Causes of Death in Mesenteric Arterial Occlusion: *

I. Local and General Effects of Devascularization of the Bowel

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ACUTE OCCLUSION of the superior mesenteric artery (SMA) by embolus, or thrombosis continues to be fatal in over 80 per cent of cases treated conservatively or by resection of nonviable bowel.[4, 6, 15] Reconstruction of the blocked vessel is not difficult, and should be technically feasible in over two thirds of those afflicted.[18] Despite this, only nine successful revascularizations of the acutely infarcted bowel have been reported [4, 8, 21, 33, 37, 43, 44, 49] (excluding, that is, deaths in the postoperative period from any cause). These almost certainly represent a small proportion of many unsuccessful attempts. It is true that virtually all patients who suffer a major mesenteric occlusion have associated cardiac, or arterial disease which decreases the number of good results, but this applies also to the victims of strokes and myocardial infarctions, neither of which is as lethal. Since acute ischemia of the bowel carries a uniquely high mortality, we have been stimulated to re-examine the mechanisms involved.

It has always been assumed that when the gut is totally deprived of its blood supply it becomes gangrenous. It has been pointed out, however, that frank sloughing and perforation are rare following a mesenteric embolus.[6, 14] Most of the experimental work in this field has been concerned with strangulation, which is a different condition from pure ischemia in that it implies obstruction, successively, of the veins, the arteries, and the lumen of, in most cases, a short length of intestine. In this situation a highly toxic fluid [10, 12] accumulates in the peritoneum, the bowel-wall rapidly necroses and eventually perforates, and the individual becomes dehydrated from loss of water and crystalloids into the distended loops above the obstruction. In occlusion of the SMA, on the other hand, the whole of the small intestine is rendered acutely ischemic while its veins remain open. Here a profound systemic disturbance takes place which may well kill the individual before complete necrosis and perforation occur. The components of this disturbance are not yet understood. They probably include redistribution of body fluid, absorption of bacterial endotoxins, and the products of tissue necrosis, septicemia and perhaps auto-immune mechanisms.[25, 29, 36]

That dehydration is one of the most lethal effects of strangulation-obstruction has been known since the work of Scott and Wangensteen,[38] Aird [1, 2] and Scott.[39] It is also a clinical observation that thrombosis of the portal, or superior mesenteric vein is followed by haemorrhage into the

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alimentary tract.[3] It has always been supposed that an arterial occlusion does not cause significant losses of body fluid because the bowel is no longer perfused with blood. However, there is some experimental evidence that revascularization of the bowel after a period of ischemia is associated with redistribution of fluid. For instance Shapiro *et al.*[41] have shown that in the rabbit there is a profound drop in blood volume following release of an experimental ligature applied for some hours to the SMA, and Lillehei, Goot and Miller[27] have continued this in the dog. Recently Zuidema *et al.*[50] have demonstrated lowering of the serum albumen and leakage of I^{131} labelled polyvinylpyrrolidone into the intestine of the dog following a two-hour period of SMA occlusion. However, the quantitative changes in blood and plasma volumes which occur during the period of ischemia have never been accurately studied.

It is the purpose of the present work to estimate the amount and nature of body fluid redistribution which takes place following occlusion of the SMA, and to correlate those with the gross and microscopic changes observed in the bowel.

Materials and Methods

A total of 26 dogs has been used. They were healthy adult mongrels of both sexes weighing between 11 and 19 kilograms. No special care was taken with their preoperative diet which consisted of Purina Dog Chow® with occasional additions of horsemeat. No antibiotics were given at any stage. Experiments were carried through, for humanitarian reasons, under intravenous nembutal anesthesia. The total dosage varied little between the control and experimental animals and approximated 5.0 mg./Kg./hr. All procedures were done with full sterility. Temperature was measured with an intra-esophageal probe, and the initial hypothermia which occurs following induction of anesthesia was controlled by the use of a heating pad. (This is important as it is probable that the rate of bowel destruction following infarction is a direct function of body temperature.[32, 34]) Blood volume was measured at the outset of the experiment by the I^{131} labelled human serum albumin technic using a Volemetron well counter. In some dogs it was additionally measured by the use of CR^{51} labelled red cells. The two values were comparable within 10 per cent, as would be expected.[20] Hematocrit was measured by spinning the heparinized post mix blood volume sample on an International microhematocrit centrifuge for four minutes at 13,000 r.p.m. Blood pressure was monitored by an intra-aortic cannula inserted via the left femoral artery, and connected to a Statham strain gauge and Sanborn Polyviso Multichannel Recorder. A small polyethylene cannula was inserted into the femoral vein for sampling.

Operative Technic. Following blood volume estimation and arterial cannulation a midline laparotomy was performed and the origin of the SMA from the aorta exposed by dividing the right leaf of the mesentery parallel to the artery. A snare tourniquet was then placed around the artery proximal to the common colic branch and led out through a small stab incision in the flank. A fine cannula was inserted into a tributary of the splenic vein in order to monitor the portal pressure. The vessels in the neighborhood of the ligament of Treitz, and at the ileocecal junction connecting the superior mesenteric territory with that of the celiac axis and and inferior mesenteric artery, were divided according to Lillehei's[27] technic in order to produce a situation more closely resembling the human, and to delimit the arterial supply to the bowel. The abdomen was then closed.

Observations. Blood pressure, portal venous pressure, and temperature were observed continuously until death, or, in the

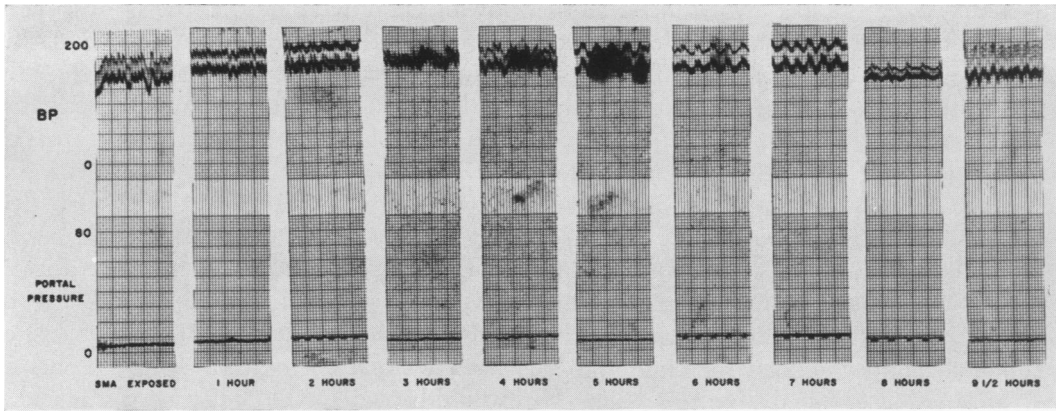

FIG. 1. Group 1 (Experiment 22). Representative experimental record. SMA is exposed but not ligated. Aortic and portal venous pressures show little change over nine hours.

case of the control animals, for a period of ten hours. Blood volume and hematocrit were measured in some animals at hourly intervals, in others at the outset and close of the experiment. The changes in blood volume, red cell mass and plasma volume were calculated and expressed as a percentage of the preoperative level. The dogs were then divided into two groups and treated in different ways.

Experimental Procedure

Group I. Laparotomy Only (6 Dogs). These animals served as controls. They were treated precisely as above and observed for a period of eight to 12 hours. The tourniquet on the SMA, which had been left loose throughout, was then removed and the animal returned to its cage.

Results. In this control group, the blood pressure was well maintained throughout (Fig. 1). However, there was a significant contraction of blood volume which in some cases amounted to as much as 20 per cent over a nine-hour period. The mean decrement was of the order of 1.0 per cent per hour. These results are comparable to those obtained by Seavers and Price [40] in a similar group of dogs. The loss appeared to be almost entirely of plasma. The reasons for it are not clear. It is probably due in part to insensible loss through lungs and skin, and in part to sequestration of blood in the portal system, or muscle venules. Another source of error is the presence of an intact spleen, which is thought to contribute ten per cent to the blood volume when it contracts [35] (Table 1). In any event a baseline is provided to show the response of the normal dog to prolonged anesthesia, laparotomy, and retroperitoneal dissection. The bowel in these cases remained normal. Of the six dogs operated upon, five survived in good health. The sixth dog died a few hours after termination of the experiment, and autopsy revealed pulmonary atelectasis and suppurative pneumonia.

Group 2. Occlusion of the SMA (20 Dogs). In this group, the effects of ischemia were studied (Fig. 2). When the arterial blood pressure and portal venous pressure appeared to be stabilized following operation, the snare tourniquet on the SMA was tightened, producing complete occlusion. Observations were then continued until death occurred. Serial biopsies of the bowel were obtained in some of the experiments. Immediately following death the bowel was removed and photographed.

Results. Effects on the Bowel. Immediately on occluding the SMA the well known sequelae were noted which were described in detail by Litten [28] and by

TABLE 1. *Results in Group 1 Experiments*

Dog	Duration of Experiment (hr.)	Anesthesia mg. Nembutal/kg./hr.	% Change in Blood Volume	% Change in Red Cell Volume	% Change in Plasma Volume	Result
4	12	3.3	− 2	+18	−18	Survived
13	9	3.9	−17	+11	−21	Died (pneumonia)
15	9	4.7	−15	+ 9	−37	Survived
14	9	3.8	− 9	0	−18	Survived
30	9	4.7	− 9	+10	−22	Survived
42	11	7.3	−11	− 7	−15	Survived
Mean 10		4.6 ± 0.5	−10.5 ± 2.4	+7 ± 3.3	−22 ± 2.9	

* The apparent gain in red cells is probably due to splenic contraction. See text.

Welch.[47] The bowel went into spasm, the arteries emptied and pale concentric stripes appeared at the sites of maximum ischemia. After some three to four hours the bowel lost its tonus and appeared cyanotic and flabby, and in five to six hours edema and frank hemorrhage began. Frequently the dog passed a bloody stool at this time. After eight to nine hours the edema was more marked, and there were areas of discoloration which were usually most prominent at the ileocecal region. A sharp demarcation between healthy and infarcted tissue appeared at the duodenojejunal junction, and at the upper part of the descending colon where the celiac and inferior mesenteric systems respectively entered. In no case was there a frank perforation of the bowel, though a few milliliters of turbid fluid accumulated in the peritoneum. An interesting finding was that the mesenteric veins were frequently distended with bubbles of gas. This has been noted in human lymphatics at operations for mesenteric embolus.[43] Since the veins were unopened, the gas must have arisen from organisms invading the bowel wall. It was also noticed that peristalsis could be evoked by pinching the bowel until late in the experiment, and sometimes in a dog that had already died.

Histological Appearances. Progressive destruction of the bowel wall was apparent as early as one hour after ligation of the SMA. The tips of the villi started to slough at this time, and formed a membrane of necrotic material and bacteria. A little later edema appeared, with hemorrhage into the interstitium. Two findings were of interest. In the first place, it was noted that whereas the arteries were almost in every case empty of blood the veins were considerably engorged, particularly toward the end of the period of ischemia (Fig. 3). Furthermore, the in-

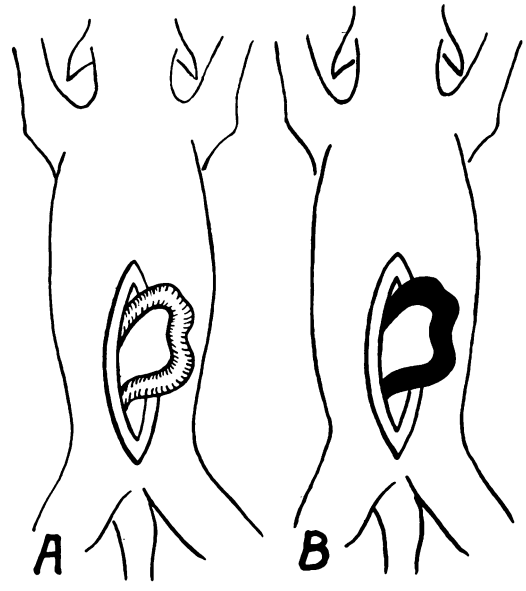

FIG. 2. The experimental set-up. A. Group 1. Control with simple exposure of the intestine and its blood supply. B. Group 2. Same procedure with sole addition of superior mesenteric artery occlusion.

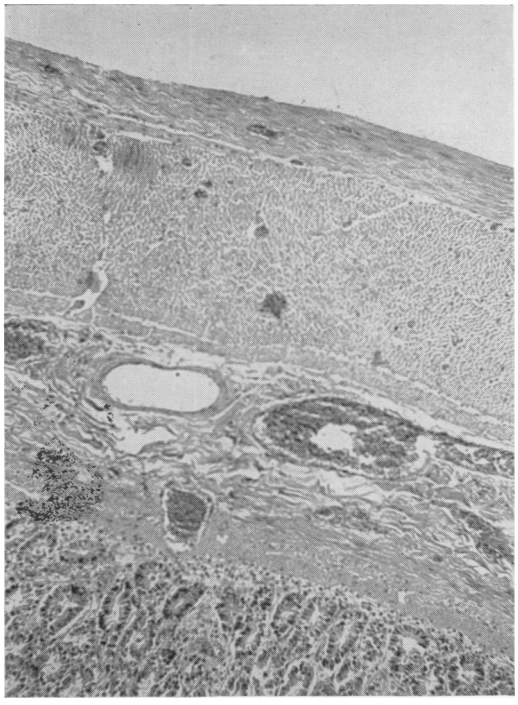

FIG. 3. Photomicrograph of arteries and veins.

flammatory response in terms of numbers of polymorphs, which was marked at two to three hours of occlusion, thereafter steadily diminished. This was probably because the available supply of inflammatory cells had been used up due to occlusion of the arterial inflow.

General Effects. Death occurred in all the dogs at a period between eight and 16 hours. There was usually a progressive decline in blood pressure after the first four hours, although in some animals the blood pressure remained elevated until a few hours before the end. The portal venous pressure was fairly constant throughout (Fig. 4). There was often a small fall immediately on tying the SMA, but thereafter, with occasional exceptions it remained steady from 5.0 to 15 mm. Hg.

The changes in blood volume were most striking. A contraction of blood volume of the order of 35 to 40 per cent, or 5.0 per cent per hour, occurred between the time of ligation of the SMA and death of the animal while the hematocrit rose steeply showing that in fact this loss was almost entirely of plasma (Table 2). This observation was not due simply to exclusion of the splanchnic circulation from the measured compartment. Had such been the case there would have been an immediate drop in blood volume on occlusion of the SMA, followed by a leveling off. In fact the blood volume diminished in a roughly linear

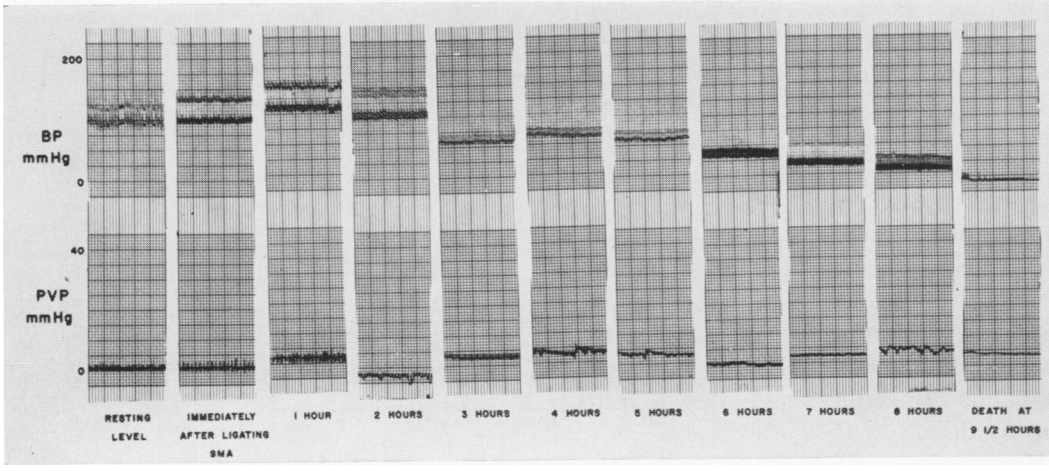

FIG. 4. Group 2 (Experiment 44). Representative experimental record. Following ligation of the SMA there is a progressive decline in arterial blood pressure and death occurs at 9½ hours. Portal venous pressure remains stable throughout.

TABLE 2. *Results in Group II Experiments*

Dog	Hours SMA Occlusion to Death	Anesthesia mg. Nembutal/ kg./hr.	% Change in Blood Volume	% Change in Red Cell Volume	% Change in Plasma Volume
6	7	5.6	−15	+29	−56
7	10	4.1	−23	+21	−36
8	10	3.8	−30	−13	−44
9	13	3.0	−40	−23	−59
10	9	5.4	−42	−13	−55
11A	8	6.2	−34	−18	−60
13	12	2.6	−36	+ 8	−67
16A	13	2.7	−38	−25	−56
18	9	3.3	−34	− 2	−68
23	10	3.3	−39	−13	−58
28	10	4.0	−40	−11	−59
33A	10	4.1	−30	−24	−38
34A	9	3.7	−21	0	−35
35A	10	4.1	−42	−27	−48
37A	11	3.7	Not obtained	—	—
44A	8	4.2	−49	−19	−60
45A	16	5.4	Not obtained	—	—
47A	14	4.3	−37	−15	−52
48A	11	4.2	Not obtained	—	—
51A	14	3.7	−24	+ 3	−38
Mean	11 ± 2.5	4.1 ± 0.2	−34 ± 2.0	−10 ± 3.4	−52 ± 2.3

fashion throughout the experimental period.

Discussion

Local Effects of Ischemia. Gross damage to the bowel occurs rapidly following occlusion of its blood supply, but it is possible that these changes do not progress as rapidly as do the physiological changes in the whole organism. This is in contrast to the situation which obtains when a short loop of bowel is involved, as in a strangulated hernia, or minor volvulus, where the subject's blood pressure and blood volume are well maintained and time is adequate for the bowel lesion to progress to complete necrosis and sloughing. The magnitude of the physiological change was demonstrated by Scott and Wangensteen in their strangulation experiments [38] to vary with the length of bowel involved. When, as in our preparations, the whole of the bowel is rendered ischemic, no perforations occur even in dogs that have died from the effects of the lesion. However, there is patchy discoloration, edema, and mucosal destruction, most marked at the ileocaecal region which is the site of maximum ischaemia.

Body Fluid Changes. Fluid loss is considerable, and appears to be borne almost entirely by the plasma compartment. This, of course, represents only a fraction of the total extracellular volume and it is probable that the amount of fluid sequestrated into the bowel or elsewhere is considerably larger than is measurable by blood volume studies. To elucidate further, it would be necessary to use crystalloidisotopes such as Br^{82} in order to measure the extent of the extracellular compartment. Red cells are also lost, which is the reason why arterial occlusion leads to a hemorrhagic infarct,[11] but the extent of the cellular loss is much less than that of plasma. The situation can be likened to that of a severe burn, and, insofar as it is justifiable to draw conclusions from the anesthetized

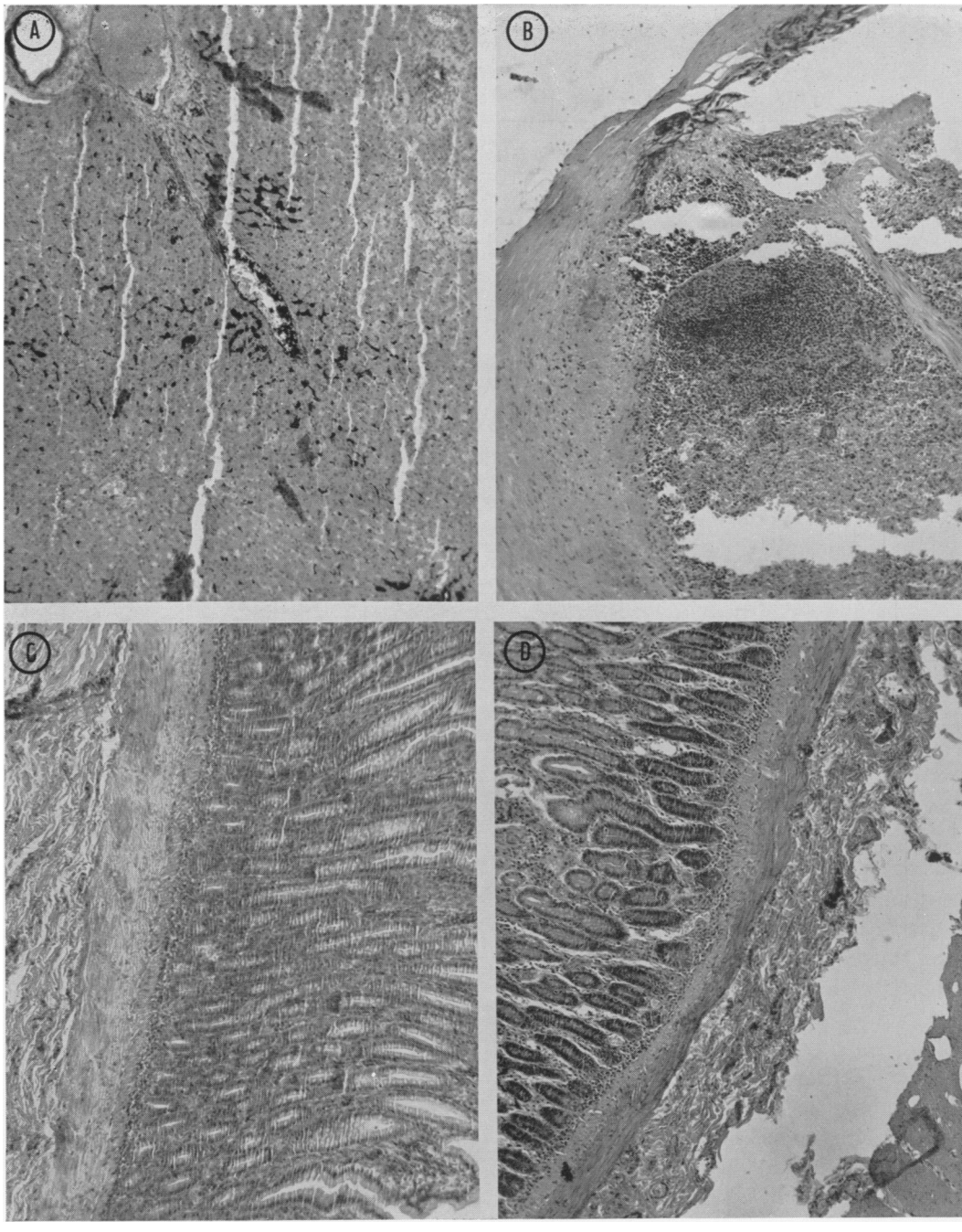

FIG. 5. India ink injections. A, B, and C are from a dog with SMA occlusion in whom India ink has been injected into the aorta. Ink has appeared in the liver (A) and the spleen (B) but not in the small bowel (C). In (D) ink has been injected into the portal vein of a similar animal and has appeared in the intestinal wall.

dog, the clinical lesson would appear to be that a human patient with a blocked SMA is in a state of hypovolemia and hemoconcentration and needs massive replacement.

The source of the hemorrhage and plasma loss is almost certainly from the veins. This was demonstrated in the classical experiments of Litten [28] who observed retrograde flow in the portal system following mesenteric artery occlusion. Furthermore, by observing the distribution of indigo injected into the aorta of a dog whose SMA had been tied, he demonstrated that there was practically no arterial collateral to the mid-gut. These observations have been borne out in the present study. In addition the histological appearances of venous engorgement, and arterial collapse suggests that hemorrhage is occurring from the veins. In three of our experiments, an injection of India ink was made into the aorta immediately after occlusion of the SMA, and sections taken from various organs a half hour and two hours later. In each case the particles were widely scattered throughout the tissues, but none was visible in the area of the infarcted bowel. In contrast injections of India ink into the portal vein produced massive extravasation of particles into the bowel (Fig. 5).

It should be emphasized that this retrograde plasma leakage from the mesenteric veins occurs in the absence of portal hypertension. A well known physiological response of dogs to trauma [16] and to endotoxin [21, 30] is pooling of blood in the portal system, with congestion of the mesenteric veins and a great rise in portal pressure. This has been termed *hepatic outflow obstruction* and is thought by some to be brought about by sphincteric contractions at the ostia of the hepatic vein.[5] However caused, the syndrome appears peculiar to the dog.[24] Although liver swelling was observed grossly on one or two occasions in the present work, there was no rise in portal pressure during the experimental period, and we feel justified in claiming that the fluid losses we recorded were due to bowel ischemia and not to hepatic outflow obstruction. There is a portal pressure, albeit a normal one, and the portal system is still receiving an inflow of blood from the celiac and inferior mesenteric routes. This pressure exerted over the enormous area of the intestinal mucosa [46] is more than adequate to account for the plasma leakage observed.

Summary

The effects of devascularization of the bowel have been studied by occluding the SMA in 20 anaesthetized dogs and observing them until death. A control group of six dogs underwent an identical operative procedure except that the SMA was not occluded.

Under the conditions of the experiment, SMA ligation was fatal in eight to 16 hours, and caused progressive destruction of bowel from the mucosa outwards, but no perforations.

During the period of arterial occlusion the blood volume contracted at the rate of 5 per cent per hour as compared with the control group where the rate was 1 per cent per hour. This loss, which was largely of plasma, seemed to originate from backflow in the portal system, although no rise in portal pressure was observed.

It is suggested that hemoconcentration is one of the lethal factors in mesenteric arterial occlusion, and that massive plasma replacement is important in the preoperative treatment.

References

For references see following article "Causes of Death in Mesenteric Arterial Occlusion: II. Observations on Revascularization of the Ischemic Bowel."