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# THE RENAL RESPONSE TO EXTRARENAL DEPLETION OF THE BLOOD VOLUME

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The concept that the kidney might regulate the extracellular fluid volume was first explicitly stated by Peters (1935), although the idea can be traced in much earlier work (Starling, 1909). Peters was particularly concerned with tubular salt reabsorption, arguing that the kidney retained osmotically active substances when the extracellular fluid volume was depleted, and conversely. A large volume of research bearing on Peters's thesis has accumulated in recent years.

Using the technique of salt depletion to achieve volume depletion, McCance & Widdowson (1937) first showed that this was associated with a drop in glomerular filtration rate (G.F.R.), and Harrison & Darrow (1939) indirectly confirmed this observation in salt and volume loss secondary to adrenal insufficiency. The latter authors interpreted this as a renal vascular response.

Studies of dehydration also bear on this problem, although dehydration involves body-fluid hypertonicity as well as volume depletion. With the advent of clearance techniques, Shannon (1936) utilized dogs, dehydrated by water deprivation, to show that G.F.R. was independent of the state of hydration except at extreme limits. He later confirmed and extended these observations in dogs with diabetes insipidus (Shannon, 1942), where dehydration to the extent of a 20% reduction in extracellular fluid volume can be attained in 24 hr. He found also that when animals with diabetes insipidus were given 0·5% saline to drink their plasma and extracellular fluid volumes were increased, and, concomitantly, the G.F.R. More important, the intravenous administration of the antidiuretic hormone, whether in physiological or massive doses, did not affect the G.F.R. regardless of the state of hydration. Studies of dehydration without starvation in man (Black, McCance & Young, 1944; McCance & Young, 1944) indicated that within the range of a 4–7% weight loss, G.F.R., renal plasma flow (R.P.F.) and plasma volume are all maintained at

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normal levels. This may have been due to the salt intake in the diet. Kenney (1949), applying a similar but greater stress, observed that a 7–8% haemoconcentration in man was associated with a significant fall in G.F.R. and R.P.F., with an essentially unchanged filtration fraction.

Rapid depletion of blood volumes may be observed on the assumption of the passive erect posture in man. This involves no change in total extracellular fluid volume, merely a distributional change. Significant among the many studies of this phenomenon are those of Brun, Knudsen & Raaschou (1945*a*, *b* and *c*), McCance (1951) and Epstein, Goodyer, Lawrason & Relman (1951). Brun maintained that responses to this procedure fall into two categories: hormonal and vascular. The hormonal response seemed to follow stimulation of the supraoptico-hypophyseal system causing active retention of water, as well as of some other system causing active retention of salt. Vascular antidiuresis involved a well-marked decrease in G.F.R. and R.P.F., with filtration fraction remaining unchanged—indicative of afferent arteriolar constriction. Epstein elaborated these views by showing that renal tubular reabsorption of water and salt still increased when the systemic blood-volume decrease of quiet standing was prevented by a simultaneous infusion of isoncotic albumin. Thus, Brun's hormonal responses are apparently associated with a localized, rather than a systemic, volume or pressure change, and can occur when the increase in serum oncotic pressure (colloid osmotic pressure, Peters, 1935) of quiet standing is largely nullified by the intravenous addition of large amounts of isoncotic albumin in normal saline. Epstein's findings agree in general with those of Lewis, Buie, Sevier & Harrison (1950) and Viar, Oliver, Eisenberg, Lombardo, Willis & Harrison (1951), who believe that a localized increase in venous pressure in the head (produced with a pneumatic cuff about the neck) leads to an increase in sodium excretion. On the other hand, increase in plasma colloidal osmotic pressure has been thought to be the primary determinant of a decrease in salt and water excretion (Greiner & Podhradszky, 1947; Welt & Orloff, 1951), particularly in experiments where hyperoncotic albumin (25% solution) is infused into reclining subjects. The latter experiment involves a sudden increase of fivefold in the serum oncotic pressure, which soon leads to a considerable expansion of the blood volume. Thus both hydrostatic and oncotic pressures seem to be able to excite Brun's hormonal responses.

The experiments herein described were made in the attempt to produce acute blood-volume depletion (and extracellular fluid volume depletion) by an extrarenal route, at controllable rates and with minimum trauma, and to observe the renal reaction to this stress. The technique consisted of introducing hyperoncotic, isosmotic solutions into the peritoneal cavity of dogs, and allowing the animals to approach new fluid equilibrium by losing isotonic extracellular fluid to this peritoneal pool until systemic and renal effects were demonstrable.

## METHODS

Ten adult female dogs, selected for leanness, were used in fifteen experiments. The character of the procedures used necessitated light nembutal anaesthesia, 25 mg./kg. Urine was collected by means of an indwelling soft rubber catheter. Arterial blood was collected by means of a cannula in the femoral artery. Renal vein blood was collected with a no. 6 straight Cournand radio-opaque cardiac catheter inserted into the right jugular vein in the neck, and run into the left renal vein with the aid of a small portable fluoroscopy unit. Systemic blood flow was measured directly with a modified Selkurt bubble flowmeter (Selkurt, 1949) inserted into a carotid-carotid circuit (inflow to and outflow from the meter in the same common carotid artery, using a low meter resistance). The instrument used is described in the appendix. Intraperitoneal pressure was measured with a simple water manometer. Concentrations of creatinine and *p*-aminohippuric acid (PAH) satisfactory for accurate clearances were obtained in the blood by an initial intravenous injection of 10 mg. PAH and 200 mg. creatinine/kg. body weight. These concentrations were maintained throughout the experiment either by a slow intravenous drip of 500 mg./100 ml. PAH in 1·0% creatinine solution into the femoral vein, or by subcutaneous injection of the same solution with 500 viscosity units of added hyaluronidase (Alidase-Searle) per litre.

Base-line values of PAH and creatinine extraction ratios and clearances, haematocrit, haemoglobin concentration, plasma chloride and protein concentrations, and urine chloride were determined in duplicate or triplicate over an hour's time. 25 ml./kg. of 12% acacia in normal saline or 12% albumen in normal saline at 37° C. were then injected intraperitoneally, and the same determinations repeated after 15 and 30 min., 1, 2, 3 and 4 hr. The total time for injection was usually 2–3 min. On several occasions 25% albumen in normal saline was used. In most cases, the initial dose of barbiturate was sufficient for the entire 3–5 hr. period; occasionally additional small amounts were required intravenously. If any dog was inadvertently too deeply anaesthetized, and base-line values were found abnormally low, the animal was not used on that particular occasion. The experiment was usually terminated after 3–4 hr. with as complete a paracentesis as possible, intravenous administration of normal saline, and clipping of all minor 'cut-down' wounds. These animals did well, and could be used again in 2–3 weeks with no obvious deleterious effects. Four of the animals received no intraperitoneal injection but were otherwise treated in the same manner in order to determine the effect of anaesthesia and lack of motion over a 4 hr. period.

Syringes for the collection of blood samples were moistened with heparin, and 5·0 ml. samples were drawn almost simultaneously from the femoral artery and renal vein. Haematocrit was determined in the usual manner. Haemoglobin concentration was determined colorimetrically in a Coleman spectrophotometer using laked blood with added concentrated $NH_3$. PAH was determined by the method of Smith, Finkelstein, Aliminosa, Crawford & Graber (1945), with the exception that plasma-protein precipitation was brought about by adding 10 vol. of 10% trichloroacetic acid to the diluted plasma. Creatinine determinations were carried out by the method of Barrett & Addis (1947) on the trichloroacetic acid filtrate. Total plasma proteins were estimated using Gornell, Bardawill & David's method (1949), and plasma and urine chlorides were determined by a Volhard microtitration as described in Peters & Van Slyke (1936). Plasma-water concentration was determined by weighing a given volume, drying it to constant weight, and then subtracting the weight of the dry solids in it.

Following Oakley's observations (1934), acacia solutions were refrigerated to prevent bacteria breakdown from producing smaller more diffusible particles. The acacia used was the purified, sterilized Lilly product.

Albumen solutions were made up from 25% solutions of salt-poor human albumen (Squibb) supplied for research by the American Red Cross.

Various calculations were used to determine the quantitative aspects of glomerular and tubular function. Clearances were determined by the usual $UV/P$ formula, the exogenous creatinine clearance being taken as the G.F.R., and the PAH clearance being taken as the effective renal plasma flow (R.P.F.). A measure of the active tubular handling of water was taken from the $U/P$

ratio for creatinine, which was the substance least affected by tubular action in this experiment. Chloride filtered was calculated from the concentration of Cl/ml. of serum water corrected for Donnan factor. The ratio of excreted chloride to filtered chloride is taken as a measure of the active tubular handling ('rejection ratio') of chloride. All chloride values tabulated are expressed either in terms of m.equiv./min. or m. equiv./l.

## RESULTS

In Fig. 1 changes in blood volume are plotted over a 3 hr. period of dialysis as reflected in the two criteria of plasma-protein concentration and haemoglobin-haematocrit. Volume ratio (or volume fraction) was obtained by setting pre-injection base-line values arbitrarily as equal to 1·0, and expressing all subsequent arterial values as fractions of these base-line figures. This calcula-

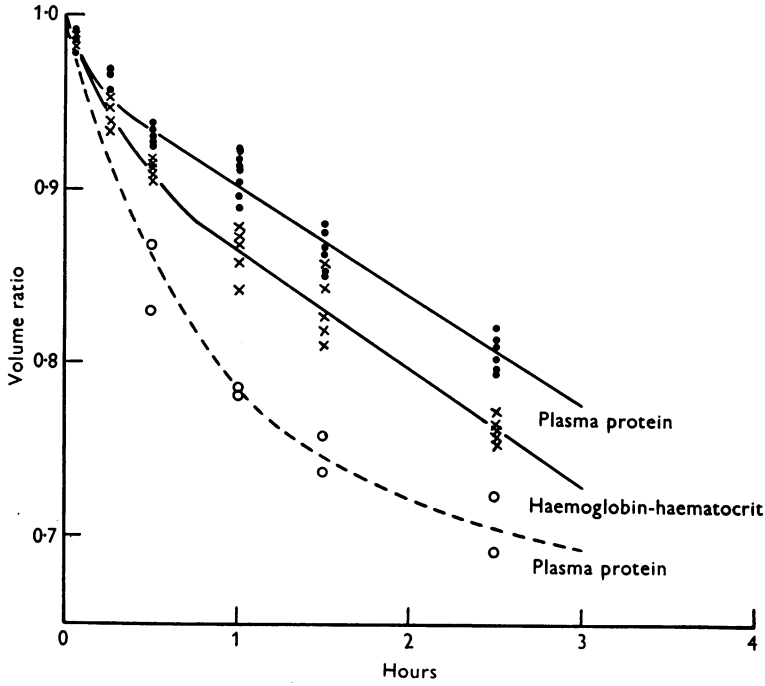


Fig. 1. Changes in blood volume induced by intraperitoneal injection of colloid in normal saline. Ordinates: volume ratio (see text). Abscissae: time after injection. —— 12% acacia or albumin (five animals); - - - - 25% albumen (one animal).

tion necessitates the assumption that total circulating red cells and plasma proteins remain constant during the peritoneal dialysis period; that is, that no net gain or loss of these substances occurred, e.g. into the peritoneal pool. The validity of this assumption will be discussed below.

Elkinton's formula (1946) was used to calculate blood volume fractions from haematocrit and haemoglobin:

$$\frac{(1-\mathrm{Hct}_2)\,(\mathrm{Hb}_1)}{(1-\mathrm{Hct}_1)\,(\mathrm{Hb}_2)} = \frac{V_2}{V_1} = \text{vol. ratio or fraction.}$$

In this case all '1' values are pre-dialysis values or base-line values, and all '2' values are determinations at varying intervals of time after initiation of peritoneal dialysis.

As can be seen by comparing the dotted with the solid lines, the only essential difference between the two colloidal concentrations is that the higher the colloidal osmotic pressure, the faster the dialysis rate, and the faster the asymptotic approach towards a new equilibrium. No difference was observed in the rate of volume change induced by the two types of colloid given in the

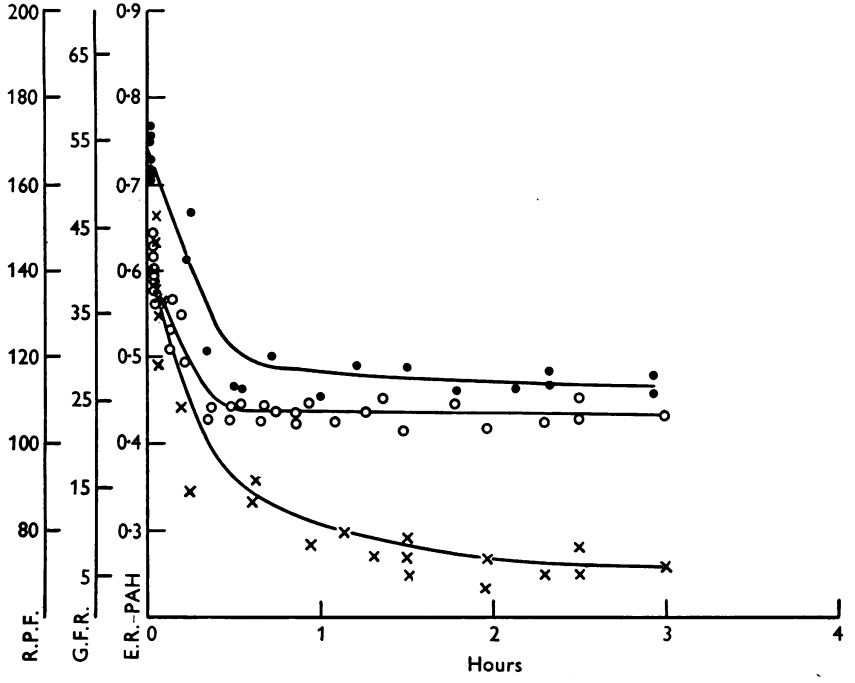


Fig. 2. Changes in renal function induced by intraperitoneal injection of colloid in normal saline. Ordinates: G.F.R., R.P.F. (renal plasma flow) and E.R.-PAH (extraction ratio of PAH). Abscissae: time after injection. ●–● extraction ratio, ○–○ G.F.R., ×–× R.P.F. Results recorded from five animals.

same concentration. It should be noted that the slope of the haemoglobin-haemotocrit curve is significantly greater than that of the plasma-protein curve within the first 45 min. after injection, but subsequently both show the same rate of change. Plasma and peritoneal fluid chloride concentrations remained unchanged at about 100 m.equiv./l. throughout the entire experiment whether 12 or 25% colloid had been given.

The results presented in Fig. 2 and Table 1 are from the experiments with 12% colloid. 25% colloid produced such rapid and extreme declines in urine volume that accurate determination of clearances was impossible.

TABLE 1. The effect of intraperitoneal injection of 12% acacia or albumen on various tubular functions at intervals after the injection. See text for method of calculation.

| | | Urine flow (ml./min.) | G.F.R. (ml./min.) | $U/P$ creatinine ratio | Serum chloride concentration (m.equiv./l.) | $A$ Chloride filtered (m.equiv./min.) | $B$ Chloride excreted (m.equiv./min.) | $B/A$ |
|---|---|---|---|---|---|---|---|---|
| Exp. 1 | Base-line | 1·8 | 42 | 23·3 | 98·7 | 3·66 | 0·063 | 0·017 |
| | 15 min. | 1·6 | 38 | 24·0 | 99·5 | 3·35 | 0·054 | 0·016 |
| | 30 min. | 1·2 | 30 | 24·8 | 100·0 | 2·66 | 0·027 | 0·010 |
| | 1 hr. | 1·05 | 27·6 | 26·2 | 99·4 | 2·42 | 0·012 | 0·005 |
| | 2 hr. | 0·89 | 25·1 | 28·4 | 99·2 | 2·20 | 0·009 | 0·004 |
| | 3 hr. | 0·70 | 24·5 | 35·1 | 99·5 | 2·15 | 0·009 | 0·004 |
| | 4 hr. | 0·64 | 24·4 | 38·2 | 99·5 | 2·14 | 0·008 | 0·004 |
| Exp. 2 | Base-line | 1·3 | 40 | 30·8 | 100·1 | 3·54 | 0·018 | 0·005 |
| | 15 min. | 1·0 | 35 | 35·0 | 101·5 | 3·14 | 0·013 | 0·004 |
| | 30 min. | 0·8 | 25 | 31·3 | 100·8 | 2·21 | 0·004 | 0·002 |
| | 1 hr. | 0·71 | 24 | 33·8 | 99·6 | 2·12 | 0·004 | 0·002 |
| | 2 hr. | 0·52 | 24 | 46·2 | 99·9 | 2·14 | 0·002 | 0·001 |
| | 3 hr. | 0·50 | 24·5 | 49·0 | 99·5 | 2·16 | 0·002 | 0·001 |
| | 4 hr. | 0·51 | 23·0 | 45·0 | 100·4 | 2·04 | 0·002 | 0·001 |
| Exp. 3 | Base-line | 2·0 | 45·0 | 22·5 | 98·9 | 3·94 | 0·024 | 0·006 |
| | 15 min. | 1·8 | 38·7 | 21·0 | 99·1 | 3·39 | 0·017 | 0·005 |
| | 30 min. | 1·5 | 34·7 | 23·4 | 99·8 | 3·06 | 0·006 | 0·002 |
| | 1 hr. | 1·1 | 29·4 | 25·7 | 100·4 | 2·61 | 0·005 | 0·002 |
| | 2 hr. | 0·80 | 25·6 | 32·3 | 99·6 | 2·25 | 0·002 | 0·001 |
| | 3 hr. | 0·55 | 25·2 | 45·6 | 99·0 | 2·20 | 0·002 | 0·001 |
| | 4 hr. | 0·42 | 25·0 | 59·5 | 98·7 | 2·18 | 0·002 | 0·001 |
| Exp. 4 | Base-line | 0·9 | 38 | 42·3 | 101·6 | 3·40 | 0·115 | 0·034 |
| | 15 min. | 0·75 | 34 | 45·4 | 100·4 | 3·02 | 0·091 | 0·030 |
| | 30 min. | 0·68 | 30·4 | 44·8 | 99·8 | 2·68 | 0·056 | 0·021 |
| | 1 hr. | 0·63 | 28·2 | 45·0 | 98·4 | 2·45 | 0·044 | 0·018 |
| | 2 hr. | 0·46 | 23·0 | 50·0 | 99·2 | 2·02 | 0·024 | 0·012 |
| | 3 hr. | 0·45 | 23·0 | 51·0 | 100·0 | 2·04 | 0·025 | 0·012 |
| | 4 hr. | 0·43 | 22·6 | 52·0 | 101·2 | 2·01 | 0·022 | 0·011 |

The changes in renal clearances, PAH and creatinine, during the period of 4 hr. dialysis are shown in Fig. 2 (five animals). There is a decrease in PAH clearance and extraction ratio, and creatinine clearance, with some increase in filtration fraction. All three curves are logarithmic in nature, and it should be emphasized that most of the change in G.F.R. and PAH clearance took place within 30 min. The absence of further change after 30 min. suggests a renal adaptation response.

The anatomy of the dog made it necessary that only the left renal vein be catheterized for blood samples, since it joins the inferior vena cava at a lesser angle than does the right, and, being longer, offers greater security against slipping of the catheter during the experiment. However, this also means that the left ovarian vein is supplying part of the input to the catheter sample (not so on the right side), and this input becomes a greater source of error when the experimental procedure produces a selective fall in the renal blood flow, thus allowing greater proportion to the ovarian return. This undoubtedly accounts for the rather large drop in extraction ratio that is shown in Fig. 2.

In Table 1 are presented detailed results concerning renal water and chloride excretion from four experiments out of the ten performed, when 12% albumen or acacia was used as the peritoneal dialysing colloid. The direction and magnitude of changes are typical of the entire group.

It can be seen that urine minute volume falls with the G.F.R., and in addition tubular reabsorption of both chloride and water progressively increase, as reflected in chloride 'rejection ratio' (B/A) and in $U/P$ creatinine ratio. The four control dogs who received no intraperitoneal colloid showed none of these changes over the period in question (3–5 hr. of anaesthesia).

In Fig. 3 are plotted the values of systemic blood flow and intra-abdominal hydrostatic pressure during the 4 hr. experimental period in all the animals. Intraperitoneal pressure remained at about 4 cm. of water, with the expected respiratory fluctuations, for at least 3 hr. after initiation of peritoneal dialysis. That is, the accumulating mass of peritoneal fluid did not exert significant

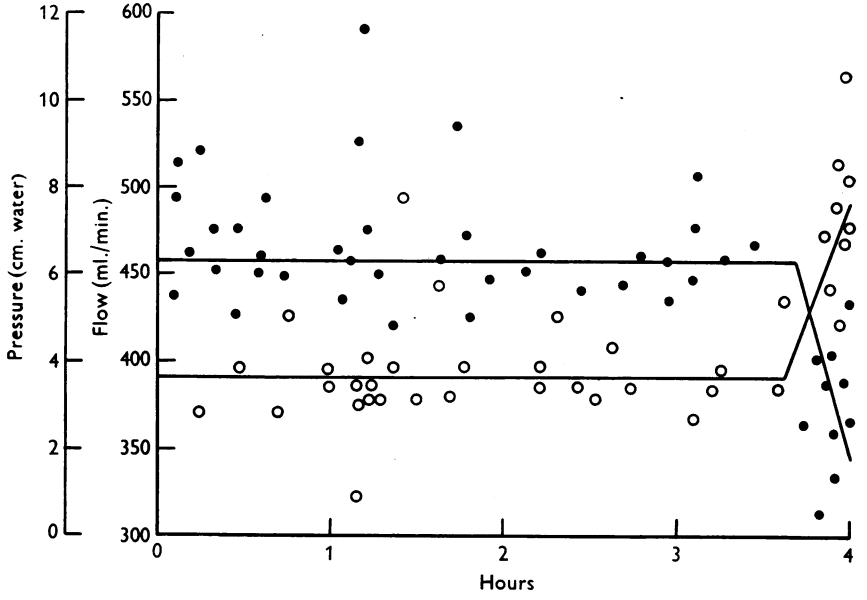


Fig. 3. Intraperitoneal pressure and carotid to carotid blood flow during peritoneal dialysis with 12% colloid in normal saline. Ordinates: intraperitoneal pressure in cm. water, and carotid blood flow in ml./min. Abscissae: time after injection. ●–● carotid flow, ○–○ intraperitoneal pressure (ten animals).

intra-abdominal pressure while the changes which have been described were taking place. Three to four hours after injection of 25 ml./kg. of 12% colloid the volume limit of the peritoneal cavity seems to have been reached, and pressure rose as indicated. At about the same time, carotid to carotid blood flow, which had previously been maintained more or less constant in the region of 400 ml./min., began to decline. Carotid artery mean pressure (not shown) was well maintained for the first 3 hr. of dialysis in every case, and rose 5–15 mm. Hg in about half of the experiments. It usually began to fall by the end of 4 hr. If the experiment was allowed to continue beyond 4 hr., massive ascites

usually developed, and about half of the animals went into shock with a large drop in systemic blood pressure and flow, and died overnight. Renal function was not determined in such a period.

## DISCUSSION

We can predict from the Starling concept of capillary fluid exchange that when two solutions of the same electrolytic osmotic pressure (O.P.) but different colloidal osmotic pressure (C.O.P.) are separated by a membrane permeable only to electrolyte, a diffusion of water and electrolyte into the compartment of highest C.O.P. results. Although migration of water slightly precedes the migration of electrolyte, the net effect is a movement of isotonic solution. At equilibrium there should be equal electrolytic O.P. on both sides of the membrane but greater total volume on the side of the originally larger colloidal concentration. The original margin of C.O.P. would then be balanced by the hydrostatic pressure of increased volume.

That this situation has been approximated here can be seen by referring to Fig. 1. As in the simple system above, the rate at which a new equilibrium is approached is a function of the C.O.P. differences between the two compartments (peritoneal cavity and vascular compartment). It has been shown (Saslow, 1939) that a 6% acacia solution has an O.P. of 246–260 mm. $H_2O$, while the C.O.P. of dog serum averages about 276 mm.$H_2O$. Therefore a 12% acacia solution corresponds to about twice the C.O.P. of dog serum, and the total injected intraperitoneal volume may be expected to double itself at equilibrium. Were theoretical equilibrium achieved when 25 ml./kg. of 12% acacia in normal saline are used, the peritoneal volume would approximate to the blood volume of the adult dog. Judging from one experience with a rather obese bitch, an excessive quantity of omental fat probably slows the rate of approach to equilibrium. We must realize that what has been presented is an extremely oversimplified picture, and that if the additional variables of lymphatic drainage of the peritoneal cavity, etc., were taken into account, true equilibrium would probably never be reached. Since the animals (left to themselves to cope with a 12% colloid load) went into shock after about 4 hr., the lymphatic drainage of the peritoneal cavity was evidently too slow to remove this amount of acacia within the necessary time. It is interesting to note that the haemoglobin-haematocrit curve indicates apparently a significantly greater fall in blood volume than does the plasma-protein curve. The author is inclined to interpret this as the result of splenic contraction in response to the first movement of fluid into the peritoneal pool. The plasma-protein concentration, therefore, would seem a more reliable indicator of blood-volume changes. The alternative possibility exists, however, that protein moved into liver cells or the peritoneal pool.

It seems, at least at the present time, that changes in the extracellular fluid

volume influence renal function by a corresponding change in the composition or volume of the serum. There seems to be no other way for the volume of the interstitial fluid to be acted upon or perceived. Theoretically, an alteration in the extracellular fluid volume could alter the circulating blood to provoke a response from the kidney in three ways: diffusible osmotic pressure (e.g. electrolytic O.P.), non-diffusible osmotic pressure (colloidal osmotic, or oncotic pressure) and hydrostatic pressure. The last two are more direct relations, while the tonicity function is a variable one depending upon the route of volume change.

The object of the experiments reported was to alter serum oncotic pressure as a function of extracellular fluid and plasma-volume depletion. Systemic hydrostatic pressure was maintained essentially constant throughout the experimental period, as was electrolyte tonicity. Logically, since the peritoneal colloid caused simultaneous depletions of both blood and extracellular fluid volumes, we can ascribe the renal reactions as causally related only to the blood-volume depletion.

Other possible incidental variables include the possibilities of toxic reaction, peritoneal pressure of the collecting dialysis pool, and anaesthesia. From experiences in the intravenous use of acacia in patients suffering from hypoproteinaemic oedema we know (Hall, 1938; Jackson & Frayser, 1939) that the drug is deposited in the liver and prolonged use gives rise to such hepatotoxic signs as impaired glucose and galactose tolerance curves, and depression of plasma-protein formation. A small percentage of allergic and anaphylactoid reactions have been reported after repeated usage, but purification of the product largely eliminated these shortly before the drug fell into disrepute as a therapeutic agent. There are no such reports yet for albumen. Against the possibility that the effects observed are toxic in nature are the following: the acacia used was the purified Lilly product; both colloids gave the same response per unit of osmotic pressure; there was a graded systemic response to different C.O.P. levels; none of the animals received the acacia intravenously or had had any previous exposure or opportunity to become sensitized to the two foreign substances; some of the animals were used twice and showed the same degree of response on each occasion.

The pressure effect of an increasing peritoneal volume on venous pressure and renal function may be evaluated by reference to the work of Bradley, Halperin & Mayer (1948) using a pneumatic abdominal binder to produce an intraperitoneal pressure of 80 mm. Hg. At that point there was an increase in venous pressure, and decreases in G.F.R., renal blood flow, glucose Tm (tubular reabsorptive capacity) and $O_2$ consumption by the kidney, as well as a decrease in urine flow. In the present experiments, however, at no time during the period of observation did the intraperitoneal pressure exceed 10 cm. $H_2O$. Pressure rose to higher levels at about the time when the animal,

if untreated, went into shock. The lack of significant intraperitoneal pressure also tends to rule out the direct effect of increased venous pressure in increasing tubular reabsorption of sodium (Blake, Wegria, Keating & Ward, 1949).

Fig. 3 shows that there was no change in carotid flow during any of the procedures, and either no change or a slight rise in blood pressure. This offers some collateral evidence that the reduction in renal blood flow was not part of an incipient or actual state of shock. There were systemic adaptations to the volume changes that maintained cerebral flow and systemic pressure for at least 3 hr. This should not be taken to mean that the renal effect was specific, for obviously each organ would be required to make its own adaptation to volume depletion in accordance with bodily need. It does suggest, however, that the renal vascular response was active. Eventually all adaptations were insufficient to prevent the animal going into shock, but the present work is concerned only with the earlier stages.

The response, then, to the stimulus of hyperoncotic volume depletion is a lowered G.F.R. and R.P.F. with some increase in the filtration fraction, and an active decrease in chloride and water excretion. It must, of course, be mentioned that increase in blood viscosity and cell concentration will undoubtedly modify the renal vascular response, but conclusions cannot be drawn from this without pertinent data. The magnitude of the vascular response is obviously a function of the rate of stress application. Shannon observed G.F.R. changes only at the end of a 24 hr. dehydration of a diabetes insipidus dog. These responses become more pronounced when the events of 24 hr. are telescoped into 1 hr.

The tubular responses are similar to those observed in other techniques of volume depletion (Brun *et al.* 1945*a*), except that the present results suggest that they can occur when plasma oncotic pressure is the primary variable. Therefore, the renal reactions to dehydration—that is, increased water and salt reabsorption—are not a necessary function of hypertonicity (Verney, 1947), for they can occur when volume and oncotic pressure are the only changing variables.

## SUMMARY

1. A technique of peritoneal dialysis induced by intraperitoneal injection of concentrated colloid solutions is described as a method of depleting blood and extracellular fluid volumes at controlled rates. The depleted serum is left with a normal electrolytic osmotic pressure, but an elevated colloid osmotic pressure.

2. The renal responses to blood-volume depletion in this manner are decreases in glomerular filtration rate, effective renal plasma flow and extraction ratio of *p*-aminohippurate, with slight significant increase in filtration fraction. There is an associated decrease in chloride and water excretion which

is believed to be in excess of the effect of a depressed glomerular filtration rate.

I should like to express my gratitude to Prof. Donald H. Barron for his counsel, equipment and time, and to Prof. R. A. McCance for rigorous instruction in both what this paper has to say and how to say it. I should also like to thank Prof. John F. Fulton for his encouragement and assistance, Dr Louis Welt and Dr Donald Seldin for many critical comments and for supplying the albumen. Dr Samuel Gelfan supplied the fluoroscopy unit. This work was financed by the George Sheffield Fund at Yale University.

## APPENDIX

The flowmeter was constructed of Pyrex glass and is illustrated in Fig. 4. All inner surfaces were siliconed to prevent adhesion of possible clots to the walls. It is preferable to have the animal well heparinized. Blood enters at *A* and

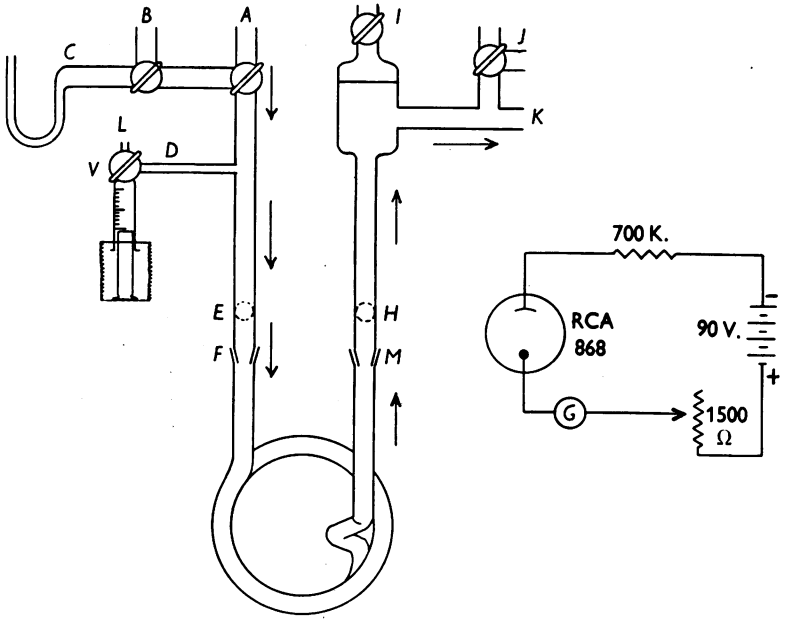


Fig. 4. Mechanical and electrical circuit diagram of photocell bubble flowmeter. See appendix for description.

normally flows in the direction of the arrows to the outflow point at *K*. The stream may be diverted to *B* or *C* for sampling or pressure measurements. Above the plane of the drawing, over the area of *E* and *H*, a small light source, directed downwards, is placed. Below the plane of the diagram in the same area is a phototube, completely shielded save for two small apertures directly under *E* and *H*. The simple circuit for powering the phototube is illustrated. RCA no. 868 was used. When blood is flowing no light will fall on the cathode. A supply of compressed air of reasonably constant pressure is attached to *L* and a small charge of air can be stored in a 2 ml. syringe held below, with a

spring supplying the barrel with tension. By turning the valve at *V* the stored air can be injected as a bubble of constant volume into the circulation up to the point *I*, where it is stored for later release, while the blood continues to flow back into the animal. As the bubble passes *E* and *H* two surges of current are recorded at *G*, since light is momentarily allowed to strike the cathode below. The time interval between the two surges may be measured most accurately by feeding the bursts into a fast-moving pen-writer. *F* and *M* are ground-glass joints for the insertion of coils of varied internal diameter (and, therefore, varied meter resistance). *E* to *H* volumes are calibrated for each separate coil used, and thus the absolute flow may be computed as vol./time. The valve at *J* permits infusion into the circulation. The total internal volume of the meter, including the bubble trap at *I*, is 30 ml., and it is charged with saline or blood with heparin before being inserted into circulation. The tubing *A* to *F* and *M* to *K* is 4 mm., and the range of *E* to *H* circulation times is 1 to 5 sec.

For a discussion of negligible temperature drop and flow anomalies caused by the bubble, see Selkurt (1949).

## REFERENCES


Barrett, E. & Addis, T. (1947). *J. clin. Invest.* **26**, 875.

Black, D. A. K., McCance, R. A. & Young, W. F. (1944). *J. Physiol.* **102**, 406.

Blake, W. D., Wegria, R., Keating, R. P. & Ward, H. P. (1949). *Amer. J. Physiol.* **157**, 1.

Bradley, S. E., Halperin, M. H. & Mayer, H. (1948). *J. clin. Invest.* **27**, 635.

Brun, C., Knudsen, E. O. E. & Raaschou, F. (1945*a*). *Acta med. scand.* **122**, 315.

Brun, C., Knudsen, E. O. E. & Raaschou, F. (1945*b*). *Acta med. scand.* **122**, 332.

Brun, C., Knudsen, E. O. E. & Raaschou, F. (1945*c*). *Acta med. scand.* **122**, 486.

Elkinton, J. R. (1946). Physiology of Body Fluids. In Fulton, J. F., *Howell's Text Book of Physiology*, 15th ed. chap. 7. New York: Saunders.

Epstein, F. H., Goodyer, A. V. N., Lawrason, F. D. & Relman, A. S. (1951). *J. clin. Invest.* **30**, 63.

Gornell, A. G., Bardawill, C. J. & David, M. M. (1949). *J. biol. Chem.* **177**, 751.

Greiner, A. & Podhradszky, L. (1947). *Lancet*, ii, 498.

Hall, W. K. (1938). *Proc. Soc. exp. Biol., N.Y.*, **38**, 46.

Harrison, H. E. & Darrow, D. C. (1939). *Amer. J. Physiol.* **125**, 631.

Jackson, R. L. & Frayser, L. (1939). *J. Pharmacol.* **65**, 440.

Kenney, R. A. (1949). *Acta med. scand.* **135**, 172.

Lewis, J. M., Jr., Buie, R. M., Sevier, S. M. & Harrison, T. R. (1950). *Circulation*, **2**, 822.

McCance, R. A. (1951). *Spec. Rep. Ser. med. Res. Coun., Lond.*, no. 275, p. 179.

McCance, R. A. & Widdowson, E. M. (1937). *J. Physiol.* **91**, 226.

McCance, R. A. & Young, W. F. (1944). *J. Physiol.* **102**, 415.

Oakley, H. B. (1934). *Trans. Faraday Soc.* **31**, 136.

Peters, J. P. (1935). *Body Water. The Exchange of Fluids in Man.* London: Ballière, Tindall and Cox.

Peters, J. P. & Van Slyke, D. D. (1936). *Quantitative Clinical Chemistry.* Vol. 1, Methods. Baltimore: Williams and Wilkins.

Saslow, G. (1939). *Proc. Soc. exp. Biol., N.Y.*, **40**, 277.

Selkurt, E. E. (1949). *J. Lab. clin. Med.* **34**, 146.

Shannon, J. A. (1936). *Amer. J. Physiol.* **117**, 206.
Shannon, J. A. (1942). *J. exp. Med.* **76**, 371.
Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. & Graber, M. (1945). *J. clin. Invest.* **24**, 388.
Starling, E. H. (1909). *The Fluids of the Body.* London: Constable.
Verney, E. B. (1947). *Proc. Roy. Soc.* B, **135**, 25.
Viar, W. N., Oliver, B. B., Eisenberg, S., Lombardo, T. A., Willis, K. & Harrison, T. R. (1951). *Circulation*, **3**, 105.
Welt, L. G. & Orloff, J. (1951). *J. clin. Invest.* **30**, 751