KAWASAKI MED. J. VOL. 10 : NO. 1, 49-61 (1984)

Morphological Studies of the Mucous Membrane of the Small Intestine of Vertebrates with an Emphasis on Comparative Anatomy

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Accepted for Publication on January 9, 1984

ABSTRACT. In order to explicate the morphological and adaptive variations occurring in the mucous membrane of the small intestine, a morphological study was conducted from a phylogenetic viewpoint of the small intestinal mucosa of fish, amphibians, reptiles, birds and mammals, including man. A tendency for the mucosa to have gradually changed from that of folds only to that of fine villi as evolution proceeded was noted. It was further noted that as the evolutionary scale is climbed, there is a tendency for both the columnar cells, which make up the epithelium, and the microvilli observed at their apices to become shorter. Another interesting discovery was that the basal lamina of the mucosal epithelium of fish living near the delta of rivers is multi-layered and has a unique wavelike laminar structure.

Key words : mucous membrane of the small intestine — villi — columnar cell — microvilli — basal lamina

The small intestinal mucosa of humans has a highly differentiated mucosa whose constituent cells are also highly differentiated both morphologically and functionally.[1] Morphological variation of the mucosa can occur due to genetic as well as dietetic factors.[2] It is also known that chronic diseases of the small intestine may cause various morphological changes and structural adaptations.[2–4] In order to get a clue as to why such changes occur, a morphological study was performed from a phylogenetic standpoint of the mucous membrane of the small intestine of fish, amphibians, reptiles, birds, and mammals, including man.

MATERIALS AND METHODS

Three flatfish (*Paralichthys olivaceus*), 3 goby (*Bathygobius fuscus*), 3 mullet (*Mugil cephalus*), 6 salamanders (*Triturus pyrrhogaster pyrrhogaster*), 6 lizards (*Takydromus tachydromoides*), 6 finches (*Lonchura striata*), and 6 rats (*Rattus norvegicus*), which were all physically normal, were included in the study. They were sacrificed under ether anesthesia, and their small intestines were removed and immediately fixed in 2.5% glutaraldehyde in phosphate buffer (pH 7.4). In the case of fish, a saline solution physiological to fish was used.[5] After observing the mucosa under a dissecting microscope, specimens were

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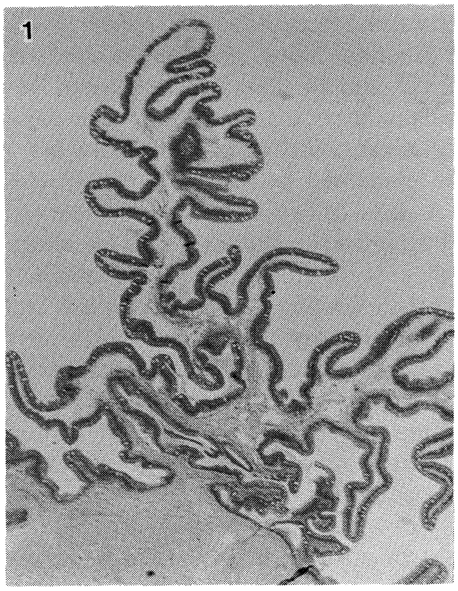
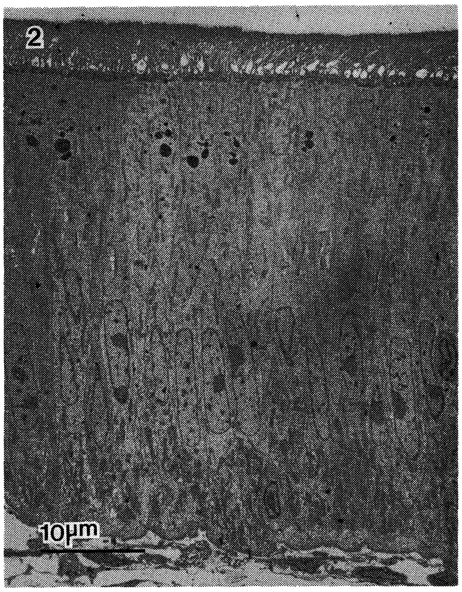
prepared for light microscopic examination with hematoxylin-eosin staining. Separate specimens were fixed for two hours in 1% osmium tetroxide and dehydrated in a graded ethanol series. Scanning electron microscopic samples were transferred to iso-amyl acetate, critical-point dried, coated with gold-palladium by evaporation and observed under a Hitachi HHS-2R scanning electron microscope. Transmission electron microscopic samples were transferred to propylene oxide and embedded in epon. Ultrathin sections were then made with a MT2-B Porter-Blum ultra-microtome, double-stained with uranyl acetate and lead citrate, and observed under a Hitachi H-500 electron microscope. The base, middle and tip of the villi from both the proximal and distal small intestine were examined. Using surgically resected materials from the ileum of three patients with Crohn's disease, the human small intestinal mucosa was observed macroscopically as well as under the dissecting, light and electron microscopes. The cases cited in the research report of Kihara concerning the small intestinal mucosa of the Japanese, especially the morphology of the villi, were referred to for comparison.[6)]

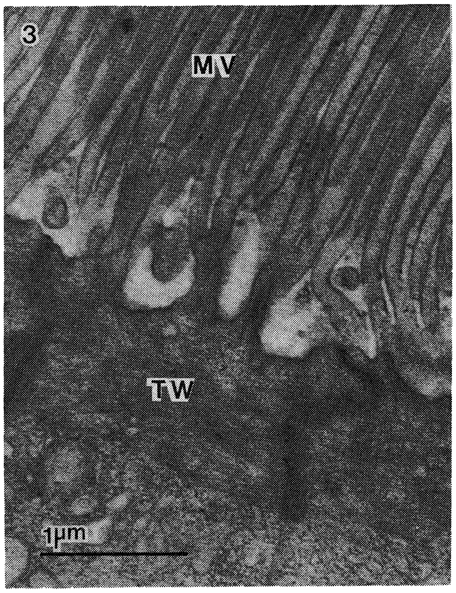
RESULTS

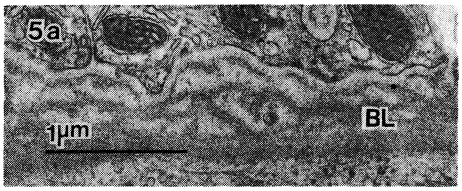
Fish. The digestive tract of the flatfish leads from the esophagus to a white saccate stomach, from there to a tubular intestine, and ends in the rectum. Four pyloric ceca can be observed surrounding the pylorus. There is hardly any morphological difference between the intestine and the rectum in the rectal region adjacent to the intestine. The folds of the intestinal lumen are divided into many branches which lie against each other in a longitudinal direction. The mucosa is covered with a simple epithelium of columnar cells, and nothing corresponding to the crypts of the mammalian small intestine was observable (Fig. 1). TEM revealed the columnar cells, consist of most of the intestinal epithelia, to be long and narrow cell with a diameter of $44.65 \pm 1.81\,\mu m$ at the middle of the villus. The cells have no interdigitation along their sides, but form junctional complexes in places with adjacent cells through desmosomes (Fig. 2). The microvilli which crowd the surface of the cells facing the inside of the lumen are long ($5.25 \pm 0.96\,\mu m$ at the middle of the villus) and branch at the base into two or three strands. There is a well developed terminal web. The surface coat over the epithelium is well developed, and numerous pinocytotic vesicles can be observed at the apices of the epithelial cells (Fig. 3). From the basal portion of the cell, there are three repetitions of lamina lucida-lamina densa followed by the zona reticularis and these lamina form a wavelike multi-layer structure (Fig. 4). Goby and mullet have a similar wavelike laminar structure at the base of the intestinal epithelium. The deep layer of lamina densa is quite thick in these fish, with that of goby being about 195 nm and that of mullet about 150 nm (Fig. 5a,b). The special lamellar structure seen from the middle to basal portion of the mucosal epithelium, said to be peculiar of fish, is poorly developed in flatfish, while it is well developed in goby and mullet.

Salamanders. A saclike stomach opens into a tubular small intestine which in turn opens into the rectum, appearing to have a slightly larger diameter.









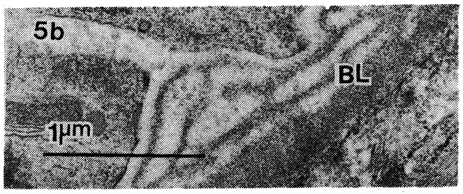


Fig. 1. Light micrograph of a section of the small intestine of the flatfish showing the complex branching of the folds. ×12.5

Fig. 2. Transmission electron micrograph of the intestinal epithelium of the flatfish. The columnar cells are long and thin, and there is no interdigitation along the sides of the cells.

Fig. 3. Apex of a columnar cell from the flatfish small intestine. The microvillus (MV) branches at its base into 3 strands. The terminal web (TW) is well developed.

Fig. 4. The basal lamina (BL) of the flatfish mueosal epithelium, having a wavelike multi-layer structure.

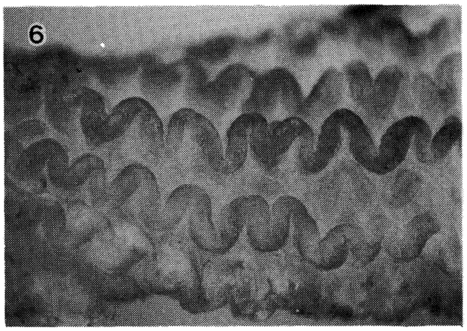
Fig. 5a. The basal lamina (BL) of the goby mucosal epithelium, having a wavelike multi-layer structure.

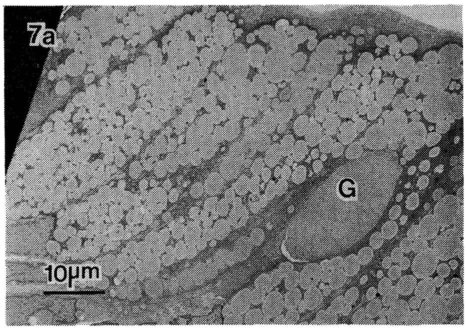
Fig. 5b. The basal lamina (BL) of the mullet mucosal epithelium, having a wavelike multi-layer structure.

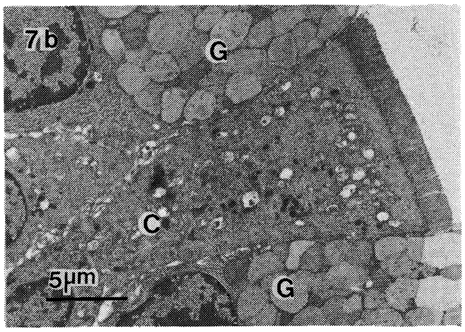
There are seven to eleven folds in the intestinal lumen which meander continuously from the pylorus to the rectal junction along the longitudinal axis (Fig. 6). Giant columnar cells 117.0±17.25 μm in diameter at the middle of the villus were observed by TEM. In salamanders dissected after one day of strict fasting, the cytoplasm of these columnar cells contained many 0.5 to 5 μm particles of lipid. Goblet cells also contained cytoplasmic fat droplets. However, in salamanders dissected after 3 days of fasting, no fat droplets were observed (Fig. 7a,b). The microvilli of the salamander columnar cells are shorter than those of the flatfish, having a length of 1.78±0.37 μm at the middle of the villus, and are not branched. The surface coating of the microvilli is thin. The central actin filaments appear within the microvilli as stakes which pierce the cytoplasm, and the terminal web is rather meager (Fig. 8). Interdigitation with adjacent columnar cells is obvious. The intercellular space at the base of the cells gives the cells a root-like appearance. Within the intercellular space many chylomicrons are observed. There is only one layer of lamina densa, and the gap between the base of the columnar cells and the basal lamina, being about 105 nm, is wider than that of other animals (Fig. 9). Though crypts as they exist in mammals are not recognizable in the salamander small intestine, nests of immature cells with scanty cytoplasm can be seen under the mucosal epithelia (Fig. 10). By extending their cytoplasm, immature cells immediately under the mucosal epithelium appear to push through and form new intestinal epithelial cells (Fig. 11).

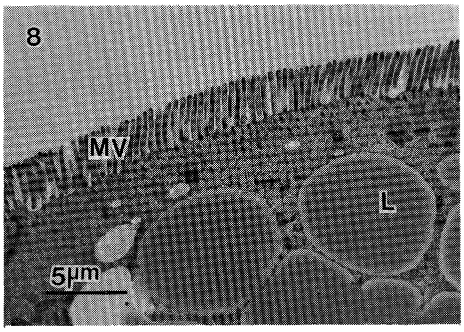
Lizards. The digestive tract of lizards consists of the esophagus, stomach, small intestine which occupies most of the abdominal cavity, a short rectum and finally the cloaca. Thirty-six continuous lumenal folds course from the pylorus to the end of the small intestine in a manner similar to that in salamanders (Fig. 12). The nuclei of the mucosal epithelial cells are not arranged as uniformly as in other animals. The columnar cells have a diameter of 35.65±9.5 μm at the middle of the villus and have 1.83±0.46 μm-long microvilli at their apices. The surface coat is thin as with salamanders. Though not as extensive as in salamanders, interdigitation along the sides of the cells and occasional desmosomes can be seen (Fig. 13,14). There is a single-layer basal lamina which somewhat resembles that of mammals (Fig. 15). Two kinds of goblet cells were observed : ones containing homogeneous mucin (Fig. 16a) and ones containing high density granules (Fig. 16b).

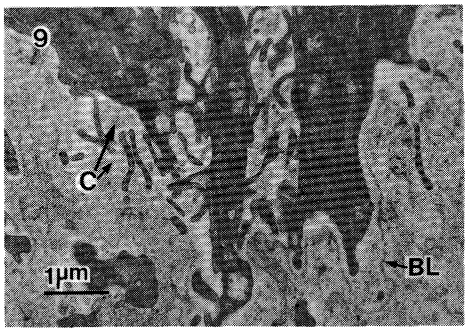
Finches. Following the esophagus, crop, proventriculus and gizzard, the duodenum arises, which then opens into the small intestine. At the distal end of the small intestine, a kind of cecum just out so as to pinch the small intestine where it leads into the rectum. The digestive tract ends in the cloaca. Tongue-like villi zigzag in a regular manner along the duodenum and intestinal lumen (Fig. 17). As observed by TEM, the columnar cells are 34.2±1.6 μm at the middle of the villi and are orderly arranged. Interdigitation along the sides of the cells is well developed (Fig. 18). The microvilli are 1.26±0.44 μm in length and have central actin filaments piercing the cytoplasm. There is a terminal web. A thick surface coat can be seen covering the microvilli (Fig. 19). The base of the columnar cells is similar to that in lizards (Fig. 20). The morphology of the columnar cells and goblet cells a likeness to that of mammals, but Paneth cells and microfold cells of the lymphoid follicle epithelium

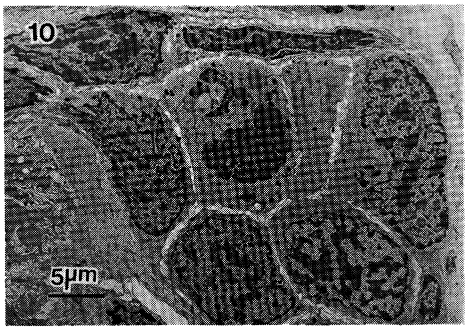


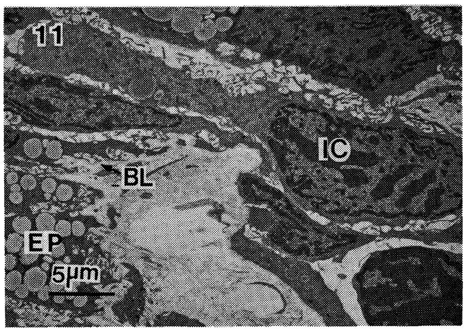












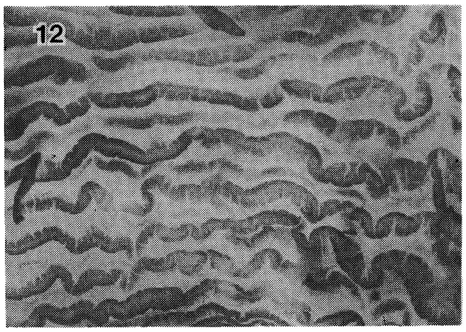
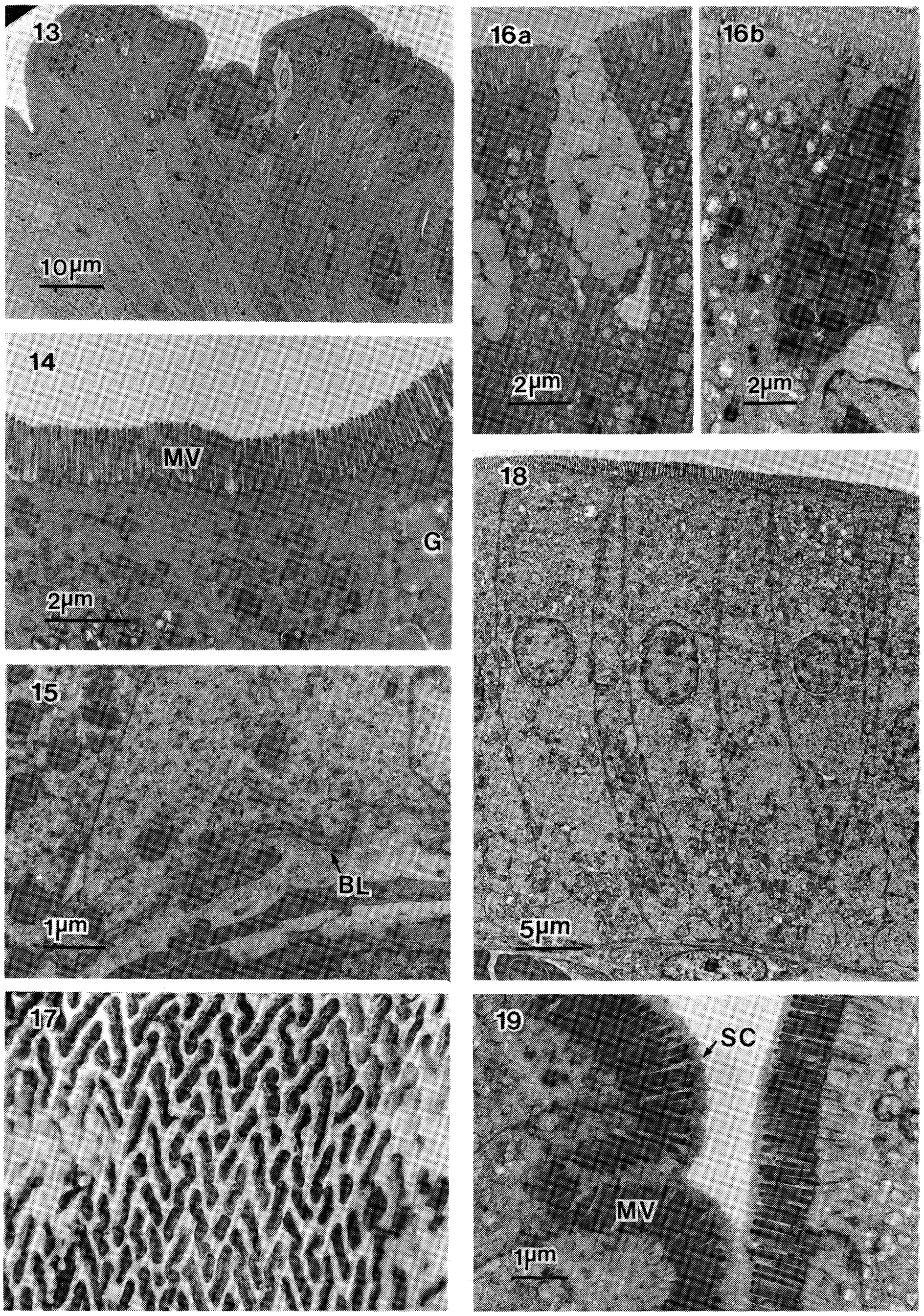


Fig. 6. The intestinal lumen of the salamander as seen under a dissecting microscope. The folds meander continuously from the pylorus to the rectal junction.

Fig. 7a. Transmission electron micrograph of the small intestinal epithelium from a salamander fasted for one day. There are abundant fat droplets in the cytoplasm. G : Goblet cell

Fig. 7b. Transmission electron micrograph of the epithelium from a salamander fasted



for three days. No fat droplets are seen in the cytoplasm. C : Columnar cell, G : Goblet cell

Fig. 8. Apex of a salamander columnar cell. L : Lipid, MV : Microvilli

Fig. 9. Base of a salamander epithelial cell. The open intercellular space gives the base of the cells a root–like appearance. Many chylomicrons (C) are apparent. BL : Basal lamina

Fig.10. Nests of immature cells with scanty cytoplasm seen under the mucosal epithelium of salamanders.
Fig.11. Immature cells of the same cell nest shown in Fig. 10 appear to extend their cytoplasm, push through the epithelium and form new epithelial cells. IC : Immature cell, BL : Basal lamina, EP : Epithelium
Fig.12. The intestinal lumen of the lizard as seen under a dissecting microscope. The folds meander continuously from the pylorus to the rectal junction.
Fig.13. Transmission electron microgsraph of an epithelial cell from the small intestine of a lizard.
Fig.14. Apex of a lizard mucosal epithelial cell. MV : Microvilli, G : Goblet cell
Fig.15. Base of a lizard columnar cell. BL : Basal lamina
Fig.16a. Goblet cells of the lizard containing homogeneous mucin.
Fig.16b. Goblet cells of the lizard containing a mixture of mucin and high density granules.
Fig.17. The intestinal lumen of the finch as seen under a dissecting microscope. The longitudinal axis is from left to right.
Fig.18. Transmission electron micrograph of an epithelial cell from the small intestine of a finch.
Fig.19. Microvilli (MV) of the finch columnar cells. The surface coat (SC) is well developed.

are not observed.

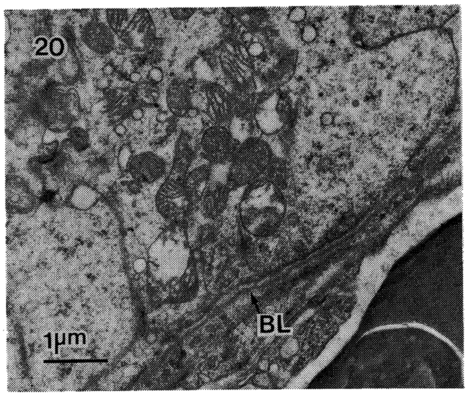
Rats. The concentric circular folds, the plicae circulares, seen in the small intestine of man are not found in the rat. The basic structure of the villi, however, is the same as in man. Tongue-like and sharply bent leaflike villi, which grow perpendicularly from the mucosal surface, densely line the intestine from the duodenum to the ileum (Fig. 21). The columnar cells covering the villi from top to bottom are 18.3±3.3 μm in diameter. However, those cells forming crypts are about 15 μm in diameter and tend to be longer higher up on the villus than in the crypt. At the middle of the villus, the microvilli are 1.00±0.36 μm in length. The central actin filaments can clearly be seen penetrating the cytoplasm (Fig. 22), and the terminal web is well developed. Along the upper sides of the cells, junctional complexes can be seen along with the union of adjacent cells through occasional desmosomes and interdigitation (Fig. 23).

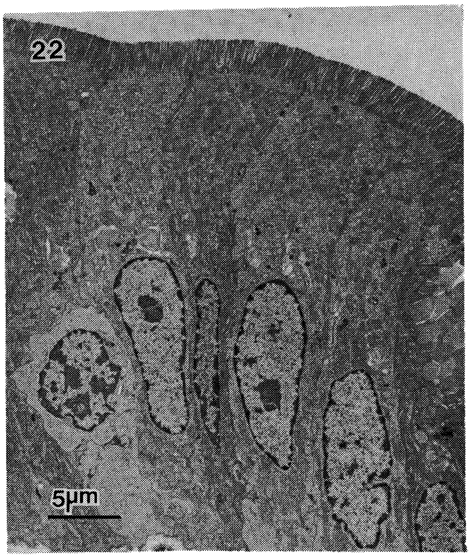
Human cases. Leaflike and tongue-like villi line the intestine from the duodenum to the proximal jejunum, while finger-like villi are prevalent in the ileum. However, upon examining the small intestinal tissue resected from the 3 patients with Crohn's disease, it was found that when the lesion spread over a wide area, the oral side of the ileum dilates and leaflike plicae circulares arise even in the ileum (Fig. 25), covered with villi which take on a leaflike or tongue-like morphology (Fig. 26). It was also confirmed that the regenerative villi on the longitudinal ulcers of Crohn's disease patients have a leaflike or tongue-like morphology.

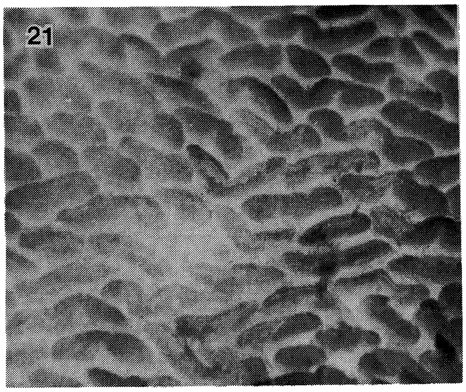
As illustrated in Figures 27 and 28, a tendency can be recognized for the columnar cells and microvilli to become shorter as the evolutionary scale is climbed from fish to mammals, though there is an exception in the case of salamanders.

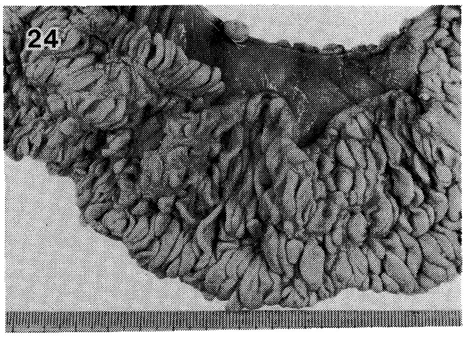
DISCUSSION

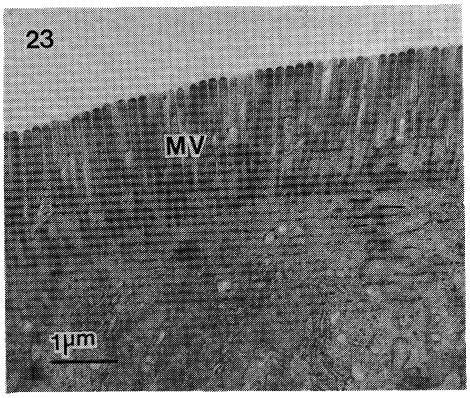
In a comparative examination of the mucosa of the small intestine of animals from fish to mammals, it can be seen that there was a tendency for mucosae made up of folds only to develop into those with fine villi as evolution











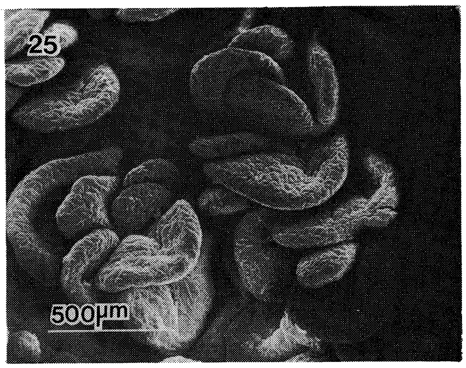


Fig. 20. Basal lamina (BL) of the finch mucosal epithelium.

Fig. 21. The intestinal lumen of the rat as seen under a dissecting microscope. Tongue and 'v'-shaped villi crowd the surface.

Fig. 22. Transmission electron micrograph of the rat mucosal epithelium.

Fig. 23. Apex of a rat columnar cell. MV : Microvilli

Fig. 24. A section of the ileum from a patient with Crohn's disease. Leaflike Kerckring's folds appear at right angles to the longitudinal direction.

Fig. 25. Tongue and leaflike villi on the surface of the folds in folds in Fig. 24.

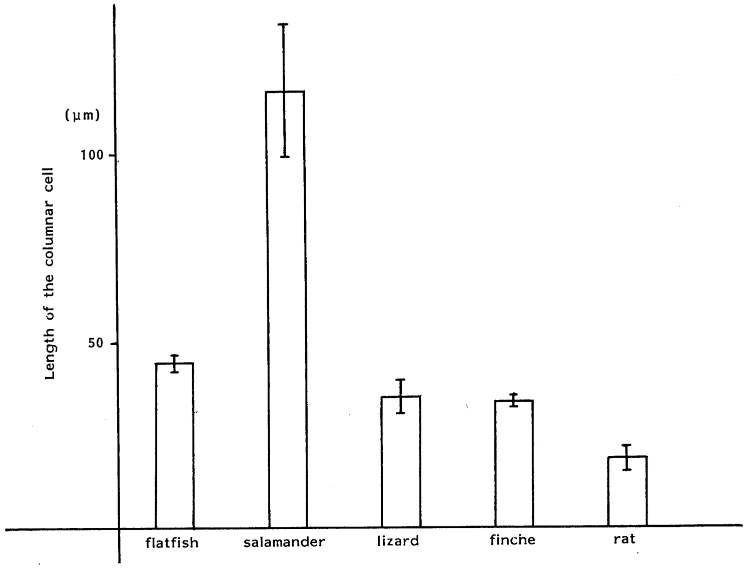


Fig. 27. Length of the columnar cell of the middle of the villus

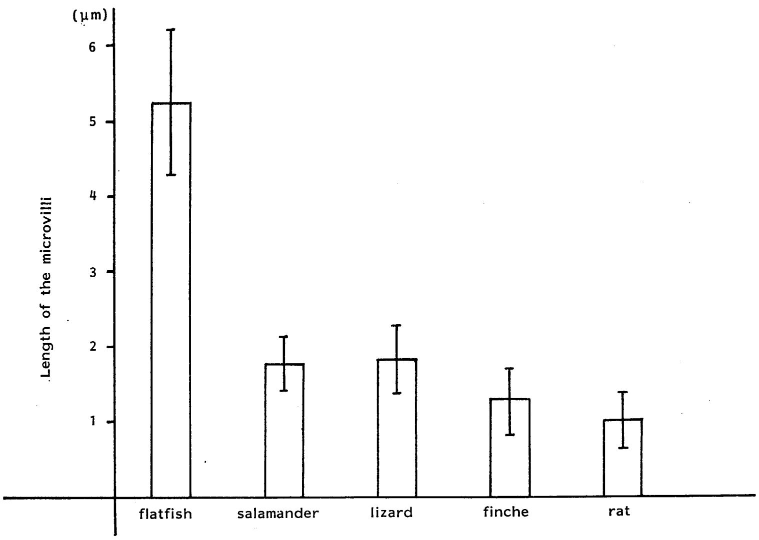


Fig. 28. Length of the microvilli at the middle of the villus

proceeded. Differences in the morphology of the folds and villi are observed among members of the same class ; in fact, Suehiro[7] reported observing longitudinal, zigzag longitudinal, horizontal ; zigzag horizontal and reticulate folds and papillate projections according to the order among fish. Among the amphibia, the author observed meandering folds which were continuous from the pylorus to the rectal junction in salamanders, though in the frog, reticulate folds reportedly take up most of the duodenum, while most of the small intestine is covered with semilunar folds up to its midpoint after which meandering folds are observed.[8] However, the change from folds to villi was definite between the reptiles and birds. The branching of the intestinal folds and the long, thin microvilli found in the flatfish seem suitable for digesting the minute food particles in the ocean, just as the longitudinal folds, which by their winding course allow for the easy expansion of the intestine, of the salamanders and lizards, seem well adapted for taking in large pieces of food without mastication. The well developed interdigitation along the sides of the columnar cells in salamanders and lizards may also be related to the expansion of the intestine. In animals not requiring expansion of the intestine, as in the flatfish, interdigitation is not found.

An increase in the surface area of the intestinal lumen is achieved with the development of villus morphology, first recognized in birds, which evolved beyond reptiles. The zigzag arrangement of villi seen in finches seems likely to be a vestige of the meandering folds of the reptiles. In higher animals the villi are thinner and more densely packed, so that the absorptive surface area is greatly increased.

Upon examining the mucosal epithelia of the small intestine of various animals, it was discovered that the size of the cells differed from animal to animal, so a comparative study of the lengths of the cells at the middle of the folds and villi in the upper small intestine was conducted. Excepting the flatfish through the salamanders, a tendency was recognized for the cells to become shorter as the evolutionary scale was climbed. Though there are numerous reports on the lengths of microvilli,[9–14] none of them are phylogenetic in orientation. In the present study, a tendency for the microvilli to have become shorter with the progress of evolution was noted. Thus viewing the results comprehensively, it seems that the tendency is for animals with mucosal folds to have long microvilli, while those with villi taking on complex morphology have short microvilli. Perhaps this tendency is an evolutionary adaptation.

The microstructural characteristics of the microvillus are the triple layered membrane, the electron dense outer and inner leaflets and the electron lucent central leaflet. The plasma membrane covering the microvillus is from 95 to 115 Å thick, and is thus thicker than the plasma membrane of the lateral and basal portions of the columnar cells (70–80 Å).[15–18] The center of the microvillus is made up of 60 Å-diameter actin filaments[15] which connect with the terminal web seen at the top of the cells. A coating of extremely fine filaments covers the surface of the microvilli.[19,20] The above characteristics are common to all the animals from fish to mammals. However, the microvilli of flatfish are branched at their base into 2 or 3 strands, a structural feature not reported elsewhere and probably peculiar to flatfish. The thickness of the surface coat covering the microvilli varies in thickness according to the kind of animal. In the flatfish, finch, rat and man the surface coat is comparatively well developed, while it is not so well developed in salamanders and lizards. The surface coat of the finch, rat and man is said to be composed of glycocalyx with S-IgA, but the composition of the surface coat of other animals is unknown.

Electron microscopic descriptions of the basal lamina of the mucosal epithelia reported to date divide the basal lamina into 3 layers: the lamina lucida, lamina densa and zona reticularis, in that order from the base of the epithelial cells.[21] In contrast to this structure of only one electron dense layer, that of the flatfish appears to have multiple wavy layers of lamina densa. This unique wavelike laminar structure is in contrast to that of other fish such as the freshwater goldfish and rainbow trout described by Yamamoto[22] and loach described by Suzuki[23] which has only one lamina densa. Globefish and parrot fish, which are saltwater fish, were observed by Ozaki[24] to have only one lamina densa. The fish on which there have been reports are either freshwater only or saltwater only fish, which may explain the differences between them and flatfish. Realizing that flatfish live near the coast, and especially during the spawning season come into shallow coastal areas where they travel through fresh water and seawater, the author additionally examined the basal lamina of goby and mullet which are delta fish. A wavelike laminar structure was observed in these fish as it was in flatfish.

It is known that the basal lamina is formed of collagen and glycoprotein and is synthesized by the epithelium.[25–28] The basal lamina functions as a transport barrier and is also said to play roles in cell differentiation, maturation and support.[21,29] In addition to these functions, the basal lamina characteristic of fish living in delta regions probably protects against the rapid changes in osmotic pressure and acts a highly selective, material transport barrier.

The large changes in lipids occurring in the cytoplasm of salamanders were the same as those observed by Green[30] in fat absorption tests using king salmon. According to Green, when the fat first enters the apical surface of the epithelial cells, it is in small granules less than 1 μm in diameter which cluster in the apical portion of the cell. As these granules move deeper into the cell, they become larger, reaching diameters of 4.5 to 6 μm, and fill the space between the nucleus and the free surface. When the cell becomes full of fat droplets, they begin to be seen in the intercellular space and in the connective tissue near the lamina propria. Finally, all the fat disappears from the cytoplasm. While such large fat droplets are seen in the epithelia of fish and amphibians, in mammals only numerous 50 mμ-diameter chylomicrons are observed. This difference may result from absorptive cells of lower animals having the capacity to store lipids temporarily.

The immature cell nests seen under the mucosal epithelium of salamanders are peculiar to these animals, and areas where cytoplasmic projections of the immature cells push through the mucosal epithelium may correspond to the crypts of mammals. Patten[31] injected H^3-thymidine into salamanders and noted that 4 hours later the nuclei of the cell nest cells were uniformly labeled, while the epithelia showed no labeling. However, 12 hours after the injection, labeled nuclei appeared in the epithelium, and with the passage of time, the number of labeled cells began to decrease starting with the cell nests. Also in the cell nests, immature goblet cells containing mucin were observed, indicating early differentiation.

The goblet cells containing high density granules observed in lizards resemble morphologically the granular goblet cells observed by Cheng[32] in the mouse small intestine. These granular goblet cells are observed within the crypts or at the base of the villi, and goblet cells further up the villi have fewer granules, such that goblet cells at the apex of the villi are normal. Thus the granular goblet cells are considered to be immature. Though they are thought to be so in lizards as well, there is no place corresponding to the mammalian crypts, and the granular goblet cells are not limited to any particular area in lizards. Marshall *et al.*[33] in their study of cell proliferation of the intestinal epithelium of tadpoles (*Xenopus laevis*) reported that in young tadpoles cell division was not limited to one particular area, but as they matured cell division became limited to the valleys of the intestinal folds. Wurth *et al.*[34] also reported that in reptiles, proliferation zones are found in the valleys of the mucosal folds.

The morphology of the mucosa of the human small intestine may vary according to eating habits.[2] Moreover, in a disease such as Crohn's disease in which the lesion spreads over a wide area of the ileum, the folds of the ileum may become like those seen in the duodenum or take on villus-like morphology. Such changes may be thought of as adaptations by the organism to maintain proper absorption or correct impaired absorption.

Acknowledgment

Thanks are due to Professor Tsuyoshi Kihara for his helpful advice, and to Mr. Yoshiki Masuda, Department of Biology and the staff of the Electron Microscopic Center for their careful technical assistance.

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