EXPERIMENTAL STUDY OF PHYSICAL FACTORS, INCLUDING FIBRIN FORMATION, INFLUENCING THE SPREAD OF FLUIDS AND SMALL PARTICLES WITHIN AND FROM THE PERITONEAL CAVITY OF THE DOG*

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Steinberg[33, 34, 36, 37, 38, 39] has maintained that the spread of infection in the peritoneal cavity from a focus such as a ruptured viscus is exceedingly rapid and that it is virtually complete within three hours. This is not in accord with the view of many clinicians, that the process may be slow enough in some instances to permit limitation of the infection by the local formation of fibroplastic exudate. That the extent and rapidity of spread may be subject to a number of variables, specifically the nature of the exudate, and the condition of the peritoneum, seemed possible, and to test this a variety of radiopaque liquid mixtures were introduced into the peritoneal cavity. Some of them were specifically designed to duplicate the physical character of intestinal contents, urine, and the contents of gangrenous appendices. The effects of the vertical and horizontal positions and ambulation on the intraperitoneal spread of the radiopaque liquids and accompanying bacteria were studied. The migration was followed with and without established peritonitis, and in the presence of enhancement and depression of the normal clotting mechanism. Simple physical factors have been shown to regulate the direction and rate of intraperitoneal spread.

EXPERIMENTAL METHODS

Roentgen Ray Methods. Mongrel dogs between 5 and 8 Kg. in weight, (whose dimensions conveniently fitted the roentgen ray facilities available) were prepared by milk and bread feeding, and control survey films of the abdomen were taken before the introduction of any radiopaque material. Intravenous Nembutal anesthesia (0.3 ml. of a 6 per cent solution per kilogram of body weight) was given before the initiation of any of the studies to be reported, and the dogs were maintained in the position of study by fixation in a canvas harness so designed as to distribute the dog's weight evenly between the pelvis, backbone and shoulder girdle. Serial roentgenograms were taken in the A-P projection with 0.2 of a second exposure at a film target distance of 34 inches, using 100 milliamperes and kilovoltages ranging from 6 to 35, depending upon the radiopaque liquid used and the thickness of the individual dog. To make quantitative measurements feasible, the lower edge of the casette was placed below the lower limit of the body surface, and in dogs of this size the upper portion of the film always extended above the diaphragm. Deviation of the central ray, in dogs of slightly different sizes, was shown to cause distortion of 5 per cent or less of the relative position of radiopaque material measured from a transverse line drawn on the roentgenogram through the midpoint of a line from the tip of the right wing of the ileum to the tip of the right transverse process of the last lumbar vertebra.

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TABLE I.—*Specific Gravity and Viscosity of Various Gastro-intestinal Contents and Peritoneal Exudates in Dogs.**

Material	Location	Sample	Specific Gravity	Viscosity
Normal G.I. Contents	Gastric	1	1.040	8.0
		2	1.184	15.0
	Jejunum	1	1.060	18.0
		2	1.140	22.0
	Ileum	1	1.020	15.0
		2	1.250	18.0
	Rt. Colon	1	1.040	30.0
		2	0.950	50.0
	Left Colon	1	1.060	120.0
		2	0.950	300.0
Gangrenous Appendiceal Contents	Appendix	1	1.062	60.0
	Appendix	2	1.047	32.0
	Appendix	3	1.028	18.0
	Appendix	4	1.034	20.0
	Appendix	5	1.040	19.0
	Appendix	6	1.032	52.0
	Appendix	7	1.026	14.0
	Appendix	8	1.038	16.0
		Average	1.038	28.9
Peritoneal Exudates	Peritoneal Cavity	1	1.021	9.4
	Peritoneal Cavity	2	1.040	25.0
	Peritoneal Cavity	3	1.027	12.2
	Peritoneal Cavity	4	1.017	12.5
	Peritoneal Cavity	5	1.018	12.2
	Peritoneal Cavity	6	1.033	25.8
	Peritoneal Cavity	7	1.005	8.1
	Peritoneal Cavity	8	1.024	9.0
	Peritoneal Cavity	9	1.015	10.0
	Peritoneal Cavity	10	1.012	9.4
	Peritoneal Cavity	11	1.021	18.4
	Peritoneal Cavity	12	1.042	12.6
		Average	1.023	13.7
Radiopaque	Mixtures			
#1	Mercury		13.00	15.0
#2	Lipiodol, 5.0 cc. Tragacanth, 5.0 cc. Albumen, 5.0 cc.		1.50	70.0
#3	Thorotrast, 5.0 cc. Tragacanth, 5.0 cc. Albumen, 5.0 cc.		1.40	40.0
#4	Thorotrast		1.50	15.0
#5	Thorotrast, 5.0 cc. Aquaphor, 2.0 cc. Petrolatum, 8.0 cc.		1.10	50.0
#6	Idochloral, 5.0 cc. Tragacanth, 5.0 cc. Albumen, 5.0 cc.		0.98	40.0
#7	Thorotrast, 3.0 cc. Aquaphor, 8.0 cc. Petrolatum, 4.0 cc.		0.94	300.0

*The mercury used was C. P. (Merck & Co., Inc.); Iodochloral (Searle); Lipiodol, 40 per cent iodine content (La Fay); Thorotrast, (Heyden Chemical Co.); albumen 5 per cent bovine albumen (Armour Laboratories, Inc.); petrolatum, neutroleum (Eimer & Amend); Aquaphor (Commercial Solvents Corp.); Tragacanth 5 per cent (Eimer & Amend).

Radiopaque liquids were made in proportions described in Table I by a high speed conical homogenizer, which resulted in stable emulsions containing small and variable proportions of trapped air. These materials yielded reproducible viscosities and specific gravities to within 10 per cent. Viscosity measurements were made with instruments appropriate to the ranges, *e.g.*, Ostwald, Hoppler and Couette technics.[4, 6, 8] The biological samples studied were stored at 4° for 24 hours before vis-

cosity determinations were performed but were returned to 37° for the measurements. Specific gravities were determined with appropriate density media by the falling drop technic[3] except for high viscosity media which were directly weighed in Gay-Lussac bottles.

Bacteriologic Technics. In those dogs in which preliminary appendiceal manipulation was carried out, initial cultures were taken of the appendiceal lumen at the time of operation. At the time of death or sacrifice, bacteriologic cultures were taken of specific areas under study. Bacteriologic smears, and segments of peritoneum and underlying tissues were taken and stained with Glynn bacteriologic stain[18] for microscopic examination. All cultures were incubated originally aerobically and anaerobically in meat infusion media (Difco), and on plain and blood broth agar. Blood cultures were prepared by adding 1 to 5 ml. of arterial blood to previously warmed plain agar broth in pour plates, mixed by rotation, and counted at six, 12, 24 and 48 hours after parallel aerobic and anaerobic incubation. The figures reported in blood cultures, are the total of both aerobic and anaerobic blood broth colony counts. Differential media which were used previously in stool evaluation were found to yield erroneous results in the presence of fresh blood, and therefore were abandoned here.

Surgical Technic. (a) *Direct Intraperitoneal Injection.* Injection of both preliminary irritant mixtures* and our radiopaque materials were performed by the cautious introduction of a 16-gauge needle through a 5 mm. nick in the skin and superficial layers of the right lower quadrant, after fixing the dog in the position for study and preliminary skin preparation. Then 1 to 2 ml. of sterile saline were injected through the syringe up to such time as the peritoneal cavity was entered. In three dogs not included in this study, injection retroperitoneally or into the lumen of the cecum was performed inadvertently. Fifteen ml. of radiopaque mixture were then injected gently over a period of five minutes and then the first roentgen ray pictures taken. The skin defect was closed tightly with a single previously laid steel wire suture.

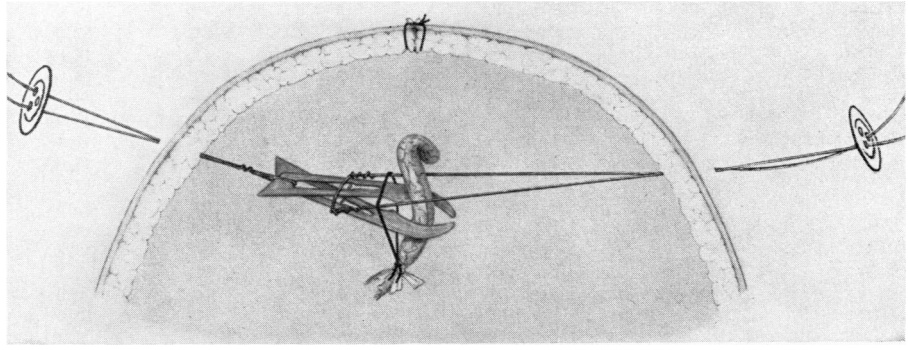


FIG. 1.—The apparatus shown was used to perforate the appendix, after its ligation and closure of the abdominal wall. Traction on the steel wires forces the No. 12 Bard Parker blades to close, amputating the tip of the appendix. Buttons on the skin surface were used to prevent retraction of the wires.

(b) *Introduction Via the Appendix.* In the immediate perforation group of dogs, the method of Zintel[40] was used for the rapid dissemination of the naturally occurring appendiceal flora for purely bacteriologic studies of spread. In other dogs, the effect of the gangrenous appendix in modifying the peritoneal reaction was investigated in the following fashion. Through a midline incision the appendix was located,

* Dr. Steinberg kindly provided us with a stock culture of *E. coli* #300 for the preparation of *coli-bactragen* according to his directions.[6]

its vessels ligated, and umbilical tape placed firmly about the base. A purse string suture was then laid in the wall, and a No. 16 needle introduced through this purse string suture and opaque media injected. The needle was withdrawn and the suture tied promptly. In those dogs which died without visible gross perforation, the appendix had been gently returned to the abdominal cavity after ligation and the wound closed in the usual fashion. In other dogs, before closure, crossed No. 12 Bard-Parker blades were left *in situ* about the appendix, as illustrated in Figure 1, to make possible subsequent accurately-timed gross perforation under roentgen ray observation.

In some dogs on closure, 1 per cent dog fibrinogen in normal saline, prepared by standard methods,[28] or dog brain thromboplastin[21] was injected intraperitoneally as the last peritoneal suture was tied. Some dogs were heparinized after the conclusion of the operative procedure by immediate administration of 0.5 mg. of heparin in Pitkins menstruum per kilogram of body weight. This was repeated every six hours until death. Dicumarin was administered to another group of dogs according to the schedule of 5 mg. per kilogram 24 hours before operation, 10 mg. per kilogram the day of the operation and 10 mg. per kilogram the day following the operation. In others, *fibrin foam* (kindly donated

TABLE II.—*Correlation of Bacterial Spread with Roentgen Ray.*

Dog No.	Localization by Culture and/or X-ray	Appendix	Left Subphrenic	Left Lumbar Gutter	Right Subphrenic	Right Lumbar Gutter	Pelvis
B	Culture	*Cl. welchii* Proteus	*Cl. welchii* Proteus	Proteus	2 Coliforms *Cl. welchii* Proteus	2 Coliforms Proteus	2 Coliforms Proteus
	X-ray Iodochloral #6	+	−	+	−	+	+
C	Culture	*Cl. welchii* 2 Coliforms	*Cl. welchii* Strep. *B. aerogenes*	*Cl. welchii* 2 Coliforms	*Cl. welchii* 2 Coliforms	2 Coliforms	2 Coliforms *Cl. welchii*
	X-ray Iodochloral #6	+	−	+	+	+	+
E	Culture	Proteus 2 Coliforms	Proteus	Proteus 2 Coliforms	Proteus 2 Coliforms	Protues 2 Coliforms	Proteus 2 Coliforms Staph
	X-ray Iodochloral #6	+	+	+	+	+	+
L	Culture	*Cl. welchii* Proteus	*E. coli* *Cl. welchii*	Proteus	*Cl. welchii* Proteus	Proteus *Cl. welchii*	*Cl. welchii*
	X-ray Iodochloral #6	+	−	+	−	+	+
M	Culture	*E. coli* *Cl. welchii*	*E. coli* *Cl. welchii*	*E. coli* *Cl. welchii* 2 Colistridis	*E. coli* *Cl. welchii*	*E. coli* *Cl. welchii*	*E. coli* *Cl. welchii*
	X-ray Thorotrast #5	+	+	+	−	+	+
N	Culture	*E. coli* Beta. Strep.	*E. coli* Beta. Strep.	Proteus Beta. Strep.	Proteus	Proteus Beta. Strep.	Proteus Beta. Strep.
	X-ray Lipiodol #2	+	−	+	+	+	+
S	Culture	Proteus Clostridium	Clostridium Coliform	Clostridium Coliform	Clostridium *Cl. welchii* *E. coli* N. H. Strep.	Clostridium *Cl. welchii* *M. tetragenes*	Clostridium *Cl. welchii* *E. coli*
	X-ray Lipiodol #2	−	−	−	−	+	+
U	Culture	Coliform Proteus N. H. Strep.	Coliform	Coliform Clostridium	Coliform Clostridium N. H. Strep.	*Cl. welchii* Clostridium N. H. Strep.	Coliform Clostridium
	X-ray Thorotrast #5	+	+	+	+	+	+

by Sharpe and Dohme) was fastened in place with the use of the supplied human thrombin, either closely adjacent to the operated appendix, or widely distributed in the pelvis, left lumbar gutter and right and left subphrenic spaces. In some dogs, metallic pellets measuring 1.0 x 1.0 cm. cut from lead or zirconium foil were widely

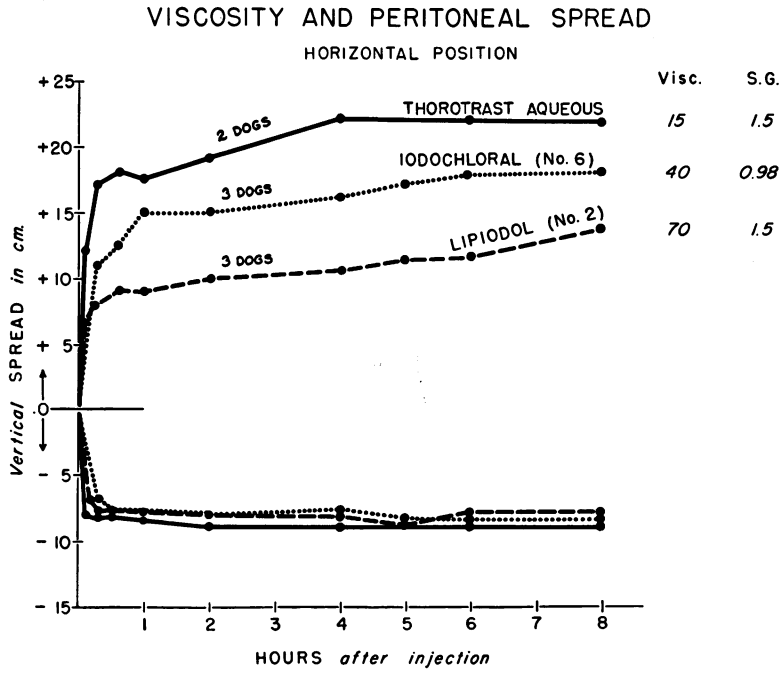


FIG. 2.—Effect of viscosity. The averaged limits of spread as measured on the roentgenograms of eight dogs injected with three different radiopaque mixtures of varying physical properties can be seen to be greater, the lower the viscosity. These dogs were maintained in the horizontal position throughout the period of these observations.

spread within the peritoneal cavity to demonstrate the capacity of the peritoneal surfaces to move and fix such large foreign bodies.

RESULTS

Spread within the Peritoneal Cavity. The nature of material being spread within the cavity is important in determining the rate and the direction of spread. With increasing viscosity, spread is slower as is shown in Figure 2. With increased specific gravity, in the dogs maintained in the vertical position, the direction of spread is that which would be predicated from the density gradient as is seen in Figure 3. After 24 hours within the lumen of the gangrenous appendix, the radiopaque materials become so diluted with intraluminal breakdown products as to retain little individuality and seem to spread quite uniformly regardless of their original physical properties. Previous irritation of the peritoneum, producing large quantities of fluid exudate, apparently speeds the spread of all radiopaque materials, although the high white cell content of this fluid may well limit the pathogenicity of the bacteria spreading with the media. Bacteria both by culture and tissue examination were found to spread more rapidly than any of the radiopaque media studied (see Table II).

The condition of the peritoneal cavity may well be a determining factor in controlling the passage of bacteria from a gangrenous appendix to the systemic circulation. Steinberg[38] was forced to inject air or administer peristalsis-inducing agents in order to insure perforation of ligated ap-

pendices before walling off occurred. In our experiments, the dogs showed paralytic ileus both clinically and fluoroscopically, and injected material simulating large bowel content failed to show any spread beyond the midline before six hours, or procedure. Tissue invasion (Fig. 4) and *in situ* bacterial multiplication were seen to be likewise enhanced by the absence of the normal clotting mechanisms.

In four of eight dogs studied, large metallic particles were collected by the omentum

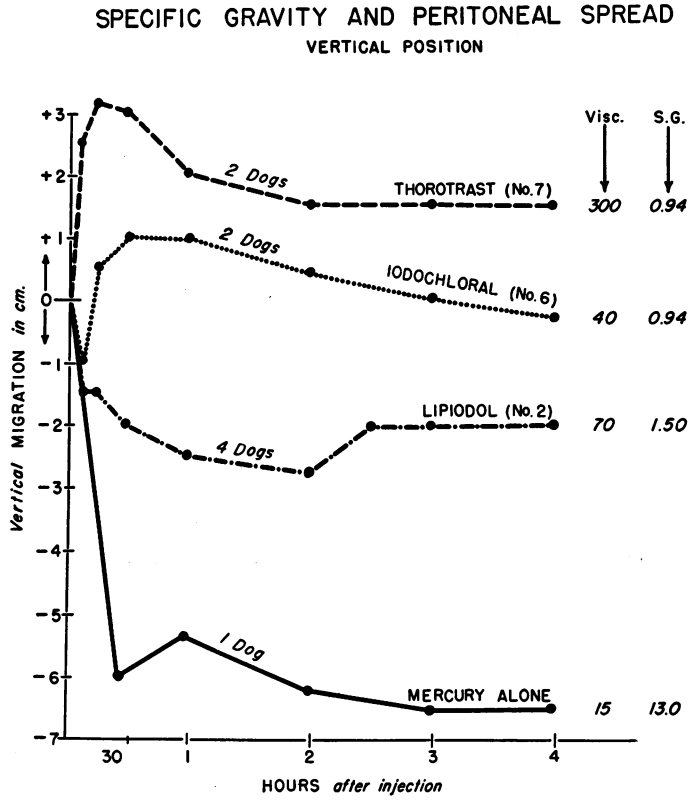
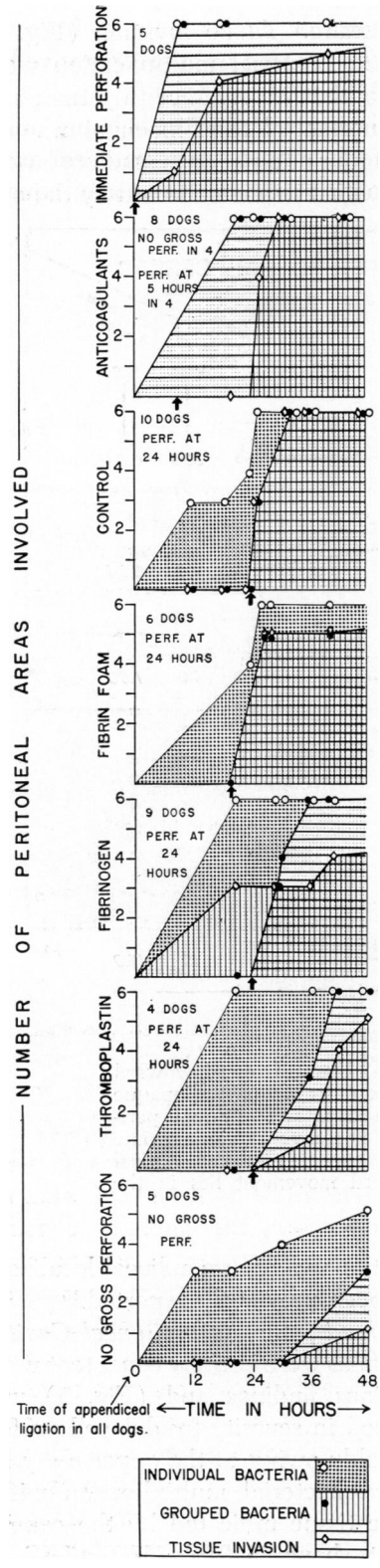


FIG. 3.—Effect of specific gravity. Upward or downward migration of the center of the radiopaque mass of four radiopaque media of different specific gravities in dogs with normal peritoneum, maintained in vertical position, is shown at various time intervals up to four hours. It would appear that the critical specific gravity for upward or downward movement lies in the range of 0.94 to 1.50.

above mid-abdomen before 12, if the dogs were maintained vertically. The presence of fibrinogen or thromboplastin was found to produce a fibrin gel in the peritoneal cavity, through which spread of all agents was markedly impeded. The presence of a systemic anticoagulant resulted in an extremely low viscosity peritoneal fluid, such as that seen without anticoagulants in the majority of dogs subjected to the Zintel into the area of appendiceal localization, as has been previously reported.[15]

Spread from the Peritoneal Cavity. Bacteriemias were entirely consistent with these previous findings and (Fig. 5) were increased in severity by delayed perforation, probably owing to the opportunity for protected bacterial multiplication within necrotic tissue indicated by the comparative counts shown in Table III.



Mortality figures are unfortunately not entirely comparable from group to group as the administration of anticoagulants in the presence of a ligated appendix was found to be so lethal a procedure that even in the absence of appendiceal perforation or any hemorrhage at autopsy, only a small fraction of these dogs could be maintained beyond 24 hours postligation, the time when the other control series were initially perforated. Accordingly, it will be noted that bacteremia figures for these dogs can be directly compared only with the five-hour delayed perforation control. The fibrinogen and thromboplastin-treated dogs perforated at 24 hours survived an average of 42 and 56 hours postperforation respectively, as compared with dogs to whom no agents were administered, and those receiving fibrin foam implants, who survived 35 and 37 hours postperforation respectively.

DISCUSSION

The mechanics of dissemination within the peritoneal cavity of foreign substances and the routes of disposal from the peritoneal cavity have been extensively studied.[1, 2, 9-12, 14, 16, 17, 22, 23, 25, 26, 28, 30-32] In general, these reports would indicate that spread within the peritoneal cavity is relatively unhampered by prior inflammation and not significantly affected by the position of the animal. Fowler's original paper, based on the just supposition that drainage by diaphragmatic lymphatics was a prime lethal factor, made no claims as regards the initial intraperitoneal dispersion of bacteria. Our results would seem to indicate

FIG. 4.—The peritoneal cavity was arbitrarily divided into six equal areas. Bacterial spread as seen by smear, section and culture was plotted against time. In the majority of dogs the area of the left subphrenic space was the last to be involved. Distinction was made between isolated bacteria on the surface of the peritoneum, bacteria in groups or colonies, and tissue invasion as manifested by free bacteria in muscle or lymphatics. It can be seen that with anticoagulants, tissue invasion is early and with fibrinogen and thromboplastin it is retarded as compared with controls.

that spread from the lower abdomen of relatively high specific gravity exudates, such as those from a gangrenous appendix, might be decreased by the semi-erect position. Urine and some contents of the small bowel of low specific gravity and low viscosity will probably spread rapidly upward with vertical position of the dog, and, being of low viscosity, would tend to spread both widely and rapidly throughout the cavity regardless of the position of the dog. Large bowel contents of relatively low specific gravity but high viscosity will tend to spread diffusely upward in the erect posture, but more slowly than either urine or small bowel contents. One can predict that the leakage of the high viscosity left colon content, such as might occur from a line of operative anastomosis, will take place far less rapidly than low viscosity small bowel contents or similar material from the large bowel resulting from preoperative intestinal antibiotics.

The spread of overwhelming numbers of bacteria within the peritoneal cavity has been presumed to be nearly equal to the spread of the radiopaque liquids. Actually the extent of solitary bacterial contamination within the cavity is somewhat more extensive than the spread of radiopaque liquids indicates. In evaluating the results of the bacteriologic studies, however, three factors must be borne in mind, first, that no peritoneal cavity opened under circumstances of the best operating technic can be sterile on closure, second, that some escape of bacteria from gangrenous gut in the absence of visible perforation is known to occur, and lastly that the integrity of a purse string closure in devitalized intestine

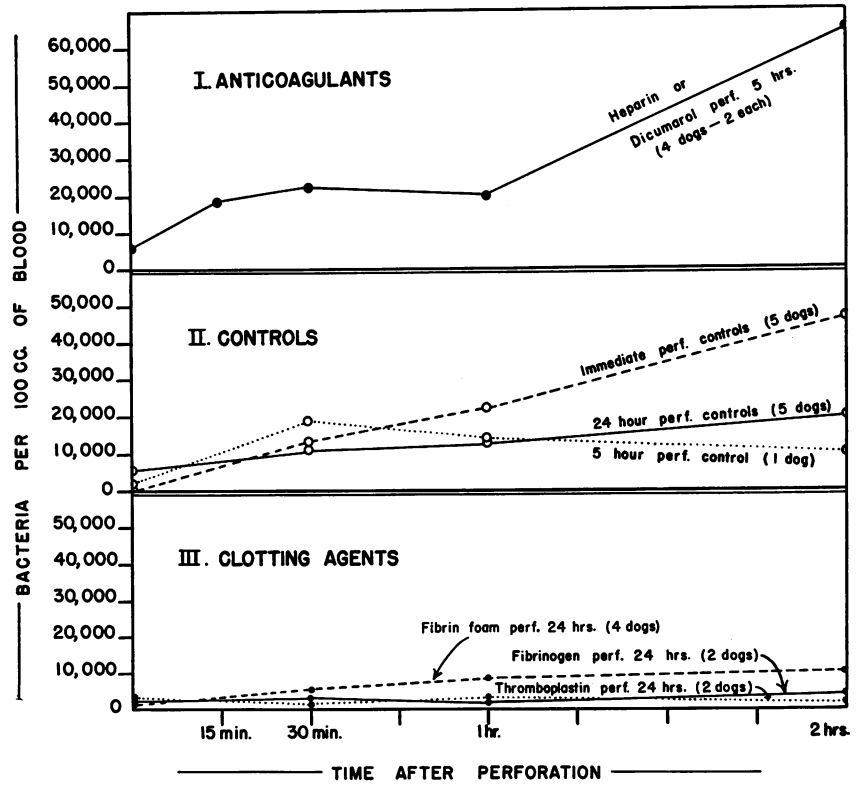


FIG. 5.—The effect of various agents on the bacteriemia seen after perforation follows fibrin formation closely. There is a significant bacteriemia seen in all dogs during the 24 hours before mechanical perforation.

(such as was used in some of these experiments) is subject to reasonable doubt.

The presence of a fresh fibrin mesh intraperitoneally appreciably slows tissue invasion and the spread of bacteria to the bloodstream, and may in part explain the results previously reported in animals with diminished plasma coagulability[19, 20] and their improvement with intraperitoneal whole blood.[29] That this is not merely the result of leukotaxine[35] secondary to fibrin breakdown[13] is shown by the apparent ineffectiveness of fibrin foam. Such reasoning makes plausible the enhanced virulence of fibrinolytic strains of bacteria intraperitoneally.[41]

Normal peritoneum can probably cope with low dosages of organisms. It is presumably the progressive overloading of local agents of resistance that determines the true extent of the peritoneal inflammation, and the explosive bacteriemia in the absence of fibrin blockade that leads to abrupt mortality.

TABLE III.

	Immediate Perforation at Time of Ligation			Perforation 24 Hours After Ligation		
	Blood	Appendix	Peritoneal Fluid	Blood	Appendix	Peritoneal Fluid
At Perforation	None	20,000	None	500/ 100 cc.	1.6 Billion/ 100 cc.	10 Million/ 100 cc.
2 Hours after Perforation	35,000/ 100 cc.	.....	1 Million/ 100 cc.	20,000/ 100 cc.	.....	10 Billion/ 100 cc.
12 Hours after Perforation	50,000/ 100 cc.	.....	100 Million/ 100 cc.	More than 500,000/ 100 cc.	.....	20 Billion/ 100 cc.
24 Hours after Perforation	200,000/ 100 cc.	.....	70 Billion/ 100 cc.	200,000/ 100 cc.	.....	50 Billion/ 100 cc.

SUMMARY

1. Radiopaque fluids and particulate matter, simulating in viscosity and specific gravity both urine and contents of various portions of the intestinal tract, spread more rapidly with low viscosity, and move under the influence of gravity according to the density difference between the radiopaque medium and the peritoneal exudate.

2. Individual bacteria spread more rapidly than any of the iodochloral, Thorotrast or Lipiodol mixtures studied.

3. Invasion of viable tissues by appendiceal flora is a slow process after contamination, with or without prior peritoneal irritation, either by injection of irritants or prior appendiceal ligation.

4. Tissue invasion and subsequent explosive bacteriemia can be reduced by the presence of an excess of intraperitoneal fibrinogen or thromboplastin and is increased in dogs receiving heparin or dicumarol. Fibrin foam was found to be without effect.

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