

## Micro-vasculature of Mucosal Structures in the Human Ileum

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Received: October 22, 2012 Revised: November 15, 2012

Accepted: November 18, 2012

Published online: February 21, 2013

### ABSTRACT

**AIM:** To study the vasculature as well as blood flow in the small intestine in health and disease in the human.

**METHOD:** Patients undergoing ileocolonoscopy in the endoscopy unit aged 3 to 82 are included. The microstructures and their vasculature were examined under white light and a spectral enhancement program (FICE, Flexible Spectral Imaging Color Enhancement).

**RESULTS:** There are two types of villi, the long, slender type and the broad, leaf-like type. The vasculature in the first type is mainly of the reverse fountain or one-up, one-down types, while that of the latter is of the reticular pattern. The Peyer's patch is vascularized by a network of blood vessels which is denser in the young and much less so as age advances. Proliferation of blood vessels is an early feature in inflammation, which resolves as inflammation subsides.

**CONCLUSION:** The new endoscopic equipment provides a new modality of investigative tool in investigating the microstructure of the small intestine.

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**Key words:** Microstructure; Villi; Vasculature; High-resolution endoscopy; FICE; Inflammation of villi; Peyer's patch

Leung YK. Micro-vasculature of Mucosal Structures in the Human Ileum. *Journal of Gastroenterology and Hepatology Research* 2013; 2(2): 403-408 Available from: URL: <http://www.ghmet.org/index./joghr/>

### INTRODUCTION

The microvascular structure of the small intestinal mucosal microstructure has always aroused attention in the scientific community,

and numerous structural architectural patterns have been proposed in animals as well as in man. However, in most of these studies the methodology employed is in the non-living animal tissue and it is not until recently, with the advent of the high-definition endoscopes with optical zoom that we are able to observe these microstructures in the small intestine directly in the living human<sup>[1,2,3,4]</sup>.

The small intestinal villous structure is of physiological significance in the digestion and absorption of nutrients that one ingests. The knowledge on the microvasculature and microcirculation of the intestinal villi are important to the understanding of the digestive and absorptive processes. In the small intestinal mucosa, the Peyer's patches are also of great significance to the intestinal immunological system, the gut-associated lymphoid system (GALT)<sup>[5,6,7]</sup>. These are lymphoid aggregates on the anti-mesenteric aspects of the small intestine that present as domes on the mucosal side which are lined by a layer of modified epithelial cells. Embedded within these cells are the M cells, which are structurally specific cells important in the uptake of antigens from the luminal side to the interior of the body<sup>[8]</sup>.

Study of such microstructures of the small intestine will also have importance in the study of certain diseases of the small intestine. Inflammation of the small intestine has a significant impact on the microvasculature, and recovery of the villi from the inflammation can also be observed from changes in the vasculature in the villi. Previous studies of the microstructures and vasculatures entail the use of dead tissues obtained from animals or the human and various treatment procedures were applied to such tissues, such as injection of dyes and then subjecting them to optical or electron microscopy for analysis. Direct observation of the microstructures of the living human small intestine under direct vision has seldom been reported.

Direct observation of the intestinal villi has been made possible with the advent of a new generation of endoscopes with high-resolution images and optical magnification. The resolution is above 1 megapixel in the video format, and the digital system can also store digital images of resolution 1280×1024. The actual magnification of the images under maximum zoom is 150 times on a regular medical grade 19 inch (48 cm) monitor. Visualization of the microvasculature is not possible under natural white light, but with a software program FICE (Flexible Spectral Imaging Color Enhancement, Fujifilm Corporation, Tokyo, Japan), blood inside the microstructures could be spectrally enhanced hence clearly visualized. Using the system, it is also possible to visualize the direction of the blood flow within the vessels.

Standard videoendoscope systems use the entire spectrum of

visible light (400-700 nm) for tissue illumination. Although the broadband, white-light illumination in conventional videoendoscopes was designed to simulate daylight and enable the endoscopist to examine tissue in its natural color, detailed assessment of particular features, such as mucosal microvasculature, is only feasible when these features are visualized at specific illumination wave-length(s) or wavelength ranges (bands).

FICE is a digital image processing technique that enhances the appearance of mucosal surface structures by using selected wavelengths of light in reconstituted virtual images. It can also be coupled with electronic or optical (zoom) magnification for enhanced visualization of mucosal details. FICE technology is software driven and uses an image-processing algorithm that is based on spectral estimation methods. In this technique, a standard image captured by a color CCD videoendoscope is sent to a spectral estimation matrix processing circuit contained in the video processor. Here, reflectance spectra of corresponding pixels that make up the conventional image are mathematically estimated. From these spectra, it is feasible to reconstruct a virtual image of a single wavelength<sup>[9]</sup>.

Three such single-wavelength images can be selected and assigned to the red, green, and blue monitor inputs, respectively, to display a composite color-enhanced FICE image in real time. Ten factory-determined, wavelength-enhanced presets are available in current FICE configured processors for a differentiated color display of the mucosa.

Light of different wavelengths has different degrees of penetration into the tissue, with the longer wavelength of the red end of the spectra being able to penetrate deeper into the tissue and the shorter wavelength of the blue end of the spectra being reflected at a shallower depth. Moreover, the spectral enhancement made use of the absorptive characteristics of hemoglobin, which absorbs light principally at 415 nm and also at 540 nm.

The early reports of the vascular anatomy of the intestinal villus, in man and animals, are classified into three forms<sup>[2,3]</sup>. Several authors described a "step-ladder" circulatory arrangement for man and rabbits. In this system, an arteriole was said to ascend on one side of the villus and a venule descend on the other, and with interconnecting capillaries, suggested the ladder shape. A "fountain" pattern with an arteriole passing up the centre of the villus to the tip where it arborized into a subepithelial capillary network has been described. These vessels converged near the base of the villus to form efferent venules.

## MATERIALS AND METHODS

This study is part of a clinical endoscopy service in a private hospital (Precious Blood Hospital) in Hong Kong that serves patients varying in age from newborn to adulthood. For the purpose of the study, 50 patients are enrolled, the youngest patient is 3 years old and the oldest is 82 years old. The indications for the endoscopy are as follows: (1) routine examination to exclude polyps or malignancy; (2) abdominal pain; (3) per rectal bleeding.

Patients with disorders suggestive of physiological dysfunction of the small intestine, such as diarrhea, were not included in this observational study.

### The ileo-colonoscopy procedure

The patients were prepared as for routine colonoscopies with PEG (polyethylene glycol) solution, and the procedures were performed under general anesthesia for patients below the age of 12 and conscious sedation for patients above the age of 13. The routine colonoscopic examinations were carried out with the author as the colonoscopist, and the ileo-cecal valve was cannulated and the terminal part of the ileum was then entered. Usually the last 10 cm

of the ileum was examined. The procedures were no different from normal routine examinations and the study was approved by the IRB (institutional review board) of the hospital and consent was also obtained from the patients or the parents in case the subject is a minor. A total of 50 patients were enrolled into the study in which detailed examination of the small intestine was conducted.

A high-resolution endoscopic system was used in the study (Fujinon 4400 processor and EC-590ZW5/L colonoscope with optical zoom, Fujifilm Corporation, Tokyo, Japan). The system was enhanced with a multiband imaging software (FICE) which is used to enhance the microvasculature of the mucosa making use of the differences in penetration of tissues of different wavelengths of light as well as the absorption characteristic of hemoglobin contained in blood. Details of spectral enhancement and FICE have been explained in the introductory part of this paper.

We attempted all ten programs of FICE in our study and found that the best result for visualization of the ileal microvasculature is obtained with preset program No. 4 which inputs images at 540 nm, 490 nm and 420 nm to the Red, Green and Blue channels of the processor, respectively.

### Examination of the ileal structures

The ileal mucosal surface was examined under white light provided by the xenon light source for pathological changes. Both the normal and abnormal (if any) parts of the mucosa were examined with increasing power of magnification until the maximum magnification of 150 times was achieved. Under normal examination, the villi appeared to be lumped together and the details could not be seen properly. Light reflection from the surface of the mucosa may also interfere with the examination. These deficiencies could be avoided by the addition of a layer of water covering the surface of the mucosa, thereby eliminating an air-mucosa interface, hence surface reflection. Moreover, the constant injection of a stream of water through the water injection orifice of the endoscope could float up the villi so as to enable the endoscopist a better examination of the details of the microstructure, and the higher refractive index of water as a transmission medium enhances the resolution by 1.3 times.

### Recording of results

The processor of the endoscopy unit has a digital recording system for JPEG images of resolution 1280×960 via a Compact Flash (CF) card. Video recording is also carried out using a DVD video recording system. The images are then examined after the procedure for details of the microstructure and microvasculature of the ileal mucosa.

## RESULTS

### The normal intestinal villi (Figures 1a and 1b)

The appearance of the intestinal villi varies from subject to subject and also within the small intestine of the same subject. In general, two types of villi were observed, one type, the majority, is long and slender with a length more than 1 mm in length, while the other type, the minority, is more roundish or globular in shape. This may be the type previously described as leaf-like; but in our observation, we have never been able to observe them side-ways so they are not thin and broad to be likened to leaves. These round villi are mostly found in areas surrounding the domes of the Peyer's patches.

The width of the long, slender type of villi averages 0.15 mm. In some healthy individuals, the villi tend to be shorter, from 0.5-0.8 mm in length. The villi are usually seen as turgid structures. Very occasionally, slight superficial wrinkles could be seen on the villous surface when it is bent. The villus could be seen as having a lighter



**Figure 1a** Endoscopic image of small intestinal villi under white light and optical magnification. Most of the villi seen are of the long, slender type. The layer of enterocyte is seen outlining the outer surface, but the blood vessels are not visualized.



**Figure 1b** A Peyer's patch in an adult under FICE enhancement.

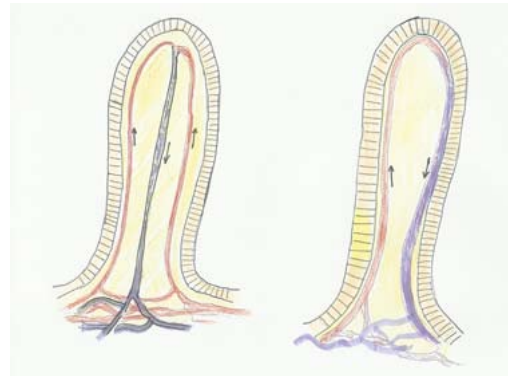
outer layer, represented by the layer of enterocytes, of a thickness of around 0.04 mm or one-quarter of the thickness of the villus, and a central core, represented by the syncytium or lamina propria. On the outer surface of the enterocytes is a thin, glistening layer that probably represents the glycocalyx of the microvilli of the enterocytes.

The round or oval villi are mostly seen around Peyer's patches. Like the long, slender ones, they also have an outer layer of enterocytes and a central stroma. The blood vessels vascularizing such villi are rather different from those of the slender villi, as described below. Globular villi are also seen in areas that are inflamed. These pathological villi represent a regenerative process, and the internal vasculature also appeared to be different from regular villi, slender or round. These are the 'large' villi previously described as having intimate connection with the vascular supply of the Peyer's patches<sup>[5,6,7]</sup>.

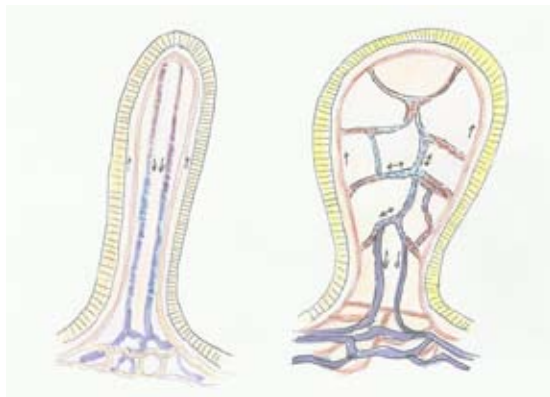
**Blood vessels of intestinal villi, (Figures 2a and 2b)**

Utilizing our system of endoscopy with spectral enhancement to scrutinize the vasculature of the villi, a complicated system that does not fall into a single pattern is observed. In most of the long and slender villi, a vascular loop that runs just beneath the layer of enterocyte is seen. In some, however, one or more additional vessels that run longitudinal to the long axis could be visualized. The direction of the blood flow seems to be going up in one of these blood vessels and down in the other, forming a complete circuit. In some villi, these two vessels are the only ones we can observe, while in others communications are seen between these two main trunks (Figures 3a, 3b and 3c).

A central, thicker blood vessel that drains the sub-enterocytic



**Figure 2a** The two commonest vascular pattern in the long, finger-like villi. Arrows indicate direction.



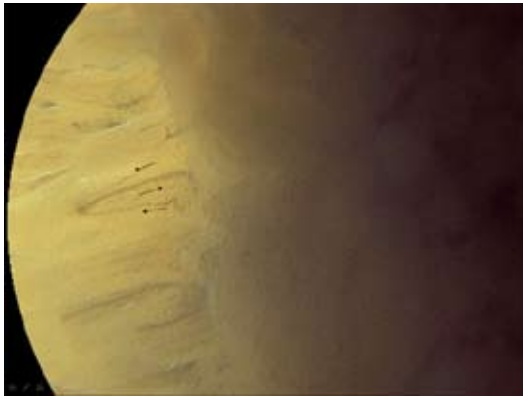
**Figure 2b** The two up and two down pattern is less common. The reticular pattern is seen in the broad, leaf-like villi. The direction of flow could be to-and-fro in those inside the villus.

layer vessels can also be seen in many villi. A tuft of small vessels is sometimes seen at the tip of the villus; with the tip draining into the central vessel the direction of flow of which is towards the serosa, therefore it probably is a venule. In other studies, a 'fountain' pattern of blood flow has been described with the central vessel being an arteriole supplying the blood to the villi which drains into the veins that run below the layer of enterocytes. This, however, is not consistent with our observation (Figure 3a).

Patterns more complicated than those described above has also been observed. A reticular pattern is seen, with the blood vessels inside the villous lamina propria having branches that interconnect with each other. The direction of blood flow in each one of these branches cannot be well established. Nevertheless, blood flow has been visualized in such branch vessels. The blood flow is episodic, suggesting the presence of sphincters inside the vascular network which control the quantity of blood flow in the villi.

In some apparently normal looking villi, a curvilinear blood vessel may be seen under the outer layer of enterocytes. This is suggestive of a corkscrew-shaped blood vessel in place of the usual straight sub-epithelial vessel. Though such a pattern is observed in inflammation and, especially in the recovery phase of inflammation of the villus, in such normally appearing villi there is no indication that it is in an inflammatory process. It is possible that such a corkscrew vessel is the result of the action of certain growth factor that stimulates blood vessel genesis, in a process of rapid development<sup>[10]</sup>.

In the ovoid, bigger villi that are mainly in the periphery of the domes of the Peyer's patches, a different pattern of blood vasculature has been observed. It may be due to the bigger internal capacity of such villi, the ordinary sub-epithelial vessels are insufficient for the physiological supply of blood hence there is usually a reticular pattern



**Figure 3a** The reverse-fountain pattern of blood flow is the most commonly seen. Arrows indicate direction of flow.



**Figure 3b** Villi with vasculature of different patterns.

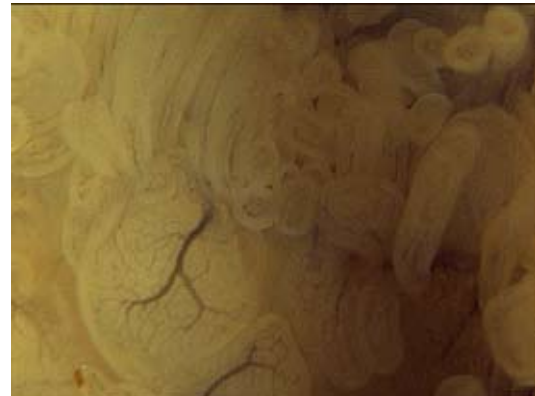


**Figure 3c** In this spectral-enhancement picture we can see that the vessels inside the villi are curved, probably spirally arranged. This indicates proliferation of blood vessels in the healing stage. The central vessel is nicely demonstrated in two of the villi.

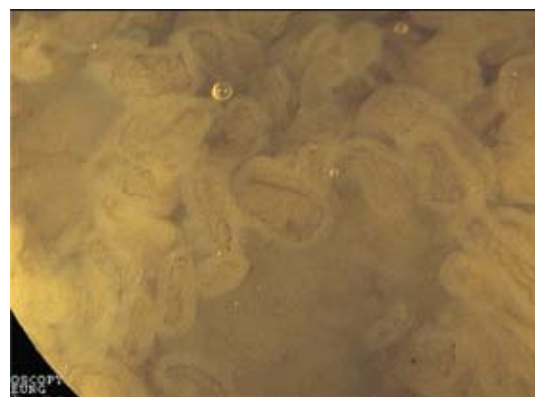
with three or four blood vessels running along the longitudinal axis of the villus. The direction of flow of the vessels in the reticular system is complex and cannot be ascertained via our endoscopic observation. In some other broad villi adjacent to Peyer's patches, a main trunk with numerous branches in the form of veins of a leaf is observed. These villi near the Peyer's patches have a vascular pattern suggestive of those of the patches themselves. It is possible that the big, central vessel is a high-endothelial venule (HEV) that may have some immunological function similar to those of the Peyer's patch<sup>[11,12]</sup>.

#### The Peyer's patches

Peyer's patches are clusters of lymphoid nodules in the wall of the intestine<sup>[8,9]</sup>. They play an important role in immune reactions of the gut. Both B and T lymphocytes have been shown to recirculate



**Figure 4a** The Peyer's patch in a 3-year-old child. The vascular pattern on the dome is reticular and well-developed. The density of blood vasculature decreases as age advances.



**Figure 4b** The vasculature on the dome of the Peyer's patch of an adult are less prominent compare with that of a child. The villi surrounding a Peyer's patch tend to be of the broad, leaf-like variety, and blood vessels are of the reticular pattern.

through them, and the IgA-secreting cells of the intestinal mucosa have their origin in this tissue. Peyer's patches lack afferent lymphatics; gut antigens may reach the lymphoid tissue via the specialized M cells<sup>[13,14]</sup>.

Observing the Peyer's patches from the mucosal side of the ileum, one can only see the dome-shaped structures that represent the superficial portion of a much deeper structure. They are more abundant in young subjects and scarcely seen in those above the age of 60. They may appear single or group in clusters of three or more domes each one measuring 0.5-1 mm in diameter. The superficial covering is smooth and devoid of the glistening reflective surface that is commonly seen in the intestinal villi. It is lined by one layer of cells about the same thickness as the enterocytes, the follicle associated epithelium (FAE) (Figure 4a).

In young individuals, it is usually possible to see aggregates of lymphoid follicles into nodules in the small intestine, especially the terminal ileum, and these lymphoid nodules project into the intestinal lumen as small elevations. The surface of such elevations are covered with regular villi, and they should not be confused with Peyer's patches which are embedded in the mucosa.

#### Blood vasculature of the Peyer's patches (Figures 4a and 4b)

A system of blood vessels that includes the high endothelial venules (HEV) which is specific to the Peyer's patch has been described in various animals, including the human. High endothelial venules (HEV) are specialized post-capillary venous swellings characterized by simple cuboidal cells as opposed to simple squamous cells found in regular venules. This allows for re-entry of lymphocytes into the

bloodstream through HEV.

In the young subject the Peyer's patches are more prominent and the blood vessels are much better observed endoscopically. In a three-year-old child, the blood vessels on the surface of the dome of one of the patches could be seen in the pattern of the veins on the surface of a leaf. This vasculature probably runs below the layer of FAE but not at the serosal side of the dome because it could be seen following the curvature of the surface of the hemispherical dome structure. The blood vessels observed is probably a HEV system, though the exact histological composition of it needs confirmation via microscopy.

In subjects in the 3<sup>rd</sup> and 4<sup>th</sup> decades of life, Peyer's patches are still found though the venous pattern on the surface of the dome we saw in the three-year-old child could no longer be seen, and the single HEV pattern remained. In others, single blood vessels without branches could be demonstrated, suggesting that the branches are so thin that are beyond the limit of detection of our system.

#### Blood vessels in inflammation and recovery (Figures 5a-5d)

Inflammation of villi, traditionally demonstrated histologically by the presence of inflammatory cellular infiltrates in the lamina propria of the villi, is specifically visualized under the current endoscopic system. Acute inflammation, as seen in villi surrounding an aphthoid ulcer in the small intestine, presents as a rosette of flattened villi sticking together and surrounding the mucus-covering ulcer (Figure 5a, b). In the severely inflamed villi, extravasation of blood into the stroma (lamina propria) starting from the tip is seen (Figure 5c). The tiny droplet of blood does not affect the layer of enterocytes, however, and the clarity of this layer is preserved even in those severely inflamed. In those which are moderately inflamed, in addition to a mild degree of blood extravasation, abnormality in the morphology of the vasculature could be seen. The blood vessels of the villi become tortuous and more numerous in number, and in many cases they become thicker in caliber, probably in response to the greater blood flow requirement in the inflamed area.

In the recovering villi (Figure 5d), inflammation with extravasation of blood is no longer observed, but the tortuosity of the blood vessels, especially in those just below the layer of enterocytes, is more marked. Many of them adopt a corkscrew appearance. These may be the result of stimulation of angiogenesis mediators which may cause the growth and proliferation of the blood vessels.

## DISCUSSION

In this study, a system for the observation of the microstructures of the small intestinal mucosa *in vivo* in the human is described. *In vivo* observation of the human tissue has numerous constraints, especially those related to medical ethics and subject safety. In the current study,



Figure 5a Villi surrounding a fissuring ulcer under white light.



Figure 5b Villi surrounding an ileal ulcer. There is extravasation of blood elements in villi surrounding the ulcer (arrow). Blood vessel proliferation is one of the features of inflammation.



Figure 5c Extravasation of blood at the tip of an inflamed villus.



Figure 5d In the recovery phase, the villous vasculature tends to be wavy, circular and redundant.

we have been able to observe the ileal villi and the domes of the Peyer's patches of the living human being, mostly under conscious conditions, as part of a clinical examination without harming the patient.

*In vivo* examination of the small intestinal microstructure has been described in the animal<sup>[3]</sup>. In that study, mice under anesthesia had their abdominal wall opened and the small intestine exteriorized and kept warm in a water bath, and the intestinal microstructure examined with a microscope with the wall either intact or cut open. The microcirculation of such an animal model might be affected by the manipulation done on the intestine; hence the observation may be different from the natural *in vivo* condition. In the current study, the use of human subject without any surgical procedures being performed is an observation model previously not described

Such a study is made possible with the advent of high-resolution

endoscopes with optical magnification which is afforded by the precise, motorized movement of a system of lenses at the tip of the endoscope upon the touch of a button at the handle of the endoscope. Examination of the blood vessels is made possible only with the development of a new spectral enhancement system. Currently being marketed are two systems making use of a similar principle. The system marketed by the Olympus Corporation makes use of a hardware system in which narrow band filters are rotated rapidly in front of the light source resulting in the formation of a composite image. In another system, that marketed by Fijifilm Fujinon, is a software system that allows the formation of composite images of different wavelengths for the examination of different tissues. In the current study, a set of specific wavelengths is chosen for the best delineation of the blood vessels in the microvasculature in the mucosal tissues.

Further development in this field in the form of confocal laser endomicroscopy has enabled the direct observation of intestinal structures magnified up to 1000 times. Visualization of the blood cells moving inside the blood vessels is made possible and this new technique could be used in the more detailed study of the vasculature and blood flow inside the villous structures<sup>[15]</sup>.

The current study provides a system of examination of the microvasculature of the mucosal tissues, and opens a new modality of research methodology in microcirculation research. The potential application of such a system is diverse. It could be used in the study of the physiological function of the gut, in the area of human nutrition, and in the transport of fluid and electrolytes into and out of the villi. Further development of such a system may include the use of polarized light for the observation of the glistening layer of the brush-border of the enterocytes to examine its changes in absorption of various nutrients. The use of phase-contrast technique incorporated into such a system may be used for the delineation of the cellular structures of the cells of the villus, thereby providing a system of *in vivo* endoscopic histological examination.

The observation of the blood vessels could be of potential interest to the gut immunologist who may be interested in the scrutiny of the function of the Peyer's patches and the transfer of macromolecules across the intestinal barrier. The change in pattern of blood vessels on the surface of the domes of the Peyer's patches is age related, and this may be of importance in the development of gut-associated immunology in the human.

Inflammation of the villi as described in the current study has interesting observations on the villous blood vessels which were not described in conventional histopathology. Inflammatory bowel disease, of which the aphthoid ulceration shown in this study could be an early lesion, might be staged according to the vascular appearance in the inflamed villi to acute, in which there is blood extravasation into the tip of the villi, chronic, in which blood vessel tortuosity is an accompaniment, and regenerative, in which corkscrew appearance of the villous blood vessels are seen.

In conclusion, our study made use of a novel endoscopic technique that could be used to examine the microvasculature of microstructures of the small intestine in the living human. Studies in human always have understandable constraints, and intubation of the ileo-cecal valve to enter the small intestine could be technically difficult to the inexperienced, especially in small children. But the technique could also be adapted to animal systems in which

experiments could be better controlled and stringent medical ethics need not be applied. The ability for researchers to visualize the microstructures of the traditional blind area of the body, the small intestine, without surgically opening up the abdomen of the animal thereby better mimicking the natural situation is probably a welcomed addition to microcirculation research.

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