THE TREATMENT OF ACUTE RENAL FAILURE BY PERITONEAL IRRIGATION*

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CERTAIN TYPES of acute renal failure need not be fatal if the period necessary for repair can be provided by utilizing an extrarenal pathway as a temporary substitute for the normal excretory function of the kidney. We have already published the experimental data[1] and one clinical experience[2] demonstrating the possibilities of continuous peritoneal irrigation for this purpose.

The peritoneal membrane has long been recognized to be an excellent dialyzing membrane, readily permeable to water and crystalloids.[3] Peritoneal irrigation makes use of this dialyzing capacity for the removal of diffusible substances from the plasma and ultimately from the extracellular fluid. Proper adjustment of the composition of the irrigating fluid prevents the depletion below normal concentration of the plasma of its normal constituents and thereby protects the chemical structure of the extracellular fluids.

We have referred elsewhere[1] to efforts by others† to utilize the peritoneum. In an experimental study in dogs[1] it was found that adequately conducted peritoneal irrigation would provide 40–75 per cent of normal kidney function in terms of urea clearance, correct acidosis, and prevent death from uremia following bilateral nephrectomy. In the present report our clinical experience with this method will be discussed.

METHOD

The irrigation fluid is modified Tyrode's solution containing the following amounts of anhydrous substances per liter: NaCl 8.0 grams, KCl 0.2 gram, $CaCl_2$ 0.1 gram, $MgCl_2$ 0.1 gram, NaH_2PO_4 0.05 gram, $NaHCO_3$ 1.0 gram, and dextrose 1.5 grams. It is prepared in large volume as follows: Fifteen liters of freshly distilled sterile water are run into a sterile 20-liter pyrex carboy. With the exception of sodium bicarbonate all the salts and the glucose for 18 liters of irrigating fluid are dissolved in two liters of distilled

* Part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

† Additional references: Bliss, S., Kastler, A. O., and Nadler, S. B., Proc. Soc. Exp. Biol. and Med., 29, 1078, 1932; Haam, E. V. and Fine, A., Pros. Soc. Exp. Biol. and Med., 30, 396, 1932; Rhoads, J. E., Am. J. Med. Sci., 196, 642, 1938; Wear, J. B., Sisk, I. R., and Trinkle, A. J., J. Urol., 39, 53, 1938; Abbott, W. B. and Shea, P., Am. J. Med. Sci., 211, 312, 1946.

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water and autoclaved. The $NaHCO_3$ for 18 liters is dissolved and autoclaved separately in a liter of distilled water. *It is important not to heat the bicarbonate solution with the other salts and glucose because of precipitation of calcium and magnesium salts and the production from glucose of toxic substances (probably aldehydes), which may be fatal.* Sterile solutions in small volume of the sodium salt of heparin (0.25–0.50 mg. per liter), of penicillin (2,500–5,000 units per liter) and of sulfadiazine (60–120 mg. per liter) together with the solutions of the salts and glucose are added to the water in the carboy at room temperature. Heparin is used to prevent the formation of fibrin and intestinal adhesions. Penicillin is used for prophylaxis against infection. Sodium sulfadiazine should not be added if renal sensitivity to sulfonamides is present or suspected.

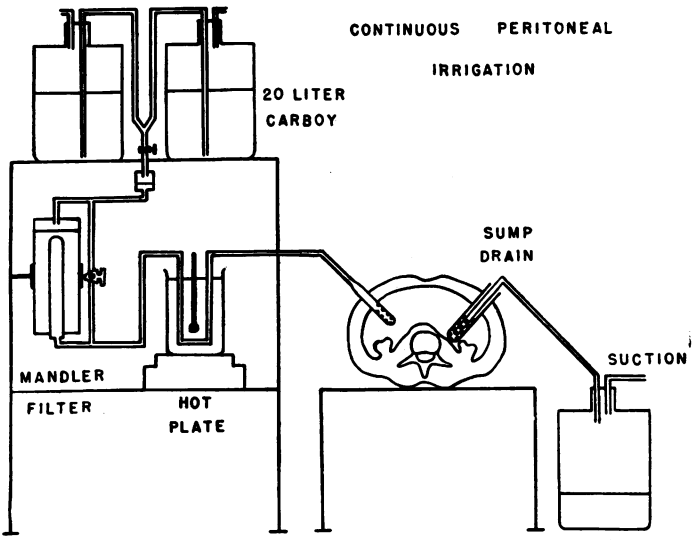

FIG. 1.—Diagrammatic representation of the circuit for continuous peritoneal irrigation.

Occasional modifications in the composition of the fluid were made, as indicated in the case reports. Further changes may be indicated as more experience is acquired. Since edema of the peritoneal membrane does not occur in consequence of irrigation, protein is not used as a rule. When protein seems indicated (as in Case 4), gelatin is used, since the large amount of protein required makes the use of human albumin impracticable, though probably preferable. If gelatin solution, which is acid in reaction, is used it should be brought to pH 7.5 with concentrated NaOH.

The fluid flows by gravity from two elevated carboys through siphon tubes, joined by a Y-tube, through a drip-bulb, then either directly or preferably through a Mandler (Berkefeld) filter to a glass U-tube in a water bath (40°C.–45°C.) and thence to the peritoneal inlet-tube (Fig. 1). The filter candle is eight inches long and one inch in diameter and permits a flow

of 40–60 cc./min. of a protein-free solution when the carboys are elevated two to three feet above the bed, as indicated in the photograph (Fig. 2). The inlet tube is a rubber catheter or a perforated small stainless steel tube. The outlet tube used in earlier cases was a whistle-tip catheter or a large-bore mushroom-tip catheter connected to a receiving carboy on the floor. The outlet tube proved unsatisfactory because of frequent plugging. Accordingly, in later cases a stainless steel sump-drain (Figs. 1 and 3), which is similar to the metal-perforated suction tube commonly available in operating rooms, was used as an outflow tube attached to a constant suction line. This has

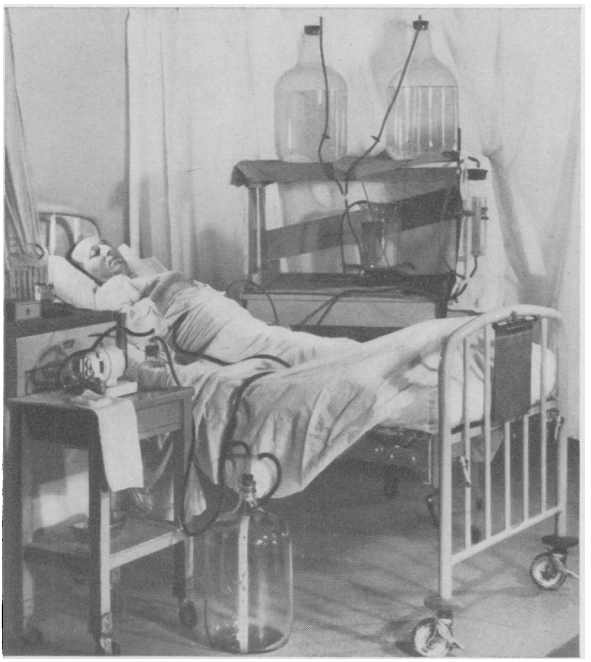

FIG. 2.—Photograph of apparatus for peritoneal irrigation.

proved entirely satisfactory and remains patent indefinitely. The inflow and the outflow tubes are inserted under local anesthesia into the peritoneal cavity, through small incisions, one in each flank. The sump-drain is directed into the cul-de-sac.

Collateral therapy, referred to in the case reports, is necessary for maintaining nutrition and water-soluble vitamin balance, correcting anemia, acidosis, hypoproteinemia and for the treatment of associated disease.

CASE REPORTS

CASE 1.—B.I.H. No. 82847: I. E., female, age 49, was transferred to us from another hospital because of uremia caused by ureteral obstruction due to recurrent carcinoma of the cervix. She had entered the other hospital complaining of headache, anorexia, nausea, vomiting, and weight loss. Examination at that time showed her to be alert and coöperative. She was afebrile. She had purpuric spots on the arms

FIG. 3-A

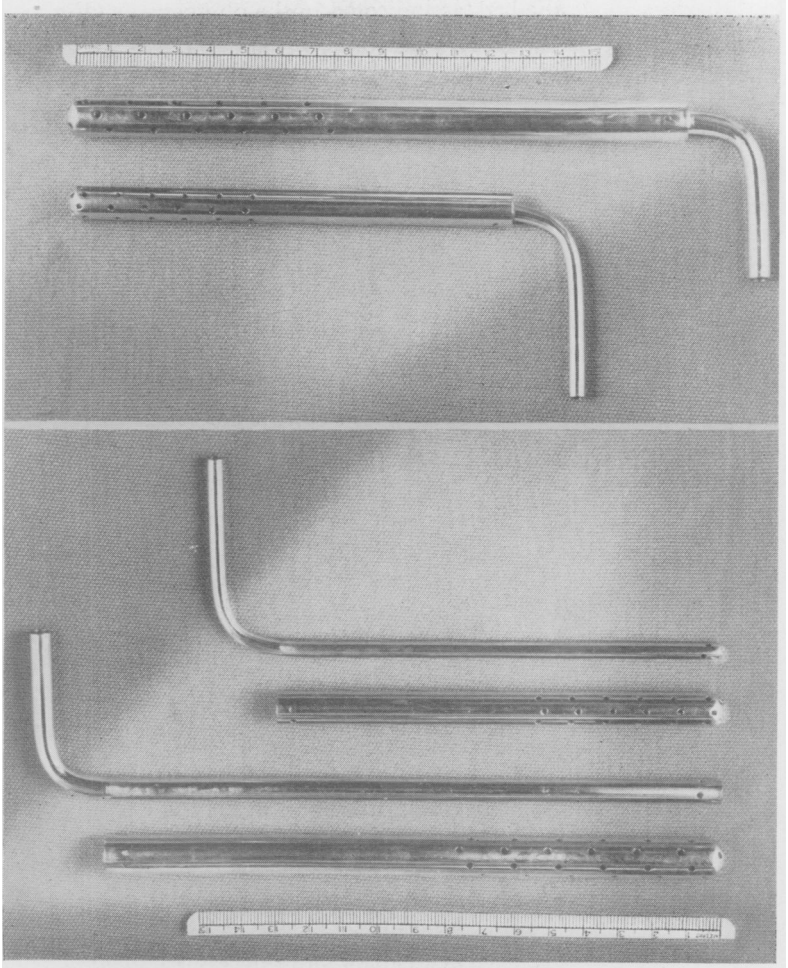

FIG. 3-B

FIG. 3-A and FIG. 3-B.—Sump-drain.

and legs and multiple fresh hemorrhages in the optic fundi. The blood pressure was 230/120. The apex of the vagina was fixed in a hard irregular tumor mass which extended laterally to fill the pelvis. The urine contained 2+ albumin and occasional white and red cells. The hemoglobin was 100 per cent. The blood N.P.N. was 105 mg. per cent, the blood urea N 83 mg. per cent. At cystoscopy, no excretion of phenolsulfonphthalein was observed from the left ureter and only 2 per cent from the right ureter in ten minutes. Catheters reached the kidneys through tortuous ureters. Retrograde pyelograms showed dilatation of both renal pelves.

Nausea and vomiting necessitated parenteral alimentation. In spite of an adequate fluid intake, the total urine output was 10 to 40 cc. per 24 hours in each of the last four days prior to transfer to this hospital. Headache increased and mental alertness diminished. A pericardial friction rub appeared. She showed generalized edema. The patient's condition and prognosis were too poor to warrant nephrostomy or ureterostomy.

Upon transfer to this hospital two mushroom catheters were placed in the peri-

TABLE I

CASE 1. BLOOD UREA CLEARANCE* BY PERITONEAL IRRIGATION TESTED FOR SHORT PERIODS AT VARYING RATES OF FLOW

Flow Rate Cc./Min.	Peritoneal Fluid Urea N Conc. Mg. %	Blood Urea Clearance Cc./Min.
19	50.4	11.2
47	32.1	14.5
58	23.9	15.6
66	13.8	9.7
83	13.0	11.7
127	11.1	14.3

* Blood urea clearance by peritoneal route was calculated in the same way as urinary urea clearance using peritoneal fluid rate of flow and urea concentration in place of urinary values.

toneal cavity, which contained a large volume of free fluid (0 day, Fig. 4). The following day, when the blood N.P.N. was 195 mg. per cent, irrigation was started. Test periods of irrigation, with one-half hour intervals in between, at rates of flow varying from 19 cc./min. to 127 cc./min. indicated a maximum clearance of blood urea when the flow rate varied 40–60 cc./min. (Table I).

The next day continuous irrigation was carried out at a rate of 45 cc./min. for 24 hours. In this period 23 grams of urea were removed and an average blood urea clearance value of 16 cc./min. was attained. After an interval of four hours irrigation was resumed for another 24 hours, this time at an average rate of 60 cc./min. In this period 24 grams of urea were removed and the blood urea clearance value was 23

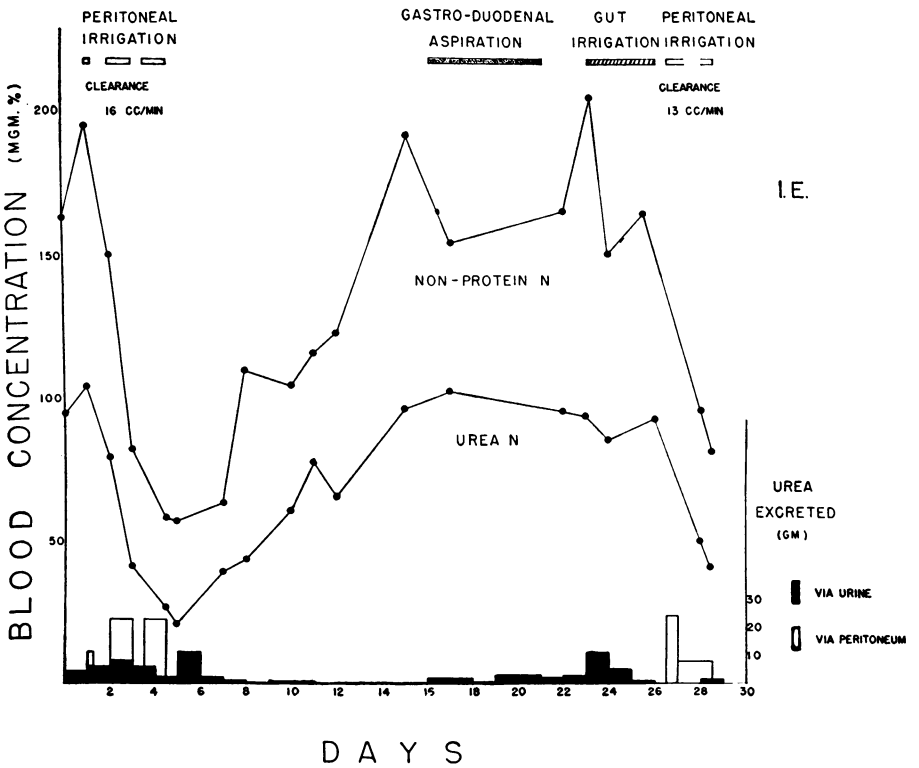

FIG. 4.—Case 1: Course of azotemia and daily urea elimination by the kidneys and by the peritoneum.

cc./min. After these two and one-half days of intermittent peritoneal irrigation, the blood N.P.N. concentration was 57 mg. per cent and the blood urea N was 21 mg. per cent. The patient was relieved entirely of headache, anorexia, nausea, and vomiting, and was alert. The blood pressure remained unchanged Transfusions were given to correct anemia. The irrigation produced no discomfort and the tubes required only occasional attention when the outflow catheter blocked.

During the period of peritoneal irrigation the volume of urine excreted increased up to 1,400 cc. per day. However the urea N content of the urine did not exceed 400 mg. per cent and total daily urinary urea excretion did not exceed ten grams. In view of the correction of the uremia and the apparent return of urine flow, peritoneal irrigation was discontinued.

Urinary output fell again and the clinical and chemical evidence of uremia gradually returned. Both peritoneal catheters were blocked. Nausea and vomiting recurred. A Miller-Abbott tube was passed and gastroduodenal suction instituted. The fluid removed was replaced by physiologic saline given intravenously. When the volume of aspirated fluid was less than 500 cc. per day its urea N content reached 64 mg. per cent, but when over 3,000 cc. per day was aspirated its urea N content was only 15 mg. per cent. Not more than one gram of urea per 24 hours was obtained by gastroduodenal aspiration. The uremic state was not improved.

Under spinal anesthesia an isolated 12-inch loop of ileum, with both ends exteriorized, was constructed in order to determine whether irrigation of the intestine in man would function adequately when peritoneal irrigation was impossible for one reason or another. Scattered omental and peritoneal metastases were found and histologic examination of one nodule disclosed undifferentiated carcinoma. No evidence of peritoneal inflammation from the preceding irrigation was found. The ends of the peritoneal catheters were firmly encased in omentum. Irrigation through the loop of

TABLE II

CASE 1: BLOOD UREA CLEARANCE BY IRRIGATION OF ILEAL LOOP TESTED FOR SHORT PERIODS AT VARYING RATES OF FLOW

Flow Rate Cc./Min.	Irrigation Fluid Urea N Conc. Mg. %	Urea Clearance Via Intestine Cc./Min.	Urea Clearance Via Intestine Cc./Min./In. Intestine Length
7.8	7.0	0.6	0.5
14.6	3.3	0.54	
15.5	2.9	0.48	.04
15.8	3.0	0.52	
32.2	1.4	0.52	
46.0	0.7	0.36	.03
63.0	0.5	0.34	
166.6	0.2	0.31	

ileum for short test periods at various rates showed so poor a clearance of blood urea (Table II) as to indicate that perfusion of a loop 200 inches long would be required to achieve a blood urea clearance of 10 cc. per minute, a rate which is approximately the minimum clearance necessary to avoid the development of uremia.[4] In the next three days, during which postoperative convalescence was entirely satisfactory, continuous irrigation through the loop at a rate of about 15 cc./min. was performed. The average urea clearance value per 24 hours was 0.56 cc./min. and the total amount of urea removed in the 24-hour period was only 0.1 Gm. (Fifty per cent magnesium sulfate irrigated through the loop was ineffective in increasing fluid and urea output and produced nausea and vomiting.) The blood urea N level was not improved and the patient's clinical condition became steadily worse. She lapsed into uremia and seemed moribund.

Two straight catheters were then introduced into the peritoneal cavity, under local anesthesia. They were passed with the aid of a stylet alongside the emerging

ends of the isolated loop of intestine. In the subsequent 24 hours, 38 liters of fluid were irrigated through the peritoneal cavity and 30 liters in the following 36 hours. An average blood urea clearance value of 13 cc./min. was attained and 35 Gm. of urea removed, with resulting satisfactory reduction in blood levels of N.P.N. and urea N. Clinical evidence of uremia disappeared. Irrigation was discontinued at this time.

Thereafter nothing was done to prevent the recurrence of uremia, steadily progressive anemia and malnutrition. The patient was kept comfortable by symptomatic therapy. She died a month and a half after irrigation therapy was ended. During this terminal period she excreted up to 1,000 cc. of urine daily and the progression of the uremic state was very slow.

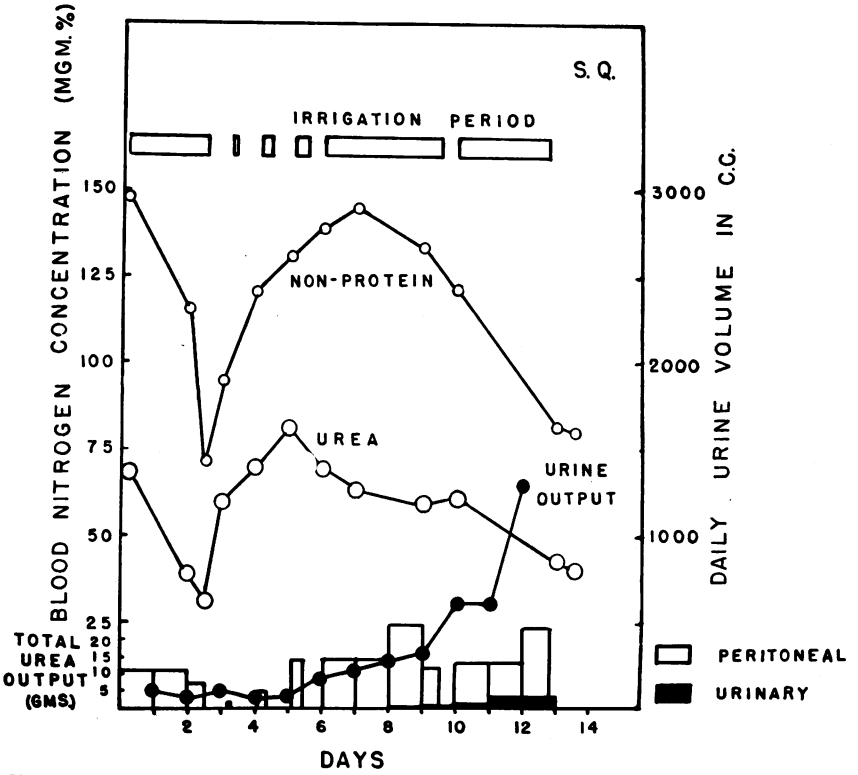

FIG. 5.—Case 2: Course of azotemia and daily urea elimination by the kidneys and by the peritoneum.

Autopsy showed the pelvis filled with carcinoma and scattered metastases in omentum and liver. The lower ureters were narrowed by tumor tissue so that there was considerable difficulty in forcing urine through them. The upper ureters were dilated. The kidneys were small and had dilated pelves and calices, surrounded by a narrowed rim of cortex. Microscopically they showed only edema and tubular degeneration. There was no evidence of peritonitis.

COMMENT: This case was our first clinical trial of continuous irrigation for uremia. It was learned that continuous peritoneal irrigation can be carried out without discomfort to the patient and without the production of peritonitis. An optimal rate of irrigation was determined and shown to be capable of rapidly reducing the blood levels of nitrogenous substances to normal with simultaneous correction of the uremic state.

It was learned further that irrigation of the intestine, which would have advantages over peritoneal irrigation if effective, is not a satisfactory substitute.

CASE 2.—B. I. H. No. 83789: S. Q., a 14-year-old girl, entered another hospital because of repeated nose bleeds of one month's duration. She was found to have a low grade fever, mycrocytic, hypochromic anemia, a loud systolic apical murmur, left axis deviation and an elevated sedimentation rate. The diagnosis of active rheumatic fever was made. She was given ferrous sulphate and 100 grains of aspirin daily. After five days of salicylate therapy, nausea, vomiting, marked hyperventilation and stupor were noted. The blood pH was 7.45 and CO_2 combining capacity was 20 volumes per cent. These findings were attributed to salicylate poisoning which is said to produce a primary respiratory alkalosis from central stimulation,[5] with a compensatory fall in alkali reserve. She was given 10 per cent CO_2 inhalations, morphine, 1.2 grams of ammonium chloride, 4,500 cc. of glucose in saline and 500 cc. of blood, later found to be incompatible. Seven hours after the transfusion she showed hemoglobinemia and hemo-

TABLE III

CASE 2: DAILY EXCRETION OF UREA BY PERITONEAL IRRIGATION AND BY THE KIDNEYS

	Peritoneal Fluid				Urine				Blood	Blood Urea Clearance (Cc./Min.)	
Days*	Volume Cc.	Flow Rate Cc./Min.	Urea N Mg. %	Total Urea Gm.	Volume Cc.	Flow Rate Cc./Min.	Urea N Mg. %	Total Urea Gm.	Urea N Mg. %	Peritoneal	Renal
0	9250	6.0	61	11.3	0	—	—	—	68	5.4	
1	9250	6.0	61	11.3	108	.08	20	.04	55	6.7	
2	9000	12.5	38	6.8	64	.05	15	.02	35	13.5	
3	2000	11.0	56	2.2	109	.08	60	.13	60	10.3	
4	3000	8.0	76	4.6	60	.04	40	.05	70	8.7	
5	9000	16.6	77	13.9	74	.05	74	.11	82	15.6	
6	18000	12.5	39	14.0	184	.13	40	.15	68	7.2	
7	18000	12.5	39	14.0	210	.15	109	.46	63	7.7	0.25
8	24000	16.6	50	24.0	260	.18	89	.46	60	13.8	0.27
9	12000	16.6	50	12.0	305	.21	122	.75	60	13.8	0.43
10	18000	12.5	37	13.3	610	.43	78	.95	62	7.5	0.54
11	18000	12.5	37	13.3	610	.43	260	3.00	55	8.4	2.01
12	36000	40.0	32	23.0	1300	.88	118	3.10	45	28.5	2.40

* From the start of irrigation; numbers correspond with days indicated in Fig. 5.

globinuria. The pH of the urine was 4.5. She was given sodium bicarbonate and sodium lactate. The temperature rose to 103° F. In the subsequent two days she voided no more than 30 cc. of urine per day. She remained hyperpneic and stuporous, with a blood CO_2 combining capacity at or below 30 volumes per cent. Diathermy to the kidney areas failed to increase urine output.

The patient was transferred to us 48 hours after the hemolytic reaction was recognized. On admission, she was pale, edematous and stuporous. She coughed frequently. There were diminished breath sounds and râles at both lung bases. The heart was enlarged, with a loud apical systolic murmur and thrill. Pulse rate was 110. The rectal temperature was 100.6° F., and the respiratory rate 30 per minute. The urine was clear and straw-colored, alkaline, sp. gr. 1.010, albumin 4+, 15–20 W.B.C. and R.B.C. The red cell count was 2.45 millions and the Hb 36 per cent. The blood N.P.N. was 78 mg. per cent. Chest roentgenograms showed mitral valvular disease, consolidation of both lower lobes, and questionable left pleural effusion.

In view of the brief duration of the anuria and the complicating illnesses, uremia was not considered the immediate primary problem. Accordingly, peritoneal irrigation was deferred for 36 hours. During this time she was given 1,000 cc. of blood in two transfusions, glucose in distilled water in small volume, parenteral penicillin (100,000

units per 24 hours) and sodium sulfadiazine (2.5 Gm. per 24 hours). Mental clarity improved and temperature and pulse returned to normal. The total urine output in this period was less than 30 cc.

Without removing the patient from bed, two whistle-tip rubber catheters were introduced, under local anesthesia, into the peritoneal cavity and irrigation was begun. Figure 5 and Table III indicate the effect of the irrigation in terms of total urea removed, changes in blood level of nonprotein and urea nitrogen and calculated urea clearance. In the early period flow rates considerably slower than optimal were used because recurring difficulty with the outflow tube led to recurring distention of the peritoneal cavity with fluid. Repeated adjustments of the outlet tube were necessary. In spite of this, significant blood urea clearance was achieved, blood nitrogen levels were markedly improved, the blood CO_2 combining capacity rose to 48 volumes per cent, and alertness returned. Nevertheless, she remained sick, exhibiting a low-grade swinging fever, evidence of congestive heart failure, pneumonia, and episodes of paroxysmal dyspnea, cyanosis and tachycardia. Gastric distention required suction drainage. The hemoglobin level was restored to 80 per cent by transfusion. She was fully digitalized and penicillin and sulfadiazine therapy were continued. Since she was no longer uremic and since the avoidance of abdominal distention was desired, peritoneal irrigation was almost completely discontinued for two days, during which the clinical and chemical evidence of uremia recurred. The CO_2 combining capacity dropped to 24 volumes per cent.

Accordingly, two large-bore mushroom-tip rubber catheters, instead of whistle-tip catheters previously used, were implanted in the peritoneal cavity through small lateral abdominal incisions made, under local anesthesia. No evidence of peritonitis was seen. Irrigation through these tubes proceeded satisfactorily although blockage of outflow did recur from time to time. The uremic state was corrected. During this period, ileus required almost continuous Miller-Abbott tube therapy. The peritoneal outflow fluid in the subsequent week remained sterile. On the last day of irrigation the colon bacillus was found in the outflow fluid. In spite of a complexity of confusing symptomatology chiefly referrable to the cardiorespiratory system, the general trend of the clinical condition was one of gradual improvement and all evidence of uremia eventually disappeared.

Meanwhile, there was evidence of recovery of renal function. On the second day of irrigation, 5.5 days after the transfusion reaction, 108 cc. of urine were excreted. On each of the subsequent four days from 60 to 110 cc. of urine were excreted. The urea content of this urine was less than 75 mg. per cent, so that the total urinary excretion of nitrogen was negligible and uremia recurred when peritoneal irrigation was interrupted. On the sixth day of irrigation the urine volume increased to 184 cc. and continued to increase thereafter until it reached 1,300 cc. on the 12th day of irrigation, or 15.5 days after renal shutdown. The urinary urea excretion, however, did not keep pace with the recovery of volume output and was still insufficient to prevent recurrence of uremia. Since improvement in kidney function seemed to be progressive, irrigation was temporarily discontinued. On the next day (16th day) when she seemed very much better and indeed apparently convalescing, she suddenly died, following a severe paroxysm of dyspnea. Postmortem examination disclosed multiple small pulmonary emboli, the sources of which were mural thrombi in the right ventricle and auricle. There was a minimal amount of rhemuatic heart disease and vegetative endocarditis. There was no peritoneal reaction of consequence at the site of the catheters but 100 cc. of turbid fluid containing the colon bacillus was found in the pelvis, which also showed a low grade inflammation with delicate, fibrinous adhesions between loops of intestine. The kidneys were swollen and pale except for congested pyramids. Microscopically, they showed a few brown granular hemoglobin casts in the tubules. Most of the tubules were dilated and lined with flattened regenerated epithelium.

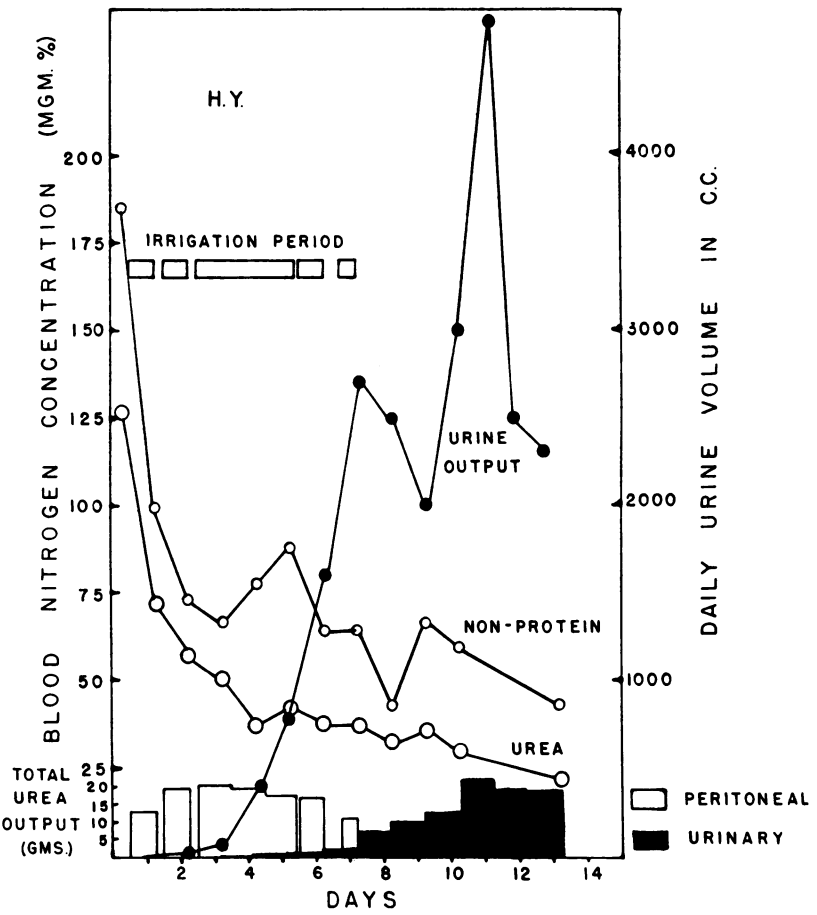

FIG. 6.—Case 3: Course of azotemia and daily urea elimination by the kidneys and by the peritoneum.

COMMENT: The immediate cause of death was multiple pulmonary emboli. In spite of the multiplicity of grave disorders complicating the acute renal shutdown, peritoneal irrigation achieved the purpose of eliminating the uremic state except during the period when the first set of catheters stopped working well. Renal shutdown was virtually complete for 13 days after the incompatible transfusion, at which time significant diuresis began (over 500 cc. per day) and the urinary urea output was increasing so that recovery sufficient to maintain electrolyte equilibrium might have been expected shortly. Although the recovery of function after renal shutdown from an incompatible transfusion begins, as a rule, at about this time, it is possible that elimination of the uremic state relieves the kidney, as it presumably must all other tissues, of an added burden which itself may prolong the recovery period. Peritoneal irrigation, therefore, may serve not only to delay death until renal recovery takes place but may also shorten the period necessary for recovery.

The colon bacillus infection of the peritoneum appeared on the 12th day of irrigation. Its extent and severity did not seem to contribute significantly to the lethal outcome.

It was clear from this experience that a catheter would not do as an outflow tube — so that in the next patient a stainless steel sump-drain was used instead. This functioned with complete satisfaction.

CASE 3.—B. I. H. No. 85197: H. Y. This case has been reported fully elsewhere.[2] A summary of the pertinent data follows: A man, age 51, developed anuria five days before admission to the hospital after 14 days of sulfathiazole therapy for an acute infection. After admission to the hospital, excessive parenteral fluids produced generalized edema and uremic intoxication became extreme. A study of the urinary tract disclosed parenchymatous renal damage. After five more days of anuria, at a time when the patient seemed moribund, peritoneal irrigation was started (0 day, Fig. 6 and Table IV). In spite of severe ileus, pulmonary edema and acidosis, the azotemia was reduced to near normal values within 48 to 72 hours. On the fourth day of irrigation, after 14 days of virtually complete anuria, urine output began and increased steadily thereafter. The urinary urea excretion reached a level capable of

TABLE IV

CASE 3: DAILY EXCRETION OF UREA BY PERITONEAL IRRIGATION AND BY THE KIDNEYS

	Peritoneal Fluid			Urine			Blood
Days*	Flow Rate Cc./Min.	Urea N Conc. Mg. %	Blood Urea Clearance Cc./Min.	Flow Rate Cc./Min.	Urea N Conc. Mg. %	Blood Urea Clearance Cc./Min.	Urea N Conc. Mg. %
1	25	24.4	8.4	—	—	—	72.7
2	33	27.4	14.5	0.02	85.0	0.03	62.2
3	25	28.1	13.8	0.04	66.0	0.05	50.6
4	25	26.0	17.2	0.28	75.0	0.55	37.8
5	13	31.2	9.5	0.55	50.0	0.65	42.8
6	35	21.0	19.4	1.10	62.5	1.82	37.8
7	29	26.5	21.0	1.87	32.5	1.65	36.7
8				1.74	145.0	7.60	33.3
9				1.40	255.0	9.70	36.8
10				2.30	193.0	14.80	30.0
11				3.30	225.0	24.70	
12				1.74	370.0	26.00	
13				1.60	392.0	28.50	22.0

* From the start of peritoneal irrigation; numbers correspond with days indicated in Figure 6.

preventing uremia on the seventh day of irrigation. At this time the irrigation was stopped. Progressive improvement in renal function continued thereafter and the patient left the hospital quite fit one week later, at which time renal function, in terms of urea clearance, was 33 per cent of normal. One month later renal function, in terms of urea clearance, was 50 per cent of normal and the P.S.P. test was normal. A year later kidney function was no better.

Pulmonary edema was considerable and distressing on the third day of irrigation. All parenteral fluids were omitted from then on. Glucose was added to the peritoneal fluid to correct starvation acidosis. At the same time troublesome ileus required tube suction, which yielded 6,000 cc. of fluid on the third and fourth days. The edema rapidly cleared thereafter. On the third day of irrigation, *E. coli* appeared in the outflow liquid, but there was no other clinical evidence of peritonitis even though this organism and leukocytes persisted until irrigation was stopped. On the first and second days after irrigation was discontinued, one million units of streptomycin in a liter of saline was injected intraperitoneally even though the patient seemed not to require chemotherapy.

COMMENT: Parenchymatous damage to the kidney from sulfathiazole is usually fatal. This patient was almost moribund when peritoneal irrigation was started. A cure seems to have been achieved in this patient by this method.

CASE 4.—C. W., a 19-year-old girl, entered another hospital for the surgical correction of cardiospasm. An esophagoplasty was done through the left chest. During the operation she received 500 cc. of Type-A blood (Rh positive). The patient's blood group was thought to have been Type A but later investigation demonstrated her to be Type-O (Rh positive). The patient's preoperative blood pressure was 100/70 mm.Hg. There was no shock during the operation. However, in the immediate postoperative period there was an abrupt drop in blood pressure to 70/40 mm.Hg. accompanied by respiratory difficulty and marked shift of the mediastinum to the right. The respiratory distress and mediastinal shift were corrected by the aspiration of bloody fluid and air from the left chest, after which the blood pressure recovered to a level of 85/55 mm.Hg. and reached normal two days later. Fifteen hundred cubic centimeters of 5 per cent glucose in water plus sodium sulfadiazine were given the afternoon of the day of operation. Mental dulness bordering upon stupor was present through the afternoon and night. The next morning the patient was found to be anuric. Spectrophotometric examination of the blood plasma disclosed the presence of a severe hemolytic transfusion reaction. A roentgenogram disclosed left pleural effusion and atelectasis. The blood N.P.N. was 70 mg. per cent, the serum chlorides 86 mEq./L and the serum CO_2 27.8 mEq./L. She was given 80 cc. of molar sodium lactate in 2,000 cc. of 5 per cent dextrose in water intravenously and 500 cc. of Type-O blood. In the 24 hours of the first postoperative day, 80 cc. of black urine were obtained from an inlying catheter. Tables V, VI, VII and VIII list the pertinent chemical findings and fluid balance data from this day onward. The fluid taken by mouth throughout the postoperative period was negligible in amount.

On the second postoperative day the patient was alert and comfortable. Laboratory data showed: blood N.P.N. 86 mg. per cent, B.U.N. 81 mg. per cent, serum chlorides 92 mEq./L, serum CO_2 29.2 mEq./L, serum sodium 133 mEq./L, serum potassium 5.2 mEq./L, and plasma protein 5.1 Gm. per cent. In the 24 hours of the second postoperative day she was given 2,000 cc. of 10 per cent glucose in water and 1,000 cc. of whole blood. Her urine output in this period was 50 cc.

On the afternoon of the second postoperative day peritoneal irrigation was instituted. An inflow tube and a sump-drain were introduced into the lateral aspects of the peritoneal cavity under local anesthesia and peritoneal irrigation at a rate of 40 cc./min. was started. The inflow fluid was passed through a Mandler (Berkefeld) filter. Penicillin and Vitamins B, C, and K were given parenterally each day. Irrigation proceeded smoothly, produced no discomfort and required no adjustment to maintain outflow. Because of recurring respiratory difficulty the patient remained in a high sitting position, which is not optimal for peritoneal irrigation.

On the third postoperative day the patient seemed well except that respiratory distress required two taps of the left chest which yielded about 2,000 cc. of bloody fluid. The blood N.P.N. was 70 mg. per cent and serum CO_2 23.3 mEq./L. She was given 2,600 cc. of 5 per cent glucose in water and 500 cc. of blood. The urine output was 30 cc. A menstrual period began. In view of the uterine bleeding and the reaccumulation of bloody fluid in the left chest, the danger from heparin in the irrigating fluid was considered but since the blood clotting time and prothrombin time were found to be normal repeatedly, heparin in the irrigating fluid was continued. The outflow fluid had a slightly uriniferous color and odor. The blood pressure had risen to 180/90. The extracellular fluid space, as measured by radioactive sodium, was found that evening to be 15,000 cc. or 29.5 per cent of the body weight (50.9 Kg.), a considerable increase over the normal extracellular space, which is 18–22 per cent of

body weight. This suggested the development of edema, which was not yet obvious clinically. It is possible that the chest fluid and the intraperitoneal fluid may have accounted in part for the increased extracellular fluid space.

The presence of edema was evident the next (fourth) day. Another chest tap was required and removed a liter of brown fluid. A transfusion of 500 cc. of blood and 2,000 cc. of 15 per cent glucose in water were given intravenously. The urine output for the day was 60 cc. The plasma sulfadiazine level was 4.9 mg. per cent, derived entirely from the irrigation fluid. Thereafter it was omitted from the irrigation fluid because of the remote possibility that it might retard renal recovery. Chest signs indicative of slight pulmonary edema were found. Digitalization was begun.

On the fifth postoperative day the patient's respirations were rapid, deep and labored. There was no evidence of recurrence of pleural effusion and the respiratory changes were attributed to a combination of pulmonary edema and acidosis. The serum CO_2 was 16.9 mEq./L, serum chlorides 110 mEq./L, blood N.P.N. 70 mg. per cent, B.U.N. 45 mg. per cent, plasma protein 5.0 Gm. per cent and the venous blood pH 7.38. By the dye and hematocrit methods the blood volume was found to be 3,500 cc. (7.1 per cent of body weight) and the plasma volume 1,950 cc. (4.0 per cent of body weight) — both values being somewhat lower than normal. Generalized edema was marked. The extracellular "thiocyanate space" was 29,400 cc., or 58 per cent of body weight. Part of this increase may have been due to an intracellular shift of normally extracellular ions as indicated by the somewhat reduced serum sodium (131.0 mEq./L.) and elevated serum potassium (6.2 mEq./L.). Fifteen hundred cubic centimeters of 10 per cent glucose in water and 600 cc. of plasma were given through the day.

By midnight the dyspnea was very marked and was not relieved by the aspiration from the left chest of 300 cc. of fluid. To reduce pulmonary edema 800 cc. of a solution containing 30 per cent glucose and 25 per cent human albumin was administered intravenously in a period of 5.5 hours. At the end of this time severe pulmonary edema with extreme dyspnea, frothy sputum, cyanosis, and loss of consciousness was manifest. Treatment included morphine (8 mg.), atropine (0.65 mg.), continuous oxygen inhalation at a positive pressure of 1 cm. of water, phlebotomy of 300 cc. and the application of venous tourniquets to the extremities. Gradual improvement occurred over a period of three hours, leaving the patient conscious but dyspneic, with poor color and with râles throughout both lungs. In the hope of removing the excess water from the patient's body by way of the peritoneal membrane, almost all sodium (as well as all other electrolytes) were eliminated from the irrigation fluid, which was made hypertonic by a combination of 5 percent gelatin and 2.5 per cent glucose. The Mandler filter was removed from the inflow circuit to allow the free passage of the gelatin. Irrigation with this solution was begun at noon of this day. By early evening the pulmonary edema seemed considerably diminished. At 10:30 P.M. the patient was found to be in extreme shock, unconsciousness, with cold, pale skin and a thin weak pulse. The systolic blood pressure which had been at a level of 150 mm.Hg. all through the day up to 6:00 P.M. was now unobtainable. The irrigation was stopped and 100 cc. of 50 per cent glucose plus 500 cc. of blood were given intravenously. The systolic blood pressure was restored to 110 mm.Hg. by midnight and it remained at that level. A slow intravenous drip of 30 per cent glucose in water was continued. Respirations remained labored and the patient remained unconscious.

The next morning the patient was still unconscious. The coma was attributed to cerebral edema. The generalized and pulmonary edema seemed definitely diminished. The blood N.P.N. was 42 mg. per cent, the B.U.N. 40 mg. per cent and the serum CO_2 20.4 mEq./L. To further reduce the edema, particularly the cerebral edema, peritoneal irrigation with 5 per cent gelatin, and 2.5 per cent glucose was resumed at noon. Within 30 minutes the blood pressure dropped to 80/50 mm.Hg. and in the subsequent 2.5 hours to 60/40, after which the irrigation was stopped and the systolic pressure

slowly returned to 100 mm.Hg. A generalized tonic and clonic convulsion, accompanied by apnea, lasting one minute, occurred. There was a marked rise in hemoglobin concentration and hematocrit from the previous day's levels of 11.6 Gm. per cent and 42 per cent, respectively, to 15.8 Gm. per cent and 57 per cent, respectively, and a concomitant fall in serum sodium and chloride from 131 and 106 mEq./L., respectively, to 114 and 88 mEq./L., respectively. Eighty cubic centimeters of molar sodium lactate was given intravenously because of the low serum sodium. The peritoneal irrigating fluid was changed to a simple solution of 5 per cent glucose in water which was brought to the physiologic concentration of sodium and chloride by the addition of sodium lactate and sodium chloride.

At 2:30 A.M. of the eighth postoperative day, the seventh day of peritoneal irrigation, convulsions recurred, the blood pressure dropped and in spite of treatment in the next four hours with sodium phenobarbital, sodium lactate and whole blood transfusion, the patient died. By the time of death the subcutaneous edema had disappeared.

The patient had never shown systemic or any local evidence of sepsis during her illness. The rectal temperature remained below 100° F. in the early postoperative days and she was completely afebrile in the two days before death. Histologic examination of the output fluid showed no leukocytes. On the last day of irrigation a very few colonies of bacteria were grown from the outflow fluid. These were identified as *Staph. albus, E. coli, Cl. welchii* and diplococci of the enterococcus type.

Postmortem examination showed typical transfusion reaction kidneys, but no other cause of death. There was no peritonitis, adhesions or evidence of tissue injury in the peritoneal cavity. Subcutaneous and cerebral edema were absent and pulmonary edema was minimal.

The report of the completed examination of the kidneys is not yet available.

COMMENT: This patient was given 500 cc. of incompatible blood while under general anesthesia and became almost completely anuric immediately thereafter. She excreted no more than 80 cc. of urine on any of the subsequent eight days of life. Peritoneal irrigation for approximately six of those days was successful in reducing the blood N.P.N. level to near normal limits. The irrigation proceeded with a minimum of adjustment, produced no discomfort, caused no intra-abdominal damage or infection, and did not interfere with the remainder of the care of the patient.

Death probably was due to incorrect management of the water balance problem. This may have been due in part to a division of responsibility in the management of this patient between ourselves and the resident staff at the hospital at which the patient was being treated. She received water in excess, as the fluid intake data demonstrated. At least partly because of this (there is also a possibility that water might be absorbed in excess of normal requirements from the irrigating fluid) she developed pulmonary and probably cerebral edema. The water was given as a vehicle for glucose to counteract starvation and acidosis, but the glucose could have been given in much higher concentration and smaller fluid volume. When the tissue edema was massive and pulmonary edema severe, hypertonic glucose was given, but concentrated albumin was also given and both were given too rapidly. Even though the plasma volume was a little less than normal, the addition of concentrated albumin proved to be unwise since the resulting rapidly induced hydremic plethora precipitated an even more severe pulmonary edema with

the disastrous results described. The treatment then needed to correct the situation resulted in a considerable depletion of an originally less than normal blood volume. The administration of oxygen at positive pressure in expiration as well as in inspiration may have further reduced cardiac output. The subsequent use of an hypertonic and salt poor irrigation fluid to reduce the edema may have reduced plasma volume more rapidly than it could be restored from interstitial fluid, so that while pulmonary edema diminished, extreme shock developed and was unrecognized for several hours, during which the patient was in a high sitting position with a very low blood pressure. Shock was subsequently corrected, but the period of poor blood flow may well have done damage which contributed to the fatal outcome. The patient never regained consciousness thereafter. A second period of peritoneal irrigation with hypertonic salt-poor fluid resulted in another drop in blood pressure.* A marked rise in hematocrit and hemoglobin concentration substantiated the impression that the plasma volume was being too rapidly reduced.

The terminal convulsions are not explained except on the basis of cerebral damage from the antecedent edema or shock or possibly because of reduced ionizable calcium, because calcium was omitted from the irrigating fluid in the last two days and the plasma calcium concentration did drop somewhat below normal.

There is no way of knowing if or when recovery of kidney function might have occurred. The dose of incompatible blood was large, but there is no reason to believe that renal healing might not have taken place if the patient could have been kept alive for the required time.

The electrolyte pattern of the plasma was kept near normal limits. Figure 7 is the diagram adapted from Gamble,[6] showing the electrolyte composition of the plasma of the patient on the sixth day of almost complete anuria (day 5, Table V) compared with that of normal plasma. On this day the patient's serum CO_2 concentration was the lowest recorded, but normal blood pH was maintained nevertheless.

The total disappearance of the edema before death was ample testimony to the efficacy of peritoneal irrigation with hypertonic solutions, for removing water from the body. In spite of the complex and disappointing developments peritoneal irrigation served its primary purpose. But it is at the same time evident that such a tool for the control of fluid and electrolyte balance cannot be successfully instituted without the exercise of extreme caution and without well considered judgment as to the kind of supplementary therapy needed for nutritional balance.

Discussion.—The foregoing experiences show emphatically that this method is still in the experimental stage. What is so far established is

* This happened so quickly that a toxic effect of the solution was suspected. To exclude the suspicion of toxic material in the irrigation solution, 300 cc. of the solution was given intravenously during 2–3 hours to an 8-Kg. dog without immediate or delayed harmful effect.

TABLE V

CASE 4: DAILY BLOOD ANALYSIS

Day*	Blood N.P.N. Mg. %	Blood Urea N Mg. %	Serum CO^2 mEq./L.	Serum Chloride mEq./L.	Serum Sodium mEq./L.	Serum Potassium mEq./L.	Serum Calcium Mg. %	Serum Phosphorus Mg. %	Serum Protein Gm. %	Serum Magnesium mEq./L.	Venous Blood pH
1	7)		27.8	86					5.1		
2	86	81	29.2	92	133	5.7					
3	70	69	23.3	94					5.1		
4	90	51	21.7	102	132	6.2			5.0		
5	70	45	16.9	110			7.8	5.8	5.0		7.38
6	60	42	22.2	106	131	5.5	7.8	6.8	5.7	2.4	
7	42	40	20.4	88	114	7.1	8.0	6.7			

* Days subsequent to transfusion reaction.

(1) that a properly performed peritoneal irrigation can eliminate all clinical and chemical evidence of the uremic state; (2) that significant improvement can be achieved within 36 to 48 hours; (3) that the total time required will vary with the duration and severity of the uremia, degree of saturation of the tissues with retained products, degree of dehydration or edema, the nutritional state, food intake, the rate of protein catabolism, the presence of associated disease and the rate of efficiency of peritoneal irrigation; (4) that irrigation will not injure the peritoneal structures; and (5) that the efficiency

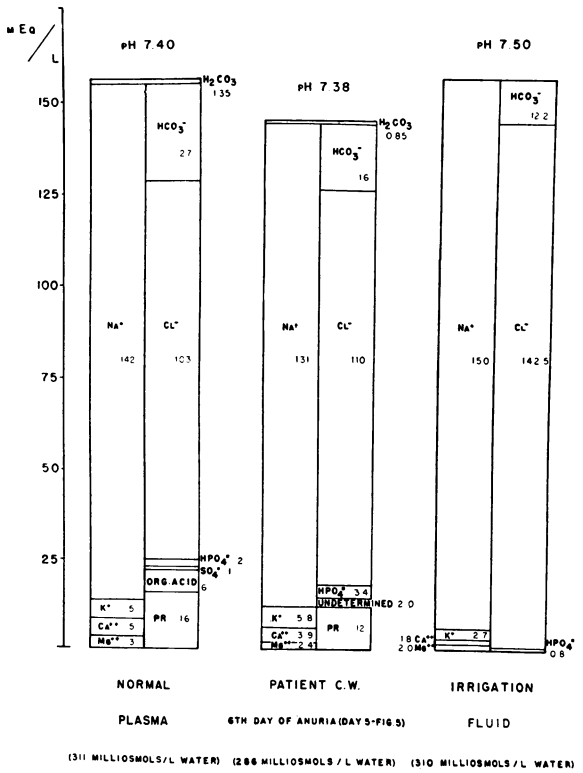

FIG. 7.—Gamble diagram[6] of the electrolyte composition of normal plasma, the plasma of Case 4, and of the peritoneal irrigation solution.

of irrigation so far as blood urea clearance is concerned does not diminish with time and exceeds the minimal degree (10 per cent–15 per cent) of renal excretory function necessary to avoid reaccumulation of nonprotein nitrogen or urea.

It is possible that the uremic state imposes a further burden on the damaged kidneys, as it does on all other tissues and that the repair of the renal injury is facilitated by the removal of the uremic state. The time necessary for repair of the renal injury and recovery of sufficient renal function can not be foretold. It will vary from one type of injury to another and from case to case with the same type of injury. Lesions capable of repair within a few weeks should be amenable to this therapy because it probably can be continued safely that long. To date the longest period we have carried the treatment is 12 days.

The danger of peritonitis has been the chief hazard. With the introduction of a bacterial filter on the inlet side of the irrigating system, with chemotherapy and with careful isolation of the abdominal wounds and tubes by proper dressings, this danger is minimized very substantially. The organisms isolated from the peritoneal drainage fluid were *E. coli* after 12 days in Case 2, *E. coli* after three days in Case 3, in which it produced no significant clinical effects, and *E. coli, Cl. welchii, Staph. albus* and enterococci in Case 4, in which at postmortem there was no evidence of peritonitis. Objection to sulfonamides on the ground of inflicting additional renal injury may be valid and may justify restricting chemotherapy to penicillin and streptomycin when available. The placing of the inflow and outflow tubes should be done with such care that the possibility of dislodgement and the need to replace them should be avoided. It is certain that a rubber catheter of whatever design as an outflow tube will not answer this need and should not be attempted. A sump-drain made of inert metal (stainless steel) is completely satisfactory and devoid of discomfort to the patient.

The most meticulous attention to fluid and electrolyte balance is continuously required. Neglect to do so, as Case 4 demonstrates, will vitiate the whole effort. In uremia "the defense of the chemical structure of the extracellular fluid is of much more importance from the point of view of survival than reduction of azotemia."[7]

Pulmonary edema was present in Cases 2, 3 and 4 — in all instances because of the intravenous administration of fluid in excess of tissue requirements for fluid in the anuric state and because of acidosis. The fluid requirement during renal suppression consists only in water lost by vaporization, which is about a liter per day, *i.e.*, 0.5 cc./Kg./hr.,[6, 8] unless fever, vomiting, diarrhea or sweating are present. All these patients received water in excess of what they required; Cases 2 and 3 before irrigation was started, in what was an obviously futile effort to stimulate diuresis; Case 3 for the first two days after it was started, and Case 4 for five days after irrigation was started. Since food intake is likely to be either inadequate or *nil*, intravenous fluid is necessary purely as a vehicle for glucose (and possibly for

amino-acids if treatment is needed for many days) to counteract starvation acidosis and to spare protein breakdown, but the fluid must be given in as small a volume as possible. Four hundred grams of glucose in 1,200 cc. of water should substantially satisfy the caloric need and prevent acidosis. It should be given slowly to avoid hydremic plethora and rapid loss of glucose into the irrigating fluid.

TABLE VI

CASE 4: DAILY URINE OUTPUT AND INTRAVENOUS FLUID ADMINISTRATION

		Fluid Intake					
Day	Urine Output Cc.	Blood Cc.	Plasma Cc.	25% Albumin Cc.	Water Cc.	Dextrose in Water %	Fluid Removed from Left Chest Cc.
0	0	500			1500	5	± 300
1	80	500			2000	5	
2	50	1000			2000	10	
3	30	500			2600	5	2000
4	60	500			2000	15	1000
5	±60		600		1500	10	
6	±60			50	800	30	300*
7	±60						

* 300 cc. venesection.

TABLE VII

CASE 4: URINE ANALYSIS

Day	N.P.N. Mg. %	Urea N Mg. %	NH^3 N Mg. %	Creatine Mg. %	Creatinine Mg. %	Gross and Microscopic Appearance
2	410	128				Black, turbid, loaded with débris; no casts or R.B.C.
3		70	55			
4	410	95		0	24	Dark brown, clear
5		40	0			
6	92	29		0	24	Amber, clear, acid, albumin 4+; many R.B.C.

TABLE VIII

CASE 4: UREA REMOVAL BY PERITONEAL IRRIGATION

	Peritoneal Fluid				
Day	Volume Cc.	Flow Rate Cc./Min.	Urea N Mg. %	Total Urea Gm.	Blood Urea Clearance by Peritoneum Cc./Min.
2	38,000	26.5	23.3	17.7	7.6
3	38,000	26.5	20.6	15.7	7.9
2	34,000	23.6	21.0	14.3	9.7
5	18,000	16.6	34.0	12.3	12.5

It is difficult to predict the exact state of affairs with reference to excretion and absorption across the peritoneal membrane with the type of irrigating fluid used and a varying state of hydration of the plasma and extracellular fluids. It is not known whether, with the type of fluid used, irrigation offers a route of exit for excess body water. We suspect that

the fluid as at present constituted is not satisfactory for this purpose. Experience with Case 4 indicates that when the peritoneal fluid is made hypertonic by 5 per cent gelatin and 2.5 per cent glucose, water can be so rapidly removed from the plasma that caution should be exercised to avoid excessive hemoconcentration. Eventually it may prove desirable to modify the electrolyte composition of the irrigating fluid, for better control of acidosis by reducing the chloride content to that of normal plasma and substituting sodium lactate buffered with lactic acid. Further, an increase in the glucose of the irrigation fluid might provide a sufficient amount to balance what is lost into the peritoneal fluid from the intravenously administered glucose, to counteract water absorption from the irrigating fluid and to provide some of the glucose for metabolic needs. If modifications needed for such purposes result in making the fluid hypertonic, their long-continued use might be impractical, because of the potentially irritating properties of such solutions. Further data will be accumulated to discover the optimal solution under most circumstances.*

The proper time to institute peritoneal irrigation is not established. It is not possible to say when any given data regarding the uremic state signify the existence of irreversible damage. Therefore, since the method can be carried on for many days safely it should be started soon after the uremia is full-blown. Meanwhile it is important not to add to the patient's burden by the harmful effects of excessive water administration, since the amount of water needed is small and as a diuretic it is futile. The time for discontinuing peritoneal irrigation can be determined readily by measurements of the return of sufficient kidney function to prevent azotemia and to sustain a normal fluid and electrolyte balance.

CONCLUSIONS

1. Continuous peritoneal irrigation with an appropriate fluid is a satisfactory method of eliminating uremia. It can be used in any case of acute renal failure in which death from uremia is likely and in which recovery of kidney function is considered possible.

2. The control of fluid and electrolyte balance is at least as important as the elimination of nitrogenous waste products, and is an integral part of this therapeutic method.

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* Since submitting this article for publication additional clinical experience (to be published) has demonstrated that the use of 2% glucose in the irrigating fluid instead of glucose at blood level concentration will prevent the production of edema from the absorption of water from the irrigating fluid. Furthermore, the absorption of glucose from 35 liters of such irrigating fluid in 24 hours was found to be some 200–300 grams of glucose. The absorbed glucose therefore reduces the basal requirement of a starving patient from 400 to 100–200 grams per 24 hours, and so reduces the amount that must be administered intravenously to prevent starvation acidosis. Two per cent glucose, moreover, is not irritating to the peritoneum.

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DISCUSSION.—DR. ARTHUR B. MCGRAW, Grosse Pointe, Mich.: I wish to add a very incomplete report on one patient, upon whom an attempt was made to use this method of Doctor Fine's. Five days before this meeting, our Pediatric Department asked me to help them set up an irrigation system such as Doctor Fine describes. We had no sump-tube of the size described by him, but we did have one small abdominal suction tube of brass, chrome plated and rather worn. We cut it down to what we felt was the proper size.

The patient was an anemic anuric six-year-old boy, suffering from glomerulonephritis superimposed on a severe nephrosis. It worked very well for one day and night, and the next day. On the third day we had a little trouble with the outflow of the tube and I think that in trying to wipe that out we may have introduced contamination into the peritoneal cavity. On the fourth day it stopped, and when I left we had decided to take it out, leave it out overnight, and then reinsert it in another location. I can only report that the child's nonprotein nitrogen dropped progressively in four days from 150 to 95. I think this is an interesting method, and it holds great promise. If we try it again with more precautions and more careful teamwork, I believe we can achieve successes such as Doctor Fine reports.

DR. EDWARD D. CHURCHILL, Boston, Mass.: The type of case selected by Doctor Fine for experimental observations tends to obscure the broad surgical application of such a method when it is perfected and ready for general clinical application. It may not be realized that, despite all the optimistic reports on the successful management of shock in this war, renal shutdown was the stone wall against which we butted our heads many times. The reduced blood volume of shock could be corrected by transfusion, but the kidneys ceased to function and many wounded men died despite the most skilled surgical procedures. The full explanation is still not clarified; the problem requires further study. The surgeons caring for these patients with anuria tried many forms of treatment: high spinal anesthesia; alkalies, to the point of severe alkalosis; and many other measures. Still the patients died in uremia. Doctor Fine's method represents one more procedure that may be applicable to men suffering from renal shutdown following severe trauma. I hope it will prove successful.

DR. ALLEN O. WHIPPLE, New York City: I have been tremendously interested in this new experimental work. Doctor Fine told me about it a few days ago, and I think he has established a point of departure in the treatment of anuria and uremia which will apply not only to surgical but to medical cases, and is a real advance. One