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The Vascularization of the Digestive Tract Studied by Scanning Electron Microscopy with Special Emphasis on the Teeth, Esophagus, Stomach, Small and Large Intestine, Pancreas, and Liver

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THE VASCULARIZATION OF THE DIGESTIVE TRACT STUDIED BY SCANNING ELECTRON MICROSCOPY WITH SPECIAL EMPHASIS ON THE TEETH, ESOPHAGUS, STOMACH, SMALL AND LARGE INTESTINE, PANCREAS, AND LIVER**

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Abstract

The periodontal vessels in adult rats show a ladder-like pattern; in guinea pigs molars, by contrast, they present a honey-comb pattern. The vascular architecture in human teeth seems to be similar to that of rabbits. In guinea pigs, rats, rabbits and humans esophagus circumferential vessels give off perforating vessels. In human esophagus the number and diameter of the vessels in the submucous venous plexus decrease from proximal to distal. In the stomach the subepithelial capillary network shows a honey-comb pattern reflecting the arrangement of the gastric pits. A local portal system between the gastric glands and the surface mucosal cells for the transport of HCO_3^- ions has been suggested. In the small intestine of humans and rabbits the existence of a dual blood supply of the villus has meanwhile been established. It consists of pericryptal capillaries for the lower portion of the villus (tuft pattern) and a direct arterial supply up to the villus tip (fountain pattern). The colonic microvasculature closely resembles that of the stomach. In the pancreas the insulo-acinar portal system is physiologically significant in that it connects the venules draining the islets with the acini. Venous sphincters in the vascular system of the exocrine pancreas of the rat are of particular functional importance. The hepatic sinusoids are supplied both by the hepatic artery and the branches of the portal vein. The peribiliary plexus is supplied by the afferent vessels of the hepatic artery, the efferent vessels drain the plexus either into the sinusoids or into the lobular vein.

Key words : Scanning electron microscope, Microvascular corrosion casts, Tooth, Esophagus, Stomach, Small intestine, Colon, Pancreas, Liver.

**This work is dedicated to Professor Dr. Alfred GISEL on the occasion of his 80th birthday.

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Introduction

Scanning electron microscopy (SEM) of vascular corrosion casts is, undoubtedly, one of the most useful methods for obtaining three-dimensional representations of circulatory pathways. First described by Murakami (1971) and repeatedly modified by Nowell and Lohse (1974), Hodde and Nowell (1980a, b), and Lametschwandtner *et al.* (1980, 1990), it is commonly used for studying the vascular architecture of different organs. Among these, the digestive tract occupies a special position, as its different segments are adapted to different physiologic functions. This is clearly reflected in their vascular supply. Considering that the function of the jejunum is mainly absorptive, while that of the stomach is mainly digestive, it would appear logical that the vessels supplying these two segments of the alimentary tract should have different roles and show different patterns.

This contribution presents our own findings on the microvasculature of selected segments of the digestive tract, i.e., the teeth, the esophagus, the stomach, the small and large intestine, the pancreas, and the liver, and reviews those of other investigators.

Material and Methods

150 albino guinea pigs (Cavia porcellus), 50 Sprague Dawley rats (200-250 g body weight) and 10 rabbits (New Zealand white, weighing 2-2.5 kg) of both sexes were used for corrosion casting. The animals were anaesthetized with pentobarbital (40 mg/kg body weight, intraperitoneally) and the thorax and abdomen were opened by a median cut. A plastic catheter (Argyle 0.8 x 19 mm, Sherwood Medical, St. Louis, MO, USA) connected to a two-way connector (LS-2, B. Braun-Melsungen, Germany) was introduced into the aortic arch via the left ventricle and ligated into place. The circulatory system was rinsed (using manual pressure) with 100-1,000 ml 37 °C heparinized Tyrode solution (5000 IU/l) until the efflux of the incised inferior vena cava was clear. Mercox CL-2B (Dainippon Ink & Chemicals, Tokyo, Japan), diluted with monomeric methylmethacrylate (v/v: 4:1, Hodde, 1981) was injected through the aortic arch. The animals bodies were left at

Figure 1. Micrographs of the guinea pig lower incisor. **Fig. 1a.** Arrowheads mark the sinusoidal veins of the periodontal ligament. Tooth, surrounding periodontal ligament and alveolar bone are removed. Bar = 400 μm.
Fig. 1b. Arrowheads show the thick sinusoidal veins of the periodontal ligament. The surrounding alveolar bone (arrows) shows thinner vessels. Asterisks mark the bordering area of the periodontal ligament (in between) and the alveolar bone. Partially decalcified cast, view from the maxilla to mandible, the tooth is removed. Bar = 500 μm.

room temperature for 2 hours and then placed into a 60 °C water bath for final polymerization of the resin overnight. Thereafter organs were dissected away, maceration was carried out in 15% potassium hydroxide at 40 °C for 2 days or longer. Vascular casts were cleaned in 5% formic acid for 30 minutes, rinsed in several passages of distilled water and finally frozen in a small volume of the latter. Some of the specimens were cut into 0.5-2 mm thick slices, using a specially adapted circular saw at -20 °C (Lametschwandtner and Lametschwandtner, 1991). All specimens were freeze-dried, mounted onto copper foils and fixed to specimen stubs with conductive silver paste, according to the method of Lametschwandtner *et al.* (1980). The specimens were evaporated with carbon and gold for 3 seconds, then sputtered with gold for 600 seconds (Aharinejad *et al.*, 1989, 1990c) and examined with a Cambridge Stereoscan 90B SEM, using an acceleration voltage of 15 kV.

Results and Discussion

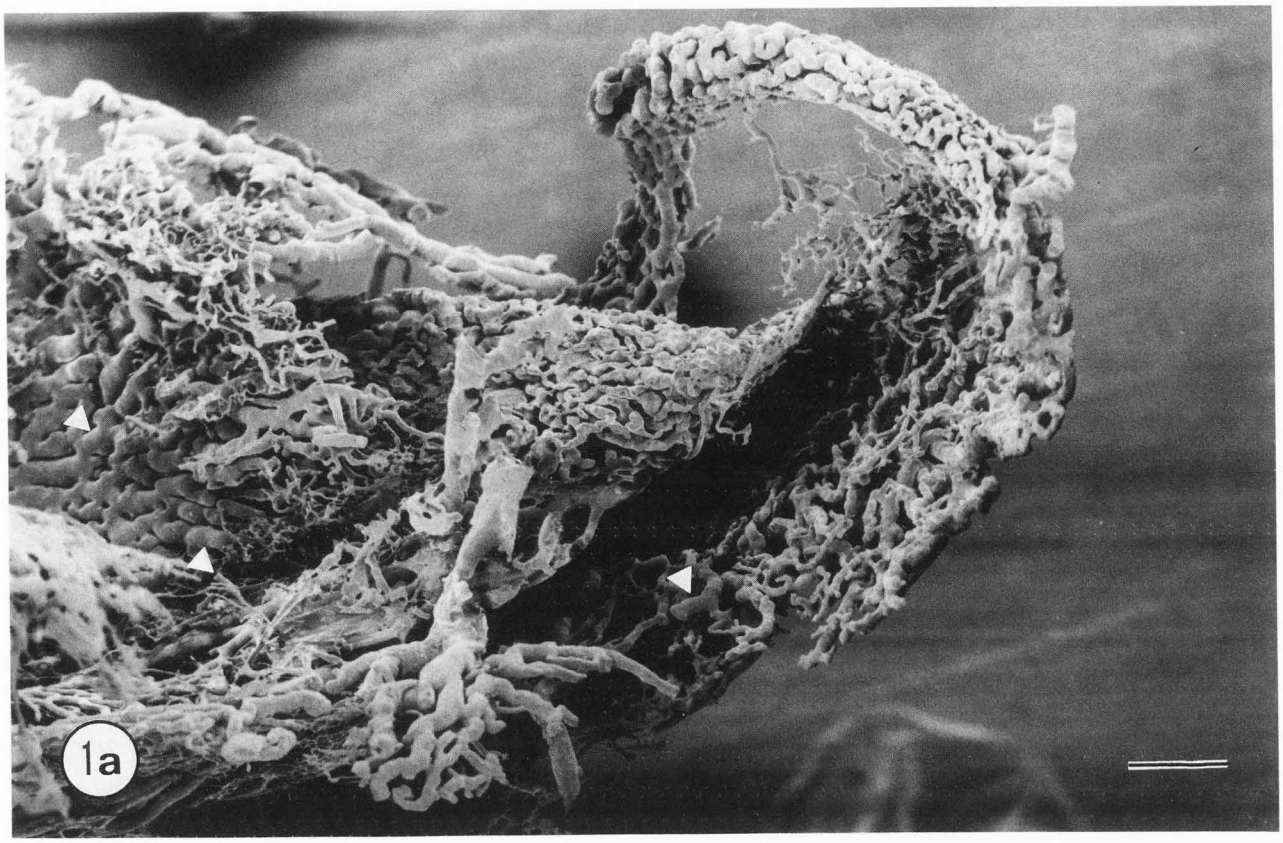
The Teeth

Reported studies of dental blood supply focus on different structures. Among them the periodontal ligament appears to have attracted particular attention (Wedl, 1881; Lepkowski, 1897, 1901; Häupel, 1931; Hayashi, 1932; Keller and Cohen, 1955; Goldman, 1956; Schuback and Goldman, 1957; Kindlova and Materna, 1959; Cohen, 1960; Kindlova and Materna, 1961; Adams, 1962; Bernick, 1962; Boyer and Neptune 1962; Franke, 1964; Fröhlich, 1964; Castelli and Dempster, 1965; Kindlova, 1965a, b; Birn, 1966; Carranza *et al.*, 1966; Kindlova, 1966; Cutright and Bhaskar, 1967; Folke and Stallard, 1967; Kindlova, 1967; Lenz, 1968; Stallard, 1968; Kindlova, 1970; Garfunkel and Sciaky, 1971; Lenz, 1974; Düker and Grossehellerforth, 1976, Mörmann and Ciancio, 1977; Gängler and Merte, 1979a, b; Skobe, 1980). While Boling (1942), James (1955), Sulzmann (1955), Bernick (1960) Boyer and Neptune (1962) and Bernick (1966) investigated the vascularization of the pulp in different mammals, the vasculature of the gingiva, the dentogingival junction and the mandible was central to the studies by Meyer (1932), Castelli (1963), Huelke and Castelli (1965) Egelberg (1966a, b), Dunker (1970), Nuki and Hock (1974), Kishi (1982), Okada *et al.* (1986) and Kishi *et al.* (1988). These investigations were based on rheography, vital microscopy, India ink - gelatin injection, Latex injection, light microscopy of paraffin-embedded specimens, fluorescence angiography and radiography with contrast application.

The above review of pertinent investigations was intended to pinpoint the problems encountered in two-dimensional studies of the vasculature. In the following comparative analysis of three-dimensional studies based on SEM results of dental blood supply will be addressed.

Periodontal ligament

Describing a dense vascular network in the periodontium, Carranza *et al.* (1966) and Egelberg (1966a, b) thought that, in inflammatory processes, this network underwent changes compatible with those of the epithelium lining the gingival sulcus and the connective tissue underlying the gingival epithelium (Folke and Stallard, 1967; Kindlova, 1967). The vessels forming these networks were also reported to be the source of the pocket fluid (Brill, 1959; Egelberg, 1966a, b; Stallard, 1968), which varies quantitatively as a function of the intensity of the inflammation (Egelberg, 1966a, b; Stallard, 1968). Kindlova (1970) found that the vessels overlying the gingival sulcal epithelium showed an arrangement other than that of the vessels overlying the oral gingival epithelium. She also described capillary loops projecting from ring-shaped vessels deep to the gingival cuff and considered these to belong to the periodontal ligament, without, however, furnishing any evidence of a functional relationship between these loops and the gingival vessels. Among the vessel layers seen after removal of the root, she distinguished one overlying the alveolus and another one supplying the enamel. While she thought the latter to have a basket shape and to show an abundance of vessels, she found the former to contain a delicate capillary network. Unlike Kindlova (1970), Gängler and Merte (1979a) described the periodontal ligament as having strikingly few vessels. Kindlova and Materna (1961), Castelli and Dempster (1965), Birn (1966), Carranza *et al.* (1966) and Folke and Stallard (1967) reported the periodontal vessels to be parallel to Sharpey's fibers and to take a perpendicular course from the cribriform plate into the periodontal ligament. They thought this arrangement protected the vessels from compression along their course through the alveolar bone and ensured that they could receive feeders at any level. Kindlova (1965a) and Carranza *et al.* (1966), by contrast, described the periodontal vessels as being parallel to the longitudinal axis of the tooth.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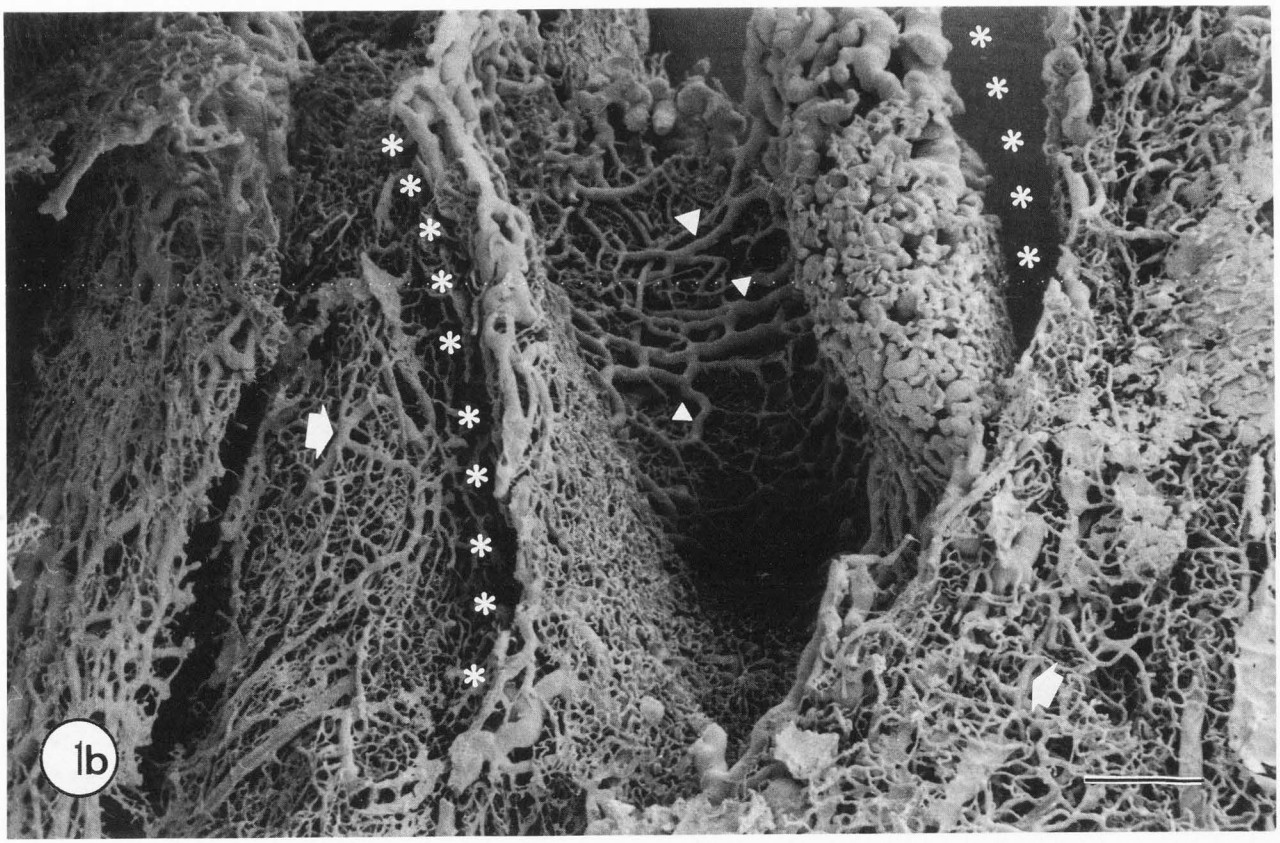
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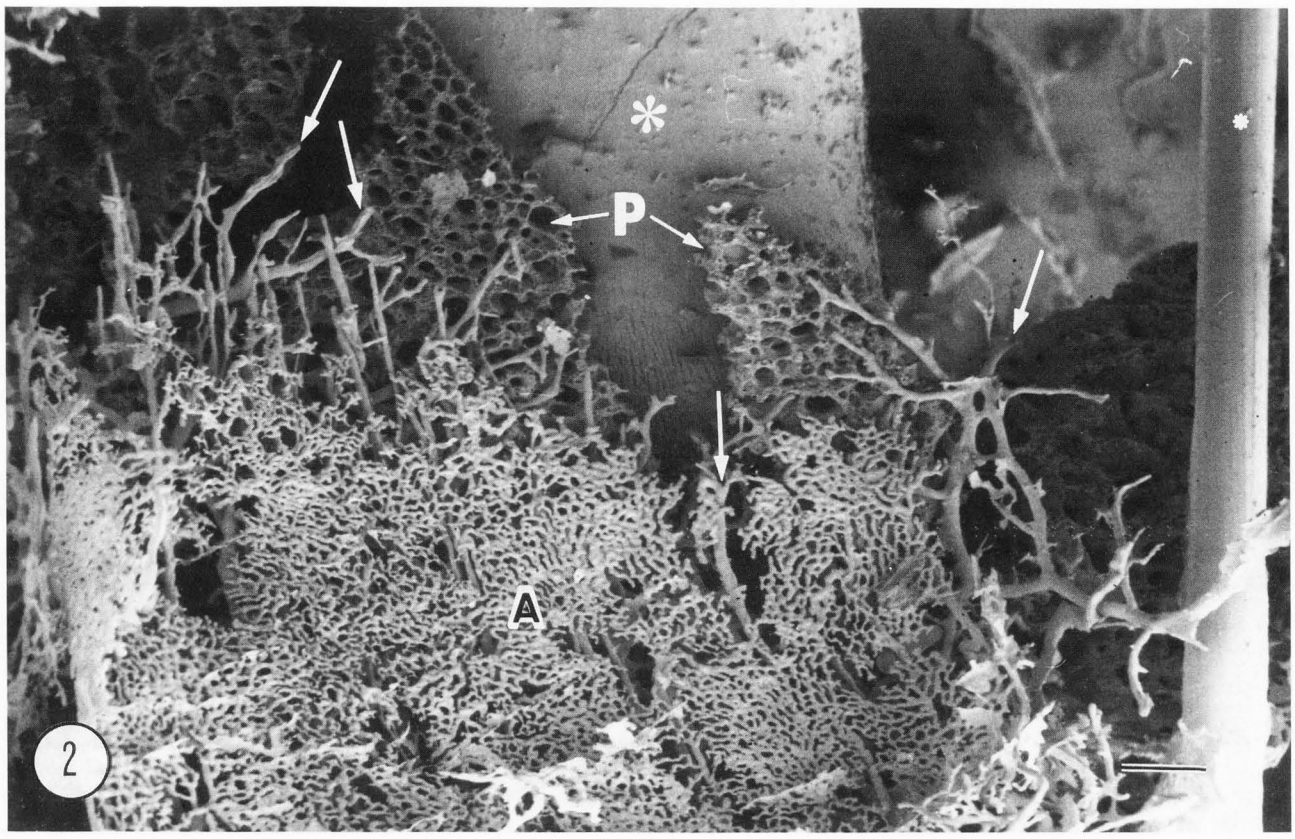
Except for the studies by Bernick (1966) and Aharinejad *et al.* (1990a, b), almost all of the investigations done to date focussed on the vasculature of the rat periodontium. Iwaku and Ozawa (1979) distinguished three vascular layers in the periodontal ligament: An innermost layer supplying the enamel and consisting of capillaries, an intermediate layer of branches from the inferior alveolar artery feeding capillaries through arteriolar vessels, and an outermost layer of sinusoidal veins connected with the innermost layer by capillaries and adjacent to the alveolar bone. Hodde *et al.* (1983) found the innermost vascular layer to be composed of two zones: a secretion zone and a maturation zone. In their interpretation, the capillary network of enamel presented a predominantly transverse pattern and no recognizable relationship to the obliquely oriented lines of Retzius. According to Hodde *et al.* (1983) the capillary network of the enamel organ received blood from longitudinally arranged arterioles, while venous drainage was through venules receiving blood from numerous sinusoidal veins. Sasaki *et al.* (1984) described the periodontal capillaries as a "blind network", Iwaku and Ozawa (1979) as ladder-like. According to Sasaki and coworkers, the periodontal capillaries arose, seen from the enamel organ, from the arteries in the central incisor region, took a parallel buccolingual course and communicated through numerous anastomoses. As the capillaries emptied into sinusoidal veins around the tooth, the authors concluded that the enamel organ was entirely supplied by arterial capillaries. Iwaku and Ozawa (1979) distinguished four zones of the inner capillary layer: a presecretion zone at the proximal end of the incisor with a circular meshwork; a secretion zone which, like the former, showed a circular meshwork, but also presented a ladder-like pattern; an early maturation zone with a predominantly ladder-like appearance, wider than the two former zones, but with thinner capillaries; and a late maturation zone without any circular meshes, which was more extensive than all other zones and contained capillaries thinner than those of the early maturation zone (shown later, Fig. 4b). This zonal arrangement is based on an earlier classification by Kallenbach *et al.* (1965).

Nakamura (1985) and Nakamura *et al.* (1987) observed that the periodontal ligament contained few blood vessels, which were mainly derived from the wall of the alveolar bone. Around the root apex, vessels were more abundant; arteries and capillaries showed a basket-shaped arrangement. In the mid-segment of the root, Nakamura and coworkers described a loose vascular layer with few loops and with arteries emerging from Kolkmann's canals and running towards the alveolar crest. In teeth exposed to experimental orthodontic movements Nakamura *et al.* (1986a, b) also reported that periodontal vessels were compressed with a bundled arrangement and a wavy pattern and that the capillaries and "twiggy vessels" increased in number. This they interpreted as evidence of the adaptability of the vasculature to dental movements. Vascular changes in the bony alveolus of osteoporotic rats were described by Yoshikawa (1987) and by Yoshikawa *et al.* (1987). These included a fence-like arrangement of the vessels between the periodontal ligament and the bone marrow and a reduction in the size of the periodontal space associated with an increase in the number of small venules and capillaries. Blood vessels overlapped everywhere and formed irregular networks. Near the root apex, vessels were compressed and formed a flat basket-shaped network. Studying vascular changes in the dog periodontal ligament during experimental movements, Matsuo *et al.* (1987) found that, one day after starting the test, vessels disappeared on the periodontal aspect exposed to the stress and the underlying bone became visible. On day 3 capillaries derived from the bone emerged; these showed several loops on day 7. On day 14 advanced bone absorption had produced a moth-eaten appearance. Changes in the microvascular pattern of the cat periodontium in an experimental tooth movement were described by Hosoyama (1989) and Kobayashi (1989). They showed that the new blood vessels arose from the pre-existing vessels, entered resorption lacunae, connected with each other, and formed the vascular layer for alveolar bone resorption, covering the bone surface. The blood vessels of the root side around the degenerate tissue initially had spear-like ends, the vessels gradually became interconnected, formed capillary loops, and encircled the degenerate tissue. The vascular layer for capillary loop formation was completed after three weeks. In addition to the mentioned papers, there are some other studies, dealing with the changes of the tooth vascular pattern under different experimental conditions, the results of which are in good agreement with those described above (Matsuo *et al.*, 1986, 1987; Okuda, 1988; Kai, 1989; Kawato, 1989). Distinguishing three vascular layers in rat tooth germs, i.e., in the mucous membrane, in the surrounding bone and on the outer surface of the enamel organ, Yoshida (1984) reported the vessels of the enamel organ to separate into an outer and an inner vascular bed during amelogenesis and to disappear, as the tooth erupts.

Fig. 2. First guinea pig molar (large asterisk) surrounded by the periodontal ligament vessels (P), showing a honey comb pattern. Arrows mark the supplying and draining vessels, A = alveolar bone. Small asterisk marks a conductive bridge. Partially decalcified specimen. View from buccal side. Bar = 250 μm.

Fig. 3. Capillary convolutions between alveolar and periodontal ligament. Bar = 25 μm.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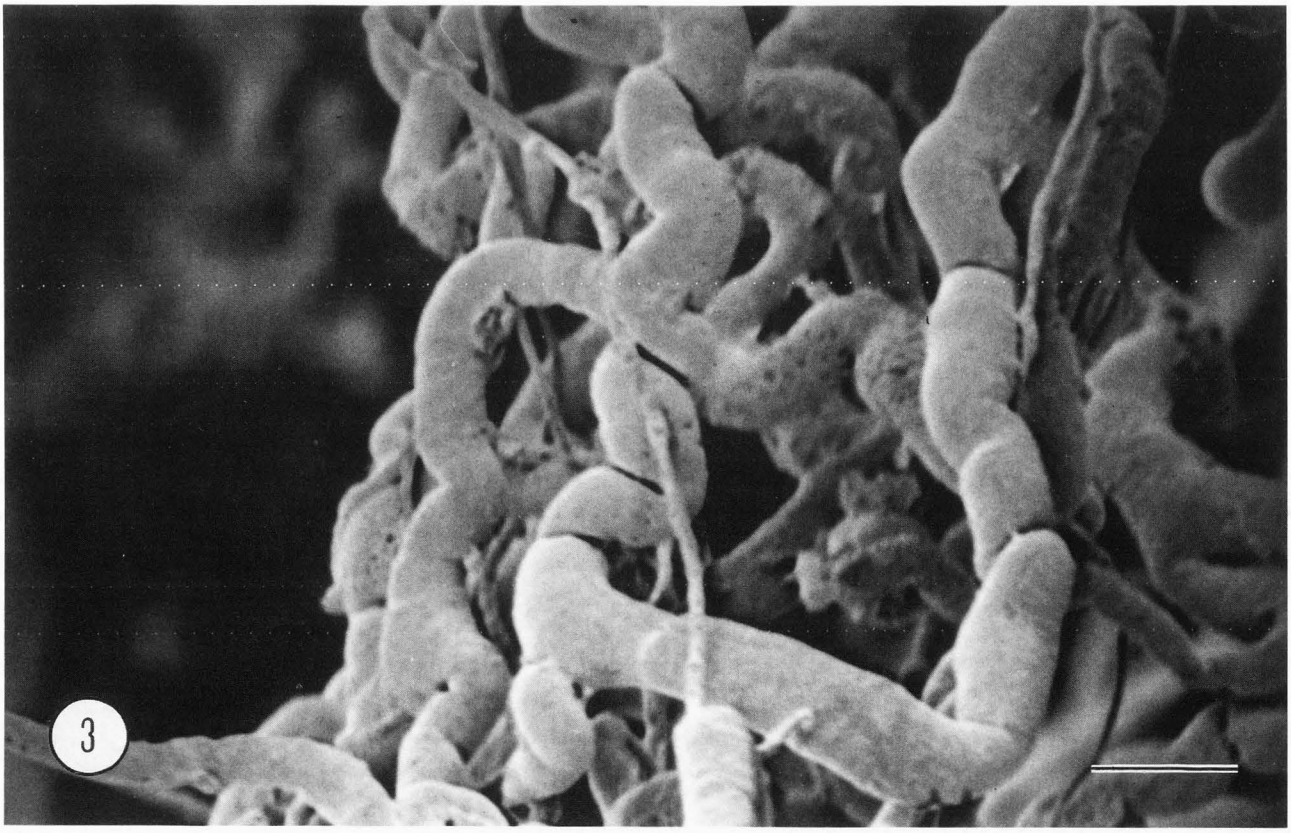
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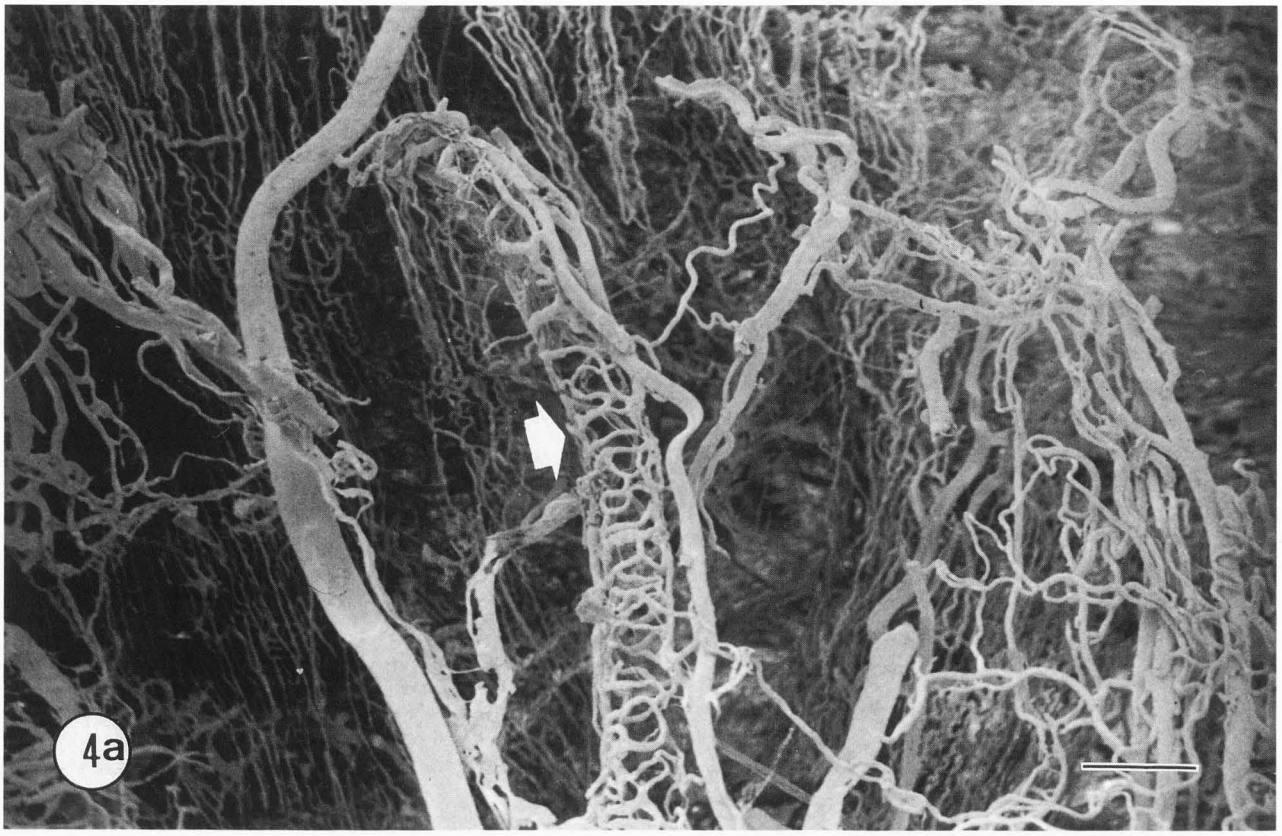
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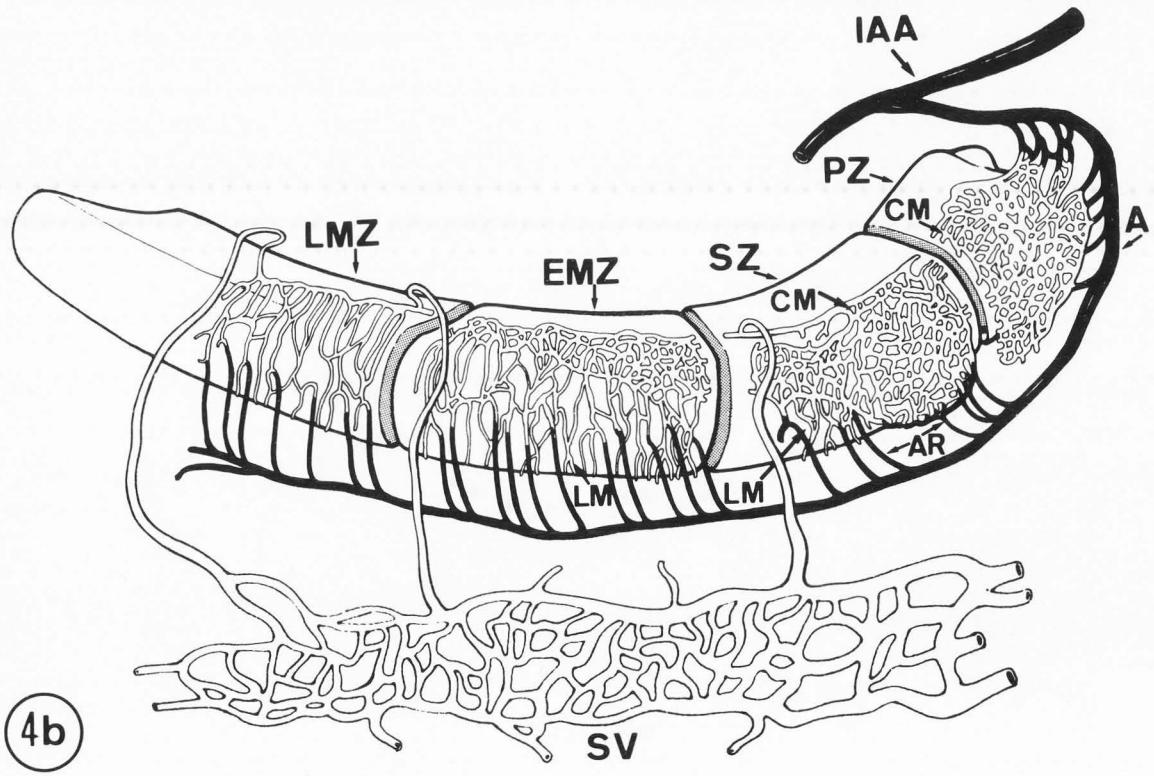
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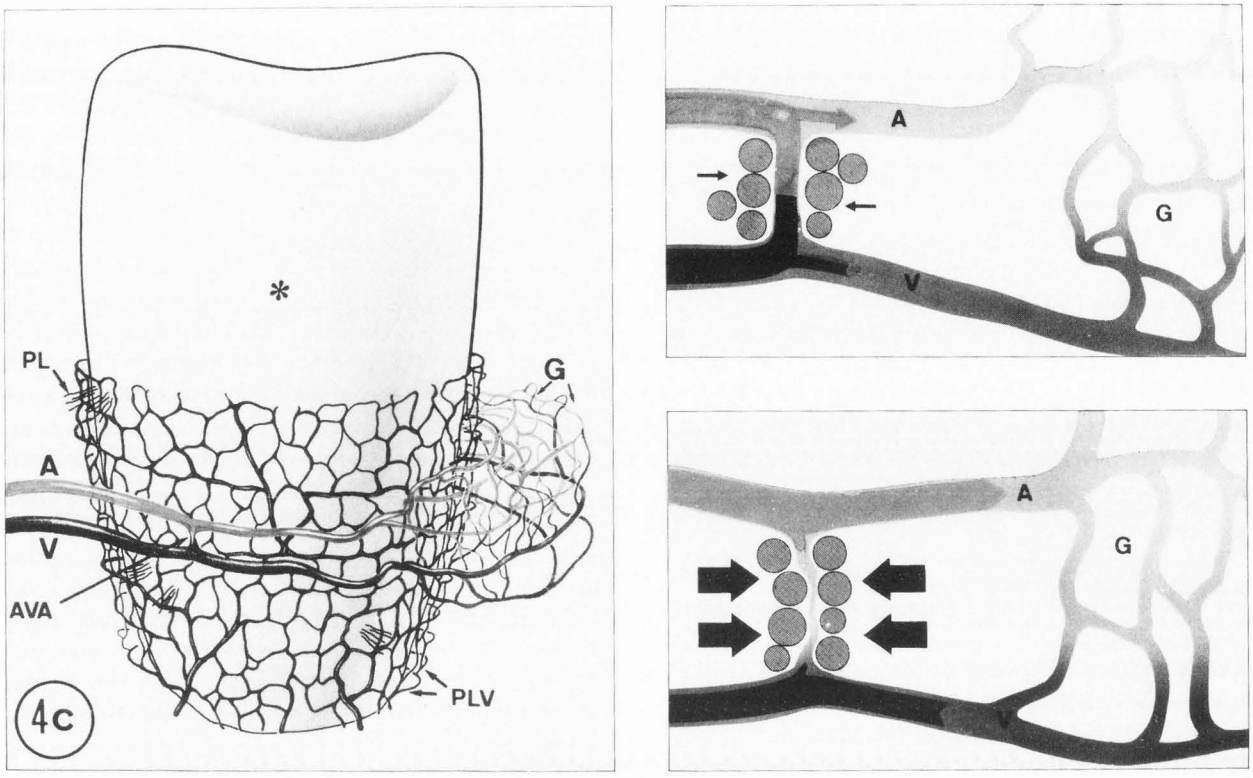


Fig. 4a. A capillary cord (arrow) supplying the molar pulp of the guinea pig. The tooth and the periodontal ligament vessels are removed. Bar = 250 μm. **Fig. 4b**. Schematic overview of changes in the microvascular bed of periodontal ligament during the amelogenesis in rats. Circular meshes (CM) disappear, they are then replaced by ladder-like meshes (LM). IAA = inferior alveolar artery; A = a branch of the IAA; AR = branches of the A; PZ = presecretion zone; SZ = secretion zone; EMZ = early maturation zone; LMZ = late maturation zone; SV = sinusoidal veins (adapted from Iwaku and Ozawa, 1979). **Fig. 4c (above)**. Diagrammatic view of the glomera (G) of the periodontal ligament (PL) around the molar (asterisk) of guinea pigs. A = afferent artery of the glomera; V = efferent vein; AVA = arterio-venous anastomosis; PLV = vessels of the periodontal ligament. Insets: The blood flow in the AVA is reduced, as the periodontal ligament fibers become taut (bold black arrows in the upper inset), so leading the glomera to get inflated.

Studies of the oral tissues in the guinea pig are scarce. Those of an earlier date (Fish and Harris, 1935; Thoma, 1950) concentrated on molar changes in the presence of vitamin deficiencies. Aharinejad *et al.* (1990a) observed a plexus of sinusoidal veins to be the dominant structure in the periodontal vasculature of the incisors (Fig. 1, unpublished data), but found a honeycomb pattern of the periodontal vessels in guinea pig molars (Fig. 2). Like in the molars, the vessels of the periodontal ligament were larger than those in the alveolar bone. They also described para-alveolar capillary convolutions between the alveolar bone and the periodontal ligament (Fig. 3). Vascular convolutions in the human dental periosteum were first reported by Wedl (1881). They were also mentioned by Häupel (1931), Meyer (1932), and Bargmann (1959). Using an India ink - gelatin injection technique, Ishimitsu (1960) found evidence of periodontal glomeruli. Their occurrence and true functions went unnoticed for a long time. 30 years after they were first described, Aharinejad *et al.* (1990a) showed that the afferent and efferent arterioles and venules of these convolutions communicated by arterio-venous anastomoses (AVAs) and suggested to replace the term glomeruli by glomera (Fig. 4c). Like earlier authors (Wedl, 1881; Bargmann, 1959), Aharinejad *et al.* (1990a) attributed mechanical functions to these glomera. They hypothesized that, as pressure built up in the alveolar pocket, the collagen fibers of the periodontal ligament became taut and the AV-anastomoses were compressed so that more blood could flow into the glomera (Fig. 4c). The resultant blood-filled saccular spaces served as buffers counteracting the pressure build-up. Conversely, the AVAs were thought to control flow in the periodontal ligament, as they channeled the blood towards the venous side in their uncompressed state so that it was removed from the exchange processes in the interstitial spaces. While sensory nerve endings were reported to be present in the human perio-

dontium (Nakamura *et al.*, 1982, 1986c), studies to show whether or not the glomera had a specific nerve supply would help to understand the function of these structures. Aharinejad *et al.* (1990a, b) also found that vessels were more abundant on the buccal than on the lingual aspect. This supports the concept of a mechanical function of the periodontal vasculature, which becomes more plausible, if one remembers that the guinea pig molars are tilted 7° away from the horizontal towards the lingual side so that the pressure moments tend to be compensated on the buccal side. Ohta *et al.* (1990) observed a glomerular vascular architecture closely to a new formed bone surface in an extracted tooth socket after an experimentally dental implantation in Macaca fuscata.

Dental pulp

In the pulp of rabbit molars, Nakamura *et al.* (1983) found contracted capillary segments to alternate with dilated ones. In rat molar pulp, Nakamura (1986) described tortuous arteries and AVAs and concluded that both played an important role in regulating blood flow. Based on SEM and transmission electron microscopy (TEM) studies in monkeys, Nakamura *et al.* (1988) showed that capillary networks in the pulp horn and in the periphery of the coronal chamber were more abundant than in the radicular pulp. The complex adrenergic innervation the authors found to be present appeared to them to be involved in regulating local blood flow.

Semba *et al.* (1983) proposed a particularly interesting concept: In the pulp of rat incisors, arterial trunks showed a median arrangement. Those in the basal part gave branches from the nearest one to the labial side towards the lip; others towards the lingual side, therefore, reached the dental incisal part. Arterioles were distributed mostly where enamel is formed and proceeded to the capillaries near the surface of the dental pulp. Capillaries ramified in a rosette-like configuration almost parallel to the surface of the dental pulp and directly below the odontoblastic layer. Then they ran along the odontoblasts, forming terminal capillaries parallel to the dental pulp surface. Venous trunks ran along both sides of arterial trunks and lined up in the sagittal plane. Semba *et al.* (1983) concluded that this vascular architecture was responsible for increasing the body fluid pressure on the labial side, while reducing it on the lingual side.

Takahashi (1985) studied maturation of the dental pulp in dogs and distinguished 4 maturation stages: (1) Completion stage of crown formation: Arterioles and venules mostly ran longitudinally in the pulp center, "terminal capillaries" were perpendicular to the capillaries. (2) Root formation stage: A main feeding artery from the distal side ran horizontally along the apex of the distal root, with several branches toward the pulp. In the pulp, these arterioles ran almost straight toward the coronal area. (3) Completion stage of root formation: In this stage the three specific vascular layers of the pulp were apparent, i.e., the terminal capillary network (loop-shaped), the capillary network (middle layer) and the venular network. These three layers were also described by Kobayashi (1983) in dogs and by Semba *et al.* (1983) in rats. Unlike in rats, dogs and rabbits, AVAs have so far not been found in the cat pulp (Kishi *et al.*, 1989b). (4) Root maturation stage: The apex of the tooth was fully matured, the size of the pulp was narrower than in the previous stage. In the coronal area several hairpin-loop "terminal capillary networks" were present; vessels of the root had a fishing net-like configuration. Terminal capillaries drained directly into the large venules; in contrast to the previous stages capillary and smaller venular networks were absent. Veno-venous anastomoses (VVAs) were present in the mesial root, a U-turn loop was mainly located in the root canal pulp. The latter with its strategic location might play a role in blood flow regulation in place of, or in addition to, the AVAs. In addition to the VVAs, Takahashi *et al.* (1982) first described AVAs in the dog pulp, confirming earlier observations by Provenza (1958) and Kramer (1968). In the authors' interpretation, the AVAs played an important role in the flow regulation of the pulp. The observations of Yoshida *et al.* (1988) contradict those of Takahashi *et al.* (1982), Takahashi (1985), Kobayashi (1983), and Semba *et al.* (1983). They did not find any evidence of 3 vascular layers in the rat pulp. They rather found that the terminal capillaries invaded the odontoblastic layer and were finally located close to the predentin. Thick capillaries became thinner with advancing dentin formation and the capillary network density increased gradually with the invasion of the odontoblastic layer. On the basis of these observations Yoshida *et al.* (1988) concluded that the capillaries played a role in dentin formation. Okada *et al.* (1990) dealt with changes in the microvascular architecture of the blood capillaries during the amelogenetic process in the rabbit upper major incisor. They distinguished a proliferation, a differentiation, a secretion, an early maturation, a late maturation and a regression zone. In their interpretation the ladder-shaped capillary network was thought to represent an intermediate form towards the succeeding zone, in which the round meshes might be suitable for supplying the nutrient elements that are needed in the differentiation of the inner enamel epithelial cells. Interestingly, the vascular architecture of the cat pulp during the maturation process (Kishi and Takahashi, 1987; Kishi *et al.* 1989b) was reported to be similar to that in rats, rabbits and dogs (Nakamura *et al.* 1983, Semba *et al.* 1983; Yoshida, 1984; Takahashi, 1985). In all species the pulp

shrank in size with age, the characteristic three vascular networks disappeared and only coarse terminal capillary networks remained. In the pulpal horn and root canal areas several circular hairpin loops occurred in the maturation stage. Together with the narrowing of the pulp cavity, the networks changed their structure suggesting that the vascular network remodeled during the maturation of the tooth (Kishi *et al.*, 1989b).

The vascular changes in the dog pulp were also investigated experimentally. Acute and chronic pulpitis was the subject studied by Kogushi *et al.* (1988) and Takahashi (1990). They found the permeability of vessels to be increased in the initial stage of acute pulpitis which was evidenced by extravasation of resin in vascular resin casts. While an expanded and tortuous granuloma-like vascular network was found around an abscess in chronic pulpitis, leukocyte extravasation in acute pulpitis was confined to venules and postcapillary venules below the dentin (Takahashi, 1990). Kogushi *et al.* (1988) showed that in acute pulpitis, the vascular architecture in necrotic areas was the same as that in normal tissue. However, there was considerable leakage of resin in necrotic areas suggesting increased permeability.

The vascular architecture of the guinea pig pulp was studied by Aharinejad *et al.* (1990a). They found cylindrical capillary cords to be present in the pulp and thought that these reflected the response of the pulp to stresses (Fig. 4a). As the pulp was exposed to continuous stresses, secondary dentin was deposited so that the pulp space was reduced in size. This prompted the authors to interpret the pulpal cords as channels surrounded by dentin.

The only SEM study on dental vessels in humans available to us is that by Kishi *et al.* (1989a), who found the pulp vasculature of humans to be strikingly similar to that in cats and dogs (e.g., terminal capillary networks).

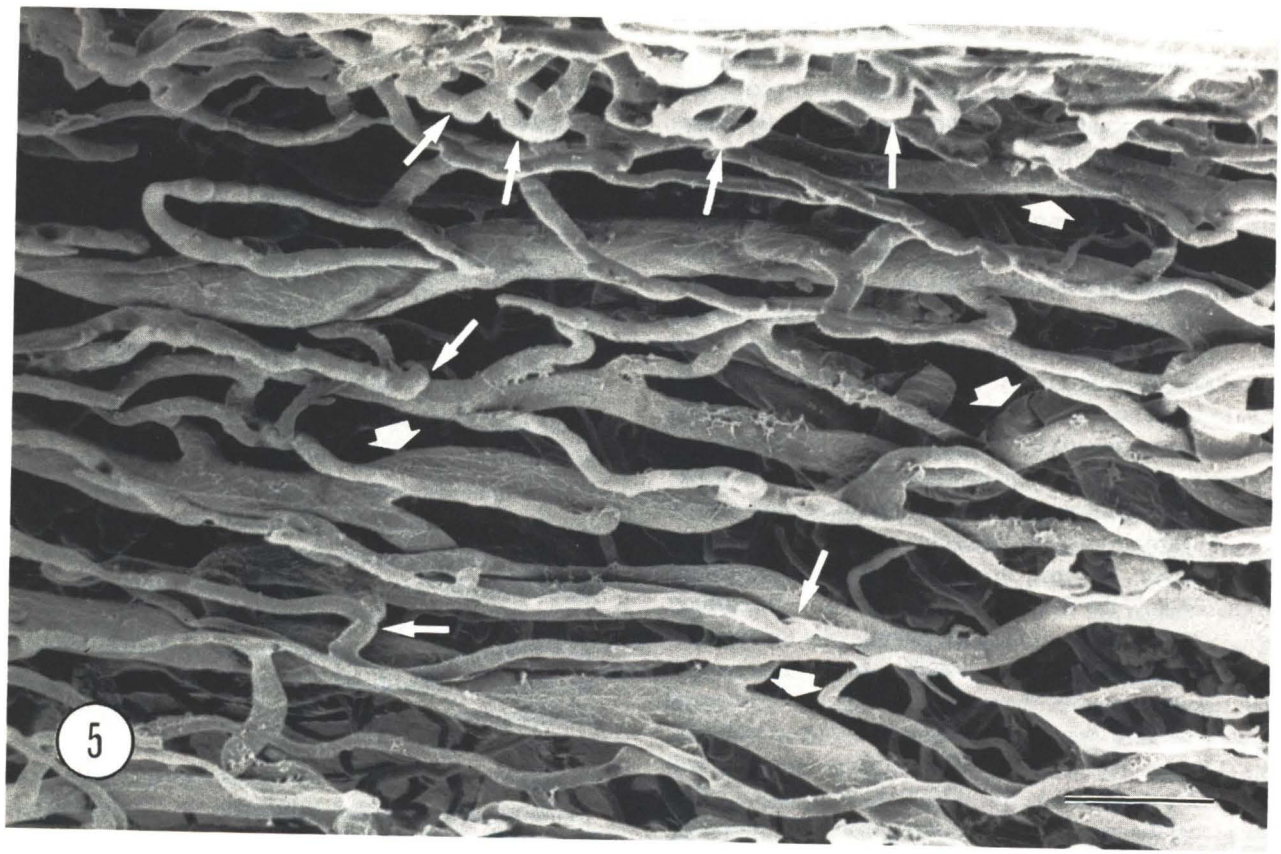
Only few studies have been published on the lymphatics of the dental pulp. The earliest one available to us is that by Schweitzer (1909). More recent investigations fall into one of two categories: Their authors either advocate (Bernick and Patek, 1969; Bernick, 1977; Frank *et al.*, 1977; Berkovitz *et al.*, 1978; Avery, 1986) or deny (Scott and Symons, 1982; Torneck, 1989) the presence of pulpal lymphatics. In the most recent investigation by Bishop and Malhorta (1990), transmission electron microscopy of the cat pulp produced conclusive evidence of their existence and prompted the authors to postulate that the lymphatics were prominently involved in the balance between the hydrostatic and osmotic pressures at the capillary ends, which was brought about by extravasation of fluid and proteins into the interstitial spaces.

In summary the microvasculature of the tooth is still poorly understood in humans and guinea pigs. Future studies should address the vascular pattern of the teeth in the presence of pulpitis and the relationships between the periodontal ligament and the alveolar bone.

The esophagus

The esophagus is of special significance. This has two reasons: (**1**) Esophageal neoplasms, while rare, often enough defy early detection and their 5-year survival rate is extremely low, i.e., 3 to 4% (National Cancer Institute, 1972; Earlam and Cunha-Melo, 1980); patient age apparently does not correlate with the prognosis (Peracchia *et al.*, 1989; Mori *et al.*, 1990). (**2**) Esophageal varices carry an extremely poor prognosis (Teres *et al.*, 1987; Westbay *et al.*, 1989); as cirrhosis of the liver is the most common cause of portal hypertension in the Western world (Hütterroth and Meyer, 1980) and as about 50% of cirrhotics die of bleeding varices (Graham and Smith, 1981), they constitute a major clinical challenge. Recent evidence suggests that esophageal varices may also be idiopathic (Motoo *et al.*, 1989). In addition the anatomical location of the esophagus, in the posterior mediastinum, is of importance particularly in thorax surgery.

In the light of these factors, the microvasculature of the esophagus is of particular interest. Therapeutic concepts for controlling esophageal cancer and esophageal varices require a full understanding of esophageal circulation. The earliest description of the vessels of the gullet is no less than 500 years old. Vesalius (1543) pictured the esophageal branches of the left gastric vessel lying close to the vagus nerves. Bartholin (1673) described the veins of the esophagus to drain into the azygos, intercostal and jugular veins. The dual drainage system of the lower third of the esophagus into the chest veins and the portal circulation was first described by Dionis (1703) and Portal (1804). Injecting the vessels with India ink, Demel (1924) made several vascular preparations of the human esophagus and found the different parts of the esophagus to have different vascular patterns. His observations suggested that, in general, the esophagus was more abundantly supplied with blood vessels at its lateral margins than at its anterior and posterior surfaces. These were relatively undersupplied, as most of the branches supplying the organ entered it from the sides. In the esophageal segment behind the tracheal bifurcation, vessels were most abundant; at the gastroesophageal junction the left margin supplied by the inferior phrenic artery lagged far behind the right one which received its supply from the left gastroepiploic artery. Kegaries (1934) observed several anastomoses between the splenic and the esophageal veins and considered them as possible sources of esophageal varices in cases of splenic anemia or Bandit's disease, independent of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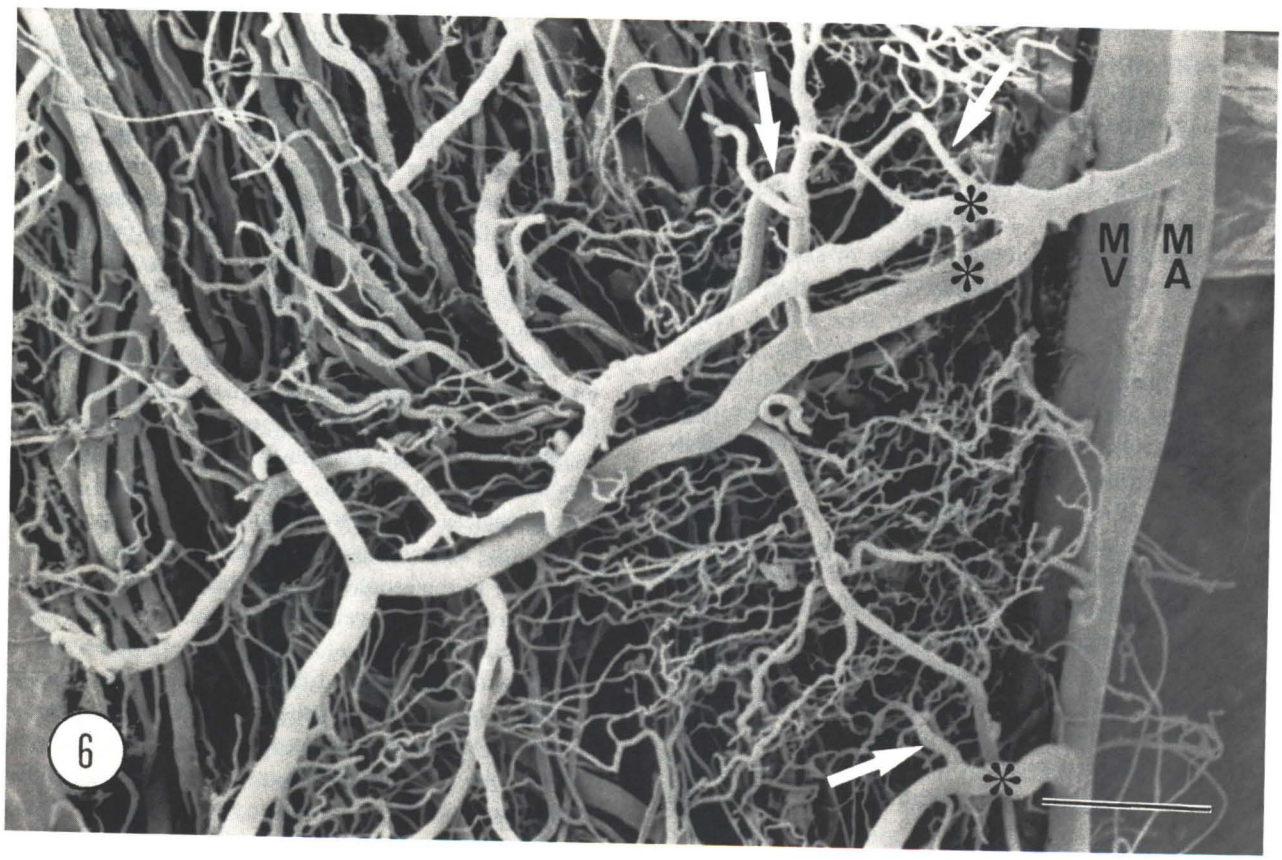
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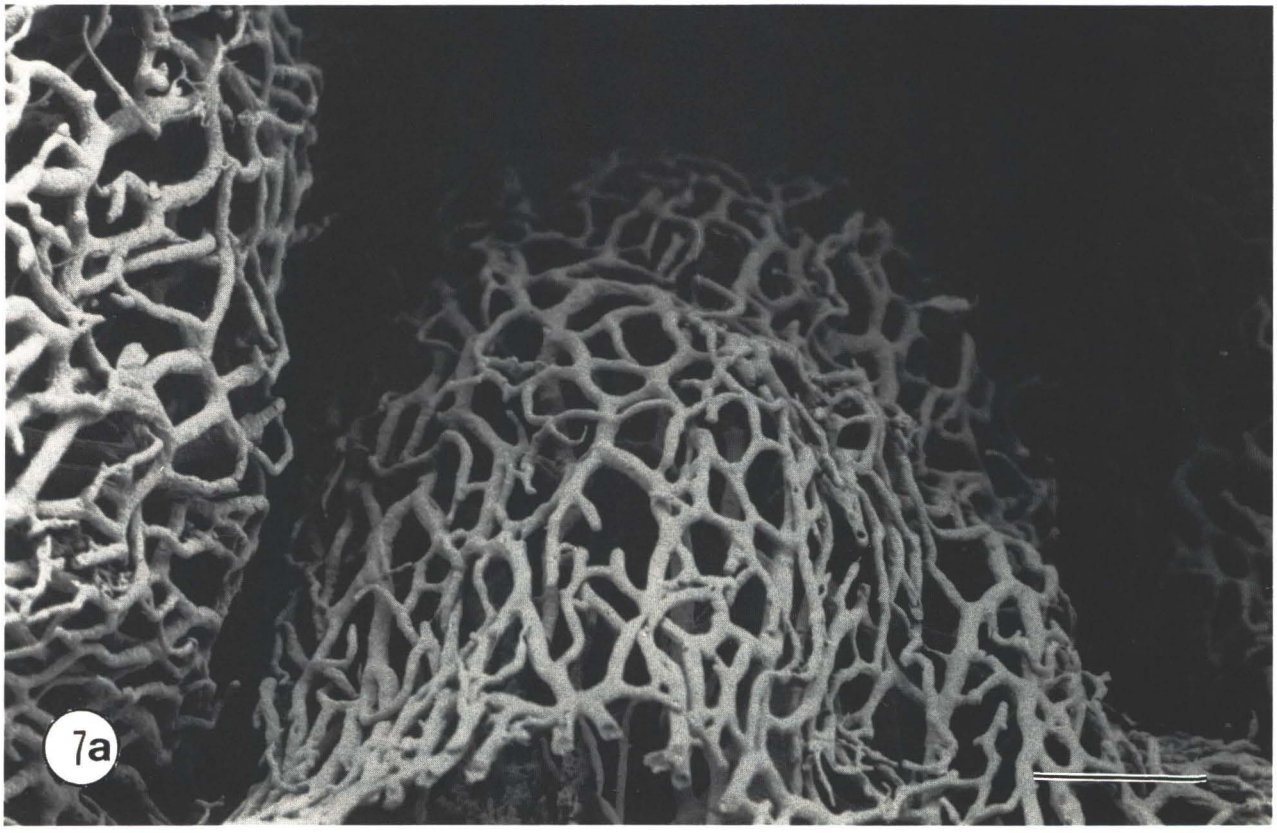
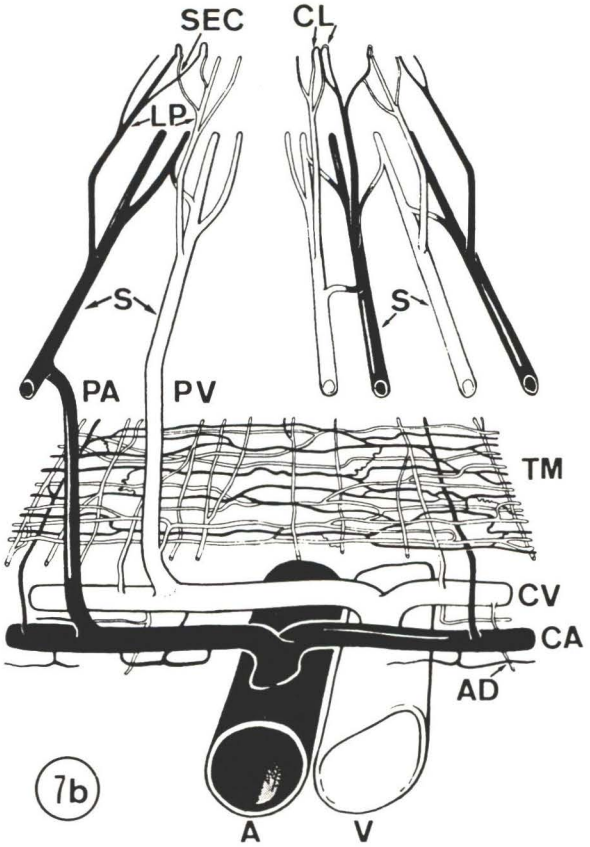


Fig. 5 (facing page, top). Longitudinally arranged subepithelial capillary network in the esophagus of the guinea pig. Note several capillary loops protruding towards the lumen (small arrows). Lamina proprial vessels are marked by bold arrows. Bar = 100 μm.

Fig. 6 (facing page, bottom). Vasculature of the rabbit esophagus. From the main longitudinal artery (MA) and vein (MV) circumferential vessels (asterisks) arise, from which in turn the perforating vessels (arrows) arise. Bar = 250 μm.

Fig. 7a (above). Subepithelial capillary network in the human esophagus without a recognizable pattern. Bar = 200 μm.

Fig. 7b (at right). Microvascular architecture of the esophagus in guinea pigs, rats, rabbits, and human, schematic drawing. A, V = main longitudinal artery and vein; CA, CV = circumferential artery and vein; PA, PV = perforating artery and vein; SEC = subepithelial capillaries; CL = capillary loops of the mucosa; LP = Lamina propria; S = submucosa; TM = Tunica muscularis; AD = adventitia. Note that the capillary loops of the mucosa are only present in guinea pigs and rats.



liver cirrhosis. He also described the submucosa of the esophagus as being richly supplied with veins situated both above and below the muscularis interna. The veins at the cardia he found to be strongly supported by loose connective tissue. As a result of his study, he thought it would be doubtful that ligation of the left coronary vein of the stomach would have any beneficial effect on bleeding esophageal varices secondary to splenic anemia or Bandit's disease. But this method, he advised, should be used in hepatic cirrhosis associated with bleeding esophageal varices. Potter and Holyoke (1950) identified a submucosal arterial plexus and suggested that conclusions as to the adequacy of intramural longitudinal arterial blood flow to compensate for an extensive interruption of the extrinsic vessels at all levels would not be justified. In 1951 the anatomist Butler published his report on the intrinsic blood drainage of the esophagus. He distinguished three groups of veins: (**1**) intrinsic veins; (**2**) venae comitantes of the vagus nerves; and (**3**) extrinsic veins, and he further subdivided group (1) as follows: (**1a**) A subepithelial venous plexus lying in the lamina propria and extending for the whole length of the esophagus. While the veins of this layer were of uniform shape, they changed at the extreme upper and the lower ends. They pierced the muscularis mucosae and drained into the submucosal veins. (**1b**) A submucous venous plexus lying between the muscularis mucosae and the circular muscle coat having diameters of 50 μm up to 1 mm. At the lower end of the esophagus these veins increased in number, but decreased in diameter. In the upper one-third of the esophagus the submucous veins increased in both diameter and number (up to 7 or 8 veins arranged in dorsal and ventral groups). (**1c**) Perforating veins which arose from the longitudinal submucous veins and perforated the muscle coats of the esophagus to reach its outer surface. They received tributaries from the muscle coat. The venae comitantes of the vagus nerves ran on the outer surface of the esophagus and connected the left gastric vein to the azygos veins. The extrinsic veins were joined by perforating veins and drained into the inferior thyroid vein in the neck region, into the azygos, hemiazygos, first intercostal, superior and inferior phrenic veins in the thorax, and into the left gastric vein in the abdomen. Butler (1951) did not observe any valves in the subepithelial or comitant veins. He further proposed that the direction of blood flow may vary during the respiratory cycle.

Studying the rat, mouse and rabbit esophagus, Günther and Lierse (1968) found the vessels to adapt to the muscular architecture in all but the lower esophageal sphincter segment of the organ. They distinguished two arterial groups, one in the adventitia and the other in the submucosa. The former was more abundant in the cranial part and the latter in the caudal part of the esophagus. Veins were also located in the layers mentioned above, but anastomoses between them were fewer than between the arteries. In their macroscopic investigation, Caix *et al.* (1981) put special emphasis on the role of the bronchial branches for the middle thoracic esophagus.

Most of the studies done since 1982 concentrated on abnormalities of the vasculature or the mucosa in the presence of esophageal varices. Spence et al. (1983a) examined the causal relationships between reflux esophagitis and bleeding in patients with esophageal varices (Wagenknecht *et al.*, 1953; Orloff, 1963). Like Orloff, Spence and coworkers did not find esophagitis to be etiologically related to bleeding from varices. What they did find, however, was that most of the patients with mucosal damage had previously undergone treatment by a Sengstaken-Blakemore tube or by sclerosing. Spence *et al.* (1983b, 1984) observed dilated intraepithelial blood-filled channels in esophageal rings removed at transection for varices. They compared rings removed from variceal patients and from patients with esophageal and gastric tumors. A small number of non-varicose patients had intraepithelial channels. However, these were significantly longer and more abundant in patients with varices. The depth of papillae and the thickness of the squamous epithelium, the area and number of subepithelial channels and the area of lamina proprial channels were also shown to be greater in variceal patients. Intraepithelial channels like those described in patients with esophageal varices were also reported to be present in normal esophagi (Kitano *et al.*, 1986; Hashizume *et al.*, 1988). In our view, the term intraepithelial channels is misleading in the normal esophagus, because the only vascularized epithelium ever identified is the stria vascularis in the inner ear. In patients with esophageal varices the intraepithelial channels were suspected to be the source of minor variceal bleeding (Spence and Terblanche, 1987).

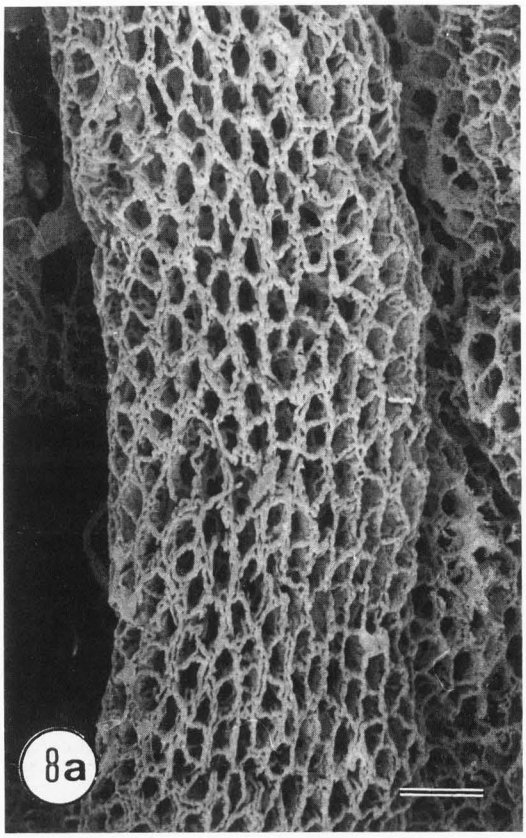
Studying the angioarchitecture of esophageal varices, Noda (1984) attributed particular importance to the veins in the lamina propria which he called "sudare-like veins" because of their arrangement. He recognized ruptured points at the oral end of the longitudinal veins in the lamina propria. Dilation of these veins was most prominent in severe varices; these veins were seen to penetrate the muscularis mucosae to connect to the submucosal veins. Unlike McCormack *et al.* (1983) who had reported flow reversal during the respiratory cycle, Noda thought that the direction of flow in variceal patients was consistently towards cranial. McCormack and coworkers also described perforators connecting esophageal varices with peri-esophageal vessels, particularly in the lower esophageal segment. These perforators caused turbulent flow which, they surmised, might be responsible for the high incidence of ruptured varices just above

the gastroesophageal junction. Noda (1984) contested this concept as, in his experience, most of the ruptures occurred in the so called critical areas where the varicose veins of the lamina propria anastomosed with the submucosal veins, i.e., in the lower esophageal segment, rather than at the gastroesophageal junction. To the judicious reader Noda's description of the location of these critical areas would seem to be inaccurate, particularly since anastomoses between the lamina propria veins and those of the submucosa were meanwhile shown to occur at any level of the esophagus in guinea pigs (Fig. 7b, shown later; Aharinejad *et al.*, 1989) as well as in rats, rabbits and humans (Aharinejad *et al.*, 1991). In fact, the latter studies established that, in humans, both the number and the diameter of the submucosal veins decreased from proximal to distal, i.e., from the pharyngoesophageal to the gastroesophageal transition zones. This would explain why most of the variceal ruptures occur at the level of the gastroesophageal junction or in the lowest esophageal segment. Resistance in the lower esophageal segment or at the level of the gastroesophageal junction is, of necessity, substantially higher than in the proximal segments of the organ. Interestingly enough, this was only seen in humans and could not be confirmed in rats, rabbits and guinea pigs (Aharinejad *et al.*, 1991).

Using a computer-assisted image analysis system, Spence (1984) distinguished three zones in variceal and normal esophagi: Zone 1 - the stomach where the mean relative area occupied by veins of the lamina propria was 2.6% in normal and 3.7% in variceal subjects; zone 2 - began at the gastroesophageal junction where the mean relative area occupied by veins of the lamina propria was up to 19.8% in normal and 37.8% in variceal subjects; zone 3 - the remainder of the esophagus where the mean relative area occupied by lamina propria veins was up to 4.9% in normal and 6.1% in the variceal specimens.

The classification of veins by Kitano *et al.* (1986) comes closer to that proposed by Butler (1951): Using macro-corrosion casting methods, they distinguished intraepithelial channels, a superficial venous plexus, deep intrinsic veins and adventitial veins in the normal esophagus, the latter anastomosing with the deep veins via perforating veins. In portal hypertensive patients all venous layers were reported to be dilated. The deep veins of Kitano and coworkers showed few interconnections, but a rich anastomosing network with superficial veins in both normal and hypertensive subjects. Furthermore, the authors showed the deep intrinsic veins to be the source of severe variceal bleeding. These veins were found to overly the superficial veins in variceal patients. Perforating veins were described as being responsible for recurrent variceal bleeding. Precise sclerotization of these veins was recommended to ensure non-bleeding intervals. While our observations would support this concept, we cannot follow the terminology used by Kitano and coworkers in two points: (**1**) relates to the existence of intraepithelial channels in normal esophagi and (**2**) to their use of the terms "superficial veins" instead of subepithelial veins and "intrinsic veins" instead of submucous veins. As mentioned earlier, we cannot accept the existence of intraepithelial channels in the normal esophagus, while we have no doubts that these may well be present in the varicose esophagus (Spence *et al.*, 1983b, 1984; Hashizume *et al.*, 1988). The controversy about the terminology can perhaps be cleared up by considering the data reported by Aharinejad *et al.* (1989; 1991): Both in guinea pigs and in rats they found two venous plexuses, in the lamina propria and in the submucosa. Arterioles arising in the lamina propria formed the "subepithelial capillary network" underneath the epithelium from which short venules reached the veins in the lamina propria (Figs. 5 and 7b). Mucosal vessels drained into the submucosal or adventitial veins through "perforating venules". In humans an additional venous plexus was present in the tunica muscularis. Found in all species they studied, perforating veins were accompanied by perforating arteries, which originated from the so called "circumferential arterioles" (Figs. 6 and 7b). The latter arose from the longitudinally arranged main adventitial arteries and extended along half the circumference of the esophagus to continue their course towards cranial or caudal. Aharinejad and coworkers attributed particular importance to the venous plexus of the lamina propria. While most of the earlier studies showed the submucosal veins to be the source of varices, their investigations (1989, 1991) suggested that the submucosal veins served as reservoirs. In the presence of portal hypertension these would become dilated and enlarged (Noda, 1984; Kitano *et al.*, 1986; Hashizume *et al.*, 1988), either overlying the venous plexus of the lamina propria to form so called major varices (Japanese Research Society for Portal Hypertension, 1980) or draining into the lamina propria veins through the perforating veins. The latter would be present as "medium-sized" or "minor" varices.

It may be of interest to recall that, in the study of portal hypertension by Ide *et al.* (1989), in the stomach only the submucosal veins were dilated, while in the esophagus both the submucosal and the lamina proprial veins were dilated. The authors attributed this difference to differences in the structure of the lamina muscularis mucosae. As the lamina muscularis mucosae was loosely structured in the esophagus, increased venous pressure in the submucosa would be readily transmitted to the vessels of the lamina propria. In the stomach, by contrast, the lamina muscularis mucosae was more compact and more firmly attached to the lamina propria so that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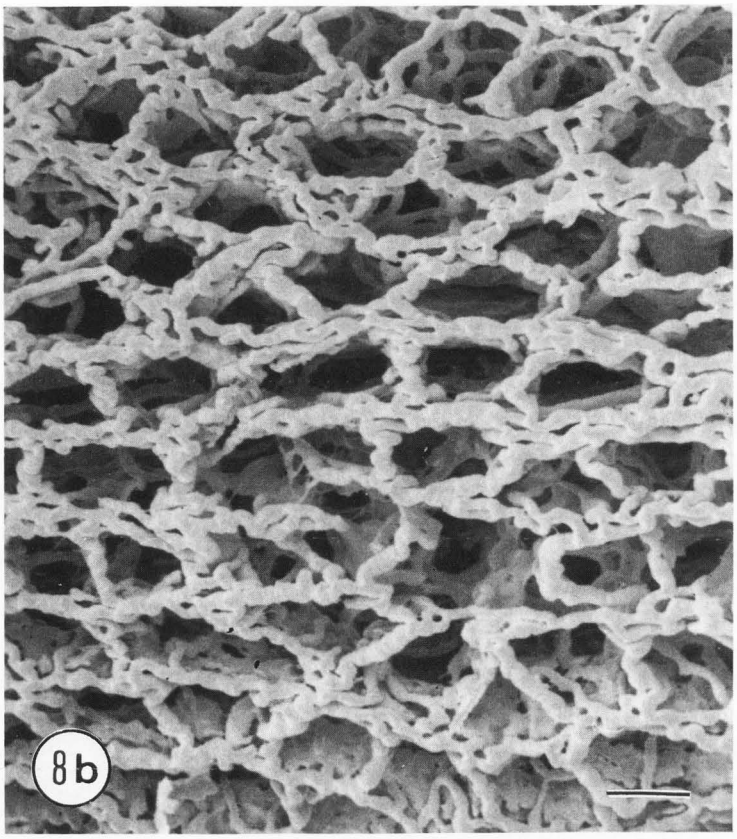
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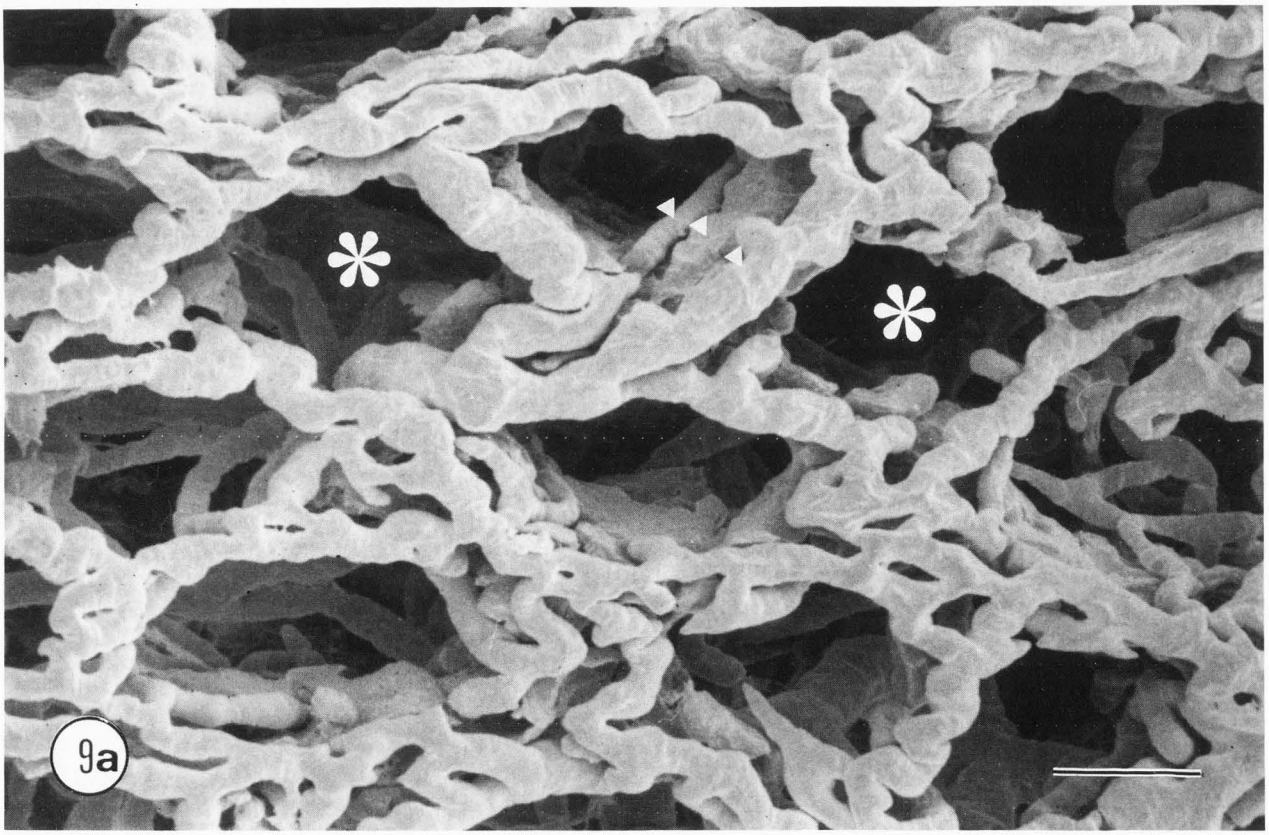
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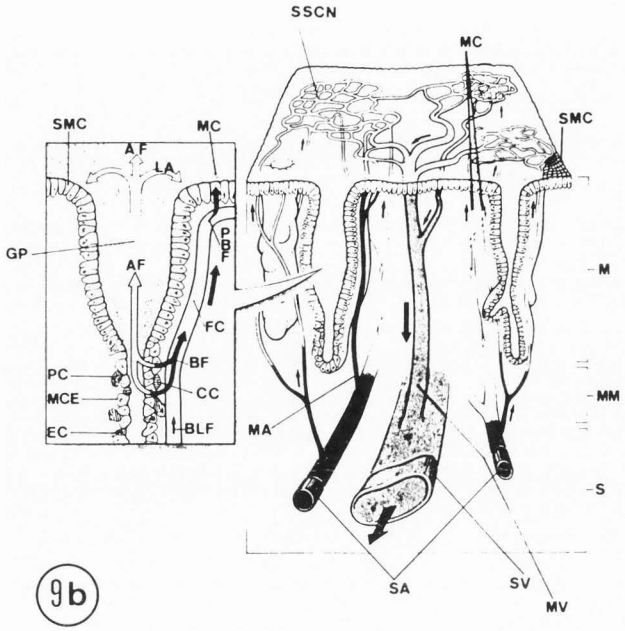

Fig. 9b. Diagram of the gastric microvascular bed in human and rats. SA, SV = submucosal arteries and veins; MA and MV = mucosal arteries and veins; SSCN = sub-surface capillary network; SMC = surface mucous cells; MC = mucosal capillaries; M = mucosa; MM = muscularis mucosae; S = submucosa. Arrows mark the direction of blood flow. Inset: Mechanism for microvascular transport of bicarbonate ions produced by parietal cells toward surface mucous cells in a local portal pattern, schematically visualized. AF = acid flow; LA = luminal acid; MC = mucous coating; SMC = surface mucous cells; GP = gastric pit; PBF = protective bicarbonate flux; FC = fenestrated capillary; BF = bicarbonate flux; PC = parietal cells; MCE = mucous cells; EC = endocrine cells; CC = chief cells; BLF = blood flow (adapted from Gannon and Perry, 1989).

Fig. 8a. Cast of a gastric mucosal fold of the guinea pig. Bar = 250 μm. **Fig. 8b**. Higher magnification of Fig. 8a. Note the honey comb pattern. Bar = 100 μm.

Fig. 9a. High magnification micrograph of the gastric subepithelial capillary network in the guinea pig. The hexagonally arranged capillaries surround the gastric pits (asterisks). The network shows two or more layers of capillaries arranged upon each other (arrowheads). Bar = 50 μm.

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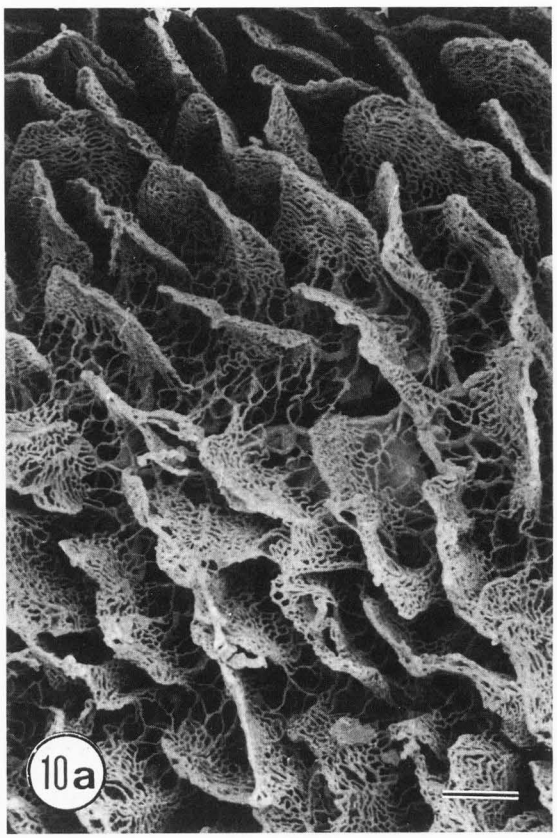
the flow in the perforating vessels would be slowed and the resultant pressure on the lamina propria veins would be reduced (Ide *et al.*, 1989). Considering the blood flow direction of lamina proprial vessels via perforating veins to circumferential veins, we think that just the opposite effect would be achieved. Pressure would be increased in the lamina proprial veins, they would become inflated.

The arrangement of the vessels in the lower third of the esophagus described by Aharinejad *et al.* (1991) in humans agrees well with the observations by Vianna *et al.* (1987). They distinguished a gastric zone, a palisade zone, a perforating and a truncal zone in the lower esophageal segment. Above the gastric zone, in the palisade zone, they described parallel veins in the submucosa. Like Vianna and coworkers, we also found these parallel veins in the submucosa, but unlike these authors we did not see any of the veins leaving the submucosa at the gastroesophageal junction to enter the lamina propria of the esophagus. In our specimens (guinea pigs, rats, rabbits, and human) the submucosal veins did not change their course at the gastroesophageal junction. In addition, we found perforating veins to be consistently present. This was not seen by Vianna *et al.* (1987), at least not in the lower esophageal segment. In the "perforating zone" Vianna *et al.* (1987) described loops which might provide for a reversal of flow. While we did not find any evidence of the loops reported by Vianna *et al.* (1987), we would be inclined to believe that the extensive anastomoses between the veins in the submucosa and the mucosa, the latter containing a vascular network without any recognizable pattern (Fig. 7a), as well as the absence or paucity of valves could serve the same purpose, i.e., to provide the morphological substrate for a reversal of flow.

Esophageal varices associated with portal hypertension would constitute a special challenge for future SEM investigations of vascular corrosion casts. Using animal models these may well be expected to shed light on some controversial issues.

The stomach

A review of all the studies dealing with the vascularization of the stomach would go far beyond the scope of this paper. Ulcers are, no doubt, a major problem in contemporary society. They have thus prompted researchers to focus their attention on the microcirculation of the stomach with a view to shedding light on the underlying pathophysiology. The oldest study in this area appears to be that of Virchow (1853). Other studies were done in dogs (Delaney and Grim, 1964; Piasecki, 1975; Gupta *et al.*, 1978; Marais, 1982), cats (Svanes *et al.*, 1975; Marais, 1988), in rats (Arabehety *et al.*, 1959; Guth and Rosenberg, 1972; Gannon *et al.*, 1982; Konerding *et al.*, 1987), in rabbits (Ohtsuka and Ohtani, 1984) and in humans (Barclay and Bently, 1949; Brown and Derr, 1952; Bell, 1967; Piasecki, 1974; Gannon *et al.*, 1984). Studying digested stomach specimens, Sugimoto and Ogata (1989) described the structure of the subepithelial tissues in the rat stomach.



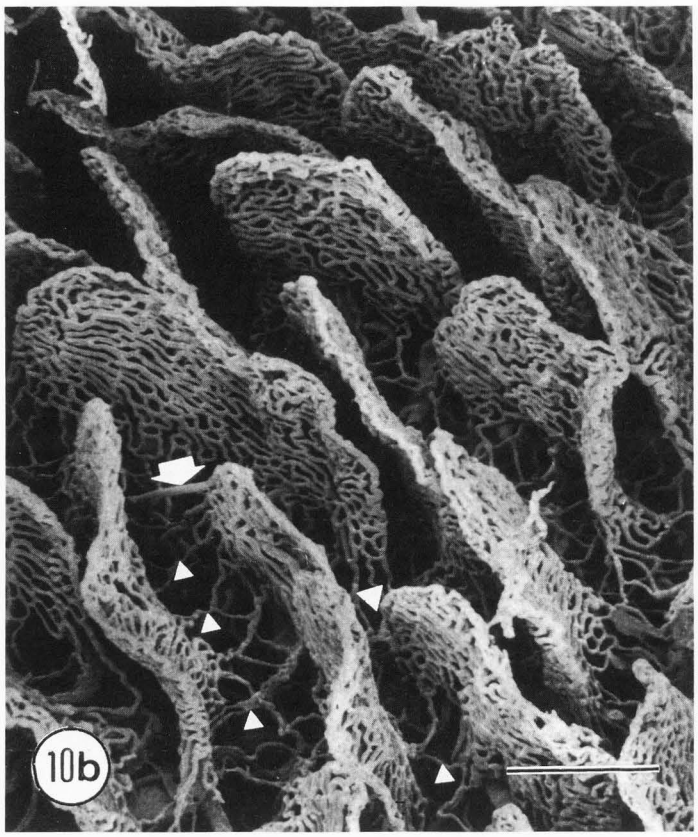


Fig. 10a. Ridge-like villi in the guinea pig small intestine. Bar = 250 μm. **Fig. 10b**. Higher magnification of Figure 10a. Arrow marks a supplying arteriole running towards the edge of the villus, large arrowhead marks a draining venule, small arrowheads mark the precryptal capillaries. Bar = 250 μm.

Accounts of the microangioarchitecture of the stomach based on SEM of vascular corrosion casts show a large measure of agreement. The mucosa is described as being supplied by small arterioles from the submucosal arterial plexus. These arterioles give off capillaries which are perpendicular to the luminal surface of the stomach and pierce the lamina propria. Just beneath the epithelium these capillaries form a polygonal network which reflects the arrangement of the gastric pits (Figs. 8 and 9a, b). This polygonal network is drained by subepithelial venules which converge into mucosal veins (Fig. 9b). Running at right angles to the mucosa, these empty into the submucosal veins (Fig. 9b). This pattern was reported for both humans and rats (Gannon, 1981b; Gannon *et al.*, 1982, 1984; Ohtani *et al.*, 1983; Ohtsuka *et al.*, 1988; Gannon and Perry, 1989).

In the rabbit stomach the submucosal arteries were found to give off short and long arterioles. The short arterioles ascended to the base of the fundic glands and broke up into a capillary network, the long ones ascended along the glands to feed the subepithelial capillary network (Ohtsuka and Ohtani, 1984; Ohtani, 1989). In the glandular neck region the two networks connected with each other and converged into common venules, which emptied into the submucosal veins. What Ohtani (1989) described for the rabbit stomach reportedly reflects the pattern in the human stomach (Raschke *et al.*, 1987). But Gannon and Perry (1989) found the mucosal microcirculation of the human stomach to be more closely related or even identical to that of rats.

Marais *et al.* (1989) reported the capillary arrangement in the dog and cat antrum to show considerable similarity, but to be less dense than in the rat stomach. In contrast to the latter species, the dog and cat mucosa, in their observations, was drained by venules with more of an acute angle to the mucosal surface. Receiving few tributaries along their course, the rat mucosal veins were described as being independent of other venous systems (Ohtsuka *et al.*, 1988; Gannon and Perry, 1989) and as exclusively serving the purpose of mucosal drainage. The physiological significance of the gastric mucosal barrier has been the subject of many investigations.

What role the vasculature plays in this context may perhaps be explained by the observations of Gannon *et al.* (1984). Their TEM studies confirmed a close proximity of the mucosal capillaries to the lamina proprial aspect of the parietal cells and a preferential spatial association of mucosal capillaries with parietal cells and suggested the existence of an intrinsic local portal transport system from the gastric glands to the hydrogen-producing parietal cells on the surface. The authors proposed the hypothesis that the bicarbonate ions released by the parietal cells, as they secreted H^+ ions, were transported from the lamina proprial surface of the parietal cells in the local portal system to be pumped into the mucous cells on the mucosal surface, thus enhancing the mucosal barrier (Fig. 9b). They furthermore hypothesized that an intramucosal local portal circulation of HCO_3^- exists. Confirmed by Ohtani *et al.* (1983), Ohtsuka *et al.* (1988) and Raschke *et al.* (1987), this hypothesis is supported by the observation that the gastric antrum where the glands lack parietal cells is the most common site of gastric ulcers. Ohtsuka *et al.* (1988) thought that the proposed upward flow of blood might transport serotonin, somatostatin and other substances produced by endocrine granulated basal cells. Conversely, metabolites produced in response to acute stress might be washed up to the mucosal surface along this transport route to cause surface ulceration (Marais *et al.*, 1989). Although described in the mucosa (Nylander and Olerud, 1961; Delaney, 1975) and the submucosa (Boutler and Parks, 1960; Hase and Moss, 1973), the existence of arterio-venous anastomoses was dismissed by Gannon and Ohtani.

Lymphatics were found to be present in the interglandular region of the deep mucosa (Ohtani, 1989). These were described as converging to thicker channels piercing the muscularis mucosae to enter the submucosal lymphatic plexus. From there, they were reported to drain into a lymphatic plexus between the inner and outer layers of the tunica muscularis propria (Ohtani and Murakami, 1987). In the tunica muscularis lymphatics were shown to be equipped with bicuspid valves. This agrees with *in vivo* observations by Nagata and Guth (1984).

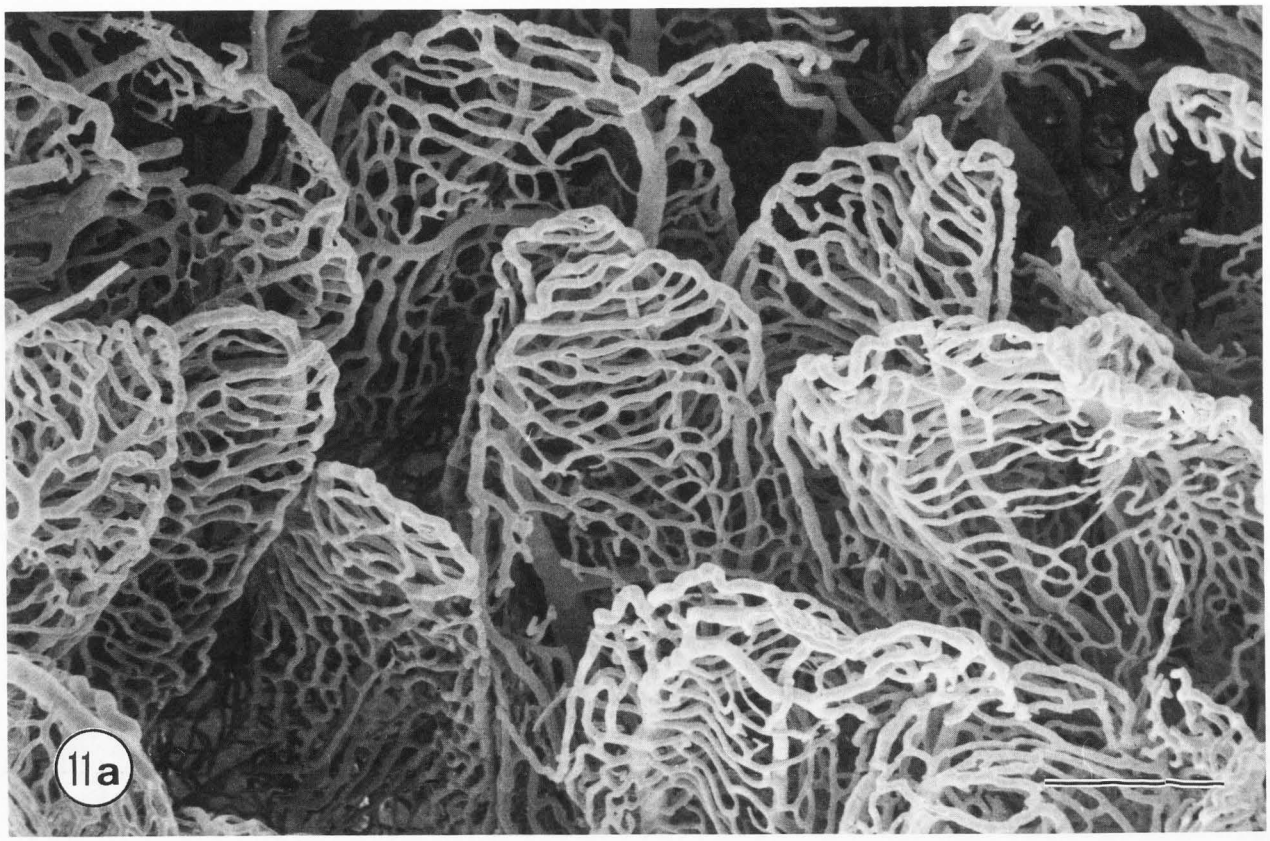
Different segments of the golden hamster stomach and that of the rat were compared by Imada *et al.* (1987) and Browning *et al.* (1983) respectively. Both groups found a two-dimensional array of vessels to be present in the lamina propria of the forestomach. This contrasted with a well developed three-dimensional capillary network along the glands and gastric pits in the glandular stomach. Imada *et al.* (1987) described the subepithelial capillaries to be thicker than those in the mucosa and accordingly called them sinusoids. At the mucosal surface they found two types of capillaries to be present, an arched type in the cephalic and a honeycomb type in the caudal region of the body. In their interpretation, all ascending vessels were arterial and all descending ones were venous. While this is in agreement with the observations by Gannon *et al.* (1982, 1984), it contradicts the data published by Ohtsuka and Ohtani (1984), who described arterioles in the lamina propria of rabbits. Imada and coworkers suggested that the difference in the density of the vascular supply in different segments of the stomach reflected the involvement of the vessels in protective mechanisms: Known to be a common site of ulceration, the antrum is comparatively poorly vascularized.

In summary, the existence of a local portal system in the gastric mucosa as well as that of vascular connections between different gastric segments, e.g., the body and the antrum, has as yet to be proven. In addition, morphologic abnormalities associated with gastric ulcers, their healing and the resultant alterations of the vascular supply should also be investigated by SEM of vascular corrosion casts. These, no doubt, are challenging subjects for future studies.

The small intestine

Accounts of the villus angioarchitecture, some of them from the previous century, vary. Henle (1873) and Frey (1876) described a step-ladder circulatory pattern in man and in rabbits. Near the turn of the century a fountain pattern was supported by Mall (1887) and Böhm and Davidoff (1900). Descriptions by Stöhr (1901), Szymonowicz (1902), Rauber and Kopsch (1909) and Schäfer (1912) have followed the tuft idea of the villus circulatory pattern. Spanner (1932) identified a much more complex pattern in human and rabbit villi than the fountain concept. Injecting the superior mesenteric artery in humans, rabbits, dogs and opossums with a mixture of Latex and India - ink, Jacobson and Noer (1952) found that humans and rabbits showed an almost identical tuft pattern. Patzelt (1936) published a detailed account of the micromorphology of the small intestine. Injecting monkey guts with silicone rubber, Reynolds *et al.* (1967) reported that the villus vascular pattern in monkeys was distinct from that of other species studied (rabbits, cats, dogs) by the presence of an additional drainage system existing side by side with the central villus vein and draining the cryptal plexus.

Among the early attempts to shed light on the villus microvasculature by SEM of vascular corrosion casts, that of Nowell and Tyler (1974), and Nowell and Lohse (1974) figure prominently. Confirming the observations of Jacobson and Noer (1952), Nopanitaya and Flores (1979) described a tuft pattern in the villi of monkeys and reported anastomoses to be present between the arterial and the venous system without specifying their location.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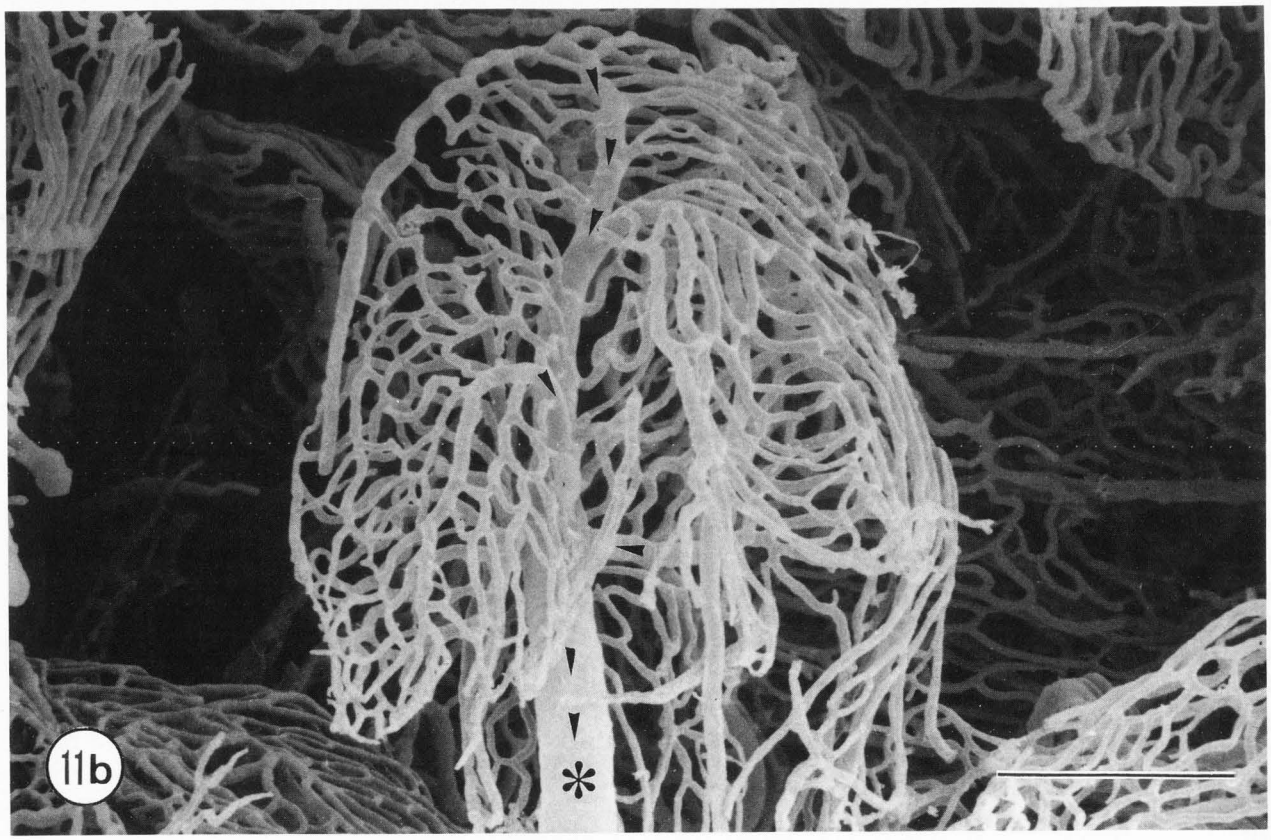
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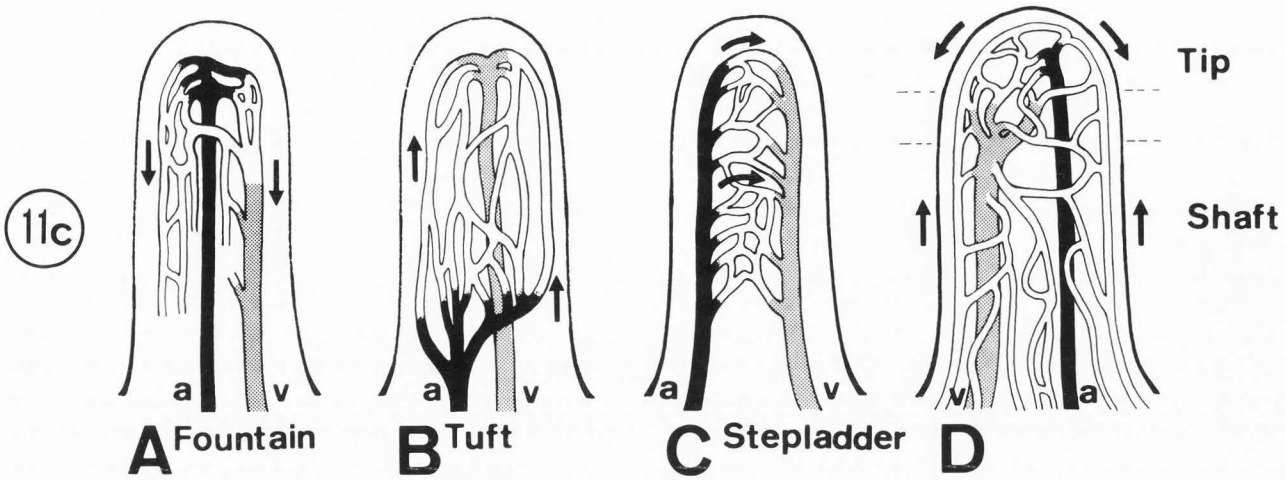


Fig. 11a, b (at left). Micrographs of the rabbit small intestinal villi. Bar = 250 μm. **Fig. 11a.** Note the different size of the villi. **Fig. 11b.** A single villus of the rabbit small intestine. The fountain pattern near the base of the villus and the tuft pattern around the shaft of the villus can be clearly identified. Both capillary systems are drained by the central efferent vein (asterisk). Arrowheads mark the direction of the blood flow.

Fig. 11c (above). Models of villus microvascular patterns in rats, rabbits and man. Dotted lines in diagram D mark watershed region between two blood flow sources to villi, i.e., direct arterial supply to the villus tip and indirect local portal supply via the periglandular capillaries (the system of the "dual blood supply"). a = artery, v = vein. Arrows mark direction of blood flow.

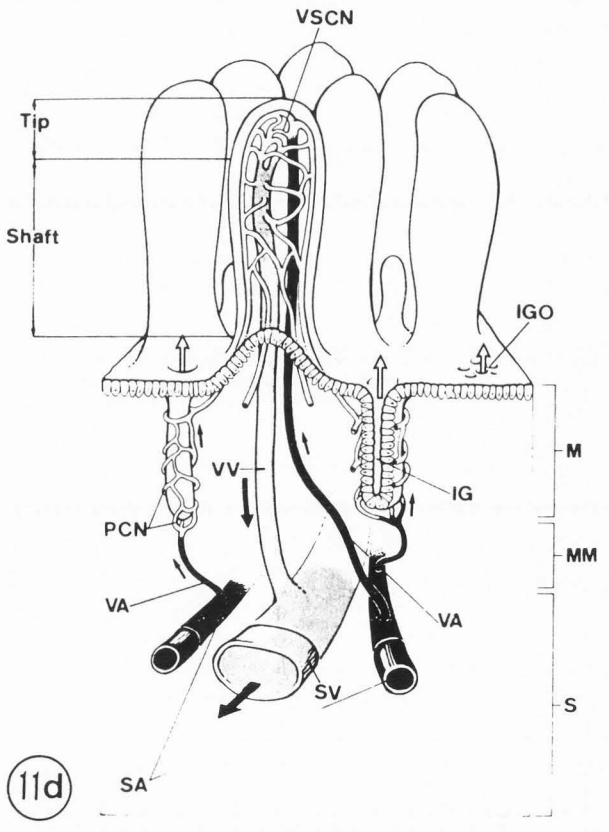


Fig. 11d (at right). Patterns of the rat and human intestinal mucosal microvasculature, shown schematically. SA, SV = submucosal arteries and veins; VA, VV = villus arteriole and venule; PCN = pericryptal capillary network; IG = Intestinal glands (crypts of Lieberkühn); IGO = intestinal glands openings; VSCN = villus subepithelial capillary network; M = mucosa; MM = Muscularis mucosae; S = submucosa. Arrows mark the blood flow direction (adapted from Gannon and Perry, 1989).

Ohashi *et al.* (1976) finally established the nature of the microcirculation in the intestinal villi, at least in rats. They classified the conflicting descriptions of earlier authors in three categories. As this classification provides for some clarity (Fig. 11c), it seems worth quoting: (**1**) Step-ladder concept: The afferent and efferent veins extend from the base to the tip of the villus (Henle, 1873; Jacobson and Noer, 1952). (**2**) Fountain pattern: The afferent artery, after reaching the tip of the villus, gives rise to capillaries which are collected at the base of the villus into the efferent vein (Fig. 11c; Bellamy *et al.*, 1973). (**3**) Tuft pattern: The afferent artery continues at the base of the villus into a tuft of capillaries which converge near the tip of the villus into the efferent vein (Fig. 11c; Reynolds *et al.*, 1967). On the basis of their own studies, Ohashi and coworkers demonstrated that the vascular bed in the mucosa was isolated from that in the tunica muscularis, both being supplied from the submucosal arterial plexus. In keeping with the two muscular layers, they found the capillary bed in the tunica muscularis to be divided into two layers (Ohtsuka *et al.*,

1988): Ascending from the submucosa to the tip of the villus, an arteriole broke up into capillaries taking a downward course on either side of the leaf-like villus. Crypts were also shown to receive capillaries from the submucosal arteries. The two capillary systems were reported to converge at the base of the villus draining into the submucosal vessels through paired efferent veins on either side of the villus. This model which Ohashi *et al.* proposed in 1976 clearly confirmed the fountain concept.

Much of what we know about the shape, microvascularization and physiology of the intestinal villi goes to the credit of Gannon and coworkers. They reported that the dog villus was a stout cylindrical structure, that cat villi were slender and finger-shaped, that rats and guinea pigs had flattened leaf-shaped villi and that the villi in humans were a mixture of all these configurations (Gannon and Perry, 1989). Their studies suggested the vascular pattern of human villi to be the same as that in rabbits (Gannon *et al.* 1980b; Gannon and Perry, 1989). Similar to Ohashi *et al.* (1976), they found that, in both species, straight capillaries connected from the top of the periglandular capillary network up the lower 3/4 of the villus to the villus vein (Gannon, 1979; Gannon *et al.*, 1980a, b, c; Ohtani *et al.*, 1983). In contrast to the rat villus with its central arteriole dividing at the tip of the villus in a T-shaped fashion to supply either side of the villus and its two veins draining the capillaries, guinea pigs were described as having an irregular capillary network, each surface being supplied by a number of arterioles to the luminal edge of the ridge and drained by several low set venules (Fig. 10). In cats a single arteriole was reported to extend to the villus tip and branch into a cylindrical capillary network which was connected to venules between the intestinal glands at the villus base. In dogs, restricted to the upper half of the villus, the arteriole connected into the villus capillary network serially along its length to the villus tip and a vein just in the same manner was connected to the capillaries. As extensive connections were present between the crypts and villus capillaries in rats (Metry *et al.*, 1983), while the lower vessels entered the submucosal veins, Gannon and Perry (1989) and Harper and Gannon (1978) thought a local portal system to be present. In such a system blood from the villus would filter down through the pericryptal plexus to the submucosa thus providing for a chemically controlled regulation mechanism, e.g., regulation of epithelial cell proliferation rate in the crypts by a blood-borne factor from the eroding villus tip.

Gannon *et al.* (1980c) proposed that the human and rabbit villi received a dual blood supply (see also Fig. 11d; Gannon *et al.*, 1980b; Gannon, 1981a; Gannon and Perry, 1989): Firstly, a fountain pattern supplying the distal approximately 20 to 30% of the villus and, secondly, a tuft pattern of supply derived from the capillary plexus surrounding the intestinal glands and supplying the basal 70 to 80% of the villus (Fig. 11). Both of these capillary systems were described as draining into the villous venule high in the villus and to consist of tortuous capillaries at the tip of the villus (fountain pattern) and of straight capillaries in the shaft (tuft pattern, Gannon *et al.*, 1980b, c; Gannon and Perry, 1989).

Except in cats, Gannon and Perry (1989) found a portal system to connect the villi with the crypts in all of the species they examined,based on this anatomy, they suggested that the blood would flow from the pericryptal plexus to the capillaries in the lower portion of the villus if the colloid osmotic pressure is raised and the hydrostatic pressure is lowered (see also Gannon *et al.*, 1980b; Gannon, 1981a). In their interpretation, this system would be ideally adapted for the uptake of fluid from the villus, i.e., for the extraction of fluid from the arteriolar end of a dual capillary network with fluid absorption into the venous end. However, these physiological variables have yet to be measured, the proposal of Gannon and Perry is only a consequence of the anatomy they observed. Their suggestion is in contrast to the concept proposed by Florey *et al.* (1941), who proposed two flows, one of blood and other of secretion fluid, in their scheme of fluid recycling from crypts to villi.

The blood supply of Brunner's glands has only been dealt with by Browning and Gannon (1984). They showed the acini to be surrounded by a basket-like plexus of fenestrated capillaries (Treasure, 1978) interconnected with capillary plexuses surrounding adjacent acini. The arterial supply and venous drainage of Brunner's glands were described as being separate from the overlying villi. As there were connections of the Brunner's gland microvascular web with the pericryptal microvascular network and as there were also connections from the latter to the villus venules en route to the submucosa at the level of the crypts, the authors thought that, in the duodenum, the capillaries of the lower portion of the villus might not receive a tuft supply of capillary blood from the pericryptal capillary network. The parallel arrangement of villi and Brunner's gland vascular beds were described as being important physiologically, because the secretion of HCO_3^- by Brunner's glands must result, stoichiometrically, in a minor degree of acidification of venous blood effluent from the glands. In addition, the authors found the degree of internal self-anastomoses of the submucosal arterial network of the duodenum to be less than in the other portions of the small intestine and interpreted this difference as suggesting that the extrinsic arteries to the duodenum were end arteries from the extramural arcades (Piasecki, 1975). The concept of arterio-venous anastomoses such as those seen in microsphere experiments (Levitt *et al.*, 1979; Dinda *et al.*, 1983) was dismissed on the basis of SEM

studies of vascular corrosion casts in all of the reports mentioned.

In rabbits and in rats the lymphatics of the small intestine were investigated by Ohtani and Ohtsuka (1985) and by Ohtani (1987). In both of these species the so called lacteals, i.e., blindly ending structures tapering towards the villus base, were described as lying underneath the subepithelial capillary network. With a diameter of 70 to 110 μm and a length of 400 to 500 μm, they pierced the muscularis mucosae to drain into the thin distal lymphatics of the submucosal lymphatic plexus (see also Ohtsuka *et al.*, 1988). In the upper portions of the rabbit small intestine with flattened conically shaped villi, two to five central lacteals were reported to be present. These converged to sinus-like vessels. The number of central lacteals was described as decreasing from proximal to distal. The submucosal plexus was found to pierce the outer longitudinal muscle fibers of the tunica muscularis to join the lymph nodes in the mesentery (Ohtani and Ohtsuka, 1985; Ohtani, 1987). In rats Ohtani (1987) described a single-layered network of lymphatics between the outer and inner layers of the tunica muscularis, which he also found to drain into the submucosal plexus. In addition, he reported that two lymphatic sinuses in the mucosa may be connected by transverse anastomoses.

The microvascularization of the lymphoid follicles in mice and rats was studied by Bhalla *et al.* (1981) and by Yamaguchi and Schoefl (1983). Peyer's patches were described as being supplied by branches of the mesenteric arteries. Upon reaching an aggregate of follicles the artery divided and gave off branches running close to the serosal surface. These interfollicular arteries segregated into horizontal arterioles running parallel to the serosal surface as well as vertical arterioles penetrating the follicles. In addition, central ascending arterioles were described arising from the horizontal or the interfollicular arteries. These traversed the germinal center or adjacent T-cell areas and broke up into subepithelial capillaries that formed a reticulum of interconnecting vessels reminiscent of a fountain pattern (Bhalla *et al.*, 1981; Yamaguchi and Schoefl, 1983; Ohtsuka *et al.*, 1988) and anastomosed with vertical arterioles or drained into subepithelial collecting venules; some joined with capillaries to surround intervening crypts. This resulted in a capillary basket beneath the crypts. Through post-capillary and collecting venules the dome-like capillary network drained into the interfollicular veins.

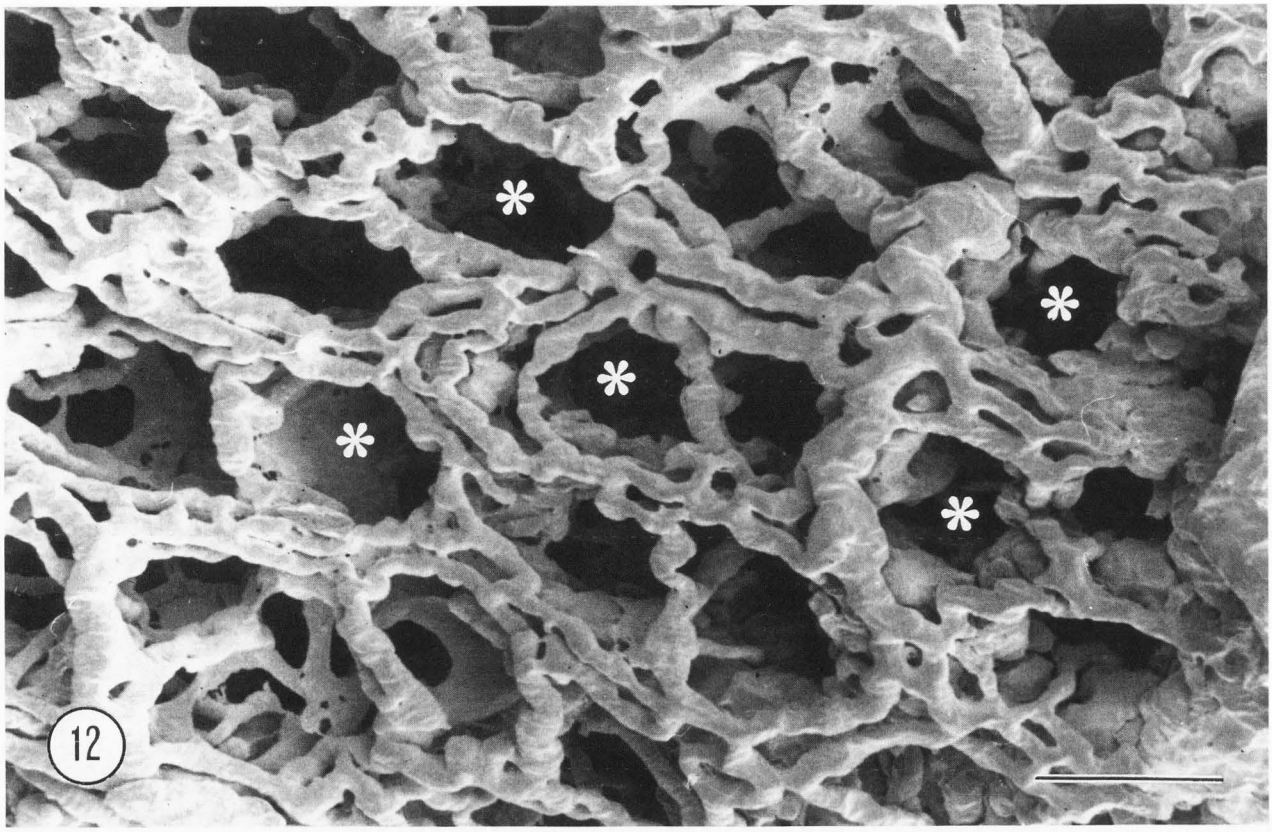
The connections between the follicles and the crypts were thought to be important physiologically, because they might provide a route for the migration of humoral factors to the crypts, which might regulate the migration of proliferating cells from the crypts to the follicle surface (Bhalla *et al.*, 1981).

The microvasculature of the small intestine is well documented. However, a number of aspects are still poorly understood, among them the three-dimensional architecture of the lymphatics in the human gut and their relations to the villus blood vessels.

The colon

Surprisingly, studies of the colonic microcirculation are scarce in spite of the multitude of clinical problems, most prominent among them the microcirculatory compromise in the presence of colonic anastomoses (Shikata and Shida, 1985; Schäfer *et al.*, 1990). The earliest account appears to be that of Albinus (1736). India - ink-gelatin injection was the technique used by several authors for studying the colonic vasculature (Eisberg, 1924; Meillere, 1927; Wolfram-Gabel *et al.*, 1986). In the illustrations of Nopanitaya *et al.* (1979) the microvascular architecture of the colonic mucosa in rabbits showed a honeycomb pattern.

Browning and Gannon (1986) published a very detailed account of the colonic vasculature. A striking similarity of the topology of colonic vessels with that in the stomach (Fig. 12) was reported by several authors (Browning and Gannon, 1986; Ohtsuka *et al.*, 1988; Gannon and Perry, 1989). The submucosal arteries were described as breaking up at the most abluminal level of the mucosa into a capillary network that ramified in the lamina propria between the colonic glands. The predominant orientation was perpendicular to the plane of the mucosal surface, but there were frequent cross-connections. At the most luminal aspect of the lamina propria the capillary net of the mucosa was reported to be connected with a polygonal plexus of microvessel rings surrounding the necks of the colonic glands. There was no evidence of a direct arteriolar supply to the luminal portion of the colonic mucosa equivalent to that apparent in the small intestinal villi; indeed, the circulation of the colonic mucosa appeared equivalent to that of the gastric glands (Fig. 13); in other words, the arteries did not or at best rarely penetrated the mucosa. Drainage of the mucosal capillaries into venules, which subsequently joined the submucosal veins (Fig. 13; Ohtsuka *et al.*, 1988), was reported to occur at the most luminal aspect of the mucosa (Browning and Gannon, 1986; Gannon and Perry, 1989). The microvascular bed of the colonic tunica muscularis is supplied and drained by submucosal vessels (Fig. 13). The tunica muscularis shows two capillary networks, an outer and an inner layer, which are, correlating to the muscular layers, arranged longitudinally and circularly respectively (Fig. 13). This arrangement of capillaries together with supplying and draining pattern is common for the tunica muscularis of the small intestine. The spatial density of colonic mucosal capillaries decreased from proximal to distal, as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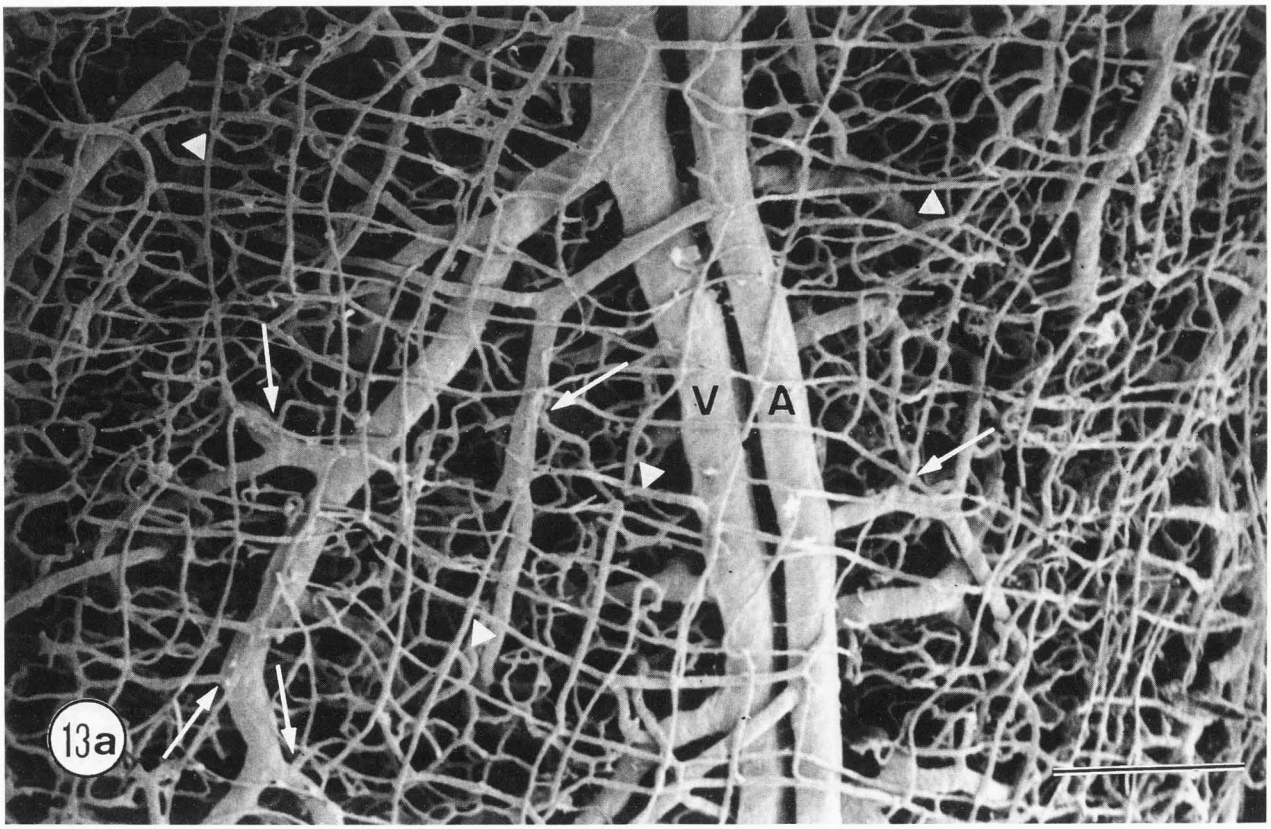
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Fig. 12 (at left). Hexagonal subepithelial capillary network of the guinea pig colon. Hexagons surround the outlets of the colonic glands (asterisks). Bar = 100 μm.

Fig. 13a (at left). Cast preparation of the guinea pig large intestine, view from outside. Submucosal vessels, A = artery, V = vein supply and drain (arrows) the tunica muscularis to form two capillary layers, arranged longitudinally and circularly (arrowheads). Bar = 250 μm.

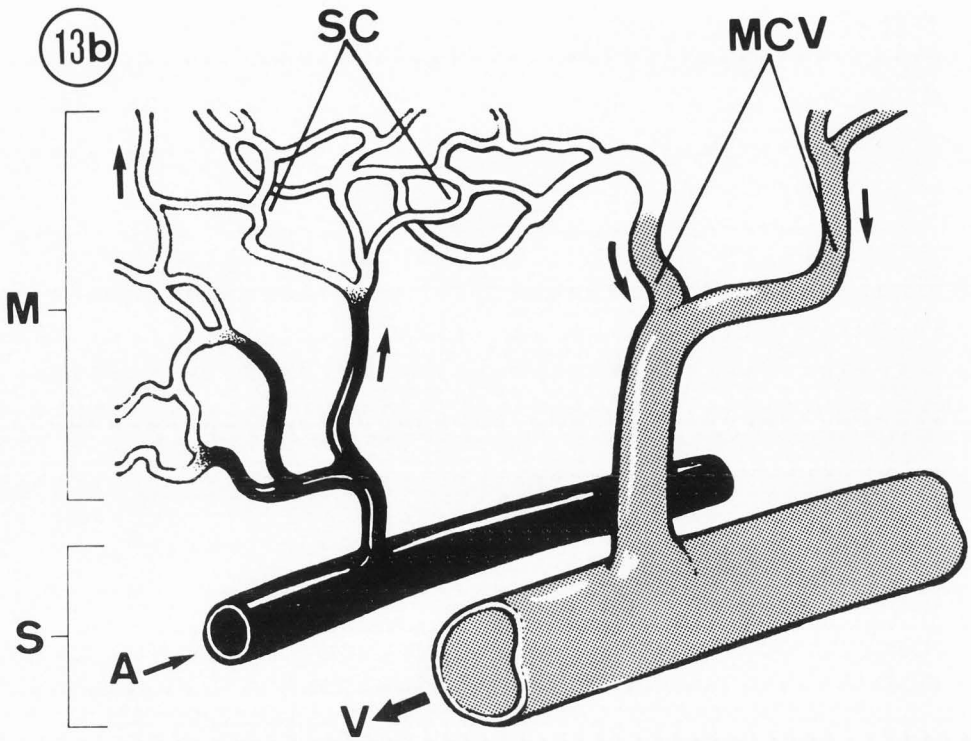

Fig. 13b (at right above). Diagram of the rat colonic mucosal microvasculature. A, V = submucosal (S) artery and vein; SC = subepithelial capillaries; MCV = mucosal collecting venules; M = mucosa. Arrows show the blood flow direction (adapted from Gannon and Perry, 1989).

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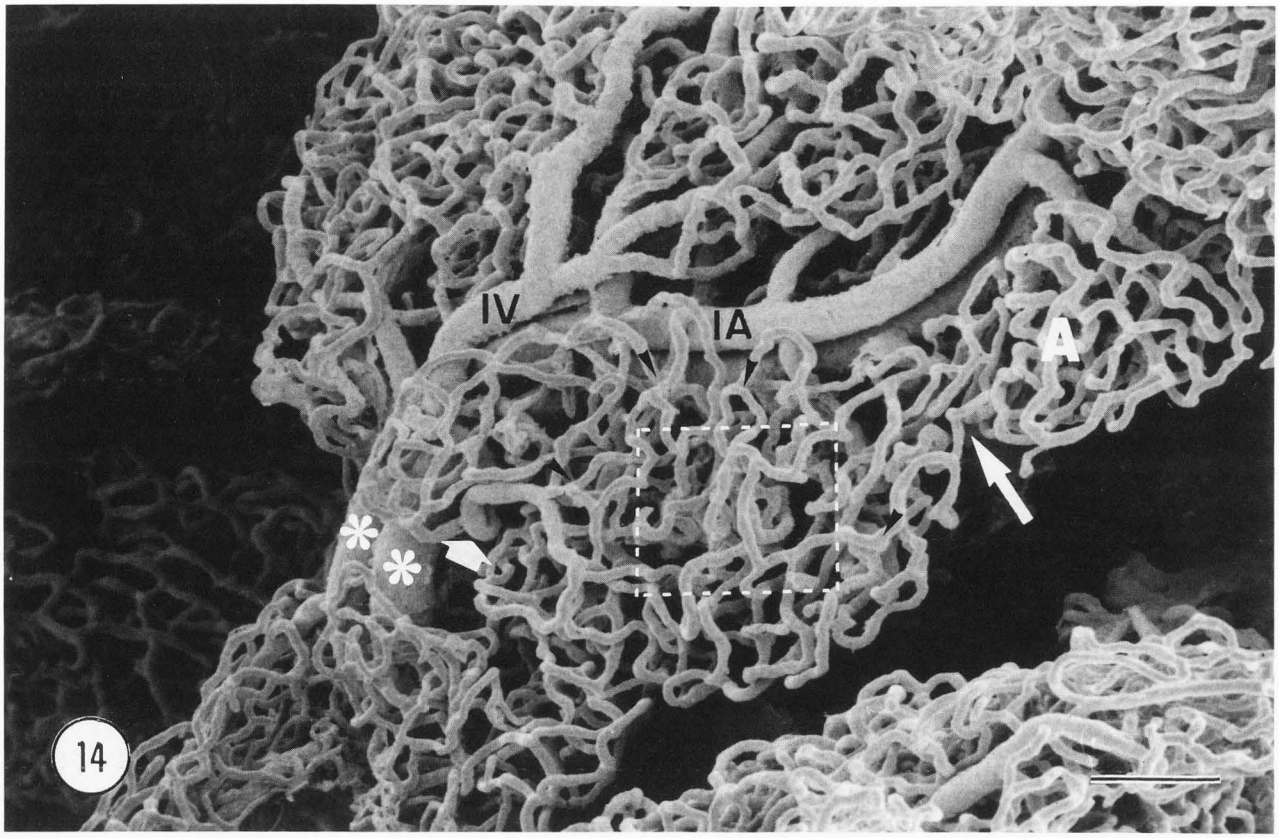
did the fenestral frequency per capillary (Browning and Gannon, 1986). This reflects physiologic conditions, as the reabsorption of water also decreases from the proximal to the distal colon. Lymphoid follicles in the rat rectum were described as having a microcirculatory pattern similar to that of Peyer's patches in the small intestine (Ohtsuka *et al.*, 1988).

The pancreas

Physiologically, the mammalian pancreas has two different functions: hormone release and enzyme secretion. In morphological terms, this would suggest the presence of two different supply systems. But there are species in which the pancreas is a single-function endocrine organ so that a simple vascular architecture should be expected to be present. As the scorpion fish (Myoxocephalus scorpius) only has endocrine cells (Syed Ali, 1985a, b) in its principal islets (Brockmann bodies; Lange, 1973; Lange *et al.*, 1975; Lange, 1984), it constitutes an interesting research object worth studying before turning to the mammalian pancreas. The scorpion fish was found to possess two endocrine islets, juxtasplenic and juxtapyloric. The juxtasplenic islet was described as being supplied by the dorsal mesenteric artery and the juxtapyloric islet received blood from a branch of the mesenteric artery. The juxtasplenic islet was found to be strawberry-like in its shape and to have dimensions of 2 x 2 x 2 mm. The mesenteric artery ramified around the circumference of the organ and displayed a corkscrew-like course after its division, penetrating the capsule and breaking up into small arterioles and capillaries. These were arranged in a radial lamellar fashion around the B and the D-cells in the center of the islet and subsequently joined sinuses, which finally opened into efferent vessels.

The pancreas of the frog (Rana temporaria and Rana esculenta) was described as being divided into three different lobes associated with the liver, the spleen and the intestine. Its supply was found to be provided by two types of capillaries, polyhedral-shaped and blind-ending, along which the endocrine cells were oriented in a palisade order (Syed Ali, 1989). Whether the polyhedral-shaped or the blind-ending capillaries are associated with a particular type of hormone producing cell is still open to discussion.

The pancreas, particularly that of the cat was repeatedly investigated by Syed Ali (Syed Ali, 1981; 1982; 1984a, b; Syed Ali and Weber, 1983). He described the interlobular artery as dividing and widening to a larger-caliber insular capillary plexus resembling a knob, a spiral or a glomerulus (Syed Ali, 1984a; Fig. 14). The islet capillaries were continuous with the capillaries of the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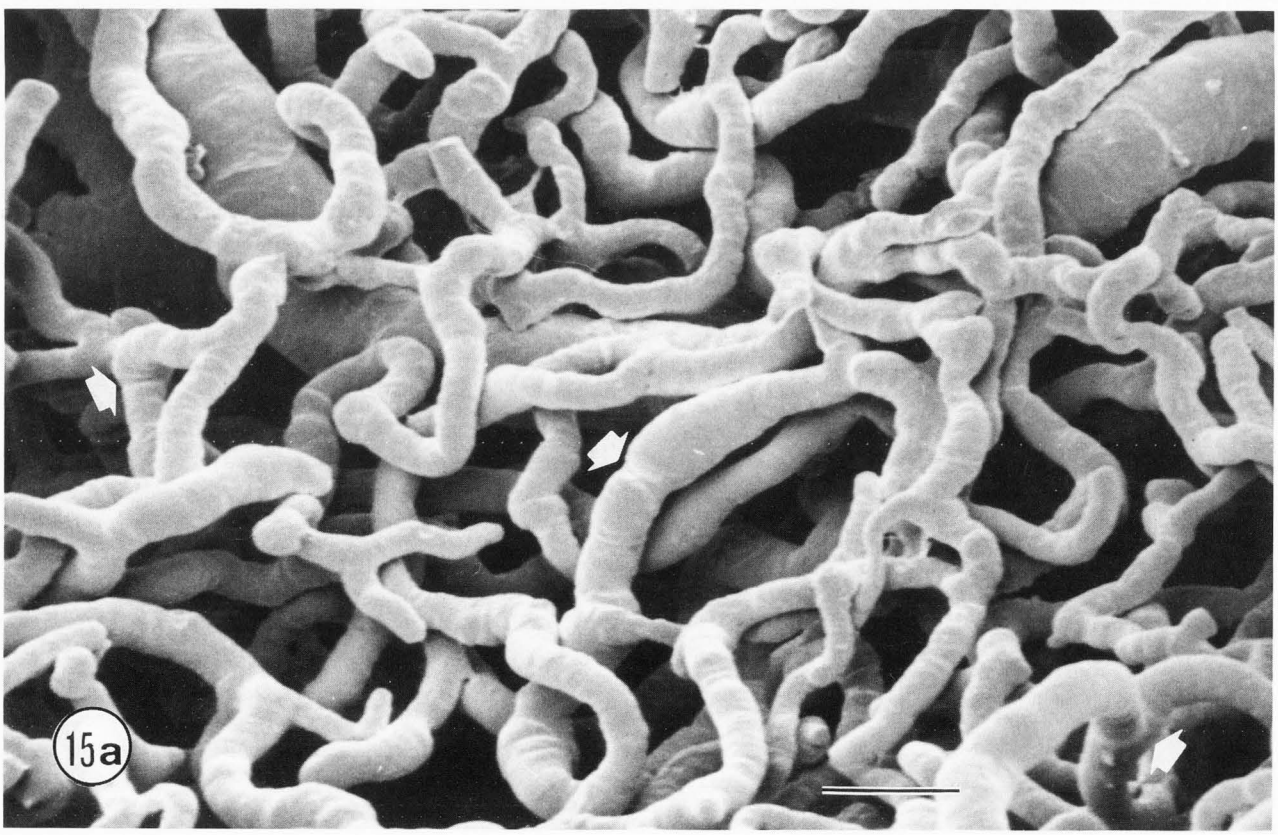
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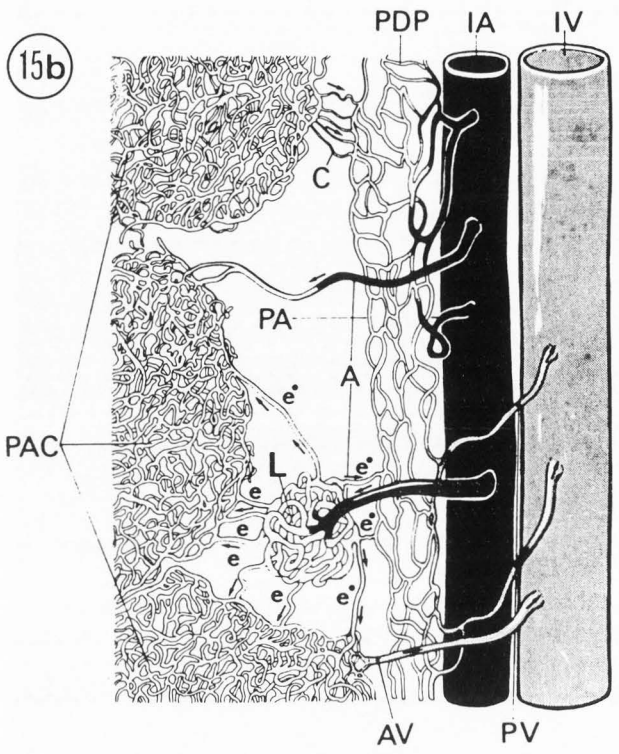


Fig. 15b. Microvascular pattern of the monkey and rat pancreas. Diagram. The periductal plexus (PDP), peri-acinar capillaries (PAC) and the islets of Langerhans (L) are supplied by branches of the interlobular artery (IA) indicated as PA and A. The efferent vessels of the islets join the acini either by shorter capillaries (e) or by longer straight vessels marked as "e" with a black point (insulo-acinar portal system), they also join the periductal plexus (insulo-ductular portal system, marked by "e" with black points). The acini by acinar veins (AV) and the periductal plexus by periductal veins (PV) empty into the interlobular vein (IV). Capillaries (C) also join the acini with the periductal plexus. Arrows mark the direction of the blood flow.

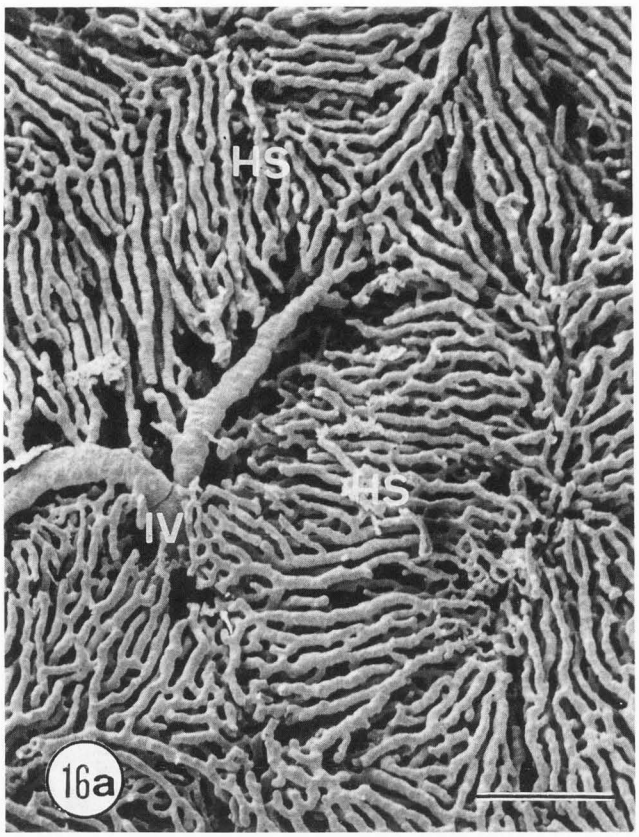
Fig. 14 (at left, top). An intralobular artery (IA) and vein (IV), tributaries of interlobular vessels (asterisks) supply and drain an islet (marked area). Note the connection (arrow) of the islet with the acinar (A) part of the pancreas via the efferent capillaries (arrowheads). The islet is also drained by an efferent venule (bold arrow) which joins the intralobular vein (IV) directly. Bar = 100 μm.

Fig. 15a (at left, bottom). Micrograph of the rat pancreas exocrine part. Circular constrictions (arrows) mark the sphincters on the cast surface of capillaries and postcapillary venules. Bar = 25 μm.

exocrine pancreas with few exceptions in which they directly joined the veins. At the endocrine - exocrine junction, ring-like constrictions were found to be present. These were interpreted as sphincters. Yoshinaga and Blank (1981), by contrast, reported sphincters which were localized at the bifurcation of the main arteries into the lobules. The sphincter-like structures seen by Syed Ali in his TEM investigations consisted of pericytes rich in glycogen and filaments and possessing cytoplasmic protrusions.

In this context, the studies by Aharinejad *et al.* (1990c) may be of interest. Combining SEM of vascular corrosion casts and TEM of ultrathin sections, they found venous sphincters to be present in the rat and mouse pancreas and reported constrictions in the capillaries themselves and at the junction between these and the postcapillary venules in the exocrine pancreas (Fig. 15). While the venous sphincters were related to accumulations of smooth muscle cells (muscular venules), the constrictions of the postcapillary venules and of the capillaries themselves were attributed to pericytes and their processes. The authors stressed the importance of avoiding relaxants when preparing vascular corrosion casts for visualizing sphincters, so that pericyte and smooth muscle cell function can be identified. In addition, they found SEM alone to be inadequate for demonstrating sphincters, because it will only show the consequences of sphincter function rather than the structure itself, which is lost during corrosion. In Syed Ali's accounts (1982, 1984a), the lobules of the cat pancreas were described as being surrounded by a vein and an artery; the capillaries were narrower in the exocrine than in the endocrine pancreas.

The vascularization of the monkey pancreas was investigated by Fujita and Murakami (1973), Murakami *et al.* (1983), and Kikuta *et al.* (1984). They described interlobular arteries as being continuous with afferent arterioles which subsequently formed the insular capillaries. Arterial terminations in the core of the organ, the site of A-cells in the monkey pancreas, were thought to be of particular importance. A similar vascular system was described for the horse and the dog (Fujita, 1973), whereas rabbits and rats (Ohtani and Fujita, 1980) were shown to have peripheral terminations at the sites of A-cell accumulations in the periphery. This system was thought to be important physiologically because, as the arterioles end at the sites of A-cell accumulation, they could transport glucagon to the B-cells where the hormone stimulates insulin release (Fujita, 1973; Fujita and Murakami, 1973; Kikuta *et al.*, 1984). Drainage of the endocrine cells was described as proceeding through the acini, i.e., the insulo-acinar portal system. This was also reported to be important physiologically, because insulin potentiates the effect of pancreozymin (Kanno and Saito,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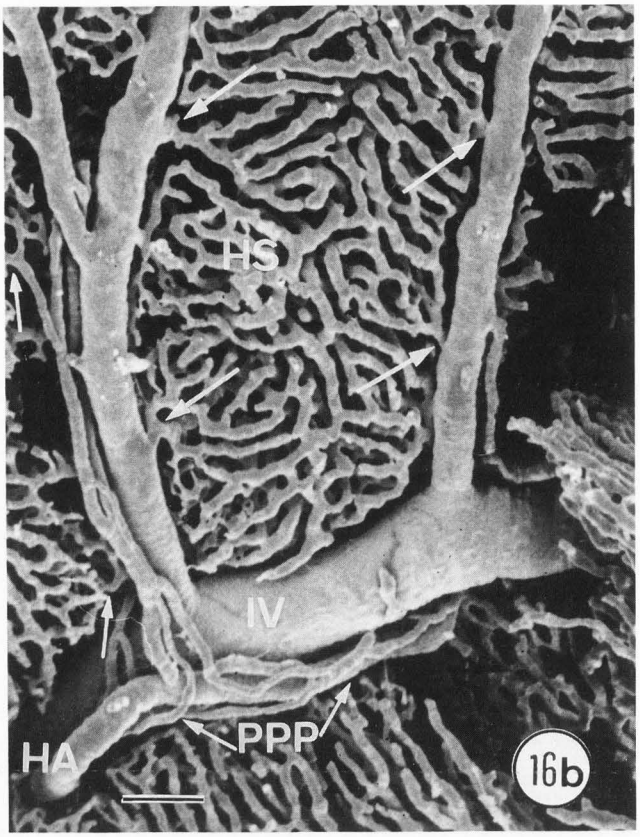
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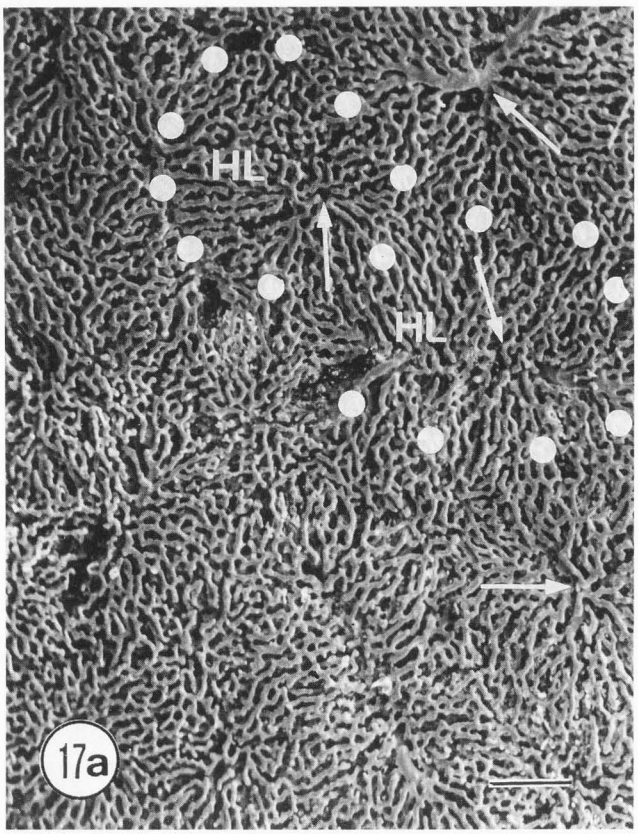
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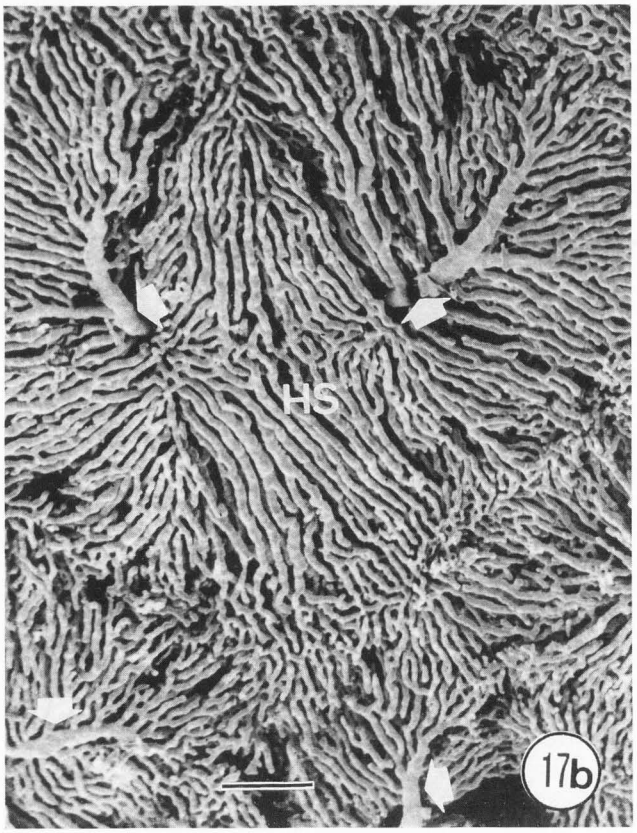
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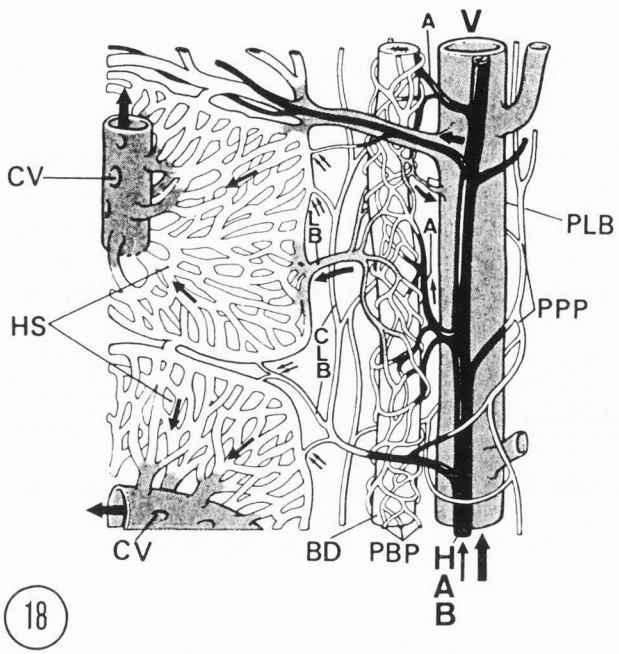

Fig. 18 (above). Schematic drawing of the rabbit liver microcirculatory pattern. V = interlobular vein; HAB = hepatic artery branch; PPP = periportal plexus; PBP = peribiliary plexus; CLB = collateral branch of the hepatic artery; PLB = prelobular branch; LB = lobular branch; A = afferent arteries of the PBP; HS = hepatic sinusoids; CV = central vein. Arrows mark the direction of the blood flow, double arrows indicate junctions between the terminals of the hepatic artery and the hepatic sinusoids.

Fig. 16. Vascular corrosion cast of the rat liver. **Fig. 16a.** The hepatic sinusoids (HS) are supplied by a branch of the interlobular vein (IV). Bar = 250 μm. **Fig. 16b.** The interlobular vein (IV) accompanied by the hepatic artery (HA) runs in the portal canal. The periportal plexus (PPP) and the hepatic sinusoids (HS) are supplied by the hepatic artery (small arrows) and the interlobular vein (large arrows). Bar = 100 μm.

Fig. 17. Micrographs of the rat liver surface. **Fig. 17a.** White points mark the hepatic lobules (HL), arrows mark the central veins. Bar = 200 μm. **Fig. 17b.** In a higher magnification the draining central veins (arrows) of the hepatic sinusoids (HS) are seen. Bar = 250 μm.

1976; Murakami *et al.*, 1983). In the initial segments of the vasa efferentia radiating from the islets, Fujita and Murakami (1973) found constrictions to be present. Their significance was, however, poorly understood for some time.

Extensive research work on the microvasculature of the rat and rabbit pancreas was undertaken by Ohtani and coworkers (Ohtani and Fujita, 1980; Ohtani, 1981a, b; Ohtani and Fujita, 1981; Ohtani, 1983; Ohtani *et al.*, 1983; Ohtani, 1984). They reported the islet of Langerhans to be supplied by an interlobular artery, vas afferens, which divided into swollen sinusoidal capillaries forming a glomus-like capillary network (Fig. 15b; Ohtani and Fujita, 1980; Ohtani *et al.*, 1983). In both rabbits and rats, the vas afferens terminated at the periphery of the islet where A-cells are located constituting a cortical capillary layer and then breaking up into branches to the deeper parts of the islet. Interlobular arteries also were reported to give rise to periductal or periductular systems called periductular plexus (Fig. 15b). Acini were described as being supplied by direct branches of the interlobular arteries: "acinar arterioles" (Fig. 15b; Ohtani, 1981b). This contrasts with observations in horses where no direct branches to the exocrine pancreas were found (Fujita, 1973).

The connections between the above three vascular systems in the rat and rabbit pancreas are complex. On the one hand, vasa efferentia were described. These were smaller in caliber than the islet capillaries and radiated from the peripheral capillary net of the acini to form a round or polygonal mesh (Fig. 15b; Ohtani and Fujita, 1980; Ohtani, 1981a, b; Ohtani and Fujita, 1981; Ohtani *et al.*, 1983). Some of the vasa efferentia were thick and quite long and broke up into the acinar capillary net after running a straight or wavy course. These vessels were called insulo-acinar portal vessels (Fig. 15b). On the other hand, some vasa efferentia were reported to be connected with the periductular plexus to form the insulo-ductular portal system (Fig. 15b; Ohtani, 1981a, b; Ohtani and Fujita, 1980, 1981). In addition, many connecting vessels were found to be present between the interacinar capillary network and the periductal plexus called acino-ductular portal vessels, they were thought to transport blood from the acini to the ducts (Fig. 15; Ohtani and Fujita, 1980; Ohtani, 1981b). And finally, there was evidence suggesting that the venules emptied into the larger vessels (probably venules) of the periductal plexus (Ohtani and Fujita, 1980) or joined with the periductular capillaries through capillary anastomoses.

Several concepts were proposed to explain the physiologic significance of these connections. The insulo-acinar portal vessels reported by earlier investigators (Wharton, 1932; Thiel, 1954) went unnoticed for many years, until Henderson (1969) furnished definitive prove of their existence assuming that the high hormone concentration in these vessels might regulate the function of the pancreatic glands. This assumption was later corroborated by Fujita and Watanabe (1973) and by Fujita *et*

al. (1976). Eventually, Kanno and Saito (1976) established the potentiating effect of insulin on pancreomyzin. The discovery by Fujita and Kobayashi (1979) of several nerve endings in the pericapillary spaces of the islets in the dog pancreas, which released VIP-like substances (Larsson *et al.*, 1978; Larsson, 1979), formed the basis for another concept. VIP and other substances, e.g., norepinephrine and dopamine, were thought to use the insulo-acinar portal vessels as a transport route to regulate the function of the exocrine pancreas in terms of a neuroparaneuronal control center (Ohtani and Fujita, 1980, 1981; Ohtani, 1983).

Explanations of the role of the insulo-ductular and acino-ductular systems are speculative at best: Islet secretions were assumed to exert their effects upon the ductal wall in very high concentrations (Ohtani and Fujita, 1980; Ohtani, 1981a, b). As the pancreatic ducts contained endocrine cells, studies were encouraged to shed light on the potential effects of insular hormones on these cells (Ohtani and Fujita, 1980). A potential regulatory effect of insular hormones on the tone of the ductal muscular vessels has also been proposed (Ohtani, 1983).

The studies by Bonner-Weir and Orci (1982) in the rat pancreas put earlier concepts into an entirely new perspective. In the rat pancreas, only small islets less than 160 μm in diameter were found to show extensive drainage routes via the acinar capillary network. In medium-sized and large islets (160 to 260 μm and greater than 260 μm in diameter) efferent capillaries at the edge of the islet were described as forming an extensive finger-like network of collecting venules over the islet. These observations prompted the authors to conclude that most of the blood from the islets would flow through the venules rather than through the insulo-acinar portal system. Contradicting the data put forward by Ohtani, Fujita and coworkers (see above), this concept has so far not been corroborated.

One major area for future research will, no doubt, have to be that of flow regulation. Although conclusive evidence of the existence of an insulo-acinar portal system has meanwhile accumulated and although this system has been attributed a role in the humoral regulation of the exocrine pancreas, the regulatory factors involved in the transport of hormones from the islets to the acini are still poorly understood. Such questions as whether the insulo-acinar vessels contain contractile elements or have a special nerve supply still need to be answered. The classification of the islets by their size (Bonner-Weir and Orci, 1982) reported in rats, but unconfirmed in other species is another area of interest for future studies. These should be designed to show whether or not islets of different size are also distinguished by the structure of their insulo-acinar systems.

The liver

A survey of literature brings to light that the hepatic vasculature and its variation patterns together with that of intrahepatic bile ducts has been the subject of extensive research for years: Julian and DeOme (1949), Hales *et al.* (1959), Lozano and Andrews (1966), Firbas *et al.* (1972), Feigl *et al.* (1973), Wicke *et al.* (1975), Motta *et al.* (1980), Nawar *et al.* (1980), Reimann *et al.* (1983), *Wisse* et al. (1985), Cagol *et al.* (1989), and Buechter *et al.* (1990). In these studies angiography, vascular corrosion casting with various resins or India - ink injecting were used as the method for visualizing of the hepatic vasculature, in order to research the anatomic or pathologic architecture of the hepatic vessels. Ohtani (1988) and Okanoue *et al.* (1988) studied the hepatocyte cytoskeleton and the collagen fibrillar frame work in human liver. Verbeke and Buyssens (1990), using light microscopy of tissue sections, reported on the intrahepatic lymphatics in the human fetus. The research work of Gupta and coworkers, doubtlessly increases our knowledge on the vascular architecture of the liver in human, chicks and dogs (Gupta and Gupta, 1976, 1979; Gupta *et al.*, 1979, 1981, 1982a, b).

As the microcorrosion casting method was developed (Murakami, 1971), the scanning electron microscopy of cast preparations allowed a three-dimensional view in the precise architecture of the hepatic vessels and the biliary tree (Hanstede and Gerrits, 1982; Murakami *et al.*, 1984). Already in the year 1971, in his pioneer paper, Murakami published the first SEM views of the hepatic microvasculature. He described, as did Schäfer *et al.* (1975), that the sinusoids were supplied both by tributaries of the portal vein (named interlobular veins) and the hepatic artery.

The blood vascular bed of the monkey liver was studied by Murakami *et al.* (1974). They described the sinusoids, in analogy to the rat liver, to be mainly supplied by the portal vein (Figs. 16a and 18), those around the final segments of the portal canal by the terminal branches and those adjacent to the more proximal segments by side branches of the portal vein. The side branches were exclusively observed in the larger portal canals, the terminal branches in the small canals. The authors concluded, in agreement with Elias and Popper (1955) and Hase and Brim (1966) that as in the rat and other mammals the hepatic sinusoids around the large portal canals were poorly supplied by the portal vein. In their course, the hepatic arteries supplied besides the hepatic sinusoids (Fig. 16b), the peribiliary plexus via the so called afferent vessels (referred to as the "peribiliary portal system") which ran in close association with the portal vein and the hepatic artery (Fig. 18; Murakami *et al.*, 1974). The afferent vessels supplied

the outermost layer of the peribiliary plexus, then entered deep to give rise to the inner capillary network (Fig. 16). The efferent vessels of the peribiliary plexus divided at the periphery of the portal canal or on the surface of the lobules to supply the hepatic sinusoids (Fig. 18). The efferent vessels were almost isolated from the portal vein and also from the hepatic artery. These findings strengthen the hypothesis of "radicular portal veins" (Olds and Stafford, 1930) and agree with those of Lozano and Andrews (1966), Hase and Brim (1966) and Mitra (1966), who reported on the "internal hepatic radicles". Furthermore, Murakami *et al.* (1974) clearly proved that the efferent vessels of the peribiliary plexus undertake a major supply to the hepatic sinusoids, particularly in the larger portal canal where the sinusoidal branches of the portal vein are scarce.

The surface of the rat liver vascular cast shows a hexagonal pattern (Fig. 17a) consisting of sinusoids which converge into the central vein (Fig. 17b; Ohtani and Murakami, 1978). In contrast to the liver in the monkey, human and cat (Murakami *et al.*, 1974; Ohtani *et al.*, 1982, 1983) where the terminal hepatic arterioles and portal venules are connected with the sinusoids at the surface of the liver, in the rat and rabbit liver such vessels are usually not observed (Ohtani and Murakami, 1978; Ohtani, 1979). Arterio-portal anastomoses between the interlobular arterioles and the accompanying interlobular veins are frequently seen in the rat (Ohtani and Murakami, 1978; Ohtani *et al.*, 1983; Ohtani and Murakami, 1985), while they are rarely present in the rabbit (Ohtani, 1979). The architecture of the peribiliary plexus is the same as in the monkey, the drainage route of the efferent veins is however, different from species to species. It either drains into the hepatic sinusoids, called "lobular branches", or into the lobular vein, designated "prelobular branches" (Ohtani, 1979; Ohtani, 1981b; Ohtani *et al.*, 1983). In the rabbit and human both branches occur at almost the same frequency (Fig. 18; Ohtani, 1979; Ohtani *et al.*, 1982; Ohtani, 1983), in the rat the prelobular branches are seen more frequently than the lobular branches (Ohtani and Murakami, 1978), while in the monkey the lobular branches occur almost exclusively with few prelobular branches (Murakami *et al.*, 1974). The peribiliary portal system (Ohtani, 1981b) has been suggested to facilitate the reabsorption of substances from bile (Henderson and Daniel, 1978) or as a transport route for released hormones of the bile duct back to the hepatic lobules (Fujita, 1977). Interestingly enough, Nopanitaya *et al.* (1978) reported on three termination routes of the hepatic artery in rats and mice: In the peribiliary plexus, the hepatic sinusoids and the portal vein. While the two former routes are meanwhile established, the direct connection of the hepatic artery and the portal vein is denied by Elias and Petty (1953), Hase and Brim (1966), Murakami *et al.* (1974), Ohtani (1979) and Kardon and Kessel (1980), other investigators accept their existence (Mitra, 1966; Ohtani and Murakami, 1978). In their comprehensive study Yamamoto *et al.*, (1985) compared the hepatic microangioarchitecture in rats, hamsters and human. The key question in their study was whether the hepatic arterioles terminate into the sinusoids or into the terminal portal venules. They showed that in the terminal portal tracts, the terminal hepatic arterioles, 7 μm in diameter, anastomosed with branches of the terminal portal veins. In the hamster and human liver, however, no arterioportal venous anastomoses were observed.

The intrahepatic lymphatics were studied by Yamamoto and Phillips (1986) and Ohtani (1989). Injecting Mercox retrogradely into the common bile duct, the resin leaked at the periphery of the lobule and filled the lymphatic vessels in the portal tract. These vessels repeatedly divided, anastomosed and formed the network surrounding the portal triad. Marked notches indicated the bicuspid valves. The entrance of the biliary constituents into the lymphatic vessels following bile duct obstruction (Bloom, 1923), was thought to be a route for the regurgitation of the bile into the blood (Yamamoto and Phillips, 1986). The resin leakage from the bile into the lymphatic vessels, indicated a possible route through which biliary substances enter the lymphatic vessels following obstruction the bile duct (Ohtani, 1989). Yamamoto and Phillips (1986) observed no anastomoses between the portal and the capsular lymphatics, they showed the resin in the lymphatics to drain from small portal tracts to the hilum of the liver.

Yogita (1982) reported on increased anastomoses between the portal and hepatic veins, in an experimental cirrhosis model in rats. Gaudio and coworkers (1988) clearly proved the proliferation of bile ducts in cholestatic rat livers. In their studies they never observed resin regurgitation into vascular sinusoidal bed, strengthening the hypothesis of the absence of direct communications between the bile canaliculi and the space of Disse, even in advanced cholestasis. Two concepts of the blood supply to regenerative nodules in liver cirrhosis oppose each other: Portal and hepatic arterial blood supply. Yamamoto *et al.* (1984) demonstrated the increased arteriolar networks around the cirrhotic nodules which in turn supplied the liver parenchyma. In contrast, portal vein branches decreased in number, distorted and compressed by surrounding connective tissue. These findings are in agreement with those of Rappaport *et al.* (1983).

Conclusions

When applied to appropriate problems, SEM studies of vascular corrosion casts can make major contributions

towards a better understanding of physiology and pathophysiology. This is amply documented by their increasing use. For instance, a portal like microcirculation is suggested to be existent in the rat sympathetic ganglia (Mekhail *et al.*, 1990). Although light and transmission electron microscopic observations support the suggestions of the authors, a three-dimensional visualizing of connections between cathecholamin containing cells and sympathetic ganglia has yet to be performed. In our opinion SEM of vascular corrosion casts in combination with TEM of tissue sections offers a more powerful instrument to solve problems in the area.

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Discussion with Reviewers

S. Syed Ali: To produce brilliant results it is advisable to wash the cast preparation in the last stage of maceration in 5-10% trichlor acetic acid solution, then osmicate with 1% OsO_4 solution in phosphate buffer or leave it in OsO_4 vapours in an exccicator for about 2 hours, followed by gold sputtering (10 nm) and viewing in SEM.
Authors: The suggested procedures of maceration, rinsing, and sputtering are useful. In our study, we used other methods which we consider to be of equal quality. In detail, the conductive bridge method of Lametschwandtner *et al.*, (1980), maceration in 15% potassium hydroxide, rinsing in formic acid and distilled water, and evaporation and sputtering with carbon and gold (Lametschwandtner *et al.*, 1990, Aharinejad *et al.*, 1990c) were used.

Reviewer IV: You have shown sphincters in pancreatic veins attributed to smooth muscle and in pancreatic capillaries attributed to pericytes. Do the two look different? Do you think arteries have sphincters? Have you done anything to contract the sphincters?
Authors: In corrosion casts there is no difference between the sphincters on capillaries or veins. Both are identified as different deep grooves on the cast surface. Arteries have, in our opinion, also sphincters. These are contractile (muscular) elements which are capable to narrow or even occlude the arterial lumen (Zweifach BW, 1989; Future trends in microcirculation research. In: Lee JS, Skalak TC, eds. Microvascular Mechanics. Hemodynamic of Systemic and Pulmonary Microcirculation, Springer, New York, pp. 3-12). In our experiments with pancreas we omitted the relaxing drugs in order to prove the intensity of the function of sphincters. They were regularly present. If relaxing drugs, however, are used the cast surface appears just smooth.

B.J. Gannon: What are "twiggy vessels"?
Authors: This term, which is used in the paper of Nakamura *et al.* (1986a, b), is not clear to us either. We feel that they used this term for small venules and arterioles, describing the changing pattern of periodontal ligament vessels under experimental tooth movement.

B.J. Gannon: How a change in flow rate in perforating vessels would reduce pressure in lamina proprial veins is not at all clear; indeed the opposite conclusion seems more appropriate on the facts presented.
Authors: We agree. This hypothesis is only a postulation of Ide *et al.* (1989), which we have cited. In our interpretation if the flow is reduced in perforating vessels, the lamina proprial vessels would become inflated, the hydrostatic pressure would increase.