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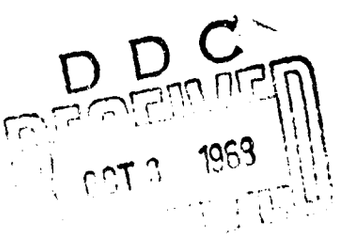

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ULTRASTRUCTURE OF CAPILLARIES IN CHRONIC INFLAMMATION

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The capillaries of the granulation tissue differ functionally and according to studies with the light-optical microscope in form as well from normal capillary vessels. In the submicroscopic order of magnitude further differences in the orthological structure are to be expected. For that reason we have analyzed more precisely a classical model of inflammation, the turpentine granuloma. Upon comparison with some reports that have been published by other investigators in the meantime, our findings show not only correspondences, but also differences in details. We bring this fact into relationship with the different etiology of the tissue modifications and structural transformation in the course of an inflammation.

Material and Method

As an extension of our previous studies of the capillaries of the skeletal muscles, an inflammation was to be generated in a cross-striated musculature. To judge by numerous preliminary investigations, the musculature of the abdominal walls of albino rats weighing 90 to 240 g is especially well suited for the performance of our experiments. But because an intramuscular injection in the region of the abdominal walls is difficult, we laid open the muscle fascia under ether or calypnon narcosis and inserted the cannula of the injection syringe subfascially. By raising the skin the position of the cannula could be checked even outside the area of the incision. After fairly deep penetration an intramuscular deposit of 1 ml (or in exceptional cases 0.5 or 0.7 ml) of oil of turpentine was injected. The abdominal wound was then sewed up. In a few other cases smaller doses (0.1-0.2 ml) were injected subcutaneously. Two hours to 21 days later we took tissue from 22 animals under ether or hexobarbital narcosis or after decapitation for examination under the electron microscope. We devoted particular

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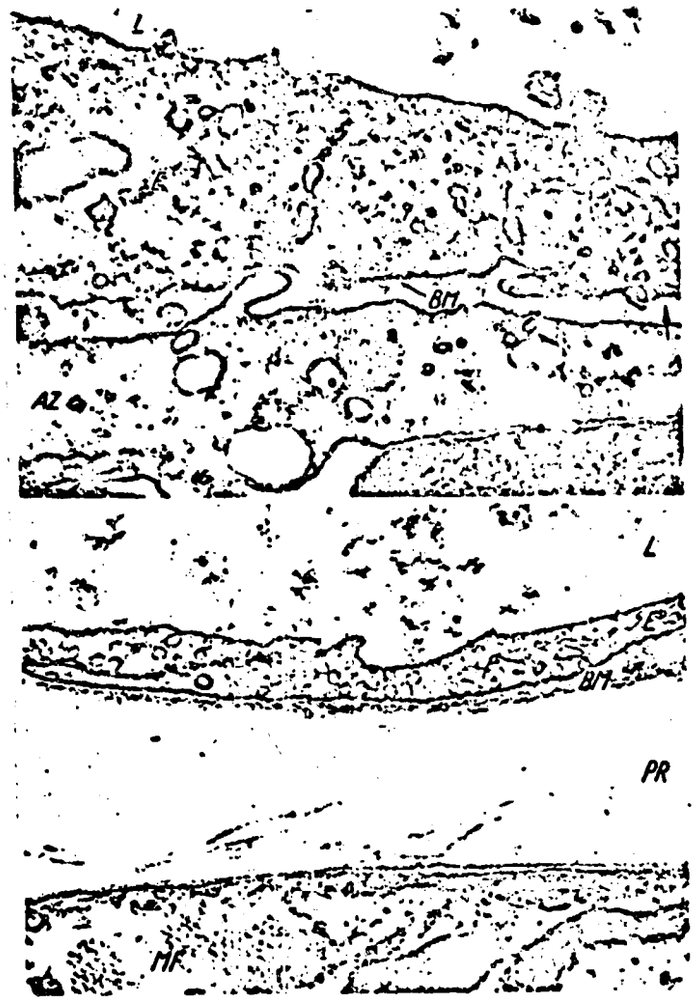

Figure 1. Comparison between a capillary vessel from chronic inflammation (above) and a normal skeletal muscle capillary (below). The basement membrane (BM) is lacking at a circumscribed place (arrow). AZ - adventitial cell, E - endothelium, L - capillary lumen, MF - muscle fiber, PR - pericapillary space. No. 1192/63 and 2138/62. 35,500 times and 36,400 times respectively.

tus is uncommonly strongly developed. The karyoplasm may be swollen and the perinuclear cisternae enlarged.

It is not only the organella of the cell that show differences from the ortholo;ical behavior of the blood capillaries; the basic plasma is much changed in various ways (Figure 3), becoming sometimes lighter, sometimes denser. In the former case the cell may be almost empty electron optically. All that is then discernible is a little osmiophilic material along with bubbles, vesicles, and granules. In contrast to this, the cell may seem much too dark because of homogeneous

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Figure 2. Osmiophilic particles intracapillarily and extracapillarily situated (arrow). The surface of the endothelium cell (E) shows extensions, some of them transversely cut. Leucocyte (Lc), Capillary lumen L. No. 1193/63, 25,560 times.

fine-grained or fine-fibered densification of the basic substance (see illustration in Fuchs, 1964). In the extreme case there is a homogeneous osmiophilic annular structure containing light bubbles and vesicles, and still showing blood cells in its interior. We consider such cells coagulation-necrotic.

Another change concerns the cell boundaries. Here the endothelia for long distances only lie loosely beside each other. At other points there are gaps in the endothelial cell bond. Big, bloatedly swollen endothelial cell segments may fill such gaps. They sometimes contain many small parts of endothelium cells, isolated from each other in the process of microtoming. Surely these formations are in part sections of the villously extended lateral walls of the endothelium cells. Such a formation is rarely photographed in its entire longitudinal extent. The same picture must arise through multiple breaks in continuity in the endothelium cell bond, whether in this way or another.

The subendothelial basement membrane is extraordinarily thin at many points. It may in places be entirely missing (Figure 1), but is usually maintained, at least locally, in

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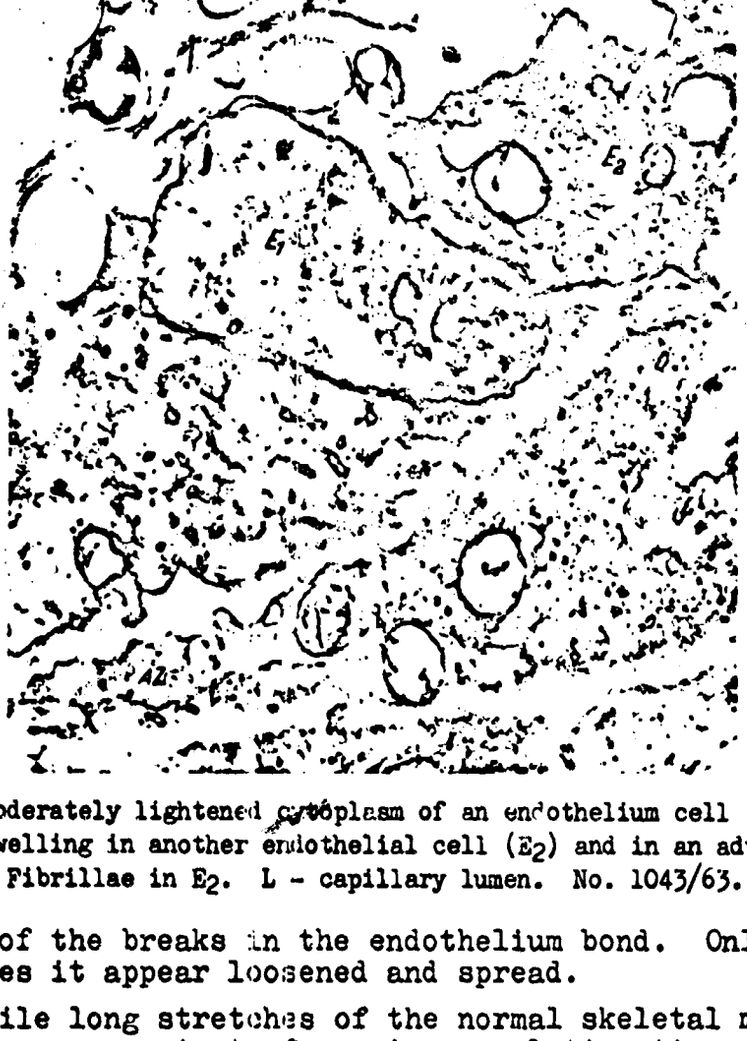

Figure 3. Moderately lightened cytoplasm of an endothelium cell (E_1). Mitochondrial swelling in another endothelial cell (E_2) and in an adventitial cell (AZ). Fibrillae in E_2. L - capillary lumen. No. 1043/63. 25600 times.

the area of the breaks in the endothelium bond. Only very rarely does it appear loosened and spread.

While long stretches of the normal skeletal muscle capillaries are pericyte-free, in granulation tissue a heavy cellular adventitia is usually developed (Figures 1,2). In these cells there are not only edematous swellings, which occur independent of simultaneous endothelial changes; these pericapillary cells can also exhibit plainly developed ergastoplasm and abundant RNPr granules. We consider a transformation of these cells and their subsequent mobilization entirely probable, especially as the cell bodies at their end can move far from the capillary wall. Locally these cells may show a marginal deposit of basement-membranelike substances.

Discussion

Inflammational tissue damage can quite generally lead to a reaction of the small blood vessels on the spot or condition the new formation of capillaries. A part of them are

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Figure 4. Schematic representation of some findings (left, normal capillary wall; right, capillary vessel from granulation tissue).

rebuilt at later stages into larger vessels, but can also be completely re-formed (Policard and Collet 1958, Schlipköter and Linder 1961).

That the cause of the inflammation and its course in a given case shape and modify the phenomena must be concluded from the variation in details of the modification of the pre-existent blood vessels. Thus in the rat colon inflamed after administration of oil of mustard (Florey 1961), in the rat skin after intracutaneous injection of sterile homologous serum (Hurley and Zeros 1961), and in the rat mesenterium after mechanical irritation (Marchesi and Florey 1960, Marchesi 1961) they are unchanged, while in the originally aseptic exudative pulmonary inflammation in experimental silicosis research (Policard, Collet, Prégermain, and Reuet 1957) capillary enlargement and cell concentration are observed (Policard, Collet, Giltaire-Ralyte, Reuet, and Desfosset 1955). Blood vessels of the rabbit ear after ultraviolet radiation show not only emigrating blood cells, but also vacuole formations of the epithelial cells (Florey and Grant 1961). These modifications are also found in our fixed muscle capillaries and in lung capillaries two days after intratracheal administration of silicon (Policard, Collet, Prégermain 1957), and in acute pancreatitis of the dog they are 1 µm in size (Williamson and Grisham 1961). These authors also observed long cell processes of the endothelia extending into the lumen, which isolate the emigrating blood cells in the later stages. Cell swellings are found in small blood vessels of the lymph nodule in hog cholera (Schulze 1963). In experimental kidney tuberculosis of the rat the basement membrane and sometimes the endothelial cells are changed (Policard, Collet, Noufflard, Prégermain 1960). During acute glomerulonephritis of man the endothelial cells are multiplied and swollen, the capillary lumina contracted, the basement membranes generally thickened and modified by the deposit of fine granular material (Farquhar, Vernier, Good 1957; Huhn, Steiner, and Movat 1962, etc.). Lastly, gaps in the covering of the endothelium may occur independent of the escape of blood cells (Movat 1962, Pappas and Tennyson 1962, Movat and Fernando 1963) and necroses may be observed (Kisch 1960). This brief enumeration of

some findings shows in what varied ways local capillaries and veinules can react to inflammatory stimuli. Admittedly, common characteristics are unrecognizable in many cases.

In our experimental arrangement new blood vessels develop, since oil of turpentine starts up a chronic inflammation. It is bactericidal, so that it prevents a mixed infection and works as a cytoplasm poison (Meier 1959) which first causes a tissue necrosis. Abundant inflammation cells do not appear until after 17 hours. A granulating inflammation is well developed after three days. Bardenheuer (1891) observed processes of new formation of blood capillaries even at this period in subcutaneous oil of turpentine granulomata of the rabbit. After a week there is a broad band of granulation tissue. Cicatrization of the field of inflammation is far advanced after a month.

Among individual phenomena attention should first be called to the thickening of the capillary endothelium observable over long stretches, found by Schoefl (1963) locally side by side with thin portions in healing muscle wounds, by Steiner, Carruthers, and Kalifat (1962) occasionally in endothelial cells of blood capillaries and Kuppfer's cells of the sinusoid in granulation tissue development in the rat liver after extrahepatic cholestasis, by Löblich and Arambašić (1961) evidently regularly in young paraffin granuloma of the rat pleura, and also by Cliff (1963) in the Sandison auricular capsule of the rabbit ear. This hypertrophy of the endothelial cells, in some cases quite pronounced, appears to be a peculiarity of many but by no means all young, growing capillaries. Löblich et al. (1961) also observed in the capillaries of chronic inflammation six weeks after beginning of the experiment a definite flattening of endothelial cells which two weeks before had been strong. The thickness of the wall covering, if we disregard the processes of growth, is also influenced by the width of the lumen, i.e. by the dilatation or relaxation of the vessels.

In our experiments and those of Schoefl (1963) the number of the small vesicles which serve for pinocytosis, but in endothelial cells principally for cytopempsis, is sometimes considerably reduced, as occurs with relatively undifferentiated cells (Pallade 1958). When nevertheless the exchange situation at the capillary wall is favorable, the continuing possibility of permeation, of direct passage of cell membrane and basic plasma in other words, should be mentioned, apart from the escape of material through the space between neighboring cells; the formation of gaps in the endothelial bond and the slighter development of the basement membrane should also be pointed out. This discontinuous arrangement of the endothelium is encountered not only in connection with escaping blood cells, but also independent of them. It occurs in inflammation, as mentioned briefly above, even in blood capillaries which remain

in place, and can be induced by the effect of histamine and serotonin (Majno and Palade 1961). Whether all these points of separation in the endothelium bond lie in the region of the cell boundaries alone we cannot state with certainty. Like Schoefl (1963), we have seen gaps near the tip of capillary branches.

In our experiments, as in intraperitoneal kieselguhr granuloma (Löblich 1961), the basement membrane is defectively developed. Schoefl (1963) speaks of a relatively incomplete basement membrane in newly formed vessels. Only on older capillaries is it better developed. Löblich and Arambašić found no basement membrane in the four-weeks stage of their experiment, but found a slight ground membrane at six weeks and a definite one in eight to ten weeks. Steiner, Carruthers, and Kalifat (1962) miss a basement membrane at the point where the capillary changes into a sinusoid. Gersh and Catchpole (1949) observe that the basement membrane disappears in inflammation and is not formed anew until later.

The heavy development of the ergastoplasm and of Palade's granules points to an intensive protein synthesis, which serves the needs of capillary growth and perhaps the demands of granulation tissue as well. Similar observations have been reported by Gusek (1962,1964), Cliff (1963), Schoefl (1963), as well as Steiner, Carruthers, and Kalifat (1962) on Kupffer's cells and Palade and Porter (1954) on fetal endothelium in tissue culture. On the other hand Löblich and Arambašić (1961) found only scantily developed ergastoplasm in small blood vessels of paraffin granuloma. By simple light microscopy Ernst (1926) found and described in the earlier stages of turpentine granuloma of the rat "the picture of pronounced swelling and basophilia of the endothelia and the existence of a definite basophilic endothelial membrane." This basophilia is to be attributed to the formation of ribonucleic acid, and is thus a sign of synthetic cell activity and not a manifestation of inflammational acidification (Ehrich 1956).

Besides edematous swelling of the cells, thickening of the basic plasma also occurs; this was observed by Steiner, Carruthers, and Kalifat (1962) in endothelial cells and interpreted as a disturbance of the hydration. Perhaps the hyaloplasm is also composed of different substances. Such very dark cells are in fact found in the electron microscopic image not only among endothelial cells; they are to be found under certain conditions in the canaliculi of Tiedemann's bodies in the starfish (Bergmann and Behrens 1964) and in the epithelia of the bile duct and liver (Steiner, Carruthers, and Kalifat 1962, David and Bartók 1963) and elsewhere.

With regard to the transmutability and the reaction forms of the adventitial cells we refer the reader to the older

studies with the light optical microscope (for bibliography see Herzog 1916) and the newer ones with the electron microscope (Amano 1958, von Albertini 1959, Gusek 1962, Gonatas et al. 1963, etc.). We have Gusek to thank for a handy summary of the possible transformations (1962). That adventitial cells are derived from fibroblasts is especially emphasized by Cliff (1963). According to Marchand (1924; additional bibliography is given there) they arise from endothelial cells through lateral fission.

A comparison of the various examples reveals both similar phenomena and differences in the capillary reaction, which we have discussed in some detail. Other lesser differences concern the frequency of cytoplasmatic fibrillae and of multivesicular bodies, the degree of cytoplasmatic edema of the endothelia, and the formation of Golgi apparatus and basic projections of the endothelia, which of course are also found orthologically (Fuchs 1953). In our model case the newly formed capillaries are certainly subject to toxic influences on the part of the oil of turpentine. The damage to many mitochondria and the cell swelling which can be generated by inhibition of glycolysis (according to Woodin 1963) might be explained in this way. In any case there is a whole gamut of modes of reaction of newly formed blood vessels, which finds a parallel in the above-described varying behavior of the more permanent blood vessels.

Summary

The newly formed blood capillaries of turpentine granuloma of the rat show both thin-walled segments and especially thick capillary endothelium, which contains relatively few small vesicles; the formation of gaps in the endothelium and a locally weakly developed basement membrane may favor the exchange function. The heavy development of the ergastoplasm and of Palade's granules points to an intensive albumin synthesis, which serves the needs of capillary growth and perhaps other requirements of the granulation tissue. Side by side with edematous swellings of the cells, inspissations of the basic plasma occur. The adventitial cell sheath is powerfully developed. The oil of turpentine obviously injures not only the original but also the newly formed blood capillaries.

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