

THE MANAGEMENT OF UREMIA BY PERFUSION OF AN ISOLATED JEJUNAL SEGMENT: WITH OBSERVATIONS OF THE DYNAMICS OF WATER AND ELECTROLYTE EXCHANGE IN THE HUMAN JEJUNUM¹

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Gamble (1) has stated that in uremia, the defense of chemical structure of the extracellular fluid is of much more importance from the point of view of survival than the reduction of azotemia. More recent knowledge of body composition extends this view and implicates body fluid-electrolyte derangements as important lethal factors in the uremic syndrome.

Since demonstration of absorption of urinary products from the intestine (2) and secretion of urea into the intestine (3), the use of intestinal perfusion has been employed by many workers in attempts to manage the uremic syndrome, as reviewed by Twiss (4) and most recently by Merrill (5). Perfusion of an isolated segment of intestine for this purpose is attractive since the remaining bowel is in continuity. Use of an isolated segment of ileum in a patient was first described by Kolff (6), and subsequent reports (4, 7-9) of perfusion of isolated ileal or mid-gut segments in patients have appeared.

Evaluation of isolated intestinal segments in dogs has been done (10-14). Seligman, Frank, and Fine (10) evaluated the urea clearance of various portions of the gastrointestinal tract in dogs and found that this is highest in the jejunum. This appears to refute earlier work (15) in dogs with isolated jejunal segments. Perfusion of the intact jejunum with a double lumen tube has been shown to remove potassium in proportion to the serum concentration (16). The classic studies of Visscher and co-workers (17) on the exchange and transfer rates of sodium and water in the ileum, as studied with radiosodium and with

deuterium oxide, emphasized the rapid exchanges and transfers involved.

The absorptive function of the ileum does not favor its use in intestinal perfusion; the important secretory function and increased surface area of the jejunum would seem to make this segment more applicable. Most of the small intestine may be resected in the adult with survival and satisfactory adaptation, as reviewed by Wangenstein (18). Massive small bowel resections are better tolerated if the terminal ileum remains. Exclusion of 50 per cent of the small intestine by an isolated segment procedure (Thiry-Vella fistula) should not produce any functional abnormality.

Intestinal perfusion is probably the only method that affords the possibility of repeated dialyses over a long period. In order to utilize it effectively, however, it is necessary to define the variables, including serum and perfusate electrolyte concentrations, serum and perfusate osmolality, rates of intestinal exchange and transfer of electrolytes and other crystalloids, and such factors as the flow rate and temperature of the perfusate solution. It is essential to preserve normal functioning of the intestinal mucosa and to be able to remove water in predictable amounts when necessary. The present report shows that the exchange of water, sodium, potassium, chloride and urea can be predicted and the method applied. The data show that complete renal function is not attained although considerable temporary improvement occurred.

It is the purpose of this paper to report an experience with the management of chronic uremia in a patient by 74 perfusions of a 50 per cent isolated jejunal segment and to present the results of a metabolic balance study carried out during his three month hospital period.

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CASE ABSTRACT

The patient² was an 18 year old rancher's son who, five years prior to admission, had acute glomerulonephritis and since that time had had slowly progressive hypertension, azotemia, albuminuria, weight loss and anemia.

Initial studies revealed the following: The patient was a well developed, thin, 18 year old boy who was markedly pale but appeared to be in relatively good spirits. Vital signs and physical examination were normal except for a blood pressure of 140/100, slight cardiac enlargement and minimal ankle edema. Weight was 53.2 Kg. Laboratory studies on admission revealed a normal white blood count, smear and differential. Hematocrit was 18 per cent and the hemoglobin was 7.5 Gm. per cent. Urinalysis showed a specific gravity of 1.012, acid reaction, albumin 4+ and no sugar; and microscopic examination revealed 10 to 15 white cells per high power field and a few fine granular casts. Quantitative urinalysis revealed 25 Gm. of albumin in 24 hours. Analyses of the plasma were: sodium, 140 mEq. per L.; potassium, 3.3 mEq. per L.; calcium, 3.0 mEq. per L.; creatinine, 18 mg. per cent; non-protein nitrogen (NPN), 176 mg. per cent; blood urea nitrogen (BUN), 145 mg. per cent. Plasma volume was 3.3 L. and total blood volume was 4.2 L. as measured with T-1824 blue dye. Total body water on Jan. 8, 1957, was 38.56 L. Chest and abdominal X-rays showed no abnormality. Review of retrograde pyelograms done two years previously disclosed no evidence of obstructive uropathy or other abnormality.

The patient was placed on a low salt, low protein diet and lost a few pounds initially. He was continued on a diet designed to provide sufficient amounts of sodium and minimal amounts of nitrogen. Six blood transfusions elevated the hematocrit to 35 per cent. On this program his clinical situation stabilized, but the azotemia was unchanged. Operation was done on Jan. 19, 1957, under local and light general anesthesia with isolation of the proximal half of the small intestine and restoration of continuity of the remaining bowel by end-to-end anastomosis. Abdominal stomas were made in both lower quadrants. Postoperatively, the patient's course for the first week was uneventful. On the eighth postoperative day, development of clinical deterioration was evident. The plasma NPN, which had been unchanged since operation, rose and on the following day had reached a value of 272 mg. per cent with a urea nitrogen of 225 mg. per cent. The patient was semicomatose at this time with occasional twitching. Accordingly, perfusion of the isolated intestinal segment was begun on Jan. 28, 1957, and was continued, usually for six hours a day, five days a week, during the remainder of the 10 weeks of his hospital stay. Having learned the perfusion technique and preparation of the perfusate solution, he was discharged on April 11, 1957, to return home to continue the perfusion schedule there. This was resumed as outlined and for the first two weeks at home his general condition was well

maintained with a urine output of 226 ± 52 ml.³ per day. Progressive oliguria continued, however, and the patient expired on May 9, 1957, after a few days of anuria. Gross autopsy⁴ revealed chronic lobular glomerulonephritis, each kidney weighing 90 Gm. Destructive arthritis with caseous exudation in the sterno-clavicular, costochondral, acromioclavicular and other joints was present. The isolated intestinal segment and remaining bowel were normal. The heart weighed 450 Gm. and an adhesive pericarditis was present without exudate. Microscopic evaluation of the tissues⁵ showed uric acid deposition in the joints and kidneys as well as widespread metastatic calcification confirmed by the demonstration of 23 to 24 per cent of the ash weight of the lung and gastric mucosa as calcium.

METHODS

During this three month study, daily dietary intake was estimated (19, 20) and urine was collected. Body weights were measured daily and after each perfusion. Fecal collections were not included routinely but one two-day stool collection was done.

Samples of plasma, urine and perfusates were analyzed for sodium and potassium (flame photometer), calcium (21), magnesium (21), chloride (22), phosphorus (23), urea nitrogen (24), non-protein nitrogen (25) and creatinine (26). Occasional analyses were done for creatine (26), uric acid (27) and glucose (28). Perfusates containing sucrose were hydrolyzed and the monosaccharide (28) was determined. Use of a modification of the Kjeldahl nitrogen method for estimation of perfusate nitrogen was necessary because of the high carbohydrate content. Osmolality was estimated with the Fiske osmometer.

Deuterium oxide in plasma and some perfusates was measured by the falling drop method (29), and total body water was calculated from the dilution of the amount infused after equilibrium (30).

Intestinal segment perfusion procedures

A. *Perfusion equipment.* An oil-filled temperature-controlled receptacle⁶ with the contained 20 L. carboy was placed on a bedside stand about one foot above the patient.

B. *Perfusate solution.* From concentrated stock solutions, 14 L. of perfusate formula was prepared each day according to requirements or for special studies. After mixing the solution in the carboy, a sample was taken for accurate analysis. A total of 32 different perfusate

³ Variances are expressed as standard deviations except where noted.

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⁵ By Dr. Bernard Klionsky, Assistant Professor of Pathology, University of Kansas School of Medicine.

⁶ Designed and made by the Physics Laboratory, University of Kansas Medical Center, under the direction of Michael Klein, Ph.D.

² Referred by Dr. John McMillin, Idaho Falls, Idaho.

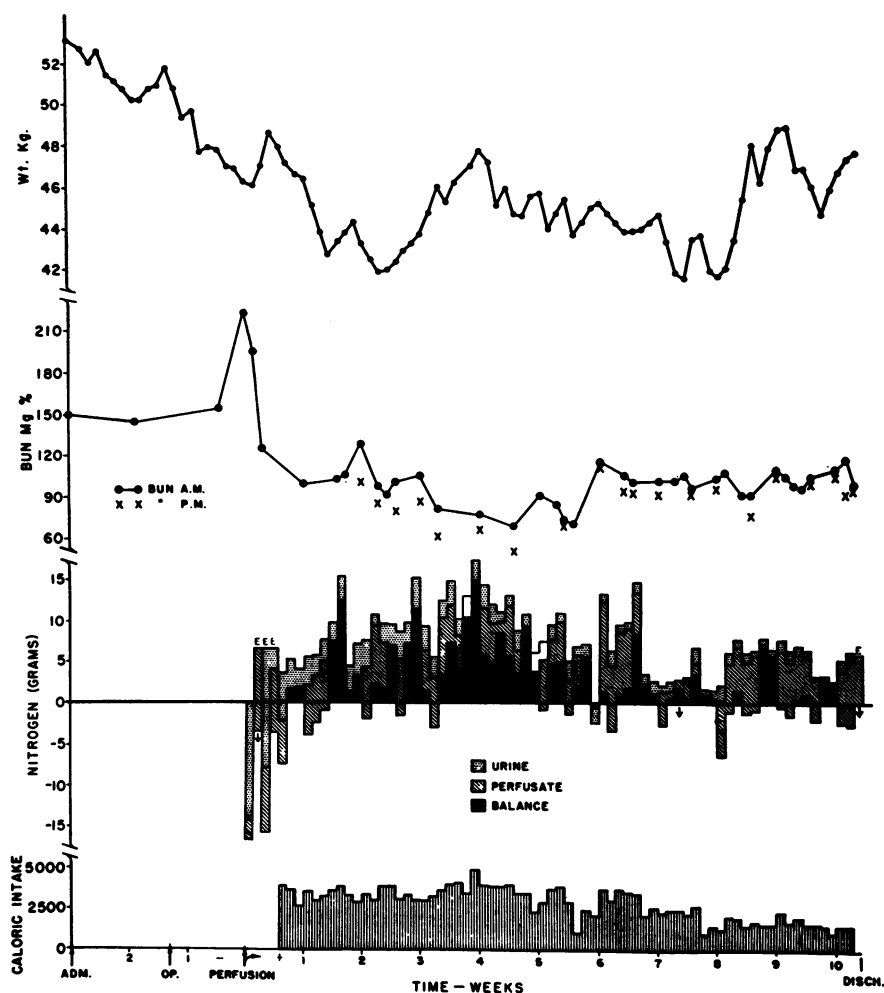


FIG. 1. NITROGEN DATA

Following initial weight loss, weight gain from two to seven weeks was associated with positive tissue nitrogen balance. Weight gain during last two weeks was related to edema. Initial decrease in blood urea nitrogen was related to urinary (60 per cent) and perfusate (40 per cent) nitrogen excretion. Progressive increased removal of nitrogen by perfusion with decreased urinary nitrogen excretion is evident. Fecal nitrogen losses of about 1 Gm. per day are not included. Intake is plotted upward from the zero line and output downward from the top of the intake line. E indicates estimated dietary nitrogen intake.

formulas was used for the 50 perfusions with wide ranges in the concentration of electrolytes and osmolality.

C. Perfusion method. The fluid was administered by siphon into the left stoma through a rotameter flowmeter and was removed from the right Foley catheter by a tube leading to a second polyethylene carboy on the floor. The flow rate was adjusted to 2 L. per hour in all routine perfusions. The effect of varying rates of flow was studied separately. During the perfusion, the patient was permitted to sit up in bed, assume any comfortable position, read, drink and eat small amounts. Water intake was not limited and was dictated only by the patient's

thirst. At the end of the perfusion period, which usually lasted six hours, 500 ml. of a perfusion solution similar to that used during the six-hour perfusion, but containing no carbohydrate, was infused into the left stoma in 15 minutes to wash out any remaining carbohydrate in order to reduce the possibility of bacterial enteritis.

Water transfer was the difference between the volume infused and the volume collected. Electrolyte transfer was calculated as the difference between the concentration of an aliquot of the initial perfusate times the volume infused and the concentration of an aliquot of the effluent perfusate times the volume collected.

Perfusions lasting six hours were usually carried out five times weekly, Monday through Friday. A total of 50 perfusions was done during a period of over 10 weeks.

RESULTS

I. Clinical

A. Hospital course. Eight days following operation, evidence of clinical deterioration included semicoma, vomiting and twitching with plasma concentrations as shown in Figures 1 and 4. Perfusion was begun on January 28, 1957, and by the next day, clinical improvement was manifested by arousal from coma, ability to get out of bed and walk, and to eat normally. Except for five days during the remainder of his hospital stay, the patient was able to be up and about and was able to leave the hospital on weekends for several hours. On the five days of inactivity, diarrhea and weakness were present, occurring during the sixth and seventh weeks after perfusions were begun.

Weight changes are represented in Figure 1. Initial weight loss was probably related to negative salt and water balance, while the postopera-

tive weight decline may be ascribed to the usual catabolic phase related to low caloric intake. For about one month after perfusion, moderate weight gain was associated with positive nitrogen balance, and the patient appeared to be gaining tissue weight. The weight gain observed later in the hospital course was related to edema, and the loss of weight after this period was due to water removal by perfusion (Figure 2).

B. Diet. The patient objected to reduction of dietary protein to less than 40 Gm. per day. Rather than have the patient partake of an unknown additional amount of food, and to ensure continued cooperation, a more acceptable diet was made available. Sodium intake is shown in Figure 3. The dietary sodium intake is not more accurate than ± 15 per cent of the values shown, but these figures more nearly represent maximum values.

C. Fecal losses. Daily fecal losses during the single 48 hour collection period were: sodium, 1.2 mEq.; potassium, 9.5 mEq.; calcium, 1.4 mEq.; magnesium, 1.5 mEq.; chloride, 1.1 mEq.; phosphorus, 100 mg.; total nitrogen, 1.0 Gm.;

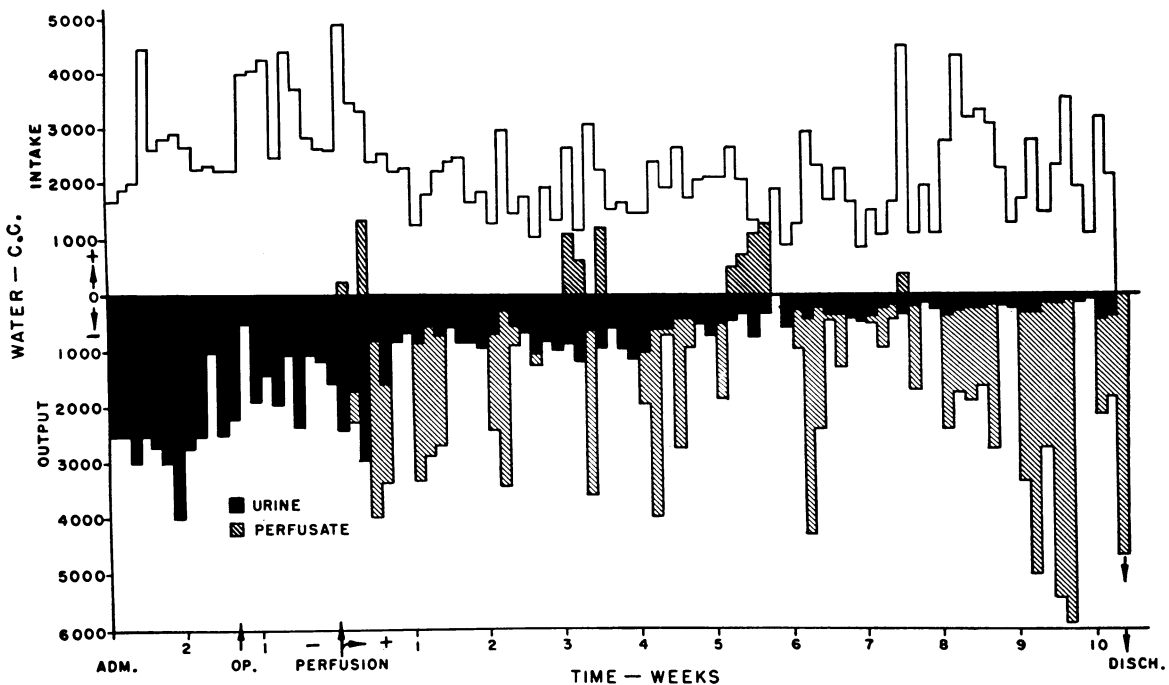


FIG. 2. URINE VOLUME, PERFUSATE WATER TRANSFER AND WATER INTAKE

Progressive decrease in urine volume with associated increased body water removal by perfusion is shown. Urine output did not increase significantly when perfusion was not done. Intake is plotted above the zero line and output below the zero line.

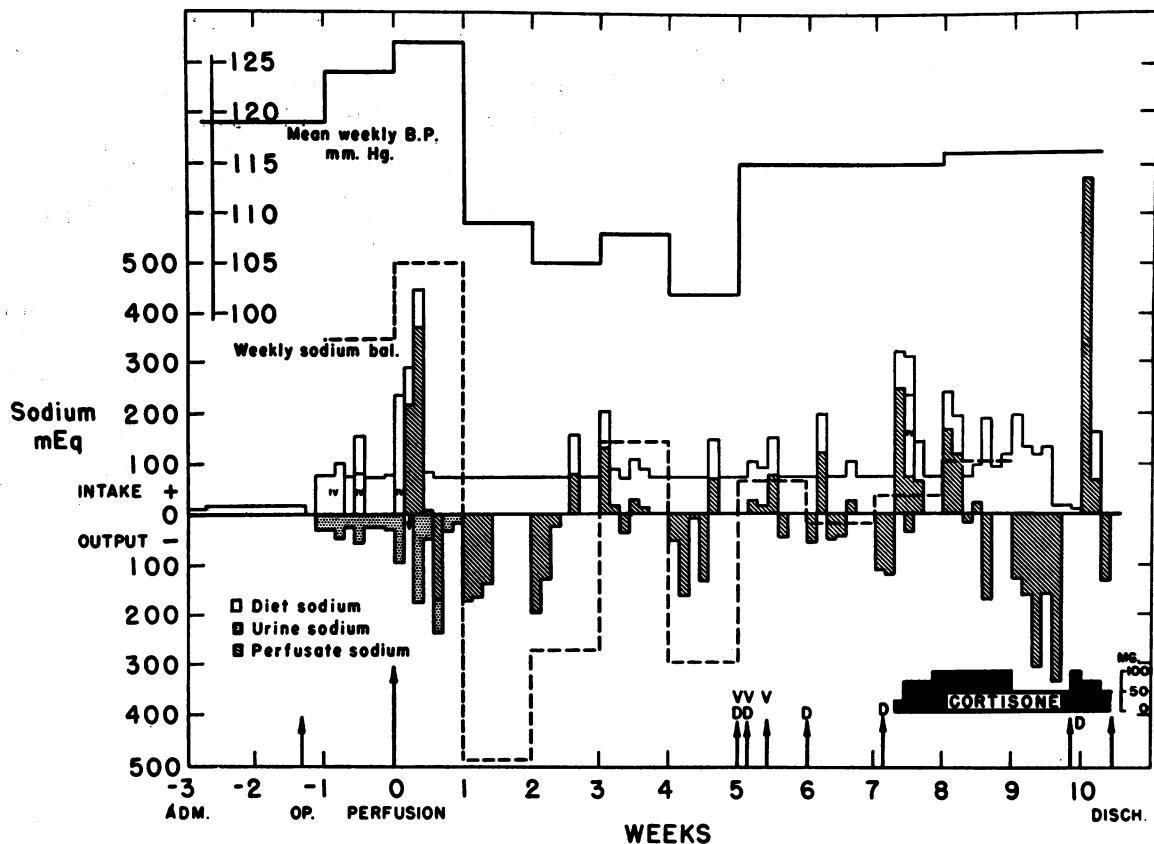


FIG. 3. SODIUM BALANCE AND THE RELATIONSHIP BETWEEN BLOOD PRESSURE AND WEEKLY PERFUSATE SODIUM BALANCE

Diagram shows correlation ($r^2 = 0.71$, $p = 0.01$) until cortisone was given. V indicates vomiting; D, diarrhea. Urine sodium excretion one week after perfusions were begun was too low (4.5 ± 4.0 mEq. per day) to be plotted on this scale. Removal of 1,103 mEq. of sodium (not plotted) during cortisone administration produced no decrease in blood pressure.

non-protein nitrogen, 0.52 Gm.; fiber nitrogen, 0.53 Gm. Stool phosphorus losses were about half of the daily urinary phosphorus excretion. Nitrogen loss data, if assumed to be representative, would decrease the nitrogen balance (Figure 1) by about one Gm. per day. Presence of diarrhea would, of course, alter these values and it is probable that electrolyte losses by this route did contribute to the hyponatremia observed on a few occasions (Figure 4).

D. Urine volume and kidney function. The urine volume, which declined gradually throughout the period of hospitalization and after discharge, is shown graphically in Figure 2. After perfusions were begun, the average daily urine output during the ensuing two and one-half months was 589 ± 477 ml. per day. During the last two

weeks of hospitalization, 24 hour urine volume had decreased to 240 ± 33 ml. declining further to 20 ± 24 ml. during the final two weeks at home. An attempt to correlate the relationship of the perfusions to the observed progressive oliguria revealed that on 49 of the days when perfusions were done, the daily urine volume was 594 ± 539 ml. On 22 days when perfusions were not done, the average 24 hour urine volume was 577 ± 296 ml., so that daily urine output was not affected by perfusions done on the same day, nor was it decreased significantly (537 ± 479 ml.) by perfusions done the previous day. Endogenous creatinine-chromogen clearance has been measured as a relative indication of renal function with realization of its limitations as a measure of glomerular filtration in advanced uremia.

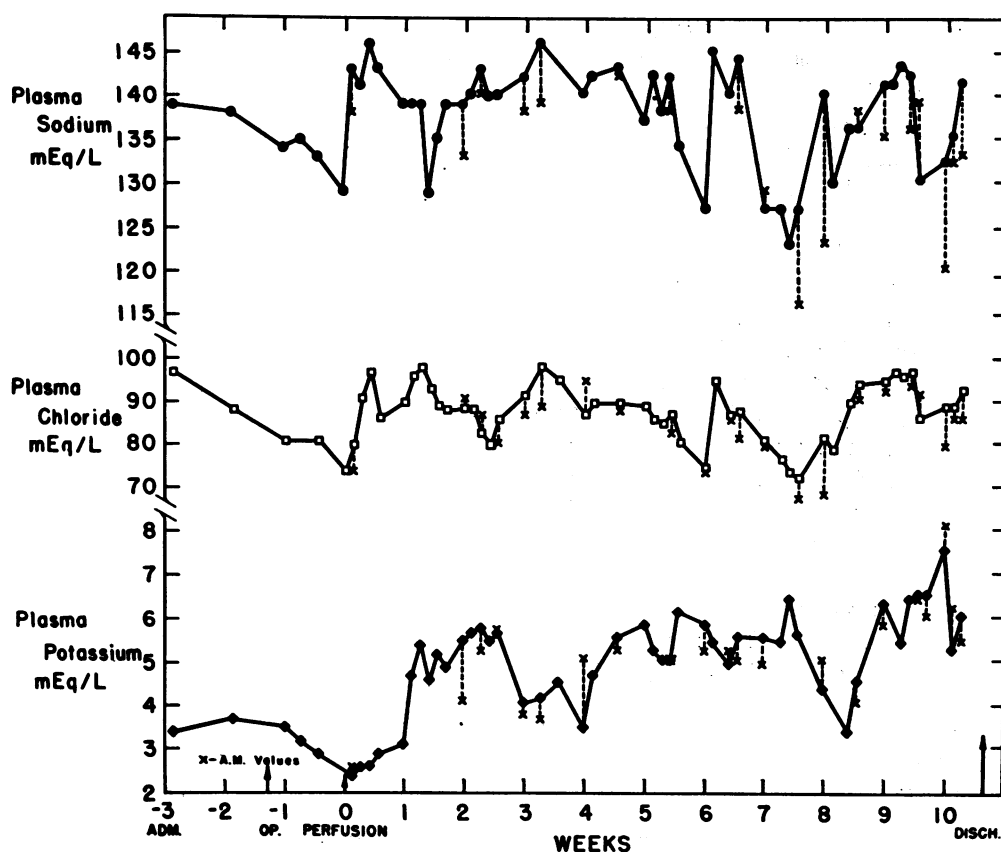


FIG. 4. PLASMA SODIUM, CHLORIDE AND POTASSIUM CONCENTRATIONS

X values represent concentrations before perfusions on 21 days when blood samples were taken before and after perfusions. Sodium and chloride concentrations generally increased toward normal after perfusions. Potassium concentrations were 5.2 ± 1.1 mEq. per L. after perfusions were started. One episode of hyperkalemia (8.2 mEq. per L.) about the tenth week was due to excessive potassium in the perfusate but was corrected readily by omission of potassium.

These data are shown in Figure 5. Sodium, chloride, calcium and magnesium excretion paralleled the decrease in urine volume. Urine osmolality during the perfusion period was 273 ± 42 mOsm. per L. Decreasing daily albumin excretion correlated with the decline in urine volume ($r^2 = 0.665$, $p = 0.001$). On days when perfusions were done, the urine accounted for 24.5 ± 11.3 per cent of the daily nitrogen excretion. During the last week of hospitalization this figure was 14.1 ± 3.65 per cent of daily nitrogen excretion, both excluding fecal losses.

E. Plasma electrolyte concentrations. Plasma sodium, potassium and chloride concentrations (Figure 4) show decreasing values until perfusions were begun, followed by restoration toward normal, accompanied by moderate urinary sodium

and chloride excretion. In general, plasma sodium and chloride concentrations were higher after perfusions than before. Depressions of sodium and chloride concentration were related either to diarrhea or to water loading. Significant alterations in plasma sodium and chloride concentrations were produced by perfusions and were related to the electrolyte and osmolar composition of the perfusate solutions. Low initial plasma potassium concentrations soon reached high normal values. On one occasion hyperkalemia (8.2 mEq. per L.) occurred due to increased potassium in the perfusate but was corrected readily by omission of potassium.

F. Deuterium studies. Total body water, as estimated by deuterium oxide dilution, was 38.56 L. (72.48 per cent of body weight) on the day

after admission. On Feb. 14, 1957, two and one-half weeks after perfusions were started, this value had decreased to 32.54 L. comprising a larger portion (77.39 per cent body weight) and reflecting a decreased lean body mass and a proportionately greater decrease in body fat compared with the initial studies.

Comparable states of hydration were observed clinically at the times of both determinations. The loss of 6.02 L. of total body water corresponded to the loss of 8.22 Kg. of lean body mass using the factor lean body mass equals 73.2 per cent H_2O (31). The patient's clinical appearance at the time of the second total body water determination corroborated these observed body compositional changes; he obviously had lost weight and had less muscle mass and subcutaneous fat than on admission.

G. Blood pressure alterations. Blood pressure data are presented in Figure 3. Blood pressure, measured two to six times daily, averaged $139 \pm$

35 mm. Hg systolic and 98 ± 9 mm. Hg diastolic, preoperatively. Postoperatively, the blood pressure was 150 ± 15 systolic and 100 ± 10 diastolic. After perfusions were begun, a general decline in blood pressure to values of 126 ± 6 systolic and 78 ± 7 diastolic one month later was observed. After this interval, mean weekly fluctuations ranging up to 134 ± 6 systolic and 98 ± 10 diastolic were noted. Mean weekly blood pressure, until cortisone was given, was correlated with weekly perfusate sodium balance as shown in Figures 3 and 6 ($r^2 = 0.71$, $p = 0.01$). Removal of sodium after cortisone was given did not reduce the blood pressure.

II. Perfusion results

A. Determination of optimal flow rate. The results of a study in which perfusion rates were varied and alternated on the same day in order to evaluate the rates of transfer of non-protein

CREATININE CHROMOGEN CLEARANCE (cc./DAY)

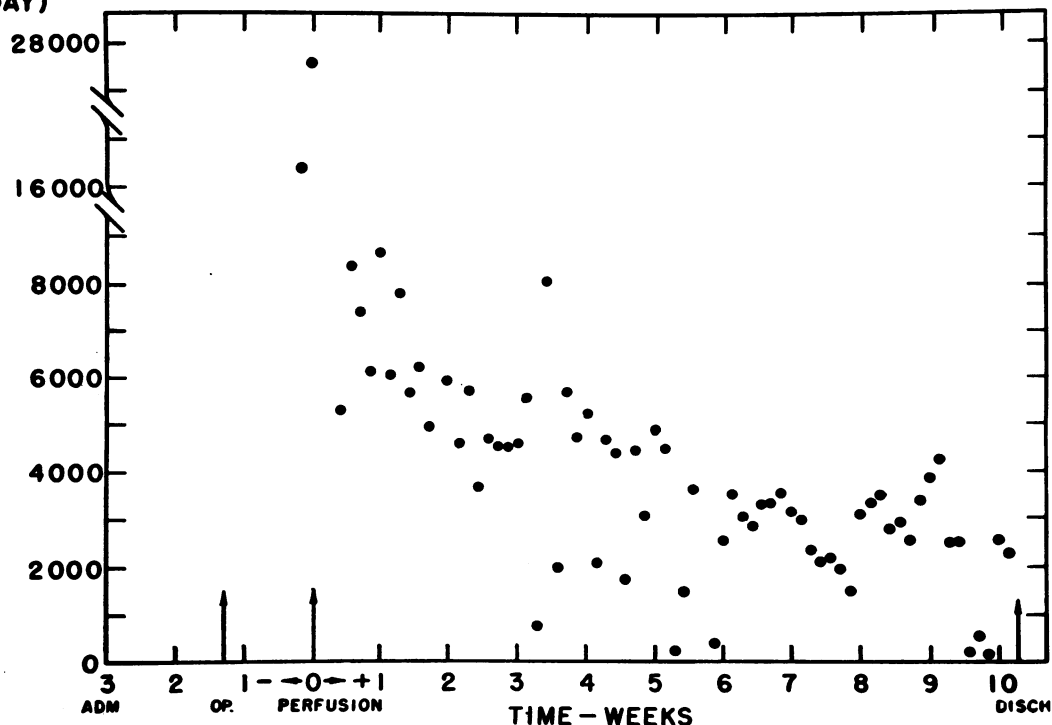


FIG. 5. ENDOGENOUS CREATININE-CHROMOGEN CLEARANCE

The progressive decrease at an average rate of 70 ml. per day is shown.

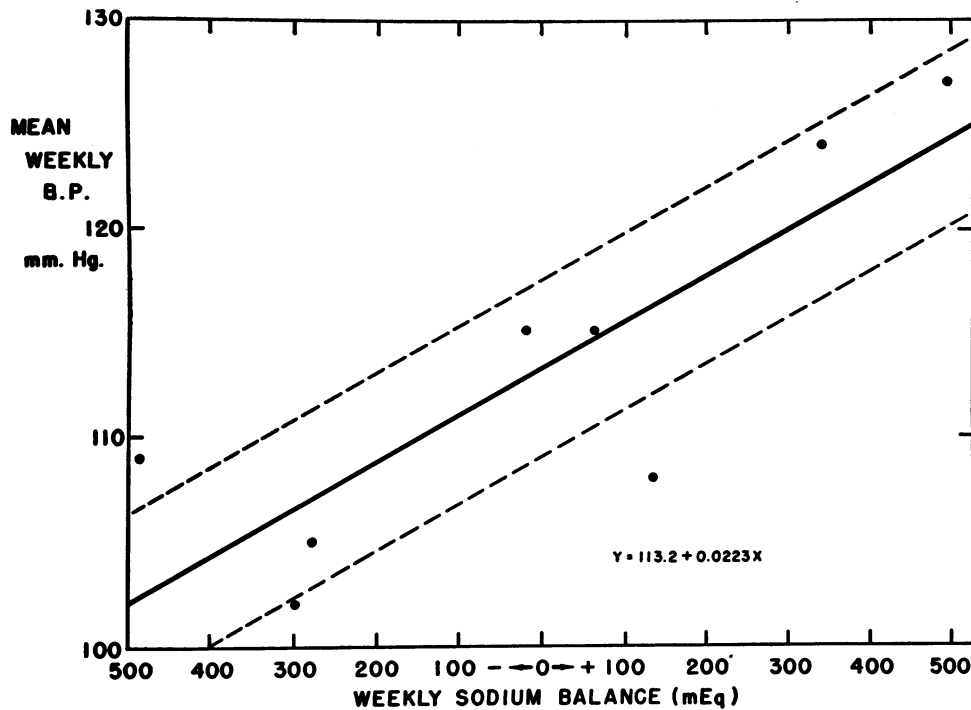


FIG. 6. THE RELATIONSHIP BETWEEN AVERAGE WEEKLY BLOOD PRESSURE AND WEEKLY PERFUSATE SODIUM BALANCE

$r^2 = 0.71$; $p = 0.01$. One standard error (dotted line) equals 4.2 mm. Hg.

nitrogen at varying rates of flow are shown graphically in Figure 7. These data indicated that the optimal flow rate for the purpose of nitrogen removal was about 2,000 ml. per hour, and this rate was used as a standard part of the perfusion procedure in this patient. This rate afforded adequate water removal (up to 1,000 ml. per hour) and electrolyte transfers when these were desired.

B. Water exchange and transfer. The passage of substances across the intestinal mucosa was found to depend upon flow rate, osmolality of the perfusate, concentration gradient between the blood and perfusate, and temperature of the perfusate. Length and surface area of the isolated intestinal segment, blood flow to the segment, and functional integrity of the intestinal mucosa were assumed not to vary sufficiently to preclude comparisons of rates observed on different perfusion days. Repetitive observations indicated that these assumptions were warranted.

1. Water transfer and osmolality. Perfusate water absorption or removal, together with urine volume and approximate (± 15 per cent) water

intake, are shown in Figure 2. On 39 days during the perfusion period, when body water was removed, the water removed by perfusion accounted for 71 ± 2.4 per cent of the total sensible water excretion. During the last 16 days, when water was removed by each of 12 perfusions, 88.2 ± 6.4 per cent of the sensible water loss was removed by the perfusions. According to the data available from 24 perfusions done at home, water removal by perfusion was continued.

Thirst occurred during perfusions in proportion to the osmolality of the perfusate solutions employed. Oral fluid intake was not limited during perfusions and occasionally up to 2 L. was taken.

The relation between the osmolality of the perfusate solutions and water absorption or removal is depicted in Figure 8. Up to 1 L. of water per hour was removed with a perfusate osmolality of 760 mOsm. per L. Removal of body water was accompanied on several occasions by obvious decrease or disappearance of edema during the six hour perfusion period. This was associated with weight loss during this interval corresponding to

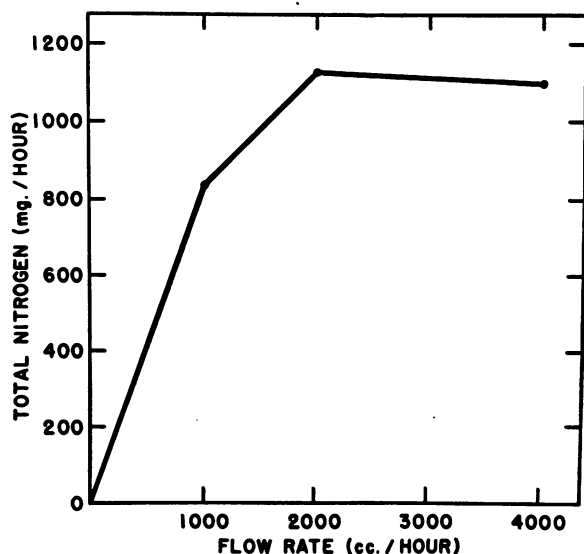


FIG. 7. EFFECT OF FLOW RATE ON NITROGEN REMOVAL.

Flow rates were varied and alternated to determine the optimum flow for nitrogen removal. Each point represents the average nitrogen removal at the flow rates indicated. Maximal nitrogen removal was obtained at approximately 2 L. per hour.

the amount of water removed. The osmolal concentration at which no water absorption or removal took place was 363 ± 62 mOsm. Plasma osmolality during the perfusion period was 299 ± 4.4 mOsm. per L.

2. *The dynamics of water exchange and clearance.* Deuterium oxide (heavy water) was used to measure the rate of exchange of water between the blood and the lumen of the isolated jejunal segment. The patient was in body water-deuterium equilibrium from a deuterium oxide infusion on the previous day for determination of total body water. A blood sample was taken, and 300 ml. of 0.2 M sucrose solution in distilled water was instilled into the intestinal segment. Serial samples were taken from the isolated segment for two hours and were analyzed for deuterium, which appeared rapidly in the intestinal lumen, reaching a concentration (0.265 volume per cent) nearly equal to that of the plasma (0.270 volume per cent) in 30 minutes. By the usual clearance formula ($C = UV/P$), the earlier 15 minute intestinal concentration (0.256 volume per cent), and correction for the water contents of plasma and the sucrose solution, plasma clearance of intestinal segment was 19.5 ml. per

minute. This is an approximation since the volume of the sucrose solution within the segment was not measured. The removal of 17 ml. per minute, by hypertonic perfusates, approximated the deuterium clearance and may therefore have represented a near-maximum rate of water removal. Perfusion for brief (15 minute) periods with dilute perfusates of about 50 mOsm. per L. concentration indicated an absorption rate of approximately 1,000 ml. per hour. These data are not included in Figure 8 because of the short perfusion times. Perfusion with plain water is known to cause mucosal damage (32) and was not done for this reason.

C. *Nitrogen transfer. Nitrogen removal.* The abrupt decrease of plasma urea nitrogen, after perfusion was begun, was associated with intestinal sodium absorption and increased urine output with considerable urine nitrogen excretion (Figure 1). The plasma urea nitrogen reached its lowest concentration (49 mg. per cent) one month after perfusions were begun, and this was associated with the peak of clinical improvement,

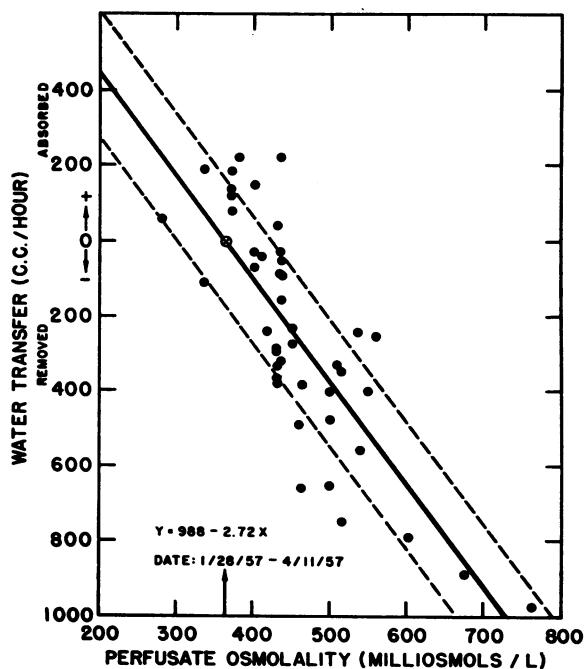


FIG. 8. EFFECT OF PERFUSATE OSMOLALITY ON WATER TRANSFER

Each point represents one perfusion. The point (X) at which no water transfer occurred was 363 ± 61 mOsm. per L. Standard error (dotted line) is 169 ml. per hour; $r^2 = 0.66$; $p = 0.001$.

positive nitrogen balance, highest caloric intake and greatest apparent tissue weight. The plasma urea nitrogen remained relatively stable with a gradual increase throughout the remainder of hospitalization. After perfusions were begun, the average morning plasma urea nitrogen for the 10 week perfusion period was 99.3 ± 12 mg. per cent. Perfusion reduced the plasma non-protein nitrogen by 8.2 ± 7.3 per cent of its initial value and the plasma urea nitrogen was decreased by 10.8 ± 7.8 per cent of the preperfusion figure.

Since the removal of water frequently was greater than the removal of nitrogen, the serum concentration proved to be less valuable than an estimate of total body urea nitrogen. The assumption that urea is distributed equally throughout total body water is well documented (33) and has been confirmed in this laboratory. Two measurements of total body water with deuterium oxide, together with nitrogen balance measurements and weight observations, permitted approximations of daily total body water values. From the products of body water values and the plasma urea nitrogen measurement, total body urea nitrogen estimations were made. Total body urea nitrogen, calculated in this way, was reduced 4.45 ± 2.25 Gm. by each perfusion on 21 days when blood samples were taken before and after perfusions. On these days, total body urea was reduced by 12.8 ± 6.5 per cent of its initial value. Urea synthesis and urinary urea excretion during the six hour interval introduced only a small variation and have not been considered in these estimations. Decrease in total body urea nitrogen, calculated in this way, agreed well with the analytical values for perfusate urea nitrogen removed; total body urea nitrogens were decreased by 14.1 ± 4.1 per cent of their initial values.

Urea nitrogen was removed at a rate of 0.8 ± 0.3 Gm. per hour and accounted for 88.6 per cent of the total nitrogen removed. This corresponds to the removal of 4.8 ± 1.8 Gm. of urea nitrogen in the usual six hour perfusion period. Total non-protein nitrogen was removed at a rate of 0.92 ± 0.32 Gm. per hour or 5.51 ± 1.92 Gm. in six hours.

2. *Urea clearance.* From the urea nitrogen removal data it is possible to calculate the urea clearance of the isolated jejunal segment by the usual clearance formula ($C = UV/P$). With an

overall average plasma urea nitrogen of 99.4 mg. per cent and a mean urea nitrogen excretion rate of 13.3 mg. per minute, the clearance is 13.4 ml. of plasma per minute, which is 17.9 per cent of normal renal plasma clearance.

D. Sodium potassium and chloride. The relations between perfusate sodium, potassium and chloride concentrations and absorption or removal rates of these electrolytes are shown by the scattergrams with linear regression equations⁷ (34), in Figure 9, which represent data obtained from 49 individual six hour perfusions over a 10 week period.

The rates of maximum removal observed for sodium, potassium and chloride are summarized in Table I. Removal rates were those observed with omission of the respective electrolytes from the perfusate solution. With the specified flow rate conditions employed, these values probably represent near maximum clearance rates for these respective electrolytes by the isolated proximal half of the small intestine in this patient. The maximum absorption rates observed depended upon the arbitrarily determined maximum concentrations of electrolytes in the perfusate solutions.

Since the intestinal transfer rates of electrolytes would seem to depend more upon the differences between the plasma concentrations and the perfusate concentrations than upon the absolute values of either, these data have been plotted graphically as shown in Figure 10 and are summarized in Table I. A high degree of significance ($p = 0.001$) for all of these correlations was found.

E. Calcium and magnesium. Observed changes in the perfusate calcium and magnesium concentrations before and after perfusions were subject to the probable error of precipitation of variable amounts of calcium and magnesium carbonate, and this precluded positive interpretation of the

$$r = \frac{NSXY - SXSY}{\sqrt{[NSX^2 - (SX)^2][NSY^2 - (SY)^2]}}$$

$$t = \sqrt{\frac{r^2(N-2)}{1-r^2}}$$

where r = coefficient of correlation; r^2 = coefficient of determination; N = number of perfusions; S = "sum of"; X = perfusate electrolyte concentration or gradient (see Table I); Y = electrolyte transfer rate in mEq. per hr. (see Table I); t = factor used to determine p value (level of significance) from table of t and p values (34).

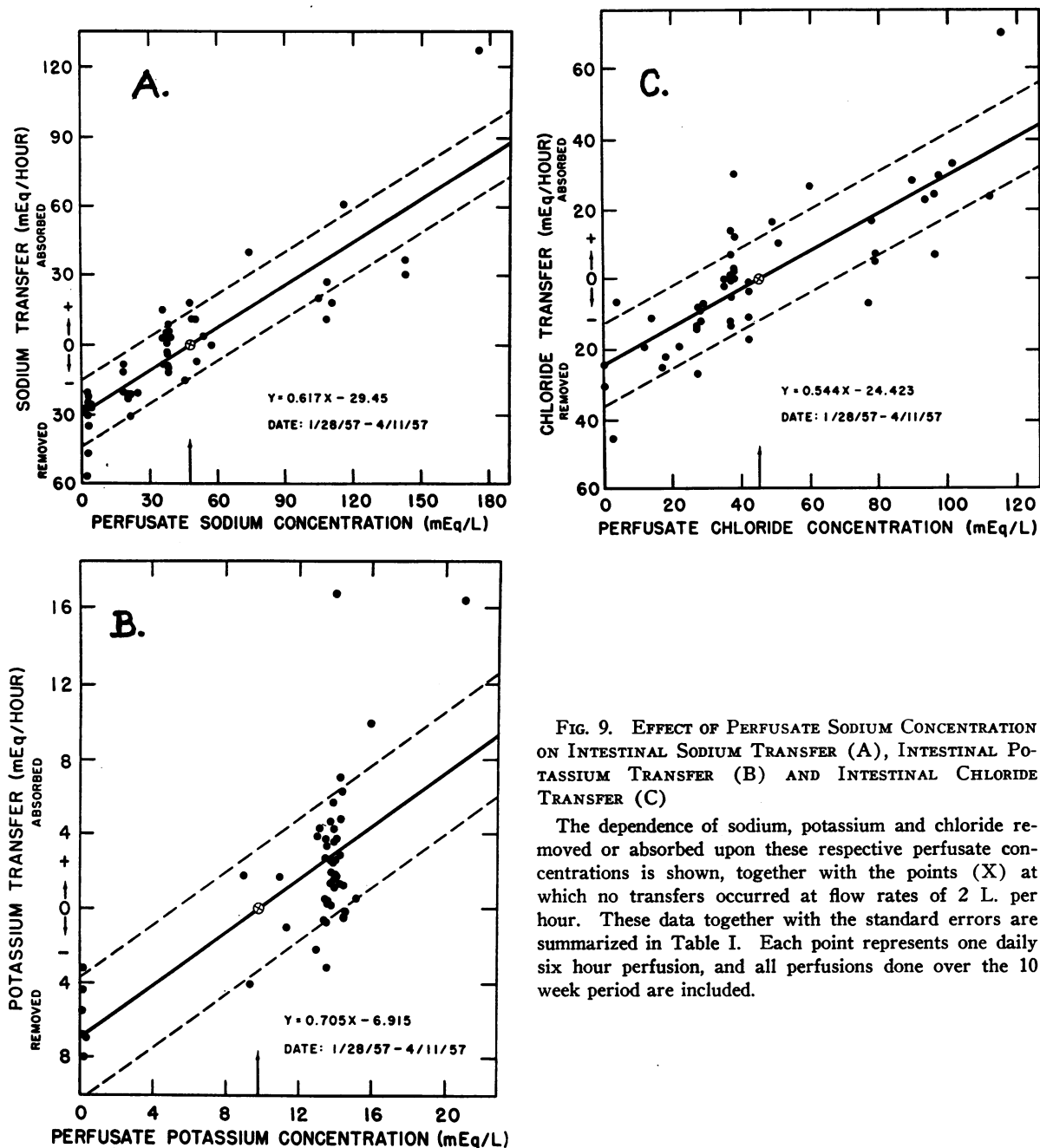


FIG. 9. EFFECT OF PERFUSATE SODIUM CONCENTRATION ON INTESTINAL SODIUM TRANSFER (A), INTESTINAL POTASSIUM TRANSFER (B) AND INTESTINAL CHLORIDE TRANSFER (C)

The dependence of sodium, potassium and chloride removed or absorbed upon these respective perfusate concentrations is shown, together with the points (X) at which no transfers occurred at flow rates of 2 L. per hour. These data together with the standard errors are summarized in Table I. Each point represents one daily six hour perfusion, and all perfusions done over the 10 week period are included.

balance data for these substances. Elevation of plasma concentrations (Figure 11) and later evidence of metastatic calcification suggest that absorption of calcium may have occurred with the perfusate concentrations employed.

F. Phosphorus. Analysis of effluent perfusates revealed that little phosphorus was removed by the perfusate, and significant changes were not

observed in plasma phosphorus concentrations before and after perfusion. Determinations of fecal and urinary phosphorus excretion indicated that these two routes accounted for the greatest excretion, even with the marked oliguria observed later in the course of the disease.

G. Creatinine and uric acid. Plasma creatinine concentrations before and after perfusion did

TABLE I
Summary of electrolyte transfers *

X	Y	Fig. no.	N	T ₀	C _{min.}	T	S. E.	Factor	r ²	p
				mEq./L.	mEq./L.	mEq./hr.	mEq./hr.	mEq./L.		
Perf. Na	Na trans.	9A	49	48	1.8	30	14	3.0	0.80	.001
Perf. K	K trans.	9B	49	10	0.1	7	3	2.5	0.50	.001
Perf. Cl	Cl trans.	9C	49	45	0.0	24	12	2.2	0.65	.001
Na grad.	Na trans.	10A	32	88			16		0.74	.001
K grad.	K trans.	10B	32	-4			4		0.52	.001
Cl grad.	Cl trans.	10C	32	44			14		0.59	.001

* Symbols are as follows: X = perfusate electrolyte or gradient, as indicated, in mEq. per L.; Y = perfusate electrolyte transfer in mEq. per hr.; Perf. = perfusate concentration, mEq. per L., X; Grad. (Gradient) = plasma concentration - perfusate concentration; Trans. (Transfer) = removal or absorption, mEq. per hr., Y; N = number of perfusions; T₀ = zero transfer concentration; C_{min.} = minimum concentration used; T = amount removed with minimum perfusate concentration; S. E. = standard error; Factor = amount to be added to or subtracted from zero transfer concentration (T₀) to produce absorption or removal, respectively, of 10 mEq. in a six hour perfusion; r² = coefficient of determination; p = probability.

not differ significantly. Assuming body water distribution of creatinine, total body creatinine before and after perfusion was calculated from total body water and plasma creatinine concentrations. Significant changes in total body creatinine were not observed. Plasma uric acid data are shown in Figure 11. The decrease observed two to four weeks after perfusions were begun was associated with the peak of clinical improvement. Significant amounts of uric acid were not removed by perfusion, however.

H. Glucose. Analyses of nine perfusate solutions showed glucose absorption of 14 ± 6.6 per cent of the amount in the perfusate per hour. This ranged from 4.50 to 27.85 Gm. per hour and was associated with plasma glucose concentrations of 138 to 162 mg. per cent. Sucrose absorption did not occur as evidenced by lack of detectable sucrose in the plasma. Some hydrolysis of sucrose was observed in the perfusate, however, with absorption of the monosaccharides.

III. Effect of withholding perfusions

On days when no perfusions were done increases in plasma urea nitrogen, non-protein nitrogen and total body urea nitrogen were related to dietary nitrogen intake.

Ten days after perfusions were started, the effect of omitting perfusions for five days was evaluated. Effective dietary nitrogen intake was 37.3 Gm. during this interval. The plasma urea nitrogen increased from 86 to 129 mg. per cent;

the NPN rose from 119 to 158 mg. per cent and total body urea nitrogen accumulated from 27.9 to 41.2 Gm., an increase of 13.3 Gm. Urine non-protein nitrogen was 15.3 Gm. The unaccounted difference of 8.7 Gm. includes fecal nitrogen loss and, possibly, positive tissue nitrogen balance. In contrast to his condition at the beginning of this interval, after three days the patient developed symptoms of nausea, anorexia, vomiting, lower extremity paresthesias and general irritability. These symptoms subsided during the next perfusion. Overall nitrogen balance was readily maintained at an acceptable compensatory plasma nitrogen concentration; the rate of nitrogen removal permitted moderate intake of protein.

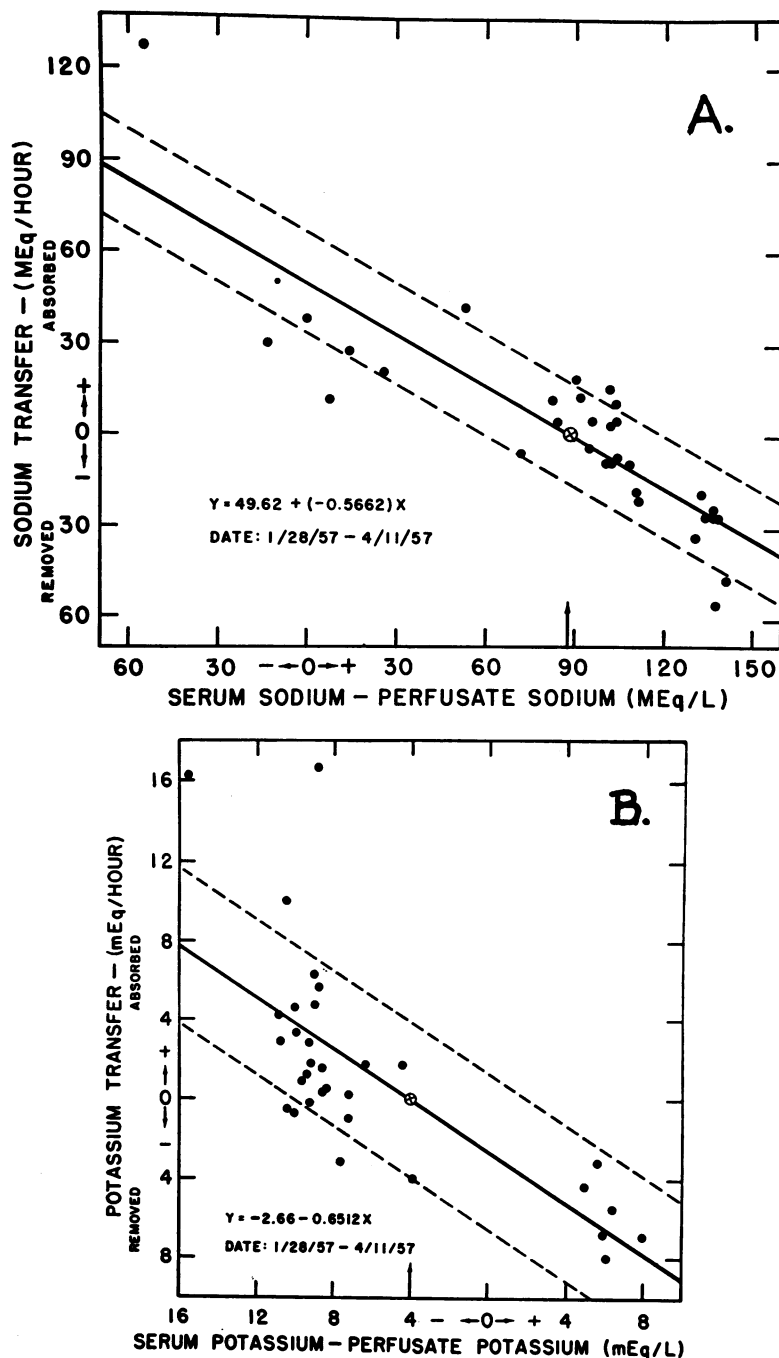
IV. Derivation of perfusate formula

The derived points (Table I) at which no electrolyte transfers occur are reference values for the preparation of the perfusate formulas. These values were altered to compensate for dietary electrolyte intake and external losses, including urine excretion. Any reasonable dietary electrolyte intake could be compensated by adjustment of the perfusate concentration to maintain zero balance, but maintenance of a fairly constant dietary electrolyte intake facilitated management. The amounts of sodium, potassium, or chloride to be removed by each daily perfusion were represented by the differences between dietary intake and urinary excretion. This difference, multiplied by the factor listed in Table I and subtracted from

the zero transfer concentration, represents the approximate overall zero balance concentration. Positive electrolyte balance occurring on days when no perfusions were done had to be considered in the preparation of subsequent perfusion formulas in order to remove excesses.

V. Maintenance of function by the isolated jejunal segment

An attempt was made to evaluate alteration in intestinal segment transfers of nitrogen and electrolytes by plotting these transfers against time.



(FIG. 10—Continued on opposite page)

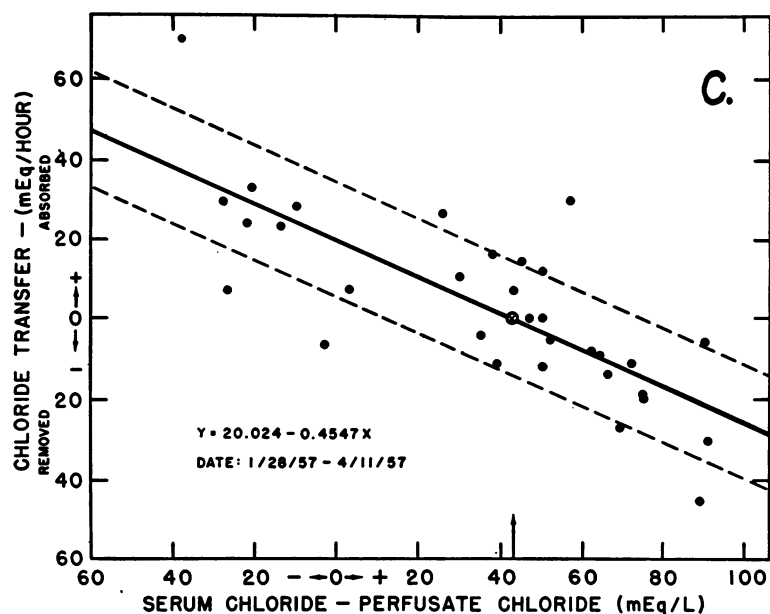


FIG. 10. EFFECT OF SODIUM, POTASSIUM AND CHLORIDE GRADIENTS ON INTESTINAL SODIUM TRANSFER (A), INTESTINAL POTASSIUM TRANSFER (B) AND INTESTINAL CHLORIDE TRANSFER (C)

Figures show the dependence of electrolyte absorption or removal on the gradient or difference between the plasma electrolyte concentration and perfusate electrolyte concentration. For any given perfusate concentration, the plasma concentration determined the actual electrolyte transfer at a flow rate of 2 L. per hour. These data, together with the standard errors, are summarized in Table I. Each point represents one daily six hour perfusion on 39 days when blood samples were taken.

The percentage of body urea nitrogen removed (14.1 ± 4.1 per cent) did not change significantly over the entire perfusion period of 10 weeks ($p = 0.65$). The electrolyte gradients (Figure 10) were the same for sodium during seven perfusions over a period of seven weeks, for potassium during 20 perfusions over a period of eight weeks, and for chloride during eight perfusions over a period of five weeks. When the ratios, electrolyte gradient/electrolyte transfer, were plotted against their respective times, no significant slope was found. Similarly, water transfer-perfusate osmolality relationship did not change during the 10 week period. It was concluded, therefore, that no alteration in transfer rates of nitrogen, sodium, potassium, chloride or water occurred during the course of the perfusions and that no evidence of deterioration of function of the isolated jejunal segment was observed. The possibility that later alteration in mucosal transfers occurred, is not, however, excluded.

VI. Course after discharge⁸

Perfusion equipment, supplies and chemicals were sent home with the patient, together with diet and complete written instructions. Perfusions had been done in the hospital by the patient and his mother for several days prior to discharge, and detailed records were also kept by them during the last week in the hospital.

The patient continued to be up and about and was able to drive a car for the first two weeks at home. The urine output, which had declined during hospitalization, continued to decrease with the following average daily urine volumes at home: first week, 317 ± 31 ml.; second week, 134 ± 73 ml.; third week, 22 ± 20 ml.; and fourth week, 17 ± 28 ml. Weight remained stable. Twenty-four perfusions were done at home with removal of 1.52 ± 0.69 L. of water during each perfusion. Ten telephone conversations were held during

⁸ Under the care of Dr. Albert Juergens, Dillon, Mont.

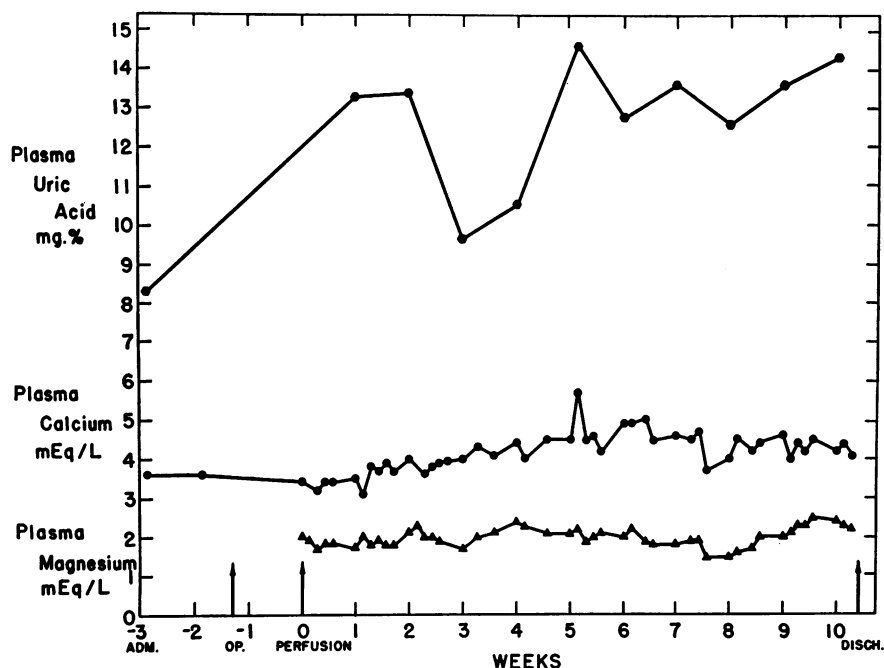


FIG. 11. PLASMA CALCIUM, MAGNESIUM, AND URIC ACID CONCENTRATIONS

Figure shows the maintenance of normal plasma calcium and magnesium concentrations and the general increase in plasma uric acid with a decrease during the third and fourth weeks, which corresponded with the peak of clinical and biochemical improvement.

which minor alterations in perfusate composition were advised on the basis of weights and clinical symptoms, suggesting sodium excesses or deficits. During the last five days, joint pains were allegedly severe and were relieved by adding sodium via the perfusate. The patient expired quietly one month after discharge. Autopsy showed depositions of uric acid and calcium sufficient to explain the eventual anuria.

DISCUSSION

From the results of the present study, afforded by changes observed during 50 separate six hour perfusions, it was possible to prepare a perfusate solution which would cause predictable changes in intestinal transfer of these electrolytes in order to correct fluid-electrolyte derangements or to maintain water and electrolyte homeostasis. The perfusate composition, at which no transfers of important electrolytes or water occur, is similar to some of those used by others (4, 5, 14).

The urea clearance of 13.4 ml. per minute for

the isolated jejunum in this study compares with a reported value of 19.1 ml. per minute with a single perfusion of the entire bowel at a flow rate of 1,332 ml. per hour (35).

Limitations of the method of perfusion of the isolated proximal half of the small intestine include inability to remove uric acid, creatinine or phosphorus in sufficient amounts to lower the plasma concentrations of these substances. It seems likely that other higher molecular weight substances similarly are not removed by the perfusion. From information presently available it would seem desirable to limit dietary uric acid and its precursors in an attempt to combat the hyperuricemia.

The possible role of sodium in the genesis of hypertension receives some support from these studies. The significant correlation of blood pressure with sodium balance seems to implicate this ion although better correlation was observed with the sodium/potassium ratio. After the patient was given cortisone, removal of sodium did not produce a fall in blood pressure.

Practical applications in perfusion management

Table I gives the perfusate concentrations at which no transfers of sodium, potassium or chloride occur. The factor in mEq. per L. to be added to or subtracted from the zero transfer concentration in order to add or remove each of these electrolytes in a six hour perfusion is also tabulated. For each 1,000 ml. of water to be added or removed in a six hour perfusion, the osmolality is decreased or increased, respectively, 61 mOsm. per L. All of these values represent approximations, since the standard deviations are about 30 per cent of the figures listed. The perfusate composition at which no transfers of electrolytes or water occurred is summarized in Table II.

The transfer data has been determined for each new patient. This was approximated by doing several careful one hour perfusions, using a few different electrolyte concentrations within the ranges reported in this study. From these data and their relationships to plasma concentrations, electrolyte transfers are graphed and calculated. This information may then be used to obtain predictable transfers of electrolytes and water.

Although the procedure is apparently capable of adjusting body water, sodium, chloride, potassium and urea adequately, it does not perform all the functions of the kidney since removal of larger molecule uremic metabolites and phosphorus in amounts sufficient to lower the plasma concentrations was not attained. Body weight and clinical symptoms were useful guides in the preparation of individual perfusate formulas.

The practical feasibility of the method is evidenced by the ability of the patient to do it at home. Availability of common salts, sugar, tap water, and perfusion carboys and tubing render

this an inexpensive adjunct. No deterioration of function of the isolated intestinal segment was observed, and present evidence from this laboratory and others (4, 14) suggests that the function of the isolated segment can be maintained for at least three years.

Patients selected for this type of management should be reasonably free from pre-existing cardiovascular complications. In the present stage of development it is believed that its use at the age extremes is not warranted. At the present time isolated jejunal segment perfusion is limited at this institution to young and middle aged adults with serious progressive renal disease.

SUMMARY

1. A patient with advanced uremia has been managed by 50 perfusions of the isolated proximal half of the small intestine in the hospital and by 24 perfusions at home.

2. With decreasing renal function and progressive oliguria, the patient remained clinically and biochemically essentially stable until anuria developed.

3. Total renal function was not achieved because of failure to remove adequate amounts of phosphate, uric acid, and probably other larger accumulated metabolites.

4. Studies of the exchange and transfer rates of water, electrolytes and other crystalloids permitted the compilation of a perfusate solution which would produce either no change or predictable transfers of these substances at perfusion flow rates of two L. per hour.

5. Urea nitrogen was removed at a rate of 0.8 ± 0.3 Gm. per hour, and urea clearance was 13.4 ml. per minute or 18 per cent of normal renal clearance.

TABLE II
Perfusate composition at which no transfers of electrolytes or water occurred

mEq./L.		Gm./L.		Gm./14 L.
Na	48	NaCl	1.35	19
K	10	KCl	0.73	10
Ca	10	CaCl ₂ ·2H ₂ O	0.74	10
Mg	2	MgCl ₂ ·6H ₂ O	0.20	3
Cl	45	Na lactate (71%)	3.90 ml.	55 ml.
Lactate	25	Sucrose	62.00	868
		or		
		glucose	36.80	515

6. Deuterium indicated a water clearance of 19.5 ml. per minute by the isolated jejunal segment.

7. Blood pressure was correlated with perfusate sodium balance until cortisone was given.

8. Isolated jejunal segment perfusion was a useful adjunct in maintaining water, electrolyte, and nitrogen homeostasis in this patient.

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