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Microvasculature of Human Colorectal Epithelial Tumors

An Electron Microscopic Study

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Summary. The ultrastructure of the microvasculature in human colorectal adenomas and carcinomas was studied, and compared with that of normal tissue. Blood vessels in adenomas were generally of normal structure, whereas carcinoma vessels displayed a variety of structural alterations. Endothelial proliferation was frequently observed in all the eleven carcinomas examined, which confirms the reports of new vessel formation in experimental malignant tumors. The presence of fenestrations in obviously abnormal endothelium was tentatively attributed to hypoxia, vascular regression or immaturity of the cells, in spite of the fact that normal capillaries in colonic mucosa are fenestrated. Some vessels showed multilayered basement membranes, various types of activated cells containing numerous lysosomal granules, and thickened perivascular tissue. These features may be a vascular response to repeated damage or a manifestation of vascular remodelling. Dilated thin-walled vessels, which were usually found at the periphery of carcinomas, were identified as venules. Small vessels located between the closely apposed carcinoma tubules were not obviously abnormal. They were nevertheless considered to be tumor-induced vessels which had undergone differentiation. The differences in vascular morphology between adenomas and carcinomas were considered to be due to their different growth patterns, growth rates and degrees of maturity.

Key words: Colonic neoplasm – Microcirculation – Ultrastructure – Pathology

Numerous studies have been performed on the morphology of tumor blood vessels. Injections, angioradiography and transparent chamber techniques

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have been used to study the growth pattern and the architecture of tumor vessels (Warren 1979a). More recently, microangiography (Eddy 1976) and resin casts combined with scanning electron microscopy (Egawa 1979) have allowed the investigation of very small details of the microvasculature. These studies have shown that tumors have a characteristic vascular architecture, which is probably determined by the growth pattern of the tumor cells (Warren 1979a). Dilated, convoluted, or tapering vessels are common in malignant tumors (Egawa 1979).

Information concerning the ultrastructure of tumor blood vessels has been obtained mostly from experimental studies of tumor angiogenesis (Warren 1970; Cavallo et al. 1973; Papadimitriou and Woods 1975). It is well recognized that tumor cells are able to induce new vessel formation via a tumor angiogenesis factor (Folkman et al. 1971; Kumar 1980). The morphogenesis and the ultrastructure of tumor-induced capillary sprouts have been described (Ausprunk and Folkman 1977), and are reminiscent of the neovascularization of inflammation or wound healing (Schoefl 1963). Although the initial development of tumor vessels is relatively well documented, little is known about the subsequent growth, differentiation and remodelling of these vessels in a well-established tumor.

It is important to stress two points concerning tumor microvasculature. Firstly, the fine structure of the microvasculature varies according to the functions or metabolic requirements of the tissues which it supplies (Wolff 1977; Majno and Joris 1978). Secondly, tumors are heterogeneous in many respects including the organization of their vascular system (Warren 1979a). Experimental tumors, which are usually poorly differentiated and have a rapid growth rate, are not ideal models of spontaneous long-lived human tumors.

With regard to human tumors, the abnormal vessels in brain tumors have been extensively studied (Long 1970; Hirano and Matsui 1975), but there are only a few brief reports describing vessels in tumors of other organs, e.g. breast (Ozzello 1971), peripheral nervous system (Hirano et al. 1972a), pituitary gland (Hirano et al. 1972b), kidney (Warren 1979a), and thyroid (Ludatscher et al. 1979). It is therefore of interest to expand our knowledge of the morphology of vessels in different human tumors as well as in experimental models. Since no published information is available on the ultrastructure of blood vessels of human colorectal epithelial tumors, the present study was undertaken to compare benign and malignant tumor vessels with those of normal mucosa.

Material and Methods

Origins of Material

1) Eleven colon carcinomas were examined. Ten were removed by colectomy and 1 polypoid carcinoma was obtained by sigmoidoscopy. One of the carcinomas was mucinous, the others were well or moderately differentiated adenocarcinomas, although some of these exhibited mucinous or poorly differentiated areas. Most of the cases were of Dukes A or B stage; there were three Dukes C carcinomas, one of them with vein invasion.

2) Seven colonic or rectal adenomas were excised by endoscopy. Among these, 5 were tubular adenomas and 2 were tubulo-villous adenomas. All were devoid of cellular atypia.

3) Normal tissue controls were represented by 6 fragments of colon mucosa, 3 of which were obtained by endoscopy near the base of pedunculated tubular adenomas, the other 3 were from colons resected for carcinoma, at a distance of more than 7 cm from the tumors. All 6 samples appeared histologically to be within normal limits.

Sampling and Preparation

The tumor and control material was obtained in the operating room at the time of endoscopy or surgery. Tumor tissues were selected from the peripheral, non-ulcerated regions of the carcinomas or the head part of the adenomas at various depths. They were immediately cut into small (1 mm^3) blocks, fixed in cold 2.5% glutaraldehyde buffered with 0.1 M sodium cacodylate (pH 7.4), then post-fixed in 2% osmium tetroxide buffered as above and embedded in Epon, using standard techniques.

Prior to thin sectioning, 1 μm sections were screened on the light microscope. In order to obtain representative samples, 3–6 blocks from each tumor were selected, taking into account the various tumor zones, and the histological patterns of tumor parenchyma and stroma. Carcinoma structures in the vicinity of residual normal tissue (such as non-tumoral glands or smooth muscle) were considered to belong to the infiltrating edge. Furthermore, the periphery of tumor lobules was also assumed to form part of the advancing edge. Areas with closely arranged carcinomatous tubules or trabecula and narrow interposed stroma were interpreted as intralobular (i.e. intratumoral). Nevertheless, the location in the tumor of many of the blocks could not be ascertained. All the tissue samples were devoid of heavy infiltration by granulocytes. As for the adenomas, both tubular and villous areas were chosen, either near to the free surface or close to the muscularis mucosa. Thirteen blocks from the control mucosa were selected to represent the different segments of the blood vessels in the lamina propria and muscularis mucosae. Vessels which could be identified by light microscopy as being small arteries or veins were excluded, and thus only the microvasculature was examined with the electron microscope. Grids were scanned systematically, and every recognizable blood vessel was photographed. In some cases, microphotographs were taken on serial sections.

Results

Tissue Preservation

Careful comparison was made between the colon mucosa of resection specimens and that of biopsy ones, in order to identify any artifacts which might have been caused by prolonged hypoxia, mechanical trauma or other unknown factors during surgical intervention. The fine structure of the vessels in colon mucosa obtained surgically was unexpectedly well preserved. The most common types of damage were the formation of extra- or intra-cellular myelin figures and the swelling of mitochondria. The smooth endoplasmic reticulum sometimes also showed some degree of swelling, but whole cell oedema was not frequent. In the most seriously injured cells, part of the cell membrane had disintegrated. Occasionally, a cell with darkened cytoplasm, of the type that has been described as "mummified" (Majno 1965), was interposed between 2 endothelial cells of normal appearance. Fenestrations existed as long as the plasma membrane remained intact, and a few gaps with isolated erythrocyte diapedesis were seen. The basement membrane sometimes appeared blurred, but was never disrupted or absent. Pericytes and smooth muscle cells showed the same types of damage as endothelial cells, but usually to a lesser extent. The degree of damage varied from vessel to vessel, and even from cell to cell within the same vessel. In comparison with the controls, the alterations summarized above were considered to be possible artifacts, and hence will not be included in the following description of vascular abnormalities. However, it should be noted that these possible artifacts were more frequent and conspicious in carcinomas than in normal mucosa taken from resections. Only on rare occasions were

endothelial swelling and gaps found in the vessels walls of adenomas or colon mucosa obtained by endoscopy.

Control Colon Mucosa

The ultrastructure of the microvasculature in our control mucosa (Fig. 1) was similar to that reported in the literature (Florey 1961; Majno 1965; Kaye et al. 1971). The thin and elongated endothelial cells contained few organelles, although pinocytic vesicles were numerous. Weibel-Palade bodies (Weibel and Palade 1964) were rare in capillary endothelial cells, but more often seen in those of venules. In the attenuated part of the capillary endothelium, fenestrations appeared frequently in groups, although some capillaries had no fenestrations in a given section. Neighboring endothelial cells overlapped slightly, and the junctions were partly sealed. Endothelial basement membranes were well defined. Flat pericytes lying close to the endothelial cells were wrapped in the same basement membrane. Fine filaments were common in pericytes, and a few small dense bands along the cytoplasmic side of the cell membrane were characteristic. The perivascular adventitia, which was presumably limited by intermittent thin fibroblasts (veil cells), was narrow and free of cellular infiltration.

Colorectal Adenomas

The fine structure of the small blood vessels in colorectal adenomas was in general similar to that in the control mucosa. However, a few endothelial cells and pericytes had an enlarged perinuclear zone with more numerous cell organelles (Fig. 2), but no capillary sprouts were observed. Some small vessels were mildly dilated and congested with erythrocytes, and occasionally, extravasation of erythrocytes was observed. Perivascular collagen fibers were often more numerous than in the control mucosa.

Colon Carcinomas

The morphology of the small blood vessels in colon carcinomas ranged from normal to markedly altered and virtually unrecognizable at lower magnifications. The vascular abnormalities were present in all the eleven cases and in a relatively large proportion of the vessels under observation. Although they varied both qualitatively and quantitatively, some features emerged, which made it possible to group the tumor vessels according to five main patterns, in order to facilitate their description. Nevertheless, some vessels showed overlap between different patterns.

Type 1. Many capillaries and small venules in the carcinomas were not markedly altered, nevertheless some slight deviations from normal were often observed. For instance, the endothelial cells were less attenuated and fenestrations were less frequently seen. The basement membrane was occasionally multilayered (Fig. 3) and the perivascular fibrous tissue was sometimes more pronounced. This type of vessel was frequently located in the

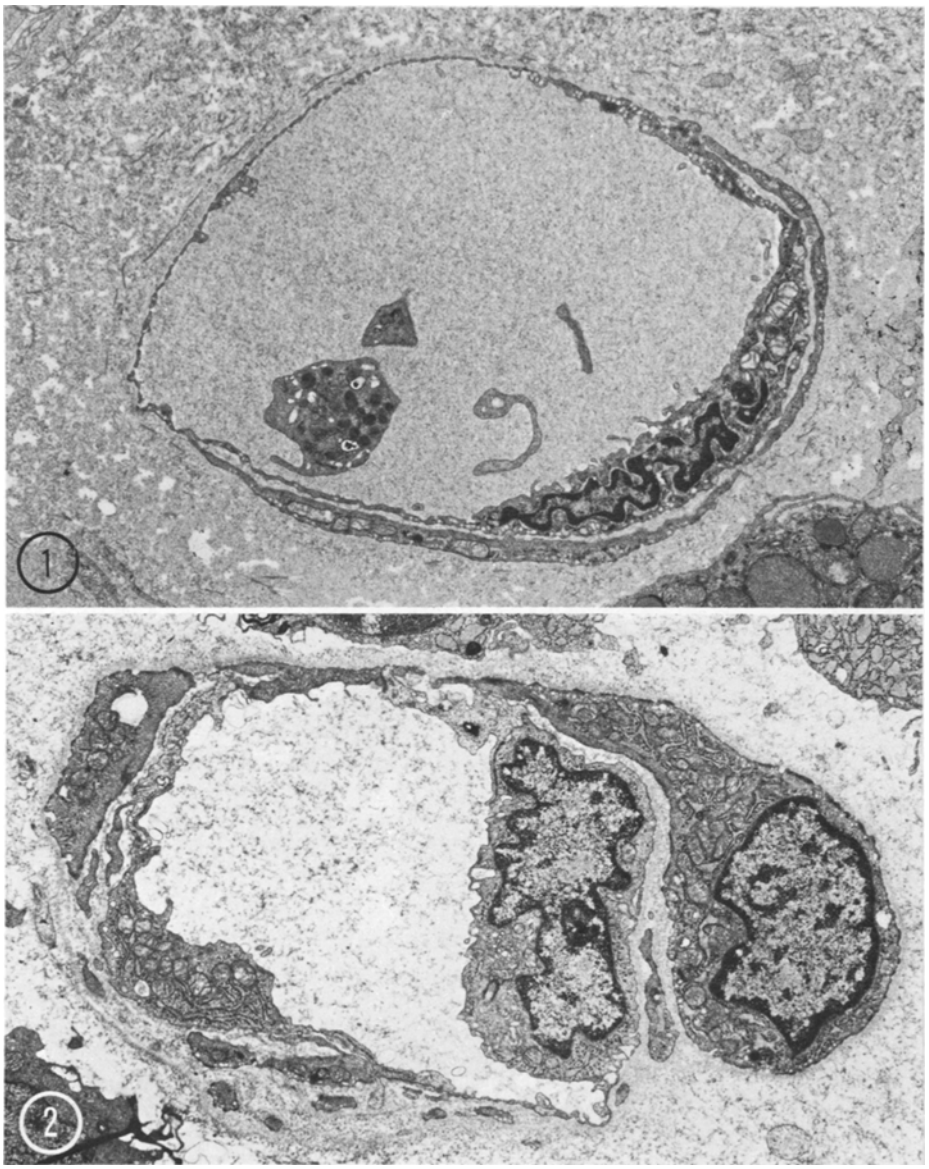

Fig. 1. Fenestrated capillary of normal colon mucosa. × 7,400

Fig. 2. Small blood vessel in adenoma. Endothelial cell and pericytes contain increased numbers of cell organelles. Perivascular tissue is slightly thickened. × 6,400

narrow stroma between the relatively well differentiated carcinomatous tubules, and was present in every carcinoma.

Type 2. The vessels in this group (Figs. 4–8) were characterized by their rounded endothelial cells and narrow, slit-like lumens, which on transverse

section were sometimes enclosed by only two endothelial cells (Fig. 4). Occasionally, some parts of the endothelial cells were flattened, but showed virtually no fenestrations. The nuclei were large and nucleoli were common. Cell organelles were more numerous and, in particular, free ribosomes and rough endoplasmic reticulum which showed dilated cisternae. A few Weibel-Palade bodies were frequently observed in the perinuclear area (Figs. 4–6). They tended to be shorter than those in normal venular endothelial cells, and the intertubular substance was less dense. Intercellular junctions were often quite long and convoluted, and equipped with several tight junctions which alternated with gaps (Fig. 6), but some junctions were unusually short and perpendicular to the endothelial basement membrane without overlap between two neighboring cells. Another remarkable feature of these vessels was the long thin intraluminal projections, which made the narrow and tortuous vascular lumens even more complex (Fig. 6). In addition, sawtooth, club-shaped and finger-like projections arising from the outer surface of the endothelium deformed or penetrated the basement membrane, which was sometimes multilayered (Fig. 7).

Some pericytes were rounded or irregular-shaped, with large nuclei, abundant cell organelles and thick processes (Fig. 8). These pericytes often had their own basement membranes separated from that of the neighboring endothelium and appeared to be less closely associated with the latter. In some vessel walls, the pericytes were less irregular in shape and their long thick processes covered a large part of the external surface of the endothelium, thus giving the vessel the appearance of a venule.

This type of vessel was found in all the 11 carcinomas. They were more often located at the infiltrating edge of the tumor or of a carcinoma lobule.

Type 3. Blood vessels of this pattern had extremely irregular contours, marked variations in the thickness of the endothelium and numerous fenestrations (Fig. 9). The thick part of the endothelial cells, which contained many organelles, was sometimes abruptly attenuated, and fenestrations were often adjacent to the wider region of the cytoplasm. The basement membrane along the fenestrated area often became faint or indistinguishable. Gaps or platelet thrombi were found in several vessels of this type, and were often associated with endothelial cell swelling or disintegration.

This type of vessel was randomly dispersed and was less frequently observed than the previous two types of vessel.

Type 4. By light microscopy or low-power electron microscopy, some small blood vessels appeared to have very thick walls, which in fact included both the capillary wall and the perivascular tissue, without a clear demarcation between these two layers (Fig. 10).

The vascular lumens were often moderately dilated and filled with circulating cells, among which granulocytes appeared in significant numbers. Endothelial cells were more numerous than in a normal vessel of the same diameter, and resembled those in type 2 vessels. Attenuation or fenestrations were sometimes present. In addition, sawtooth projections were common, and a few sprouts budded off from the vessels. Multilayered basement mem-

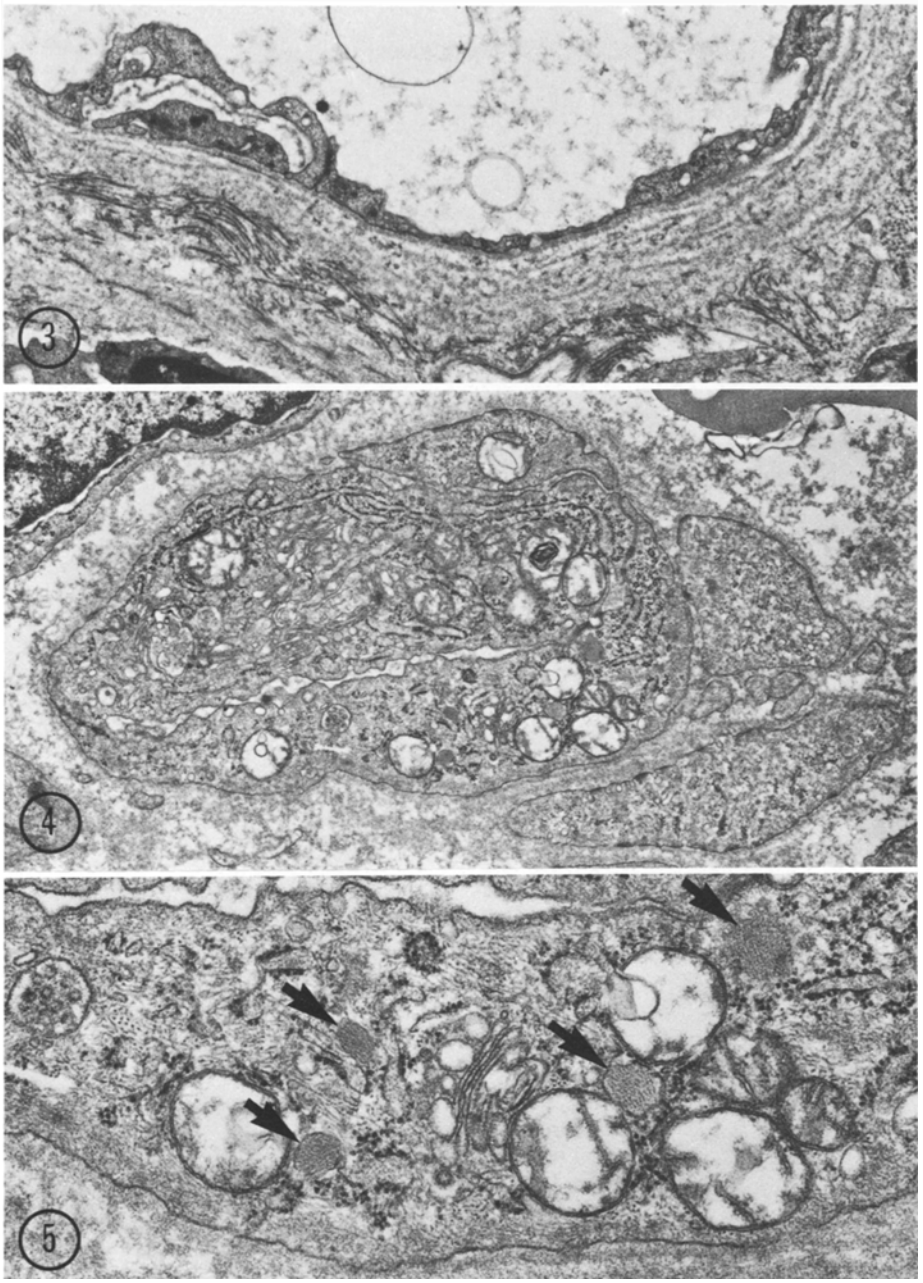

Fig. 3. Type 1 vessel in carcinoma. Basement membrane is multilayered. ×11,000

Fig. 4 and 5. Capillary sprout (type 2 vessel) in carcinoma

Fig. 4. Thickened endothelial cells contain numerous cell organelles. Pericytes are also thickened. ×11,000

Fig. 5. Higher magnification of the endothelial cell shown in the lower part of Fig. 4. Among the numerous organelles there are four Weibel-Palade bodies (*arrows*). ×33,000

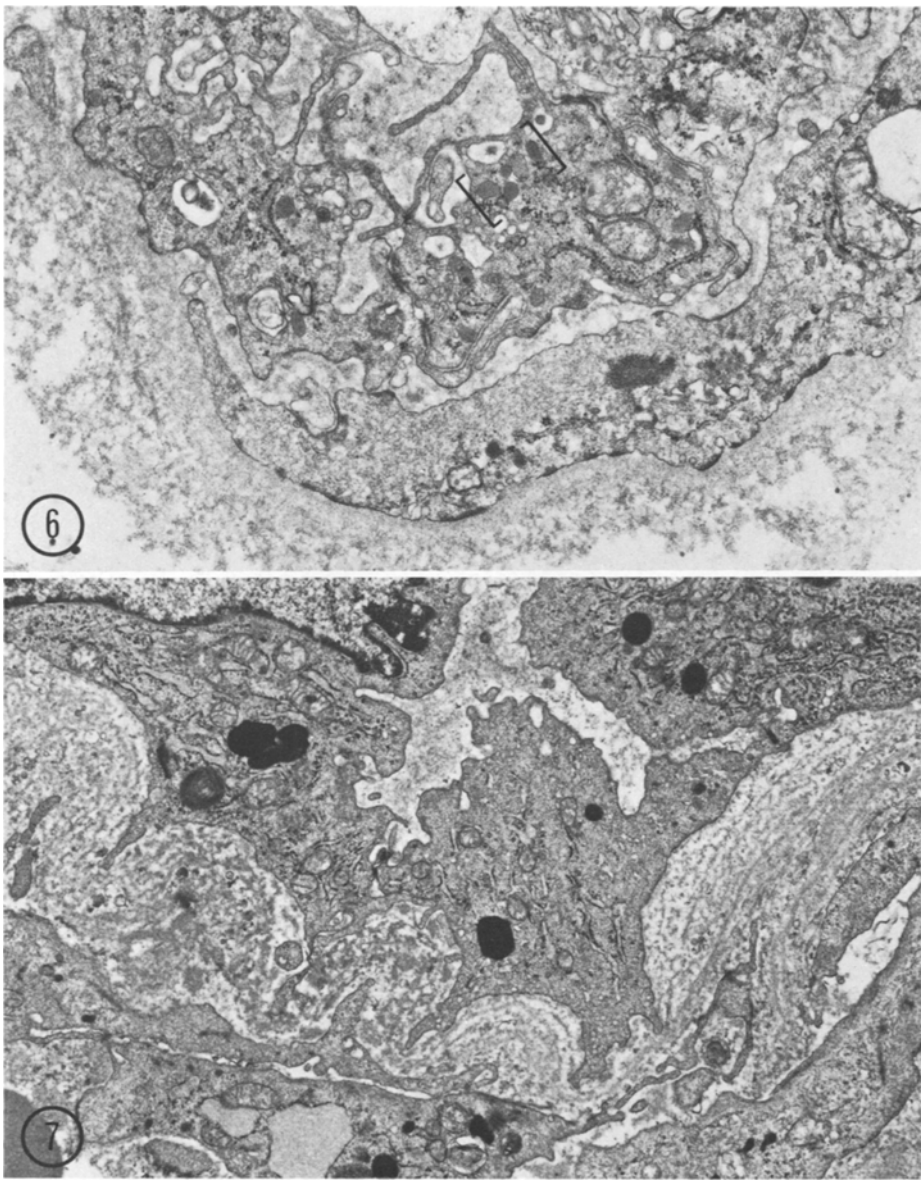

Fig. 6 and 7. Type 2 vessel in carcinoma

Fig. 6. Villous projections are present at the luminal side of endothelial cells, in which there are many Weibel-Palade bodies. The framed area contains a group of five such bodies, one transversly sectioned. Intercellular junctions are long and convoluted. Pericytes have small dense bands along the cell membrane. × 9,000

Fig. 7. Multilayered basement membrane is deformed and penetrated by endothelial projections. Many very dense bodies are present in the endothelial cells. × 17,000

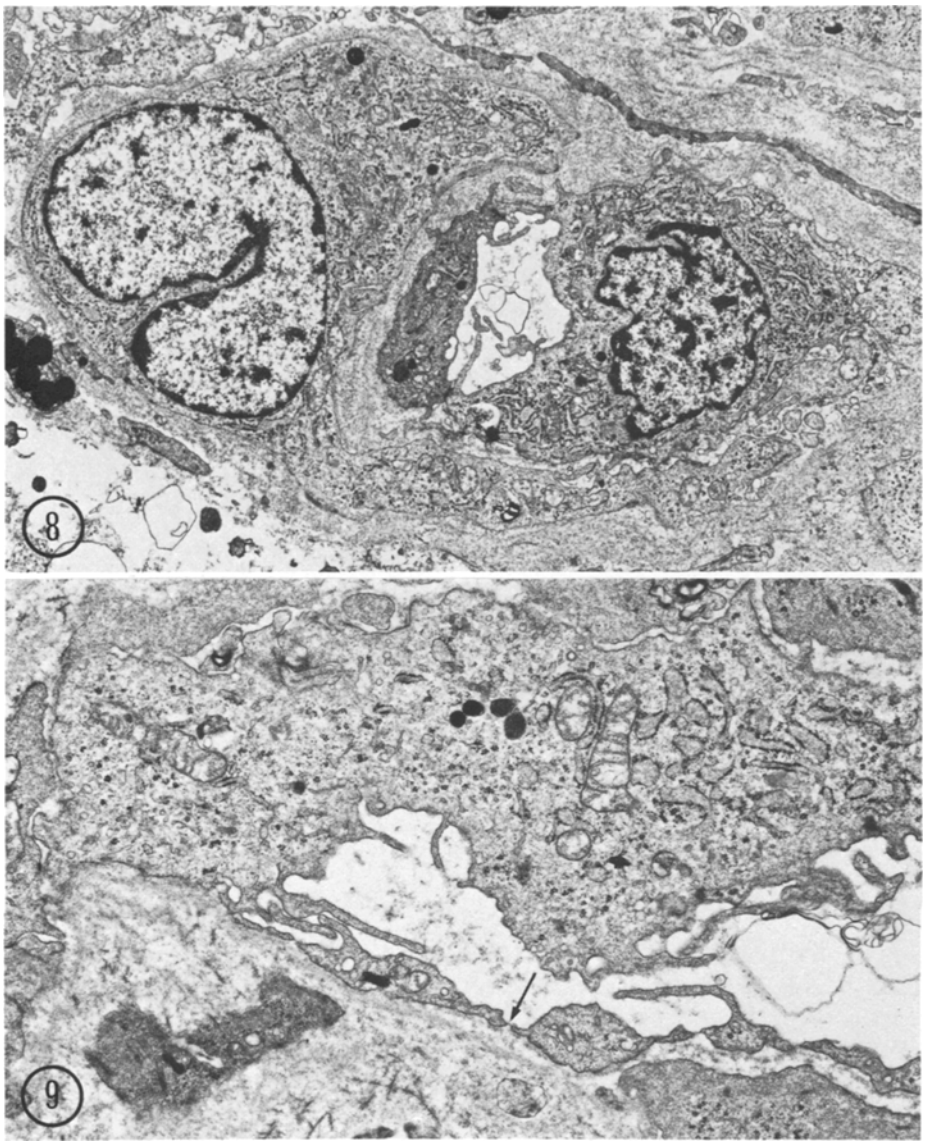

Fig. 8. A large pericyte in the wall of a type 2 vessel in carcinoma. ×5,100

Fig. 9. Type 3 vessel in carcinoma. Endothelial cells show alternating thick and thin regions. Fenestrations can be seen (*arrow*). ×11,000

brane mixed with structureless electron dense material, granules and cell debris filled the enlarged space between the endothelium and pericytes. The latter were often irregular in shape.

The very thick perivascular sheath was composed of large numbers of collagen fibers and numerous cells, including lymphocytes, macrophages,

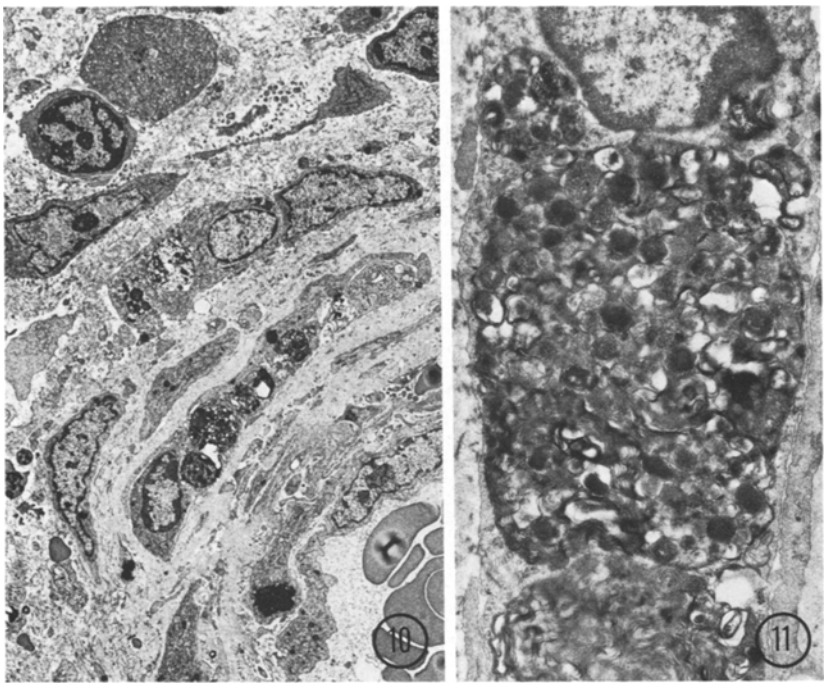

Fig. 10 and 11. Type 4 vessel in carcinoma.

Fig. 10. Perivascular tissue is markedly thickened and numerous small or large dense bodies are present in various kinds of cells. × 2,200

Fig. 11. Large granular bodies in a perivascular cell. × 12,000

active fibroblasts and extravasated erythrocytes and granulocytes, which were in various steps of degeneration. Many cells, however, could not be identified. Small but very dense bodies (Figs. 7, 9 and 10), some of which were clearly membrane-bound, were present in endothelial cells, pericytes and fibroblasts. A larger type of membrane-bound body of heterogeneous density and containing myelin figures, was also observed in various cells (Fig. 11). These bodies were interpreted as lysosomes, phagosomes or autophagosomes and some of these contained remnants of granulocytes.

This type of vessel was not restricted to a particular location in the carcinoma, and was only observed in a few cases.

Type 5. These were exceedingly dilated thin-walled vessels. Under the light microscope, it was difficult to be sure whether these were blood vessels or lymphatics (Fig. 12). The vessel walls were very thin, consisting of only one or occasionally two layers of cells, and the lumens were wide, and contained a few red blood cells or were occasionally empty. Using electron microscopy, it was evident that these were thin-walled venules. There was

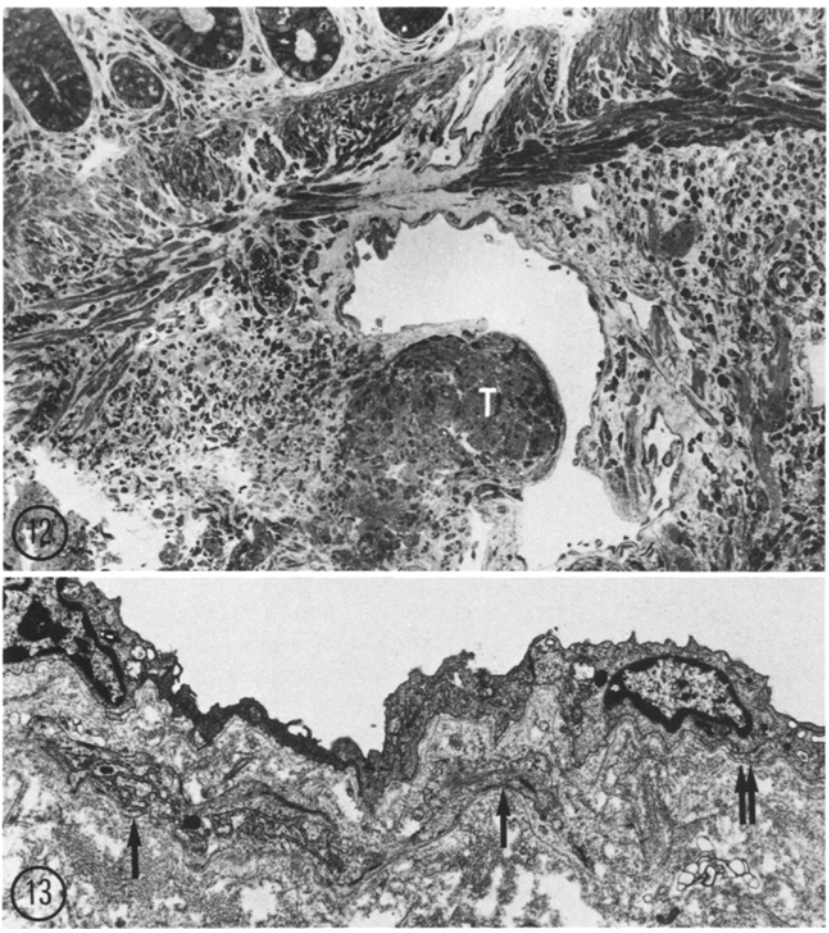

Fig. 12 and 13. Type 5 vessel in carcinoma.

Fig. 12. Light micrograph of an Epon embedded section. A thin-vessel in the submucosa is deformed by a mass of tumor cells (*T*). ×130

Fig. 13. Thin section adjacent to that illustrated in Fig. 12. Endothelial basement membrane is well-defined (*double arrows*). A discontinuous smooth muscle layer is identifiable (*arrows*) ×4,500

always a distinct but discontinuous layer of smooth muscle cells (Fig. 13) beneath the endothelium, which was mostly of normal appearance. A few fenestrations and Weibel-Palade bodies were occasionally found. The basement membrane was usually well defined, and sometimes consisted of multiple layers. Moreover, at intervals along the vessel wall, small branching vessels were occasionally observed.

These vessels were generally located at the border of the carcinoma, close to the tumor cells. In one case of moderately to poorly differentiated

adenocarcinoma with vein invasion and mesenteric lymph node metastasis, a mass of tumor cells deformed the thin vessel wall, although it did not penetrate the endothelium (Fig. 12).

Discussion

The present observations demonstrate that small blood vessels of colorectal adenomas are almost identical to those of control mucosa, whereas carcinoma vessels display a variety of structural alterations. Before discussing our observations in detail, some of the factors which may influence vascular morphology should be considered.

An effort has been made during this study to identify morphological artifacts resulting from surgical intervention. Both control mucosa and carcinoma samples included specimens from biopsy as well as from resection and the morphology of the tissues obtained by these two methods was compared. Some of the abnormalities observed in the surgical specimens, such as cell oedema, membrane disintegration, gap formation, haemorrhage and fresh thrombi are considered to be possible artifacts due to hypoxia and mechanical trauma during surgery. Nevertheless, these features were more frequent and more severe in carcinoma vessels than in those of control mucosa, even though both were from the same resected colon. This suggests that some hypoxia may be the result of progressive malfunction and deterioration of the vascular network as the tumor grows (Vogel 1965; Tannock 1970; Gullino 1978). Furthermore, mechanical damage may have occurred before the operation, because of the location of the tumors. Tissues were carefully sampled from the peripheral non-ulcerated areas of the carcinomas and were devoid of heavy infiltration by granulocytes. Nevertheless, the possibility of inflammation must be taken into consideration.

Blood vessels in colon carcinomas were described according to five patterns. Although this is an arbitrary classification, each pattern showed some characteristic features, which may represent a particular type of vascular response.

Endothelial Proliferation and Neovascularization

Endothelial proliferation was obvious in all the eleven colon carcinomas, regardless of their histological type or degree of invasiveness. Proliferating endothelial cells were identified in thin sections by characteristic features which have been reported in the literature (Cavallo et al. 1973; Hirano and Matsui 1975), and are illustrated in Figs. 4–8.

Weibel-Palade bodies were rare in normal capillary endothelial cells of colon mucosa, but were more frequently observed in venular endothelial cells, and in particular in the proliferating cells of carcinoma vessels. They were usually shorter and of lower density than those in normal vessels, which may be a sign of the immaturity of these bodies (Sengle and Stoebner 1970). Weibel-Palade bodies have been found to occur in significant numbers in human brain tumors (Hirano and Matsui 1975; Kumar et al. 1980). The latter group also reported an increased number of Weibel-Palade bodies in chick chorioallantoic membranes treated with tumor angiogenesis factor, and suggested that these bodies might be a marker for budding capillaries.

Large proliferating pericytes were a striking feature of many of the carcinoma vessels, and in agreement with the report by Cavallo et al. (1973), their occurrence accompanied endothelial proliferation. Some of the pericytes had lost their normal orientation and were dissociated from the endothelium. These features have been either ascribed to the "activation" of pericytes by various stimuli (Movat and Fernando 1964; Cotran 1967), or assumed to be evidence for pericytes being derived from primitive mesenchymal cells (Crocker et al. 1970).

The type 2 vessels in the carcinomas were composed of typical young endothelial cells, and conformed morphologically to the capillary sprouts most often described in the literature. Two types of sprouts have been described in experimental wound healing and in tumors respectively by Schoefl (1963) and Warren (1979b). One type is pointed or tapering, the other is club-shaped or saccular. Schoefl (1963) inferred that the sprouts pushed forward along a path of least resistance, and that the different forms of sprouts were due to the irregularity of the substrate along which the endothelial cells advanced; whereas Warren (1979b) suggested that saccular sprouts appeared to be derived most frequently from venules and the tapering type from capillary networks. While the type 2 vessels described in the present study may be equivalent to the tapering sprout, the vessels of type 3 and type 4 could not be unequivocally identified as sprouts, although they bore some resemblance to the saccular type illustrated in the report by Warren (1979b). Unlike the experimental models using transparent chambers, the present approach using thin sections of human material did not permit the identification of a sprout by its anatomical location.

The frequent presence of proliferating endothelial cells and newly formed vessels in colon carcinomas may be related to the angiogenic property of tumor cells (Folkman and Cotran 1976). There is well documented experimental evidence that, at the advancing edge of a growing tumor, there is an ingrowth of capillary sprouts from the host's pre-existing capillaries or venules (Warren 1970; Ausprunk and Folkman 1977). Presumably, in a human tumor of significant size, the advancing front would not only be limited to the edge of the tumor, but might also include the border of carcinoma tubules or lobules which extend forward into the stroma. This would explain the wide-spread occurrence of growing vessels in our samples. In contrast to the location of capillary sprouts, the normal-looking type 1 vessels were more often seen in the narrow stroma between the closely apposed intralobular carcinoma tubules. It is unlikely that these are pre-existing small vessels which have not been destroyed by tumor cells, and they are probably tumor-induced vessels which have undergone differentiation.

Fenestrations

It was not surprising to find fenestrated endothelium in the wall of some well differentiated (type 1) vessels, since the capillary endothelium of colon mucosa is normally fenestrated. However, since the type 3 vessels demonstrated so many abnormalities, it is doubtful whether in this situation, the presence of fenestrations is a sign of endothelial differentiation. It is more probable that they developed under abnormal conditions. Anomalous fenestrations have been reported in normally non-fenestrated endothelium in some tumors (Ozzello 1971; Hirano and Matsui 1975) and under a variety

of conditions (Wolff 1977). Some of the vessels included in type 3 were composed of young endothelial cells and were obviously newly formed. In this context, it is of interest to note that Schoefl (1963) reported extremely attenuated segments, resembling fenestrations, in the endothelium of capillary sprouts. There are two other possible explanations for the abundance of fenestrations in the type 3 vessels. First, these vessels might be in regression as a part of the process of vascular remodelling in the carcinoma. The presence of fenestrations associated with endothelial cell degeneration and platelet thrombi, which were also observed in some of the type 3 vessels, has been described by Ausprunk et al. (1978) in a study of regressing capillaries. The second possibility is that the fenestrations were formed under hypoxia. Luft and Hechter (1957) observed fenestrated capillaries in the cow adrenal cortex, if the tissue was fixed 1–2 h after the death of the animal, but if it was perfused with warm serum during that interval, the capillaries were non-fenestrated.

"Thick-Walled" Vessels

The type 4 vessels were characterized, at the light microscope level, by extremely thick walls. This appearance was mainly due to thickening of the perivascular tissue and also to some extent that of the capillary wall, and the endothelial cells, pericytes and fibroblasts in this region appeared to be activated. The multiple layers of basement membrane interspersed with cell debris may imply that repeated episodes of endothelial cell degeneration and regeneration have taken place, as has been suggested by Vracko and Benditt (1970).

Apart from the above mentioned features, the presence of proliferating endothelial cells, pericytes and fibroblasts containing numerous lysosomes, together with extravasated granulocytes and numerous collagen fibers may constitute a vascular response to prolonged injury. Although some of these features resemble those induced by various sublethal, experimental stimuli (Cotran 1967), the marked thickening of the vessel wall and perivascular sheath, as illustrated in this paper, has not been previously reported. It is possible that the vascular abnormalities of the type 4 vessels resulted from repeated mechanical trauma or mild infections, to which a long-lived human tumor in the bowel wall is often exposed. On the other hand, the possibility that these carcinoma vessels were undergoing repeated remodelling as the tumor grew cannot be excluded. It is unfortunate that little is known about the sequence of events involved in vascular remodelling in tumors.

Dilated Thin-Walled Vessels

The dilated thin-walled vessels in the peripheral region of the colon carcinomas had well-defined basement membranes, a few fenestrations, a smooth muscle layer and small vascular branches, which together characterize them as venules. The discontinuity of the smooth muscle layer may be due to

excessive stretching during vessel dilation, the cause of which is unknown. The content of the lumen did not always aid in the identification of the vessel. It is possible that blood cells were washed out more easily from a dilated lumen than from a small one during tissue preparation and this would explain their scarcity in these sections.

Since these dilated thin-walled vessels were often located at the periphery of carcinomas and were composed of mature endothelium and smooth muscle cells, it was presumed that they were pre-existing colon vessels. This is consistent with the findings of other authors, who have described that, before budding off capillary sprouts, the parent vessels in front of the growing tumor become engorged and dilated (Ausprunk and Folkman 1977). This type of vessel may also correspond to the giant capillaries (Warren 1979a) or large venules (Liotta et al. 1974) which have been identified as a site of tumor cell intravasation. In this respect, it is interesting to have encountered in the present study a deformed thin-walled vessel, which appeared to be in the process of being invaded by an outgrowth of tumor cells (Fig. 12).

Comparison between Adenomas and Carcinomas

It is clear that, while capillary sprouts and vascular abnormalities were commonly seen in colon carcinomas, no sprout was observed in the adenomas and vascular changes were only slight. Being true neoplasms, the adenomas would be expected to have a vascular network in addition to the normal vasculature of the colon mucosa. Unfortunately, there is little information about the vascularization of benign tumors (Brem et al. 1978; Ludatscher et al. 1979). Tumor-associated angiogenesis has been mostly studied in experimental malignant tumors, however, some data obtained from studies on wound healing may help to explain the above mentioned differences between benign and malignant tumors. During wound healing, there are two patterns of vascular growth (Schoefl 1963): 1) by sprouting, and 2) by elongation of the pre-existing capillary loops, probably by the intercalation of young endothelial cells among the old ones (Chalkley 1946). Schoefl (1963) found that sprouts usually coincided with more severe injury, whereas lengthening of the loops prevailed in the milder cases, and it was suggested that these two patterns might reflect different speeds of vascular growth, possibly depending on the intensity of the stimulus. Following this hypothesis, the different frequencies of capillary sprouts in adenomas and in carcinomas might also imply a difference in the growth rate of their blood vessels. As cited above, the expansion of the vascular network at the advancing edge of a malignant tumor takes the form of sprounting. In contrast, the scarcity of capillary sprouts in the adenomas is consistent with their non-invasive growth pattern and relatively slow rate of growth. In these tumors, lengthening of the vessels may be the most important means of expansion in the vascular network. The gradual elongation of the blood vessels may also facilitate the maintenance of their structure and allow their differentiation. Therefore, although adenomas are located in

the same unfavorable environment as carcinomas, their vessels may not be as vulnerable to damage as the immature ones in carcinomas, hence the rare occurrence of abnormalities in adenomas. Moreover, the mechanisms of defence against mechanical and bacterial trauma, which are present in normal colon mucosa (Donnellan 1965), may be defective or destroyed in colon carcinomas, but may be maintained, at least to some extent in adenomas.

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