Microvasculature as Studied by the Microvascular Corrosion Casting/Scanning Electron Microscope Method. I. Endocrine and Digestive System

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Summary. This paper reviews firstly the microvascular corrosion casting/scanning electron microscope method and secondly the microvascular organization of endocrine and digestive system as revealed by this technique. Detailed descriptions of the microvascular arrangement of the hypophysis, pineal body, thyroid gland, pancreas, adrenal gland, salivary gland, liver, stomach and small intestine are given. Various hypotheses are also proposed regarding the physiological significance of the microcirculatory patterns observed.

The study of microcirculation is currently advancing from a physiologic, pharmacologic, and pathologic, as well as clinical, point of view. While many relevant and detailed anatomical studies were completed some time ago, within the last decade the microvascular corrosion casting/scanning electron microscope (SEM) method (MURAKAMI, 1971, 1975, 1978; CANNON, 1978, 1981) has unraveled the microvascular organization of many organs and tissues previously visualized less clearly by conventional light (LM) or transmission electron microscopy (TEM).

It appears to be time to review the microvascular organization in organs and tissues revealed by the microvascular corrosion casting/SEM method. Such a review will hopefully provide the morphological basis for further advances in the field of microcirculation research. This paper will deal with the microvascular organization in the endocrine and digestive systems.

METHODOLOGY

Preparation of corrosion media

The casting medium of partially polymerized methacrylate introduced by Murakami (1971) has given the best casts for SEM. The problem of obtaining consistent partial polymerization of methyl methacrylate monomer has been largely overcome by the use of ultra-violet light for the decomposition of the organic initiator rather than applied heat (80°C) (see Gannon, 1981b). Mercox is a commercially prepared methacrylate
medium; the best results are obtained if it is diluted with methyl methacrylate monomer to give a viscosity of 3–5 centistoke (OHTANI and MURAKAMI, 1978). Other microvascular casting media are available (e.g. Batson’s plastic, Trylon, Valtex, Geon, Microfill) without the partial polymerization procedure.

Injection and corrosion casting

Any organs can be injected, provided they have vessels large enough to cannulate. Specimens obtained at an autopsy can also be used, provided their blood vessels have not been occluded with coagulated blood or excessively damaged by autolysis. Non-fixed tissues or organs generally give better filling of the microvascular beds, although the surface morphology of the casts shows more detail in fixed tissues. The method of corrosion casting is described in detail elsewhere (MURAKAMI, 1971, 1978; GANNON, 1978).

SEM observation of microvascular casts

Prior to SEM, the vascular casts may be coated with heavy metals such as gold and platinum. Exposure of the casts to osmium vapor also gives substantial conductivity (MURAKAMI et al., 1973; KUBOTsu and UEDA, 1980). To expose deep structures of particular interest, the specimens should be microdissected under a stereo light microscope with fine forceps, prior to SEM. In order to elucidate the connections and arrangements of particular vessels, analysis of stereo-pairs of micrographs with tilt separation of 4–10° is also useful. So, too is successive microdissection followed by SEM. Characterization of particular vessel casts such as arterial or venous, is aided not only by the observation of the shape of endothelial nuclear imprints under high magnification (HODDE et al., 1977) but also by a systematic study of vessel connections in three dimensions (OHTANI et al., 1983). Arterial or venous partial casts are also useful in visualizing the basic distribution pattern of the arterial or venous system, as well as identifying with more certainty, vessels in complex complete networks as either arterial or venous (e.g. GANNON et al., 1983).

Merits and limitations of microvascular corrosion casting/SEM method

The merits of this technique are well documented (HODDE and NOWELL, 1980): 1) The large depth of field and the wide range of magnification of SEM have permitted detailed analysis of the spatial organization of the microvascular networks, 2) microdissection followed by SEM, and stereoscopic observation of the micrographs has facilitated the evaluation of the relationships between blood vessels, 3) luminal surface structures can be observed on the surface of the casts under high magnification. This has facilitated identification of vessel types and the possible location of sphincters or contracted segments of vascular smooth muscle in the vessel wall.

Limitations of this method should also be recognized. Spatial relationships of vessels to the tissue elements, and the structure of the vessel wall, cannot be examined in vascular casts. For such information the corrosion technique must be supplemented by other methods (e.g., LM and TEM of intact and/or dye-injected tissue). The three-dimensional relationship of the vessels to the tissue elements can be observed by SEM following removal of stromal connective tissue (EVAN et al., 1976; SHIMADA, 1981; OHTANI et al, 1983). Ultrastructural details must be revealed with TEM. Direction of blood flow can often be observed by intravital microscopy, or analyzed by the microsphere injection technique. Intravital microscopy, in conjunction with SEM of microvascular corrosion casts of the same region as examined in vivo, will allow a more detailed analysis of circulatory patterns in particular networks (OHTANI, 1983).
ENDOCRINE SYSTEM

1. Hypophysis

Since the description of a portal system in the human hypophysis was presented by Popa and Fielding (1930a, b), the hypophyseal microcirculation has attracted much study. SEM of vascular casts has clarified hypophyseal microcirculation in mammals (Murakami, 1975a; Page and Bergland, 1977; Page et al., 1978; Ohtani, 1981b) and lower vertebrates (Lametschwandtner et al., 1975, 1977a, b, c).

Microvascular architecture of the hypophysis

The superior hypophyseal arteries, derived from the cerebral arterial circle or internal

Fig. 1. Vascular cast of the rat hypophysis (dorsal view). The median eminence (ME) is supplied by the superior hypophyseal arteries (shA), arising from the internal carotid arteries (icA). The pars posterior (PP) is supplied by the inferior hypophyseal arteries (ihA) and drains into the cavernous sinus (cS) via the posterior hypophyseal vein (phV). The pars anterior (PA) drains into the cavernous sinus through the lateral hypophyseal veins (lhV). ×18
Fig. 2-4. Legends on the opposite page.
carotid artery, penetrate the median eminence where they form two vascular layers: the external and internal plexus (Fig. 1, 2). The internal plexus consists of numerous sinusoidal capillary loops projecting into the inner portion of the median eminence (Fig. 1–3). The outer layer, a capillary and arteriolar network, encloses the inner layer. A number of capillaries connect the external layer with the internal plexus. Middle hypophyseal arteries descend into the infundibular stalk where they divide into an outer layer (a reticular capillary network) and an inner layer of capillary loops similar to those seen in the median eminence. The capillary loops in the median eminence are collected largely into so-called long portal vessels which descend along the pars tuberalis to break up into capillaries in the pars anterior (Fig. 2, 4). The capillary loops in the infundibular stalk are connected with so-called short portal vessels, which enter the pars anterior to be connected to its capillary network (Fig. 5). The short portal vessels in the rat and mouse are not as well developed as in the monkey. The pars anterior drains into the lateral hypophyseal veins (Wislocki and King, 1936; Wislocki, 1937) which lead into the cavernous sinus. It should be emphasized that the adenohypophysis has no direct arterial supply, in contrast to the conclusion of Wislocki and King (1936) and Harris (1947) (Fig. 5).

Fig. 5. Diagram of the vascular organization of the dog hypophysis (mid-sagittal view). The vascular routes drawn in broken lines are found between the lateral margin of the pars intermedia and the pars anterior. The most probable direction of blood flow is indicated by arrows. shA, mhA, ihA superior, middle and inferior hypophyseal artery, lhV, phV lateral and posterior hypophyseal vein, lp, sp long and short portal vessel, ME median eminence, PA pars anterior, PI pars intermedia, PP pars posterior, and 3rd V third ventricle.

Fig. 2. Vascular cast of the rat hypophysis (anterior view). The portal vessels (P) connect the capillary bed of the median eminence (ME) with that of the pars anterior (PA). shA superior hypophyseal artery, mhA middle hypophyseal artery. x17

Fig. 3. Vascular cast of the rat median eminence viewed from above. Its endothelial surface consists of numerous capillary coils which project toward the ventricle. x236

Fig. 4. Para-sagittal view of the rat hypophysis. Note that the capillaries of the pars posterior (PP) are denser and smaller than those of the pars anterior (PA). P portal vessel, ME median eminence. x39
The intermediate lobe is rather poorly vascularized. The capillaries in the pars posterior (or infundibular process) extend into the pars intermedia where they are collected into thicker vessels, probably of capillary or venular nature, which are presumed to be connected with the vasculature in the pars anterior (Fig. 5).

The pars posterior is supplied by the inferior hypophyseal arteries arising from the internal carotid arteries, and it drains into veins leading to the cavernous sinus. The capillary network of the infundibular stalk also connects with that of the pars posterior.

The superior hypophyseal arteries supply the hypothalamus as well as the median eminence. Although a portal route from the median eminence to the hypothalamus has been reported (Török, 1964; Holmes, 1967; Akbayev, 1971), SEM of vascular casts revealed that these two areas are not linked via such portal vessels but have their own direct arterial supplies (Murakami, 1975a). The vessels ascending into the hypothalamus are usually arterioles of 15–30 μm in diameter. Noteworthily, the capillaries connected with the descending limbs of the capillary loops in the median eminence, before joining the portal vessels, often run very closely adjacent to the arterioles extending into the hypothalamus. Possible significance of this will be discussed later. The upper part of the median eminence drains predominantly into the long portal vessels, but also has some drainage into the systemic veins (Murakami, 1975).

Can the neural hormones be carried via vascular routes to the adenohypophysis?

Figure 5 shows the most likely flow direction within the hypophysis as deduced from the SEM of vascular casts. Popa and Fielding (1930a, b) believed that blood flowed from the pars anterior to the median eminence. However, it is now widely accepted that neurohormones secreted by the axon terminals from the hypothalamus are taken up into the capillary loops of the infundibulum (both of the median eminence and infundibular stalk) and transported through the portal vessels to the adenohypophysis to modify its endocrine function. Furthermore, Knigge and Scott (1970) suggested that the specialized ependymal cells, the tanycytes (a name coined by Horstmann, 1954), function as a link between the cerebrospinal fluid (CSF) and the portal system of the hypophysis. It has been demonstrated that mammalian CSF contains numerous bioactive peptides such as vasopressin, neurophysin, TRH, lutenizing hormone releasing hormone, somatostatin, angiotensin, ACTH, growth hormone, TSH, prolactin, and sleep factors (Ishikawa, 1973; Knigge and Joseph, 1974; Heller et al., 1968; Pavel, 1973; Robinson and Zimmerman, 1973; Allen et al., 1974; Pappenheimer et al., 1967). Investigations into the median basal hypothalmus using tracers and labeled hormones have suggested that bioactive substances might be transported into the portal system via tanycytes and thus might influence the activity of the adenohypophyseal cells (Scott et al., 1974).

Noteworthy is the possibility that the portal vessels between the infundibular process (or pars posterior) and the pars anterior might transport the neurohormones, including vasopressin, to the pars anterior (Fig. 5). This vascular route is of particular interest, since vasopressin is reported to play a role in the release of ACTH from the adenohypophysis, assisting the action of corticotropin releasing hormones (CRH) (Yates, et al., 1971).

Are hypophyseal hormones transported directly to the brain?

Bergland and Page (1979) discussed extensively the possibility that blood might flow from the adenohypophysis to the brain, on the assumption that there is little capacity for blood flow from the voluminous sinusoids of the adenohypophysis to the cavernous
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We will reevaluate their hypotheses based on our own SEM observations of vascular casts and propose some new concepts.

Whether or not the adenohypophysis has sufficient drainage capacity directly into the cavernous sinus, is the first question to be considered. The neurohypophysis has a rich direct arterial supply whereas the adenohypophysis has no direct arterial supply. The vascular casts of the sinusoids in the adenohypophysis are significantly larger in diameter than those in the neurohypophysis (Fig. 4). These two facts suggest that the sinusoids in the adenohypophysis are at much lower hydrostatic pressure than those in the neurohypophysis. Thus, the most probable flow direction is from the neurohypophysis to the adenohypophysis, as previously mentioned (Fig. 5). Since the cavernous sinus is a rather tough structure, it is unlikely to expand as the sinusoids of the adenohypophysis could, following plastic perfusion, which could lead to an overestimate of the volume difference between sinusoids and their drainage vessels. Furthermore, one should bear in mind that outflow capacity should be compared with its inflow capacity. In considering the actual blood flow, the comparison of the total vascular volume of the organ with the volume of its drainage vessels does not show whether or not the organ has enough drainage capacity. To date, there is no physiological data about the inflow and outflow capacities of the adenohypophysis.

Is there any possibility that the inflow volume of the adenohypophysis exceeds the outflow through the cavernous sinus? This would force some adenohypophysyal blood to flow reversely towards the neurohypophysis. Vasoconstriction in the neurohypophysis, whether regional or total, is likely to reduce the inflow into the adenohypophysis through the short portal vessels; however this reduction of inflow through the short portal vessels from the neurohypophysis might be partly or totally compensated by an increase in flow through the long portal vessels from the median eminence. Regional vasoconstriction of the adenohypophysis near its drainage vessels would reduce the outflow into the cavernous sinus, and might cause a redirection of flow into and out of the adenohypophysis via the two portal vessel groups. However, nothing is known about blood flow control in the adenohypophysis.

Do some hypophyseal portal vessels serve as efferent vessels? Since the neurohypophysyal cells are bathed by a high concentration of potent vasodilators and vasoconstrictors (Carraway, Demers and Leemar, 1976) and the microvessels in the neurohypophysis are well innervated and have much juxtaposed smooth muscle (Bergland and Torack, 1969), regional vasodilation, as well as vasoconstriction, of the neurohypophysis seems likely to occur. The vasoconstriction, or orchestrated repetition of vasoconstriction and vasodilation in the neurohypophysis could allow blood flow into the neurohypophysis through some of the portal vessels. Thus, the flow direction through the portal vessels may be reversible as previously proposed (Bergland and Page, 1979) (Fig. 6). Such reversal of flow from the adenohypophysis to the neurohypophysis could then allow a circular blood flow in the hypophysis (Fig. 7). This hypothesis is consistent with the reported high concentrations of the adenohypophyseal hormones in portal blood (Oliver, Mical and Porter, 1977).

Is there any direct transport route from the infundibulum to the hypothalamus? Although the outer vascular plexus of the infundibulum seems to have some capillary connections with the hypothalamus, careful microdissection of vascular casts, followed by SEM observation, revealed that most of the vessels running from the median eminence to the hypothalamus arise directly from the arteries and are arterioles (herein called hypothalamic ascending arteriole; Murakami, 1975a). It seems unlikely that blood in the capillaries of the median eminence could be transported to the
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hypothalamus, in view of the arteriolar nature of the connecting vessels. Attention should be given to the close spatial relationships between the hypothalamic ascending arterioles and the capillaries connected with the hypophyseal portal vessels (Fig. 8). This may represent a countercurrent exchange system which allows the hormones in the capillaries to be transferred into the arterioles and thus transported to the hypothalamus.

Can tanycytes transport hormones directly to the brain? Studies with horse-radish peroxidase suggest that the tanycyte transport may lead toward the ventricle (Nakai and Naito, 1975). No evidence is available that tanycytes can transport hormones from the infundibulum to the ventricle.

Fig. 6 and 7. Fig. 6 shows the possibility of flow reversal in the portal vessels which link the neurohypophysis and the adenohypophysis: such reversal flow could allow some degree of circular flow within the hypophysis (Fig. 7). The portal vessels close to the median plane are shown in solid lines, while those located laterally are in broken lines.
Fig. 8. This diagram shows the close spatial relationship of the hypothalamic ascending arteriole (see text) to the distal limbs of the capillary loops, and their collecting venules of the median eminence. The close proximity between the arterioles (red) and the venules (blue) may represent a countercurrent exchange system. Thus, some fraction of the neurohormones secreted into the capillary loops may be drawn into the arterioles and transported to the hypothalamus, where, they presumably act as feedback control. Arrows indicate the flow direction deduced from the observation of vascular casts. (Tracing of the SEM view by T. Murakami: Cell 7, 17, 1975).

Fig. 9. Vascular cast of the rat thyroid. Many round or oval basket-like networks of capillaries for the follicles (F) are seen. The interfollicular arteriole (a), after reaching the one pole of the follicle, abruptly breaks up into capillaries which in turn are collected into the interfollicular venule (v) at the opposite pole of the follicle. ×150
2. Thyroid gland

Thyroid follicles are known to be encapsulated by a capillary network, due to the work of Billroth (1882). SEM of vascular casts has shown basket-like networks of capillaries surrounding the follicles (Fig. 9). As in other endocrine organs, the capillaries surrounding the follicle are larger in caliber and the networks are more dense, which suggests the involvement of the blood vessels in hormone production and distribution. SEM of acid-digested tissue has shown the spatial relationship of the blood capillary networks to the follicles. This technique has also revealed that the lymph capillaries (approx. 20–100 μm in diameter) form loose meshworks, each of which contains one to six or more follicles (Shimada, 1981). Thus, the hormones secreted from the follicles can be taken up into blood capillaries and the lymphatic vessels as well.

The microvascular architecture surrounding the follicles shows species differences (Bargmann, 1939; Fujita and Murakami, 1974). In the dog and rat, the capillary network surrounding each follicle is often shared with that of the adjacent follicle (Fig. 9). Furthermore, wide avascular spaces often occur between adjacent follicles, suggesting
their direct contact at the sites (Fig. 10). In the monkey, however, adjacent capillary “baskets” tend to be independent (Fujita and Murakami, 1974).

3. Pancreas

The pancreas is made up of oval lobules 1–3 mm in diameter. Each lobule consists of exocrine tissue and endocrine islets scattered in between. A close anatomical and physiological relationship of the exocrine and endocrine portions has attracted attention of researchers and the vascular connections between them have been reported under

![Vascular cast of the rat pancreas. A periductal plexus (PdP) is seen as being supplied by an arteriole (indicated by white arrow head) and drained by venules (black arrow heads) which lead into interlobular vein (V). The intralobular arterioles (a) are seen breaking up into periacinar capillaries near the surface of the lobule. The intralobular venules (v) run within the centre of the lobule. A interlobular artery, x 75. (Micrograph from O. Ohtani and T. Fujita: Biomed. Res. 1, 135, 1980).](image-url)
the concept of the insulo-acinar portal system (Fujita, 1973; Fujita and Watanabe, 1973; Henderson, 1969). Also microcirculation of the pancreatic duct system has been subjected to recent studies (Ohtani and Fujita, 1980; Ohtani, 1983).

The interlobular arteries of the pancreas usually run with the interlobular veins along the ducts. The intralobular arterioles, tending to run in a more central part of the lobule, are generally not accompanied by the intralobular venules (Fig. 12). The intralobular arterioles can be classified into three categories by their destinations: 1) the insular arterioles which break up into the glomus-like capillary network characteristic of the islet of Langerhans (Fig. 13), 2) the acinar arterioles which tend to run long distances in the periphery of the lobules, then branching out into capillaries around the exocrine acini (Fig. 12, 13), 3) the periductular arterioles which supply the periductular capillary plexus of the duct system (Fig. 12) (Ohtani and Fujita, 1981).

**Fig. 12.** Vascular cast of the rabbit pancreas. An islet (I) is seen issuing a larger and longer efferent vessel (e) which is more appropriately termed an "insulo-acinar portal" vessel. Note a periductal plexus (PdP) is connected with the periacinar capillaries through small vessels of capillary or venular size (indicated by black arrow heads). An arteriole is seen in the lower right section of the picture (white arrow head), directly supplying the periacinar capillaries. A, V interlobular artery and vein. ×125. (Micrograph from O. Ohtani and T. Fujita: Biomed. Res. 1, 136, 1980).
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Microcirculation within the islet

The capillary network of the islet is normally supplied by one or two, but sometimes more, insular arterioles, and is usually drained through efferent vessels, called "insuloacinar portal" vessels (see below), into the periacinar capillary network (Fig. 12, 13). Some of the efferent vessels of islets in the rat drain directly into venules or veins without joining the periacinar capillary network: Islets with these connections are usually located near large veins, and not well surrounded by exocrine acini (OHTANI, 1983).

The microvascular pattern within the islets shows some species differences. In the rat and rabbit, the afferent arterioles usually end in the peripheral zone (area of A and D cells), and efferent vessels arise in deeper portions (area of B cells) of the islets (Fujita et al., 1976; Ohtani and Fujita, 1980) (Fig. 12, 13). In the monkey and horse, the afferent arterioles penetrate deep into the core zone (area of A and D cells) of the islets, and numerous efferent vessels radiate from the peripheral zone (area of B cells)
of the islets (FuJITA, 1973; FuJITA and MurAKAMI, 1973). The guinea pig islets, where A and D cells are rather evenly dispersed among B cells, tend to have a vascular pattern intermediate between that of the monkey and the rat (OHTANI, unpublished data). The vascular pattern within these islets suggests that blood flows from the area of A and D cells to that of B cells. Therefore glucagon released from A cells, and somatostatin from D cells, can be transferred by microcirculation to their first target, the B cells (FuJITA, 1973). It is widely accepted that glucagon stimulates the secretion of insulin, and somatostatin inhibits it.

**Insulo-acinar portal circulation**

The vascular route from the islet through its efferent vessels to the exocrine acini may properly constitute a "portal system," and has been referred to as the "insulo-acinar portal system" (FuJITA, 1973). Most of the efferent vessels of the islets in the monkey and guinea pig are of capillary size, whereas the islets of the rabbit and rat frequently have wider efferent vessels (probably venular) which run a rather, long distance before breaking up into the second, periacinar capillary plexus (Fig. 12). These vessels may better deserve the name of "portal" vessels.

The insulo-acinar portal system is also seen in the lower vertebrates, such as in the Japanese rat racer snake. In this snake, at least two kinds of islets have been noticed: several large oval islets 1 mm × 0.5 mm size (Fig. 14) and many small islets of less than

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**Fig. 14.** Vascular cast of the pancreas of the Japanese rat racer snake, *Elaphe quadrivirgata* (Boie). Illustrated in the center of the picture is a large islet (I) (approx. 1 mm × 0.45 mm) that drains directly into the systemic vein (indicated by an arrow head). a Afferent vessel of the islet, V vein. ×65
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300 μm in diameter (Fig. 15). The smaller islets show the typical insulo-acinar portal circulation pattern (Fig. 15), whereas the larger ones tend to drain directly into the systemic veins (Fig. 14). It is worthy to note that the larger islets are often found near the spleen or even surrounded by the parenchyma of the spleen, which suggests a functional correlation.

Intravital microscopy of the living pancreas in situ has revealed that blood leaving the islet flows through the portal vessels to the exocrine acini (rabbit: FRASER and HENDERSON, 1980; rat: OHTANI, 1983).

It is considered that through the insulo-acinar portal vessels, insular hormones and neurohormones (FUJITA and KOBAYASHI, 1979) are transferred in high concentrations to the exocrine pancreas to control its secretory activity. Evidence favoring this view has accumulated: insulin potentiates the effect of pancreozymin upon the exocrine pancreas (KANNO and SAITO, 1976); injection of glucagon causes degranulation of exocrine cells (SALTER, DAVIDSON and BEST, 1957); somatostatin inhibits the pancreatic enzyme secretion stimulated by cholecystokinin (DOLLINGER et al., 1976); and pancreatic polypeptide inhibits the secretion and cholecystokinin effect upon the exocrine pancreas (Lin et al., 1977).

Periductular circulation

The ducts and ductules of the pancreas have a well developed subepithelial plexus of capillaries which are sinusoidal in appearance (Fig. 12). In addition to its direct arterial
supply and venous drainage into the intra- or interlobular veins, the ductular (and ductal) plexus receives blood from the acinar portion via two other sources. First, blood flows into the periductal veins via vessels, both of capillary and venular size (Fig. 11): second, the periductular and periductal plexus is connected with the lobular capillary network by a few vessels of capillary size (OHTANI and FUJITA, 1980) (Fig. 12). Intravital microscopy of the rat pancreas has confirmed that blood flow through these vessels is from the lobule to the duct (OHTANI, 1983).

Rat islets frequently have a close anatomical relationship to the periductal and periductular plexus. Such islets receive branches from the interlobular (or intralobular) arteries. Their efferent vessels partially drain into the periductular or periductal plexus as well as into the periacinar capillary plexus (OHTANI and FUJITA, 1980) (Fig. 16). Blood flow from these islets to the periductular capillary plexus has been observed by intravital microscopy (OHTANI, 1983). It has been proposed that insular secretions are transferred, either directly through the insulo-ductular route or indirectly through

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**Fig. 16.** Vascular casts of the rat pancreas. An islet (I) located close to the periductular plexus (PdP) (a) and two islets attaching to the periductular plexus (b) are seen. The efferent vessels (indicated by arrow heads) of the islets are connected with the periductal, or periductular plexus. A Artery, a arteriole supplying both the periductular (or ductal) plexus and the islets, V vein, v venule. a: x 123, b: x 237
the insulo-acinar circulation, in high concentrations to the duct wall as short distance hormones which affect the duct system of the pancreas (OHTANI and FUJITA, 1980).

In conclusion, the microvascular organization of the pancreas (Fig. 17) provides the anatomical basis for the concept that the islets of Langerhans are the controlling centers of pancreatic functions (FUJITA and KOBAYASHI, 1979).

4. Adrenal gland

The adrenal gland derives its blood supply from several adrenal arteries leading into the subcapsular plexus on the surface of the gland. From the subcapsular plexus arise numerous arterioles and capillaries which course deep into the cortex, thus forming a cortical capillary bed. At the cortico-medullary junction, cortical capillaries abruptly

![Fig. 17. Diagram showing the arrangement of the pancreatic circulation.](image)

![Fig. 18. Vascular cast of the mouse adrenal gland showing the microvascular arrangement of the cortex (C) and medulla (M). Arrow head shows medullary artery, A adrenal artery, CV central vein. × 67](image)
converge into venous sinusoids (also called peripheral radicles of the central vein): in the medulla, these gradually collect to reach the central vein (Ohtani, 1981b; Kikuta and Murakami, 1982) (Fig. 18, 19). In addition, several small arteries, termed arteriae medullae, penetrate through the cortex and form a capillary bed to directly supply the medullary tissue. This capillary bed drains into the tributaries of the central vein, including the venous sinusoids (Fig. 18, 19).

It is currently accepted that phenylethanolamine-N-methyl transferase (which transfers a methyl group from S-adenosyl methionine to noradrenalin, which in turn yields adrenalin) is induced in the presence of glucocorticoids (Wurtman and Axelrod, 1966; Pohorecky and Wurtman, 1971). The N-methyl transferase is known to exist only in adrenalin-storing cells (A cells). Animals whose adrenal cortex is anatomically separated from the medulla can synthesize only noradrenalin, and not adrenalin (Coupland, 1953). Thus, it seems logical to postulate that noradrenalin (NA) cells will be closely located to the capillaries arising from the arteriae medullae. On the other hand, if A cells are positioned close to the venous sinusoids, blood reaching the A cells will have come from the cortex and so contain high concentrations of corticosteroids. However, to date there is no evidence of selective distribution of arterial or venous blood to either A or NA cells.

As in many other capillary beds, blood in the capillaries of the adrenal medulla may reverse its flow. Since adrenal medullary tissues are bathed in potent vasoconstrictors (e.g. noradrenalin), regional constrictions of arterioles or precapillary sphincters would likely occur. Such arteriolar constrictions could allow flow reversal from the venous sinusoids to arterial capillaries. As a result, blood containing corticosteroids in high concentrations could reach A cells. TEM has shown that the venous sinusoids of the adrenal medulla have fenestrated endothelial cells (Kikuta and Murakami, 1982) and a wide pericapillary space which could provide a transport route for corticosteroids to A cells.

5. Pineal body

Through clinical and experimental studies, it had been assumed that pineal body had an antigonadotropic effect. When Lerner et al. (1958) succeeded in isolating melatonin, this body became a subject of intensive investigation. In addition to photic influence on the secretory activity in the pineal body (Wurtman et al., 1964), its endocrine effects on the central nervous system have been proposed (Anton-Tay and Wurtman, 1969; Nir, Behrozi, Assael et al., 1969; Quay, 1965, 1970). In fishes, there exists a reciprocal
relationship between the dorsal sac size and the length of the pineal stalk (Hafeez, 1971). Some functional relationship between the pineal body and the choroid epithelium has been proposed. Furthermore, Friedrich-Freksa (1932) suggested that pineal secretion possibly controls permeability of the choroid plexus and formation of CSF.

Vascular architecture of the pineal body

The pineal body is a highly vascularized tissue (Hodde and Velteman, 1979) (Fig. 20), containing a network composed almost entirely of capillary-sized vessels. Each of the pineal lobules has a distinct capillary network, although there exist many interconnecting vessels between them. TEM and SEM have revealed the pineal capillaries are fenestrated (Milofsky, 1957; Wolfe, 1965; Moller et al., 1978; Krstic, 1979). The pericapillary spaces anastomose extensively with the pineal canaliculi, whose extensions reach almost every pineal cell (Krstic, 1979).

The posterior cerebral arteries supply the pineal body (Kappers, 1960; Smith, 1971; Hodde and Velteman, 1979). The pineal microcirculation drains into several pineal veins which lead, in turn, into either the great cerebral or cerebellar veins (Von Bartheld and Moll, 1954; Kappers, 1960; Smith, 1971). The topographical relationship of the pineal body to the large intracranial veins shows some species differences. There is no evidence for a portal system associated with the pineal body analogous to the hypophyseal portal system (Kappers, 1960; Smith, 1971; Hodde, 1978).

Are there any vascular routes from the pineal to the brain?

Since a portal system does not exist in the vicinity of the pineal, there appears to be no direct vascular route which would allow transport of the pineal secretions to particular regions of the brain. Following retrograde India ink perfusion of the pineal region, Quay (1973) concluded that the great cerebral vein could provide a vascular route for carrying pineal hormones to the brain, especially to the choroid plexus. However, his results were obtained by means of forced retrograde perfusion in postmortem preparations; other methods will have to be employed to substantiate this proposal.

Does the pineal secrete directly into the third ventricle?

The topographical relationship of the pineal to the third ventricle shows substantial species differences. In fishes and birds, the pineal is in direct contact with the CSF of the third ventricle through the pineal recess. In the rat, it has no direct contact with the ventricle, whereas in the hamster and guinea pig, the proximal part of the pineal reaches the ventricle. In the human, pineal parenchyme protrudes into the pineal
recess, thus investing the acervuli (Krstić, 1981). In the hamster, the pinealocytes could secrete their hormones directly into the CSF of the third ventricle, since this animal has a specialized structure where pinealocytes are in direct contact with the CSF. In the guinea pig and human, the third ventricle surface of the pineal is covered with ependyma (Krapp, 1978; Krstić, 1981), through which pineal secretions may pass. Studies with fluorescence microscopy have suggested a possibility of transcellular transport across the ependyma (Fleischhauer, 1972).

The capsule of the pineal consists of a few layers of flattened cells whose extensions frequently display rounded perforations of 0.5–1 μm in diameter (Krstić, 1979). These perforations could serve as transport routes between the pineal parenchyma and the CSF in the subarachnoid space.

DIGESTIVE SYSTEM

1. Salivary glands

Salivary gland microvasculature has been studied by the vascular corrosion casting/SEM method (rat; Ohtani, 1981b, Ohtani et al., 1983). The arterioles of the salivary gland run, generally, along the intralobular duct system and break up into capillaries to surround the acini, intercalated ducts and convoluted ducts (Fig. 21). The striated duct is surrounded by a sinusoidal capillary network which receives blood from the capillary networks surrounding the acini, intercalated ducts and convoluted ducts, through primarily two types of vessels. Firstly, the capillaries of the secretory portion drain into the sinusoidal capillary network around the striated ducts, through venules which may constitute a “portal system.” Secondly, the venules from the secretory portion join those running closely along the striated ducts, forming part of the vascular plexus around these ducts (Fig. 22, 23). Thus, circulation of the secretory portion of the salivary gland is linked with intralobular striated duct circulation through portal vessels or venules (sheep parotid: Blair-West et al., 1969; canine parotid: Burgen et al., 1958; rat submandibular, sublingual and parotid: Ohtani et al., 1983). It is likely that blood flows from the secretory portion of the gland through the portal vessels to the duct system (Blair-West et al., 1969; Ohtani et al., 1983).

Fig. 21. Diagram showing the microcirculatory bed and its relationship to the tissue element in the rat salivary gland. AC acinus, ID intercalated duct, CD convoluted duct, SD striated duct, ED excretory duct, PV portal vessel.
The interlobular, or excretory, ducts are surrounded by a dense subepithelial capillary network which is directly supplied by the interlobular arteries and drains into the interlobular veins (Fig. 24). In contrast to the intralobular ducts, the vessels around the interlobular ducts are independent of those around the acini (Ohtani et al., 1983).

No arterio-venous anastomoses (AVA) have been found in the gland, although arterio-arterial (AAA) and veno-venous anastomoses (VVA) are frequently observed along the ducts (Fig. 24). VVA and AAA, together with what are presumably sphincters at the confluent sites of the efferent venules of the periductal plexus and at the commencement of the afferent arterioles, may participate in regulating the duct circulation.

2. Liver

The liver lobule, as seen in the vascular casts, is represented by a dense network of extensively interconnected sinusoids which converge into the central vein (Fig. 25, 26). The vascular casts of the liver surface show a more or less hexagonal pattern consisting of the tapered origin of the central, or collecting vein and sinusoids converging into it (Ohtani and Murakami, 1978). The terminal hepatic arterioles and portal venules also
appear connected with the sinusoids on the surface of the liver in the monkey, human and cat (Murakami et al., 1974; Ohtani et al., 1982; Ohtani, unpublished data). In the rat and rabbit, such vessels are usually not seen on the liver surface (Ohtani and Murakami, 1978; Ohtani, 1979).

In general, the interlobular (or hepatic) artery runs within the stroma of the portal tract and is accompanied by the much wider interlobular (portal) vein (Fig. 26). In many places, the interlobular veins give off short side branches which abruptly diverge into the hepatic sinusoids at the margins of the lobule (Fig. 26). The interlobular arteries largely contribute to formation of a peribiliary (or periductal) plexus, from which efferent vessels join the sinusoids close to the portal tract or to the interlobular veins (see below). Other arterial branches bypass the peribiliary plexus and empty into the sinusoids, either directly or after supplying the connective tissue in the portal tract.
The interlobular arterioles occasionally anastomose with the accompanying interlobular venules (arterio-portal anastomoses) (Wakim, 1941; Wakim and Mann, 1942; Knisley et al., 1948; Bloch, 1955; Mitra, 1966; Del Rio Lozano and Andrews, 1966; Ohtani and Murakami, 1978) (Fig. 27). Such arterio-portal anastomoses are frequently seen in the rat (Ohtani and Murakami, 1978), while rarely in the rabbit (Ohtani, 1979). Neither arterio-hepatic vein anastomoses (Andrews and Maegraith, 1953) nor intralobular arterioles (Elias and Petty, 1953) have been confirmed by the SEM of vascular casts (Ohtani and Murakami, 1978; Ohtani, 1979; Ohtani, Murakami and Jones, 1982).

**Peribiliary portal system**

As noted by Mall (1906) and confirmed by later injection studies (Andrews, Maegraith and Wenyon, 1949), most branches of the interlobular arteries supply the bile ducts to
form a dense capillary network, termed the "peribiliary plexus" (Fig. 26, 28, 29). Larger peribiliary plexus usually consists of two vascular layers: an inner network of subepithelial capillaries, and an outer layer of arterioles, arising from the interlobular artery, and venules collecting from the inner capillaries (Fig. 30). Smaller plexus, in contrast, is composed of a single capillary network (Fig. 26). The peribiliary plexus is collected into independent vessels leading either to the hepatic sinusoids or interlobular veins (rat: OHTANI and MURAKAMI, 1978; OHTANI, 1981a; rabbit: OHTANI, 1979; human: OHTANI et al., 1982) (Fig. 26, 28, 29). The former route which drains into the hepatic sinusoids is designated the "lobular branch" (Fig. 26, 29). The latter, which ends in the inter-
lobular vein, is designated the "prelobular branch" (Fig. 26, 28) (OHTANI, 1979). The occurrence of the lobular and prelobular branches of the peribiliary plexus seems to vary from species to species. In the rabbit and human, both branches occur at almost the same frequency (OHTANI, 1979; OHTANI et al., 1982). In the rat, the prelobular branches are seen more frequently than the lobular branches (OHTANI and MURAKAMI, 1978), whereas in the monkey, the lobular branches occur almost exclusively with few prelobular branches (MURAKAMI, ITOSHIMA and SHIMADA, 1974). In lower vertebrates, e.g. the bullfrog, Rana catesbeiana, a similarly arranged peribiliary plexus is seen, in that efferent vessels tend to be drained more frequently into the hepatic sinusoids via the lobular branches (Fig. 31).

Since the peribiliary plexus has an elaborate capillary network of efferent vessels
Fig. 27-29. Legends on the opposite page.
reentering the hepatic sinusoids, the vascular route from the peribiliary plexus to the hepatic sinusoids through the peribiliary efferent vessels qualifies for the term of "portal" system, and should be referred to as the "peribiliary portal system" as proposed by Murakami et al. (1974).

The possible function of the peribiliary portal system has been considered in terms of a countercurrent mechanism which could facilitate the reabsorption of substance from bile (Henderson and Daniel, 1978). It has also been suggested that hormones released, in response to chemical information in the bile, from the basal-granulated (endocrine) cells in the bile ductules, might be transferred by this portal system back to the hepatic lobule to exert their actions upon hepatocytes (Fujita, 1977).

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Fig. 30. Vascular cast of the rabbit intrahepatic bile duct (large sized peribiliary plexus). Note that the plexus consists of two vascular layers; an inner network of subepithelial capillaries and an outer plexus of venules and arterioles. ×140. (Micrograph from O. Ohtani, Arch. histol. jap. 42: 160, 1979).

Fig. 27. Microdissected vascular cast of the rat liver. Anastomoses between the interlobular (or portal) vein (P) and the terminal branch of the hepatic artery (A) are seen (indicated by arrowheads). HS hepatic sinusoids. ×160

Fig. 28. Microdissected vascular cast of the rat liver. Note that the peribiliary plexus (PhP) receives arterioles (a) and emits efferent vessels (ep) leading into the interlobular vein (P). A hepatic artery, CV central vein, HS hepatic sinusoid. ×48

Fig. 29. Microdissected vascular cast of the rabbit liver. An efferent venule (el) of the peribiliary plexus (PhP) is seen draining into the hepatic sinusoids (HS). A hepatic artery, P interlobular (or portal) vein. ×50
3. Stomach

The microvascular organization of the stomach is diagrammatically summarized in Figure 32. Arteries supplying the stomach enter the serosa, divide into large branches which penetrate the muscularis externa and enter the submucosa where they form submucosal arterial plexus. The arteries of the submucosal plexus supply both the muscularis externa, and the mucosal layer. A number of terminal branches of the submucosal arteries ascend for short distances at right angles to the submucosal plane, towards the luminal surface. There, arterioles break up into capillaries near the base of the mucosa. Capillaries are associated with individual gastric glands, but adjacent areas have numerous cross-connections (Fig. 33). The luminal aspect of the vascular casts shows a honeycomb-like network of capillaries with infrequently placed draining vessels (Fig. 34). The mucosal capillaries are collected into mucosal venules near the luminal surface (Fig. 34). These straight venules descend at a right angle to the submucosal plane to join with the submucosal venous plexus (Fig. 33). In addition to these straight mucosal venules, some capillaries around the bottom of the gastric gland are drained into venules which lead into the submucosal venous plexus. The capillary sheets of the muscularis externa also drain into the submucosal venous plexus.

Although arterio-venous anastomoses (AVAs) in the submucosal vascular plexus have been described (Barlow, Bently and Walder, 1951, Oka, 1970; Hase and Moss, 1973), they were not found by SEM of vascular corrosion casts (Gannon et al., 1982), nor indicated in recent physiological studies. Guth and Rosenberg (1972), by in vivo microscopy, also failed to find AVAs in the submucosa or superficial mucosa.

As a result of SEM of vascular casts, and in vivo microscopy in the rat’s stomach, it is now known that blood must travel upward from the submucosal arterioles through the mucosal capillaries to the mucosal venules, which drain only from just below the luminal surface.

Physiological experiments have shown that secretion of $H^+$ by the parietal cell is associated with an equivalent extrusion of $HCO_3^-$ from the parietal cells into the adjacent interstitial space (Teorell, 1951). The fenestrated mucosal capillaries are located close to the parietal cells of the gastric glands, which, together with the direction of mucosal blood flow, suggest that the alkaline tide of the actively secreting
parietal cell will be transferred to the abluminal aspect of the surface epithelial cells, thus increasing the capacity of these cells to secrete HCO₃⁻ and to neutralize back diffusion of H⁺ ions (Gannon et al., 1982).

Gastrin, which is secreted by the antrum, has a powerful stimulatory effect on acid secretion by the parietal cells in the fundus. Although there is no evidence for the existence of a portal system analogous to the hypophyseal portal system, it would be of interest to search for any microcirculatory connections between the antrum and the fundus of the stomach (Henderson and Daniel, 1978).

4. Small intestine

The microvasculature of the small intestine has been well investigated by SEM of vascular casts, generally in the rat (Ohashi, Kita and Murakami, 1976); and specifically in villi of the cat, rabbit and human (Gannon, Gore and Rogers, 1981). The microvascular arrangement of the small intestine is summarized in Figure 35.

The microvascular bed of the intestinal mucosa is independent from those of the tunica muscularis; both are separately supplied by and drained into the submucosal
Fig. 33-34. Legends on the opposite page.
vascular network (OHASHI, KITA and MURAKAMI, 1976). The tunica muscularis has two capillary networks, an outer and inner layer of capillaries arranged along the longitudinal and circular muscles, respectively (Fig. 36).

The base of the crypt is richly supplied by a basket-shaped capillary network, from which small interconnected vessels (probably capillary in nature) ascend along the crypt and form a capillary ring around its opening (see below). Near the bottom of the crypt, some capillaries are drained into venules which lead into the submucosal venous plexus (Fig. 37).

The villous microvasculature shows species differences. In the rat, an arteriole running centrally through the flattened, tongue shaped villus connects at its tip with a plexus of cross connected capillaries immediately beneath the epithelium (Fig. 38). At 30-70% of the villous height below the tip, this plexus converges into venules. There are usually two venules per villus in the proximal part of the intestine, and often three in the distal part. The villous venules are situated more or less symmetri-

**Fig. 33.** Mucosal capillaries of the rat stomach corpus. a Submucosal arteriole that breaks up into mucosal capillaries (C), r mucosal venule. ×110

**Fig. 34.** Vascular cast of the rat stomach corpus. Note that the luminal aspect shows a honeycomb-like network of capillaries and commencements of the mucosal venules (r). ×87
Fig. 36. Vascular cast of the rat jejunum. The serosal aspect of the muscularis externa shows two layers of microvessels among longitudinal and circular muscles crossing at approximately right angles. A, V submucosal artery and vein. × 180

Fig. 37. Vascular cast of the rat jejunum. Submucosal aspect of the mucosa. Muscular capillaries have been dissected away. A, V submucosal artery and vein. × 135
cally in the villous core, aligned with the single arteriole (Fig. 38). Near the villous base (some 80% of the villous height below the tip) the subepithelial capillary plexus continues as a series of straighter vessels, with the capillary rings surrounding the opening of the crypts adjacent to the villus (Fig. 39). In the cat, an arteriole located centrally in the villus connects at the villous tip with a cylindrically shaped plexus of subepithelial capillaries. These capillaries from the villous tip to the base where the plexus connects with venules, and thus forms a classical fountain pattern of vessels (Gannon, Gore and Rogers, 1981). The villous microvascular architecture of the rabbit and human is similar to that of rat in many respects, but different in that, in the rabbit and human, an arteriole and a venule are situated asymmetrically in the villous core, and the level of connection of the subepithelial capillary plexus with the villous venules is some 20–40% (rabbit) and 15–25% (human) of the villous height below the tip (Gannon, Gore and Rogers, 1981).

The microvascular organization of the small intestine shows some regional differences. In the duodenum, the capillary plexus around the duodenal glands of Brunner is located in the submucosal layer and is well developed (Fig. 40). In the distal part of the small intestine, especially in the ileum, between the villi there are dome-like networks of capillaries surrounding the lymphatic follicles of Peyer's patches (Fig. 41) (see below).
**Microrvascular organization of fetal villi**

The microvascular casts of the flatter finger shaped villi of the full term rabbit fetus show a classical step-ladder pattern. An arteriole arises from the submucosal artery and ascends along the apical margin of the villus, giving off subepithelial capillaries en route. The villous venule descends along the other apical margin of the villus, collecting subepithelial capillaries en route and connects with the submucosal vein (Fig. 42). Thus, villi in the full term rabbit fetus show a microvascular pattern different from that seen in the adult. The detailed developmental change of the villous microvasculature will be the subject of a separate communication.

**Does a vascular countercurrent mechanism operate in the villi?**

The microvascular arrangement of the cat villi, based on the physiological experiments on this animal seems to be consistent with a countercurrent mechanism (Lundgren, 1967, 1978; Hallback et al., 1979). It has been found that there is an osmotic gradient in the cat villus, with osmolarity greatest at the tip (Lundgren, 1974; Winne, 1975). However, in villi of the adult rabbit, for example, countercurrent exchange may not occur because of the spatial separation of arterioles from villous capillaries and the villous venules, and also because blood in over 60% of the height of the villous capillary plexus flows concurrent with the arterial flow (Gannon, Gore and Rogers, 1981). The differing vascular organizations of mammalian villi do not support the concept of a common and general villous countercurrent vascular mechanism.

**Does a portal circulation exist between the crypt and villous base?**

In vivo microscopy shows that blood flows from the base of the crypt plexus to the base of the villus (rabbit: Gannon et al., 1981, Gannon, 1981a; rat: Ohtani, unpublished data), where the crypt plexus connects with villous capillaries. The connecting vessels between the crypt and the villous base are capillary size with few interconnections. Thus, while these connecting vessels are not large (unlike the hepatic portal vein), functionally, they may be regarded as portal vessels. It is postulated that hormones released from the basal-granulated, or endocrine cells (which are condensed at the deeper portion of the crypt and are richly supplied by a capillary network) can be efficiently transported to act in the villous base (Ohashi et al., 1976).
**Microcirculation of Peyer's patch**

In the rat Peyer's patch (or intestinal lymphoid follicle), one or more arterioles ascending through the follicle connect with the capillary network immediately beneath the epithelium. An adequate blood supply to the apical region of the follicle is thus ensured (BHALLA, MURAKAMI and OWEN, 1981). This region of follicle is occupied by M cells and is involved in transporting antigen from the intestinal lumen to the underlying lymphoid tissue (OWEN, 1977). In addition to the arterioles ascending through the follicle, the Peyer's patch is supplied by two other sets of arterioles: a horizontal set running parallel to the serosal surface, and a vertical set penetrating the follicle. The capillary plexus of the follicle collects into venules which, in turn, lead into postcapillary venules around the follicle periphery where lymphocytes are known to migrate from the blood vessels to the follicle parenchyme (BHALLA et al., 1981).

**CONCLUSION**

SEM of microvascular corrosion casts has clearly shown that each organ has its own specific microvascular architecture, most often reflecting the local morphology.
However, some common characteristics are also found. As well known, capillaries in endocrine tissues are much higher in density and thicker in caliber (i.e. sinusoidal, as confirmed by other methods) than those found in other tissues. The duct systems in the pancreas, liver and salivary gland, as well as the intestinal villi possess well developed subepithelial capillary networks, which strongly suggest their extensive involvement in secretory and/or absorptive activities. In some organs the microvasculatures form portal systems, so that the substances secreted and/or absorbed into the blood vessels can be transported effectively through short vascular routes to their target cells as typically seen in the insulo-acinar, hypophyseal and peribiliary portal systems. The close arterio-venous (or capillary) relationship seen in cat villi may represent a counter-current exchange system (LUNDGREN, 1974), similar to the system known to operate in the renal medulla.

There are substantial differences in microvascular organization, as seen in the intestinal villi, efferent vessels of the islets of Langerhans and those of the peribiliary plexus. In order to investigate the involvement of microcirculation in the function of various organs in the human, one should first seek an appropriate animal model, i.e. one with similar microvascular organization.

In this paper we have proposed some hypotheses concerning the microcirculatory patterns and their significance, based on available literature and on our own observations both by SEM of vascular casts and by intravital microscopy. However, we would...
like to stress that our investigation is only at the initial stage of describing the structure of the numerous and variable microvascular networks in different regions of the body. Intensive studies are required in this field, not only from the anatomical, but also from physiological, pharmacological, pathological and clinical points of view.

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Fig. 42. Diagram showing the villous microcirculation of the full term rabbit fetus. SMA, SMV submucosal artery and vein, MA, MV mucosal arteriole and venule.

REFERENCES

Akmayev, I. G.: Morphological aspects of the hypothalamic-hypophyseal system. II. Functional morphology of pituitary microcirculation. Z. Zellforsch. 116: 178–194 (1971).

Allen, J. P., J. W. Kendall, R. McGilbra and C. Voncura: Immunoreactive ACTH in cerebrospinal fluid. J. clin. Endocrinol. 38: 586–593 (1974).

Andrews, W. H. H and B. G. Maegraith: Anatomical and physiological evidence of the hepatic artery and hepatic vein within the mammalian liver. Nature 171: 222–223 (1953).

Andrews, W. H. H., B. G. Maegraith and C. E. M. Wenyon: Studies on the liver circulation. II. The microanatomy of the hepatic circulation. Ann. trop. Med. 43: 229–237 (1949).

Anton-Tay, F. and R. J. Wurtman: Regional uptake of $^3$H-melatonin from blood or cerebrospinal fluid by rat brain. Nature 221: 474–475 (1969).

Bargmann, W.: Die Schilddrüse. In: Mollendorff's Handbuch der mikroskopischen Anatomie des Menschen. Springer, Berlin, 1939 (Vol. VI/2, p. 1–136).

Barlow, T. E., F. H. Bentley and D. N. Walder: Arteries, veins and arterio-venous anastomoses in human stomach. Surg. Gynecol. Obstet. 93: 657–671 (1951).

Bergland, R. M. and R. B. Page: Pituitary-brain vascular relations: A new paradigm. Science 204: 18–24 (1979).

Bergland, R. M. and R. M. Torack: An electron microscopic study of the human infundibulum Z. Zellforsch. 99: 1–12 (1969).

Bhalla, D. K., T. Murakami and R. L. Owen: Microcirculation of intestinal lymphoid follicles in rat Peyer's patches. Gastroenterol. 81: 481–491 (1981).
Billroth, T: Die allgemeine Pathologie und Therapie. 10 Aufl. G. Reimer, Berlin, 1882 (Cit. from W. Bargmann).

Blair-West, J. R., J. P. Coghlan, D. A. Denton, J. Nelson, R. D. Wright and A. Yamauchi: Ionic, histological and vascular factors in the reaction of the sheep's parotid to high and low mineralocorticoid status. Physiol. 205: 563–579 (1969).

Bloch, E. H.: The in vivo microscopic vascular anatomy and physiology of the liver as demonstrated with the quartz rod method of transillumination. Angiology 6: 340–349 (1955).

Burgen, A. S. V. and P. Seeman: The role of the salivary duct system in the formation of the saliva. Canadian J. Biochem. Physiol. 36: 119–143 (1958).

Carraway, R. E., L. M. Demers and S. E. Leemar: Hyperglycemic effect of neurotensin, a hypothalamic peptide. Endocrinology 99: 1452–1462 (1976).

Coupland, R. E.: On the morphology and adrenaline, noradrenaline content of chromaffin tissue. J. Endocrinol. 9: 194–202 (1953).

Del Rio Lozano, I. and W. H. H. Andrews: A study by mean of vascular casts of small vessels related to the mammalian portal vein. J. Anat. 100: 655–673 (1966).

Dollinger, H. C., S. Raptis and E. F. Pfeiffer: Effects of somatostatin on exocrine and endocrine pancreatic function stimulated by intestinal hormones in man. Horm. Metab. Res. 8: 74–78 (1976).

Elias, H. and D. Petty: Terminal distribution of the hepatic artery. Anat. Rec. 116: 9–18 (1953).

Evan, A. P., W. G. Dail, D. Dammrose and C. Palmer: Scanning electron microscopy of cell surface following removal of extracellular material. Anat. Rec. 185: 433–446 (1976).

Fleischhauer, K.: Ependyma and subependymal layer. In (ed. by) G. H. Bourne: The structure and function of nervous tissue. Academic Press, New York-London, 1972 (Vol. VI, p. 1–4).

Fraser, P. A. and J. R. Henderson: The arrangement of endocrine and exocrine pancreatic microcirculation observed in the living rabbit. Quart. J. exp. Physiol. 65: 151–158 (1980).

Friedrich-Freksa, H.: Entwicklung, Bau und Bedeutung der Parietalgegend bei Teleostiern. Z. wiss. Zool., 14: 52–142 (1932).

Fujita, H. and T. Murakami: Scanning electron microscopy on the distribution of the minute blood vessels in the thyroid gland of the dog, rat and rhesus monkey. Arch. histol. jap. 36: 181–188 (1974).

Fujita, T.: Insulo-acinar portal system in the horse pancreas. Arch. histol. jap. 35: 161–171 (1973).

Fujita, T. and S. Kobayashi: Proposal of a neurosecretory system in the pancreas. An electron microscope study in the dog. Arch. histol. jap. 42: 277–295 (1979).

Fujita, T. and T. Murakami: Microcirculation of monkey pancreas with special reference to the insulo-acinar portal system. A scanning electron microscope study of vascular casts. Arch. histol. jap. 35: 255–263 (1973).

Fujita, T. and Y. Watanabe: The effect of islet hormones upon the exocrine pancreas. In: (ed. by) T. Fujita: Gastro-entero-pancreatic endocrine system. A cell-biological approach. Igaku Shoin, Tokyo, 1973 (p. 161–173).

Fujita, T., Y. Yanatori and T. Murakami: Insulo-acinar axis, its vascular basis and its functional and morphological changes caused by CCK-PZ and caerulein. In: (ed. by) T. Fujita: Endocrine gut and pancreas. Elsevier, Amsterdam, 1976 (p. 347–357).

Gannon, B. J.: Vascular casting. In: (ed. by) Hayat: Principles and techniques of scanning electron microscopy. Van Nostrand Reinhold, New York, 1978 (Vol. 6, p. 170–193).

Gannon, B. J.: The co-existence of fountain and tuft patterns of blood supply in individual intestinal villi of rabbit and man: resolution of an old controversy. Bibliotheca Anat. 20: 130–133 (1981a).

Gannon, B. J., J. Browning and P. O’Brien: Preparation of microvascular corrosion casting media: procedures for partial polymerization of methyl methacrylate using ultraviolet light. Biomed. Res. 2, Suppl.: 227–233 (1981b).

Gannon, B. J., J. Browning and P. A. W. Rogers: Is there an anatomical basis for a vascular counter-current mechanism in rabbit and human intestinal villi? Biomed. Res. 2, Suppl.: 235–241 (1981).
Guth, P. H. and A. Rosenberg: In vivo microscopy of gastric microcirculation. Dig. Dis. 17: 391–398 (1972).

Hafeez, M. A.: Light microscopic studies on the pineal organ in teleost fishes with special regard to its function. J. Morphol. 134: 281–313 (1971).

Hallback, D.-A., M. Jodal, A. Sjoquist and D. Lundgren: Villous osmolarity and intestinal transport of water and electrolytes. Acta physiol. Scand. 107: 115–126 (1979).

Harris, G. W.: The blood vessels of the rabbit’s pituitary gland, and the significance of pars and zona tuberalis. J. Anat. 81: 343–351 (1947).

Hase, T. and B. J. Moss: Microvascular changes of gastric mucosa in the development of stress ulcer in rats. Gastroenterol. 65: 224–234 (1973).

Heller, H., S. H. Hasan and A. O. Saifi: Antidiuretic activity in the cerebrospinal fluid. J. Endocrinol. 41: 273–280 (1968).

Henderson, J. R.: Why are the islets of Langerhans? Lancet ii: 469–470 (1969).

Henderson, J. R. and P. M. Daniel: Portal circulations and their relation to countercurrent systems. Quart. J. exp, Physiol. 63: 355–369 (1978).

Hodde, K. C., A. Miodonski, C. Bakker and W. A. M. Veltman: SEM of microcorrosion casts with special attention on arterio-venous differences and application to rat’s cochlea. SEM/1977/II, IIT Research Institute, Chicago, 1977 (p. 477–484).

Hodde, K. C. and J. A. Nowell: SEM of micro-corrosion casts. In: SEM/1980/II, SEM Inc., AMF O’Hare, IL, 1980 (p. 89–106).

Hodde, K. C. and W. A. M. Veltman: The vascularization of the pineal gland (epiphysis cerebri) of the rat. SEM/1979/III, SEM Inc., AMF O’Hare, IL, 1979 (p. 369–374).

Holmes, R. L.: The vascular pattern of the median eminence of the hypophysis in the macaque. Pol. primat. 7: 216–230 (1967).

Horstmann, E.: Die Faserglia des Selachiergehirns. Z. Zellforsch. 39: 588–617 (1954).

Ishikawa, H.: Study on the existence of TRH in the cerebrospinal fluid in humans. Biochem. biophys. Res. Commun. 120:3–1209 (1973).

Kanno, T. and A. Saito: The potentiating influences of insulin on pancreozymin-induced hyperpolarization and amylase release in the pancreatic acinar cell. J. Physiol. 261: 505–521 (1976).

Kappers, J. A. : The development, topographical relations and innervation of the epiphysis cerebri in the albino rat. Z. Zellforsch. 52: 163–215 (1960).

Kikuta, A. and T. Murakami: Microcirculation of the rat adrenal gland: A scanning electron microscope study of vascular casts. Amer. J. Anat. 164: 19–28 (1982).

Knigge, K. M. and S. A. Joseph: Thyrotrophin releasing factor (TRF) in CSF of third ventricle of rat brain. Acta endocrinol. (Kbh) 76: 209–213 (1974).

Knigge, K. M. and D. E. Scott: Structure and function of the median eminence. Amer. J. Anat. 129: 223–244 (1970).

Knisley, M. H., E. H. Bloch and L. Warner: Selective phagocytosis. I. Microscopic observations concerning the regulation of the blood flow through the liver and other organs and the mechanism and rate of phagocytic removal of particles from the blood. Biol. Str. 4: 1–93 (1948).

Krapp, C.: The ependyma on the pineal of the guinea pig (Cavia cobaya). A scanning electron microscopic investigation. Anat. Embryol. 152: 217–222 (1978).

Krstic, R. V.: Scanning electron microscopic study of the freeze-fractured pineal body of the rat. Cell Tiss. Res. 201: 129–135 (1979).

———: Contribution of scanning electron microscopy to the study of brain ventricles, circumventricular organs and the pineal organ. Biomed. Res. 2, Suppl.: 129–137 (1981).

Kubotsu, A. and M. Ueda: A new conductive treatment of the specimen for scanning electron microscopy. J. Electron Microsc. (Tokyo), 29: 45–53 (1980).

Lametschwandtner, A. and P. Simonosberger: Light and scanning electron microscopical studies of the hypothalmo-adenohypophysial portal vessels of the toad, Bufo bufo L. Cell Tiss. Res. 162: 131–139 (1975).

Lametschwandtner, A., P. Simonosberger and H. Adam: Vascularization of the pars distalis of the hypophysis in the toad, Bufo bufo L. A comparative LM and SEM study I. Cell Tiss. Res. 179: 1–10 (1977a).
Lametschwandtner, A., P. Simonsberger and H. Adam: Vascularization of the pars intermedia of the hypophysis in the toad, Bufo bufo L. A comparative LM and SEM study II. Cell Tiss. Res. 179: 11–16 (1977b).

Lerner, A. B., J. D. Case, Y. Takahashi, T. H. Lee and W. Mori: Isolation of melatonin, the pineal gland factor that lightens melanocytes. J. Amer. Chem. Soc. 80: 2587 (1958).

Lin, T.-M., D. C. Evans, R. E. Chance and G. F. Spray: Bovine pancreatic peptide: Action on gastric and pancreatic secretion in dogs. Amer. J. Physiol. 1: E311–315 (1977).

Lundgren, O.: Studies on blood flow distribution and countercurrent exchange in the small intestine. Acta Physiol. Scand. Suppl. 303: 1–42 (1967).

Mall, F. P.: A study of the structural unit of the liver. Amer. J. Anat. 5: 227–308 (1906).

Milofsky, A. H.: The fine structure of the pineal body in the rat, with special reference to parenchyma. Anat. Rec. 127: 435–436 (1957).

Mitra, S. K.: The terminal distribution of the hepatic artery with special reference to arterioportal anastomosis. J. Anat. 100: 651–663 (1966).

Moller, M., B. Van Deurs and E. Westergaard: Vascular permeability to proteins and peptides in the mouse pineal gland. Cell Tiss. Res. 195: 1–15 (1978).

Murai, T.: Application of the scanning electron microscope to the study of the fine distribution of the blood vessels. Arch. histol. jap. 32: 445–454 (1971).

---: Pliable methacrylate casts of blood vessels: use in a scanning electron microscope study of the microcirculation in rat hypophysis. Arch. histol. jap. 38: 151–168 (1975a).

---: Injection replica scanning electron microscope method for studying the fine distribution of the blood vessels. (In Japanese) Cell (Tokyo) 7: 11–18 (1975b).

---: Methyl-methacrylate injection replica method. In: (ed. by) M. A. Hayat: Principles and techniques of scanning electron microscopy. Van Nostrand Reinhold, New York, 1978 (Vol. 6, p. 159–169).

Murakami, T., T. Itoshima and Y. Shimada: Peribiliary portal system in the monkey liver as evidenced by the injection replica scanning electron microscope method. Arch. histol. jap. 37: 245–260 (1974).

Murakami, T., M. Unehira, H. Kawakami and A. Kubotsu: Osmium impregnation of methyl methacrylate vascular casts for scanning electron microscopy. Arch. histol. jap. 36: 119–124 (1973).

Nakai, Y. and N. Naito: Uptake and bidirectional transport of peroxidase injected into the blood and cerebrospinal fluid by ependymal cells of the median eminence. In: (ed. by) K. M. Knigge, D. E. Scott, H. Kobayashi and S. Ishii: Brain-endocrine interaction. II. The ventricular system. Karger, Basel, 1975 (p. 94–108).

Nir, I., K. Behroozi, M. Assael, I. Ivriani and F. G. Sulman: Changes in the electrical activity of the brain following pinealectomy. Neuroendocrinol. 4: 122–127 (1969).

Ohashi, Y., S. Kita and T. Murakami: Microcirculation of the rat small intestine as studied by the injection replica SEM method. Arch. histol. jap. 39: 271–282 (1976).

Ohtani, O.: The peribiliary portal system in the rabbit liver. Arch. histol. jap. 42: 153–167 (1979).

---: Microcirculation studies by the Injection replica method. Biomed. Res. 2, Suppl. 1: 219–226 (1981a).

---: Microcirculation studies by the injection replica method with special reference to the portal circulations. In (ed. by) D. J. Allen, M. P. Motta and L. A. J. DiDio.: Three-dimensional microanatomy of cell and tissue surfaces. Elsevier North Holland, New York, 1981b (p. 51–70).

---: Microcirculation of the pancreas: A correlative study of intravital microscopy with scanning electron microscopy of vascular corrosion casts. Arch. histol. jap. 46, (1983, in press).

Ohtani, O. and T. Fujita: Microcirculation of the pancreas with special reference to the periduc-
tular circulation. A scanning electron microscope study of vascular casts. Biomed. Res. 1: 130–140 (1980).

Ohtani, O. and T. Murakami: Insulo-acinar portal system of the pancreas. A scanning electron microscope study of corrosion casts. In: (ed. by) E. A. Vidrio and M. A. Galina: Progress in clinical and biological Research. Vol. 59B, Advance in the morphology of cells and tissues. Alan R. Liss Inc., New York, 1981 (p. 111–120).

Ohtani, O., and T. Murakami: Peribiliary portal system in the rat liver as studied by the injection replica SEM method. In: (ed. by) R. P. Becker and O. Johari: Scanning electron microscopy/1978/II. SEM Inc., AMF O'Hare, IL, 1978 (p. 241–244).

Ohtani, O., T. Murakami and A. L. Jones: Scanning electron microscopy of replicated liver blood vessels in man and some other animals with special reference to the peribiliary portal system. In: (ed. by) P. M. Motta and L. J. A. DiDio: Basic and clinical hepatology. Martinus Nijhoff Publishers, The Hague-Boston-London, 1982 (p. 85–96).

Ohtani, O., A. Ohtsuka, J. Lipsett and B. Gannon: The microvasculature of rat salivary glands: A scanning electron microscopic study. Acta. anat. (1983, in press).

Oka, S.: Studies on the microcirculation of gastro-intestinal mucosa. (In Japanese). Saishin Igaku 25: 1705–1713 (1970).

Oliver, C., R. S. Mical and J. C. Porter: Hypothalamic-pituitary vasculature: evidence for retrograde blood flow in the pituitary stalk. Endocrinology 101: 598–604 (1977).

Owen, R. L.: Sequential uptake of horseradish peroxidase by lymphoid follicle epithelium of Peyer’s patches in the normal unobstructed mouse intestine: an ultrastructural study. Gastroenterol. 72: 440–451 (1977).

Page, R. B. and R. M. Bergland: The neurohypophyseal capillary bed. I. Anatomy and arterial supply. Amer. J. Anat. 148: 345–358 (1977).

Page, R. B., A. E. Leure-du Pree and R. Bergland: The neurohypophyseal capillary bed. II. Specialization within median eminence. Amer. J. Anat. 153: 33–66 (1978).

Pappenheimer, J. R., T. B. Miller and C. A. Goodrich: Sleep promoting effects of cerebrospinal fluid from sleep-deprived goats. Proc. Nat. Acad. Sci. (Wash.) 58: 513–517 (1967).

Pavel, S.: Arginine vasotoxin release into cerebrospinal fluid of cats induced by melatonin. Nature 246: 183–184 (1973).

Pohorecky, L. A. and R. J. Wurtman: Adrenocortical control of epinephrine synthesis. Pharmacol. Rev. 23: 1–35 (1971).

Popa, G. and U. Fielding: The vascular link between the pituitary and the hypothalamus. Lancet ii: 238–240 (1930a).

Quay, W. B.: Experimental evidence for pineal participation in homeostasis of brain composition. Progr. Brain Res. 10: 646–653 (1965).

Rabin, R. G. and E. A. Zimmerman: Cerebrospinal fluid and ependymal neurophysin. J. clin. Invest. 52: 1260–1267 (1973).

Salter, J. M., W. F. Davidson and C. H. Best: The pathological effects of large amounts of glucagon. Diabetes 6: 248–255 (1957).

Scott, D. E., G. Krobisch-Dudley and K. M. Knigge: The ventricular system in neuroendocrine mechanism. II. In vivo monoamine transport by ependyma of the median eminence. Cell Tiss. Res. 154, 1–16 (1974).

Shimada, T.: Lymph and blood capillaries as studied by a new SEM technique. Biomed. Res. 2, Suppl.: 243–248 (1981).

Smith, A. R.: The topographical relations of the rabbit pineal gland to the large intracranial veins. Brain Res. 30: 339–348 (1971).

Teorell, T.: The acid-base balance of the secreting isolated gastric mucosa. J. Physiol. 114: 267–276 (1951).
Török, B.: Structure of the vascular connections of the hypothalamo-hypophyseal region. Acta anat. 59: 84-89 (1964).

Von Bartheld, F. and J. Moll: The vascular system of the mouse epiphysis with remarks on the comparative anatomy of the venous trunks in the epiphyseal area. Acta. anat. 22: 227-235 (1954).

Wakim, K. G.: The intrahepatic circulation of blood in the intact animal: preliminary report. Proc. Staff Meet. Mayo Clin. 16: 198 (1941).

Wakim, K. G. and F. C. Mann: The intrahepatic circulation of blood. Anat. Rec. 82: 233-253 (1942).

Winne, D.: The influence of villous countercurrent exchange on intestinal absorption. J. Theor. Biol. 53: 145-176 (1975).

Wislocki, G. B.: The vascular supply of the hypophysis cerebri of the cat. Anat. Rec. 69: 361-387 (1937).

Wislocki, G. B. and L. S. King: The permeability of the hypophysis and hypothalamus to vital dyes, with a study of the hypophyseal vascular supply. Amer. J. Anat. 58: 421-427 (1936).

Wolfe, D. E.: The epiphyseal cell: an electron microscopic study of its intercellular relationships and intracellular morphology in the pineal body of the albino rat. In: (ed. by). J. A. Kappers and J. P. Schade: Progress in brain research, Vol. 10. Structure and function of the epiphysis cerebri. Elsevier, Amsterdam- London- New York, 1965 (p. 332-386).

Wurtman, R. J. and J. Axelrod: Control of enzymatic synthesis of adrenaline in the adrenal medulla by adrenal cortical steroid. J. Biol. Chem. 241: 2301-2305 (1966).

Wurtman, R. J., J. Axelrod and J. E. Fischer: Melatonin synthesis in the pineal gland: Effect of light mediated by the sympathetic nervous system. Science 143: 1328-1330 (1964).

Yates, F. E., S. M. Russell, M. F. Dallman, G. A. Hedge, S. M. McCann and A. P. S. Dhariwal: Potentiation by vasopressin of corticotropin release induced by corticotropin-releasing factor. Endocrinology 88: 3-15 (1971).