ted to peritoneal irrigation for uremia suggests that the mechanism of invasion in these patients was similar to that in the foregoing experiments.

Summary. Chemical peritonitis induced by repeated injections of monolate or gum-tragacanth in rabbits and dogs results in the appearance of *E. coli* in pure culture, in small to moderate numbers, in the inflamed peritoneum. Once this contamination is established, it continues for some time after the injections are discontinued. Eventually all cultures are sterile.

By exclusion of all other possible sources of contamination of the inflamed peritoneum, it appears that the *E. coli* found in the peritoneal exudate is derived from the intestinal lumen by transmural migration.

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17114. Transmural Migration of Intestinal Bacteria During Peritoneal Irrigation in Uremic Dogs.*

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Peritonitis due to *Escherichia coli* in pure culture occurs readily during peritoneal irrigation for the treatment of acute renal failure.[1] Clinical data suggested that the peritonitis was due to invasion of the peritoneum by the transmural migration of *E. coli* from the intestinal lumen.[1]

In a previous experimental study[2] it was demonstrated that transmural migration of *E. coli* can be induced by the intraperitoneal injection of strong irritants, but that bacterial peritonitis does not ensue. It was then considered desirable to determine whether the irrigating fluid used in treating acute renal failure can also provoke a bacterial invasion of the peritoneal cavity from the gut. The data to follow demonstrate that bacterial contamination is produced following intraperitoneal administration of this irrigating fluid in uremic dogs but not in normal dogs and that prophylactic oral antibiotic therapy is effective in preventing it.

Method. Normal dogs, and dogs made uremic by removal of both kidneys 24-72 hours previously, were treated as follows: Fifteen hundred to 3000 cc of sterile irrigating fluid‡ was injected into the peritoneal cavity by needle puncture under rigid sterile precautions. The fluid, as it escaped from the needle, just before and just after the puncture, was inoculated into dextrose broth. At the same time, swabs of the site of puncture of the skin, which had been prepared by shav-

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1 Frank, H. A., Seligman, A. M., and Fine, J., *Ann. Surg.*, 1948, **128**, 561.

2 Schweinburg, F. B., and Heimberg, F., PROC. SOC. EXP. BIOL. AND MED., 1949, **71**, 146.

‡ The 2 solutions used for infusion were those which had been used in patients for peritoneal irrigation.[1] Each was used in about half of the experiments. As there was no difference in their effect, the results are not considered separately.

	Solution A (g/l)	*Solution B* (g/l)
NaCl	7.25	7.4
KCl	0.19	0.05
$CaCl_2$	0.095	0.05
$MgCl_2 \cdot 6H_2O$	0.2025	0.22
$NaHCO_3$	1.5	0.77
Dextrose	9.5	5.0
Gelatin§	4.75	10.0
pH after sterilization	7.9	7.2-7.6

§ We are indebted to the Atlantic Gelatin Company for the gelatin used in these experiments.

TABLE I. Summary of Experiments.

Dog No.	Preliminary treatment		Infusion, days	Total vol. infused (cc) × 1000	Organisms in peritoneal fluid*		Cause of death	Gross peritonitis	
					E. coli, day	Others			
1	None		11	10.5	0	0	Distemper	No	
2	”		13	16.9	0	0	Sacrificed	”	
3	”		16½	40	0	0	”	”	
4	Bilateral nephrectomy	(1)†	9	10	6‡	0	Uremia	”	
5	” ”	(1)	4	9.4	0	0	Pulmonary edema	”	
6	” ”	(1)	6	11.4	5	*A. aerogenes*	Uremia	”	
7	” ”	(2)	9	19.2	7	”	”	”	
8	” ”	(2)	11	30.1	9	”	”	”	
9	” ”	(2)	14	44.9	7	”			
						Para-coli	”	”	
10	” ”	(3)	3	7.2	0	0	”	”	
11	” ”	(3)	5½	10.5	6	*A. aerogenes*		Fibrinopurulent	
						B. pyocyaneus	”	peritonitis	
12	” ”	(3)	9	37.8	12	*A. aerogenes*	”	No	
13	” ”	(3)	4	11.8	4	*A. aerogenes*	” enteritis	Diffuse hemorrhagic	
						B. megatherium		peritonitis	
14	” ”	(3)	13	39.5	7	0	”	No	
15	” ”	(1)	8½	39.2	8	0	”	No; no foreign body reaction	Sterile rubber tubing in peritoneal cavity
16	” ”	(1)	2	5.5	0	0	Pneumonia	Fibrinous adhesions about foreign bodies	Sterile stainless steel and rubber tubing in peritoneal cavity
17	” ”	(2)	4½	14.5	3	*Strep. fecalis*	Uremia	No; no foreign body reaction	Same
18	Sulfathalidine and streptomycin orally 5 days, then bilateral nephrectomy	(2)	6	18.5	0	0	”	No	
19	Sulfathalidine and streptomycin orally 4 days, then bilateral nephrectomy	(2)	5	17.8	0	0	”	”	
20	Same	(3)	12	44.7	0	0	Sacrificed	”	
21	Same	(3)	9	38.6	0	0	Uremia	”	

*Organisms, when present, persisted from the day first found until death, with the exception of inconstant growth of *A. aerogenes* in Dog 9.
† Days before start of infusions.
‡ Days after start of infusions.

ing, alcohol and zephiran, were also inoculated into dextrose broth. To establish the initial sterility of the peritoneal cavity, fluid aspirated from the peritoneal cavity shortly after the first infusion was inoculated into dextrose broth, on agar and endo plates and into anaerobic media.‖ Infusions were given twice daily and the foregoing procedures were repeated on each occasion, except that just preceding each subsequent infusion all the fluid which could be aspirated was removed and a sample inoculated into the various media. Cultures were observed for 10 days unless they became positive earlier.

Three normal dogs (No. 1-3) received a total of 10-40 liters in a period of 11-16 days. In 2, very little of the infused fluid was recovered by aspiration, but in the third, 30 of the 40 liters given were recovered.

Eighteen dogs were made uremic by removal of both kidneys. They are divided into 3 groups. The first group of 11 (No. 4-14) was treated in the same way as the normal dogs, but the food and fluid offered postoperatively was not consumed. In the second group of 3 (No. 15-17) a sterile foreign body (a rubber or stainless steel tube or both) was placed in the peritoneal cavity at the time of nephrectomy. In the third group of 4 (No. 18-21) 0.10 g of streptomycin and 1.0 g of sulfathalidine were given orally for 4-5 days prior to nephrectomy. Daily aerobic and anaerobic cultures of the stool were prepared and observed for several days preceding nephrectomy.

Blood was taken for culture from all dogs every second day until death.

Results (Table I) *Normal Dogs.* In all 3 normal dogs a few leucocytes per high power field appeared in the peritoneal fluid for the first time on the third day of the infusions. They increased only slightly in number thereafter. The peritoneum at the end of the experimental period was smooth, glossy, and entirely free of any reaction. No growth was obtained in any of the peritoneal fluid cultures. It is, therefore, evident that exposure of the peritoneal cavity of a normal dog to these irrigating fluids for much of each day for a period of some 2 weeks does not produce detectable bacterial contamination.

In 10 rabbits treated and observed in the same way for 14-16 days, the results were precisely the same.

Uremic Dogs. Untreated dogs survive not more than 3-4 days after bilateral nephrectomy. Two of the 11 dogs in Group I (No. 4-14) died on the 3rd and 4th day of infusion respectively. The aspirated fluid remained sterile. In the remaining 9, the aspirated fluid was sterile for the first 3 days of infusion. Leucocytes in the aspirated fluid appeared for the first time on the 2nd or 3rd day, and increased only slightly in number thereafter. Positive cultures were obtained for the first time from the fourth to the ninth day of infusion, and remained positive in all 9 dogs until death, which occurred 5-16 days after the infusions were started. *E. coli* was the contaminating organism in all instances; in pure culture in 2, together with *Aerobacter aerogenes* in 7. The number of colonies was always small, with *E. coli* predominating, except in Dog. 11. No clostridia were found in any of the anaerobic cultures. Only 2 dogs (No. 11 and No. 13) developed purulent peritonitis. In Dog 11, *E. coli, A. aerogenes* and *Pseudomonas aeruginosa* (*B. pyocyaneus*) were isolated. In Dog 13, *E. coli* and *Bacillus megatherium* were isolated.

In Group II (Dogs 15-17), contamination appeared for the first time on the 8th day of infusion in Dog 15, and on the 3rd day in Dog 17. Peritonitis did not develop in these dogs. Dog 16, which died of pneumonia 72 hours after nephrectomy, showed a sterile peritoneal inflammation after 48 hours of infusion. It appears that the sterile foreign body does not influence the time or degree of invasion of the peritoneal cavity by intestinal organisms.

In Group III (Dogs 18-21), the standard stool cultures remained sterile. A fecal suspension three times as dense as the standard yielded scanty growth of *Streptococcus fecalis* and diphtheroids, but no *E. coli* or clostridia. None of the four dogs in this group showed bacterial contamination of the aspirated fluid at any time, although the leucocyte response was the same as in the other

‖ Anaerobic cultures were done in 6 of the uremic dogs.

nephrectomized dogs. Their survival times were 5, 6, 9 and 12 days after the start of the infusions.

Death was due to uremia in all dogs in all 3 groups (except Dog 16) with purulent peritonitis contributing in Dogs 11 & 13.

The blood cultures were uniformly sterile. Cultures from the skin of the abdomen and of the irrigating fluid were always sterile before the infusion. Exceptionally a scanty growth was obtained from the skin after the infusion was given. The organisms recovered were the usual skin inhabitants, *i.e. Staphylococcus albus, Bacillus subtilis,* diphtheroids or sarcinae, and not the intestinal flora recovered from the aspirated fluid (Table I).

Discussion. The bacteria recovered from the aspirated fluid are clearly of intestinal origin, 1, because of the species found and 2, because their elimination from the intestine by oral chemotherapy prevents peritoneal contamination. The route of invasion is transmural, since the blood cultures were negative. The number of bacteria recovered in cultures was always small. Presumably this number is a measure of the balance between the number invading and the number leaving or being destroyed. It has been observed[3] that the peritoneum of dogs can destroy or eliminate a large number of bacteria without reacting with severe inflammation. Since the peritoneal cultures were uniformly negative in normal irrigated dogs, it appears that the uremic state makes the intestinal wall more permeable to bacteria or reduces the ability of the peritoneum to destroy them. The fact that only two of the fourteen uremic dogs which showed invasion developed purulent peritonitis may be due to the small number of invading bacteria or to the considerable natural resistance of the dog to these organisms.

It is noteworthy that the organisms recovered from the uremic dogs were the same as those from uremic patients treated with the same irrigating fluid.[1] Since the leucocyte response to the fluid in the normal animal is very slight, the fluid is at most a very mild stimulus to inflammation. Since neither the irrigating fluid alone nor uremia alone[1] is capable of producing peritoneal contamination, it appears that both factors acting together are responsible for the bacterial contamination. The precise role played by the uremic state is not clear. The fact that many of the uremic dogs showed an edematous intestinal wall at autopsy suggests that transmural migration may be due to the edema resulting from the absence of renal excretion, and that the uremia itself, so far as this phenomenon is concerned, is merely coincidental. However, in our clinical experience, the incidence of peritoneal contamination in irrigated patients was no less in those in whom overhydration was avoided. The ready development of *E. coli* peritonitis in man following contamination, as compared to animals, may be due to a lower natural resistance to *E. coli,* which the uremic state may further reduce.

This experimental study suggests that the treatment of acute renal failure in man by peritoneal irrigation may prove less hazardous, if a sufficient reduction of intestinal bacteria can be accomplished before treatment and maintained during treatment.

Summary and conclusions. Repeated intraperitoneal infusion of the fluid used for peritoneal irrigation in uremic patients, administered aseptically to healthy rabbits and dogs for 11-16 days, produced a moderate leukocytic response, but the peritoneum remained free of bacteria or visible inflammatory reaction. In uremic dogs, however, bacterial contamination of the peritoneal fluid developed after the 4th day of irrigation. The micro-organisms found were *E. coli* alone or with *A. aerogenes.* Occasionally, several other species, normally found in the intestine, appeared; but clostridia were never found. Preliminary oral administration of streptomycin and sulfathalidine prevented contamination of the peritoneal fluid. Blood cultures were uniformly sterile throughout the period of observation. It is concluded that irrigation of the peritoneal cavity of uremic dogs causes transmural migration of intestinal bacteria and that oral chemotherapy can prevent such contamination.

[3] Steinberg, B., Goldblatt, H., *Arch. Int. Med.,* 1927, **39**, 446; 1927, **39**, 449.

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