Virchows Arch [Pathol Anat] (1985) 406:133–148

Virchows Archiv A

Organisation of experimental thrombosis by blood cells

Evidence of the transformation of mononuclear cells into myofibroblasts and endothelial cells*

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Summary. To clarify whether thrombus organisation was carried out by local cell activity or by elements of the circulating blood we developed an artifical prosthesis, made of an impermeable polyurethane material with an athrombogenic surface but with a central part consisting of a DACRON velour ring which was thrombogenic. We implanted these devices into the aorta of 10 sheep. In these animals, organisation of the central thrombus by local aortic cells could be excluded. After varying periods of time (2–84 days), the device was removed and the organized thrombus investigated by light and electron microscopy. From our investigations the organisation process with the development of mesenchymal cellular elements proceeded in 3 steps: (1) The activation of the mononuclear macrophage system (2), the appearance of myofibroblastic cells and (3) endothelial formation. The activation of the mononuclear macrophage system is probably induced by chemospecific products of metabolism arising from aging thrombotic material. Apart from mononuclear elements such as monocytes, macrophages, and giant cells we observed fibroblast-like and myofibroblast-like cells. The matrix contained collagen. Endothelium developed on the surface of the organizing thrombus. The final stage was characterized by the formation of a pseudovessel wall, which followed the pattern of the vascular model. Our findings support the hypothesis that a thrombus may be organized by cells derived from the circulating blood.

Key words: Experimental thrombus organisation – Mononuclear cell – Mesenchymal transformation – Mesenchymal cell – Myofibroblastic cell – Endothelial cell – Dualistic genesis

* Dedicated to Prof. Dr. J.H. Holzner on the occasion of his 60th birthday.

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Introduction

The origin of cellular elements in the organisation of thrombosis, in tissue formation in vascular replacement, and in the proliferation and organisation processes in arteriosclerosis is controversial. The problem is to decide whether local cells of the vessel wall or of the surrounding tissue have a capacity for ingrowth, or whether the cells of the blood stream are capable of transformation into the various cells of the organized tissue.

Metchnikoff's (1892) assumption that white blood cells might develop into fibroblasts had to fight against the theory of morphological determination. Although since 1960 experimental results have suggested that various mesenchymal cells derive from the circulating blood (Halpert et al. 1960; Hülliger and Allgöwer 1961; Ghani and Tibbs 1962), this theory has not been generally accepted. The principle of cellular pathology, suggesting that organs (i.e. arteries) and organic systems (i.e. soft tissue) can determine successor cells only from local elements, has persisted. The monocyte in particular was found to be incapable of such a transformation, in histochemical (Leder 1967) and parabiotic (Ross et al. 1970) experiments.

It is also true that the character of the mononuclear cell in the blood stream is uncertain. There is some evidence that there exists a pool of circulating stem cells (Leu 1973; Fliedner 1978).

In the course of work connected with the development of an artificial ventricle and investigations of its lining (Bernhard et al. 1969; Feigl 1976) it appeared that some mesenchymal elements must develop from the circulating blood. We thought that this question called for renewed investigation and therefore developed a reproducible model (Feigl et al. 1979; Matejka et al. 1980) to investigate the morphological details of thrombus organisation under conditions where local cells were definitely excluded.

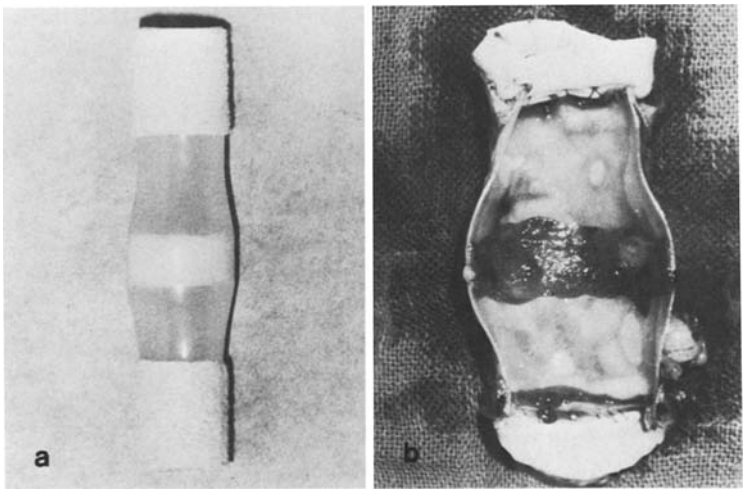

Fig. 1. a Unopened prosthesis, ready to be implanted by end to end anastomosis into the aorta. **b** Opened prosthesis; note central thrombotic ring

Material and methods

Grafts, 6 cm long, with a diameter of 1.5 cm, of AVCOTHANE 51 (now Cardiothane 51, Kontron, Inc., a complex of polyurethane, silicon and copolymer of both) were implanted into the thoracic aorta of 10 sheep, end to end (Fig. 1a). Avcothane 51 is impermeable for migration from the surrounding tissue, and the inner surface towards the circulating blood is athrombogenic (Horcher 1977). A DACRON velour measuring 1 cm was fixed in the center on the inner wall of the graft (Fig. 2). DACRON velour is thrombogenic and the thrombosis formed was meant to work as a trap for the cells of the blood stream (Fig. 1b). At each end, the graft tube was equipped with narrow strips of DACRON prosthesis, to achieve better haemostasis in the stich channels.

The prostheses were removed from the sacrificed animals after periods varying from 2–84 days (2, 6, 7, 10, 17, 18, 21, 28, 48, 84 d). Fixation of the thrombosed material taken from the DACRON fibrils was by 5% buffered formaldehyde for light microscopy, and by 2.5% buffered glutaraldehyde (0.1% cacodylate, pH 7.4) for electron microscopy. For light microscopy, H & E staining' PAS staining and Goldner's trichrome stains were used. For electron microscopy, postfixation was with osmium-ferrocyanide. The ultra thin serial sections were cut with a LBK-4802A ultramicrotome and then stained according to the method of Reynolds (1963). Electron microscopy was done on a ZEISS EM 95.

Results

Light microscopy

Two days after implantation. The DACRON fibrils were covered by blood clot consisting of dense fibrin, white blood cells, and erythrocytes. The relative proportions of polymorphonuclear leucocytes (PMNs) and mononuclear cells reflected the blood picture. There were a few cells with an elongated nucleus and little cytoplasm. One multinucleated giant cell adhered to the DACRON.

Facing the circulating blood, we found a loose layer whose border towards the lumen consisted of a sharply defined strip of eosinophilic material composed of granular material among fibrin fibers. This layer contained macrophages with a foamy cytoplasm and a few cells with elongated nuclei with dense chromatin and little cytoplasm.

Six and 7 days after implantation. Dense fibrin adhered to the DACRON fibrils. Only a few blood cells were within the fibrin. The number of PMNs had decreased. The relative percentage of mononuclear cells was higher now. There were also some cells with elongated nuclei as well as foreign body giant cells in the neighbourhood of the DACRON fibrils.

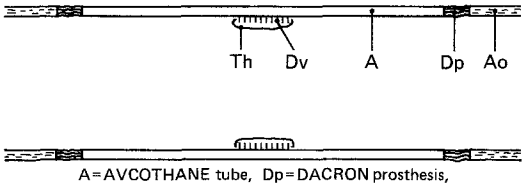

Fig. 2. Longitudinal section of the prosthesis

A=AVCOTHANE tube, Dp=DACRON prosthesis, Dv=DACRON velour, Ao=Aorta, Th=Thrombus

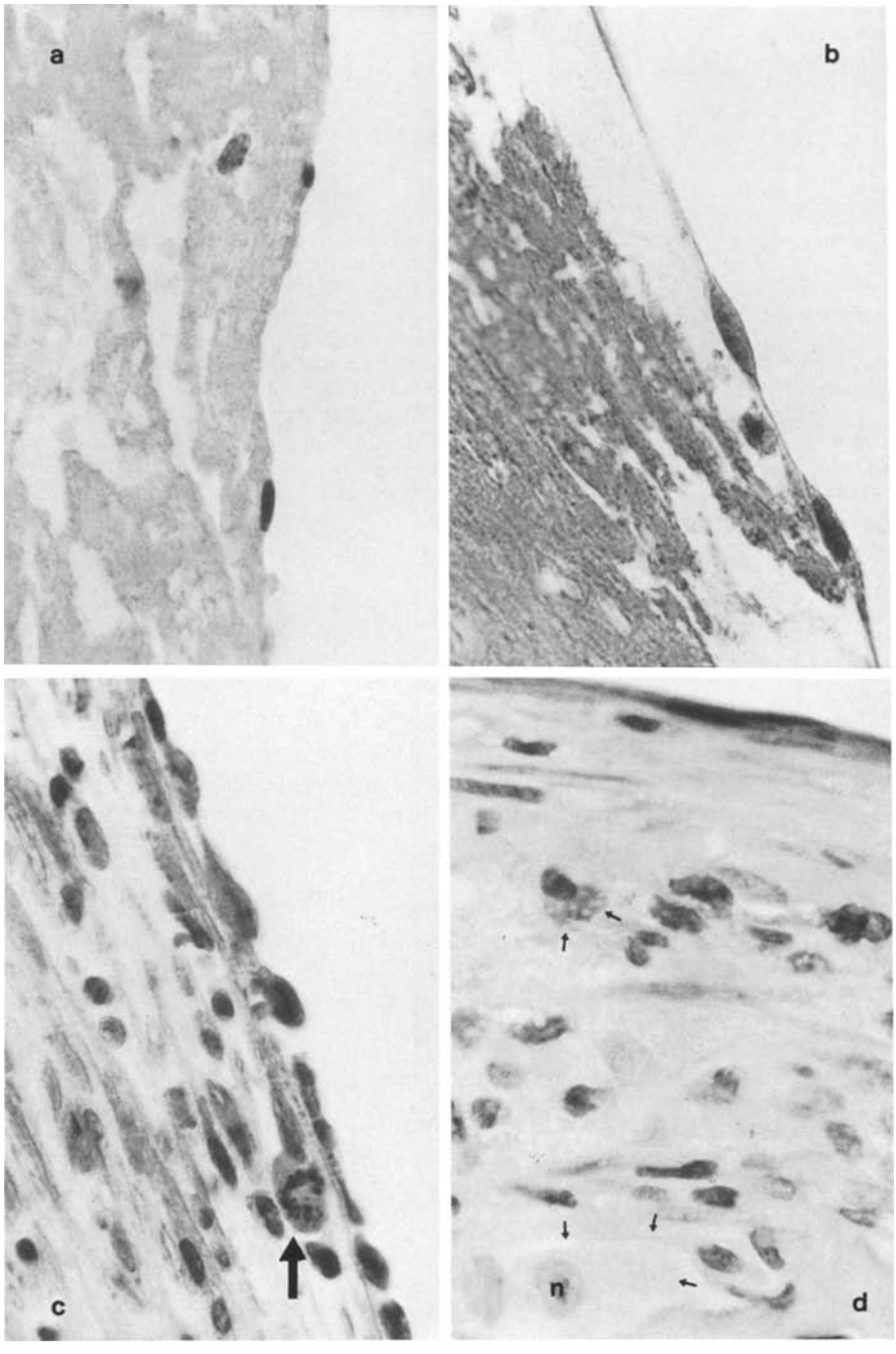

Fig. 3. **a** Inner layer of the thrombus. Loose granular material with fibrin and one slightly elongated cell. Two cells are attached to the surface (HE, ×1000, 10d). **b** Endothelial like cells covering the rather unorganized surface of the thrombus (HE, ×1,000, 18 d). c A plaque of proliferating connective tissue cells with a mitotic figure (*arrow*) and some mononuclear round cells. On top of the plaque prominent endothelial like cells (HE, ×1,000, 18 d). **d** A cluster of differently shaped macrophages with foamy, partly granular cytoplasm and some spindle cells (HE, ×1000, 18 d)

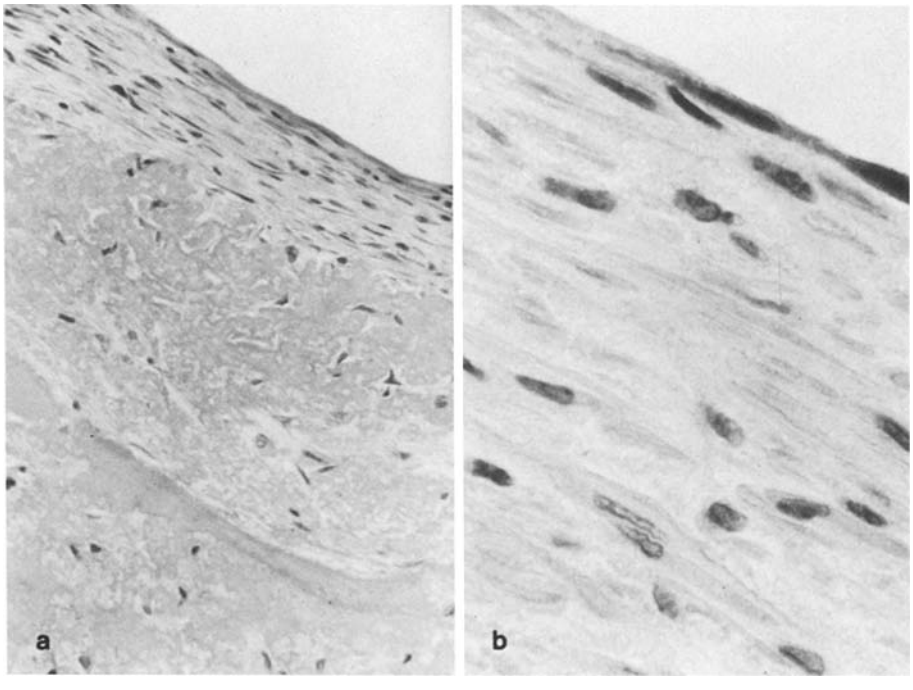

Fig. 4. **a** A zone of neointima lying on a fibrin clot containing few macrophages, stellate cells and spindle cells, organizing the thrombus (HE, ×400, 18 d). **b** Neointima with spindle cells showing morphological criteria of smooth muscle cells (HE, ×1000, 84 d)

The loose inner layer showed increased cellularity. There were round cells with dark, chromatin dense nuclei which were slightly crenated (reminiscent of monocytes). We also found cells with a dark, oval nucleus and no detectable cytoplasm. In between there were a few PMNs as well as macrophages with large nuclei, loose chromatin and nucleoli. In one section we found, on the loose inner layer, one elongated endothelial-like cell.

Ten days after implantation (Fig. 3a). Adjacent to DACRON fibrils, fibrin had become more dense, but cellular elements had decreased. In between the few blood cells some spindle cells with dark, rather long nuclei and little cytoplasm appeared. Foreign body giant cells adhered to the DACRON fibrils.

The surface of the loose inner layer consisted of adhesive elongated endothelial-like cells and a few round cells. Underneath and embedded into loose fibrin we found an increasing number of macrophages with foamy cytoplasm which showed a positive PAS-reaction.

Seventeen and 18 days after implantation (Figs. 3b–d, 4a). Dense fibrin containing few cells was adjacent to the DACRON fibrils. Within the inner layer consisting of loose fibrin there were plaque-like proliferations of spin-

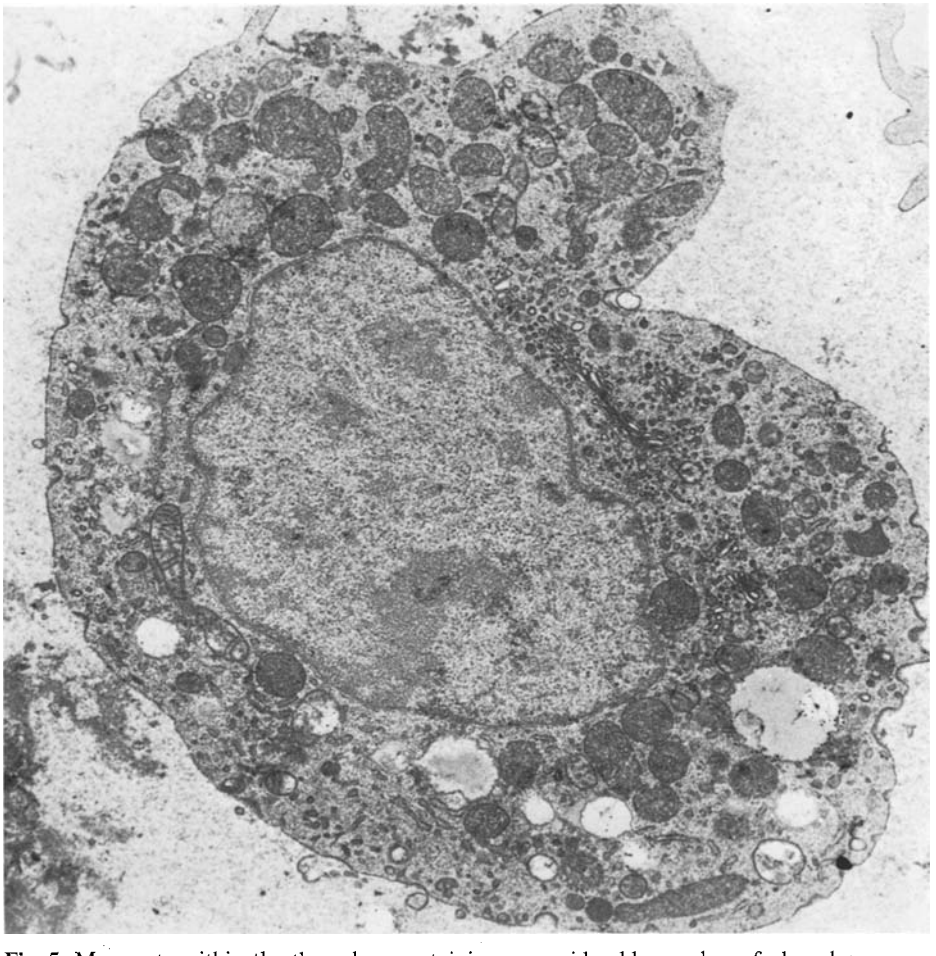

Fig. 5. Monocyte within the thrombus containing a considerable number of phagolysosomes and mitochondria (× 14600, 7 d)

dle cells in addition to macrophages. On the surface we found endothelial cells of various length which were interconnected. Underneath, the spindle-shaped cells were directed parallel to the blood flow. In only a few areas did the proliferating cells have a disorderly arrangement. Some of the spindle cells had mitotic nuclei.

Twenty-one, 28 and 48 days after implantation. The organizing procedure in the inner layer of the blood clot was histologically and cytologically similar to the one found in 18 d-old clots. Plaque-like proliferations of spindle cells were present, and most were arranged in layers parallel to the blood stream. Organisation proceeded at different speed in various animals. Re-thrombosis was evident at some points and the formation of new layers of endothelial cells occured. Around the DACRON fibrils a homoge-

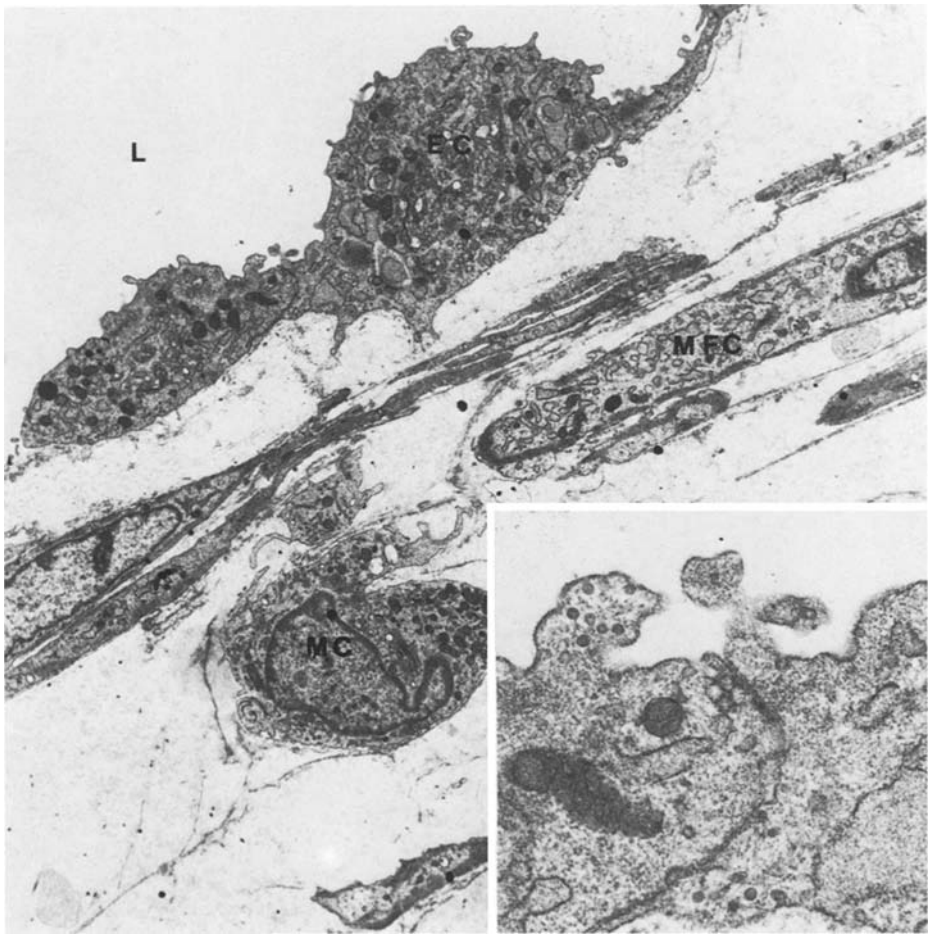

Fig. 6. Endothelium like cells (*EC*) cover the thrombus surface. Underneath mononuclear cells (*MC*) and partly elongated cells reminiscent of myofibroblastic cells (*MEC*). *L* = Lumen (× 5400, 28 d). *Inset:* Tight junction between ECs (× 27000)

neous eosinophilic fibrin layer appeared. The number of enclosed cells was still small.

Eighty-four days after implantation (Fig. 4b). A complete endothelium lined the inner layer. The density of endothelial cells varied. Their nuclei often projected into the lumen. Underneath, spindle cells were oriented in the direction of the blood stream. The ends of their nuclei were mainly pointed, and the chromatin was loose; a few had round nuclei, several nucleoli and dense chromatin. Occasionally some macrophages are embedded, their cytoplasm sometimes containing haemosiderin. Cell and tissue differentiation did not progress uniformly. In some areas organisation resembling a pseudo vessel wall was evident, while in some deep areas and also in certain parts

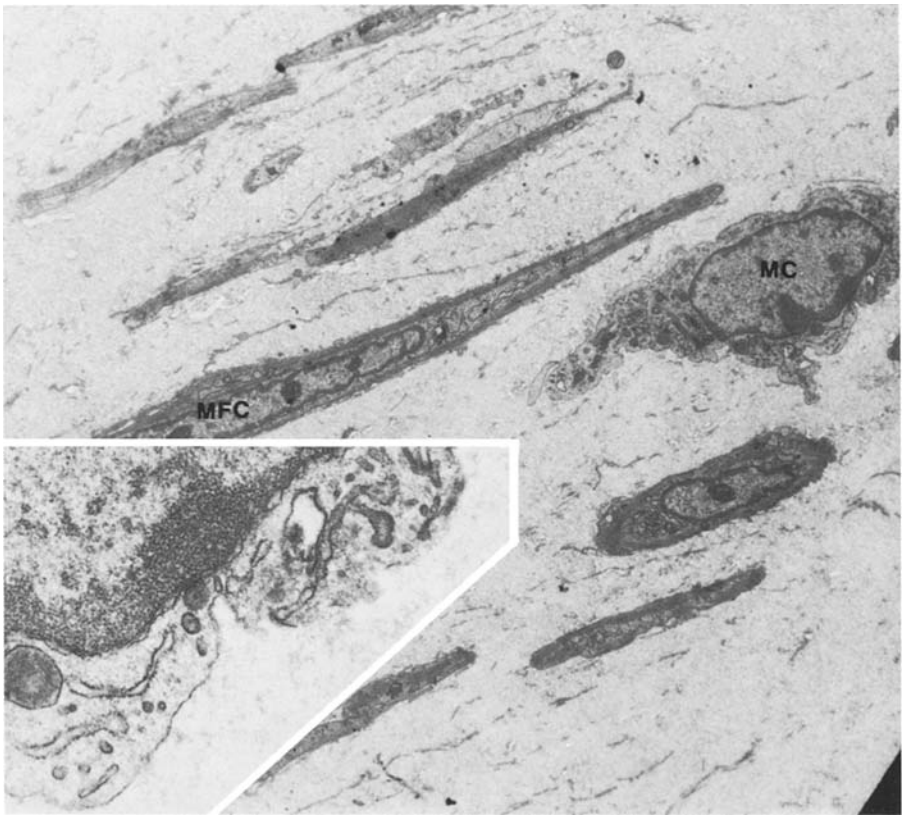

Fig. 7. Myofibroblastic cells (*MFC*) and mononuclear cells (*MC*) containing phagolysosomes and rough endoplasmatic reticulum (×14600, 28 d). *Inset*: Detail of MC (×27000)

of the surface, unorganized thrombus was still present. Thus processes of different age coexisted.

Electron microscopy

After seven days of implantation the inner layer of the thrombus revealed thrombocytes and monocytes (Fig. 5) whose cytoplasm was rich in organelles and phagolysosomes. After 28 days the surface of the thrombus was partly covered by a layer of cells. They were elongated and showed an endothelium-like arrangement (Fig. 6). They sometimes showed features of monocytes and contained smooth and rough endoplasmic reticulum which was sometimes dilatated. Tight junctions were also present (Fig. 6 Inset), Weibel-Palade bodies were not found. Underneath these surface cells there were mononuclear cells as well as myofibroblasts (Figs. 6, 7). The mononuclear cells contained phagolysosomes and rough endoplasmic reticulum (Figs. 7, 8). Myofibroblasts contained myofilaments near the cytoplasmic

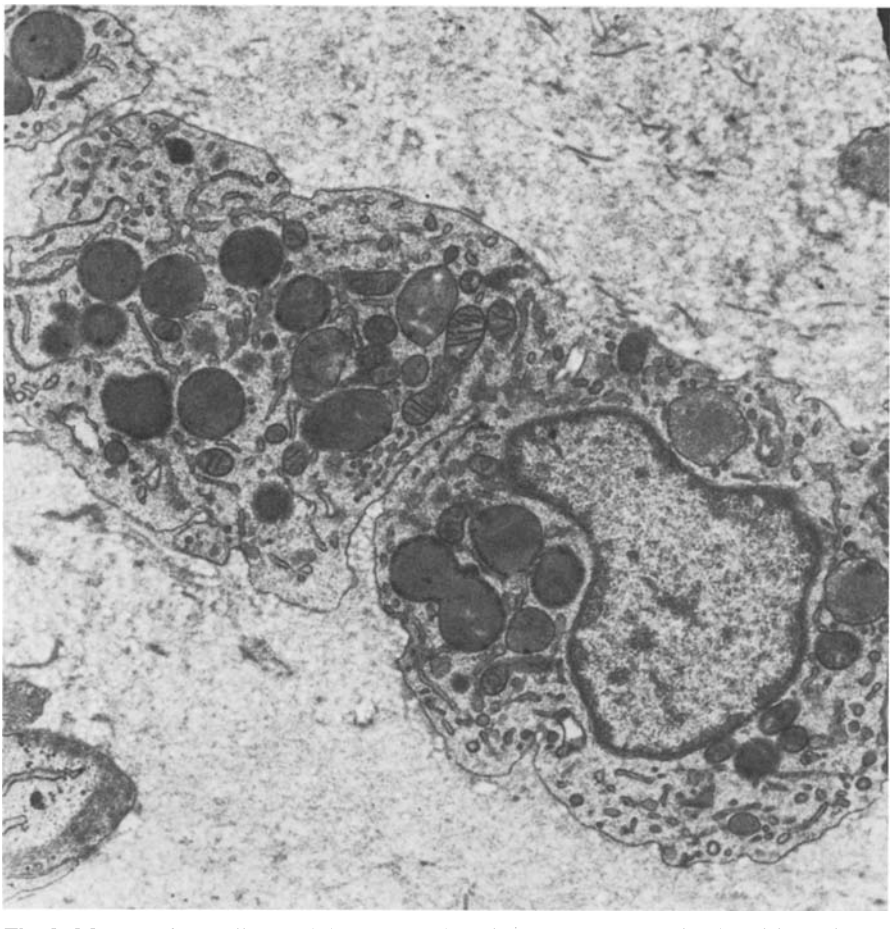

Fig. 8. Mononuclear cell containing many phagolysosomes, some mitochondria and sporadically rough endoplasmatic reticulum (× 14600, 28 d)

membrane, and they also were rich in rough endoplasmic reticulum (Fig. 9a).
After 84 days, cells corresponding to smooth muscle cells appeared (Fig. 9b). Basement membrane material was present on the cell surface. The matrix surrounding these cells was rich in collagen fibers.

In numerous SEM specimens we could not, at any time, detect thrombus on the AVCOTHANE surface (Fig. 11) nor was there a creeping-out of cells from the adjacent aortic segments into the AVCOTHANE. The DACRON ring was covered by at least some thrombotic material at all time periods.

Discussion

Considering all these experiments it seems justified to postulate that reparative processes within thrombosis can occur by two separate mechanisms:

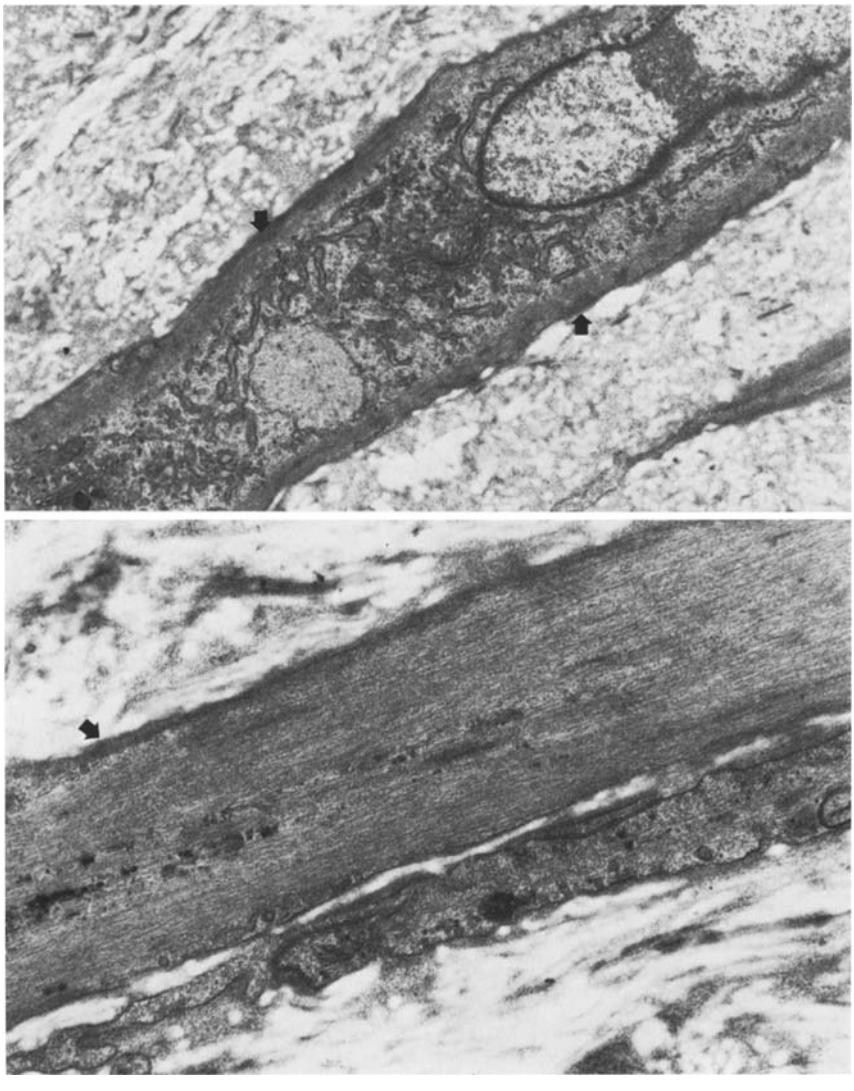

Fig. 9. a Myofibroblastic cell with myofilaments showing focal densities near the cytoplasmic membrane (*arrows*) in addition **b** Smooth muscle cell containing a lot of myofilaments and glycogen granules. On the cell surface basement membrane like material is recognized (*arrow*) (× 27000, 84 d)

1. Organisation through ingrowth of granulation tissue
2. Self-organisation through cells of the circulating blood.

Organization by cells of the surrounding vessel wall (cells of local origin) can be detected by the ingrowth of capillaries. This type of organisation was demonstrated by Virchow's (1871) investigations of the healing process and later confirmed by Marchand (1901) and Aschoff (1924). Their evidence received further support from autoradiographic investigations in parabiotic

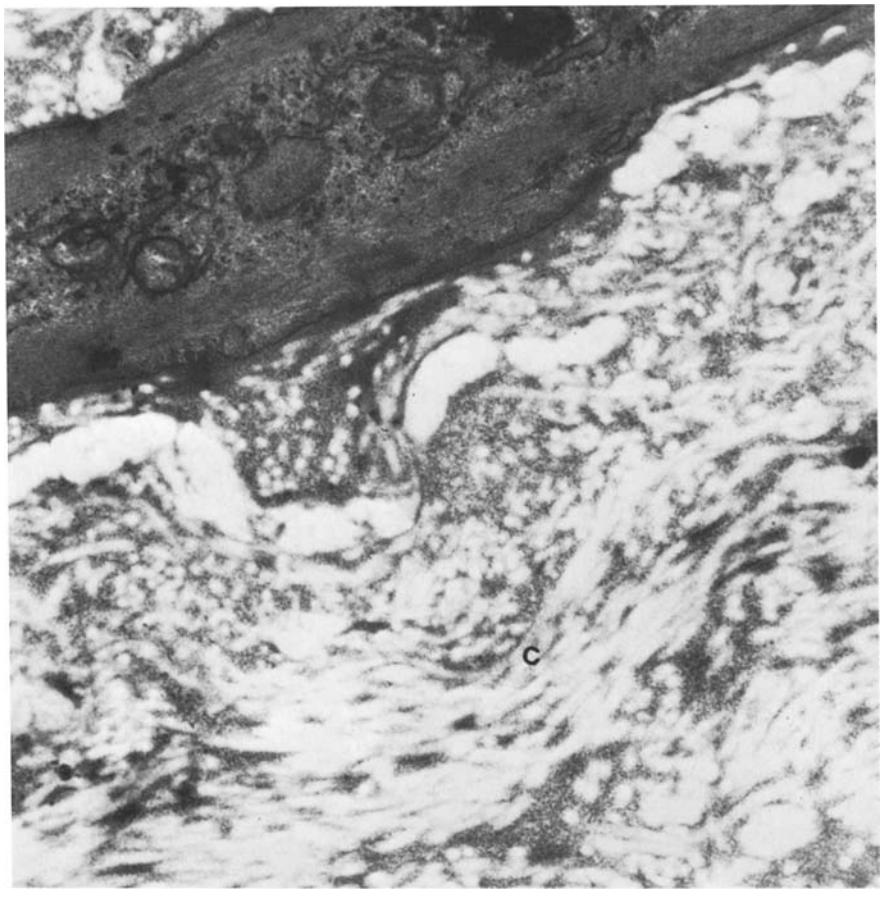

Fig. 10. In the neighbourhood of smooth muscle cells collagen material (*C*) with fibres showing a wavy appereance are observed (× 27000, 28 d)

"inbred" rats by Ross et al. (1970), which indicated that the fibroblasts of healing wounds were of local origin and did not develop from haematogenic monocytic cells. In contrast, there also is past experimental evidence that a thrombus is capable of self-organisation, namely, that some cells of the thrombus can transform into tissue cells. These latter observations support the opinion of Cohnheim (1867), Metchnikoff (1892) and Maximow (1902), that leucocytes within an inflammatory area might transform into fibroblasts. Experimental data on this topic for blood vessels began to be published from the early sixties on (Halpert et al. 1960; Hülliger and Allgöwer 1961; Ghani and Tibbs 1962; Stampfl 1962; Stump et al. 1963; O'Neal et al. 1964; Still et al. 1967; Stirling and Tsapogas 1969; Helpap and Cremer 1972; Leu 1973; Krupp 1976).

In vivo it is difficult to separate these two mechanisms, which proceed simultaneously. Following investigations of an artificial ventricle (Feigl

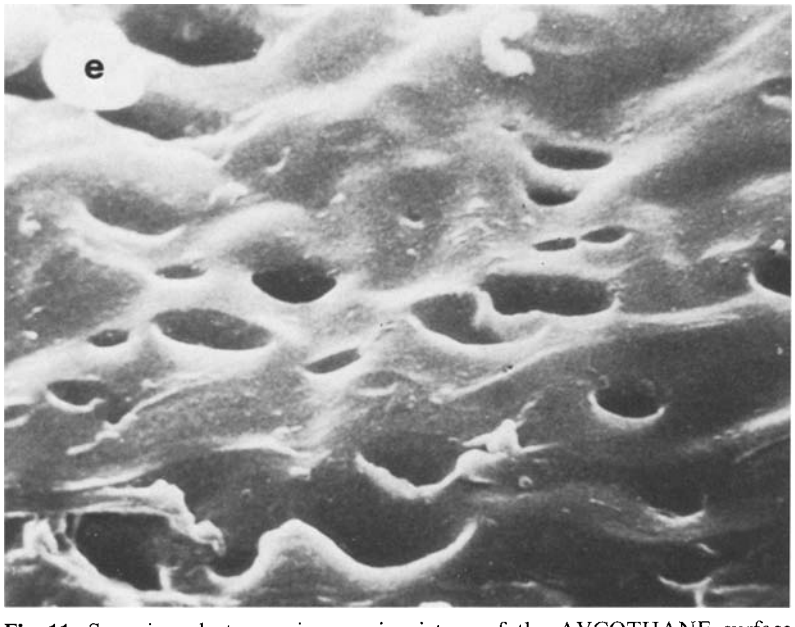

Fig. 11. Scanning electron microscopic picture of the AVCOTHANE surface. Thrombosis is absent, Erythrocyte (*e*) (× 2500, 84 d)

1976) we developed the present experimental model which allowed us to observe self-organisation of the thrombus by cells of the blood stream.

Over a period of 2 to 84 days we observed cellular processes which we could separate into 3 stages:

1. Activation of the mononuclear macrophage system
2. Emergence of myofibroblasts
3. Formation of an endothelium.

It has to be emphasized that the first process seems to be necessary for the second one, while the third step takes place independently.

1. Activation of the mononuclear macrophage system

The area close to the lumen consisting of loose material is the area at which thrombus organisation starts and continues. After 2 days, blood cells in the thrombus were still in the same relative proportions as in the circulating blood. After 7 days there was a relative increase of monocytic cells and a relative decrease of PMNs. Light microscopy showed fine granular eosinophilic material which, investigated by electron microscopy, was a platelet thrombus consisting of activated thrombocytes with abundant pseudopodia. Thrombocytes were in close contact to monocytic cells, and fibrin fibers were in between. The remarkable piling up of monocytic cells suggests a chemotactic mechanism.

Chemotactic proteins could be considered to be metabolic products of fibrinogen and fibrin (Hausmann 1972), fibronectin (Hynes 1982) or the

complementory factors C5 and C3 (Hammerschmidt 1978). Some platelet specific proteins such as the chemospecific factor (Weksler 1971) and the "human platelet derived growth factor" (Antoniades 1983) also show chemotactic reactions. Most of these substances also have a strong chemotactic effect on PMNs. Thus the accumulation of predominantly mononuclear cells in the loose inner layer is not adequately explained by chemotaxis only. It is also possible that the monocytes accumulate because of their capacity to adhere to surfaces. Therefore it should be considered that newly formed platelets and fibrin aggregates are possibly covered by adhesive monocytes. Maturation and protein synthesis of monocytes (Musson 1983) is stimulated by serum components. The "colony stimulating factor" (Tushinski and Stanley 1983) and the "platelet activating factor" (Hartung et al. 1983) also influence protein synthesis.

The giant cells which we observed in our grafts seem to be a foreign body reaction (White et al. 1979) against the DACRON fibrils.

Further morphological changes develop in animals of 7 and 10 days of age: the kidney shaped nucleus of mononuclear cells shows indentations (dumb-bell like) and elongation (reminiscent of fibroblasts). Other mononuclear cells have a nucleolus and their cytoplasm contains phagocytized amorphus material characteristic of cells of the mononuclear macrophage system. The transformation of monocytes into cells of the mononuclear macrophage system is generally accepted (van Furth 1982). Even granuloma formation is observed (for review see Spector 1980). The transformation is of importance in the genesis of arteriosclerosis (Gerrity 1981; 1981a; Stary 1983; Vos et al. 1983).

2. Emergence of myofibroblasts

In older thrombi, mononuclear cells found in the well oxygenated area near the blood stream were progressively transformed. Beside macrophages there were clusters of cells showing mitosis (Fig. 3c). In these proliferating areas an increasing number of spindle-cells appeared with increasing age of the thrombus. They had characteristics of both fibroblasts (rough endoplasmatic reticulum) and smooth muscle cells (myofilaments, pinocytotic vesicles and basement membrane). The cells resembled those described by Gabbiani as myofibroblasts (1971). We saw collagen embedded in organized fibrin in the vicinity of these cells.

Earlier evidence that cells of the blood can transform into fibroblasts has been disputed (Jurkowa and Knieriem 1970, Poole et al. 1971, Ross and Glomset 1973). This type of organisation may be important only in the area of the thrombus close to the lumen. It seems to be less important in arteriosclerosis and in vessel formation (Glagov and Ts'ao 1976, Gebrane et al. 1983).

3. Formation of endothelium

After 2 days the surface of a thrombus was formed of a thin, sharply bordered fibrin strip. The initial appearance of endothelium-like cells was

in a 10 day old thrombus. The number of elongated and endothelium-like cells was greater in older thrombi. These surface cells initially showed no connection among each other. Later, a single layer of connecting surface cells had developed.

Stump et al. (1963) were the first to consider these endothelial cells to be derived from blood borne cells. Morphological details of re-endothelialisation had already been described in the experiments of Stampfl (1962). Freudenberg and Riese (1976) demonstrated that in damaged endothelium the surrounding surviving endothelial cells did not show increased DNA synthesis. The lack of cell proliferation indicated that the reconstruction of the endothelium was not by endothelial cells from the neighbourhood. In our experiment, endothelium formation on thrombi did not depend on the stage of organisation of the underlying thrombus material. We observed endothelial cell layers in areas of the thrombus in which evidence of organisation was lacking (10 days).

The end product in our experimental set up was a pseudovessel wall with smooth muscle cells and a considerable amount of collagen. Typical elastin was not demonstrable. There was no evidence of clefts with an endothelial lining in the organising thrombi as described by some previous authors (Still et al. 1967) and which were found in our left ventricular bypass after 165 days (Sinzinger and Feigl, unpublished data). Furthermore, capillary formation (Stirling and Tsapogas 1969) was absent during the period of our investigations.

Source of the cells

Our principal aim was to study whether or not thrombotic material is capable of self organisation. Our results indicate that the embedded cells participate in the construction of a pseudovessel wall. Perhaps descriptive morphological findings alone cannot be considered as proof that myofibroblasts and smooth muscle cells derive from a monocyte-macrophage cell line. But there is other supportive evidence.

Blood monocytes do not represent a homogenous cell population (Kaplan and Gaudernack 1982, Franklin et al. 1982, van Vourhis et al. 1983), and retrodifferentiation processes of the mature cell (Uriel 1979) can take place. Beyond this, some authors postulate the presence of circulating, multipotent, mononuclear blood cells (Leu 1973). Circulating blood stem cells, although rare, were found by Fliedner (1978).

Endothelial cells, fibroblasts, and smooth muscle cells (Weber et al. 1979, Takahashi and Harker 1983) could possibly be brought into the circulation by surgical trauma, but in our earliest specimens of organizing thrombi we could not detect any evidence of such cells by electron microscopy.

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Accepted January 29, 1985