Ischaemic colitis in the experimental animal

I Comparison of the effects of acute and subacute vascular occlusion

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SUMMARY Acute ligation of the common colic and caudal mesenteric artery in the dog led to ischaemic colitis, whereas the acute ligation of the common colic artery and gradual occlusion of the caudal mesenteric artery by an ameroid plastic device did not lead to ischaemic disease. These findings suggest that the collateral blood vessels do not open up rapidly enough to prevent ischaemic change when the two major arteries are acutely ligated.

For a number of years, attempts have been made to render the large bowel ischaemic experimentally. Boley *et al.* (1963) carried out experiments in which they ligated the colonic arteries in dogs and they also undertook other studies in which either venous or combined arterial and venous interruption was effected. They produced appearances some of which resembled ischaemic colitis in man.

Marston *et al.* (1969) adopted similar techniques which involved acute ligation of the common colic, the caudal mesenteric, and the marginal arteries in the dog. The extent of devascularisation ranged from the acute ligation of the caudal mesenteric artery alone, to subtotal devascularisation where all three arteries were ligated at once. Definite structural lesions were produced which varied in timing and severity according to the degree of the devascularisation procedure.

Boley *et al.* (1965) investigated the effects of blockage of the vasa recta with microsphere emboli. Ceramic and glass microspheres varying in diameter from 35 to 100 microns were injected into the caudal mesenteric artery in dogs. This resulted in a spectrum of pathological change ranging from minimal mucosal oedema to rapid total intestinal necrosis, the severity depending on the size and quantity of the spheres injected. The larger the quantity and the smaller the spheres the greater was the damage produced.

Using the Seldinger technique, Ranniger and Scheiner (1967) injected lead pellets into the cranial (superior) mesenteric artery of dogs and found that the degree of vascular embarrassment produced

depended on the number of pellets introduced. If several adjacent intramural branches were occluded the acute ischaemia led to gangrene and perforation of the bowel within 15 hours, in spite of collateral circulation.

De Villiers (1966) perfused an isolated loop of colon in the dog with Ringer's solution, thus producing anaemic anoxia. After four hours the normal vascular supply was restored but yet ischaemic changes in the colon rapidly developed.

Marcuson *et al.* (1972) have produced ischaemic change in the colon of the dog after venous obstruction. Acute ligation alone of the veins draining the colon did not lead to thrombosis but local intravascular injection of thrombin combined with venous ligation readily induced venous thrombosis. Marked structural changes occurred in the colon but there were important differences between the appearances of experimental arterial and venous lesions. In effect, this procedure leads to the development of stagnant anoxia.

The purpose of the present study was to compare the effects on the colon of acute vascular interruption with the effects of a more gradual occlusion of the same vessels.

Experimental method

GROUP I ACUTE LIGATION OF COMMON COLIC AND CAUDAL (INFERIOR) MESENTERIC ARTERIES
The common colic artery, which is the first branch of the cranial mesenteric artery in the dog, leaves the main trunk about 2·5 cm from its aortic origin. In order to expose the common colic artery the

spleen was packed into the left hypochondrium and the peritoneum over the cranial mesenteric artery was incised.

There are many lymph channels which drain into a large lymph node just to the left side of the cranial mesenteric trunk. These channels had to be divided in some of the experiments so that the origin of the common colic artery could be visualised. When the trunk of the common colic artery was visualised it was tied in two places and the artery was cut between the two ligatures.

The caudal mesenteric artery is easily traced as it leaves the anterior wall of the aorta low down opposite the fifth or sixth lumbar vertebra. It was ligated and divided close to its origin.

GROUP II ACUTE LIGATION OF COMMON
COLIC ARTERY AND GRADUAL OCCLUSION
OF CAUDAL MESENTERIC ARTERY

The common colic artery was ligated, as in group I. An occlusive device of ameroid casein plastic material was placed on the caudal mesenteric artery close to its origin from the aorta. When implanted in the body this material absorbs fluid from the tissues, thus causing the ameroid to swell gradually. To prepare the device a 1 cm length of casein plastic was cut from a 12 mm diameter circular rod and a 2 mm diameter hole was bored down the centre of the segment. A metal ring was prepared to surround the length of plastic.

After this, a narrow groove was cut in the plastic and the metal ring so that the artery of the dog could be easily placed within the device. The purpose of the metal ring was to limit swelling of the ameroid in an outward direction, thus ensuring a more definite narrowing of the central channel resulting in compression of the artery.

When the occlusive device was placed on the artery the metal ring was first rotated so that the artery could not slip out of the plastic and then it was squeezed with a pair of forceps to ensure that the metal ring fitted snugly round the ameroid material (Fig. 1).

POST-OPERATIVE ASSESSMENT OF DOGS

General assessment of dogs
In addition to assessment of the dogs's general health attention was paid to the following:
1. *Diarrhoea* This was assessed on the basis of either an increase in the number of stools or an alteration in their nature to a more fluid consistency.
2. *Bleeding* This was ascertained on macroscopic grounds only and the dog's faeces and anus were inspected for blood.
3. *Sigmoidoscopy* Sigmoidoscopy was performed using a 30 cm long instrument. This allowed inspection to almost the splenic flexure in every instance.

Barium enema examination
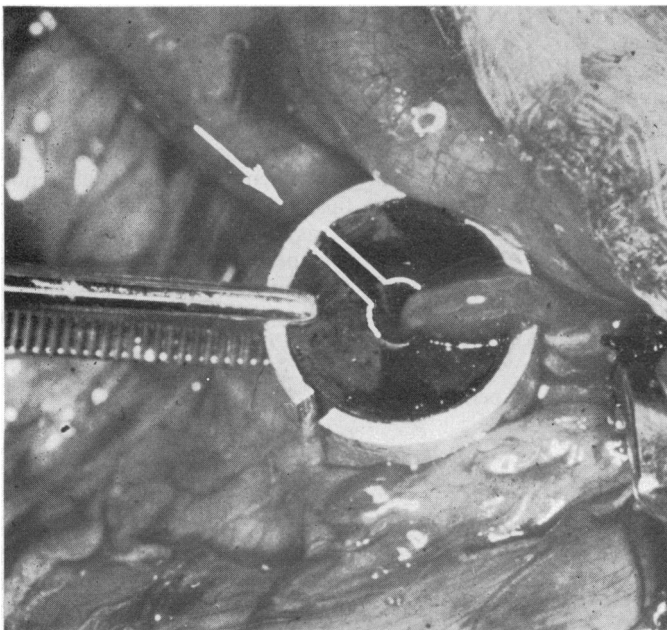*Sedation and anaesthesia* Before carrying out barium enema examinations, the animals were

Fig. 1 *Caudal mesenteric artery secured within the ameroid device.*

sedated with diazepam 20-30 mg intramuscularly, or were lightly anaesthetised using either ketamine hydrochloride with diazepam or Immobilon. When the x-ray examination was being performed in the first few hours after a surgical procedure, the residual sedation after the anaesthetic was usually adequate.

Barium was made up using Micropaque (92% w/w barium sulphate). Eight volumes of powder to seven volumes of water, yielding a 'standard' mix, were used initially, but a more dilute mix proved to be more satisfactory. Barium was introduced into the large bowel through a Foley catheter.

Position of animal The examination was started with the animal lying in the left lateral position. It was found that for complete screening of the dog's colon, it was necessary to turn the animal onto its back and occasionally to tilt its head in a downward direction. As the dog was turned from lying on its left side into the dorsal position and then over onto its right side, the ascending colon and caecum usually filled with contrast.

Methods of recording The whole procedure was monitored on an image intensifier and recorded on video tape. Standard radiographic plates were exposed to record particular features.

Results

GROUP I EFFECTS OF ACUTE LIGATION OF COMMON COLIC ARTERY AND CAUDAL (INFERIOR) MESENTERIC ARTERY

After the acute ligation of both the common colic and caudal mesenteric arteries all animals in this group developed evidence of ischaemic disease. The interval between acute arterial ligation and the onset of diarrhoea and/or bleeding varied considerably. Diarrhoea was the first sign in three of the dogs, and a mixture of blood and diarrhoea occurred in the remaining two. In the other dog that had bleeding this was slight and was noted at sigmoidoscopy. The table shows the variation of the physical signs of ischaemic colitis in this group. None of the dogs died from the disease; two of them were killed for pathological examination at 72 and 106 hours

Table *Physical signs of ischaemic colitis in group I*

Dog	Diarrhoea	Bleeding	Sigmoidoscopy changes
1	+++	++	Yes
2	++	−	Yes
3	++	+	Yes
4	++	−	Yes
5	+++	++	Yes
P	<0·005	NS	<0·005

P = Statistical analysis derived using Fisher probability test.

respectively after ligation of their mesenteric vessels.

During sigmoidoscopic examination the presence of fluid faeces in the lumen was noted in every instance and frank bleeding was present in three dogs. A prominent feature soon after initiation of the ischaemia was the increased irritability and spasm noted when the sigmoidoscope was being passed. Mucosal and submucosal changes were readily noted within a few hours of ligation of both main vessels. Mucosal oedema was the earliest sign but within a short time the mucosa became friable, granular, and haemorrhagic. Ecchymoses and mucosal swelling were prominent features, sometimes as early as four hours after the vascular ligation.

Regression of the endoscopic appearances was noted from the third day onwards and within 10 to 21 days the mucosal appearance had returned to normal.

During radiological examination of the large bowel, spasm was common and on occasion this made the introduction of the barium difficult. The earliest radiological signs were oedema and swelling of the mucosal folds leading to the formation of narrow grooves between adjacent folds which, when filled with barium, gave a 'spiked' or 'sawtooth' margin to the bowel (Fig. 2). These changes were often seen within four hours of vascular interuption. Subsequently, swelling of mucosa and submucosa became more prominent and confluent. 'Thumbprinting' was demonstrable as early as 12 hours after vascular occlusion and definitive 'pseudo-tumour' formation as shown in Fig. 3 usually followed within the next 24 to 48 hours.

GROUP II EFFECTS OF ACUTE LIGATION OF COMMON COLIC ARTERY AND GRADUAL OCCLUSION OF CAUDAL (INFERIOR) MESENTERIC ARTERY

In a series of preliminary experiments, it had been shown that the ameroid device led to complete vascular occlusion within three weeks of its application (Fig. 4). The dogs were carefully assessed each day and there was no evidence of diarrhoea or bleeding either in the kennels or on sigmoidoscopic examination.

Discussion

In the present studies, acute ligation of the two major arteries to the colon caused sufficient vascular embarrassment to lead to ischaemic colitis in all five dogs. Marston *et al.* (1969) found that not all dogs which had this procedure carried out suffered from the disease. In their experiments, sigmoidoscopy and barium enema examinations were performed on the
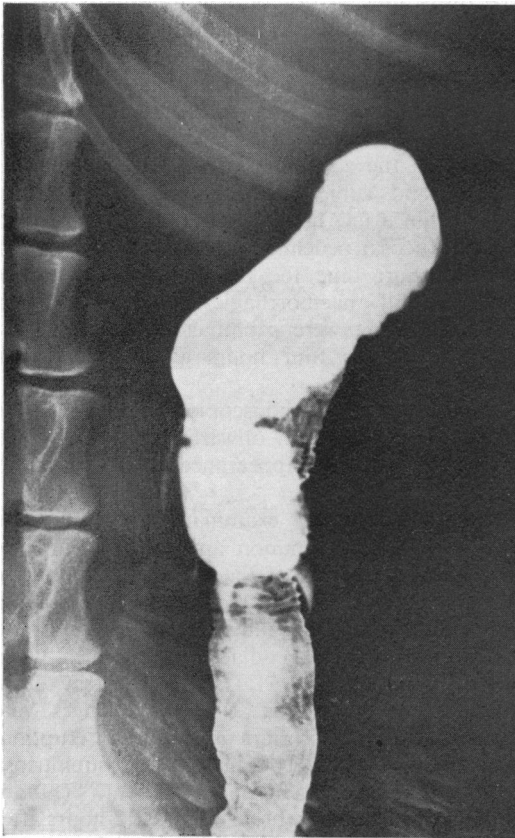
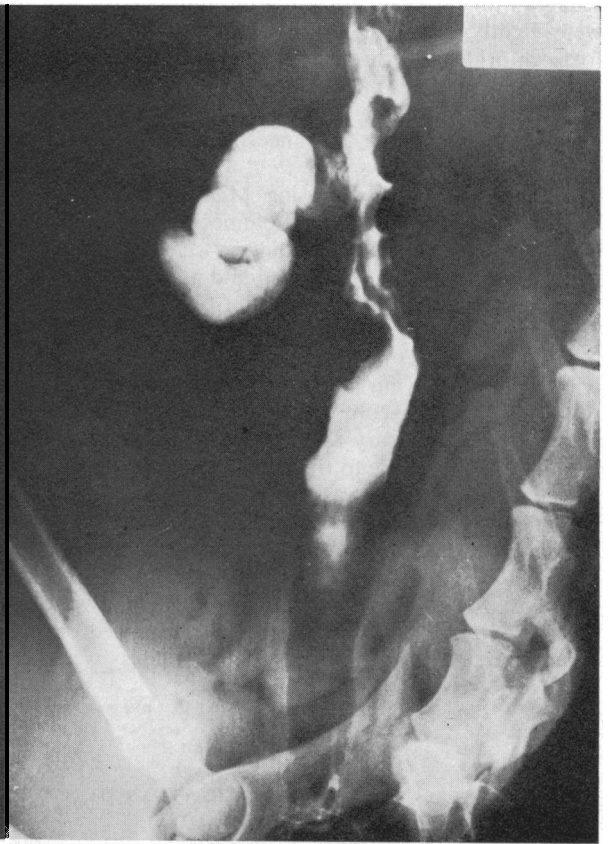Fig. 2 *Early formation of 'saw tooth' pattern at barium enema.*

Fig. 3 *'Thumbprinting' and 'pseudotumour' formation noted 36 hours after acute ligation of the common colic and the caudal mesenteric arteries.*

first, 14th, and 42nd days after acute ligation. It would have been of interest to know if any pathological changes occurred in the period between the first and 14th days.

In the present studies, within the first 36 hours of the acute ligation of both major arteries, bleeding was present in two dogs and diarrhoea in all five. The most prominent pathological features, however, were present between the second and eighth days. After this, ulcers began to disappear and the submucosal haematomata were rapidly absorbed. Marston *et al.* (1969) had previously shown that the acute ligation of the caudal mesenteric artery alone does not usually lead to ischaemic colitis, though in one case a stricture was associated with this procedure.

If two major arteries are acutely ligated then cellular anoxia occurs before the collateral blood vessels have time to open up. The acute cellular anoxia produced seems to unleash a number of mechanisms which further deplete oxygen reserves. Initially, there appears to be a breakdown of the mucosal barrier so that bacteria and other substances in the gut lumen are able to invade the bowel wall. The bacteria then evoke an inflammatory reaction in the bowel wall and this further depletes the oxygen available to the mucosal cell (Pheils, 1969). Marston *et al.* (1969) state that the size of the occluded blood vessels, the duration of the occlusion, the efficiency of the collateral circulation, and the bacteria present in the bowel lumen are all important factors in determining the outcome of vascular occlusion.

GRADUAL REDUCTION IN BLOOD FLOW
In man, gradual occlusion secondary to atherosclerosis is very common in the mesenteric blood vessels (Griffiths, 1956; Knoepp *et al.*, 1970) and as the arterial lumen is narrowed according to Poiseuille's law, the flow is drastically reduced. Whitaker (1968) showed that with increasing age in man there

Fig. 4 *Thrombosed caudal mesenteric artery three weeks after the ameroid device had been applied. (Device removed before the photograph was taken.)*

was a linear decline in mean blood flow in the inferior mesenteric artery, so that a flow of the order of 120 ml per minute in the fourth decade is reduced to approximately 10-15 ml per minute in the eighth decade.

In the present studies no evidence of ischaemic colitis was produced after the acute ligation of the common colic artery and the gradual occlusion, over two to three weeks, of the caudal mesenteric artery—that is, group II. It appears that the dog is able to compensate to deal with this degree of interference with the vascular supply, providing that the devascularisation is gradual in onset. The present work suggests that the marginal artery is capable of providing adequate circulation to the dog's colon even when both of its major supply arteries are occluded. These findings are to some extent comparable with those of Blalock and Levy (1939) and Popovsky (1966) who by chronic techniques occluded the mesenteric blood vessels with either Goldblatt clamps or ameroid devices without any obvious

detriment. Similar work was done on the 'superior' mesenteric artery alone by Laufman (1943). All these workers reported the subsequent development of a profuse collateral circulation.

In similar circumstances in man, if the two major vessels supplying the colon are occluded it is still possible that the cellular integrity of the colon may be maintained by perfusion through the marginal artery from its proximal and distal anastomoses. In 1913, in the Cavendish Lecture on the surgery of the large intestine, Lord Moynihan stated: 'My own view is that, however vessels are ligated and whatever sacrifice of the mesentery may be thought necessary, it is almost impossible to deprive the cut end of the colon, when resection is being done, of an adequate blood supply—the marginal artery affords an ample supply of blood to all parts. The importance of the marginal artery as far as the procedure of intestinal resection is concerned cannot be overestimated'.

RADIOLOGICAL APPEARANCES

Barium enema examination was very rewarding in the early stages of the disease and, indeed, mucosal oedema was noticed as early as four hours after the production of ischaemia. This usually took the form of a fine 'sawtooth' irregularity which over the next 24 hours changed into conventional 'thumbprints'.

There are no reports in the literature of the time taken for experimentally induced colonic ischaemia to be demonstrated on barium enema, but in clinical practice most radiological investigations of this disease usually take place some days after the onset of spontaneous ischaemia, due primarily to delay in considering the possibility of ischaemic colitis and, secondly, reluctance by some workers to perform barium enema examination in acute diseases of the colon. Thus, it is possible to miss the radiological evidence for the disease completely. In these experiments all dogs with evidence of ischaemic disease or barium enema examination had returned to normal within 10 to 14 days. Spasm of the colon disappeared first and thumbprinting gradually disappeared some days later. Dense thumbprints or pseudo-tumours were seen and these corresponded with submucosal oedema, haemorrhage, and haematomata. No ulceration was seen on barium enema examination.

No strictures were noted in the present studies and this is probably because the degree of devascularisation on an acute basis was insufficient to lead to permanent damage to the colonic muscle and replacement fibrosis. In experiments by Marston *et al.* (1969) strictures were found in three animals after acute ligation of the caudal mesenteric and marginal arteries and in one after the ligation of the common colic, the caudal mesenteric, and the marginal arteries.

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