A comparative radiographic and pathological study of intestinal vaso-architecture in Crohn’s disease and in ulcerative colitis

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SUMMARY  Vascular changes were seen in specimens with lesions of Crohn’s disease as well as in ulcerative colitis.

In Crohn’s disease, the vasculature in the bowel wall was rearranged secondary to thickening of the intestinal coats. An anatomical relationship was often found between the ulcers and the point where arteries break through the muscularis propria. The vasculature was markedly increased in areas with deep ulcers and transmural inflammation, but in areas with only small ulcers and mild inflammatory reaction vascular changes were barely discernible or absent. Occlusive vascular changes were uncommon and not visible in the radiographs.

In active ulcerative colitis hypervascularity was more marked than in Crohn’s disease, but was confined to the mucosa and adjacent parts of the submucosa. In ‘burnt-out’ atrophy vascularity was not increased and only minor changes in the submucosal arteries were observed.

The observations did not suggest that the vascular alterations are of primary importance for the formation of lesions in either disease.

Vascular changes in Crohn’s disease, as compared with those in ulcerative colitis, have long been the subject of varying descriptions and conflicting interpretations (Warren and Sommers, 1954; van Patter, Bargen, Dockerty, Feldman, Mayo, and Waugh, 1954; Reifferscheid and Wolfram, 1962; Meadows and Batsakis, 1963; Bacaner, 1966; Knutson, Lunderquist, and Lunderquist, 1968; and others).

Vascularity in nonspecific chronic inflammatory disorders of the intestine may be discussed in terms of abdominal angiography in vivo. This method allows only macroscopic evaluation of vascular anatomy but no direct correlation with histopathological changes. On the other hand, studies of histological sections do not allow the tracing of vessels or an evaluation of the overall vascularity.

In order to bridge this gap a technique was sought which would allow assessment of general vascular patterns, tracing of individual or groups of vessels, and direct correlation of vascular and histological changes. This could be achieved by combining a modification of an infrequently used radiographic technique (MacAlister, Margulis, Heinbecker, and Spjut, 1962) and specially prepared large histological sections. Our interest was primarily focused on changes in Crohn’s disease, but for comparative purposes the study was extended to include normal specimens and specimens from patients with ulcerative colitis.

Technique

RADIOGRAPHY

Within one hour of removal, 10 ml of 10% solution of procaine sulphate was injected into the operative specimen of the bowel through an arterial catheter to counteract possible vasospasm. Immediately thereafter a solidifying barium sulphate suspension (Schlesinger, 1957) was injected manually. The injection was stopped as soon as firm resistance was met. After 20 minutes,
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by which time the contrast suspension began to coagulate, the intact specimen was radiographed. The gut was then slit up along the mesenteric attachment, spread out flat, and re-radiographed.

A peak voltage of 50 kV, and fine grain industrial x-ray film (Gevaert Structurix D4) were used (Fig. 1a).

After fixation of the specimen in 10% formalin

Fig. 1a

Fig. 1b

Fig. 1c

Fig. 1 Normal small bowel. a Slit-up specimen of terminal ileum showing winding mural arteries in most aboral segment. b Radiograph of transverse section, 8 mm thick. c Large histological section, 5 μ thick. Haematoxylin and eosin, × 2.
for about five days, eight to 12 transverse sections of the entire specimen were cut. The sections were placed on a non-radiographic single emulsion film (Gevapan 100) and radiographed in the axial (Figs. 1b and 2b) and frontal projections. Their exact location in the specimen could be determined with the aid of the previous survey radiographs. For radiography of transverse sections, a low-voltage x-ray source (8-15 kV) with a beryllium window was used.

HISTOLOGY
After radiography, the transverse sections, which were 0.7-0.8 cm thick and up to 10 cm long, were prepared and embedded in large blocks of paraplast or paraffin using the method described by Ent and Roberts (1968). Large histological sections, 5 μ in thickness, were then cut, and stained with haematoxylin-eosin. In addition, smaller sections were stained with elastic tissue stain.

Comments
The combined radiographic and histological technique using large sections, which has not been previously used for the study of intestinal vasculature, enabled us to locate the intramural vasculature in relation to other structures of the

Fig. 2a

Fig. 2b

Fig. 2c

Fig. 2 Normal colon. a Slit-up specimen: irregularly spaced wide and narrow arteriae rectae. b Radiograph of transverse section. c Large histological section. Haematoxylin and eosin, × 2.
bowel wall by comparative studies of the radiographs and the corresponding histological sections, even when only short arterial segments were visible in the sections.

Material

The above technique was consistently carried out on 13 operative specimens of which nine showed lesions of Crohn's disease and four of ulcerative colitis. All except one of the patients, from whom the specimens had been taken, had undergone both multiple small- and large-bowel radiological examinations and mesenteric angiography before operation. The histological diagnosis, employing conventional criteria (Crohn and Yarnis, 1958; Lockhart-Mummery and Morson, 1964; Morson, 1968), was not in doubt in any of these cases. Epitheloid cell granulomas were present in all specimens with Crohn's disease, and all those with ulcerative colitis had both rectal and colonic changes characteristic of ulcerative colitis.

The control material consisted of nine necropsy specimens from young subjects with no evidence of gastrointestinal disease. The barium sulphate was injected and the specimens were fixed within five to six hours after death to minimize the effect of autolysis.

Results

Normal specimens

The vascular pattern of the intestine was well visualized and conformed with previously published anatomical descriptions of the intestinal vessels (for review, see Michels, 1955).

The arteriae rectae of the ileum, originating from the third to fifth generation of arcades, were evenly spaced, smooth, and of fairly uniform calibre (0.4-0.8 mm). Along the terminal 5 to 10
centimetres of the ileum they were often replaced by an irregular network of fine arteries, anastomosing with the colonic arteries (Fig. 1a).

The colonic arteriae rectae differed considerably in calibre from each other (0.2-1.2 mm) and originated from the marginal artery at irregular intervals (Fig. 2a).

The mural branches of the arteriae rectae were best traced in the radiographs of the transverse sections (Figs. 1b and c, and 2b and c). In the colon they usually penetrated the muscularis at the margins of the taeniae musculares. The submucosal branches of the arteriae rectae followed an undulating course in the plane of the bowel wall, parallel to and approximately 2 to 3 mm beneath the mucosal surface. They finally branched into fine arteries, supplying the mucosa, the submucosa, the muscularis, and the subserosa.

The contrast medium could usually be seen in the villous arteries of the small bowel and in other minute branches down to a size of 20 µ.

**Crohn's Disease**

Vascular changes were present in most, but not in all, transverse sections with histologically

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**Fig. 3b** Tortuous mural vessels in area at arrow in a c and d show the site of increased vascularity to the thickened submucosa.
demonstrable lesions of Crohn's disease. The changes seemed to conform to a pattern that could be recognized in most of the approximately 100 sections studied, and varied with the severity of the inflammatory reaction.

Severe Crohn's disease

Increased vascularity was the rule in areas with deep ulcers and fissures, inflammatory cell infiltration, and extensive oedema. The mesenteric arteries were not noticeably widened, but the number of arteriae rectae supplying the involved area appeared increased which at least in part was due to shortening of the bowel. In small-bowel lesions about 1·2-2·0 such arteries originated per centimetre which was more than twice the frequency found in normal specimens (Figs 3a and b). The arteriae rectae were moderately widened and in the transverse section radiographs numerous mural arteries were seen to follow a tortuous course (Fig. 4).

In addition, both extra- and intramural arteries were displaced, secondary to the fibrosis and oedema. The arterial arcades were often distorted and stretched along the margin of the bowel due to shrinkage of the mesentery. The distance between the mucosal surface and the submucosal arteries was increased to 4-10 mm, owing to the submucosal oedema (Figs 3 and 4).

In colonic segments with clearly 'transmural' inflammation some transverse sections showed an increase of vasculature in all layers of the gut (Fig. 5), but more frequently the thickened colonic wall showed two layers of arteries, one dense and irregular in the submucosa and another, less dense, in the inflamed subserosa (Fig. 6). The two layers were separated by the thickened muscularis propria.

In the ileum as well as in the colon an anatomical relationship was frequently observed between ulcers and vascularity. From their point of entrance through the muscularis, the arteriae rectae sent multiple branches through the submucosa towards the mucosa. These piercing arteries branched into numerous small arteries around the floor, or in close vicinity, of the ulcers and also in the structures known as 'cobble stones' (Figs. 6 and 7). The connexion between ulcers and vascular anatomy could not always be demonstrated, but the relationship was often striking. In the colon, most deep ulcers and fissures were found adjacent to the margins of the taeniae, where the arteries entered through the muscularis propria.

Except for these conspicuous alterations (hypervascularity, double layers of arteries, and a fairly close relationship between ulcers and vessels) noted in advanced disease, few vascular changes were visible. Inflammation was often seen to follow vascular, and lymphatic, pathways and many granulomas were located in the vascular sheaths.

Sections stained with both haematoxylin and eosin and elastic tissue were used for the study of vascular changes. Thickening of arterial walls, caused by intimal and medial hyperplasia, and narrowing of the lumina were only observed in a few specimens. These changes occurred in areas of marked inflammation and fibrosis, and did not involve major mural arteries. The oblitative
Fig. 5  Crohn's disease of the colon.  

a  Slit-up specimen: wide arteriae rectae with spiralling end branches.  
b  Radiograph of transverse section showing increased vascularity in all coats.  
c  Histology: fibrosis, oedema, and fissure.  
Haematoxylin and eosin, × 2.
changes were similar to those seen in other chronic inflammatory lesions, e.g., in areas adjacent to peptic ulcers of the stomach.

No histological changes compatible with thrombosis or infarction were observed.

*Moderate or mild Crohn’s disease*

In areas with only few ulcers and moderate oedema, vascular changes were less marked and occurred then in the form of moderate displacement of the mural vessels in relation to the mucosal surface, secondary to the oedema of the bowel wall. The degree of vascularity was closely related to the intensity of the inflammatory reaction. In some areas with only mild inflammation the survey angiograms appeared normal, although slightly tortuous mural arteries could be recognized in the radiographs of the transverse
Fig. 8 Mild Crohn's disease, small bowel. 

a. Normal vascularity in thin-walled specimen. 

b. Large histological section. Minute lesions at arrow (×2). 

c. Area at arrow, magnified ×20: small ulcers surrounded by local inflammation. Haemotoxylin and eosin.
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sections. In small or large bowel segments with only superficial ulcers, and slight cellular infiltration in their immediate vicinity, the vascular pattern in the survey radiographs as well as in the radiographs of the transverse sections appeared normal (Fig. 8).

Comments
Opinions differ regarding the appearance and the significance of vascular changes in Crohn's disease. Several authors contend that ischaemia plays a role in the formation of lesions in this disorder. Warren and Sommers (1954) stated that oedema of the submucosa causes narrowing and occlusion of the arterial lumina, and that such interference with the blood supply is one of the causes of ulcer formation, and Reifferscheid and Wolfram (1962) claimed that not only the ulcers, but also the lymphangitis and lymphoedema were secondary to vascular impairment. Meadows and Batsakis (1963), in a histological study, considered that hyperaemia occurred in early stages.
of the lesions, but that the appearance of severe and expansive ulcers coincided with angiofibroblastic proliferation. Radioisotope studies of mesenteric blood flow (Bacaner, 1966) indicated that mesenteric circulation in Crohn's disease was decreased compared with that in controls and in ulcerative colitis. The concept of ischaemic changes in Crohn's disease was also supported by one of us in an earlier publication, based on abdominal angiography (Brahme, 1966).

Opinions differ also regarding obstructing changes of the arterial walls. Williams (1964) as well as McGovern and Goulston (1968) observed obstructive vasculitis only occasionally. According to Knutson et al (1968), intimal and medial hyperplastic with narrowing of arterial lumina is a common and significant finding in Crohn's disease.

Several of the above observations are not compatible with the common notion of hyperaemia of the serosa seen at operation, and the frequent finding of intense reddening of the mucosa in the slit-up specimens, although, admittedly, a similar appearance may also be noted in cases of haemorrhagic intestinal infarction after occlusion of major mesenteric arteries.

The findings in the present series, in which the specimens were prepared specially for examination of arterial vasculature, did not support the concept that ischaemia is the cause of ulcer formation in Crohn's disease. Instead, moderate or marked hyperaemia was common in affected areas and was then associated with signs of active inflammation.

In addition to an increased number of visible mural arteries, tortuosity of these arteries was common. The appearance of the intestinal mural
arteries in Crohn's disease was similar to that seen in, eg, arteriovenous fistulae or in collateral arteries bridging an occlusion, which suggests an increased haemodynamic load on previously narrow vessels. No occlusions of major mural arteries were observed in the radiographs or in the histology in the present series.

The study also showed that in areas with small lesions, associated with minor inflammatory reactions, few or no vascular changes could be seen. That such areas with only minute changes of Crohn's disease may appear normal to palpation and at gross inspection has been noted already by Rappaport, Burgoyne, and Smetana (1951). To the experienced surgeon it is a well known fact.

Abdominal angiography for the preoperative diagnosis of Crohn's disease has not gained universal acceptance, partly due to the difficulty in visualizing vascular changes in areas with moderate or small lesions. Although the present study was not concerned with blood flow but with anatomy, such diagnostic difficulties may be explained by the finding of only minor vascular changes in areas with only mild inflammatory changes.

That ileal ulcers in Crohn's disease are related mainly to the mesenteric attachment, and thereby to the point of entrance of vessels, has been shown previously (Crohn, Ginzburg, and Oppenheimer, 1932; van Patter et al, 1954). That the ulcers in the colon are similarly related to the point of entrance of arteries through the muscularis was repeatedly seen in the present study. Our study offers no certain explanation for this relationship but it may suggest that the inflammatory process in Crohn's disease progresses along the lymphatics in the perivascular sheaths.

**ULCERATIVE COLITIS**

All specimens with ulcerative colitis had longstanding changes. Three showed evidence of active inflammation, and one of old, atrophic lesions. None of the specimens showed evidence of 'toxic dilatation' or gross carcinoma.

Hypervascularity was marked in the survey angiograms of specimens with active inflammation (Fig. 9a). The width of the colonic marginal artery was increased and the colonic arteriae rectae were up to 2 mm wide, as compared with about 1.2 mm or less in most normals. The number of large arteriae rectae counted along the mesocolic attachment was increased two to fourfold, probably because of widening of previously narrow vessels.

In the angiograms of the transverse sections the hypervascularity was seen to be confined to the mucosa and submucosa. The normally few and slender submucosal arteries were markedly widened, assuming almost the appearance of veins, and were numerous and tortuous (Fig. 9b and c). Histologically, the inflammatory lesions were confined to the mucosa, the muscularis mucosae, and to the uppermost layer of the submucosa. No endarteritic changes were observed in the specimens of the series. The ulcers, most of which were shallow, were not anatomically related to specific vascular features, but were irregularly scattered in the mucosa.

In one specimen large pseudopolyps protruded from the surface as irregular tags. These were seen to be supplied by large branches of submucosal arteries (Fig. 10).

In one case with chronic atrophic and little active inflammation, vascularity as seen in survey angiograms could not be differentiated from that of normal specimens, but in the radiographs of transverse sections tortuosity of the intramural arteries was occasionally observed. Areas of patchy, superficial premalignant changes of the mucosa, not penetrating the muscularis mucosae, were also encountered in this specimen. The arteries in these areas did not differ in appearance.

**Fig. 11** Atrophic ulcerative colitis. (Above) Radiograph: a few tortuous submucosal arteries. (Below) Histology: signs of early malignancy in mucosa. Haematoxylin and eosin, ×18.
from those in areas without incipient malignancy (Fig. 11).

Comments
The vascular pattern observed in ulcerative colitis was in agreement with the previously well known fact that the inflammatory changes are confined predominantly to the mucosa and to the adjacent layers of submucosa and that vascularity is increased. The submucosal arteries were much wider in active ulcerative colitis than in the specimens with Crohn's disease.

To facilitate the preparation of the specimens before the onset of autolysis, multiple arterial catheters were inserted at operation before the removal of the specimens. For this assistance we thank Dr A. Wenckert, of the Department of Surgery.

References


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Gut 1970 11: 928-940
doi: 10.1136/gut.11.11.928

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