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THE EFFECT OF SODIUM DEPLETION ON THE RENAL RESPONSE TO WATER-LOADING IN DOGS

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SUMMARY

1. Dogs depleted of sodium by peritoneal dialysis with glucose solution (5 g/100 ml.) showed a significant reduction in plasma sodium concentration, in inulin clearance and in plasma and extracellular fluid volume. The plasma protein concentration and haematocrit were increased.

2. By the second day of salt depletion the plasma and extracellular fluid volumes, plasma protein concentration and haematocrit all showed some recovery towards normal values.

3. A water-load of 2·5 % of body weight did not cause diuresis or natriuresis when given on the first day of depletion, but initiated a water diuresis when given on the second day.

4. A water-load of 5 % of body weight caused diuresis but not natriuresis, when given on either day of salt depletion.

5. The physiological interpretation of these results is discussed.

INTRODUCTION

Since the work of Darrow & Yannet (1935) on the production of sodium depletion in various animals by peritoneal dialysis with glucose (5 g/100 ml.), various workers have noted that the usual diuretic response to water may be modified by the salt depletion. Cizek & Huang (1951) compared the effects of a water-load of about 4 % of body weight, when given to a dog within 24 hr of salt depletion by peritoneal dialysis, and when given at any time following this, the animals being maintained on a salt-poor diet. The acutely depleted dogs showed a low-normal diuretic response, while the chronic animals showed normal or supernormal responses. Leaf & Mamby (1952) found a lack of diuretic response when a water-load of 3 % of body weight was administered to dogs 24 hr after salt depletion by peritoneal dialysis. Leaf & Mamby maintained one of their dialysed dogs on a salt-free diet for 8 days, and this animal did not show a diuresis in response to water-loading when tested on the 3rd, 5th and 8th days of salt depletion.

Thus it would seem likely that the ability of salt-depleted dogs to excrete a water-load is determined by at least two factors. The first is the size of the water-load and the second is the duration of salt depletion before the test is made. Since the first 24 hr appeared to be crucial in this respect, experiments were designed to test the ability of the salt-depleted dog to excrete water-loads of varying size immediately after the completion of dialysis and also on the following day, some 20 hr, later. A number of other measurements were also made in an attempt to interpret the differing responses to water-loading.

METHODS

The experiments were carried out on a group of seven episiotomized anoestrous bitches weighing between 9 and 18 kg. The dogs were fed with their normal meat diet, as preliminary experiments demonstrated that a stricter control of the diet was not necessary in the experiments to be described in this paper. Electrolyte excretion rates were reduced to uniformly low rates during the period of salt depletion, which contrasts with the wide fluctuations measured in salt-replete animals (Coxon & Ramsay, 1967). All the animals were trained to lie quietly on the operating table for up to 6 hr at a time without physical restraint, and were accustomed to the passing of a stomach tube, bladder catheterization, repeated venepuncture and other minor procedures. The various measurements were made either immediately after the completion of peritoneal dialysis, or 20 hr later. When the measurements were made immediately, the animal is referred to in the remainder of this paper as a day-one depleted dog and when the measurements were made the following day (i.e. 20 hr later), as a day-two depleted dog.

Salt depletion was produced by infusing 7 % of the body weight with sterile glucose solution (5 g/100 ml.) into the peritoneal cavity through a trochar and cannula. The whole procedure was carried out under light thiopentone anaesthesia, from which the animals always recovered within 20 min. Preliminary experiments had shown that the plasma sodium and protein concentrations had stabilized at their new levels within 4 hr after introduction of the intraperitoneal glucose solution. Hence, after 4 hr the cannula was reinserted into the peritoneal cavity under local procaine hydrochloride anaesthesia and the fluid removed. If the response of the animals to water-loading was not to be tested immediately after the depletion procedure, the animals were left until the following morning without food and with access to only 50 ml. of distilled water, which they usually did not drink.

The response to water-loading was tested by giving the animals in a single dose either 25 or 50 ml. water/kg body wt. by stomach tube. The bladder was catheterized and urine samples collected at least every half-an-hour for 3 hr using a careful wash-out technique which has been described previously (Ramsay & Coxon, 1967). Blood samples were taken by venepuncture at approximately 30 min intervals, and measurements of plasma, sodium, plasma specific gravity, haematocrit and occasionally plasma osmolality were made. On the first day of depletion the dogs were intolerant of the larger water-load and often vomited, and so it was only possible to obtain results on three of the dogs for this part of the experiment. In this way, each animal's response to a water-load of 2·5 % of body weight was tested when normal, day-one depleted or day-two depleted, and in some instances the response to a water-load of double this amount was also tested.

Estimations of plasma sodium, potassium and protein concentrations and haematocrit values were made in the normal state, and on the first and second days of sodium depletion, and similar comparisons were made of rates of urinary excretion of water, sodium and potassium. A comparison of the inulin and para-aminohippurate clearance in the normal and day-two depleted dogs was also made. Difficulties in obtaining sufficient blood and an inadequate rate of urine flow made it impossible to measure these values on the day-one depleted dogs. Determinations of plasma and extracellular fluid volumes were made on four of the seven dogs when salt replete, immediately after completion of peritoneal dialysis, and on the following day, that is, on our normal day-one and day-two depleted dogs respectively. These measurements were made on the same dogs and under the same conditions of depletion during separate experiments, when the response to water-loading was not tested.

Estimations of sodium and potassium were carried out in the EEL flame photometer after appropriate dilution. Plasma and urine osmolality were measured by the freezing-point method using a model 'H' Fiske osmometer. Plasma specific gravity was measured by the method of Phillips, Van Slyke, Hamilton, Dole, Emerson & Archibald (1950), and the plasma protein concentration calculated from this using the formula of Van Slyke, Hiller, Phillips, Hamilton, Dole, Archibald & Eder (1950). (In this calculation, the assumption was made that the relationship between plasma protein concentration and plasma specific gravity was the same for dog and human plasma.) Plasma volume was measured by the method of Courtice (1943) employing the intravenous injection of Evans Blue. The extracellular fluid volume was estimated from the volume of distribution of sodium thiosulphate using the method of Cardozo & Edelman (1952). The measurement of the renal clearance of inulin and para-aminohippurate was carried out by the subcutaneous injection method (Ramsay & Coxon, 1967), inulin being estimated by the method of Roe, Epstein & Goldstein (1949), and para-aminohippurate by that of Bratton & Marshall (1939).

RESULTS

Immediately following the completion of peritoneal dialysis, all the animals exhibited depression and lethargy similar to that noted by Cizek and his co-workers (Cizek, Semple, Huang & Gregersen, 1951). The degree of 'depression', however, did not seem to be so severe in our dogs. By the second day, all the animals had recovered their usual friskiness. During this period, the dogs showed a marked oligodipsia, consuming a maximum of 50 ml. of distilled water, and more often none at all.

It was not practicable to make all the measurements on the urine of all seven dogs in the depleted state for two reasons. The dogs were intolerant of water-loading when sodium-depleted, and tended to vomit the water within a few minutes of giving it. This was particularly noticeable in the day-one depleted dogs. Secondly, after depletion there was a marked tendency for the bladder mucosa to bleed, especially when the urine flows were low. When such trauma occurred, the experiment was stopped. For these reasons values are not available for all seven dogs when depleted, despite many attempts to obtain more data. Occasionally data have been obtained on the same dog more than once, and these have been included in preparing Figs. 2 and 5.

The response to a water-load of 2·5 % body weight

When 25 ml. water/kg body wt. was administered to the day-one depleted dogs there was no increase in urinary flow and no increase in sodium excretion. This is illustrated in Fig. 1. Such a water-load causes a large increase in urine flow together with a natriuresis in the normal dog maintained on a synthetic diet of known and constant salt content (Coxon

& Ramsay, 1967). Thus our day-one depleted dogs failed to excrete a water load of 2·5 % of body weight.

However, when a similar amount of water was given on the second day of depletion a diuretic response comparable to that observed in the normal

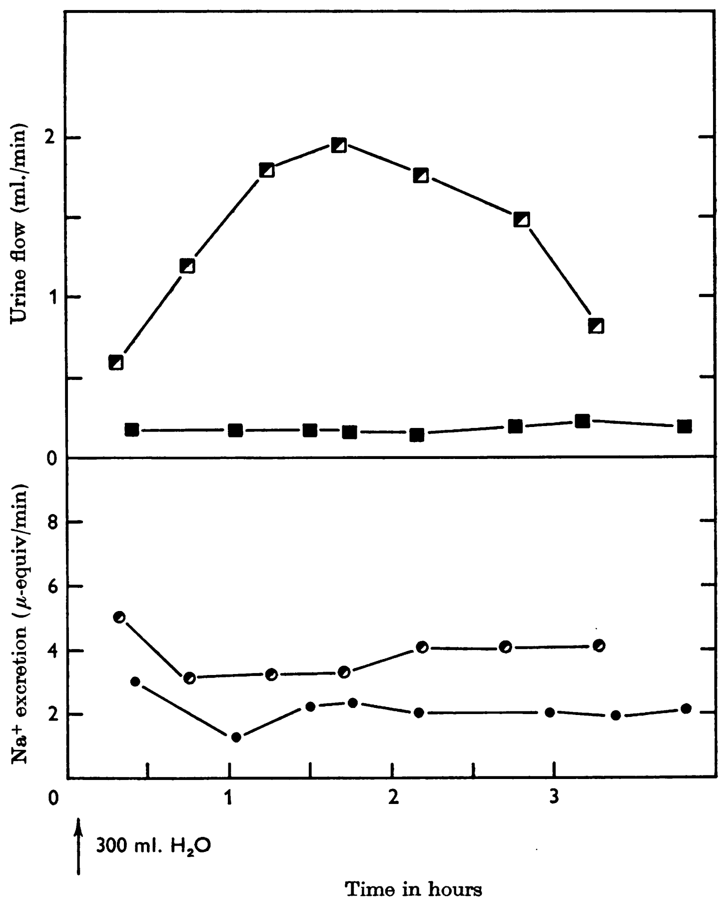

Fig. 1. The effect of administering a water-load of 2·5 % of body weight on urine flow and rate of sodium excretion in a day-one depleted dog (filled symbols) and a day-two depleted dog (half-open symbols).

animal was obtained. Occasionally, the diuresis was slightly delayed in onset. By contrast with the normal animal, there was no change in sodium excretion (Fig. 1).

That water was absorbed from the gastrointestinal tract was shown by a fall in the specific gravity of the plasma and the haematocrit.

The results on the effect of giving the water-load of 2·5 % body weight to all the dogs are collected together in Fig. 2. This shows a plot of urinary flow against sodium excretion 2 hr after the administration of the water to normal, day-one and day-two depleted animals. Inspection of the data shows that at a time of 2 hr the differences in the behaviour of the three groups become most apparent. The normal dogs showed urine and sodium excretion rates that were increased above basal levels. The day-one depleted dogs exhibited neither a diuresis nor a natriuresis. The day-two depleted dogs gave urine flows which were higher than those measured before water-loading, but this was not accompanied by natriuresis.

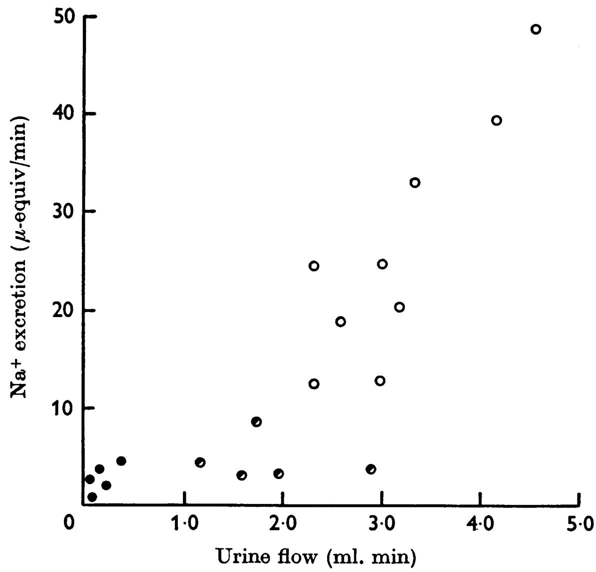

Fig. 2. The rate of sodium excretion is plotted against the rate of urine flow 2 hr after administering a water-load of 2·5 % body weight for all dogs. Open symbols, normal dogs maintained on a normal diet. Filled symbols, day-one depleted dogs. Half-open symbols, day-two depleted dogs.

The response to a water-load of 5 % body weight

The day-one depleted dogs when given this larger load responded with a diuresis similar to that in the normal animal, but again, without change in sodium output (Fig. 3). The diuresis was delayed in onset for about an hour, but it was of comparable size and duration to the normal. Unfortunately, as has already been mentioned, only three of the dogs could tolerate this amount of water immediately after peritoneal dialysis without vomiting.

The water-load of 5 % body weight, when given to the day-two depleted animals, resulted in a brisk diuresis, but again, no natriuresis (Fig. 4).

These results are grouped together in Fig. 5. As during some of these experiments involving the larger water-load there was a decrease in the rate

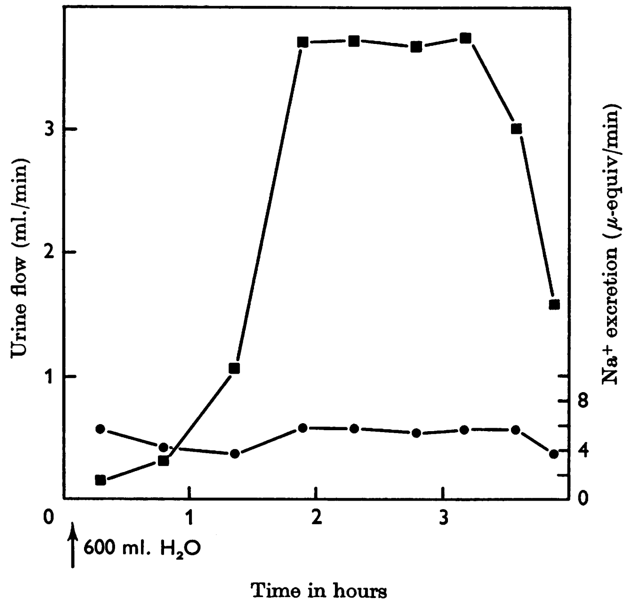

Fig. 3. The effect of administering a water-load of 5% of body weight on urine flow (square symbols) and rate of sodium excretion (circles) to a day-one depleted dog.

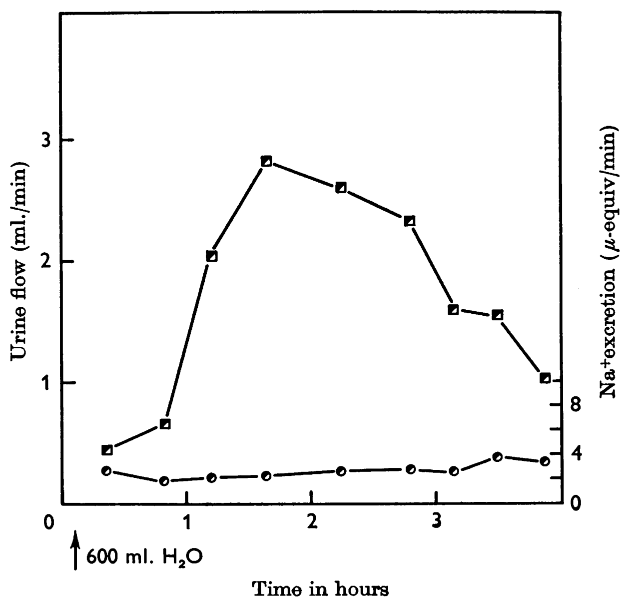

Fig. 4. The effect of administering a water-load of 5% of body weight on urine flow (square symbols) and rate of sodium excretion (circles) to a day-two depleted dog.

of sodium excretion, this point has been emphasized by plotting the change in the rate of sodium excretion against urine flow 2 hr after giving the water-load. The normal dogs show both an increase in urine flow and sodium excretion, whereas the depleted dogs show an increase in urine output, but no change in sodium output.

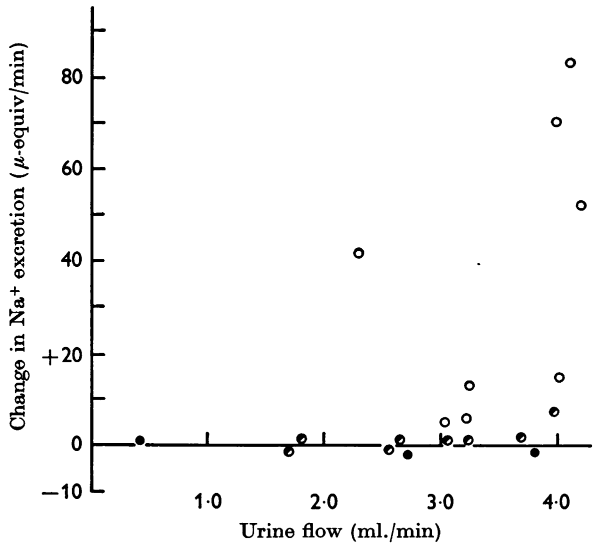

Fig. 5. The change in sodium excretion is plotted against the rate of urine flow 2 hr after administering a water-load of 5 % body weight for all the dogs. Open symbols, dogs maintained on a normal diet. Filled symbols, day-one depleted dogs. Half-open symbols, day-two depleted dogs.

There were no significant changes in potassium excretion in these experiments. In the depleted dogs the excretion rates of potassium before loading were $3\cdot0 \pm 2\cdot97$ and $5\cdot5 \pm 2\cdot83$ μ-equiv/min ($n = 7$) in the day-one and day-two depletions respectively. During the course of the experiment, the potassium excretion tended to drift towards approximately 2 μ-equiv/min by the end of 3 hr.

Other features of the sodium-depleted state

The effect of sodium depletion on various parameters are summarized in Table 1. They are considered in more detail below.

Plasma sodium. The plasma sodium concentration was reduced from a normal value of $145 \pm 3\cdot8$ m-equiv/l. to $120 \pm 4\cdot1$ m-equiv/l. on the first day of depletion. This change was highly significant ($P < 0\cdot001$, $n = 7$). There was no change in plasma sodium concentration between the first and second day of depletion.

Plasma osmolality. Osmolality measurements were made in two of the experiments and there was no direct relationship between the fall in plasma sodium concentration and the fall in osmolality. For example, in one of the animals, although the plasma sodium fell from 142 to 118 m-equiv/l. during depletion, plasma osmolality was only reduced from 304 to 282 m-osmoles/kg, whereas the calculated change in osmolality considering the observed fall in the plasma sodium with its attendant monovalent anions, should have been from 304 to 256 m-osmoles/kg, i.e. a fall of 48 m-osmoles. However, some of this discrepancy may be accounted for by the plasma glucose level which was raised from 80 to 183 mg/100 ml., which corresponds to a change from 5 to 11 m-osmoles/kg, assuming an osmotic coefficient for glucose of unity at this concentration (Robinson & Stokes, 1959). The remainder of the discrepancy could not be accounted for with the measurements at our disposal. It was certainly not due to urea, which in this dog contributed 4 m-osmoles/kg instead of the normal 2 m-osmoles/kg. Similar changes were noted in the second animal.

TABLE 1. To show various measurements that were made on normal, day-one and day-two salt-depleted dogs. The mean values and standard deviations of the observations are shown

Observations	Number of animals	Normal	Day-one depleted	Day-two depleted
Plasma sodium (m-equiv/l.)	7	$145 \pm 3\cdot8$	$120 \pm 4\cdot1$	$120 \pm 4\cdot3$
Plasma potassium (m-equiv/l.)	7	$4\cdot4 \pm 0\cdot54$	$4\cdot5 \pm 0\cdot11$	$4\cdot3 \pm 0\cdot29$
Plasma protein (g/100 ml.)	7	$5\cdot93 \pm 0\cdot54$	$7\cdot89 \pm 0\cdot33$	$6\cdot78 \pm 0\cdot25$
Haematocrit (%)	7	$48\cdot2 \pm 2\cdot50$	$67\cdot1 \pm 4\cdot88$	$59\cdot3 \pm 3\cdot59$
Plasma volume (ml./kg body wt.)	4	$43\cdot3 \pm 3\cdot6$	$30\cdot7 \pm 2\cdot4$	$38\cdot7 \pm 2\cdot3$
Extracellular fluid volume (ml./kg body wt.)	4	$239 \pm 9\cdot0$	$169 \pm 16\cdot5$	$198 \pm 10\cdot0$
Basal urine flow (ml./min)	7	$0\cdot21 \pm 0\cdot04$	$0\cdot09 \pm 0\cdot07$	$0\cdot16 \pm 0\cdot06$
Inulin clearance (ml./min/kg body wt.)	7	$3\cdot33 \pm 0\cdot59$	—	$2\cdot70 \pm 0\cdot91$
Para-aminohippurate clearance (ml./min/kg body wt.)	7	$11\cdot98 \pm 2\cdot96$	—	$11\cdot50 \pm 2\cdot6$

By the second day of depletion when plasma osmolality had fallen to 274 m-osmoles/kg, the contribution from glucose had fallen to 5 m-osmoles. Thus overnight the small fall in osmolality (8 m-osmoles) is nearly accounted for by the reduction in plasma glucose. Stern & Coxon (1964) have shown similar changes in the guinea-pig when subjected to peritoneal dialysis with (5 g./100 ml.) glucose.

Plasma potassium. Plasma potassium levels remained constant throughout the procedure.

Plasma protein concentration. There was a highly significant increase in plasma protein concentration between the normal and day-one depleted dogs of 33% ($P < 0\cdot01$, $n = 7$). Although there was some fall by the second day of depletion, plasma protein concentration was still higher than that in the normal dog by 14 % ($P < 0{\cdot}001$, $n = 7$). Thus there is a considerable decrease in plasma protein concentration, and hence colloid osmotic pressure, between the first and second day of depletion ($P < 0{\cdot}002$, $n = 7$).

Haematocrit. The changes in haematocrit followed a similar pattern to the changes in plasma protein concentration. On the first day of depletion there was an increase in haematocrit of 39 % ($P < 0{\cdot}001$, $n = 7$), which had fallen to a significantly lower level by the second day ($P < 0{\cdot}01$, $n = 7$). The haematocrit of the day-two depleted dogs was significantly higher than that of the normal dogs by 23 % of the original value ($P < 0{\cdot}001$, $n = 7$).

Plasma volume. Immediately after peritoneal dialysis the plasma volume had decreased to 71 % of the normal value ($P < 0{\cdot}001$, $n = 4$). By the second day of depletion, the plasma volume had increased to 89 % of the normal value, although it was still significantly reduced below normal ($P < 0{\cdot}01$, $n = 4$).

Extracellular fluid volume. The extracellular fluid volume was reduced to 71 % of its normal value on the first day of depletion ($P < 0{\cdot}001$, $n = 4$). By the second day of depletion, the extracellular fluid volume was 83 % of the normal value, although it was still significantly reduced below normal ($P < 0{\cdot}001$, $n = 4$). From data presented in Table 1, it may be seen that the plasma volume decreased by 12·6 ml./kg body wt. on the first day of depletion, and the interstitial fluid volume by 58 ml./kg body wt. Between the first and second day of depletion the plasma volume increased by 8·0 ml./kg body wt., and the interstitial fluid volume by 21 ml./kg body wt. Thus although the plasma volume had increased by 26 % between the first and second day of depletion, the interstitial fluid volume only increased by 15 %. This provides more evidence in favour of the view that the interstitial compartment contributes proportionately more fluid to extracellular fluid loss than does the plasma, in conditions of salt depletion (Mellors, Muntwyler & Mautz, 1942).

Basal rate of excretion of sodium and potassium. The basal excretion rate of sodium in the day-one and day-two depleted dogs, measured for a period of $\frac{1}{2}$ hr before water-loading, was found to be $2{\cdot}6 \pm 1{\cdot}71$ and $3{\cdot}0 \pm 1{\cdot}07$ m-equiv/min respectively, and of potassium $3{\cdot}9 \pm 2{\cdot}97$ and $5{\cdot}5 \pm 2{\cdot}82$ m-equiv/min ($n = 7$). These levels, especially of sodium, are lower than in the normal animal on a controlled diet and are more constant.

Glomerular filtration rate. As has already been mentioned, it was only possible to obtain renal clearance measurements on the day-two depleted animals, when there was a decrease of 19 % ($P < 0{\cdot}001$) from the normal values.

Para-aminohippurate clearance. Again, values for change in para-aminohippurate clearance are only available for the second day of depletion. There was no significant change in this value from the normal.

DISCUSSION

Holmes (1940) and Holmes & Cizek (1951) studied the effects of salt depletion on the water intake and diuretic response to large quantities of water in the dog. The salt depletion was induced by a series of intravenous injections of 50 % sucrose, 20 ml./kg, spaced 3–7 days apart. During this period, the animals were maintained on a low salt diet providing approximately 1·2 m-equiv sodium per day. Holmes & Cizek demonstrated an absence of diuretic response to a water load, however large, when administered during the first 24 hr of salt depletion, but a normal diuretic response when the water was given later in the period of salt-deficiency. The antidiuresis was accompanied by a raised glomerular filtration rate.

Such experiments are complicated by the fact that intravenous sucrose may cause renal damage, associated with a period of temporary anuria (Helmholz & Bollman, 1939). In the experiments of Holmes & Cizek (1951) lack of diuresis was correlated with the number of sucrose injections the animals had received, and the time after the injections, rather than with the degree of salt depletion present.

Cizek *et al.* (1951) depleted seven dogs of salt acutely by peritoneal dialysis with 5 % glucose for 3 hr, and then maintained them on a salt-deficient diet for several weeks. They demonstrated that this procedure results in an increased water intake throughout the period of salt depletion. Unfortunately, they only compared the diuretic response to a water-load before and during salt depletion in one animal. This animal showed a normal diuretic response to water-loading, although it should be noted that the observations were made at the end of the first week of depletion.

It is clear from the results of Cizek & Huang (1951) mentioned in the introduction that there were differences in the diuretic responses of salt-depleted dogs to water-loading which depended upon the time after salt-depletion at which the response was tested. However, they state that plasma volume, plasma protein and haematocrit remain essentially unchanged throughout the period of depletion. They did not make any measurements until 16 hr after peritoneal dialysis, and from our data marked changes would have taken place by then. By the second day of depletion plasma protein concentration, haematocrit, plasma volume and extracellular fluid volume have all returned part way towards normal. Our data do not allow us to say whether further changes would take place if salt depletion had been maintained, but the experience of other workers would suggest that these values would be essentially unchanged from the second day of depletion throughout the period of salt depletion.

The results presented are concerned with various differences occurring between day-one and day-two. Hence, any changes in renal function over this period are obviously of great importance. In our experiments the day-two depleted dogs showed a significant decrease in inulin clearance and an essentially normal para-aminohippurate clearance. Although it proved impossible to carry out these estimations on the day-one depleted dogs, an approximate comparison of glomerular filtration was obtained from inspection of the rate of disappearance of sodium thiosulphate from the plasma, data which had been used for calculation of the extracellular fluid volume by the method of Cardozo & Edelman (1952). Gilman, Phillips & Koelle (1946) showed that if inulin and thiosulphate clearances are measured at the same time in the dog they are identical. Thus, comparison of the rates of disappearance of thiosulphate from the plasma after a single intravenous injection in the normal, day-one and day-two depleted dogs should provide an indication of glomerular function. This showed a reduction in glomerular filtration in the day-two depleted dogs, as had measurement of inulin clearance, and indicated that this was no higher on the first day of depletion.

Previous studies on the effect of salt-depletion on glomerular filtration rate in the dog have not yielded clear-cut results. Harrison & Darrow (1939) noted in one experiment that creatinine clearance decreased to 20 ml./min from a control value of 65 ml./min 24 hr after an unspecified degree of salt-depletion attained by peritoneal dialysis. On the other hand, studies on the chronically salt-depleted dog by Tank & Herrin (1953) have demonstrated an increased creatinine clearance. In the experiments of Holmes & Cizek (1951) already quoted, an increase in creatinine clearance was invariably found even within 24 hr of depletion. However, Shannon (1936) and Sellwood & Verney (1955) have demonstrated that either administration of water or infusion of saline causes an increase in glomerular filtration rate. In a previous paper (Ramsay & Coxon, 1967) we have also demonstrated that intravenous administration of saline, at rates similar to those employed in the classical infusion method for the measurement of renal clearance, causes a significant increase in inulin clearance. As the infusion method has been used to determine glomerular filtration rates by all these workers, this might account for the discrepancy in the values actually observed. We used the subcutaneous injection method to measure glomerular filtration rates, which does not involve intravenous administration of fluid, and always found a significant decrease in glomerular filtration rate after salt depletion.

This reasoning was supported by observations on three of our dogs, when the classical infusion method was used to measure inulin clearance during salt depletion. The solution was prepared in 0·73 % saline so that the plasma sodium concentration of the depleted dog would not rise during the infusion. The initial clearance period, about 45 min after commencing infusion, showed an inulin clearance lower than that in the normal dog. However, the inulin clearance increased in each further clearance period, until after another 45 min the inulin clearance was always higher than in the salt replete animal. Thus in our experiments sodium depletion invariably caused a decrease in the glomerular filtration rate unless a saline infusion was given.

There is minor disagreement between our results and those of Leaf & Mamby (1952), who found that a water load of 3 % body weight was not excreted when given 24 hr after peritoneal dialysis, and, in the one animal they tested, even 1 week after this. The most probable reason for the difference is that the doses of 2·5–3 % of body weight of water are very close to the critical amount which we have found necessary for the depleted dog to show a diuresis. It is possible that Leaf & Mamby's dogs were more depleted than ours, since they used a larger quantity of 5 % glucose for the peritoneal dialysis, but this is not reflected in the plasma sodium values.

However, Cizek & Huang (1951) showed that sodium depleted dogs would excrete a water load of 4 % of body weight when given by mouth within 24 hr of peritoneal dialysis. This is in agreement with our own data, where an oral load of water of 5 % of body weight causes a diuretic response, even immediately after peritoneal dialysis.

The interesting problem is why the smaller water load should be treated in a different way by the day-one and day-two depleted dogs. One possibility, especially as the day-one depleted dogs tended to vomit their water load, was that there might be a decrease in the rate of water absorption from the gastrointestinal tract. However, study of the dilution of the plasma protein concentration after administration of the water load suggested that this was not the case, for in all experiments administration of water was followed by a reduction in the plasma protein concentration, indicating that absorption of the water was proceeding.

The reduced urinary flow and sodium excretion (see p. 625) measured before water loading could be accounted for by the low filtration rates measured in the sodium-depleted state. Alternatively, this could be explained by an enhanced tubular reabsorptive capacity for both sodium and water. Rosnagle & Farrell (1956) have demonstrated a twofold increase in aldosterone secretion rate in adrenal venous blood in five dogs salt-depleted by peritoneal dialysis. Leaf & Mamby (1952) demonstrated that the acutely salt-depleted dog secretes greater amounts of antidiuretic hormone than the normal. Share (1961) has amply confirmed these observations using more refined assay techniques. However, although our animals should have an increased tubular reabsorptive capacity for both sodium and water, errors inherent in the measurement of glomerular filtration rate do not allow an accurate assessment of glomerular-tubular balance for salt and water to be made (Wesson, 1957).

Many authors have shown that expansion of either the plasma or extracellular fluid volume may cause an increase in urinary flow and in sodium excretion in the normal dog (e.g. Sonnenberg & Pearce, 1962). These effects do not appear to depend on a change in the osmolality of the plasma. In our depleted animals, the plasma and extracellular fluid volumes were significantly different on the first and second days of sodium depletion. Experiments designed to investigate the effect of changing either plasma or extracellular fluid volume on the response of the salt-depleted dogs to water-loading are described in a further paper (Coxon & Ramsay, 1968).

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