THE EFFECT OF CHEMOTHERAPY ON THE ILEUM SUBJECTED TO VASCULAR INJURY

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THE EXTENT to which intestinal flora aggravate the damage to the intestine inflicted by vascular injury has not been clearly demonstrated. The recent introduction of potent intestinal antiseptics,[1-7] succinylsulfathiazole and pthalysulfathiazole in particular, has made it possible to undertake such a study.

In a preliminary study Sarnoff and Poth[8] found that succinylsulfathiazole conferred a protective effect upon a 50-cm. segment of ileum with occluded venous return, by preventing perforation and permitting recovery of bowel integrity. In this report data is presented demonstrating the usefulness of chemotherapy in experimental venous obstruction and in strangulation obstruction of the ileum of the dog.

METHOD

In the morphinized dog under ether anesthesia a 50-cm. loop of terminal ileum is exposed through an abdominal incision, with aseptic precautions. The accompanying mesentery is freed from adjacent mesentery by incision along its entire length from bowel to root of mesentery without injury to the vessels serving the rest of the intestine. All the veins in the isolated mesentery, which can be identified, are divided between ligatures. The division of the mesentery adjacent to the ends of the loop is carried to intestinal serosa, so that no identifiable vascular communication with adjacent loops remains. The incision is closed (Fig. 1).

One series of dogs, Group I A, so treated, received no preoperative chemotherapy. Another, Group I B, received preoperative chemotherapy as follows: Of 16 dogs, seven received 0.5 Gm./Kg. of succinylsulfathiazole daily in their food or by gavage,* and nine received 1.0 Gm./Kg. of succinylsulfathiazole daily by gavage. Water was allowed postoperatively but food was withheld for 48 hours. All blood specimens were taken from the femoral artery. Hematocrit, plasma volume and plasma protein concentration were obtained immediately prior to venous occlusion and again 24 hours later.

The plasma volume was determined by the methods of Gibson and Evelyn,[9] and of Gregerson and Gibson,[10] using the photo-electric colorimeter. Plasma protein concentration was determined from the plasma specific gravity (pycnometry method of Phillips, *et al.*[11]), and the conversion formula of Weech, *et al.*[12]

* Three of these also received the drug in the same dose by gavage or in their food for two weeks postoperatively.

Autopsy was performed immediately after death or, in the case of surviving animals, after they were sacrificed at varying intervals postoperatively. Evidence was obtained on the source of collateral venous supply in the surviving animals and sections were taken for microscopic study.

When the venous return of a loop of ileum is treated as described, the following changes are observed. After five minutes cyanosis is obvious,

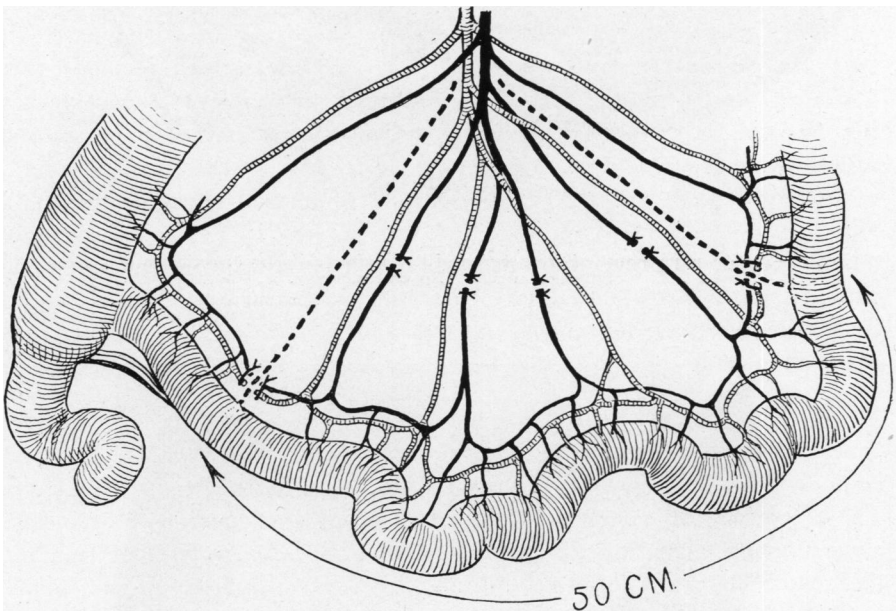

FIG. 1.—Schematic diagram indicating procedure for occlusion of venous return of ileum.

and after 15 minutes arterial pulsations disappear and the distended veins have pressures approaching the arterial diastolic pressure. After two hours the loop is deep purple, swollen and juicy, and the mesentery shows extravasation of blood as far proximally as the ligatures on the veins. The volume flow through such a loop approaches zero since, if exteriorized, the temperature of the loop approaches that of the environment, while adjacent loops are near body temperature.

In a second group of dogs, the foregoing procedure was repeated but the chemotherapy applied was as follows: Nine (Group II A) received succinylsulfathiazole locally (1.0 Gm./Kg.), introduced at the time of operation by needle and syringe into the lumen just proximal to the loop and gently distributed in the area. No other chemotherapy was administered. In eight others, Group II B, the only chemotherapy administered was sodium sulfathiazole intravenously (0.1 Gm./Kg.) immediately postoperatively and 0.05 Gm./Kg. twice daily for one to two days thereafter.

In a third group (III) of 17 dogs, under evipal anesthesia, strangulation obstruction of a 35-cm. loop of terminal ileum, exposed under aseptic precautions through an abdominal incision, was produced by tying a rubber

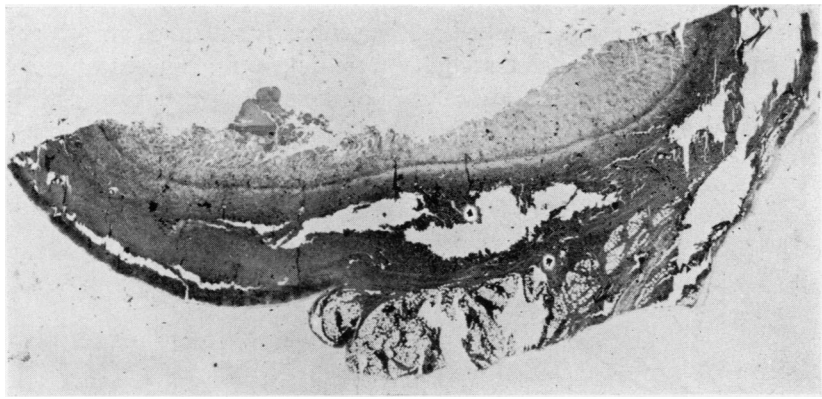

FIG. 2.—A. Gross appearance of cross-section of ileum after 24 hours of occlusion of venous return of ileum. No chemotherapy.

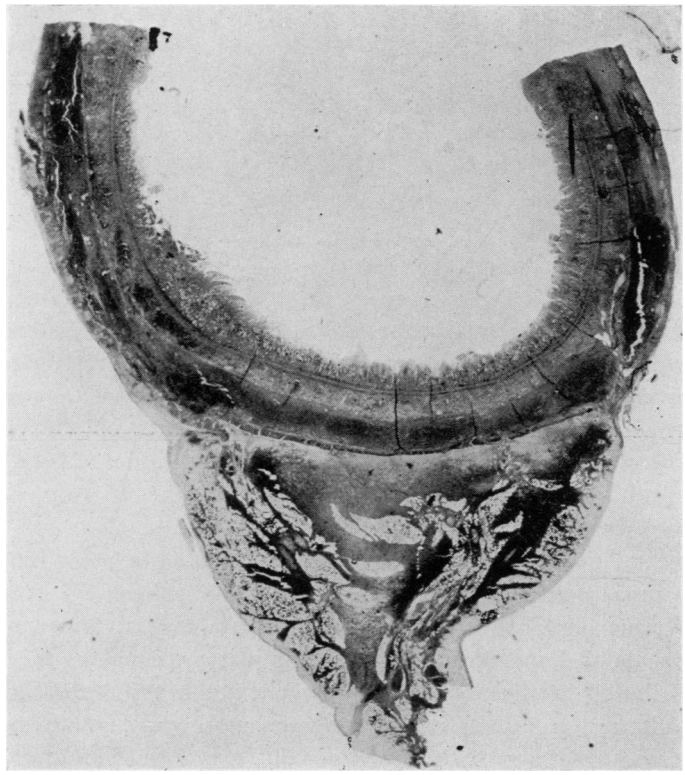

FIG. 2.—B. Gross appearance of cross-section of ileum after 24 hours of occlusion of venous return of ileum. Succinylsulfathiazole by mouth for ten days prior of venous occlusion.

band around the base of the loop so as to produce venous obstruction, as evidenced by cyanosis, without occluding arterial flow. Twelve to fourteen hours later the incision was opened, under light ether anesthesia, and the rubber band released. Many of the dogs, of course, showed evidence of shock. All had copious bloody peritoneal fluid. Nine dogs were treated immediately thereafter by an infusion of 5%-7% gelatin, in a volume equivalent to 60% of the dog's calculated blood volume. The remainder were treated likewise, but they also received chemotherapy as follows: One Gm./Kg. of succinylsulfathiazole by syringe and needle into the loop proximal to the released loop and the same amount by mouth daily for two days thereafter; in addition sodium sulfathiazole 0.1 Gm./Kg. was given in the gelatin infusion and 0.05 Gm./Kg. intravenously twice daily for two days thereafter.

TABLE I

SURVIVAL TIME FOLLOWING VENOUS OCCLUSION OF 50-CM. LOOP OF TERMINAL ILEUM

Control Group			Treated Group (see text)		
Dog No.	Survival Time in Hours	Sacrificed Days Postoper.	Dog No.	Survival Time in Hours	Sacrificed Days Postoper.
1	47	..	1	..	15
2	..	23	2	..	22
3	40	..	3	42	..
4	..	13	4	..	30
5	42	..	5	..	60
6	42	..	6	..	3
7	36	..	7	..	10
8	39	..	8	43	..
9	84	..	9	..	6
10	..	10	10	24	..
11	20	..	11	..	51
12	38	..	12	..	51
13	6.5 days	..	13	..	51
14	35	..	14	..	30
15	45	..	15	48	..
16	37	..	16	..	30
17	37	..			
18	35	..			
19	12	..			
20	34	..			
21	30	..			
22	20	..			
23	40	..			
	Average wt. = 9.5 Kg.	Mortality 87%		Average wt. = 9.3 Kg.	Mortality 25%

RESULTS

Group I (Table I): Venous Occlusion With Preoperative Peroral Chemotherapy.

In this group of dogs, with simple venous occlusion of a loop of ileum, 23 untreated control dogs (Group I A) showed a mortality of 87 per cent, death occurring in all but two of these dogs in less than 47 hours. The group of 16 dogs receiving chemotherapy (Group I B), showed a mortality of 25 per cent within 48 hours. The remainder survived, and were sacrificed at intervals varying from 3-60 days postoperatively. The surviving dogs lost weight, but appeared reasonably well and took food from the second postoperative day.

In Table II data on changes during the first 24 hours postoperatively in blood and plasma volume, hematocrit and plasma proteins are listed. It is clear that no significant alterations occurred in these categories in both the treated and untreated groups of dogs. Therefore, when death occurred, it could not be attributed to shock resulting from blood loss arising from the vascular damage. The autopsy findings demonstrate that in the untreated group (I A) death was due to partial or complete dissolution of the loop, with resulting peritonitis. The four treated dogs which died differed from the untreated dogs in that no perforation was present. Nevertheless two showed gross evidence of peritonitis.

TABLE II

BLOOD CHANGES 24 HOURS AFTER VENOUS OCCLUSION OF ILEAL LOOP

Dog No.	Blood Volume % Change	Plasma Volume % Change	Hematocrit % Change	Plasma Proteins % Change	Survival Time Hrs.
Control					
8	−11.8	+ 6.4	− 9.5	−10.0	39
9	−20.5	−22.8	− 2.3	−15.0	84
10	− 6.0	− 3.0	− 1.8	−13.9	s‡
12	−23.6	−31.7	+ 5.2	+ 3.0	38
23	− 4.8	−10.5	+ 3.0	0	40
—	—	—	—	—	—
Average	−13.3	−12.3	— 1.1	−17.2	—
Treated					
5	− 4.8	−12.2	+ 4.0	− 8.5	s‡
6	−12.8	0	− 6.5	− 8.0	s‡
7	−10.5	− 7.0	− 2.1	− 7.8	s‡
8	−27.7	−17.5	− 8.4	−11.1	43
9	−18.5	−14.4	− 2.8	− 8.0	s‡
1†	−29.5	−26.7	− 1.4	0	s‡
2†	−25.2	−23.4	− 2.5	− 7.2	s‡
3†	−11.3	+ 3.0	− 7.0	−16.7	42
4†	−18.7	−21.7	+ 1.5	− 1.3	s‡
—	—	—	—	—	—
Average	−14.9*	−10.2	− 3.2	− 8.8	

‡s = Survived until sacrificed.

† Preoperative blood volume estimated as 10% of the dog's weight in kilograms. Preoperative plasma volume calculated from preoperative blood volume and hematocrit.

* Calculated for Dogs 5–9, inclusive.

Examination of the loops from surviving animals showed that venous collateral supply to the damaged segment was provided from three sources:

(a). The omentum, which was usually found adherent to the damaged segment.

(b). The mesentery of the damaged loop showed numerous functioning venous channels, evidently submacroscopic vessels, not detectable in the mesentery at the time of venous occlusion, which had become dilated.

(c) Adherent neighboring loops of bowel which oozed freely when separated. Gross inspection of the damaged loops at the time of sacrifice showed slight mottling, a somewhat larger luminal diameter, less active peristalsis than adjacent loops. The mucous membrane was intact and the mesentery showed some fibrosis.

Sections for microscopic study were taken at varying intervals after

operation in the treated group. Examination of these sections yielded the following information:

Twenty-four hours after operation: Ulcerative necrosis of the mucosa with polymorphonuclear infiltration. Tissue from submucosa to serosa hemorrhagic but relatively intact. Process of repair evident in deep portion of mucosa and in muscularis. Lymphatics distended. Arteries contracted. No bacteria seen.

Three days after operation: Massive hemorrhage into the mesentery, the entire muscularis and between mucosal glands and mucularis mucosae. Superficial portion of the villi edematous. In places superficial necrosis of the mucosa and replacement with granulation tissue. Fibrin deposits on the serosa. Almost complete absence of thrombosis.

Six days after operation: Hemorrhage into mesentery and the muscularis. Fibroblasts and lymphocytic infiltration of the mesentery and submucosa. The venules and capillaries of the submucosa distended. Extensive slough of mucosa with granulation tissue replacement. Fibrin deposits on thickened serosa. No evidence of thrombosis.

Ten days after operation: Fibrosis, and lymphocytic infiltration of the mesentery, thickening and lymphocytic infiltration of serosa. The mucosa, submucosa and muscularis are not remarkable.

Twenty-two days after operation: Lymphocytic infiltration of mesentery. Occasional organized mural thrombus in mesenteric veins. Intestine otherwise normal.

Thirty days after operation: Except for some thickening of the serosa at the site of adhesions and some fibrosis in the mesentery, tissue is indistinguishable from normal bowel.

TABLE III

EFFECT OF CHEMOTHERAPY ON MORTALITY AND PERFORATION FOLLOWING VENOUS OCCLUSION OF A 50-CM. LOOP OF ILEUM

	Group	No. of Dogs*	Mortality Rate	Perforation Rate in Animals that Died
I A	No chemotherapy	23	87%	75%
II A	Intraluminal chemotherapy at time of venous occlusion (succinylsulfathiazole)	9	66%	0
II B	Intravenous chemotherapy for 24–48 hours following venous occlusion (sodium sulfathiazole)	8	50%	0
I B	Preoperative chemotherapy (succinylsulfathiazole)	16	25%	0

* Average weight in different series: 9.3 – 10.4 Kg.

Group II: Venous Occlusion With Simultaneous Chemotherapy.

(A) *Local Instillation of Succinylsulfathiazole:* Of nine dogs in this group (II A, Table III) six succumbed in under 48 hours. There were no perforations, however, in any of these six animals, although in two the wall was quite thin and gross peritonitis was present. The remaining three survived, and showed the gross findings already described for survivors in Group I B.

(B) *Intravenous Sodium Sulfathiazole:* Of eight dogs (Group II B, Table III), which received intravenous therapy as described, four died, but, as in the locally treated group, no perforations were present. The remaining four survived and showed, when sacrificed, the usual findings seen in surviving animals.

Group III: Strangulation Obstruction.

Of nine dogs with strangulation obstruction (released after 12-14 hours) which received an adequate volume of a blood substitute (gelatin) but no chemotherapy, none survived, death occurring from gangrene of the loop and diffuse peritonitis. Survival was less than 20 hours after release of the strangulation in all but two, which survived six days. In the latter two, autopsy showed peritonitis but no obvious perforations; the remainder showed perforations.

Of a similar series of nine dogs, which received chemotherapy as described, three survived and six died. Two of the six which died showed perforations and peritonitis at autopsy; a third showed peritonitis too but no perforation, the loop having apparently recovered; two more showed no perforation but gangrene was present, while the sixth showed neither, and died of bilateral pneumonia. Of the nine treated dogs, therefore, the chemotherapy prevented death in three, perforations in seven and peritonitis in five. The survival time in the five which died was 2, 4, 4, 2 and 5 days as compared to an average of 20 hours for the dogs not receiving sulfonamides. The three surviving dogs showed a remarkable degree of recovery of the loop. All layers of the intestine showed a somewhat dusky, deep brownish-red discoloration; there was slight edema of the mucosa, which, however, was intact throughout. The mesentery was slightly cloudy and thickened, and the serosal surface of the intestine showed patches of fibrin in addition to easily separated adhesions between adjacent surfaces. The only evidence of ileus was very slight dilatation of the proximal intestine in a few of the dogs. The vascular supply to the loop was apparently normal by gross inspection.

In view of the fact that the loop in 87 per cent of the dogs not receiving sulfonamides showed partial to complete necrosis, the protective effect of chemotherapy is obvious.

DISCUSSION.—Numerous quantitative studies[13, 14] have demonstrated that severe vascular damage to the intestine can be rapidly fatal from loss of blood volume alone. For the clinical surgeon, the therapeutic problem, therefore, is made somewhat less difficult by the provision of blood volume replacement. But the primary lethal factor of secondary infection through a permeable bowel wall remains, so that resection not only of devitalized but of questionably viable loops constitutes a cardinal principle in the surgical treatment of strangulation and of mesenteric thrombosis.

The remarkable feature of sulfonamide action in the experiments de-

scribed is their apparent ability to forestall complete necrosis. Presumably, they do so by suppressing the thrombotic action of tissue juices or bacterial products in an area of threatened devitalization and so allow time for effective collateral supply to become established. The microscopic evidence in surviving animals is that remarkably little thrombosis is evident in the obstructed veins, whereas in the one microscopic section of an early stage in the rapid disintegration of a loop in an untreated dog, thrombosis of the veins was widespread.

There is no evidence to assume that the protective effect of the sulfonamides in these experiments is achieved by any other mechanism, *e.g.*, one which might directly or indirectly prevent a substantial fall in blood volume. No significant fall in blood or plasma volume was observed in treated or untreated dogs with simple venous occlusion, while in strangulation obstruction the loss in blood volume was adequately replaced in the treated and untreated series. Advance chemotherapy might have provided for more protection than was obtained in these strangulation experiments. But while such data should be secured, they have little practical bearing on the clinical problem of strangulation, since it is not a condition that can be anticipated.

The foregoing experiments suggest the potentialities of sufonamide therapy. The maximal effect possible with the relatively insoluble sulfonamides can be secured in elective bowel surgery. Since they require at least several days to produce a substantial bacterial depopulation of the intestine, their administration would not be appropriate in acute conditions in which vascular damage is already present, unless peritonitis may be anticipated; *e.g.*, in incomplete, but diffuse, mesenteric thrombosis, in which viability is problematical and in which resection is not advisable because of too extensive involvement of the intestine. The soluble sulfonamides have a certain limited usefulness at, and subsequent to, the time of operation for a strangulation, which is released but not resected, as the experiments of Groups II and III indicate, since perforation is frequently avoided by their use. Their administration in conjunction with the local instillation of the less soluble sulfonamides may be of not inconsiderable value in elective bowel surgery. For if a point in a suture line becomes partially devitalized because of a technical error or an unavoidable postoperative complication, the threat of peritonitis may be forestalled if bacterial permeation is kept to a minimum by these agents.

CONCLUSIONS

1. The lethal effect of the simple vascular occlusion produced in these experiments is not attributable to a crucial fall in blood volume, but to peritonitis with, or without, gross perforation.

2. The protective effect of succinylsulfathiazole is maximal when applied well in advance of production of the vascular injury, while chemotherapy at

the time of, or subsequent to, the production of the vascular injury is also effective but to a distinctly lesser extent than advance chemotherapy.

3. The data suggests the probable usefulness of chemotherapy in corresponding clinical states in man.

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