Virchows Arch [Pathol Anat] (1985) 406:165–177

Virchows Archiv A

Relation between arterial intimal thickening and the vasa-vasorum

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Summary. The histopathological data presented support a new concept for the origin of the cells which cause intimal thickening of arteries. Arterial segments, isolated between ligatures, when examined by intravascular contrast techniques, showed penetration of vasa-vasora and formation of intra-arterial granulation tissue which produced myointimal thickening. Transitional forms between pericytes and myointimal cells were found. In autoradiographic studies on the incorporation of 3H-thymidine, DNA synthesis was first seen in the adventitia, fundamentally in the vasa-vasora pericytes, and in the adjacent media, and later in the intimal thickening. In arterial segments between ligatures typical intimal thickening was produced when intra-arterial granulation tissue was formed and the ligatures were removed thus restoring the circulation. These results were not produced when the arterial segment was sectioned lengthways between ligatures. It is suggested that this intimal thickening originates in cells from the vasa-vasora, in particular from pericytes.

Key words: Pericytes – Intimal thickening – Vasa-vasora – Smooth muscle cells

Introduction

According to most authors, intimal thickening of arteries is produced by smooth muscle cells of the medial layer (Abou-Haila et al. 1978; Benditt 1977; Bhawan et al. 1977; Clowes et al. 1978; Glagov and Ts'ao 1975; Guyton and Karnovsky 1979; Hassler 1970; Orcel et al. 1974; Potvliege and Bourgain 1979; Ross and Glomset 1973; Ross and Glomset 1976; Schaub et al. 1981; Stemerman and Ross 1972; Stemerman et al. 1977). This hypothesis is based on the following: 1) the cells present in the intimal

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thickening (myointimal cells) correspond in appearance to smooth muscle cells (Benditt 1977; Bhawan et al. 1977; Clowes et al. 1978; Glagov and Ts'ao 1975; Guyton and Karnovsky 1979; Potvliege and Bourgain 1979; Ross and Glomset 1973; Ross and Glomset 1976; Schaub et al. 1981; Stemerman and Ross 1972; Stemerman et al. 1977); 2) these myointimal cells show the same early enzymatic reaction as cells of the innermost third part of the medial layer (Abou-Haila et al. 1978; Orcel et al. 1974); 3) muscle cells from the media have been observed to cross the "gaps" of the internal elastic laminae, suggesting a capacity to move through this membrane (Glagov and Ts'ao 1975; Guyton and Karnovsky 1979; Schaub et al. 1981; Stemerman and Ross 1972); 4) tritiated thymidine is incorporated in the internal zone of the medium layer, prior to appearing in the intimal layer (Hassler 1970; Webster et al. 1974). Other, less convincing, hypotheses regarding intimal thickening are: 1) an endothelial origin (Gebrane et al. 1982; Haust et al. 1960; Hassler 1970; Mehrotra 1953; Reddy and Cliff 1979); 2) from subendothelial cells, multipotent mesenchymal cells of the intima (Irey and Norris 1973; Sparagen et al. 1962; Zollinger 1967); 3) from transformed mononuclear cells of the circulating blood (Buck 1961, O'Neal et al. 1964; Stump et al. 1972); 4) two or more of the previous origins combined (Gebrane et al. 1982; Gerrity and Cliff 1972). Stary (1974) carried out a detailed review of the literature concerning the histogenetic problems of the proliferating cells in atherosclerotic plaques, ranging from 1884 and Zahn's hypotheses, which attributed the healing of arterial injuries to the proliferation of endothelial cells, up to the date of this his own latest work, with special reference to the contributions made by autoradiographic studies.

The present work describes another possible origin of the intimal thickening, that is from the vasa-vasora, which can produce an intra-arterial granulation tissue with a tendancy to form a myointimal plate when the arterial circulation has been interrupted, or alternatively, an equivalent form of response by migration and proliferation of the pericytes of the vasa-vasora when arterial flow remains unchanged after arterial injury.

Materials and methods

In this study 264 experiments were performed, in both femoral arteries of 132 male, adult Sprague Dawley rats, with an average weight of 300 g. These rats were anaesthetized by the intraperitoneal injection of a solution of nembutal. An inguinal incision was made and a segment 1.5 cm long of the femoral artery was dissected.

The study was divided into 7 groups: 6 groups of 40 experiments and 1 group of 24 experiments destined for autoradiographic procedures. In all groups the control was carried out on healthy animals. In the first six groups the following procedures (Table 1) were performed:

1. Ligatures were applied to the proximal and distal parts of the dissected segment (free from blood).
2. The ligatures were applied as in group 1, but the segment contained blood.
3. In this group, the segment was sectioned nearest the distal ligature, so that one of its edges remained open to interstitial tissue.
4. The ligatures were applied as in groups 1 and 2, but before the arteries were removed

Table 1. Material and methods

Group	Number of animals (experiments)	Experimental design[a]	Techniques
1	20 (40)	Proximal and distal ligatures (free from blood)	Histology: H&E, mallory trichrome, orcein (elastic) and electron microscopy
2	20 (40)	Same as above but the dissected segment contains blood	
3	20 (40)	Arterial segment, sectioned nearest the distal ligature	
4	20 (40)	Ligatures as group 1 and 2 but before the arteries were removed barium was perfused	Barium as contrast medium and same as 1, 2, and 3
5	20 (40)	Ligatures as group 1 and 2 but opened after 8 days (circulation re-established/ 10 to 27 days)	Same as 1, 2, and 3
6	20 (40)	The isolated arterial segment was sectioned lengthways. a) Along the upper side (10 exp.) b) Upper and lower side (10 exp.) c) Distal half on upper side (10 exp.) d) Upper and lower sides (10 exp.)	
7	12 (24)	Ligatures as group 2 and animals sacrificed 1 to 12 days after operation	Autoradiography (tritiated thymidine)
Total	132 (264)		

[a] Animals sacrificed 8 to 27 days after operation, except for group 7.

an aqueous barium solution (micropaque) was introduced by arterial perfusion, as a contrast medium.

5. The ligatures were applied as in groups 1 and 2 but removed after eight days.
6. The arterial segment isolated between ligatures was sectioned lengthways: a) along the whole of its length, on the upper side (10 experiments), on the upper and lower sides (10 experiments) and b) in the distal half, on the upper side (10 experiments) and on the upper and lower sides (10 experiments).

The rats were sacrificed under general anaesthetic 8–27 days after the operation. The arterial segments were removed and fixed in a solution of formalin. Serial sections in paraffin were prepared either transverse or longitudinally according to the specimen. Sections were stained with haematoxylin and eosin, Mallory trichromie and Orcein.

For electron microscopy the arterial segments were double-fixed in a glutaraldehyde solution diluted to 2% with sodium cacodylate buffer, post-fixed in 1% osmium tetroxide in cacodylate buffer, dehydrated in ethanol and embedded in epoxy resin. Areas for electron microscopy were selected by examining thick sections stained with toluidine blue. After double staining with uranyl acetate and lead citrate, the ultra-thin sections were examined in a JEOL 100B Electron Microscope.

In the 7th group, destined for autoradiographic procedures, the ligatures were applied as in group 2 and the rats were killed 1 to 12 days after operation. At 90 min before they were killed tritiated thymidine (3H-thymidine-methyl; Nuclear Ibérica. España) in a isotonic saline solution was injected into the vena cava at a dose of 1 mC/g of body weight. The arterial segments were removed and fixed in a solution of formalin. Serial sections in paraffin

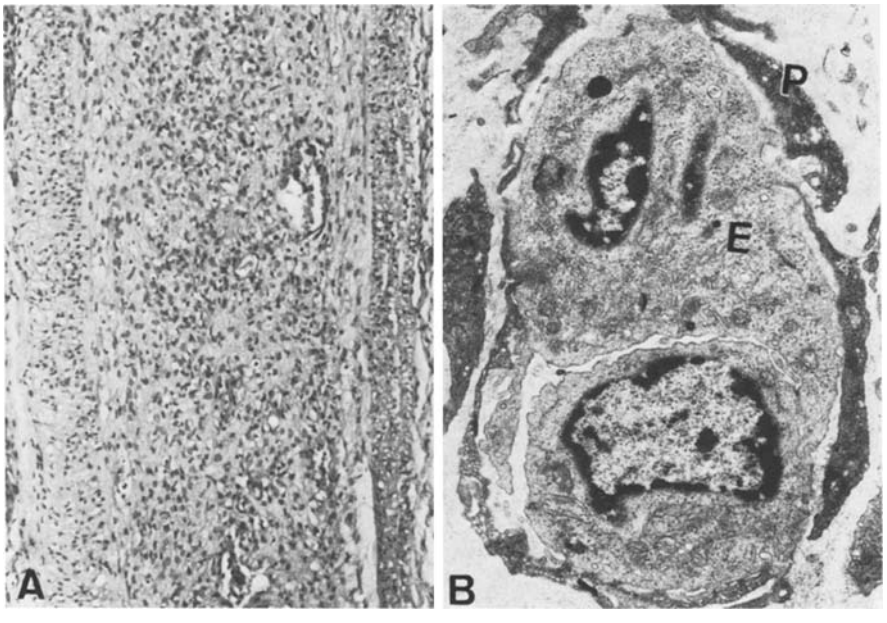

Fig. 1 A. Arterial segment 10 days after ligature. The arterial lumen is filled with granulation tissue (× 40). **B** Vascular growth in the intra-arterial granulation tissue. Endothelial cells (*E*) and electron dense pericytes (*P*) are prominent (× 10,000)

were prepared longitudinally and pretreated and dipped in Ilford's emulsion, dyed and stored in the dark at 5° C for 15 to 25 days. The autoradiograms were developed in Kodak D 19 solution, fixed in acid fixer, washed and stained with haematoxylin.

Results

In the experimental group 1 in which two ligatures were applied at the proximal and distal ends of the dissected segment free of blood, the following histopathological features were observed.

1. Eight to ten days after arterial ligature, typical granulation tissue is present in the arterial lumen (Fig. 1 A). The internal elastic lamina is discontinuous and irregularly fragmented. The granulation tissue vessels are connected to those of the adventitia, and under the E.M. they showed electron-dense pericytes (Fig. 1 B). These cells can be observed detaching themselves from the vascular walls (Fig. 2) and transitional forms between pericytes and interstitial cells are found together with a few macrophages.
2. Ten to eighteen days after arterial ligature many interstitial cells – at an intermediate stage between myofibroblasts and smooth muscle cells – are found below the internal elastic lamina. These cells (Fig. 3 A) are relatively small, oval, fusiform or stellate in shape with multiple cytoplasmic processes. The indented nuclei of these cells are hyperchromatic and

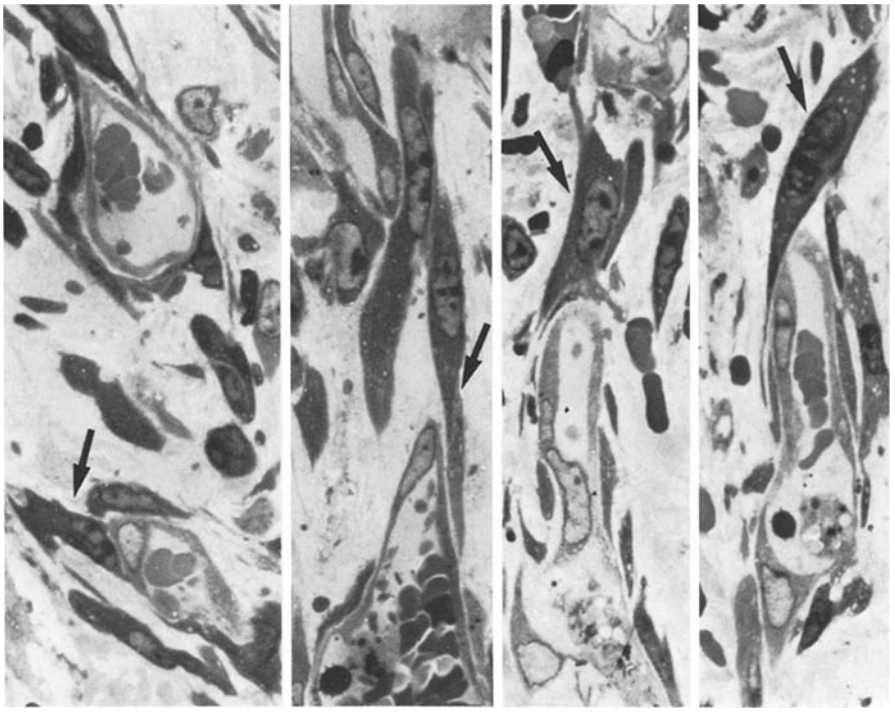

Fig. 2. Arterial segment 8 days after ligature. Intra-arterial granulation tissue. Several images of pericytes (*arrows*) as they detach themselves from the vascular walls (× 440)

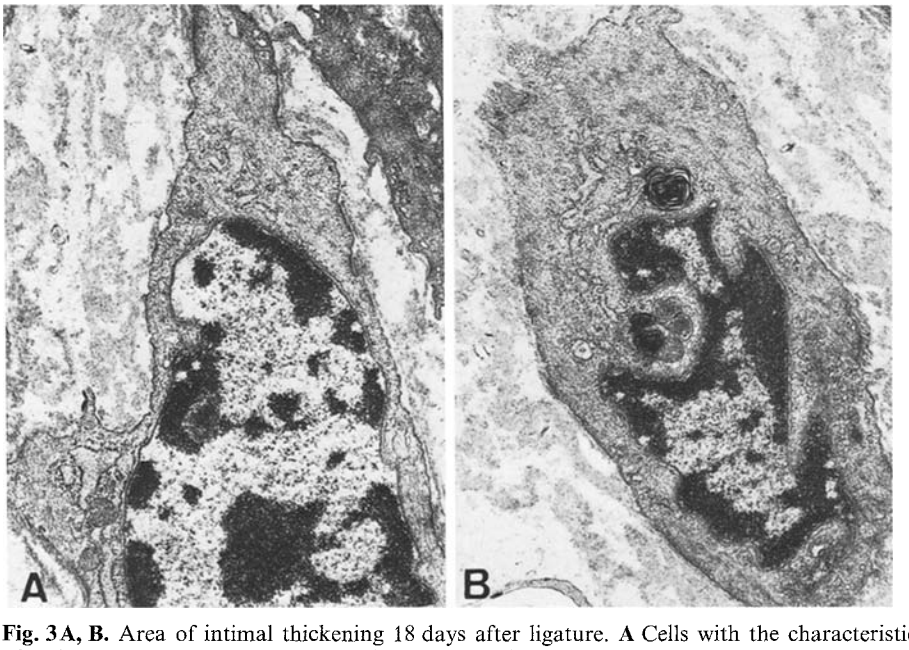

Fig. 3A, B. Area of intimal thickening 18 days after ligature. **A** Cells with the characteristics of an intermediate stage between myofibroblasts and smooth muscle cells. Abundant intracytoplasmic filaments and moderately developed R.E.R. can be seen (× 15,000). **B** Smooth muscle cell in the area of intimal thickening (× 15,000)

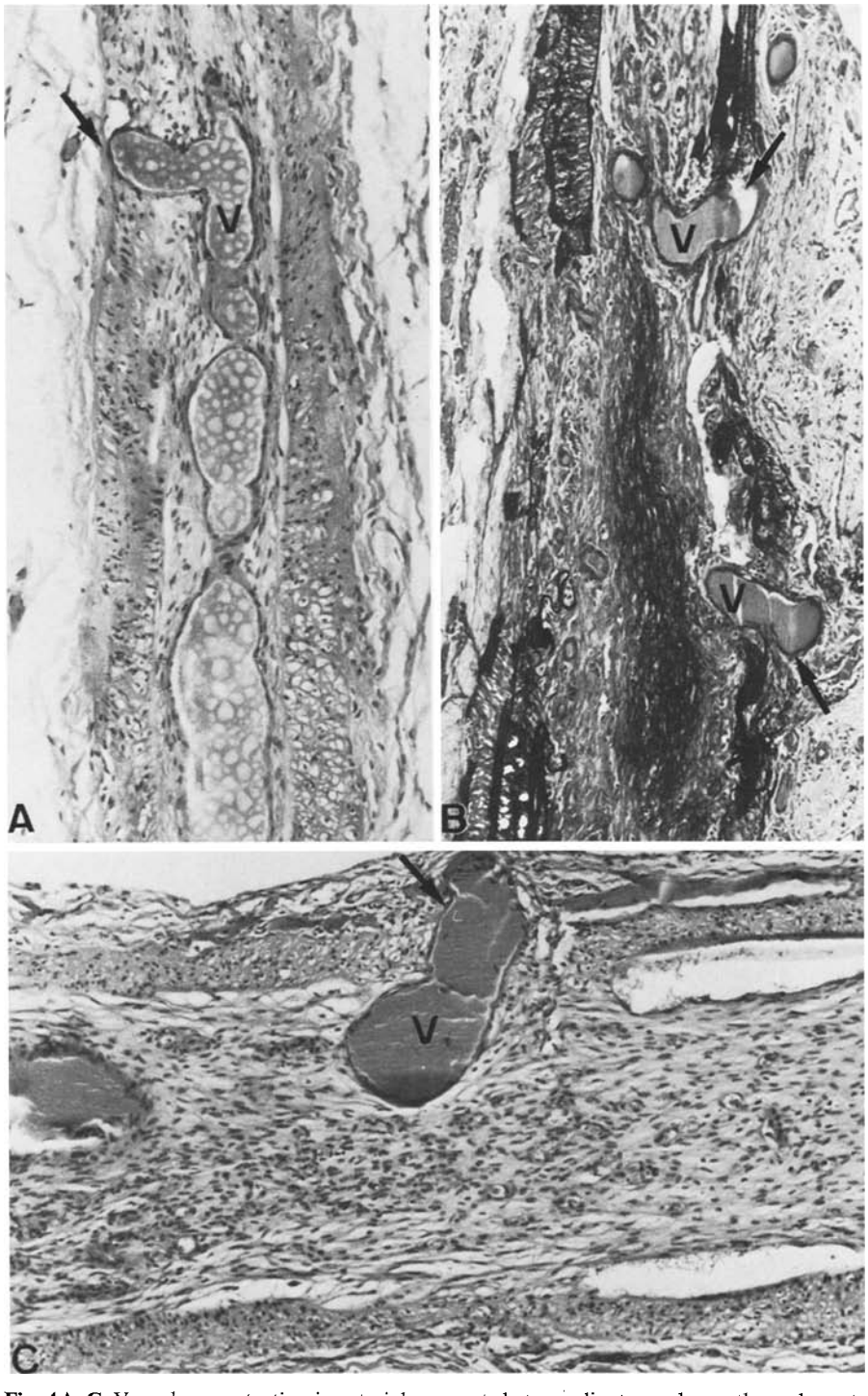

Fig. 4A–C. Vascular penetration in arterial segments between ligatures shown through contrast technique. The points at which the vessels enter the intra-arterial wall can be seen (*arrows*), as well as part of their intra-arterial tract (V). **A** H.E. (×60); **B** Orcein (×60); **C** H.E. (×90)

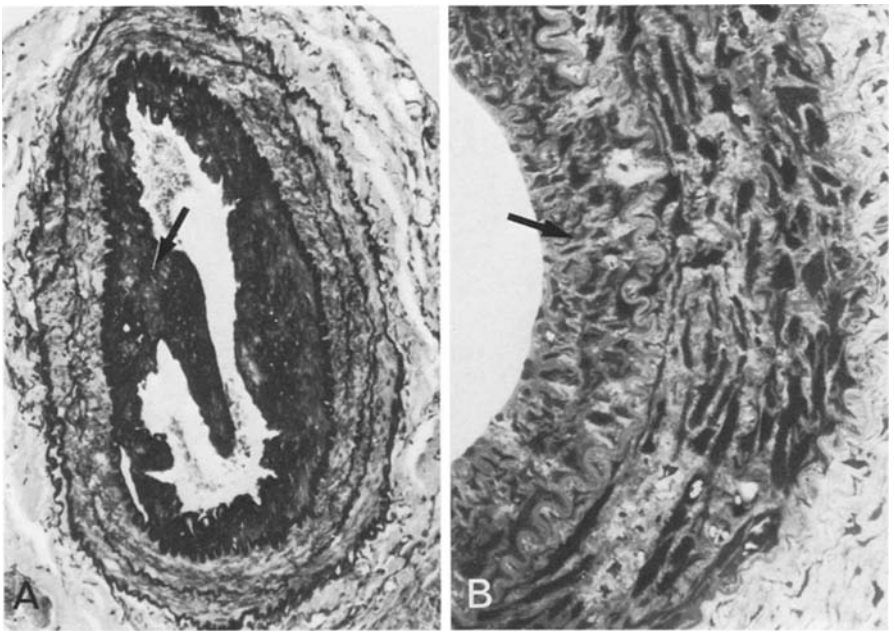

Fig. 5A. Intimal thickening in arterial segment which remained ligated for 8 days, eighteen days after removal of ligatures. Orcein (× 80). **B** Semi-thin section of the intimal thickening in a similar case to that of **A**. Toluidine blue (× 240)

the cytoplasm showed dilated rough endoplasmic reticulum and myofilaments with dense structures; occasional mitoses are present. Basal membrane-like material surrounded these cells and collagen fibrils, together with small immature elastic fibres, are also found. Some of the granulation tissue vessels are involuted or are dilated with thickened walls (arteriole-like vessels).

3. Eighteen to twenty eight days after arterial ligature most of the intimal spindle cells have the appearance of small well-differentiated smooth muscle cells (Fig. 3B). Collagen fibres and small islands of newly formed elastin, sometimes coalescent as an elastic lamina, are found in the interstitial area. At this stage the process of microvessel involution is complete and the arteriole-like vessels are more prominent, resembling recanalised arteries. In one such instance the intimal thickening is narrower, and all components are well differentiated smooth muscle cells.

In experimental group 2 in which the ligature was applied as in group 1 but the segment contained blood, and in group 3 in which the isolated segment was sectioned proximally to the distal ligature, histopathological phenomena similar to the previously described group are found.

In the arterial segments which had contrast material introduced before their removal (group 4) the micro-circulation is shown in the intra-arterial territory between the ligatures, connected to the vasa-vasora which cross

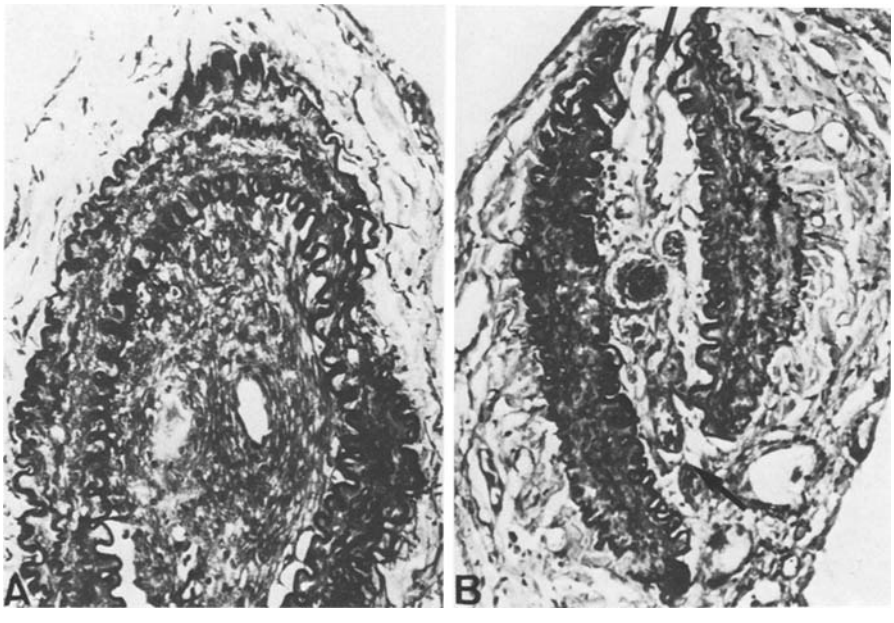

Fig. 6A. Intimal thickening, with characteristic muscle-elastic transformation in arterial segment between ligatures. Orcein (×90). **B** In the isolated arterial segment sectioned longitudinally (*arrows*) there is lax connective tissue but no muscle elastic transformation. Orcein (×90)

the arterial walls in different areas, leaving intervals of this wall unaltered (Fig. 4).

In group 5, in which ligatures were removed at 8 days, when intra-arterial granulation tissue was present, the circulation is re-established through the segment between days 10 to 27 and intimal thickening similar to that produced by other procedures is observed (Fig. 5). This intimal thickening contained small smooth muscle cells, collagen and elastic fibres and basement membrane-like material. The orientation of the cells is longitudinal with the circular orientation of media smooth muscle cells.

In the isolated arterial segments sectioned longitudinally (group 6) there is no formation of the characteristic intimal thickening. There is an impaired differentiation of the granulation tissue in relation to muscle-elastic structures, forming connective tissue (Fig. 6) which varied from lax to collagenised; adipocytes are also observed.

The autoradiographic studies (group 7) show a considerably increased DNA synthesis in the arterial segments between ligatures as compared with the normal arteries. On each of the days of this experiment labelling is observed in the arterial adventitia, especially in pericytes and to a lesser extent in endothelial and fibroblastic cells; while in the control arteries occasional labelled adventitial cells are observed. At 1–2 days or more after the operation an increased number of labelled cells in the tunica media is evident. There is also an increased number of labelled cells in the new

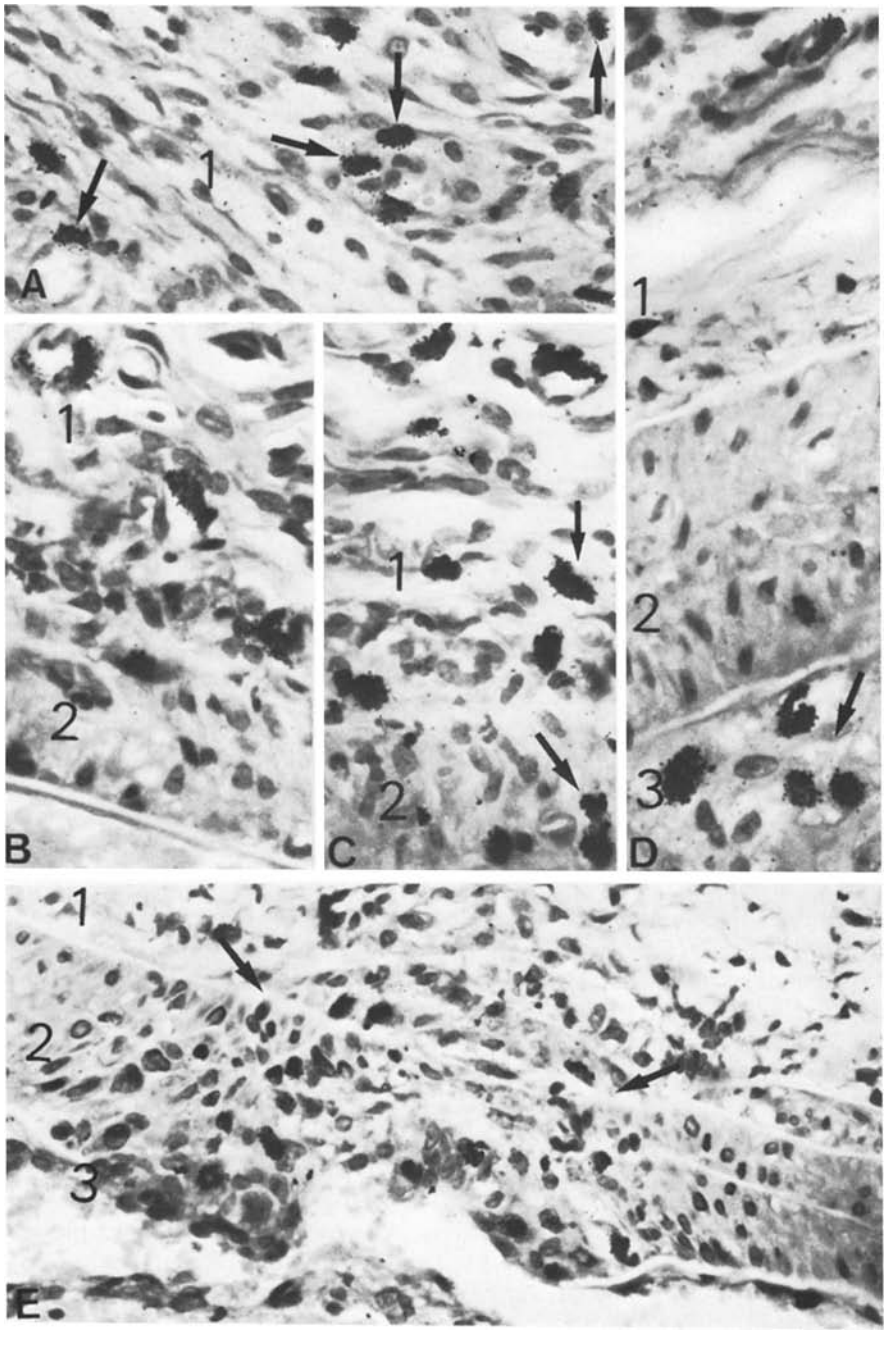

Fig. 7A–E. Autoradiograms from arterial segments between ligatures. *1* = adventitia, *2* = medium layer, *3* = intimal thickening. Hematoxylin. Obvious increase in the number of labelled cells (*arrows*). **A** Adventitia in artery that was ligated 2 days before sacrifice; there are numerous labelled cells which closely resemble pericytes. **B** and **C** Ligated 4 days before sacrifice. Labelled cells in adventitia and media. **D** Ligated 6 days before sacrifice. Labelled cells in adventitia and intimal thickening. **E** Ligated 8 days before sacrifice. Cell trails (*arrows*) which extend from the adventitia to the lumen with an increase in the labeling percentage

Table 2. Percentage of total cells labelled in ligated femoral artery

Days after operation	1	2	3	4	5	6	7	8	9	10	11	12
Location												
Intimal thickening	0	0	0	4.1[a]	13.5	12.6	9.3	3.1	7.3	4.2	6.1	4.1
Tunica media	0.5	2	5.2	6.7	7.1	7.3	8.4	2.1	6.7	5.3	4.8	3.8
Adventitia	3.3	6.4	9.1	4.3	8.2	6.5	3.3	4.1	3.2	6.8	2.2	1.5

[a] Results are obtained from 5 longitudinal sections of femoral artery. The labelling percentage of cells for normal femoral artery was less than 0.04 for endothelial cells, 0.002 for medial smooth muscle cells and 0.08 for adventitial cells

intimal layer at 4 days or more after the operation. In longitudinal sections of the arteries one can observe the penetration of the cell trails which extend from the periarterial tissues to the lumen and which show an increasing gradient of labelling percentage. The quantification of the cells labelled with 3H-thymidine is shown in Table 2.

Discussion

In these experiments the intimal thickening, which arose from intra-arterial granulation tissue, had the same characteristics of that attributed to other sources: smooth muscle cells of the media (Abou-Haila et al. 1978; Benditt 1977; Bhawan et al. 1977; Clowes et al. 1978; Glagov and Ts'ao 1975; Guyton and Karnovsky 1979; Hassler 1970; Orcel et al. 1974; Potvliege and Bourgain 1979; Ross and Glomset 1973; Ross and Glomset 1976; Schaub et al. 1981; Stemerman and Ross 1972; Stemerman et al. 1977); subendothelial cells (Irey and Norris 1973, Sparagen et al. 1962), endothelial cells (Gebrane et al. 1982; Haust et al. 1960; Hassler 1970; Mehrotra 1953; Reddy and Cliff 1979), blood cells (Buck 1961; O'Neal et al. 1964; Stump et al. 1972), and combinations of these cell types.

The results of the first three groups of experiments may be summarized as follows: 1) The arterial wall shows changes localised in the endothelial layer and internal elastic lamina. 2) Vasa-vasora, in certain areas of the segment, spirally penetrate and dissect the different layers of the arterial wall, reaching the lumen. 3) Intra-arterial granulation tissue originates in the intra-arterial pre-existent fibrin leaving cavities containing fluid blood. 4) The points of vascular growth in the different areas of penetration coalesce with each other and the cavities in the midst of the intra-arterial granulation tissue. 5) Interstitial cells are produced which show some characteristics of pericytes, myofibroblasts or smooth muscle cells; their relation with the pericytes which detach themselves from the vascular walls may be observed. Intercellular material similar to the basal membrane, collagen and young elastic fibres, are produced concurrently. 6) The penetrating vasa-vasora, on joining and fusing with the cavities containing fluid blood, produce one or two lumens which are more or less centrally disposed. Peripheral

capillaries in the mass of intra-arterial granulation tissue regress at this stage. 7) The arterialised vessel becomes predominant while the interstitial cells acquire the definite characteristics of smooth muscle cells. 8) The resulting myointimal thickening is indistinguishable from that previously described by other authors. These results are not produced when the arterial segments isolated between ligatures are sectioned lengthways.

These results, whilst suggesting an alternative origin for the myointimal cells, also question the generally accepted concept that intimal cells are derived from medial smooth muscle cells. Moreover in this last case the medial smooth muscle cells should be multipotential, movable elements with tensile and biosynthetic properties. In this respect, differences in orientation, size and distribution of organelles between smooth muscle cells of the media and myointimal cells are evident.

Observing the muscle fibre proteins by immunofluorescence, vimentin and desmin antibodies and electrophoretic analysis, shows a quantitative difference between muscle cells of the media and those in intimal thickening. Vimentin-rich cells are responsible for intimal thickening (Gabbiani et al. 1982; Rungger-Brändle and Gabbiani 1983), this and their morphological characteristics, suggest some analogies of structure and behavior between myofibroblasts and these intimal smooth muscle cells (Rungger-Brändle and Gabbiani 1983).

The penetration of micro-vessels from the adventitial layer of the artery is refuted by some authors (Bhawan et al. 1977) despite the fact that these micro-vessels are seen in the intraarterial granulation tissue. These authors suggest that the vessels come from the endothelial layer crossing the areas of the ligatures; the introduction of contrast material, at the moment of extracting the arterial segment, has enabled us to show an intricate network which connects the newly-formed tissue in the arterial lumen with the periarterial areas.

We believe it is very important to carry out these observations on longitudinal arterial sections, a recommendation which has already been made previously in relation to different studies on atherosclerosis (Doerr 1970). It seems evident that most of the vessels which penetrate the arterial walls follow a dissecting, spiral path looking for those points with an easier access, which may be related to the passages of the intramural fluids – Flüssigkeitsstrassen – which predominate in the ostium of the branches and in the concavities of the kinks. An extensive account of the data on the origin and purpose of the passages of the intramural fluid, of the theory of perfusion in atherosclerosis, and of the opinions of other authors in this field – among whom Richard Thoma stands out – can be found in the work of Doerr (1970).

It is unlikely that the particular conditions of the arterial segment between ligatures produces this particular response because, on taking off these ligatures eight days after applying them, the intimal thickening observed in these recanalized vessels was indistinguishable from that produced by other experimental procedures.

Although activity in the media of the arteries was demonstrated in our

study with tritiated thymidine in arterial segments between ligatures, label was also present in the adventitial pericytes from 1 to 12 days after injury suggesting that adventitial pericytes may be transformed into migrating cells within the media, which later reach the intimal region. Making use of two types of injury of the rabbit aorta, suture placement and electrocauterization, and autoradiographic localization of tritiated thymidine uptake Webster et al. (1974) maintain that intimal thickening is produced by smooth muscle cells of the media layer, but they also point to the fact that another arterial response to injury is that of the adventitial perithelial cells (pericytes) and that an apparent source of new medial smooth muscle cells is the migrating perithelial cells.

The suggestion that myointimal cells originate from vasa-vasora, probably from their pericytes, provides an alternative interpretation to previous data. Factors liberated from platelets (Harker et al. 1976; Ross et al. 1974; Rutherford and Ross 1976), like components normally present in plasma, have not only the capacity to stimulate the growth of smooth muscle cells but also of endothelial cells, fibroblasts and possibly other cells (Rutherford and Ross 1976).

We believe that intimal thickening results from a similar mechanism to that of the organisation of thrombus, with subsequent events depending on whether or not the arterial circulation has been interrupted. When it has been interrupted there is both a penetration of the vasa-vasora and a myointimal differentiation from pericytes, whereas when the arterial circulation has remained unchanged there is no vasa-vasora penetration and the intimal thickening originates from the pericytes migrating from the arterial vasa-vasora, as an equivalent response.

References

Abou-Haila A, Hadjiisky P, Roland J, Orcel L (1978) Etude histochimique et histoenzymatique de l'endartérite expérimentale du lapin. I. L'Endartérite fémorale. Paroi Artérielle/Arterial Wall. 4:189–205

Benditt EP (1977) Implications of the monoclonal character of human atherosclerotic plaques. Am J Pathol 86:693–702

Bhawan J, Joris I, Degirolami U, Majno G (1977) Effect of occlusion on large vessels. Am J Pathol 88:355–380

Buck RC (1961) Intimal thickening after ligature of arteries: An electron microscopic study. Circ Res 9:418–426

Clowes AW, Collazzo RE, Karnovsky MJ (1978) A morphologic and permeability study of luminal smooth muscle cells after arterial injury in the rat. Lab Invest 39:141–150

Doerr W (1970) Allgemeine Pathologie der Organe des Kreislaufes. In: Büchner F, Letterer E, Roulet FC (eds) Handbuch der Allgemeinen Pathologie, Band III, Teil 4. Springer, Berlin Heidelberg New York, pp 570, 572–580, 616

Gabbiani G, Rungger-Brändle E, Dechastonay C, Frank WW (1982) Vimentin-containing smooth muscle cells are responsible for aortic intimal thickening after endothelial injury. Lab Invest 47:265–269

Gebrane J, Roland J, Orcel L (1982) Experimental diffuse intimal thickening of the femoral arteries in the rabbit. Virchows Arch [Pathol Anat] 396:41–59

Gerrity RG, Cliff WJ (1972) The aortic tunica intima in young and aging rats. Exp Mol Pathol 16:382–402

Glagov S, Ts'ao Ch (1975) Restitution of aortic wall after sustained necrotizing transmural ligation injury. Role of blood cells and artery cells. Am J Pathol 79:7–30
Guyton JR, Karnovsky MJ (1979) Smooth muscle cell proliferation in the occluded rat carotid artery. Am J Pathol 94:585–602
Haust MD, More RH, Movat HZ (1960) The role of smooth muscle cells in the fibrogenesis of arteriosclerosis. Am J Pathol 37:377–389
Harker LA, Ross R, Slichter SJ, Scott CR (1976) Homocystine-induced arteriosclerosis: The role of endothelial cell injury and platelet response in its genesis. J Clin Invest 58:731–741
Hassler O (1970) The origin of the cells constituting arterial intimal thickening. An experimental autoradiographic study with the use of 3H-thymidin. Lab Invest 22:286–293
Irey NS, Norris HJ (1973) Intimal vascular lesions associated with female reproductive steroids. Arch Pathol 96:227–234
Mehrotra RML (1953) An experimental study of the changes which occur in ligated arteries and veins. J Pathol Bacteriol 65:307–313
O'Neal RM, Jordan JL, Rabin R, De Bakey ME, Halpert B (1964) Cells grown on isolated intravascular dacron tub: an electron microscopy study. Exp Mol Pathol 3:403–412
Orcel L, Hadjiisky P, Roland J (1974) Réactivité histoenzymatique des cellules de l'épaississement diffus de l'íntima de l'artére fémorale enveloppée d'un tube de polyéthyléne. Paroi Artérielle/Arterial Wall 2:65
Potvliege PR, Bourgain RH (1979) Thrombosis induced in vivo in the femoral artery of rats. An electron microscopic study of myointimal growth. Br J Exp Pathol 60:382–388
Reddy GSR, Cliff WJ (1979) Morphologic changes in arterial grafts in rabbit ears. Lab Invest 40:109–121
Ross R, Glomset JA (1973) Atherosclerosis and the arterial smooth muscle cell. Proliferation of smooth muscle is a key event in the genesis of the lesions of atherosclerosis. Science 180:1332–1339
Ross R, Glomset JA (1976) The pathogenesis of atherosclerosis. N Engl J Med 295:369–377; 420–425
Ross R, Glomset J, Kariya B, Harker L (1974) A platelet-dependent serum factor that stimulates the proliferation of arterial smooth muscle cells in vitro. Proc Natl Acad Sci 71:1207–1210
Rungger-Brändle E, Gabbiani G (1983) The role of cytoskeletal and cytocontractile elements in pathologic processes. Am J Pathol 110:361–392
Rutherford RB, Ross R (1976) Platelet factors stimulate fibroblasts and smooth muscle cells quiescent in plasma serum to proliferate. J Cell Biol 69:196–203
Schaub RG, Rawlings CA, Keith JC (1981) Platelet adhesion and myointimal proliferation in canine pulmonary arteries. Am J Pathol 104:13–22
Sparagen SC, Bond VP, Dahl LK (1962) Role of hyperplasia in vascular lesions of cholesterol-fed rabbits studies with thymidine 3H autoradiography. Cir Res 11:329–336
Stary HC (1974) Proliferation of arterial cells in atherosclerosis. In: Wagner WD, Clarkson TB (eds) Arterial mesenchyme and arteriosclerosis. Adv Exp Med Biol, vol 43. Plenum, New York, pp 59–81
Stemerman MB, Ross R (1972) Experimental arteriosclerosis. I. Fibrous plaque formation in primates, an electron microscope study. J Exp Med 136:769–789
Stemerman MB, Spaet TH, Pitlick F, Cintron J, Lejnieks I, Tiell ML (1977) The pattern of reendothelialization and intimal thickening. Am J Pathol 87:125–137
Stump MM, Jordan GL Jr., DeBakey ME, Halpert B (1972) Endothelium grown from circulating blood on isolated intravascular dacron tub. Am J Pathol 43:361–367
Webster WS, Bishop SP, Geer JC (1974) Experimental production of longitudinal smooth muscle cells in the intima of muscular arteries. Lab Invest 39:370–374
Zollinger HU (1967) Adaptative Intimafibrose der Arterien. Virchows Arch [Pathol Anat] 342:154–164

Accepted December 17, 1984