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Ischaemic colitis in the experimental animal

II Role of hypovolaemia in the production of the disease

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SUMMARY Hypovolaemia alone did not lead to ischaemic colitis but when venesection was induced immediately after the acute ligation of the common colic artery large bowel ischaemia ensued. Similarly, hypovolaemia induced one month after two major blood vessels had been occluded led to ischaemic colitis. These findings suggest that states of low blood flow in the presence of previous arterial constriction or blockage may lead to enough reduction in mesenteric perfusion for intestinal ischaemia to develop. Using an electromagnetic flowmeter placed in the cranial mesenteric artery of the dog, it was shown that hypovolaemia may lead to 50-75% reduction in mesenteric blood flow without producing any significant change in the systemic blood pressure.

From an aetiological point of view, the classification of mesenteric ischaemia into occlusive and non-occlusive types seems justifiable. Those patients with demonstrable vascular blockage are referred to as suffering from occlusive disease while others without blockage are classified as having non-occlusive vascular disease.

If the bowel is dependent on a diseased vascular tree, mucosal damage may develop because splanchnic vasoconstriction occurs in an effort to meet the demands from the rest of the body (Williams *et al.*, 1967). Among 45 patients with acute mesenteric vascular insufficiency, Britt and Cheek (1969) showed that 36% were due to non-occlusive disease.

Montessori and Liepa (1970) described two groups of patients who occasionally develop the signs and symptoms of ischaemic colitis of a non-occlusive variety—namely, (1) patients who had major surgery or trauma, and (2) patients with severe cardiovascular disease where the intestinal episode was precipitated by an acute myocardial infarction, severe congestive cardiac failure, or shock. Jensen and Smith (1956) mentioned that recent abdominal surgery was the second most common factor associated with mesenteric infarction. The operation being carried out was usually either a splenectomy or removal of an abdominal neoplasm.

The severity of the colonic ischaemia in non-occlusive disease may be as great as that in the occlusive variety, and Herrington (1965) described a group of patients with complete mural infarction at one end of the spectrum and mild mucosal abnormalities at the other, in which no occlusion was demonstrated.

In a leading article (*Lancet*, 1964) it was suggested that intestinal lesions may follow an episode of hypotension which reduces the pressure at the stenosed orifice of an artery resulting in widespread peripheral shut-down, causing patchy necrosis of the mucosa. These ideas were again stated by Hedberg and Kirsner (1965) in the *Annals of Internal Medicine* which goes on to associate cardiovascular decompensation with resultant low blood flow in the mesenteric vessels. Low blood flow states may be further aggravated by the presence of a large number of adrenergic constrictor receptors in the mesenteric vessels which act to restrict flow to a greater extent, after excessive sympathetic stimulation. As early as 1919, Gesell postulated that compensatory vasoconstriction resulting from shock reduced blood flow to the intestinal mucosa to such an extent that mucosal necrosis could take place. However, no attempt to investigate the hypothesis has so far been reported.

The present study was undertaken to investigate the role of reduced perfusion pressure in the aetiology of ischaemic colitis.

Experimental method

As in the experiments in part I the greyhound was used. There were five dogs in each group.

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GROUP I: HYPOVOLAEMIA ALONE

Thirty per cent (about 1137 ml (two pints)) of the dog's blood volume was withdrawn from the femoral artery over a period of 60 minutes using a Medicut cannula. The arterial pressure was monitored throughout and recorded on a pen recorder.

The blood was collected in polyethylene bags containing sodium citrate and after maintaining the hypovolaemic state for three hours the blood was transfused into the animal again within the next two hours.

GROUP II: ACUTE LIGATION OF COMMON COLIC ARTERY AND GRADUAL OCCLUSION OF CAUDAL MESENTERIC ARTERY FOLLOWED FOUR WEEKS LATER BY HYPOVOLAEMIA

In this group of experiments the initial procedure was similar to that described in part I of this communication. The common colic artery was ligated and an ameroid occlusive device was placed on the caudal mesenteric artery to cause its gradual occlusion over the next two to four weeks. Four weeks after the operation the blood volume was reduced, as described above for group I—that is, 30% of the blood volume was removed and hypovolaemia was maintained for three hours before retransfusion of the dog's own blood.

GROUP III: ACUTE LIGATION OF CAUDAL MESENTERIC ARTERY WITH HYPOVOLAEMIA INDUCED IMMEDIATELY AFTER LIGATION PROCEDURE

Figure 1 illustrates diagrammatically the ligation of the caudal mesenteric artery. The blood flow in the cranial mesenteric artery was measured using an electromagnetic flowmeter before the ligation of the caudal mesenteric artery and throughout the period of hypovolaemia and restoration of blood volume. The amount of blood withdrawn and the period of hypovolaemia was similar to groups I and II.

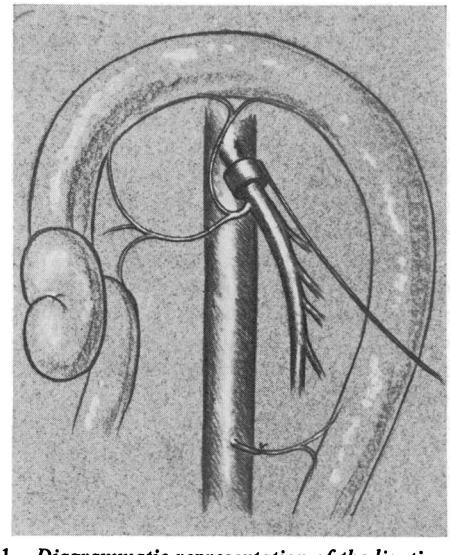

Fig. 1 *Diagrammatic representation of the ligation of the caudal mesenteric artery. Blood flow probe on the cranial mesenteric artery.*

Results

GROUP I: HYPOVOLAEMIA ALONE

When hypovolaemia was induced by removal of 30% of the dog's blood volume over the period of one hour, the systemic blood pressure and flow in the cranial (superior) mesenteric artery were continuously monitored. None of the five animals in this group developed ischaemic colitis.

In some of the experiments there was considerable change in the mesenteric blood flow after hypovolaemia but this was paralleled by only minimal change in the systemic blood pressure. In fact, in one animal the systemic blood pressure (systolic) actually rose from 180 to 185 mm Hg, while a 75% reduction in mesenteric blood flow occurred. The effects of hypovolaemia on systemic blood pressure and blood flow as measured in the cranial mesenteric artery are demonstrated in Table 1.

GROUP II: ACUTE LIGATION OF COMMON COLIC ARTERY WITH GRADUAL OCCLUSION OF CAUDAL MESENTERIC ARTERY FOLLOWED FOUR WEEKS LATER BY HYPOVOLAEMIA

When the initial procedure of acutely ligating one major artery and gradually occluding a second was carried out, there was no evidence of ischaemic colitis on careful observation during a four-week period of recovery. At this stage, when the dogs were subjected to hypovolaemia, as in group I, signs of ischaemia became detectable within a matter of a few hours. Table 2 summarises the physical, endoscopic, and radiological changes in all five dogs at the stage at which hypovolaemia was produced.

Table 1 *Percentage reduction is systemic blood pressure associated with 50 and 75% reduction in mesenteric blood flow induced by hypovolaemia*

Dog	*Systemic blood pressure associated with reduction in mesenteric flow of:*		*Percentage reduction in systemic blood pressure associated with reduction in mesenteric flow of:*	
	50%	*75%*	*50%*	*75%*
1	135/100	125/80	25	30·6
2	150/105	150/110	0	0
3	180/110	185/130	0	0
4	150/105	150/110	10·9	10·9
5	130/85	110/75	13·4	26·7

Table 2 *Physical, endoscopic, and radiological signs of ischaemic colitis in group II*

Dog	*Diarrhoea*	*Bleeding*	*Typical changes on:*	
			Sigmoido-scopy	*Barium enema*
1	++	+	Yes	Yes
2	++	++	Yes	Not done
3	++	−	Yes	Yes
4	++	−	Yes	Yes
5	++	−	Yes	Yes
P	<0·005	NS	<0·005	<0·02

Barium enema examinations were performed on all except one animal which has already started to bleed per rectum three hours after hypovolaemia had been induced. In the other four dogs early mucosal oedema was noted within the first four hours of the completion of blood withdrawal.

GROUP III: ACUTE LIGATION OF COMMON COLIC ARTERY PLUS IMMEDIATE HYPOVOLAEMIA

In this set of experiments, when only the major artery was ligated and immediate hypovolaemia induced, all the dogs showed marked evidence of large bowel ischaemia, although one did not have diarrhoea. However, sigmoidoscopy and barium enema were carried, out which confirmed the diagnosis of ischaemic colitis in this dog. Table 3 summarises the physical and endoscopic signs of ischaemic colitis in this group.

The segments of colon affected by ischaemia were more confined in group 3 than in group 2. The localised nature of the lesion typically encountered in group 3 is shown in Fig. 2. Although the pathological changes were more concentrated in a single area, vesicles, ulceration, haemorrhage, and submucosal haematomata were still prominent features (Fig. 3).

Within four hours of induced ischaemia of the colon, it was possible to demonstrate changes on barium enema examination. The earliest change was increased irritability of the colon and this was often manifested by the presence of a stripping wave, as shown in Fig. 4a. The spasm associated with the stripping wave was usually short-lived and when the barium distended the colon a 'sawtooth' pattern, indicative of early mucosal oedema was present (Fig. 4b).

Table 3 *Physical and endoscopic signs of ischaemic colitis produced in group III*

Dog	*Diarrhoea*	*Bleeding*	*Typical changes on sigmoidoscopy*
1	++	−	+
2	++	+	+
3	++	+	+
4	++	+	+
5	−	+	+
P	<0·02	<0·02	<0·005

P = Statistical significance derived using Fisher probability test.

During the next 48 to 72 hours the change demonstrated by barium enema varied with the degree of ischaemia. In some instances, when the physical signs and sigmoidoscopic evidence of ischaemic colitis were not marked, then the 'sawtooth' appearance tended to diminish slowly. Figure 4d demonstrates changes at three days in the same animal as shown in Fig. 4a, b, and c.

One of the most notable features was shortening of the colon after ischaemia and again this feature is shown in Fig. 4d.

In animals which had the common colic artery ligated, hypovolaemia occasionally resulted in radiological changes in the terminal small bowel within the first 36 hours. Among these changes a shallow 'sawtooth' abnormality consistently featured, the appearances in the small bowel and colon being not unlike those seen in malabsorptive diarrhoea in man, rather than in ischaemic colitis (Fig. 5).

In animals with more severe ischaemic involvement of the colon, other features such as the more conventional 'thumbprinting' and pseudo-tumours became demonstrable. These factors are shown on barium enema carried out on the third day after induced ischaemia (Fig. 6). From the third to the seventh days the most marked evidence of ischaemic involvement with the development of large pseudotumours with marked oedema was demonstrated (Fig. 7).

In the majority of animals which had two arteries occluded the ischaemic process induced by subsequent hypovolaemia often led to involvement of the rectum.

In all the animals which had barium studies the radiological features of ischaemic colitis disappeared within 14 days.

Discussion

BLOOD FLOW

General considerations

The flow of a fluid through a tube is governed mainly by three factors—namely, quantity, pressure, and resistance. Poiseuille resolved these factors into a formula to show that the quantity of fluid flowing through a tube depended on the pressure difference at either end and the resistance factors relating to both the tube and the viscosity of the fluid. However, blood does not fall into the category of a Newtonian

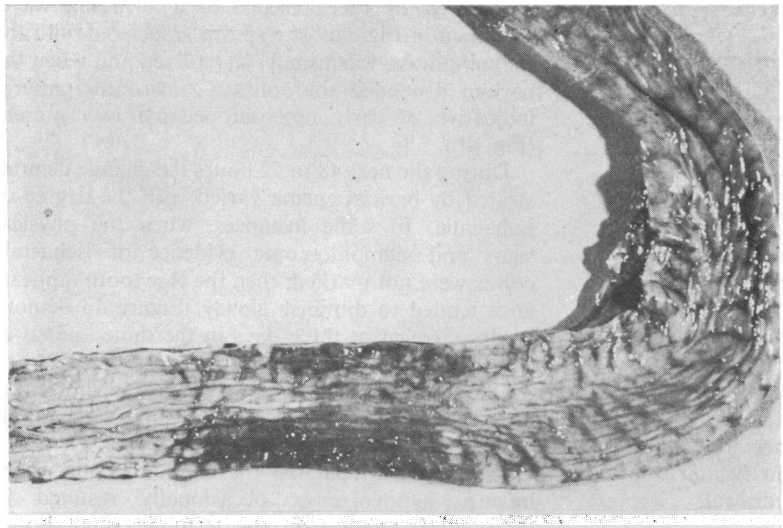

Fig. 2 *Localised nature of ischaemia in the colon, corresponding to area supplied by the caudal mesenteric artery. Group III.*

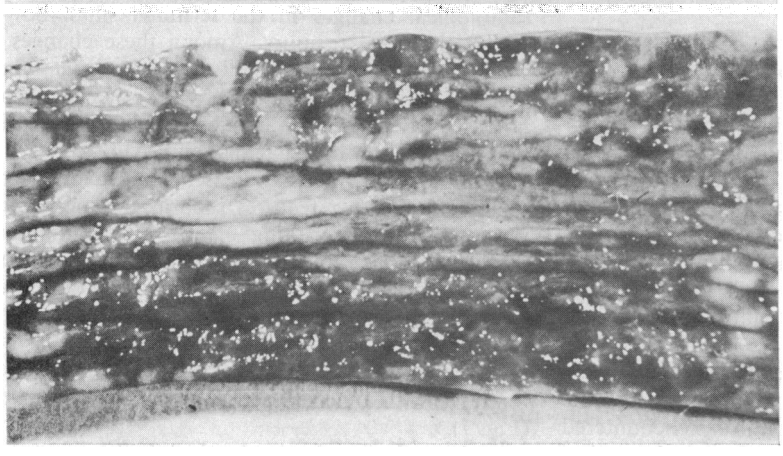

Fig. 3 *Enlargement of the ischaemic area in Fig. 2 showing vesicles, ulceration, haemorrhage, etc.*

fluid, which is defined as a liquid which does not vary with the rate of shear and remains constant at different rates of laminar flow. Consequently, its viscosity characteristics are referred to as anomalous.

Factors affecting anomalous viscosity are haematocrit, shear rate, radius and length of tube, and temperature. Turbulence is a factor only in very large blood vessels and in the heart, otherwise laminar flow occurs in the non-diseased peripheral vascular system.

For blood vessels of medium size, according to Poiseuille's law, blood flow varies directly with the fourth part of the radius of the lumen. Therefore, if viscosity of the blood, loss of energy through friction, and length of blood vessel concerned are constant, the diameter of the vessel is the critical factor in determining the volume of blood flow (Derrick *et al.*, 1959).

Perfusion through mesenteric blood vessels is therefore influenced by two factors (1) the diameter of the blood vessels, and (2) the activity of natural distant regulators in the sympathetic nervous system which further alter their size.

Selkurt *et al.* (1958) have shown that the effective radius of the vessel varies with intraluminal pressure and that the important factors influencing vascular resistance are: (1) critical closure—that is, at some small arteriovenous pressure difference the blood vessels close, (2) passive expansion of blood vessels, and (3) anomalous viscosity of blood.

With low perfusion pressures all three factors are important, whereas in the middle range passive expansion of blood vessels and viscosity are important. The chief factor contributing to the continued decrement of vascular resistance at high perfusion pressures is anomalous viscosity. Now, if the factors

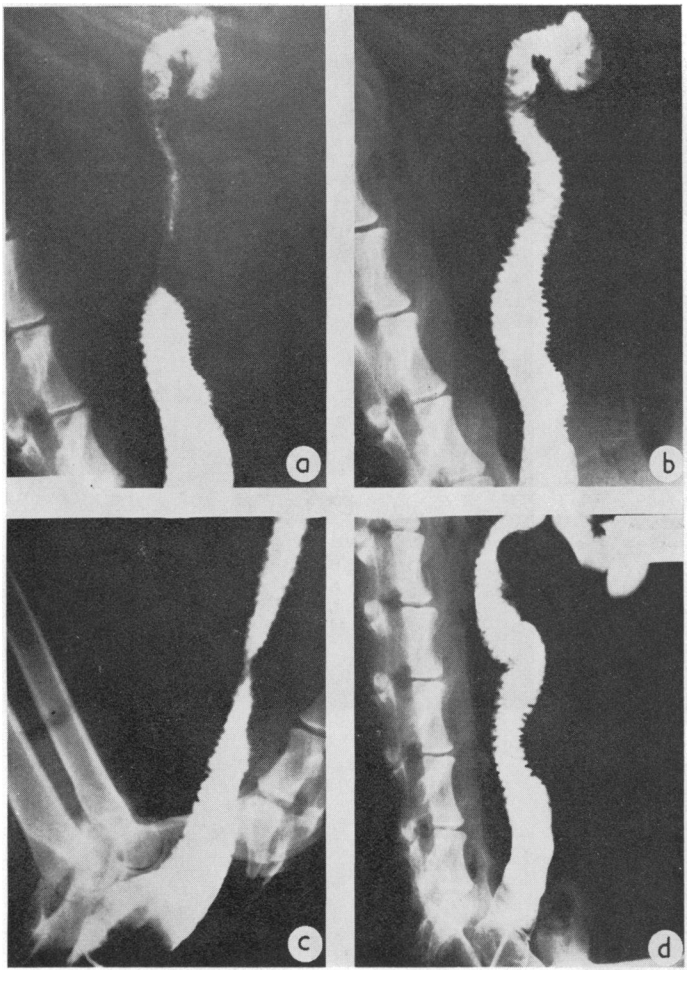

Fig. 4 (*a*) '*Stripping wave*'. (*b*) '*Stripping wave*' *filling out to* '*saw-tooth pattern*'. (*c*) *Lower portion of the colon shown in Fig. 4b.* (*d*) *Shortening of the colon at three days, in the same animal as in 4a, b, and c.*

affecting anomalous viscosity are constant then the phenomena of critical closure and passive expansion of blood vessels are of prime importance.

The law of Laplace states that transmural pressure

$$P_{TM} = \frac{\text{Tension in the vessel wall}}{\text{Radius}}$$

Thus, when the intravascular pressure drops below a certain point, critical closure may occur and the vessel will collapse. Marston *et al.* (1966) 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.

An important additional factor which governs the outcome of vascular occlusion is the condition of the general circulation (Russell, 1950). This is particularly important because, even if the collateral blood vessels do open up, blood must be supplied to them with a suitable head of pressure for adequate perfusion to occur. The cardiac output may drop considerably because of fluid loss secondary to mucosal ischaemia, resulting in further strain on the general circulation (Marston, 1967).

Microcirculation

The effects of low mesenteric blood flow in dogs have been described by Matsumoto *et al.* (1967). Their experiments involved the continuous observation of the bowel wall and mesentery in shock. With the aid of a biomicroscope they showed that at pre-shock levels there was no definite change in the microcirculation. As the blood pressure was lowered there was slowing of the blood flow in arterioles and veins and each red blood cell became visible. With reduc-

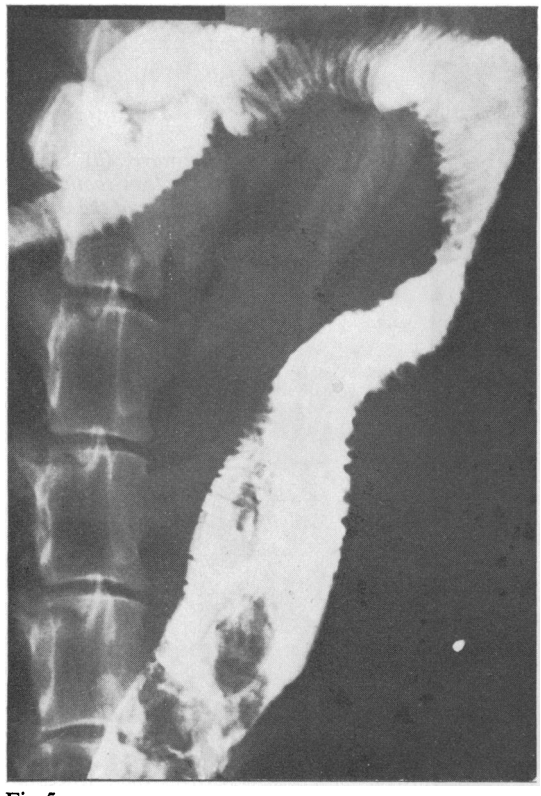

Fig 5

Fig 6

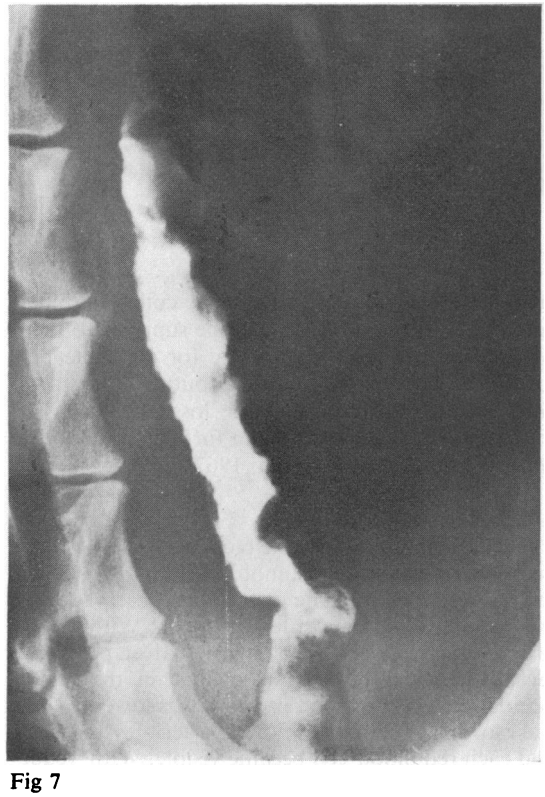

Fig 7

Fig. 5 *Malabsorptive type picture, within 36 hours after hypovolaemia.*

Fig. 6 *Thumbprinting and early pseudotumour formation on the third day after induced hypovolaemia.*

Fig. 7 *Pseudo tumour formation five days after the onset of ischaemic colitis.*

tion of 40 to 50% of blood volume arterioles were maximally constricted and flow became very slow, the venules were full, and the cells were rolling or striking against the walls. Platelet aggregates were seen and they lodged at bifurcations of blood vessels, occluding the flow.

In earlier work, Grayson and Mendel (1965) showed that in low flow states in the mesenteric circulation there was stagnation in more capillaries with distension at the venous end, causing in effect vascular 'obstruction' and subsequent pooling of blood. In the present studies small microthromboses occurred in the blood vessels of the lamina propria and this vascular interruption tended to initiate a process of ulceration with considerable inflammatory infiltrate. These findings are similar to those of Rosati and Augur (1971) who described multiple fibrin thrombi in the capillaries and venules of the lamina propria and submucosa in a patient with ischaemic enterocolitis secondary to the effects of phaeochromocytoma.

In the second group of animals in which the blood volume was reduced four weeks after the acute ligation of the common colic artery and the gradual occlusion of the caudal mesenteric artery, all five animals developed signs of ischaemic colitis. Before blood flow was reduced by hypovolaemia there was sufficient perfusion of the colon to keep it in health and there were no signs of large bowel ischaemia. However, the further encroachment caused by hypovolaemia on an already impaired circulation was sufficient to cause ischaemic disease in every instance.

As described above, thrombosis occurs with low flow states. In the present studies (group II) microvascular thrombosis was a common pathological entity and was associated with the formation of vesicles and their subsequent ulceration and haemorrhage.

In experimental work in dogs, Hardaway and McKay (1959) demonstrated that a bleeding tendency always accompanies the episode of intravescular clotting due to the appearance of a circulating anticoagulant like heparin and a drop in circulating fibrinogen and platelets, which have been already used up in the thrombotic process. Vascular blockage followed by bleeding, as occurs in the process of infarction, was clearly seen in the formation of ulcers in the present studies.

Low blood flow states may have a similar effect on the microvasculature as that produced by injecting microspheres into the caudal mesenteric artery of dogs (Boley *et al.*, 1965). In low blood flow states, as described above (Matsumoto *et al.*, 1967), it was reported that platelet aggregates lodged at the bifurcations of blood vessels occluding the flow. If enough blood vessels are blocked then logically the most dependent part of the bowel wall—namely, the mucosa—will have insufficient oxygen and ischaemia occurs. When microspheres were injected in experiments by Boley *et al.* (1965) and Ranniger and Scheiner (1967) the microspheres lodged at the bifurcation of blood vessels. The latter authors showed that the important factor in producing ischaemic disease is the quantity of microspheres injected. This is not surprising, as the microspheres must have effectively blocked most of the blood vessels in the bowel wall resulting in haemorrhage, ulceration, and infarction.

In the third group of the current experiments in which ischaemic colitis was produced after the acute ligation of one artery followed immediately by hypovolaemia, the affected segment was more localised but bleeding was more profuse than in experiments in which two arteries were acutely ligated without hypovolaemia (see Part I).

The severe effects of the combined procedure of acute ligation of one major artery and immediate hypovolaemia may be explained on the basis of acute limitation of blood flow resulting in severe impairment of perfusion through the marginal artery. The ligation of both major arteries, however, may lead to a more moderate impairment of cell function, since the integrity of the colon is maintained by the efficient marginal artery which still has a sufficient blood flow supplied by a healthy circulation.

These findings may be relevant to the clinical situation where the inferior mesenteric artery may be sacrificed at aneurysectomy. Often the inferior mesenteric artery is already thrombosed before surgical intervention but, if not, it is always ligated before replacement of the aorta by prosthesis. Patients with aortic aneurysms frequently have widespread arteriosclerosis, so if a mesenteric blood vessel is ligated at surgery and/or the heart has difficulty in maintaining normal perfusion, colonic ischaemia may develop rapidly. Large bowel ischaemia may be severe after reconstructive surgery to the aorta leading to gangrene in 1% of patients and less severe bowel disturbances of bleeding and diarrhoea in up to 15% of patients (Eastcott, 1966).

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