected, they may cause graft failure, these local abnormalities, since they can be prevented or corrected, are not among the factors that determine the ultimate intrinsic serviceability of the graft. The lesions that are all-important with respect to structural durability are the intrinsic lesions, namely, atherosclerosis, intimal thickening, and aneurysmal dilatation (the latter often being a manifestation of

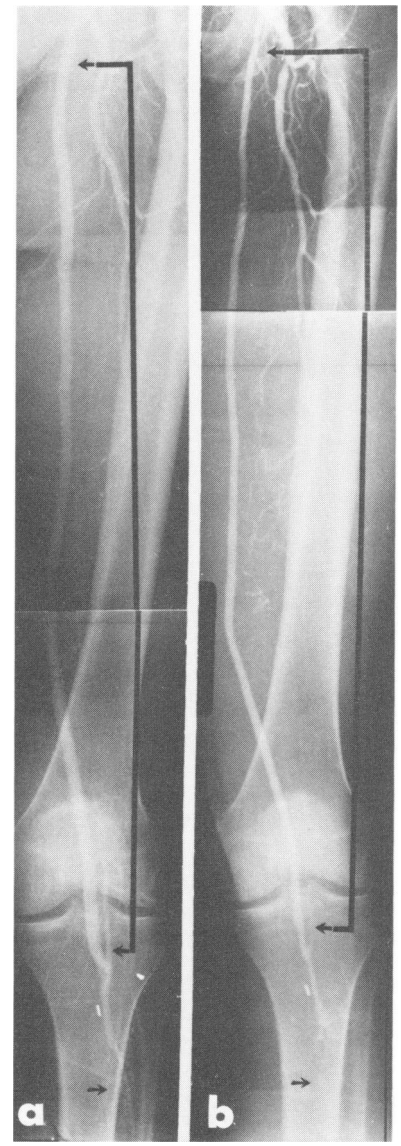



FIG. 3. Angiograms of femoro-popliteal autogenous vein bypass (a) two weeks and (b) 19 months postoperatively. Stream-line-like narrowing of the lumen along most of the graft due, in this case, to deposition of fibrin clots on the intimal surface (layering). See also Figs. C7 and C8 for corresponding microscopic changes.

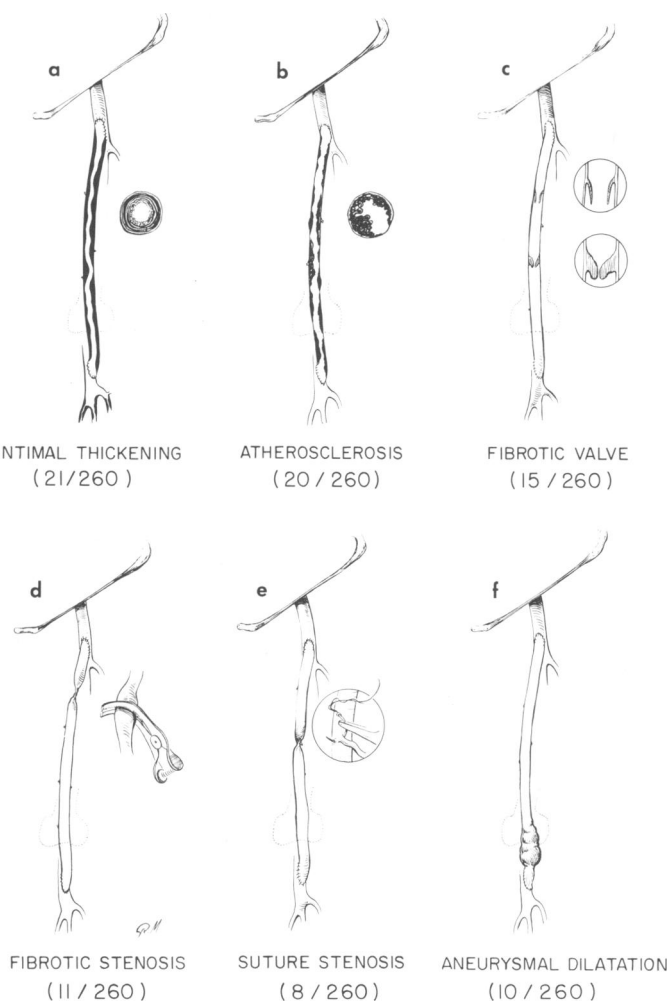



FIG. 2. Schematic representation of morphologic changes of venous autografts seen in angiograms.

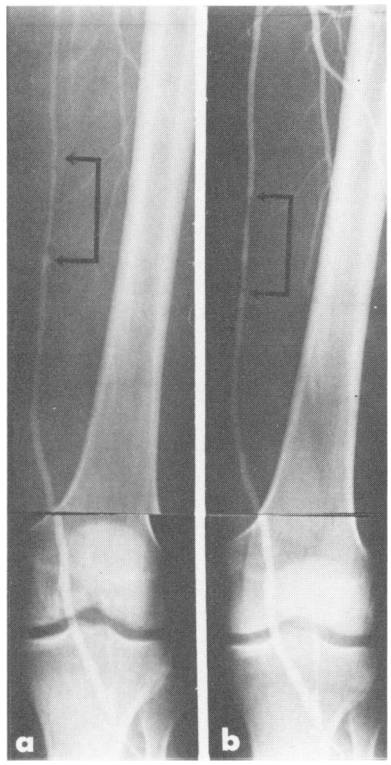


FIG. 4. Angiogram of femoro-popliteal venous autograft with atherosclerosis (a) three months and (b) 4.5 years after the primary operation. See also Figs. C10, C11, C12 from the same case.

atherosclerosis); all these alterations tend to be diffuse.

When calculating the frequency of the anatomic abnormalities, another restriction must be kept in mind. Because of the statistical bias inevitable in the selection of cases for surgical correction, the incidence of the anatomic changes of importance for the ultimate fate of the graft should be established on grounds of the findings in autopsy rather than in operative specimens.

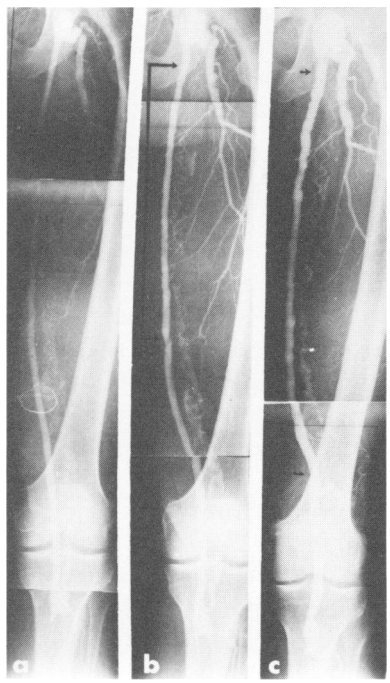


FIG. 5. Angiograms of femoro-popliteal venous autograft showing the evolution of atherosclerotic changes (b) 2 years and (c) 5 years postoperatively. See also Fig. C13 from the same case.

Among the autopsy specimens examined in this investigation, two were normal, one presented a very small area of mild traumatic stenosis, three showed diffuse atherosclerosis of modest degree, one showed atherosclerosis with local dilatation, and one showed diffuse intimal hypertrophy.

*Gross and Microscopic Anatomy of Normal Graft Incorporation.*—The concept of normality in judging the process of incorporation of a graft is defined as that anatomic picture that does not lead to structural changes unfavorable to normal function. Grossly, such grafts resemble to varying degrees the macroscopic appearances of a normal saphenous vein (Fig. C3). The only deviation from the appearance of an intact healthy saphenous vein that the naked eye can detect is the thickness of the wall which is usually increased. Microscopically a rather characteristic set of histologic features subsume this "normal" appearance (see below).

The microscopic features affect all three regions of the wall: intima, media, and adventitia. The intensity of change varies from layer to layer, and also from one region of the vein to another. Even grafts that are in-

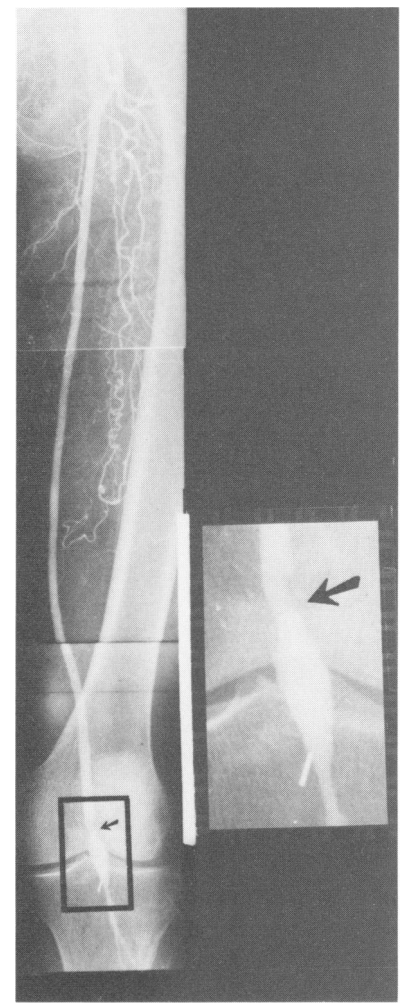


FIG. 6. Angiographic appearance of sharply localized atheroma four years, 9 months after femoro-popliteal autogenous vein bypass. Further findings of the same case are shown in Figs. C14, C15, and C16.

volved in atherosclerotic changes may show segments that appear to be normal.

To gain a clear comprehension of the changes of incorporation, one must recall the *normal histological appearances of the saphenous vein* (Fig. C1).

The histologic features of the (greater) saphenous vein are unique among venous structures. Because of its anatomic location that creates hemodynamic stresses unusual for a vein, it is thick-walled and very rich in smooth muscle and elastic tissue elements. The smooth muscle fibers are arranged in an inner longitudinal and an outer circular layer, extending through the entire thickness of the wall except the immediate subendothelial layer of collagen tissue and the outer portions of the loose connective tissue of the adventitia. In between the smooth muscle fibers of the media collagen fibers are interspersed forming about 20 percent of the total tissue mass. The intimal surface is bounded by a single layer of flat endothelial cells that rest on a narrow band of collagen tissue. As already mentioned, smooth muscle elements intrude to the very level of the subendothelial collagen tissue. The subendothelial collagen band and the intermingled smooth muscle elements, which at this level form scattered delicate bundles, are usually de-

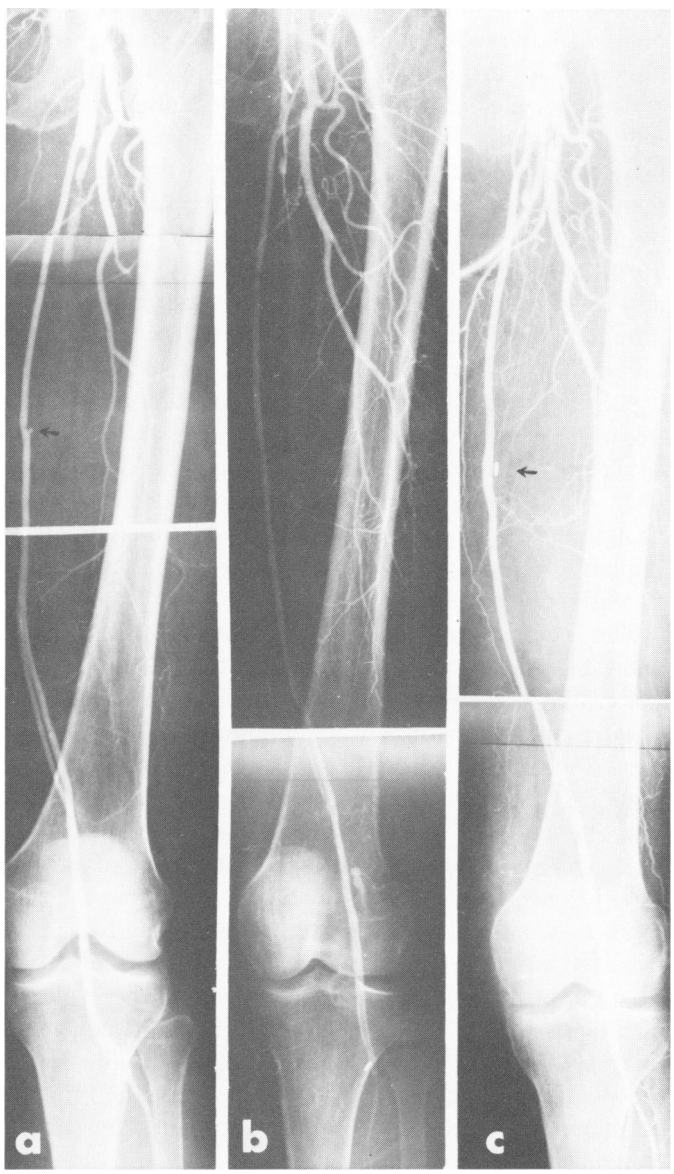



FIG. 7. Angiograms of femoro-popliteal venous autograft (a) 2 weeks and (b) 19 months postoperatively, and (c) 2 weeks after secondary repair. Arrow points to venous valve with thick fibrous cusps that have caused a well-marked stenosis. Clip (in c) marks site of repair.

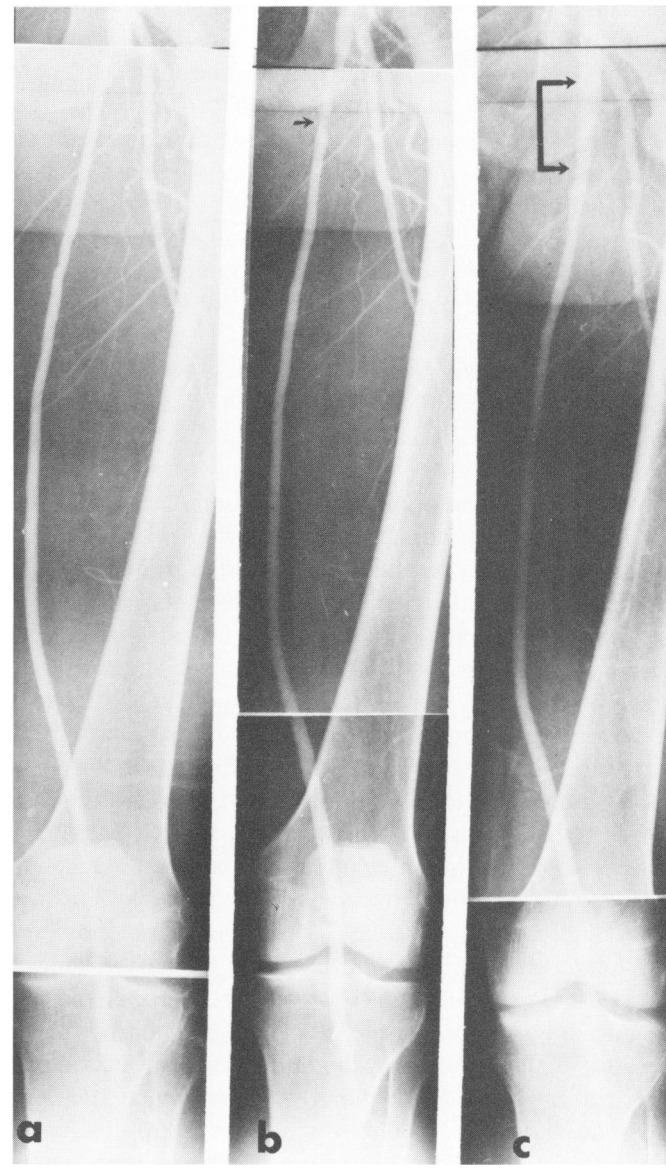



FIG. 8. Angiograms of femoro-popliteal venous autograft showing fibrotic (traumatic) stenosis (a) 3 months after primary operation (the lesion is not yet recognizable), (b) 15 months after the primary operation, and (c) 2 weeks after secondary correction.

marcated from the media by an elastic lamina that often forms a continuous circular layer, much as the inner elastic lamina of a muscular artery. The adventitia, in a strict sense is not an intrinsic part of the vein wall. It is usually sharply marked off from the tightly structured circular muscle layer of the media by elements of loose composition that are intermingled with irregularly scattered elastic and, to a less extent, smooth muscle fibers. Nutrient blood vessels are fairly abundant in the adventitia but penetrate only to the outer layers of the media.

The most striking change in the process of *normal incorporation* occurs in the smooth muscle elements (Figs. C2, C4, C16). From the earliest to the latest observations covering a span of time of from 6 to 96 months of implantation, a diminution of the smooth muscle fibers is evident. The proportion of the smooth muscle elements preserved varies and is difficult to correlate with the only readily definable factor influencing it: the length of implantation. Some late specimens may have occasionally more smooth muscle preserved than some earlier ones, very likely because of the existence of a host of unrecognizable factors that may hasten the devitalization of the smooth muscle fibers. (It is known, for instance, that the length of warm ischemia time after removal has distinct effects on the survival of smooth muscle tissue. A similar role must be assigned to mechanical trauma, ambient hydrogen ion concentration, and type of preserving solution.) Upon the whole, however, the longer the implantation the fewer the smooth muscle elements. It should be also noted that at times the persistence of smooth muscle elements is confined to two sharply defined regions: the immediate subendothelial and the outer medial regions, a phenomenon that may be related to the availability of blood supply. As the smooth muscle fibers disappear, they are replaced by collagen tissue which thus tends to form an increasingly more prominent proportion of the substance of the venous wall as the time of implantation lengthens. All the specimens we examined, however, had retained some, usually significant, amounts of smooth muscle tissue. (These observations are in accord with those of Wyatt on experimental preparations.[19,28])

The intimal changes seen after implantation, although of nearly universal occurrence, must be regarded as an abnormal histologic event and will be described under the heading of morbid anatomy.

The adventitia displays quite consistent and characteristic modifications of its structure. There is an ingrowth of vascular elements usually limited to the adventitia and outer media. The elastic elements in the adventitia are usually hypertrophic, and at times markedly so.

*Gross and Microscopic Anatomy of Morbid Changes.*—As mentioned earlier, the histologic alterations that have the decisive role in determining the ultimate functional fate of the graft are intimal thickening and atherosclerotic degeneration. Both are diffuse processes (though they often show regional accentuation) and both are very common. In fact, some degree of intimal thickening is present in all grafts, and it is discussed under the heading of morbid anatomy mainly because it represents a tissue change adverse to continued normal function.

The process of intimal thickening, a rather inelegant but necessary designation, is a complex one. At least two distinct pathological processes appear to underlie the changes that are described by this term. One process is the result of the response of the subendothelial venous wall—the subendothelial collagen and smooth muscle fibers—to the altered hemodynamic conditions in the lumen. It is manifested by an overgrowth of the subendothelial elements, mainly the subendothelial smooth muscle fibers (Figs. C9, C16). This reaction to the increased intraluminal pressure was seen in every specimen examined except those in which its place was taken by a second variant of intimal thickening: the so-called fibrin layering. Fibrin layering is a process of deposition and organization of successive films of fibrin clot on the intimal surface when the restricted outflow tract or turbulent flow at the distal anastomosis reduces the velocity of blood flow (Figs. C7, C8). Subendothelial hypertrophy is a very graded and slow process and is much less readily discernible in angiograms than fibrin layering, which progresses rather rapidly. Both of these changes are a threat to the continued function of the implant, but the danger of closure from layering is patently more serious.

The atherosclerotic changes are both grossly (Figs. 11 and C14) and microscopically (Figs. C12, C13, and C15) quite amazingly similar to those seen in arteries. Early fibrotic plaques with the beginning of lipid infiltration mark the earliest phase. The changes may be followed sequentially to the development of the entire atherosclerotic complex with its amorphous necrotic center, underlying collagen base, and ulcerated intimal surface, usually covered by a layer of fibrin clot. These alterations are usually diffuse, but occasionally may be sharply localized perhaps due to some local mechanical factor. There appears to be a time dependence in the evolution of atherosclerotic changes. The older the specimen the more likely to show the change and the more severe the degree of change. About 80 percent of the implants examined two years or more after implantation showed evidence of atherosclerosis.

*The Possible Role of Atherogenic Factors.*—Since systemic veins show an almost absolute resistance to the development of atherosclerosis, the question naturally arises whether the relatively high incidence of athero-

matous change in the veins used as arterial conduits in the lower extremity might not be the result of the presence of particularly strong atherogenic factors in the patients. We tested this assumption by comparing the incidence of certain atherogenic factors in the two groups of patients—one with and the other without atherosclerotic changes in their grafts. A summary of these data is displayed in Table 10. In the first columns are listed the selected atherogenic factors and in the next two columns their incidence in the two groups being compared. It is readily seen that no significant differences were demonstrated.

TABLE 10. *Incidence of Atherogenic Factors in 22 Patients with and 244 Patients without Atheromatous Graft Changes*

| Atherogenic Factor | Cases with the Atherogenic Factor Present | | | |
|---|---|---|---|---|
| | (A) Grafts with Atherosclerosis | | (B) Grafts without Atherosclerosis | |
| | No.* | % | No. | % |
| Males | 18/22 | 81.8 | 185/244 | 75.8 |
| Total Lipids >900 mg./100 ml. | 7/22 | 31.8 | 55/153 | 35.0 |
| Cholesterol >300 mg./100 ml. | 2/21 | 9.5 | 14/190 | 7.4 |
| Triglycerides >140 mg./100 ml. | 8/14 | 57.2 | 47/71 | 66.2 |
| Cigarettes >1 pack/day | 12/21 | 57.1 | 101/237 | 42.6 |
| Associated Diabetes | 11/22 | 50.0 | 93/244 | 38.1 |
| Systemic** Involvement by Atherosclerosis | 14/22 | 63.7 | 179/243 | 73.7 |

* Denominator: Number of patients for whom the presence of the named factor was determined.

Numerator: Number of patients in whom the factor was in abnormal range.

** More than two organ systems involved.

Note: Range of ages: Group A = 50–75 years; Group B = 28–84 years.

Mean of ages: Group A = 61.1 years; Group B = 63.1 years.

## Comments

*Validity of Angiographic Interpretation.* Throughout the exposition of this study, morphological changes in the graft were interchangeably expressed in terms of angiography and anatomic description. The question is justified whether this process of equating angiographic shadows with changes that are structural and tridimensional is valid. The answer to this question must be given in terms of the evolution of this process of interpretation. When these angiographic findings were first encountered they were merely recognized as some sort of morphological defect, but no anatomic meaning was attached to them. As either postmortem or intraoperative exploration showed the nature of the lesions, certain angiographic appearances assumed anatomical significance. With increasing experience the interpretation became secure enough to permit extrapolation from angiographic shadow to anatomic structure. We have repeatedly observed morphological lesions that were first described in speculative anatomic terms only to be proven later to correspond precisely to the supposition of the tentative diagnosis. It seems justified to say that this process has reached a clinically acceptable degree of accuracy.

*Assessment of the Value of Autogenous Vein Grafts.* In any attempt to evaluate the worth of saphenous vein grafts in the lower extremity, a clear distinction must be made between the tissue acceptance of these autografts and their functional usefulness. Tissue acceptance is almost absolute. No histologic changes associated with homogeneic implants or foreign body implants can ever be observed. Not only is there no trace of rejection, but, in addition, the anatomic structure of the vein shows some changes that favor durability; the hypertrophy and hyperplasia of the connective tissue and elastic tissue elements of the adventitia are particularly significant in this respect. A particularly fortunate aspect of the incorporation of the graft is the generally good preservation of the smooth muscle elements. As will be pointed out below, the frequent absence of a normal intima and the changes in the subendothelial elements when an intima is preserved undoubtedly constitute a serious deficiency but their significance, under normal hemodynamic conditions, is a long-term one.

In regard to the functional value, it must be considered under two aspects. The potential causes of graft deterioration appear alarmingly common if one considers the crude statistical incidence (32.7%) of the lesions observed. From this observation alone one would predict that about one-third of the implants will develop serious defects most of which would threaten the long-term function of the graft. As has already been mentioned briefly, however, about one-half of the potential defects are preventable or remediable (if detected early enough). Fastidious technic should avoid traumatic and suture fibrosis and, if recognized promptly, fibrotic valve stenosis should be readily corrected.

There still remain, however, the intrinsic lesions to which the graft is susceptible, namely, atheroclerosis and intimal thickening. Atherosclerosis in particular appears to be an inevitable ultimate abnormality that overtakes these implants commonly, and perhaps even universally, if they stay *in situ* long enough.[26,27] Fortunately, atherosclerosis evolves very slowly, taking 4 to 6 years for development to a threatening degree. Subendothelial hypertrophy is also a progressive alteration and it follows a similarly insidious course. Both subendothelial hypertrophy and mural layering are undoubtedly a major threat to patency whenever the distal hemodynamics are unsatisfactory. Under these conditions, apparently the

same process is destined to occur in the autogenous vein graft as has been observed abundantly in synthetic femoro-popliteal prostheses but, fortunately, at a slower rate and less commonly.

*Relevance to the Question of Pathogenesis of Atherosclerosis.* The observations made on the atherosclerotic changes in these grafts have a particularly exciting theoretical implication. Since in the majority of the grafts with atherosclerosis no strong biochemical factor can be detected, the autogenous vein constitutes a good experimental model for testing the importance of hemodynamic factors in the causation of atherosclerosis. Since in the same individual a peripheral vein will be totally immune to the process of atherogenesis when it is under the hemodynamic conditions of the venous system, but becomes fairly readily involved in the atherosclerotic process when it is placed on the arterial side of the circuit, the conclusion is inescapable that the primary cause of the atherosclerotic involvement is hemodynamic.

*Correlation with Coronary Surgery.* Another interesting speculative aspect of these findings is their possible significance in the evaluation of the use of saphenous venous autografts in the aorto-coronary circuit. Considering the most important factors relevant to the longevity of the graft, the two clinical uses are readily comparable. The vein material is the same, the surgical technical steps are alike, and the hemodynamic factors are similar. The differences are mainly qualitative and relate to the blood pressure relationships, tissue environment and the distal hemodynamics. Unfortunately all the differences are in the disfavor of the aorto-coronary procedure. The arterial blood pressure is higher, the tissue bed in which the graft is placed is less receptive (less capable of creating a true environment for good incorporation of the graft which is partly without tissue support) and the arterial outflow circuit is greatly constricted. These considerations suggest that the same intrinsic structural lesions may be expected in the vein grafts used as aorto-coronary bypasses but possibly with an accelerated tempo of development. The sporadic reports on the anatomic changes in aorto-coronary venous autografts[11,13,14,16,17] strongly suggest that this assumption is correct.

*The Question of Prophylaxis.*—An analysis of the behavior of these grafts emphasizes the importance of certain sample prophylactic measures in our attempt to prolong their usefulness. The avoidance of trauma in freeing the vein graft is an obvious requirement. Less evident is the need for the reduction of the time interval during which the vein graft is deprived of its blood supply at normal temperature ("warm-ischemia time"). This need can be met by allowing blood flow to continue through the vein while it is being prepared and while its tributaries are being tied, and by placing it in a cold isotonic glucose solution at a pH near 7.0 while it is being stored before insertion. Very close postoperative observation of the grafts (preferably by angiography) for the earliest possible detection of changes that might be remediable also appears to be highly desirable.

FIG. C1. Normal greater saphenous vein. Transverse section. ×175. *Note:* In this and all following microscopic sections, the stain, unless otherwise noted, is by the Gomori trichrome method, and the intimal surface is directed to the right. In the Gomori trichrome technic collagen stains green or greenish blue (the more mature the collagen fiber, the deeper the greenish hue), smooth muscle red, fibrin red, and elastic tissue violet. The approximate boundaries of the layers of the wall are marked by short black bars. I = intima, M = media, A = adventitia.

FIG. C2. Greater saphenous vein after 31 months of implantation showing normal incorporation. ×130.

FIG. C3. Grossly normal greater saphenous vein recovered 90 months after implantation. Uppermost segment represents the region of proximal anastomosis.

FIG. C4. Microscopic section of graft in Fig. C3. *Left:* Gomori stain; *right:* Orcein elastica stain. ×28.

FIG. C5. Fibrotic valve cusps seen at surgical exposure.

FIG. C6. Microscopic section of fibrotic valve in Fig. C5. ×35.

FIG. C7. Microscopic section of greater saphenous vein recovered 16 months after implantation. Fresh fibrin clots on intimal surface overlying partly organized older fibrin layers of different ages. *Cf.* Fig. 3. ×70.

FIG. C8. Section of greater saphenous vein recovered 20 months after implantation. Intima consists principally of organized fibrin clot with minimal smooth muscle elements. A more mature variant of intimal fibrin layering seen in Fig. C7. *Cf.* Fig. 3. ×100.

FIG. C9. Microscopic section of greater saphenous vein 19 months after implantation. Marked subendothelial hypertrophy with abundant smooth muscle elements. ×63.

FIG. C10. Arteriogram of greater saphenous venous autograft in midthigh with superimposed graft specimen showing atherosclerosis, 78 months after implantation.

FIG. C11. Operating-room photograph. *At bottom:* diseased segment of venous autograft in midthigh (seen also in Fig. C10) exposed at time of replacement 78 months after implantation. *At top:* vein segment used for replacement.

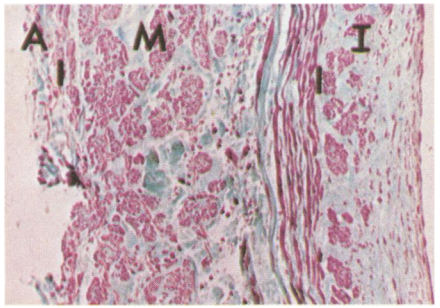
FIG. C12. Microscopic section of atheromatous lesion of diseased vein in Fig. C11. ×115.

FIG. C13. Microscopic section of ulcerated subintimal atheroma in greater saphenous venous autograft recovered 63 months after implantation. For angiographic appearance, see Fig. 5. ×35.

FIG. C14. Atheromatous intimal ulceration localized to vicinity of distal anastomosis in a greater saphenous venous autograft 58 months after implantation. Postmortem specimen superimposed on arteriogram. For antemortem angiogram, see Fig. 6.

FIG. C15. Microscopic section of atheromatous ulceration in Fig. C14. ×28.

FIG. C16. Microscopic section from midshaft of graft in Fig. C14 showing normal incorporation. (Intima thick and rich in smooth muscle fibers; media markedly narrowed, with few smooth muscle elements; adventitia normal.) ×35.



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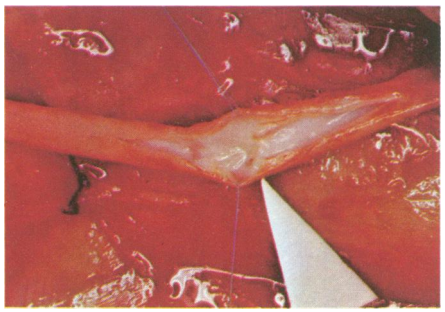
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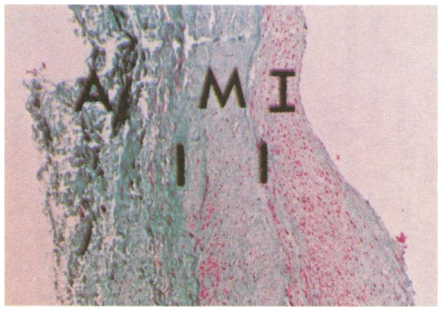

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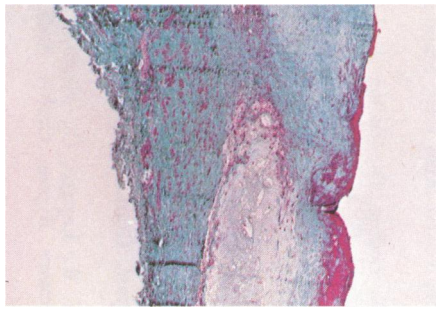
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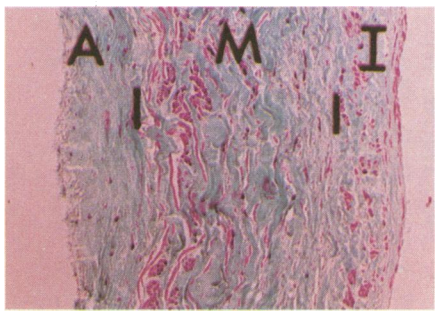

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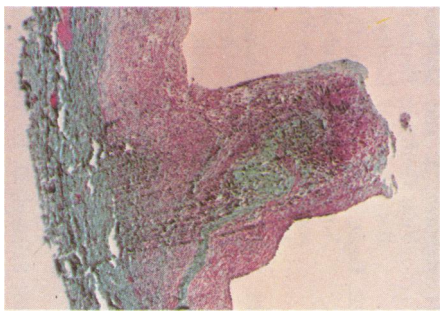
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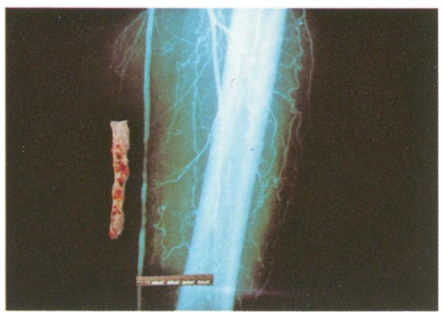
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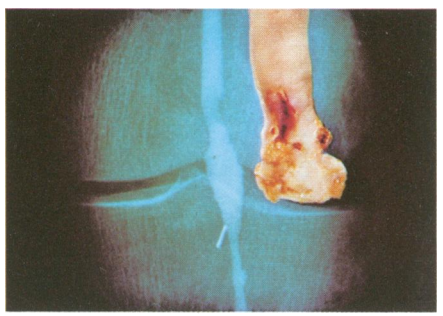
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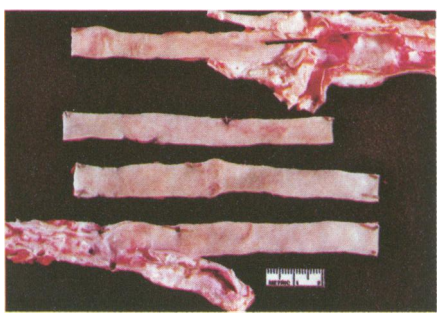
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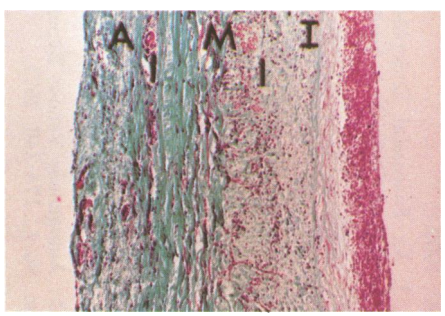

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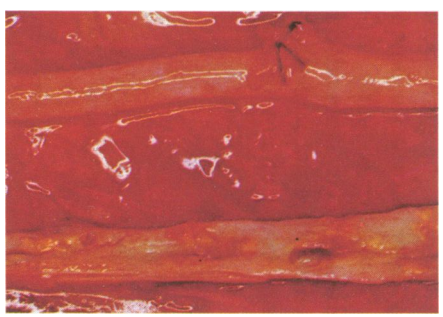
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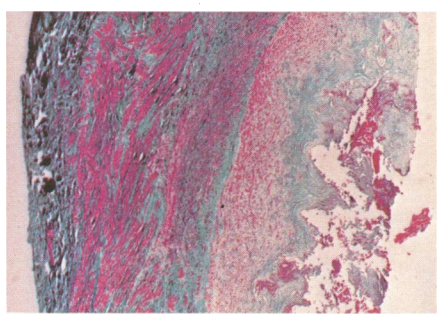
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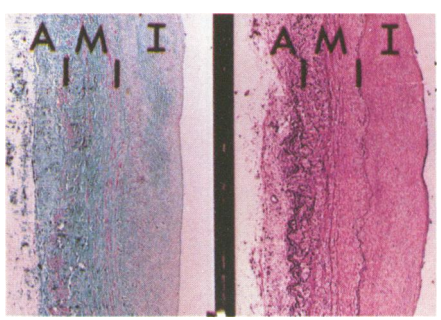

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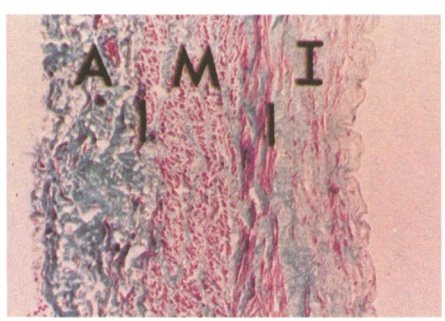

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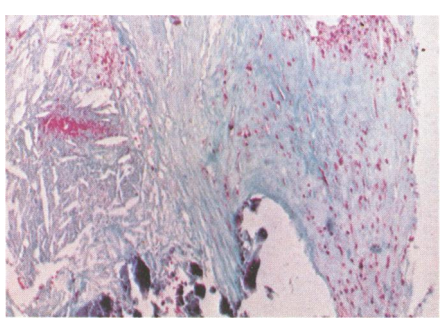
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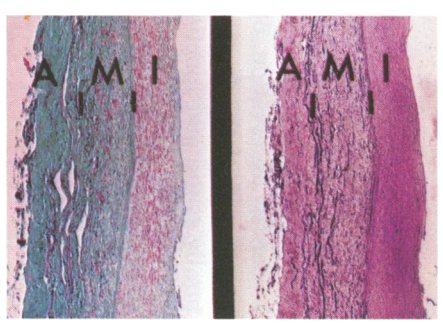

C16

## Conclusions

Autogenous vein transplants used as arterial substitutes in the femoro-popliteal and femoro-infrapopliteal regions shown excellent tissue acceptance, and the femoropopliteal grafts yield good functional results. After 5 years of observation, 64%, and after 10 years of observation, 44% of the femoro-popliteal grafts appear structurally sound and functionally unimpaired.

Structural defects develop in 32.7 percent of the grafts as the result of technical mishaps (stenosis due to improper suturing and to instrumental trauma) and due to intrinsic tissue changes (subendothelial hypertrophy, layering of intimal thrombi, fibrosis of venous valves, and atherosclerosis). All of these changes are progressive and may lead to the loss of patency of the graft. Some of these can be avoided by greater care in technique and others can be corrected if discovered early. Atherosclerosis and intimal thickening (i.e., subendothelial hypertrophy and fibrin layering) are not remediable and will continue to be a major cause of loss of graft function.

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### Discussion

Dr. Jere W. Lord, Jr. (New York City): There are two points of many which Dr. Szilagyi made that I would like to comment upon. One is that most of us thought early and late failures in vein graft bypasses were due to technical operative errors, and more commonly, progression of the atherosclerotic process in the inflow tract above or in the outflow tract below.

Our experience in the last 3 years confirms his presentation. Our failures have usually been due to intrinsic diseases of the vein graft. Two conditions in particular should be mentioned. First, fusion of a venous valve. In reversed vein bypass grafts,