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The Physiological Response of the Small Bowel of the Dog to Ischemia Including Prolonged *in Vitro* Preservation of the Bowel with Successful Replacement and Survival *

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"I have finally kum tu the konklusion that a good reliable sett ov bowels is worth more tu a man than enny quantity ov brains."—Josh Billings

NEW surgical technics and ideas for treating conditions involving the bowel and/or its vasculature have been slow to evolve. This apparently is because of misgivings that anastomoses involving these vessels, especially the vein, will not remain open. In addition, there is insufficient knowledge about the ability of the small bowel to survive complete or partial occlusion of its vasculature while conditions affecting the superior mesenteric vessels are dealt with. Finally, there are no studies available concerning the fate of the small bowel after complete severance of its connections with the central nervous system and after division of all its lymphatic drainage, events which would necessarily follow any extensive surgery in and about the superior mesenteric vessels, nor is the fate of bowel homografts known. If these and related questions could first be answered in the experimental laboratory, a more effective start could perhaps be made in treating some of the formidable problems affecting the bowel and its vasculature.

Methods and Procedures

In carrying out studies on the effect of varying degrees of ischemia on the small bowel of the dog, we made serial determinations of the plasma volume, hematocrit and plasma hemoglobin before, during, and following experiments as well as making gross and microscopic observations on the bowel itself. We had previously found in hemorrhagic [4, 5] and Gram-negative endotoxic [6, 7] shock experiments that these three plasma measurements were sensitive indicators of intestinal ischemia and allowed us to predict the ultimate fate of the bowel and the dog before pathognomonic changes had occurred.

The plasma volumes were determined by a micromethod using T-1824, the injected dye being weighed and the plasma ana-

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lyzed in microcuvettes in the Beckman DU Spectrophotometer.[8] This method utilizing small amounts of the dye, 0.1 and 0.2 ml., allowed us to make accurate serial measurements of plasma volume. Plasma hemoglobins were determined using the method of Flink and Watson.[1] Hematocrit determinations were made in Wintrobe tubes after spinning for 3000 r.p.m. for 30 minutes.

Determination of the Ability of the Bowel to Withstand Partial or Circulatory Arrest at Normal Temperatures

Group I. Occlusion of the Superior Mesenteric Artery Only for three to 3.5 Hours: Ten adult mongrel dogs of either sex and weighing 12 to 20 Kg. were sedated with morphine sulfate, 2 mg./Kg., intramuscularly after fasting for 18 hours. They were then placed on an operating table and the hematocrit, plasma volume and plasma hemoglobin determined after the femoral artery and vein were cannulated. Following this, they were lightly anesthetized with pentobarbital and the abdominal cavity entered through the midline. A Potts' bulldog clamp was placed on the superior mesenteric artery near its origin from the aorta and proximal to all branches. The collateral blood supply to the small bowel was not disturbed. The abdomen was then closed and the animals observed. At 90- to 120-minute intervals following clamping of the superior mesenteric artery, the hematocrit, plasma hemoglobin and plasma volume were again determined.

In three hours after clamping the superior mesenteric artery in five of the dogs and in 3.5 hours in the other five dogs, the abdominal cavity was re-entered and the Potts' clamp removed from the superior mesenteric artery and the abdomen again closed and the animals allowed to awaken. Following unclamping of the superior mesenteric artery, plasma volumes, hematocrits and plasma hemoglobins were again made at 1.5 to two-hour intervals for periods up to eight hours.

Group II. Occlusion of the Superior Mesenteric Artery for Five Hours: In another group of ten dogs in which the superior mesenteric artery was clamped in the manner described above, the clamp was not released until five hours had elapsed. These dogs were followed in the manner also described above.

Group III. Effect of Intestinal Antibiotics on Superior Mesenteric Arterial Occlusion: Five dogs were given 6 Gm. of sulfasuxidine, 4 Gm. of neomycin and 2 ounces of milk of magnesia daily for five days. All medications were given in large gelatin veterinary capsules which were placed by hand in the esophagus of the dog to make sure each dose was received. With this regimen, we had previously found that the dog's stool was sterile on the sixth day.[3] On the sixth day, these dogs were prepared for an experiment exactly as described above and the superior mesenteric artery occluded near its origin for five hours. Following release of the occlusion, these dogs were followed as described above.

Groups IV and V. Occlusion of the Superior Mesenteric Artery and All Collaterals to the Small Bowel: The 20 adult mongrel dogs in these groups were prepared as described above and the abdominal cavity opened and the superior mesenteric artery occluded. In addition, all collaterals to the small bowel from the celiac axis and the inferior mesenteric artery were also occluded in the following manner. At a point on the duodenum just distal to the pancreas, the duodenal mesentery was divided between clamps down to the superior mesenteric vein. Similarly at a point in the ileal mesentery just proximal to the ileocecal valve, the mesentery was also divided between clamps down to the superior mesenteric vessels. A small communicating artery along the anti-mesenteric border of the terminal ileum joining the inferior mesenteric arterial system with the superior

mesenteric system was also divided and ligated. Finally, to occlude all intramural collateral circulation, noncrushing clamps were placed across the proximal duodenum and the terminal ileum at the points where the mesentery had been divided (Fig. 1).

In 10 of the above dogs in which all collateral arterial blood supply to the small bowel was divided, the superior mesenteric artery was clamped for three hours in five dogs and in 3.5 hours in the five other dogs (Group IV). The peritoneal cavity was closed during the period of occlusion as in Groups I, II, and III. In the ten other dogs in which all collaterals to the small bowel were divided, the superior mesenteric artery was clamped for only two hours, Group V, and the peritoneal cavity left open which allowed the bowel to cool to room temperature, 25 to 28° C. All dogs in Groups IV and V were followed in the manner described above after the release of the superior mesenteric arterial occlusion.

Group VI. Effect of Hypothermia on Total Circulatory Occlusion to the Small Bowel: Having learned the safe period of partial or total occlusion of the arterial circulation of the small bowel at normal temperatures, we proceeded to the next phase of our investigation. Many organ systems are protected at least to some degree against the deleterious effects of circulatory arrest or ischemia by lowering their temperature.[2, 12, 13, 16] In the present study, we wished to see the effect of hypothermia on the ischemic bowel alone without adding the variable of general body hypothermia. To do this the following procedure was done.

The dogs were prepared as described above and the abdominal cavity entered. The superior mesenteric vessels were carefully isolated but not clamped. All collateral blood supply to the small bowel was divided in the manner described above, leaving the small bowel from the proximal duodenum to the cecum supplied only by the superior mesenteric vessels. These vessels were then both clamped with Potts' bulldog clamps and the vessels cannulated just distal to the clamps with #14 F. plastic catheters. The arterial catheter was then attached to tubing from a Sigmamotor pump and normal saline at 5–10° C. was pumped into the superior mesenteric arterial system at a rate of 100 to 150 ml./minute. The saline was allowed to drain freely from the superior mesenteric vein catheter into an open beaker and was not reused (Fig. 2). In a few minutes the superior mesenteric system was washed almost completely free of blood and the temperature of the bowel had fallen to below 10° C.

Initially, in pilot experiments, we continued the saline perfusion for the entire period of the superior mesenteric occlusion. We also initially bubbled oxygen into the cold saline before perfusing it into the superior mesenteric artery since a signifi-

OCCLUSION OF SUPERIOR MESENTERIC VESSELS AND ALL COLLATERAL BLOOD SUPPLY TO THE SMALL BOWEL

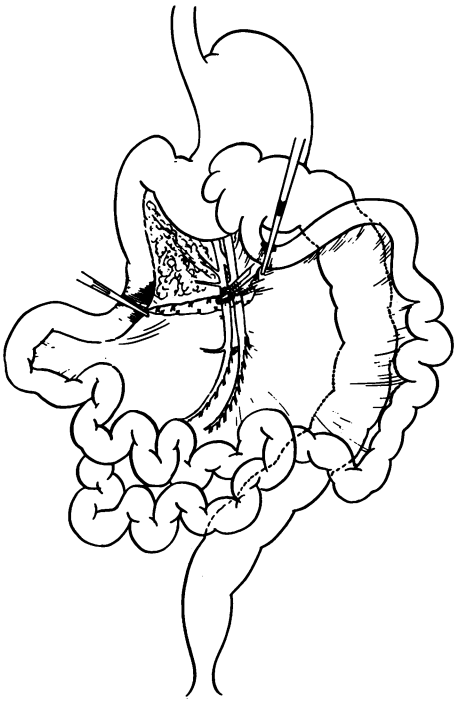

FIG. 1. Interruption of all small bowel circulation.

IN VIVO COOLING OF THE SMALL BOWEL

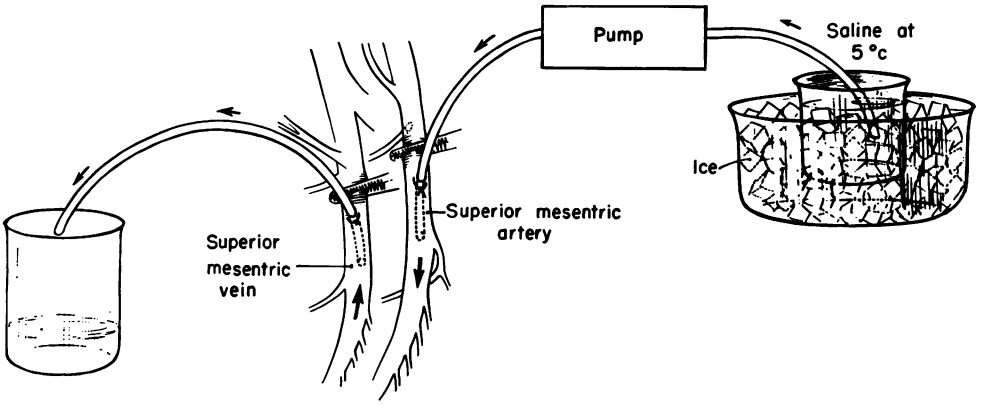

FIG. 2. *In vivo* cooling of the small bowel.

cant amount of oxygen can be held in solution by liquids at this temperature.[2] But, because of edema of the bowel attendant on prolonged saline perfusion we soon learned to stop perfusion as soon as the temperature of the bowel dropped below 10° C. For once this temperature had been reached, there was little or no spontaneous rewarming of the bowel itself. Moreover, subsequent results showed that the bowel did not require oxygen to survive at this low temperature. Heat lamps and heating pads were used during these experiments to keep the general body temperature of the dogs above 35° C.

At the end of a five-hour period, the catheters were removed from the superior mesenteric vessels and the cannulation sites in these vessels carefully repaired with 6-0 arterial silk. The noncrushing clamps were removed from the duodenum and the terminal ileum followed by the removal of the Potts' clamps from the superior mesenteric artery and vein. To prevent precipitous drops in the general body temperature of the dog as circulation was once more resumed through the cold bowel, the peritoneal cavity was flooded with warm saline at 40–42° C. for 15 to 20 minutes following resumption of the superior mesenteric circulation. This measure effectively prevented any change in the body temperature following reopening of the superior mesenteric vessels. The abdominal cavity was then closed and the animals followed as described above.

In all experiments sterile technic was used and 1 million units of penicillin and 1 Gm. of streptomycin were left in the peritoneal cavity before closing it. In all experiments nonsurviving dogs were autopsied and visceral organs examined and representative specimens saved for microscopic section. All survivors were also sacrificed and autopsied at periods varying from three days to three weeks following an experiment.

Results of In Vivo Experiments

In Table 1 is a summary of results in the experiments just described. Most dogs tolerated clamping of the superior mesenteric artery for three or 3.5 hours, Group I, if all collateral circulation to the bowel was left undisturbed. Of the three dogs dying in this group, two had occlusion of the superior mesenteric artery for 3.5 hours and the other occlusion for three hours. When the period of superior mesenteric occlusion was extended to five hours, Group II, almost all the dogs died from gangrenous small bowel in 36 hours or less despite the

TABLE 1. *In Vivo Experiments**

Group	No. Dogs	Type Occlusion	Duration of Occlusion (hours)	Maximum Values Within 8 Hours Following Release of Occlusion: Plasma Volume Loss (%)	Hematocrit Increase (%)	Plasma Hgb. Increase (mg. %)	No. of Survivors (48 hours or more)
I	10	S.M.A. only	3–3.5	24.9 ±4.3	25.1 ±6.93	25.2 ±9.7	7
II	10	S.M.A. only	5	44.9 ±12	30.9 ±6.9	108 ±49	1
III	5	S.M.A. only 5 days pre-treatment. Neomycin-sulfasuxadine	5	34.7 ±11	27.4 ±7.4	97.2 ±31.6	0
IV	10	S.M.A. and all collaterals	3–3.5	37.7 ±8.8	30.1 ±5.1	75 ±20.2	1
V	10	S.M.A. and all** collaterals	2	16.3 ±7.9	16.4 ±7.7	20.4 ±10.8	8
VI	10	S.M.A. and all collaterals. Intestinal hypothermia to 5° C.	5	26.5 ±9.9	28.1 ±8.7	18.6 ±8.9	9

* Mean values with standard deviations.
** Peritoneal cavity left open and small bowel allowed to cool to room temperature, 25–28° C.

presence of the collateral circulation. It is interesting that sterilization of the bowel contents prior to an experiment did not increase the number of survivors from this lethal five-hour period of superior mesenteric arterial occlusion, Group III.

In contrast to the findings when the superior mesenteric artery alone was occluded for three or 3.5 hours were the results of occlusion of all collateral arterial circulation to the small bowel in addition to a three- or 3.5-hour occlusion of the superior mesenteric artery, Group IV. All but one of these dogs died within 36 hours of gangrenous small bowel.

The majority of the dogs in Group V survived a two-hour occlusion of the superior mesenteric artery along with complete occlusion of all collateral blood supply. Allowing the bowel to cool to room temperature, 25 to 28° C., no doubt contributed to the favorable results obtained in this group. However, if the bowel was cooled to below 10° C., Group VI, then complete interruption of all arterial circulation to the bowel for five hours was well tolerated by all but one dog. It should be noted in this hypothermia group, VI, that several of the dogs surviving the five-hour period of occlusion died from three to seven days following an experiment. Death was usually due to pneumonia and in every case the bowel was normal at autopsy.

These results in Group VI clearly show that profound hypothermia of the bowel gives significant protection against total circulatory arrest of the bowel. Moreover, we are not yet sure that five hours is the upper limit of safe circulatory arrest of the cooled bowel, for experiments presently in prog-

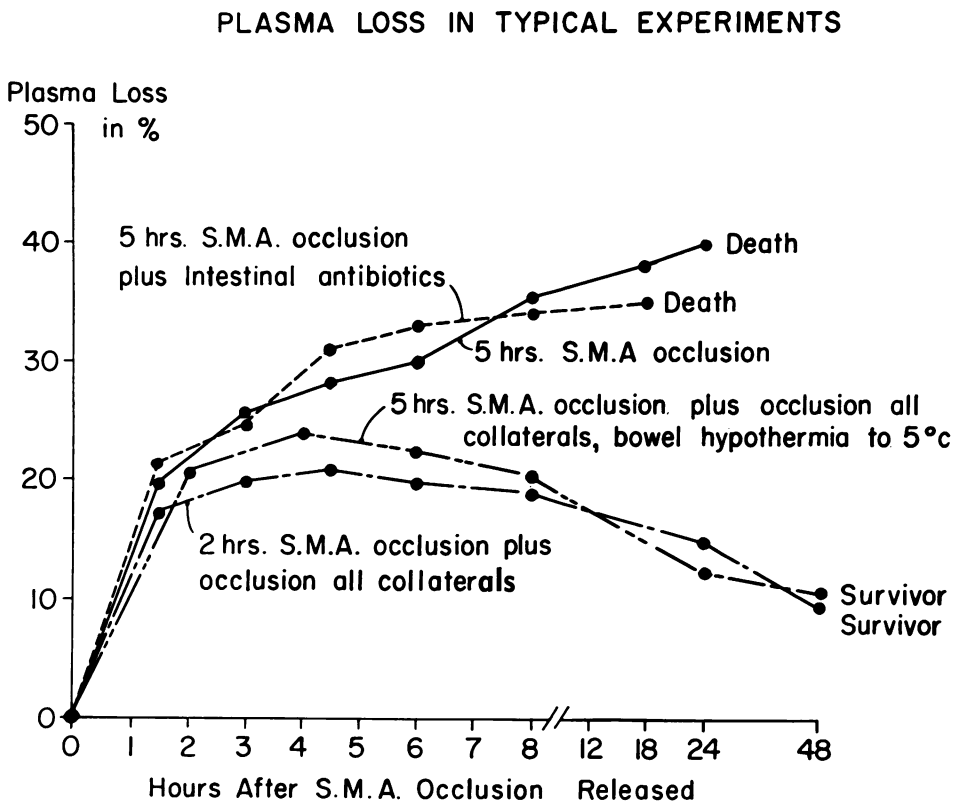

FIG. 3. Plasma volume and hematocrit findings in typical experiments.

ress suggest that circulatory arrest may be tolerable for periods of seven hours or more when the bowel is at 5° C.

Plasma Measurements

The plasma volume and hematocrit measurements show that intestinal ischemia is associated with significant plasma losses into the damaged bowel. They also show that, generally, the extent of the plasma loss and the hematocrit increase is directly proportional to the severity of the intestinal ischemia or to the period of total or partial circulatory occlusion unless the bowel is protected by lowering its temperature. The plasma volume losses in the dogs having lethal periods of intestinal ischemia, Groups II, III, and IV, were significantly higher than in those dogs having sublethal periods of intestinal ischemia, Groups I, V, and VI. Actually the volume losses in dogs dying of gangrenous bowel were even higher than those shown in the first eight hours after release of the superior mesenteric arterial occlusion because losses continued to occur into the necrotic bowel until death occurred, Figure 3 compares plasma volume and hematocrit findings in typical experiments of lethal and nonlethal arterial occlusion of the bowel in which the animals were followed for periods up to 24 hours. In some other dogs suffering fatal superior mesenteric occlusions, we gave liberal amounts of saline and blood some hours after release of the occlusion but this was of only temporary benefit.

Plasma hemoglobin levels invariably rose to high levels in those dogs eventually dying of gangrenous bowel, while levels in

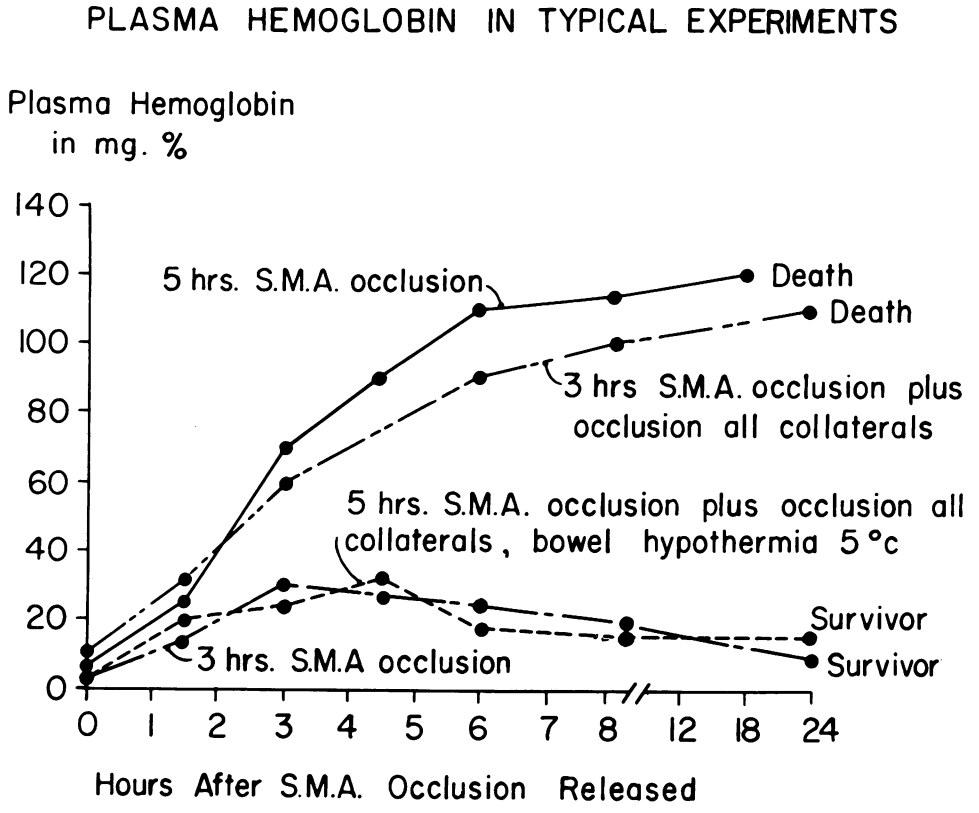

FIG. 4. Plasma hemoglobin findings in typical experiments.

dogs in nonfatal experiments increased only moderately in the first eight hours after occlusion and then fell toward normal by the day following an experiment (Fig. 4).

The results of these *in vivo* experiments defining the safe periods of intestinal ischemia under the designated conditions formed the basis for the second half of this study in which we removed the small bowel from the peritoneal cavity and later returned it, after varying periods *in vitro*, to the peritoneal cavity as an autograft or as a homograft.

In Vitro Studies of the Small Bowel with Later Replacement

In working out methods to isolate the superior mesenteric vessels and interrupt collateral circulation to the small bowel, we saw that it would be possible to take out all the small bowel preserving its vasculature, save for the first few centimeters of duodenum the arterial supply of which came from the celiac axis. This would allow a single arterial and venous anastomosis to re-establish the blood supply to this resected small bowel when desired.

In Figure 5 is pictured the anatomy of the superior mesenteric vessels in the dog. The common colic artery supplying the proximal colon is the first branch of the superior mesenteric artery, arising from its anterior surface about 15 mm. from the origin from the aorta. Immediately distal to this branch the inferior pancreaticoduodenal branch arises from the right posterior surface. There is usually then about 8 to 10 mm. of artery in which no branches originate and this is the area where the artery was divided and later reanastomosed. In some of the dogs the inferior pancreaticoduodenal artery came off 5 to 8 mm. distal

ANATOMY OF SUPERIOR MESENTERIC VESSELS

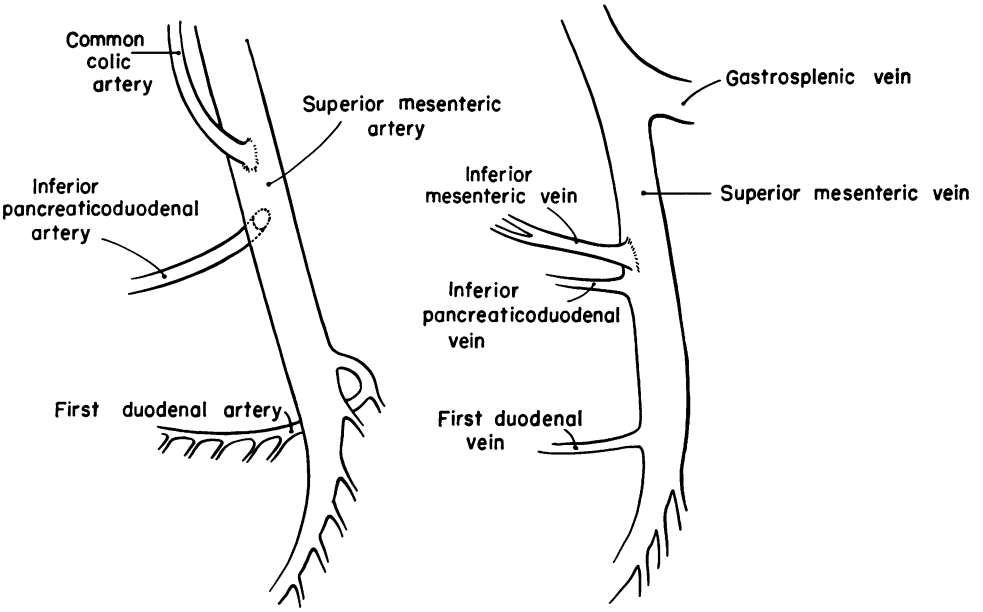

FIG. 5. Anatomy of the superior mesenteric vessels in the dog.

to the common colic artery so that this artery had to be sacrificed in order to have room to reanastomose the superior mesenteric artery. Taking this branch always necessitated resecting the distal half of the pancreas.

In the case of the superior mesenteric vein, it was necessary to carefully preserve the inferior mesenteric tributary. This vein, although small, drains almost the entire colon and accidental division of it invariably required the resection of the entire colon down to the rectum. The inferior pancreatico-duodenal vein joins the superior mesenteric vein just a mm. or two distal to the inferior mesenteric vein on the right lateral surface. There is then a distance of 15 to 20 mm. of superior mesenteric vein distal to this tributary which is clear of any other tributaries from the small bowel. It is in this area that we divided and later reanastomosed this vein.

The results of the *in vivo* experiments indicated that the bowel could withstand at least two hours of total circulatory arrest by merely allowing it to cool to room temperature. There seemed no reason then that we could not remove the bowel completely from the peritoneal cavity if we reconstituted circulation by the two-hour time limit. Moreover, if by some means we lowered the temperature of the removed bowel to below 10° C., there appeared to be no need to replace the bowel in the peritoneal cavity and re-establish its circulation for periods at least up to five hours. The question remained, however, whether this removed bowel would regain normal function and survive indefinitely following reconstitution of circulation and continuity with the remainder of the digestive tract in the face of complete severance of all nervous and lymphatic tissues which could not be rejoined.

The Operative Procedure: Adult mongrel dogs of both sexes weighing from 15 to 25 Kg. were prepared in the manner outlined above and a control plasma vol-

ume, hematocrit, and plasma hemoglobin obtained. They were then anesthetized with thiopental and using sterile technic the abdominal cavity was opened widely in the midline. The ligamentous attachments of the distal duodenum and proximal jejunum to the colon and the dorsal parietal peritoneum were first divided. Then, working along the right side of the ileocecal mesentery, the superior mesenteric vein was exposed just proximal to the confluence of the numerous tributaries from the small bowel. Following this, the dissection was continued on the left side of the ileocecal mesentery exposing the superior mesenteric artery. This was followed by a careful dissection, division, and ligation of all nervous and lymphatic tissue around the superior mesenteric artery, being careful to preserve all branches of this artery. All tissue surrounding the superior mesenteric vein was likewise divided carefully preserving all tributaries and taking special care with the inferior mesenteric vein (Fig. 6). The duodenum was divided about 5 to 8 cm. from the pylorus and the duodenal mesentery then divided down to the superior mesenteric vessels. The ileum was divided about 1 cm. from the ileocecal valve and

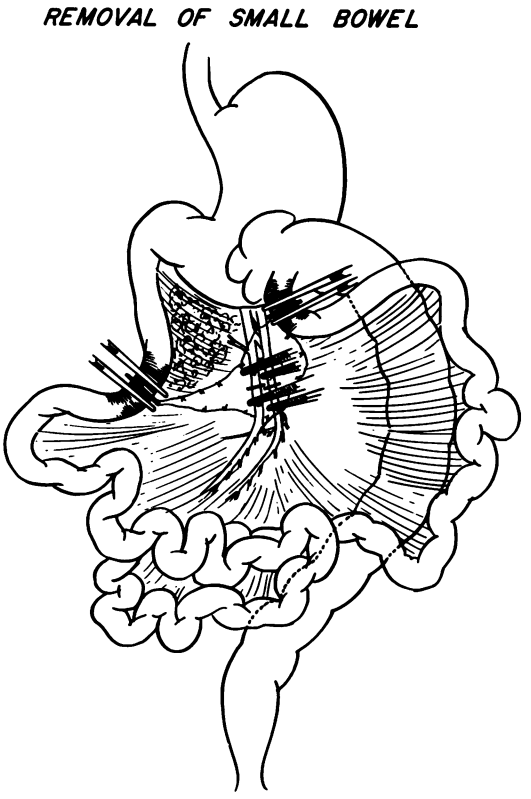

FIG. 6. Resection of the small bowel preserving its vasculature.

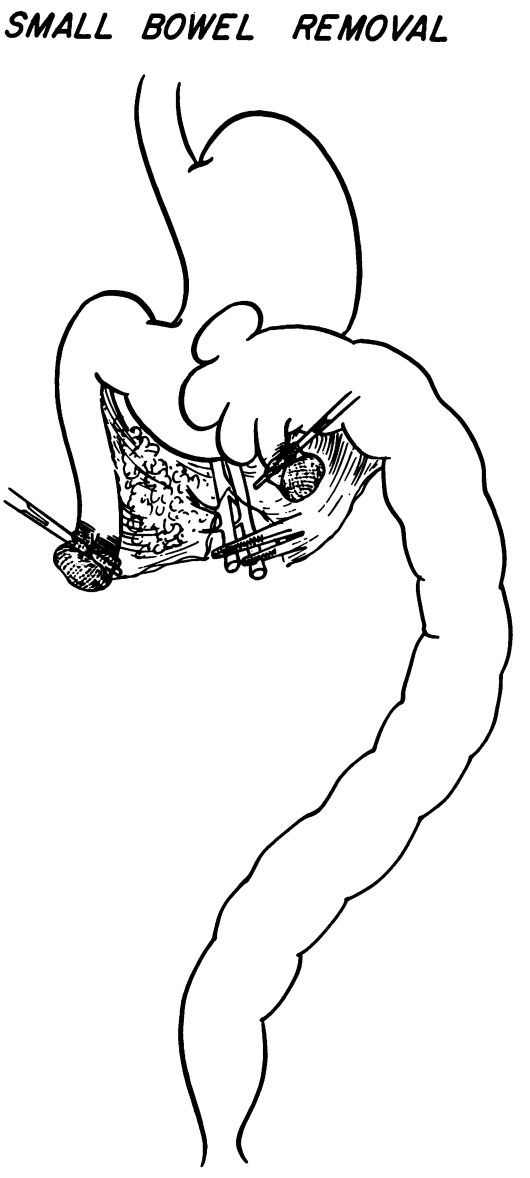

FIG. 7. Small bowel removed leaving colon and proximal duodenum.

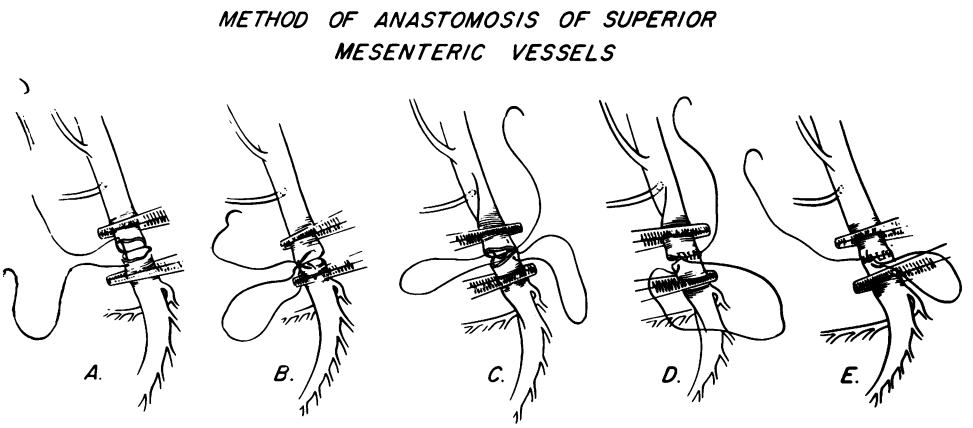

FIG. 8. Technique of anastomosing the superior mesenteric vessels.

its mesentery divided, down to the superior mesenteric vessels. This left the small bowel pedicled on the superior mesenteric vessels. Straight Potts' patent ductus clamps were placed on the artery first, allowing all possible blood to drain from the bowel before 5 mg. of heparin in 5 ml. of normal saline was injected into the artery distal to the clamp. Straight Kapp-Beck clamps, the most satisfactory clamps for veins in our estimation, were then applied to the superior mesenteric vein and both the artery and vein divided between the clamps. This allowed us to lift the entire small bowel from the peritoneal cavity leaving only the colon, stomach and a few cm. of duodenum remaining (Fig. 7).

The removed bowel was placed on a sterile towel where it was kept for periods of one to two hours. During this time, the abdominal cavity of the dog was either left open or closed temporarily with towel clips. At the time appointed for replacement, the abdominal cavity was reopened and the bowel placed back in the peritoneal cavity, being careful to place the bowel in its normal relationships to the remaining short segment of duodenum and the colon. The anastomosis of the artery was done first using an over and over suture of 6-0 arterial silk followed by the vein. In anastomosing these vessels whose internal diameter was usually no more than 3 mm. and in the case of the artery often less, we settled on a technique which proved simple and quick (Fig. 8). Using this method, we could at all times be suturing anteriorly.

After completing the vessels anastomoses, all clamps were removed and the bowel invariably regained its normal pink color and peristalsis promptly returned. The distal duodenum was then joined to the proximal duodenum making a one layer closed anastomosis with 5-0 silk over Wangensteen aseptic anastomosis clamps. By the same technic the terminal ileum was joined to the colon after resecting the cecum to facilitate the anastomosis. The gaps in the mesentery of the anastomosed bowel were closed and the root of the mesentery was sutured to the dorsal parietal peritoneum between the aorta and inferior vena cava to give support to the bowel and prevent torsion of the mesentery around the superior mesenteric vessels (Fig. 9). The procedure was completed by a copious rinsing of the peritoneal cavity with sterile saline followed by closure of the abdominal wound, after leaving penicillin and streptomycin in the peritoneal cavity.

A second plasma volume, hematocrit and plasma hemoglobin was done about two

hours after resumption of superior mesenteric circulation. In some cases, these measurements were repeated again at four hours and 24 hours following the replacement of the bowel.

Prolonged In Vitro Preservation of the Small Bowel

In another group of dogs the small bowel was removed in the manner described above and cooled. At first, we cooled the bowel by perfusing it with cold saline via the superior mesenteric artery exactly as we had done in the *in vivo* hypothermia experiments, but we soon found a simpler method. The removed bowel was placed in a sterile plastic bag and then immersed in a beaker of cold saline at 5° C. The beaker was then placed in an ordinary refrigerator. By this means, a temperature of 5° C. could be maintained indefinitely. Four to five hours after being removed, the bowel was taken from the refrigerator and returned to the peritoneal cavity of the dog where its continuity was restored as described above and the dog then followed.

Homografts of the Small Bowel: After much practice, the ease with which the small bowel could be removed and replaced when desired prompted us to study homografts of the small bowel.

Two dogs of similar build and weight, weighing at least 17 Kg. or greater, were operated upon simultaneously after the preoperative measurements outlined above. In addition, these dogs were given two or three days of preoperative treatment with 6 Gm. of sulfasuxidine and 3 Gm. of neomycin orally. This was done in an effort to give all possible protection to the intestinal anastomoses in these homografted dogs.

The small bowel of each was removed and switched to the other, restoring the vascular and intestinal continuity of the homografted bowel in the manner outlined above. These dogs were followed with daily measurements of hematocrit, plasma hemoglobin, white count and plasma volume.

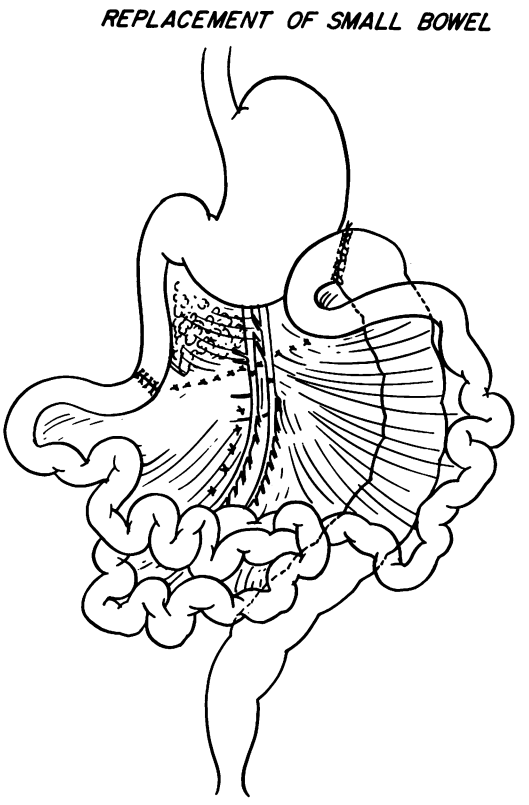

FIG. 9. Replacement of the small bowel. The root of the mesentery has been sutured to the parietal peritoneum to the right of the superior mesenteric vessels.

Results of In Vitro Bowel Studies with Replacement

At first we made innumerable technical errors and it was only after some 50 or more experiments that we developed a procedure which was successful. Careful division and ligation of lymph vessels was of utmost importance, for following replacement of the bowel, varying amounts of edema appeared both in the bowel wall and in the mesentery. This was associated with much oozing of lymph and blood if care had not been taken in the initial removal of the bowel. This edema was most noticeable in bowels which had been cooled to 5° C. and in homografted bowels. Early in the study we used liberal amounts of blood and dextran but it was not until we

TABLE 2. *In Vitro Experiments**

Group	No. Dogs	Maximum Values in 4 Hours Following Replacement of Bowel: Plasma Volume Loss (%)	Hematocrit Increase (%)	Plasma Hgb. Increase (mg. %)
VII. Bowel replacement within 2 hours	10	27.6 ±14.8	20.1 ±11.3	20.5 ±27.9
VIII. Bowel replacement after 4–5 hours *in vitro* hypothermia at 5° C.	10	35.4 ±18	31.0 ±7.1	17.9 ±15

* Mean values with standard deviations.

avoided their use that we began to obtain any permanent survivors. This was true for both heparinized or citrated blood. For plasma losses, which as will be seen were large, we found our best results using only normal saline intravenously.

An initial problem of superior mesenteric venous obstruction by torsion of the bowel around the vessels was solved by tacking the root of the mesentery down to the parietal peritoneum. Our biggest problem was and still remains postoperative pneumonia. This was especially common in dogs in which the bowel was held *in vitro* for long periods of time necessitating keeping the dog under anesthesia for periods of up to ten hours. It helped somewhat to use thiopental rather than pentobarbital so that the dogs awakened more quickly following the procedure. In addition, while the bowel was being refrigerated, we closed the dogs' abdominal incisions and turned them on their abdomens and allowed them to become quite light. By this we hoped to promote deeper respirations and prevent atelectasis. The use of positive pressure respiration in our hands caused more problems than it solved. It was particularly prone to drastically lower the dogs general body temperature over a prolonged period of use.

Another problem was that of anastomosing the small bowel after four to five hours of *in vitro* hypothermia. Although pink and viable it became very edematous and did not hold stitches well so that death from anastomotic leakage on the third or fourth day was not uncommon in these experiments.

After encountering these and other difficulties, we did a series of 20 experiments, ten in which the bowel was held *in vitro* up to two hours before being replaced, Group VII, and ten others in which the bowel was cooled to 5° C. and not replaced until four to five hours had passed, Group VIII. Table 2 gives a summary of the plasma findings in these dogs. Plasma losses in the hypothermia group, VIII, were large and correlated with the edema which occurred in the bowel wall and mesentery. In addition, the lumen of the replaced bowel usually filled with a white watery mucus after resumption of circulation. While losses of plasma were quite large in this group of dogs, similar to findings in fatal superior mesenteric occlusion described above, the plasma hemoglobin did not rise to levels associated with irreversible changes in the intestinal mucosa due to necrosis and hemorrhage and the dogs did not develop bloody diarrhea. This indicated that the intestine, although damaged by the prolonged period without circulation, had not

TABLE 3. *Group VII Survival When Bowel Replaced Within Two Hours*

Dogs #	Survival (days)	Cause of Death	Condition of Bowel at Autopsy
1551	16	Multiple lung abscesses	Normal
1450	Permanent	—	—
1612	Permanent	—	—
1790	—	Intussusception	Normal
1674	4	Rupture S.M.A. anastomosis	Ischemic
1396	Permanent	—	Normal at sacrifice 3 mo.
102	Permanent	—	—
449	Permanent	—	Normal at sacrifice 3 mo.
1555	Permanent	—	Normal at sacrifice 3 wks.
1597	Permanent	—	—

irreversibly lost its integrity. Plasma losses in dogs in which the bowel was only held *in vitro* for two hours or less were, as one might expect, less extensive.

After determining the plasma changes in these dogs after surgery, we started intravenous fluids, usually consisting of 300 to 600 ml. of normal saline in 5 per cent dextrose. For intravenous nutrition after the day of surgery, we generally used 600 ml. of 10 per cent dextrose in half normal saline daily, allowing oral intake on the fourth postoperative day.

Long-Term Results: In Tables 3 and 4 are detailed the length of survival of dogs in these experiments, their cause of death and the condition of the bowel at autopsy. In the ten dogs in which circulation was restored to the bowel by two hours, all but three recovered and were permanent survivors. Three of these survivors were sacrificed at intervals of three weeks and three months following the procedure and the bowel was normal grossly and microscopically. The peritoneal cavity was clean and there were surprisingly few adhesions. The remaining survivors are still alive at the present time. The bowels of two of the fatalities were normal at autopsy with the exception of the area affected in one dog by an ileo-ileal intussusception which caused obstruction and death. There was no trouble in any dog with clotting of the venous anastomosis and the rupture of the

TABLE 4. *Group VIII Survival When Bowel Replaced Within Five Hours After In Vitro Hypothermia to 5° C.*

Dog #	Survival (days)	Cause of Death	Condition of Bowel at Autopsy
1928	4	Pneumonia	Normal
204	Permanent	—	—
221	3	Pneumonia	Normal
426	5	Pneumonia	Normal
387	16	Rupture S.M.A. anastomosis	Ischemic
76	3	Pneumonia	Normal
568	Permanent	—	Normal at sacrifice 3 wks.
96	3	Pneumonia and heart worms	Normal
500	3	Leak of prox. bowel anastomosis	Normal
77	4	Leak of prox. bowel anastomosis	Normal

TABLE 5. *Fate of Small Bowel Homografts*

Total No. of Dogs Receiving Homografts	Number of Dogs Surviving			
	0–2 Days	3–5 Days	6 Days	7 Days
8	3	2	1	2

superior mesenteric arterial anastomosis in one dog apparently resulted from an abscess around the vessels.

In dogs in which the bowel was held *in vitro* for four to five hours, the long-term results were not as good although the longest survivor has now lived six months and has become pregnant since surgery. The other survivor was sacrificed at three weeks and the bowel was grossly and microscopically normal. The others died in three to 16 days of pneumonia, leak of an intestinal anastomosis or rupture of a superior mesenteric arterial anantomosis due to infection. In every case, however, the bowel was viable and could not be distinguished from the proximal duodenum or colon which had been left in place. In addition plasma hemoglobins taken on these dogs prior to death were normal, indicating a normal intestinal mucosa. Another interesting finding at autopsy in this hypothermia group, VIII, was that all edema of the bowel and mesentery, which had been so evident immediately after replacement, had disappeared.

Nutrition of Survivors

After recovering from the effects of these procedures, survivors appeared to have no nutritional difficulties save for a gradual fall in hematocrit for the first few days after surgery. This may have been due to the return of edema fluid in the bowel and mesentery to the circulation, since plasma volumes in these dogs gradually returned toward normal during this period without the use of blood or dextran.

The stools of these dogs appeared normal after about ten days and there was then no evidence for impaired fat absorption from the severed lymphatics. Before survivors were sacrificed weeks or months following an experiment, these dogs were reoperated upon and patent-blue dye was injected into a lymph duct in the small bowel mesentery. This dye quickly appeared in the lymphatics around the portal vein and in the thoracic duct indicating a prompt regrowth of lymphatics. This probably explains the apparently normal fat absorption in these dogs. Studies of nerve regeneration are presently being made.

Homograft Results: Eight dogs have received small bowel homografts at the present time (Table 5). The plasma findings in these dogs paralled those already discussed for dogs in Groups VII and VIII. Edema of the homografted bowel and mesentery occurred immediately after circulation was established and was even more severe in these dogs than the hypothermia group, VIII. Yet, the bowel was viable and functioned for periods up to seven days. Plasma hemoglobins were never elevated in any of these dogs prior to death and at autopsy the homografted bowel appeared grossly and microscopically normal. The cause of death in each case could be attributed to other causes. Thus we do not think that we have yet reached the true rejection period and further experiments in this field are in progress.

Discussion and Conclusions

The results of occluding only the superior mesenteric artery *in vivo* agree with those results previously reported by others.[9, 10, 15] These investigators all found that a majority of dogs will survive three to four hours of superior mesenteric occlusion only. But, the applicability of these studies to humans has been challenged by Noer [11] who maintains that the collateral blood supply of canine small bowel both intramurally and via the arcuate arteries is much better developed in dogs than in man.

If partial occlusion results in the dog can-

not be applied to man because of differences in extent of collateral circulation, then total occlusion results reported here are more easily applicable since the factor of collaterals is eliminated. That collaterals are important in superior mesenteric arterial occlusion in the dog is seen by the fact that the tolerable period of superior mesenteric arterial occlusion is about halved if collaterals are occluded as well, that is, unless intestinal hypothermia is instituted to protect the bowel. It should be stressed that in these studies we were careful never to allow superior mesenteric venous obstruction to occur with an intact arterial blood supply to the intestine because, in this situation, we have found, as have others,[9, 10] that as little as one hour of venous obstruction is usually fatal.

The similarities in the dog between the findings in superior mesenteric arterial occlusion, irreversible hemorrhagic shock and irreversible Gram-negative endotoxic shock are many. In all three conditions the characteristic findings in the irreversible state are an increasing hematocrit, a progressive plasma loss and arising plasma hemoglobin. In all three, we have found that intestinal antibiotics per se will not prevent the development of the irreversible state.[6] Again in all three, although plasma volume losses are large, mere replacement of such losses is of only temporary benefit and the animals proceed inexorably to death because of the underlying bowel pathology which is responsible for these plasma losses.[4, 6] These bowel findings are intimately related to the development of the irreversible state and are not only responsible for marked fluid losses but also for the rise in plasma hemoglobin which is the harbinger of impending death in these conditions. The elevated plasma hemoglobin like the plasma volume loss is not apparently lethal in itself but indicates that the integrity of the intestinal mucosa has been lost and that blood is accumulating within the intestinal lumen. There it is hemolyzed and then reabsorbed again into the circulation through the necrotic mucosa, doubtless along with other toxic products resulting from mucosal necrosis.[5]

It is interesting that irreversible hemorrhagic shock with its inevitable hemorrhagic bowel necrosis occurs only after 4 to 5 hours of profound oligemic hypotension followed by retransfusion. So, also, the characteristic bowel finding in superior mesenteric arterial occlusion occurs only after four to five hours of occlusion followed by release of the occlusion. If the superior mesenteric occlusion is maintained permanently, however, along with division of collaterals, the characteristic plasma findings do not occur until much later and survival is also prolonged although eventual death occurs. This is because fluid losses are minimized and the toxic products of intestinal necrosis are not washed directly into the general circulation by release of the occlusion but are denied access to the circulation until they have permeated through the bowel wall and then been reabsorbed from the peritoneal cavity.

The ability of the bowel to regain its viability after periods of *in vitro* "suspended animation" of four to five hours indicates that, in the dog at least, one need have no fear of severing all lymphatic and nervous tissues to the bowel. The lymphatics regenerated quickly and extensively so that we detected no gross disturbances in fat absorption or in the general nutrition of these dogs. Moreover, the ease with which these small vessels can be anastomosed and the rarity of thrombosis in the vein as well as the artery indicate that one could have confidence that similar anastomosis in much larger human superior mesenteric vessels would also be successful.

A most important finding was that we never found evidence of any thrombosis in the small peripheral bowel vessels as a result of stasis for four to five hours. This may be due to heparin but in some dogs we did not inject heparin into the superior

mesenteric artery before removing the bowel and our results in these dogs were the same as in the others. It may be that blood in the *in vitro* organ, similar to blood in a cadaver, will not clot or that the profound lowering of the temperature also impedes clotting.

There is no obvious explanation for our failure to get good results in the bowel replacement studies when blood was used for replacement other than to draw the parallel with recent findings in severe burns. Stirman *et al.*[14] have reported that a significantly greater number of patients with severe burns survived if given saline rather than blood. In a sense, the large measured plasma losses in these experiments indicate that the ischemic intestine resembles a severe burn, its severity depending on the duration of ischemia.

Fate of Homografts: This aspect of the study is just underway. We do not know what the ultimate fate of homografts will be since we have not yet had a homografted dog reject his new bowel. Bowel homografts will probably be rejected by the usual three-week deadline but the peculiar circumstance of the bowel with its myriad of antigens and bacteria may alter this physiologic deadline in a yet unknown way. Certainly healing of bowel anastomoses has occurred and the bowel has functioned up to seven days.

Finally, what relation has all the above to unsolved clinical problems? We believe that the beginnings of successful methods for treating pseudomembraneous enterocolitis, thrombosis and embolism of the superior mesenteric vessels, malignancies involving the bowel and/or its vessels, the radiation syndrome and other related conditions will be made in the experimental laboratory. We hope this study has helped provide impetus for such a beginning.

Summary

The majority of adult mongrel dogs tolerated up to 3.5 hours of superior mesenteric arterial occlusion if the collateral circulation to the small bowel was not disturbed. If all collateral circulation to the bowel was occluded as well, then most dogs died following a three to 3.5-hour occlusion of the superior mesenteric artery. Interruption of all circulation to the small bowel for two hours was tolerated if the bowel was allowed to cool to room temperature, 25 to 28° C. If, however, the bowel was cooled to 5° C., then it was safe to interrupt all circulation to the small bowel for at least five hours. Knowing this, we removed the entire small bowel, save for the first few centimeters of duodenum, and held it *in vitro*. No external cooling of the bowel was required if it was returned to the peritoneal cavity and circulation reestablished by two hours. If cooled to 5° C. *in vitro,* it was not necessary to re-establish circulation for up to five hours. In every case the bowel retained its viability and many of the dogs having such a procedure survived for weeks or months, indicating that the bowel could survive complete severance of all connections with the central nervous and lymphatic systems and that anastomoses of the superior mesenteric vessels, especially those of the veins, would remain open. This technic was also used to successfully make small bowel homografts in dogs which have so far lasted up to seven days.

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Discussion

Dr. Owen H. Wangensteen: You will agree with me, I am certain, that this is quite an accomplishment that Dr. Lillehei and his associates reported today. In fact, I believe it would be fair to say it is an adventure in the exploration of adversity. Dr. Lillehei and his associates have overcome a number of handicaps; the technical problem of making the anastomoses on relatively small vessels has been largely resolved in their hands.

There may be those who might suggest that their achievement represents only a stunt. I will remind you that Benjamin Franklin once asked in passing judgment upon the promise of a matter of debatable merit: "What is the good of a newborn baby?" Well, who can tell?

It occurs to me that Dr. Lillehei and his associates will presently address themselves to employment of shorter segments of bowel, establishing the vascular connections and making the intestinal anastomoses at a later date. There may be less risk of loss of the homograft for the recipient if the homograft transplant is done in this manner.

I have had personally no experience with this type of procedure. However, my associates and I during the past year have had considerable experience with the use of hypothermia under a number of conditions. In yesterday's discussion, I reported the surprising diminution of intestinal and gastric motility accompanying hypothermia. A similar startling reduction in secretion also attends hypothermia. In the normothermic rabbit, if one ligates the base of the appendix, rupture will follow in 70 per cent of instances in ten hours owing to the increase in intraluminal pressure—which actually may approximate systolic blood pressure. In the hypothermic rabbit, secretion from the obstructed appendix is considerably less, and so to with intraluminal pressure. Moreover, this same disparity in behavior is observed also in closed duodenal loops. The diminution of intestinal secretion and motility accompanying cooling suggests that mild systemic hypothermia to 34° C. may be a device of some value in the management of intractable diarrhea, which may threaten life. Perhaps someone in this group will presently have the opportunity to explore the utility of such a suggestion.

My colleagues, Drs. Peter A. Salmon, Ward O. Griffen, Jr., and I have also explored strychnine absorption from short closed jejunal loops, a technic which Dr. Louis Sperling and I examined more