THE INFREQUENCY OF LIPID DEPOSITION IN SCLEROTIC VEINS *

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It is well recognized that the walls of veins may become thickened and fibrous with advancing age or when exposed to prolonged increase in intravascular tension. The changes are usually designated by the term phlebosclerosis. In a recent systematic study of the popliteal vein, Lev and Saphir[1] described this lesion. It is also apparent that the degree of sclerosis found in veins seldom approaches that of arteries in severity or extent. Whether or not phlebosclerosis and arteriosclerosis constitute essentially analogous processes is a matter of controversy. If the view is accepted that arteriosclerosis is a regressive lesion with many variable anatomical alterations of which none is of prime importance, there is little reason to regard phlebosclerosis as an independent process. By many observers, however, the deposition of lipid is considered to be an essential, early feature of the common type of arterial lesion generally termed atherosclerosis. Much evidence has been advanced to support each of these two conflicting interpretations.

If atherosclerosis results from lipid deposition, it would be necessary to demonstrate such deposits in veins in order to prove that phlebosclerosis is related to the common form of arterial disease. There appear to be some differences of opinion as to the frequency with which lipid deposits are found in veins.[2] The present study was undertaken to investigate this feature of phlebosclerosis. Varicose veins of the lower extremity were selected for examination, not only because of their availability due to the frequency with which they are excised, but also because these vessels are subjected to severe mechanical stress and show profound anatomical alterations. Moreover, in such incompetent varicose veins the blood pressure frequently approaches normal arterial pressure when the body is in an upright position.[3] Finally, phlebosclerosis related to advancing age has been described more frequently in the vessels of the legs than elsewhere in the venous system. If atherosclerotic changes occur in veins, they should most logically be found in varicosities of the lower limbs.

MATERIALS AND METHODS

Routine random histologic sections of 24 specimens of varicose saphenous veins and 4 post-phlebitic popliteal veins were available

* This investigation was supported by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service.
Received for publication, July 2, 1952.

from the surgical pathology files of Bellevue Hospital. These were stained with hematoxylin and eosin, trichrome, and Weigert-van Gieson techniques. This material was fixed in Bouin's solution and preserved in 80 per cent alcohol and was therefore not suitable for fat stains. In addition, portions of 19 varicose saphenous and one postphlebitic popliteal veins received from the operating room were fixed in 10 per cent formalin. These measured from 20 to 45 cm. in length. Some had been turned inside out with the intima exposed during stripping. The rest were opened so that the intimal surface could be inspected. The vessels were stained grossly by immersion in Sudan IV for 3 minutes after dipping in 70 per cent alcohol. They were then rinsed in several washings of 70 per cent alcohol and returned to 10 per cent formalin. By this technique the adventitial fat is stained bright scarlet. Similar techniques have been used to demonstrate intimal lipid in arteries. The intima of the veins was examined under magnifying lenses for evidence of intimal lipid deposition. At least three frozen sections were cut from representative or suspected areas of each vessel and restained by the usual technique with Sudan IV.

Various age groups were included. Of the 48 specimens, at least 35 were from patients over 40 years old and 21 were from patients over 50 years of age. Varicosities were known to have been present longer than 6 years in 24 cases and longer than 11 years in 19. In 11 cases there were associated ulcers of the legs. The sex was recorded for 43 cases and of these 30 were men.

Results

Gross Findings

The lumina of the excised varicose veins were relatively small upon gross examination, indicating that a great deal of contraction had occurred during removal. This accounted for some of the increased thickness of the walls of the veins but there was undoubtedly a marked overgrowth of tissue. The walls of the veins measured up to 3 mm. in width and were many times thicker than in normal veins of comparable size. Many were even thicker than small muscular arteries. There was some unevenness in this overgrowth in different areas. It was somewhat more pronounced in the regions where tributary branches entered. Small, relatively thin-walled, aneurysmal outpouchings up to 1.0 cm. in depth were common. The walls of the veins were firm and inelastic. The intimal surfaces were smooth and pearly gray. In two instances, minute deposits of calcium were detectable grossly but the walls of vessels were never rigid or brittle. No intimal plaques and no

lipid deposits were found in any of the stained gross specimens. The valves of the veins were semilunar, bicuspid, and symmetrically formed. Their leaflets were extremely delicate. No evidence of valvular alteration resulting from incompetence could be made out.

In three veins, areas of thrombosis with organization were noted. In one of these, a fibrous cord-like structure, 7 cm. in length and 1.5 mm. in thickness, partly filled the lumen of a vein and was attached at several points to the adjacent wall. This was obviously an organized thrombus. After staining with Sudan IV, small focal collections of lipid up to 4 mm. across were found on the surface of this cord-like structure but not in its depths and not in the adjacent intimal surface of the vein itself.

Microscopic Findings

No trace of lipid was found in the intima or media of any of the Sudan-stained frozen sections prepared from various areas of the veins removed from 20 patients, although the adventitial fat stained as usual. In the paraffin sections of all 48 cases studied, there was no evidence of lipid deposition. No fat-laden phagocytes, cholesterol crystal spaces, or atheromatous deposits of any sort were found. There was no discrete intimal plaque formation, although in transverse sections the intimal thickening was often irregular. Some of the irregularity appeared to be due to contraction of the vessel wall.

The increased thickness of the wall of the vein was due to a marked hypertrophy of smooth muscle and a proliferation of connective tissue in all three layers. The smooth muscle hypertrophy was often pronounced and of a degree never found in any type of arterial lesion. The boundaries of the various layers were more readily identified in longitudinal than in cross sections.

The intima was usually thickened over wide areas and consisted of cellular fibrous tissue that frequently contained a heavy complement of smooth muscle. The cellular constituents tended to be longitudinally disposed and at right angles to the circular muscle groups in the media. In Weigert stains, delicate elastic fibrils were seen to extend through the intimal layer, but splitting or reduplication of the internal elastic lamella into several layers of equal thickness, a finding that is very common in arteries, was usually not observed. Complete hyalinization of the thickened intima was never noted.

The smooth muscle of the media was often greatly increased. The smooth muscle cells were sometimes arranged in small bundles separated by interlacing strands of connective tissue so that the media frequently had an almost lobulated appearance. This arrangement is

present in the normal media of veins but is usually indistinct because the amount of interwoven fibrous tissue is ordinarily scanty. In the hypertrophied media of varicose veins this pattern may be exaggerated by the overgrowth. In some instances of marked medial fibrosis, the smooth muscle cells were widely spread apart. The intramural nutrient vessels that normally penetrate the media of veins were also rendered more conspicuous in the walls of varicose veins. They could easily be traced in the fibrous tissue, coursing from the adventitia through the media to the subintimal zone. In two instances small deposits of calcium were found histologically. These simulated the very early stages of medial calcification or Mönckeberg's sclerosis of arteries.

The adventitia of varicose veins was also increased in thickness and compactness. While consisting largely of fibrous tissue, incomplete layers of smooth muscle often were found. These layers were readily distinguished from the medial muscle as they tended to course perpendicular to the medial muscle and more or less parallel to the intima.

In the single case of organized parietal thrombosis described grossly, compact groups of fat-laden phagocytes and extracellular lipid masses were found just beneath the surface of the thrombus, reproducing in every respect the histologic details of early intimal lipid streaks commonly found in arteries. The wall of the adjacent vein, however, contained no lipid. In one of the other two vessels with organizing thrombi, masses of extracellular lipid were noted. In this instance, however, the thrombus was incompletely organized and the lipid material was limited to the area of old thrombus that had not been converted into fibrous tissue.

Discussion

The histopathologic differences between sclerosis of varicose veins and of arteries are sufficiently pronounced to suggest that the mode of development of the two processes may be unrelated. The most striking difference is the regular absence of lipid deposition in veins. Lipid has been described in veins in other situations but it occurs either as very scanty deposits or under very exceptional circumstances. Lev and Saphir[4] noted small deposits of lipid in sclerotic iliac and popliteal veins but regarded this as a secondary phenomenon probably related to previous degenerative changes. Geiringer[5] found that the localized intimal fibrous plaque that is frequently found in the inferior vena cava near its point of origin from the iliac veins was sometimes faintly impregnated with lipid. He noted small fat droplets in the center of some lesions of this type. It should be pointed out that fat stains on hyalinized connective tissue, whatever its location, frequently reveal it

to contain a light film of stainable lipid. Thickened auricular endocardial plaques in rheumatic heart disease are often impregnated with lipid in this manner.

It is perhaps this finding of lipid as an obviously secondary manifestation in a variety of old scar tissues that provides one basis for the opinion that such deposits in arteries, although more pronounced, are nevertheless of the same nature. Arterial lipid deposits, however, occur early in the course of atherosclerosis before hyalinized fibrous tissue has formed and are found as large, free masses of lipid material such as are not ordinarily seen in association with hyalinized connective tissue in extravascular locations.

Apparently, true venous atherosclerosis can occur in exceptional cases. Benda[6] described this lesion in the pulmonary veins of a patient with hypercholesterolemia, chronic nephritis, thyroid tumor, and renal xanthomata. He also stated that small quantities of lipid are sometimes demonstrable in varices and in the portal vein in portal hypertension. He emphasized, however, that nothing equivalent to arterial atherosclerosis is ever found in veins. We have observed a single case of rather pronounced intimal lipid deposition in the main pulmonary veins (Figs. 11 and 12) of a young woman with severe mitral stenosis and severe diabetes. Because of this observation, the pulmonary veins in 10 other cases of severe mitral stenosis were inspected closely. In one of these, two minute flecks of intimal lipid measuring 2 and 4 mm. across, respectively, were found at points of branching in major veins at the hilum of the lung. This patient was a 45-year-old woman with no clinical evidence of diabetes and in whom no blood cholesterol studies had been done. In addition to mitral stenosis, there was massive thrombosis of the left auricle and the thrombi occluded the points of entrance of the main pulmonary veins. In the other 9 cases no gross or microscopic evidence of lipid deposition was found in the pulmonary veins. We have not been able to demonstrate lipid in the portal vein in cases with severe cirrhosis. In one cavernous angioma of a vertebra studied recently, there was marked intimal fibrosis of large venous channels but no obvious lipid deposition. It may be concluded that lipid deposition does not ordinarily play a significant rôle in phlebosclerosis.

The question may be raised as to whether the immunity of veins to lipid deposition under ordinary conditions depends upon the inability of lipid to enter the vein wall or upon the ease with which lipid can be transported through it and eliminated without deposition. Small lipid deposits are not unusual in the main pulmonary arteries of persons over 40 years of age. The resistance of veins to lipid deposition cannot,

therefore, be attributed to peculiarities of serum lipid composition in venous blood since these arteries transport venous blood. The relatively low blood pressure in veins probably contributes to the failure of lipid deposition. As already indicated, however, the blood pressure in varicosities of the lower limbs often greatly exceeds normal pulmonary arterial pressure in upright positions. The differences between arterial and venous pressures cannot, therefore, explain completely the refractiveness of veins to lipidosis. This is further indicated by the observation that organized thrombi within varicose veins may become impregnated with lipid while the vein wall itself is uninvolved.

It seems likely that differences in structure between arteries and veins that are maintained even after the vessels become sclerotic may explain in large measure the differences in susceptibility to lipid deposition. Filtration experiments on excised vessels[7] have shown that serum colloids, including lipoproteins, are able to pass through vein walls with considerably greater ease than through those of arteries. During the course of such artificial filtrations, lipid is usually deposited in the tissues of the arterial wall. In veins such deposits are either very scanty or absent.

It is of interest that the pulmonary vein is apparently the only one susceptible to atheromatous changes even if the unusual combination of abnormally high pressure and blood lipid levels is required to produce such lesions. The pulmonary veins do not differ strikingly in structure from other large veins although the medial muscle is often more compact and the elastica more fully developed. The unique feature of pulmonary veins that distinguishes them from all others is that they transport arterial blood. The paucity of intramural vascularity in the intima and inner medial layers of normal arteries has given rise to the belief that these vessels derive part of their nutrition by diffusion through the intimal surface. The question may be raised, therefore, as to whether vessels that transport arterial blood, including the pulmonary veins, are not so constructed as to receive fluid transudate directly from the lumen in contradistinction to vessels that carry venous blood. The rich intramural vascularity of systemic veins suggests that their nutrition may be maintained largely through the capillary circulation. This interpretation would support the theory that the development of atherosclerosis depends upon the penetration of lipid-containing fluid from the blood through the intimal surfaces.

Summary and Conclusions

A study of 4 popliteal veins removed following thrombophlebitis and of 44 varicose saphenous veins revealed marked thickening of all

three layers of vessel walls due to fibrosis and hypertrophy of smooth muscle. No evidence of lipid deposition was observed. Atheromatous lesions were found in an organizing thrombus within one of these veins but not in the wall of the vein itself. Analysis of the factors concerned in the development of phlebosclerosis suggests that this process is not analogous to arterial atherosclerosis. It is further suggested that the resistance of veins to lipid deposition may depend in large measure upon their structural characteristics rather than upon the hemodynamics of venous blood flow or upon alterations in the pattern of serum lipids of venous blood.

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[*Illustrations follow*]

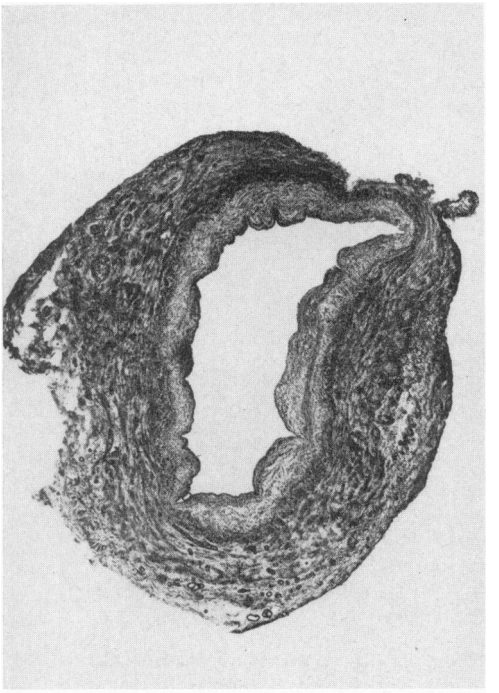
LEGENDS FOR FIGURES

FIG. 1. Marked thickening of the wall of a varicose saphenous vein. The light gray fibrous intima is uniformly thickened. Hematoxylin and eosin stain. × 15.

FIG. 2. Transverse section through the wall of a varicose vein. The thickened intima contains groups of longitudinal smooth muscle cells. The smooth muscle of the media is spread apart by fibrous tissue. The adventitia is very thick and fibrous. It contains groups of longitudinal smooth muscle bundles. Hematoxylin and eosin stain. × 90.

FIG. 3. The smooth muscle of the media is markedly hypertrophied. It is arranged in trabeculae separated by thin strands of connective tissue. Trichrome stain. × 86.

FIG. 4. The intimal smooth muscle is hypertrophied. It may be seen to course at right angles to the medial smooth muscle. Hematoxylin and eosin stain. × 90.



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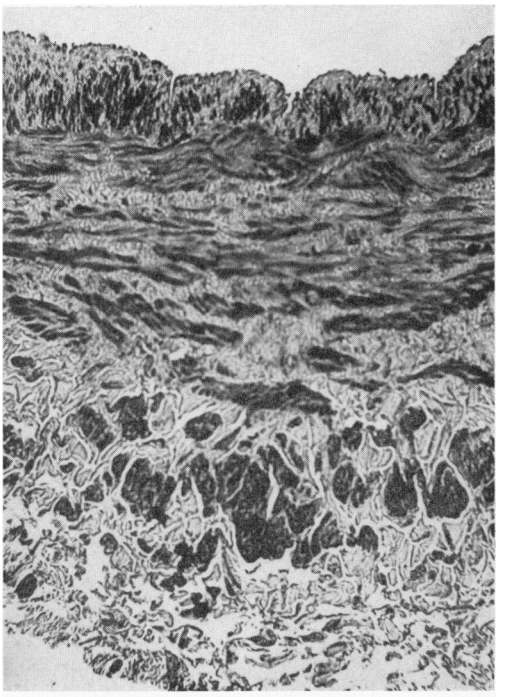

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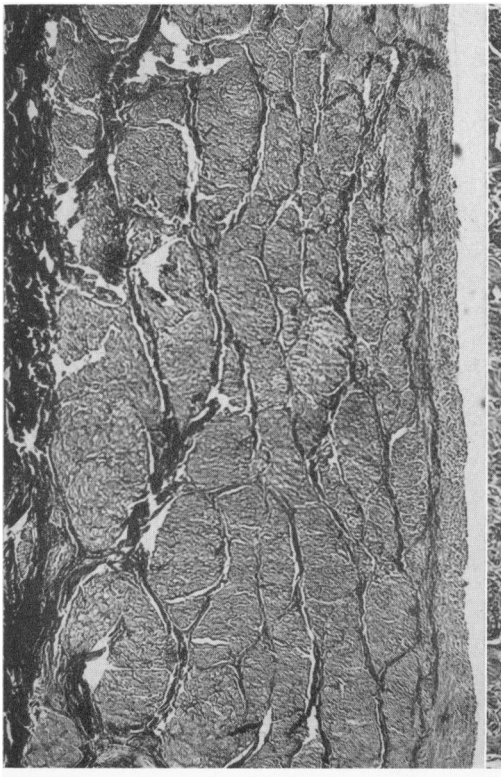

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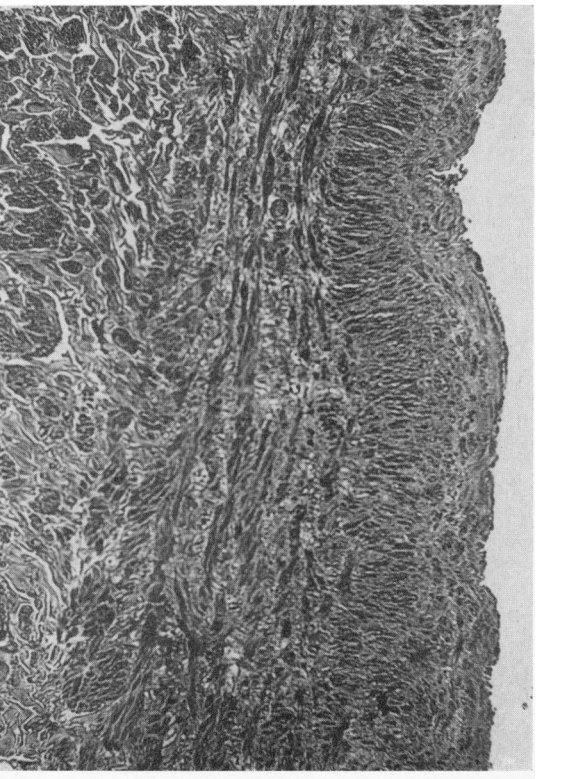

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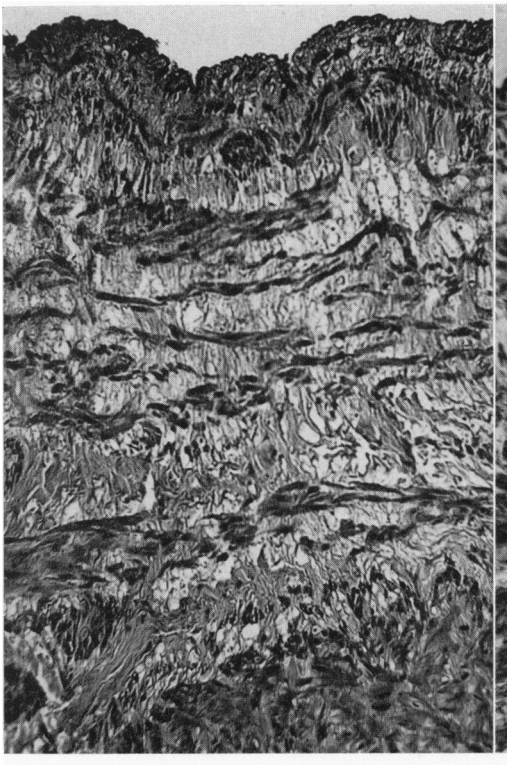
FIG. 5. The smooth muscle cells of the media in this varicose vein are widely separated by fibrous tissue. The zones of transition of the three layers are obscured. Hematoxylin and eosin stain. × 134.

FIG. 6. Longitudinal section of varicose vein showing marked intimal fibrosis. Several penetrating blood vessels may be noted. Hematoxylin and eosin stain. × 115.

FIG. 7. Weigert's elastic tissue and van Gieson's stain. The internal elastica does not appear as a distinct lamella but is granular and frayed. Granular fragments of elastic tissue are present in the media. × 124.

FIG. 8. Weigert's elastic tissue and van Gieson's stain. The amount of elastic tissue at the junction of the thickened intima and media is increased but there is no splitting or reduplication of elastic fibers. Delicate elastic fibrils extend throughout the intima. × 153.



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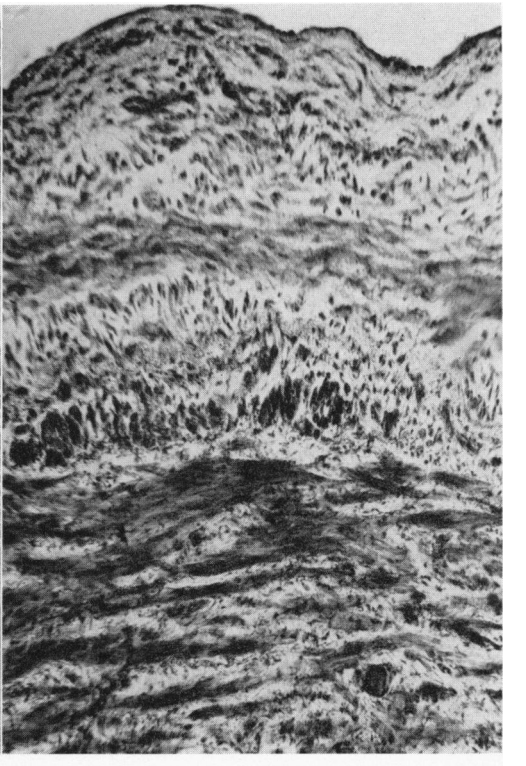

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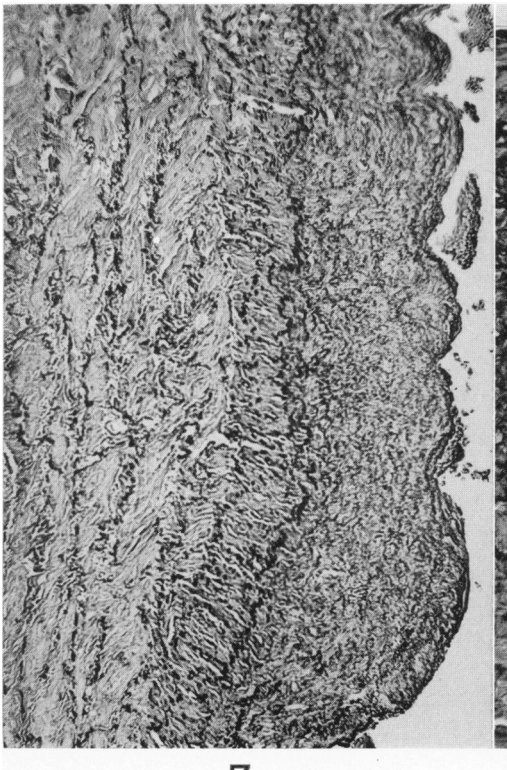

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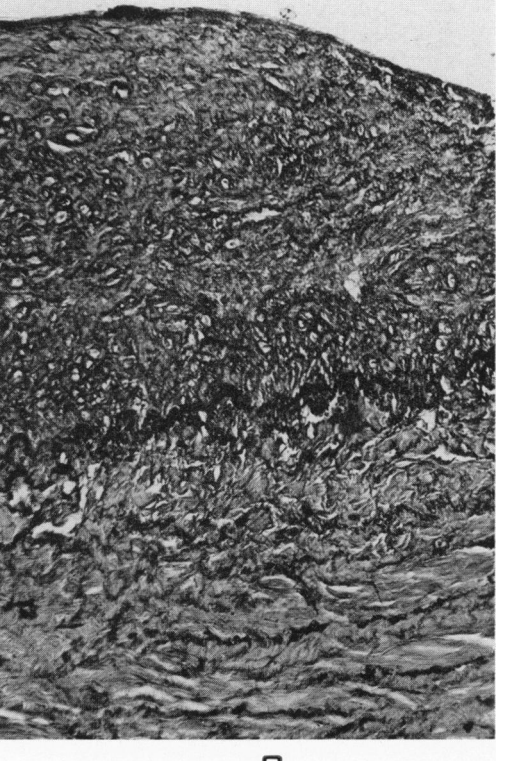

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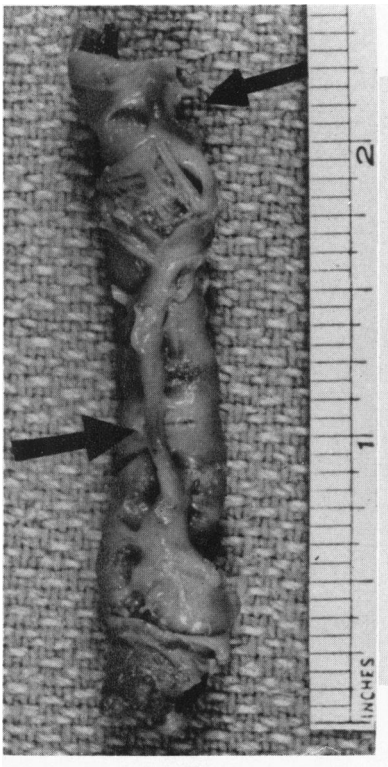
FIG. 9. Intimal surface of varicose vein stained with Sudan IV. A cord-like organized thrombus is attached to the intima at a number of points. The arrows indicate dark areas of lipid deposition in the thrombus.

FIG. 10. Cross section through the vein shown in Figure 9. The organized parietal thrombus is seen to fill the lumen partly. Near its surface is a dark area of lipid deposition. Frozen section, Sudan IV stain. × 7.

FIG. 11. Frozen section of a pulmonary vein from a 28-year-old woman with marked mitral stenosis and diabetes. The black material in the thickened intima represents lipid deposits. Sudan IV stain. × 115.

FIG. 12. Higher magnification of the vessel shown in Figure 11. Heavy deposits of lipid are present in the thickened intima. Rounded globules of fat also may be noted. Frozen section, Sudan IV stain. × 220.



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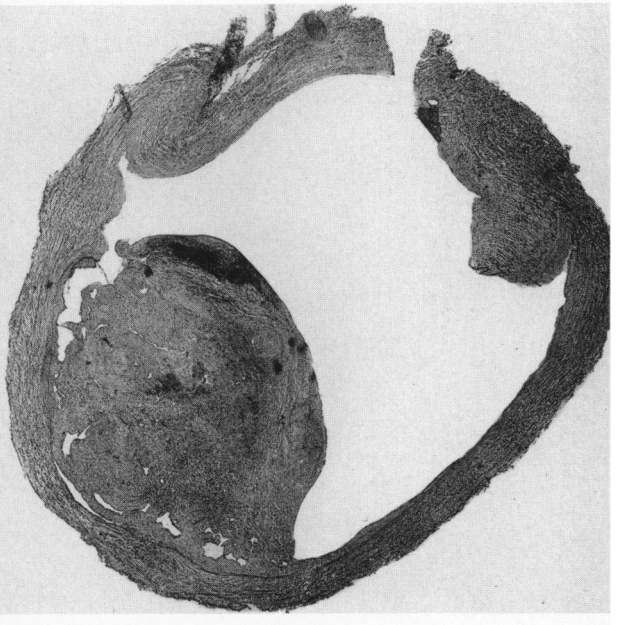

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