# Elimination of the Lethal Properties of Gangrenous Bowel Segments

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PIONEERING experiments of Hartwell and Hoguet [6] first called attention to the need for intravenous fluids and electrolytes in the management of simple intestinal obstruction. Clinical utilization of this modality is now considered a component of preoperative preparation and is responsible for increasingly favorable results in the treatment of simple intestinal obstruction.

Two factors are responsible for the more severe pathophysiologic changes which occur in strangulation obstruction. The first is blood loss, which can be replaced effectively to correct shock in strangulation obstruction.[5] The second is related to the gangrenous segment of bowel which generates and releases toxic materials into the peritoneal cavity, resulting in general body tissue exposure to gram negative bacterial endotoxins. It is necessary to weigh the relative benefits of early operation in strangulation obstruction, in the absence of thorough preoperative preparation, against delayed operation with continuing exposure to toxic materials from the dead bowel segment. Both approaches have drawbacks which account for mortality rates in excess of those in simple obstruction.

Bacteria produce toxic materials in strangulation obstruction,[3] and antibiotics in the lumen of the bowel eliminate the capacity for toxin production and convert the bowel to a harmless hematoma.[2] Since delivery of antibiotics into the lumen of a strangulated segment of bowel is not feasible, experimental studies were designed to explore the efficacy of antibiotics administered by other routes.

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## Materials and Methods

Adult, mongrel dogs were separated into two major divisions: donor and recipient animals. Various forms of treatment were administered to donor animals only. Recipient animals received no treatment and served to indicate whether or not the gangrenous segment of bowel had lethal potential.

*Donors:* (244 dogs) These animals received nothing orally for 12 hours before the operative procedure. After the abdomen had been shaved and cleaned with soap and Zephiran Chloride solution, the ileum was delivered through a midline incision. The segment of bowel to be strangulated was transected at each extremity, and the two ends were closed. The blood vessels to be ligated were then isolated in the mesentery and tied. An end-to-end anastomosis was constructed so as to establish intestinal continuity around the gangrenous segment (Fig. 1). The abdomen was then closed. Each donor dog received 500 cc. of Ringer's Lactate solution intravenously during the initial 8-hour period after stangulation. A similar volume of this intravenous solution was also administered 20 hours after stran-

TABLE 1. *Comparative Efficacy of Three Antibiotics in Eliminating the Lethal Properties of a 10 cm. Segment of Ileum following Venous Strangulation*

| Antibiotic Used to Treat Donor Animals | Dose of Antibiotic (mg./Kg.) | No. Recipient Animals Exposed to Treated Segments | 48-Hour Survivors Among Recipients | % Survivors | P Value |
|---|---|---|---|---|---|
| Kantrex | 14 | 20 | 3 | 15 | <.001 |
| Chloromycetin | 14 | 20 | 7 | 35 | <.005 |
| Keflin | 28 | 20 | 16 | 80 | |

gulation of the bowel segment. Twenty-eight hours after strangulation, the abdomen of donor animals was opened; the gangrenous segment of bowel was removed and placed within the abdomen of a normal, recipient animal (Fig. 2).

*Recipients:* Normal dogs were lightly anesthetized with intravenous Nembutal, and the gangrenous segment was placed in the peritoneal cavity through a small, midline incision. Sterile operative technic was observed throughout the operative period. After the abdomen had been closed, these animals were placed in cages for observation. No therapeutic agents were administered, but food and water were made available. Animals which lived for 48 hours were considered survivors.

*Series I. Comparative Efficacy of Various Antibiotics in Eliminating the Lethal Properties of 10 cm. Bowel Segments after Venous Strangulation.*

*Procedure for Donors:* The dose of each antibiotic was calculated to approximate clinical levels. Each donor animal received two intravenous doses of antibiotic, one at the time of strangulation and a second approximately 20 hours later.

Group 1. (20 dogs) These animals were given Kantrex in the amount of 14 mg./Kg.

Group 2. (20 dogs) Chloromycetin (14 mg./Kg.) was used for these dogs.

Group 3. (20 dogs) Animals of this group received Keflin (28 mg./Kg.).

*Results in Recipients:*

Group 1. (20 dogs) Where Kantrex was used for donor treatment, 3 recipient animals (15%) survived for 48 hours.

Group 2. (20 dogs) Seven (35%) recipient animals survived (48 hours) following treatment of donor animals with Chloromycetin.

Group 3. (20 dogs) Sixteen recipient dogs (80%) survived for 48 hours when Keflin was used for donor treatment (Table 1).

*Series II. The Influence of Keflin upon the Lethal Characteristics of Gangrenous 10 cm. Bowel Segment following Arterial Strangulation.*

*Procedure for Donors:* Gangrene was produced by ligation of the arterial supply to the bowel segment (Fig. 4). Two doses

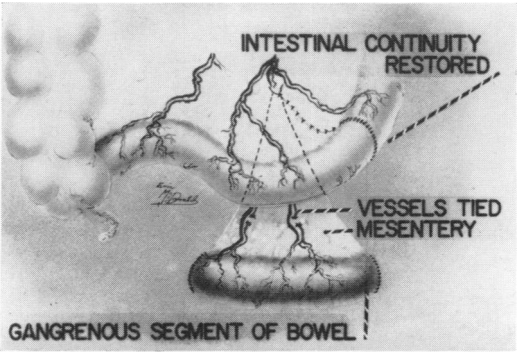


FIG. 1. Method used for producing strangulation in isolated bowel segments.

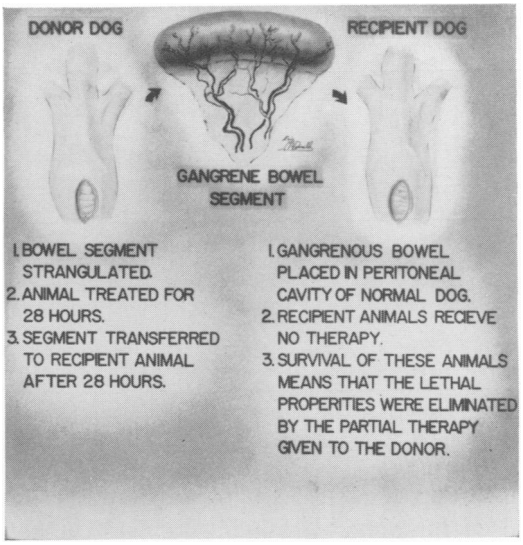


FIG. 2. Procedure for transferring gangrenous bowel segments from donor to recipient animals.

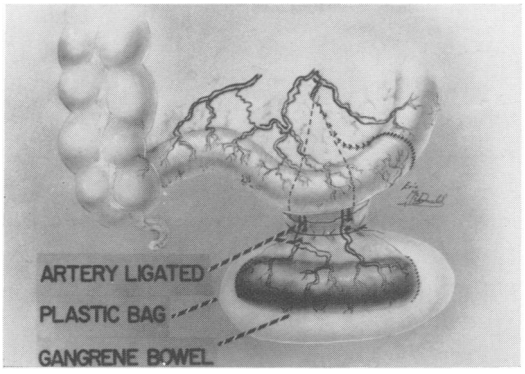


FIG. 3. Use of a plastic bag to eliminate peritoneal exposure of gangrenous bowel segment.

of Keflin in the amount of 28 mg./Kg. were given intravenously to all donor dogs.

Group 1. (20 dogs) No antibiotics were given to this control group, and the segment was completely exposed to peritoneum.

Group 2. (20 dogs) These dogs received Keflin intravenously. The gangrenous segment of bowel was placed in a plastic bag so that peritoneal exposure was eliminated (Fig. 3).

Group 3. (20 dogs) Same treatment as animals in Group 2 except that no plastic bag was used, and, therefore, the segment was completely exposed.

*Results in Recipients:*

Group 1. (20 dogs) There were seven (35%) survivors among recipients receiving bowel segments from untreated (control) donors.

Group 2. (20 dogs) When donors were treated with intravenous Keflin and the altered bowel segment was placed in a plastic bag, there were only 3 (15%) survivors among recipients.

Group 3. (20 dogs) In animals treated with intravenous Keflin with full peritoneal exposure in the absence of the plastic bag, 17 dogs (85%) survived (Table 2).

*Series III. The Effects of Keflin upon the Lethal Potential of 20 cm. Segments of Strangulated Ileum.*

*Procedure for Donors:* Arterial strangulation was utilized for all animals (Fig. 5).

Group 1. (20 dogs) These animals received intravenous Keflin in the amount of 28 mg./Kg. Two such doses were given during the 28-hour period of treatment.

Group 2. (16 dogs) These animals were managed similarly to those in Group 1, except that the intravenous dose of Keflin was increased to 56 mg./Kg.

Group 3. (16 dogs) Similar to Group 2 with the exception that the Keflin (56 mg./Kg.) was given intraperitoneally. Two doses were given during the period of treatment.

Group 4. (16 dogs) These animals were managed similarly to those in Group 3, except that 5 intraperitoneal doses of Keflin were given during the treatment period.

*Results in Recipients:*

Group 1. (20 dogs) There were only 5 (25%) survivors among recipients whose donors were treated with 28 mg. of Keflin/Kg.

Group 2. (16 dogs) The larger dose (56 mg./Kg.) of intravenous Keflin resulted in survival of only 4 animals (25%).

TABLE 2. *The Influence of Intravenous Keflin (28 mg./Kg.) upon the Lethal Characteristics of 10 cm. Segments of Ileum following Arterial Strangulation*

| Donor Animals | No. Recipient Animals Exposed to Strangulated Segments | 48-Hour Survivors among Recipients | % Survivors |
|---|---|---|---|
| No antibiotic (Control animals) | 20 | 7 | 35 |
| Strangulated bowel placed in plastic bag | 20 | 3 | 15 |
| Strangulated bowel free in peritoneal cavity | 20 | 17 | 85 |

TABLE 3. *The Efficacy of Keflin in Controlling the Lethal Potential of 20 cm. Segments of Ileum after Arterial Strangulation*

| No. Donor Animals | Dose of Keflin Given to Donor Animals (mg./Kg.) | No. of Times of Antibiotic Administration to Donor in 28-Hour Period | Route of Antibiotic Administration | 48-Hour Survivors among Recipients | % Survivors | P Value |
|---|---|---|---|---|---|---|
| 20 | 28 | 2 | Intravenous | 5 | 25 | |
| 16 | 56 | 2 | Intravenous | 4 | 25 | <.02 |
| 16 | 56 | 2 | Intraperitoneal | 11 | 69 | |
| 16 | 56 | 5 | Intraperitoneal | 15 | 94 | |

Group 3. (16 dogs) When larger doses of Keflin (56 mg./Kg.) were given intraperitoneally, the survival rate increased to 11 dogs (69%).

Group 4. (16 dogs) With the more frequent administration of larger doses of Keflin to donors the survival rate of recipients increased to 15 (94%) (Table 3).

*Series IV. The Efficacy of Keflin in Neutralizing the Lethal Properites of 30 cm. Segments of Gangrenous Ileum.*

*Procedure for Donors:* Arterial strangulation was produced in donor animals (Fig. 6). Keflin was given intraperitoneally in amounts of 56 mg./Kg. Five doses were given during the treatment period.

Group 1. (20 dogs) Antibiotic administration was started at the same time that strangulation was produced. Keflin was dissolved in the minimal amount of saline necessary.

Group 2. (20 dogs) Same as Group 1, except that each dose of Keflin was diluted in 100 cc. of saline.

Group 3. (20 dogs) Antibiotic administration was delayed for 4 hours after bowel strangulation, otherwise the management was the same as for Group 1.

*Results in Recipients:*

Group 1. (20 dogs) There were 16 (80%) survivors among the recipients of 30 cm. segments of gangrenous bowel in this group.

TABLE 4. *The Efficacy of Intraperitoneal Keflin (56 mg./Kg.—5 doses) in Controlling the Lethal Potential of 30 cm. Segments of Ileum after Arterial Strangulation*

| Group | Donor Animals | Keflin | 48-Hour Survivors among Recipients | % Survivors |
|---|---|---|---|---|
| 1 | 20 | Started at time of bowel strangulation | 16 | 80 |
| 2 | 20 | Each dose diluted in 100 cc saline and started at time of bowel strangulation | 16 | 80 |
| 3 | 20 | Same as Group 1 except that antibiotic administration was delayed for 4 hours after strangulation | 15 | 75 |

Group 2. (20 dogs) Survivors among this group numbered 16 (80%) where the antibiotic was diluted before it was placed within the peritoneal cavity.

Group 3. (20 dogs) Delayed administration of Keflin was followed by the survival of 15 recipients (75%) (Table 4).

## Discussion

The clinical course of strangulation obstruction can be divided into three stages, depending upon the degree of exposure to toxic materials from the gangrenous segment of bowel. Stage I represents circumstances in which the toxic materials are limited to the lumen of the bowel so that no significant body exposure has occurred. Stage II exists when the strangulation fluid has escaped from the altered bowel segment and is pooled in the peritoneal cavity, but significant transperitoneal absorption has not yet taken place. Stage III represents an advanced period in which toxins have escaped from the bowel, crossed the peritoneal cavity, entered the blood vessels and lymphatics, and have been distributed to most body tissues. Previous experimental studies have shown that some of the deleterious effects of strangulation fluid can be neutralized by certain antibiotics.[4] A more significant accomplishment would be neutralization or elimination of the source of the toxins as in the above experiments. When the intravenous route was utilized, Keflin provided superior results. It is true that larger doses of Keflin were used, but the other antibiotics were administered in doses at upper clinical levels. Perhaps the lack of significant side effects with larger doses of Keflin represents a distinct advantage for this antibiotic when used under these circumstances. Apparently the efficacy of antibiotics in neutralizing gangrenous bowel products is related to the concentration of the drug in the peritoneal cavity. It appears that the antibiotic permeated the peritoneal lining into peritoneal fluids and thus neutralized gangrenous bowel products. When the segment be-

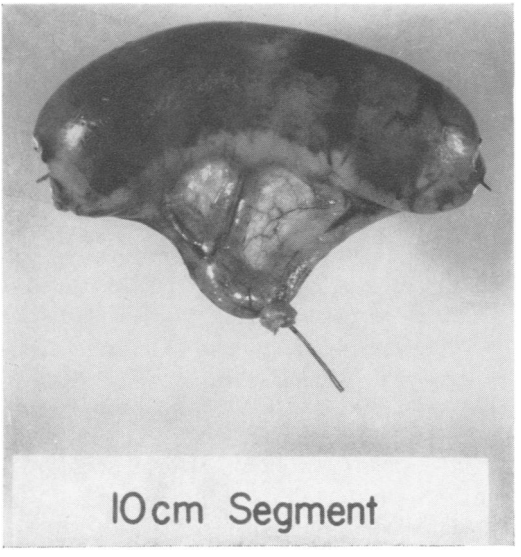


FIG. 4. Gangrenous bowel segment 10 cm. in length.

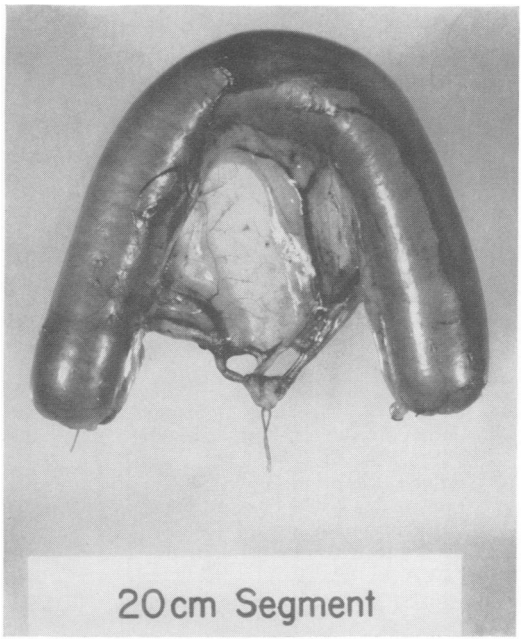


FIG. 5. Gangrenous bowel segment 20 cm. in length.

comes permeable enough for fluid to leak out, this provides a route for the antibiotic so that permeation of all layers of the bowel occurs.

This process was prevented by placing the segment in a plastic bag so that antibiotics were prevented from gaining access to the altered segments. The importance of a high level of peritoneal antibiotics was further substantiated by the results obtained in Series III. Survival rates of recipients were increased from 25 to 69% by changing the route of antibiotic administration from intravenous to intraperitoneal. This evidence is support for clinical utilization of intraperitoneal antibiotics in peritonitis. This experiment also supports the concept that the dose of antibiotic necessary for neutralization is proportional to the length of bowel involved and the number of bacteria. This feature was observed during experiments on peritonitis.[1]

Results in Series IV suggest that intraperitoneal antibiotics may be administered in dilute form without impairment of antibacterial effectiveness. This may be of importance clinically since concentrated antibiotic solutions might result in peritoneal irritation. Antibiotic administration can be effective in eliminating the lethality of gangrenous bowel even when initiated four hours after the onset of strangulation.

Since there are no absolute criteria by which strangulation can be diagnosed short of laparotomy, the question arises as to whether or not all patients with apparent simple intestinal obstruction should receive intraperitoneal antibiotics during the preoperative period. This practice might prevent progress of a simple to a strangulated obstruction. In cases of frank gangrenous bowel obstruction, the beneficial effects of intraperitoneal antibiotics has been alluded to. Such an approach might be effective in strangulation obstruction, where opportunity for improvement remains.

## Summary

When given experimentally in dogs by the intravenous route and in doses consistent with clinical usage, Keflin appeared

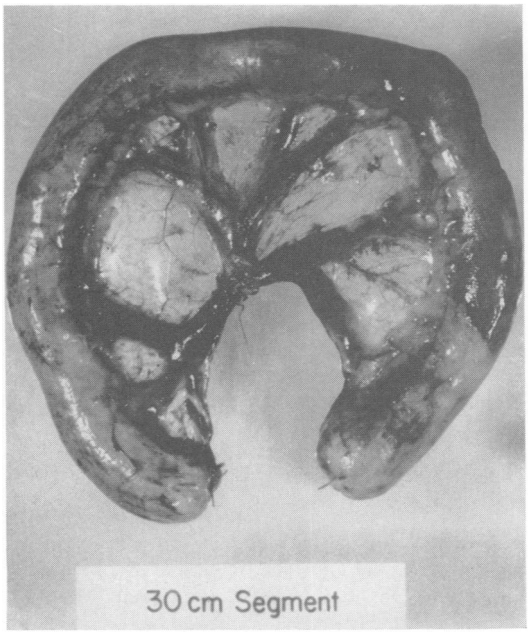


FIG. 6. Usual appearance of 30 cm. segment of gangrenous bowel.

more effective than Kantrex or Chloromycetin in neutralizing the lethal potential of gangrenous 10 cm. segments of ileum. The ability of an antibiotic to neutralize such segments appears directly related to the concentration achieved within the peritoneal cavity. Where other factors were constant, the intraperitoneal route of antibiotic administration gave best results. Neither dilution of the antibiotic solution in 100 cc. of saline nor delay of injection up to 4 hours after the onset of strangulation significantly affected the results. It is possible to neutralize the lethal characteristics of experimental gangrenous bowel segments up to 30 cm. in length for periods up to 28 hours by the intraperitoneal administration of Keflin.

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### Discussion

Dr. J. Englebert Dunphy (San Francisco): I would like to say a word about this condition's direct applicability to patients. The very nature of Dr. Barnett's experiment does eliminate intestinal obstruction, which, of course, as we know, with a gangrenous loop in man is a very important feature of the ultimate demise of the patient.

I believe we can divide intestinal obstruction into three groups, speaking primarily of small bowel obstruction. In the early patient with mechanical obstruction there may be a vascular factor—we do not know. In this situation there is no answer except immediate, early operation. This should be undertaken in every patient.

The second group are those patients who come in after 4 or 5 days with obvious pure mechanical obstruction. A gangrenous segment would have been fatal in that period of time. In this group one can be quite relaxed and have ample time to prepare the patient for operation.

The in-between group manifests symptoms for 48 hours or thereabouts, which presents great difficulty in selecting the ideal time to operate. To me, one of the most challenging experiences of the clinical surgeon is to prudently delay operation sufficiently so that the patient may be reasonably conditioned, and at the same time to operate as quickly as possible in dealing with potential or actual gangrenous bowel. In this area Dr. Barnett's studies may give us some additional leeway.

I do not believe that the particular antibiotic used in his experiments is necessarily acceptable as the best in man. The important point is: Wide spectrum antibiotics, intelligently used early, provide some time to prepare the critically ill patient for the definitive operation. In the end there is still only one way to treat intestinal obstruction, and that is to operate.

Dr. Richard C. Clay (Miami): One thing, I believe, that deserves attention in this regard is that not only evil humors, but vegetative bacteria may pass through the wall of gangrenous but unperforated bowel. Sometime recently I had the occasion—the misfortune, I guess I should say—to treat, however successfully, a case of tetanus resulting from organisms which passed through the wall of gangrenous but unperforated bowel. These organisms were recovered from the peritoneal fluid. Of course, the culture was delayed, and the patient was well on the way to recovery from obvious tetanus by the time the organism was identified.

This has led me to believe that when gangrenous bowel, or even appendix, is encountered the patient should be considered to have a wound of high risk for development of tetanus. The patient, if previously immunized, should receive a booster dose of toxoid, otherwise a dose of human antitoxin at this time.

As you all know, the presence of tetanus organisms in the intestines of a fairly large percent-