PROLONGED WATER DEPRIVATION IN THE DOG 1

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Evidence of intracellular as well as of extracellular water depletion was obtained during periods of water deprivation in some experiments on pyloric obstruction in dogs. The object of this control study was to observe the exchanges of body water and salts as conditioned by the strict deprivation of water.

Kerpel-Fronius (1) showed that in fasting rabbits deprived of water, the concentration of sodium in serum rose and the ratio of potassium to nitrogen excreted exceeded that in cell fluid. These findings were interpreted as indicating a loss of both intracellular and extracellular water. Nadal, Pedersen, and Maddock (2) obtained somewhat similar evidence in human subjects. Both of these papers emphasized the contrast between the intra- and extracellular water depletion that arose from a primary loss of pure water, and the predominantly extracellular depletion where fluids containing salt are lost. But the distinction was not made between the cell water released with potassium and that lost on an osmotic basis.

Darrow and Yannet (3) and Hastings and Eichelberger (4, 5) have shown that water is freely diffusible across cell membranes and that it shifts according to the osmotic concentration of the bases which are restrained on either side. Evidence has accumulated, however, that these bases are not entirely restrained. The factors which control their movements are not clear, but such movements must ultimately control the distribution of water between the two phases. Sodium is known to displace intracellular potassium under certain nutritional (6) and hormonal (7) stimuli. But the conditions are still obscure under which sodium and potassium cross the cell boundary in response to changes of ionic concentration and of water volume.

The following experiments in prolonged water deprivation constitute an attempt to define the range of variation of total ionic concentration and of volume of body fluids, to observe the associated renal reactions, and to differentiate the mechanisms by which cell water is released.

METHODS

In serum, the concentration of chloride was determined by the method of Hald (8), sodium and potassium by the method of Hald (9), sodium sulfocyanate by the method of Crandall and Anderson (10) as adapted to the photoelectric colorimeter by Elkinton and Taffel (11), and water content by the difference between wet and dry weights. The whole blood non-protein nitrogen was measured by the microkjeldahl technique.

In *urine*, chloride was determined by the Volhard-Harvey titration (12), sodium by the method of Butler and Tuthill (13), potassium by the method of Hald (9), sodium sulfocyanate by Elkinton and Taffel's (11) modification of the method of Crandall and Anderson (10), and total nitrogen by macro-kjeldahl.

EXPERIMENTAL PROCEDURE

Four normal dogs were deprived of water and food for periods of 11 to 20 days. During these periods, the balances of water, chloride, sodium, potassium, and nitrogen were measured. From these balances, and from studies of the distribution of sodium sulfocyanate, the exchanges of water and salt in the animals were calculated.

The dogs were kept in metabolic cages and all urine was collected. No fecal analyses were made since the amount of feces obtained was insignificant, owing to the starvation. The weight change, however, was corrected for the 2 small stools passed by 1 dog, as well as for losses of tissue and blood in surgical procedures and blood analyses, respectively. The dogs were weighed at the beginning and end of each period on scales with an accuracy of ± 10 grams.

Blood for analysis was taken from the jugular vein; that portion for determination of the non-protein nitrogen was oxalated, the rest was allowed to separate into clot and serum. The urine collected was preserved with thymol at 5° C.

The distribution volume of sulfocyanate was determined several times in 3 of the 4 dogs. A 1 per cent solution of sodium sulfocyanate was injected intravenously from a calibrated burette and the serum concentration and urinary excretion determined at the end of a 4-hour interval (11). To insure complete urinary recovery, the animal was catheterized and the bladder was washed 3 times with normal saline solution.

Two of the dogs (Dogs 6 and 8) had laparotomies and 1 (Dog 7) received anesthesia, as controls for the operative transection of the pylorus in the previous experiments. Each dog received a small infusion of 5 per cent glucose and 0.9 per cent sodium chloride solution postoperatively.

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Dog 6 was rehydrated on the twentieth day, Dog 7 died on the eleventh day, and Dogs 8 and 9 were killed on the fifteenth day when Dog 8 was moribund.

CALCULATIONS

Total water changes (ΔW) were calculated from weight changes corrected for solids lost and the metabolic mixture, as estimated according to the method of Newburgh (14, 15):

$$\Delta W = \Delta W t.' + (C + 0.49P + F),$$
(1)

where the protein burned (P) was calculated from the nitrogen excretion, the carbohydrate burned (C) was assumed to equal the carbohydrate given, and the fat burned was calculated in the following ways. Method A: The total caloric expenditure of the fasting dog, as determined by direct calorimetry by Anderson and Lusk (16), was approximately 2.0 calories per kilogram per hour, decreasing 1.5 per cent per day. The fat burned was calculated from the total calories:

$$F = (\text{Total cal.} - P + C \text{ cal.})/9.3.$$
 (2)

Method B: The fat burned was calculated from the insensible weight loss (IL) by Lavietes' formula (17):

$$F = (IL - 2.12C - 1.69P)/3.78.$$
 (3)

 ΔW was calculated from both figures for fat burned and the average taken (Table III).

Extracellular volume changes (ΔE) were measured directly by the distribution of sodium sulfocyanate (11):

$$E_{\rm SCN} = \frac{\rm Net \ retention \ NaSCN \ in \ mgm.}{\rm Serum \ concentration \ in \ mgm. \ per \ liter}$$
(4)

and from the chloride and sodium balances:

$$E_{\rm Cl_2} = \frac{(E_1 {\rm Cl_1}) + b_{\rm Cl}}{{\rm Cl_2}},$$
 (5)

$$E_{Na_2} = \frac{(E_1 Na_1) + b_{Na}}{Na_2},$$
 (6)

where:

 b_{Cl} and b_{Na} = balances of Cl and Na,

 E_1 = initial extracellular fluid volume,

$$Cl_1$$
 and Cl_2 = initial and final concentrations of Cl in extracellular water,

 Na_1 and Na_2 = initial and final concentrations of Na in extracellular water.

In this calculation, it was assumed that the initial extracellular fluid volume (E_1) equalled either 27 per cent (18) of the body weight (Dog 6), or that the chloride and sodium spaces were identical with the sulfocyanate space (Dogs 7, 8, and 9). The concentrations of Cl, Na, and K in extracellular water (*ECW*) were calculated from the serum concentrations (s) by the use of a Donnan factor of 0.95:

$$Cl_{BCW} = Cl_{\bullet}/(W_{\bullet} \times 0.95), \qquad (7)$$

$$Na_{BCW} = (Na_* \times 0.95)/W_*, \qquad (8)$$

$$\mathbf{K}_{BCW} = (\mathbf{K}_s \times 0.95) / W_s, \tag{9}$$

where $W_s = \text{grams of water in 100 grams of serum.}^3$

In Dogs 8 and 9, the distribution volume 4 of the radioactive isotope of Cl (E_{Cl}^{28}) was determined at the end of the experiment. For further calculations,

$$\Delta E = E_2 - E_1, \tag{10}$$

where E_2 was taken to be the average of E_{Cl_2} and E_{Na_2} .

The change in intracellular water volume (ΔI) was estimated in two ways. In the first method, ΔI was taken to equal the difference between the total water change (ΔW) and the extracellular water change (ΔE) :

$$\Delta I_I = \Delta W - \Delta E. \tag{11}$$

In the second method, ΔI was calculated as the sum of 3 decrements: (1) cell water lost with the consumption of protein during fasting (ΔI_P) , (2) cell water lost with potassium released in excess of nitrogen $(\Delta I_{\mathbf{K}}')$, and (3) cell water lost by osmotic shift $(\Delta I_{\Delta B})$:

$$\Delta I_{II} = \Delta I_P + \Delta I_{\mathbf{K}}' + \Delta I_{\Delta B}. \tag{12}$$

The formulae for the first 2 decrements are derived from the ratios of water and potassium to protein in the cell fluid of skeletal muscle as determined in 20 normal dogs by Hastings (4):

> $H_2O = 0.27$ liters per 100 grams protein, K = 38 m. Eq. per 100 grams protein,

assuming 92.6 per cent of the solids to be protein (Darrow (19)). Thus:

$$\Delta I_P = 2.7 \times P, \tag{13}$$

where P = protein burned in kilograms, and

$$\Delta I_{\mathbf{K}}' = b_{\mathbf{K}}'/B_2, \tag{14}$$

where B_2 = the total concentration of ionically active base in the cell (see below),

$$b_{\mathbf{K}'} = b_{\mathbf{K}I} - b_{\mathbf{K}P} =$$
balance of excess K, (15)

$$b_{\mathbf{K}P} = 380 \times P =$$
balance of K lost with protein, (16)

$$b_{\mathbf{K}I} = b_{\mathbf{K}} - b_{\mathbf{K}E} =$$
balance of intracellular K, (17)

$$b_{\mathbf{K}\mathbf{E}} = (\mathbf{K}_{\mathbf{E}\mathbf{C}\mathbf{W}_2} \times E_2) - (\mathbf{K}_{\mathbf{E}\mathbf{C}\mathbf{W}_1} \times E_1)$$

= balance of extracellular K, (18)

 $b_{\mathbf{K}}$ = total balance of K.

The concentration of potassium in serum was determined on old samples and the results appear slightly elevated. This does not, however, affect the correction for extracellular $K(b_{Kg})$. The high value at the end of the experiment in Dog 7 is undoubtedly due to the blood being drawn after death. As serum was not available for analysis in Dog 6, a value for K_{ECW} was assumed.

The calculation of the third decrement $(\Delta I \Delta B)$ involves an assumption that the total concentration of ionized base in cell water is equal to that in extracellular water, the latter value being taken to be 10 m. Eq. per liter greater than the sodium concentration. The calculation also required a value for the initial intracellular water volume. This was derived by arbitrarily assuming the total body water to be 65 per cent of the body weight. Published

⁴ Determined with the collaboration of Drs. A. W. Winkler and A. J. Eisenman.

⁴ Had W_{\bullet} been calculated per 100 cc. of serum, the values for ΔE and ΔI in Table V would be changed by not more than 5 per cent.

(20)

values of water content of whole dogs, as determined by desiccation, range from 55 per cent for fat dogs to 68 per cent for lean dogs (18, 20). The dogs used were lean. Thus:

 $I_1 = (0.65 \,\mathrm{Wt.}) - E_1,$

$$\Delta I_{\Delta B} = -I_1 \Delta B/B_2, \qquad (19)$$

where

$$\Delta B = B_2 - B_1, \qquad (21)$$

$$B = \text{Na}_{BCW} + 10 \text{ m. Eq. per liter.}$$
(22)

Balances of water, chloride, and sodium include corrections for losses in blood drawn for analysis (Table I). The nitrogen balance (b_N) consists of the urinary excretion (b_N) corrected for change in non-protein nitrogen content in the body fluids. This correction was made by approximating the total body water from the body weight; the correction was for the most part negligible.

RESULTS

The concentration of sodium in serum rose in each dog, indicating an increase in total ionic concentration in the body fluids (Table II). The extent of the increase was 15 to 41 m. Eq. per liter. The larger increases were observed in the dog that died and in the dog that became moribund. The extracellular water loss varied from 20 per cent to 38 per cent of the initial extracellular volume (Table IV). In each experiment, it was exceeded by the calculated total water loss, indicating that a substantial portion of the water lost came from the cells (Table V). Intracellular water loss as calculated by difference (ΔI_I) varied from 30 to 55 per cent of the initial volume. In 3 of the 4 dogs, the percentage water losses from each of the 2 phases were approximately equal.

The total amount of water lost from the cells could be differentiated into three processes (Table V, Figure 1). Cell water was lost with protein consumed as the result of fasting (ΔI_P) . The rise in total ionic concentration as measured by the concentration of sodium in serum accounted for a second decrement of cell water on a purely osmotic basis $(\Delta I_{\Delta B})$. The potassium excretion was considerably in excess of the amount calculated to accompany the nitrogen excretion. The passage of extra potassium from the cell released a third decrement of cell water $(\Delta I_K')$. The sum of these decrements (ΔI_{II}) was in reasonable

 TABLE I

 Exchange of water, electrolytes, and nitrogen

 Quantities expressed per individual period.

| | | Intoko porenterel | | | Output | | | | | | | |
|-----|---|---------------------------|-------------------------------------|----------------|-------------------------------------|---|--|--|---|-----------------------------------|---|--|
| Dog | Period | od Urine | | | | | | Blood * | | | | |
| | | H ₂ O | Na | CI | H ₃ O | Na | Сі | к | N | H ₁ O | Na | CI |
| б | days 1 to 4 5 to 8 9 to 12 13 to 16 17 to 20 | cc. 600† 20‡ 20‡ | <i>m. Eq.</i> 46.5 2.5 2.5 | m. Eq. 46.5 | сс. 430 130 55 25 25 | m. Eq. 34.0 11.5 0.4 0.1 0 | <i>m. Eq.</i> 34.8 17.4 8.6 1.5 0.8 | <i>m. Eq.</i> 19.7 22.4 17.6 9.0 12.5 | grams 5.66 7.61 5.13 2.80 2.79 | сс. 24 16 16 24 26 | m. Eq. 3.8 2.5 2.5 3.7 4.3 | <i>m. Eq.</i> 2.1 1.4 1.4 2.1 2.6 |
| 7 | 1 to 2 3 to 4 5 to 6 7 to 11 | 105† 20‡ | 3.9 | 3.9 | 255 78 72 65 | 33.2 9.6 3.5 1.0 | 23.6 6.9 3.5 5.4 | 21.4 21.6 16.2 16.5 | 4.24 4.37 3.92 3.55 | 25 27 33 29 | 1.7 2.0 2.5 2.3 | 1.3 1.5 2.0 1.7 |
| 8 | 1 to 2 3 to 4 5 to 6 7 to 12 13 to 15 | 209† 40‡ 30‡ | 11.6 4.9 2.5 | 11.6 2.0 | 1155§ 106 170 150 45 | 74.0 16.8 21.2 10.3 1.8 | 54.2 12.1 23.8 9.4 0 | 33.3 33.8 38.2 54.5 21.6 | 6.58 5.95 8.91 13.97 3.38 | 25 29 37 29 38 | 1.8 2.1 2.7 2.1 3.2 | 1.2 1.5 2.0 1.6 2.6 |
| 9 | 1 to 2 3 to 4 5 to 6 7 to 12 13 to 15 | 200† 40‡ 30‡ | 11.6 4.9 2.5 | 11.6 2.0 | 479 60 174 375 139 | 52.7 3.1 19.0 22.8 0.2 | 39.0 1.4 14.1 16.3 2.2 | 33.6 19.6 48.3 74.8 20.7 | 6.35 3.55 8.40 19.68 9.35 | 25 29 39 29 41 | 1.8 2.1 3.0 2.1 3.2 | 1.3 1.5 2.3 1.6 2.5 |

* Blood drawn for analyses.

† Postoperative and control infusions.

NaSCN given for measurement of volume of distribution.
 Unexplained diuresis, possibly due to pyrogens in infused fluid.

TABLE II Analyses of blood and serum Time at end of day indicated.

| Dee | Time | Blood | Serum | | | | | | |
|-----|------|------------------|---------------------|---------------------|---------------------|------------------|--|--|--|
| Dog | Time | NPN | Na | Cl | к | H ₂ O | | | |
| | day | mgm. per cent | m. Eq. per liter | m. Eq. per liter | m. Eq. per liter | per cent | | | |
| 6 | 0 | 24 | 143.8 | 108.6 | | 94.8 | | | |
| | 4 | 35 | 148.0 | 115.2 | | 95.0 | | | |
| | 8 | 31 | 150.2 | 110.0 | | 94.7 | | | |
| | | 33 | 147.0 | 118.7 | | 94.8 | | | |
| | 16 | 31 | 157.0 | 123.2 | | 94.5 | | | |
| | . 20 | 33 | 159.6 | 129.9 | | 94.7 | | | |
| 7 | 0 | 28 | 145.1 | 110.1 | 6.51 | 92.6 | | | |
| | 6 | 35 | 161.3 | 125.1 | 5.72 | 91.2 | | | |
| | 11* | 270 | 186.1 | 129.5 | 9.38 | 88.0 | | | |
| 8 | 0 | 35 | 147.1 | 102.4 | 5.62 | 93.3 | | | |
| | 6 | 53 | 151.4 | 111.5 | 5.07 | 91.1 | | | |
| | 12 | 53 | 165.1 | 125.4 | 5.17 | 89.3 | | | |
| | 15† | 152 | 170.2 | 133.0 | 6.44 | 89.3 | | | |
| 9 | 0 | 27 | 146.8 | 106.9 | 6.19 | 91.6 | | | |
| | 6 | 27 | 151.5 | 113.4 | 5.52 | 90.4 | | | |
| | 12 | 31 | 156.1 | 123.6 | 6.90 | 90.6 | | | |
| | 15 | 34 | 162.2 | 127.9 | 5.18 | 90.6 | | | |

* Died. Blood for analysis taken 20 to 40 minutes postmortem.

† Moribund.

agreement in 3 of the 4 dogs, with the difference between the extracellular and the total water loss as calculated from the weight change, (ΔI_I) (Figure 1).

In the urine, the concentrations of sodium and of chloride diminished to the vanishing point, whereas the potassium concentration steadily increased, (Figure 2). Non-protein nitrogen of blood did not rise until the terminal stages, and the specific gravity of the urine remained high.

DISCUSSION

Assumptions. The experimental results cast some light on the assumptions used in the calculations. In each experiment, the extracellular volume loss as calculated by the chloride balance exceeded that by the sodium balance and by sulfocyanate distribution, (Table IV). In the dog muscles analyzed by Hastings (4), the sodium space was 16 per cent greater than the chloride space. If ΔE_{c1} is calculated from an initial volume which is 20 per cent smaller than the sulfocyanate space, the agreement between ΔE_{c1} , ΔE_{Na} , and ΔE_{SCN} is closer.

The assumptions that intracellular and extracellular ionized base concentrations are equal and that potassium excretion measures the loss of ionized base from the cells, appear justified by the fairly good agreement in 3 dogs between the

| TABLE | III |
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|-------|-----|

Estimation of metabolic mixture

Data are expressed cumulatively from the beginning of the experiment to the end of the day indicated.

| | Time | | Change | Nitrogen | Protein | 0 | Meth | od A | Method B | |
|-----|-------------------------------|--|---|-------------------------------------|-------------------------------|----------------------------|--------------------------------------|---------------------------------|--------------------------------------|---------------------------------|
| Dog | | Weight | t of weight | | | hydrate | Total calories | (2) * fat | Insensible weight loss | (3) fat |
| | day | kgm. | kgm. | grams | grams | grams | | grams | kgm. | grams |
| 6 | 0 4 8 12 16 20 | 7.54 6.85 6.28 5.82 5.36 4.92 | -0.69 -1.26 -1.72 -2.18 -2.62 | 6.2 13.6 18.8 21.6 24.4 | 39 85 118 135 153 | 15 15 15 15 15 | 1360 2633 3820 4920 5932 | 123 239 411 528 564 | 0.84 1.26 1.67 2.08 2.49 | 197 287 380 462 582 |
| 7 | 0 6 11 | 7.07 5.50 4.76 | -1.55 -2.29 | 12.8 22.4 | 80 140 | 4 4 | 1907 3454 | 168 300 | 1.18 1.83 | 274 419 |
| 8 | 0 6 12 15 | 13.87 11.20 9.78 9.29 | -2.61 -4.02 -4.50 | 23.0 37.0 44.8 | 144 231 280 | 6 6 6 | 3750 7140 8700 | 337 663 809 | 1.34 2.57 2.99 | 287 575 663 |
| 9 | 0 6 12 15 | 15.71 13.72 12.30 11.69 | -1.90 -3.27 -3.87 | 18.3 38.3 47.8 | 115 239 299 | 6 6 6 | 4244 8080 9841 | 403 761 924 | 1.33 2.30 2.75 | 298 498 588 |

* Number at head of column indicates equation in text (Calculations) from which data are derived.

| Dog | Time | (8) † Na _{<i>BCW</i>} | (7) Cl _{<i>BCW</i>} | (4) E _{8CN} | (6) E _{N8} | (5) E _{Cl} | * E _{Cl} * |
|-----|------|-----------------------------------|---------------------------------|-------------------------|------------------------|------------------------|------------------------|
| | day | m. Eq. per liter | m. Eq. per liter | liters | liters | liters | liters |
| 6 | 0 | 144.0 | 120.4 | | 2.04 | 2.04 | |
| - | 4 | 148.0 | 126.7 | | 2.04 | 2.02 | |
| | 8 | 150.9 | 128.9 | | 1.91 | 1.84 | |
| | 12 | 148.0 | 131.8 | | 1.94 | 1.72 | |
| | 16 | 157.8 | 137.3 | | 1.80 | 1.63 | |
| | 20 | 160.1 | 144.3 | | 1.76 | 1.53 | |
| 7 | 0 | 148.8 | 125.2 | 2.12 | 2.12 | 2.12 | |
| | 6 | 168.2 | 144.3 | 1.66 | 1.61 | 1.60 | |
| | 11 | 200.2 | 155.0 | | 1.33 | 1.45 | |
| 8 | 0 | 149.8 | 115.6 | 3.90 | 3.90 | 3.90 | |
| | 6 | 158.1 | 128.9 | 3.09 | 3.04 | 2.86 | l |
| | 12 | 175.8 | 147.9 | | 2.67 | 2.42 | |
| | 15 | . 181.1 | 156.7 | 2.53 | 2.59 | 2.28 | 2.60 |
| 9 | 0 | 152.1 | 122.7 | 3.90 | 3.90 | 3.90 | |
| | 6 | 159.2 | 132.2 | 3.60 | 3.32 | 3.26 | |
| | 12 | 163.8 | 143.7 | | 3.07 | 2.88 | 1 |
| | 15 | 170.2 | 148.7 | 3.01 | 2.95 | 2.76 | 2.90 |
| | 1 | | | 1 | 1 | 1 | 1 |

TABLE IV Calculation of extracellular fluid volume Time at end of day indicated.

* Measured by means of radioactive chloride, Cl²⁸. † Number at head of column indicates equation in text (Calculations) from which data are derived.

intracellular water loss calculated by difference from the weight loss (ΔI_I) and the sum (ΔI_{II}) of the decrements ΔI_P , $\Delta I_{\mathbf{K}}'$, and $\Delta I_{\Delta B}$, which were calculated from these assumptions. In 1 dog (Dog 6), ΔI_I greatly exceeded ΔI_{II} . The experiment was performed in the heat of midsummer. If the discrepancy were due to the provision of more water of oxidation than was calculated, the total heat production would have to be doubled and the proportion of heat lost by vaporization of water reduced by one-half. This is a less likely explanation than that the dog sweated and the salt recoveries were too low.

Exchange of bases. In water deprivation, the obligatory vaporization of water for the removal of heat entails a loss of water without salt. Hypertonicity of body fluids is the result in the absence of a compensatory salt excretion. Salt excretion, as well as the distribution of the water loss between the 2 phases of body water, is conditioned by the behavior of the extra- and intracellular bases. Study of base exchange is facilitated in the dog by the usual absence of an extrarenal route for the elimination of salt.

The excretion of sodium, as well as of chloride,

| TABLE | v |
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|-------|---|

Allocation of water loss Data are expressed cumulatively from the beginning of the experiment to the end of the day indicated.

| Dog | Time | (1) * ∆₩ | (10) ΔE | (11) ΔI_I | (13) Δ <i>I</i> _P | (19) ΔΙ _{ΔΒ} | (14) ΔΙ _Κ ΄ | (12) ΔI _{II} |
|-----|------|--------------------|---------------|----------------------|---------------------------------|--------------------------|---------------------------|--------------------------|
| 6 | day | <i>liters</i> | <i>liters</i> | <i>liters</i> | <i>liters</i> | liters | <i>liters</i> | liters |
| | 4 | -0.50 | -0.01 | -0.49 | -0.10 | -0.07 | -0.03 | -0.20 |
| | 8 | -0.95 | -0.17 | -0.78 | -0.23 | -0.12 | -0.06 | -0.41 |
| | 12 | -1.26 | -0.21 | -1.05 | -0.32 | -0.07 | -0.09 | -0.48 |
| | 16 | -1.61 | -0.33 | -1.28 | -0.36 | -0.24 | -0.10 | -0.70 |
| | 20 | -1.96 | -0.40 | -1.56 | -0.41 | -0.27 | -0.12 | -0.80 |
| 7 | 6 | -1.29 | -0.52 | -0.77 | -0.22 | -0.26 | -0.14 | -0.62 |
| | 11 | -1.86 | -0.73 | -1.13 | -0.38 | -0.60 | -0.11 | -1.09 |
| 8 | 6 | -2.23 | -0.95 | -1.28 | 0.39 | -0.24 | -0.26 | -0.89 |
| | 12 | -3.29 | -1.36 | -1.93 | 0.62 | -0.72 | -0.34 | -1.68 |
| | 15 | -3.62 | -1.47 | -2.15 | 0.76 | -0.83 | -0.36 | -1.95 |
| 9 | 6 | -1.49 | -0.61 | -0.88 | -0.31 | -0.26 | -0.31 | 0.88 |
| | 12 | -2.52 | -0.93 | -1.59 | -0.65 | -0.44 | -0.47 | 1.56 |
| | 15 | -2.97 | -1.05 | -1.92 | -0.81 | -0.63 | -0.41 | 1.85 |

* Number at head of column indicates equation in text (Calculations) from which data are derived.

practically ceased under the conditions of our experiment. The high specific gravity of the urine and the adequate excretion of non-protein nitrogen are evidence against failure of renal function. Sodium and chloride must have been almost completely reabsorbed in the tubules despite the increasingly high concentration of these substances in the serum, a phenomenon noted by Kerpel-Fronius.

Although these animals were completely deprived of water, water was provided for vaporization and for an adequate excretion of urine. To provide this amount of water, the extracellular reservoir would have been completely exhausted if cell water had not been made available. A larger sodium excretion would increase the extracellular water loss. By retention of sodium, less of such water was lost, and the rise in sodium concentration made, on an osmotic basis, a fraction of cell water available $(\Delta I_{\Delta B})$. In addition, cell water was released, not only as a result of the fasting state (ΔI_P) , but also as a result of the washing out of excess potassium ($\Delta I_{\mathbf{K}}'$). Consequently, the cells shared both the hypertonicity and the reduction of volume. Under a compulsion to lose base, the preferential excretion of potassium over sodium increased intracellular and decreased extracellular water loss.

Schwartz, Smith, and Winkler (21) have observed a similar phenomenon following the injection of a combined solution of sodium chloride and sodium sulfate. A preferential excretion of



FIG. 1. DECREMENTS OF INTRACELLULAR WATER DURING WATER DEPRIVATION

Columns represent cell water loss cumulatively from the beginning of the experiment to the end of the day indicated. Decrements are represented as follows: water lost osmotically $(\Delta I_{\Delta B})$, solid black; water lost with K in excess of nitrogen $(\Delta I_{K}')$, cross-hatched; water lost with protein due to fasting (ΔI_{P}) , dotted columns. Total cell water loss taken as the difference between total water and extracellular water losses (ΔI_{I}) , blank columns.

sulfate over chloride and sodium, with a resultant rise in concentration of chloride and sodium in the serum, made available a fraction of cell water when water for excretion was greatly limited. The analogy of this experiment to the behavior of the animal deprived of water is clear.

The nature and extent of stimuli for the release of potassium in excess of nitrogen are unknown. Potassium is released from cells during hemorrhage (22). This condition shares with water deprivation the common factor of depleted extracellular volume, although anoxia may be an important factor. Evidence of a similar response under conditions lacking the teleological implications of our experiment has been produced by Gamble (23). He described an increased potassium excretion during sodium chloride ingestion by a patient who was not deprived of water. Stewart and Rourke (24) found a small increase in potassium excretion in patients receiving infusions of isotonic saline, which phenomenon they attributed to the preceding anesthesia and surgical trauma. A preliminary experiment in this laboratory (25) has revealed that the injection of hypertonic saline solution into a non-fasting dog not deprived of water is followed by a definite loss of potassium in excess of nitrogen. Such a loss of excess potassium did not occur following the injection of hypotonic saline solution or during a series of 24-hour control periods. Schwartz, Smith, and Winkler (21) have shown, in the acute experiment referred to above, that a large excretion of potassium took place during the 4 hours immediately following the intravenous injection of hypertonic saline solution. The data of Darrow and Yannet (3) also show a consistent excess potassium loss following the administration of hypertonic saline solution to 4 dogs depleted of sodium. The precise nature of this phenomenon of potassium release awaits elucidation.

Significance. In water deprivation, the release of potassium mitigates, at the expense of cell fluid, not only the rise in total ionic concentration but also the depletion of extracellular volume. Perhaps the survival value of the sacrifice of cell water lies in the maintenance of an adequate circulation. Dill (26) found that the burro, an animal acclimatized to an environment of great heat, sweats almost pure water and thereby distributes the water loss over both phases of body fluid. The concentration of salt in the sweat of Dill and his colleagues diminished as they became acclimatized to the heat of Boulder Dam. It is not known whether over a long period of time man can make this adjustment to the same degree as the burro. But the studies of Kerpel-Fronius (1) and of Nadal, Pedersen, and Maddock (2) have clearly shown that, in dehydration where sodium is also lost in large amounts, depletion of the extracellular phase alone leads to early diminution of plasma volume and consequent circulatory failure.

Heretofore, in studies of the effects of tropical and industrial heat, attention has centered on the loss and restoration of salt in the presence of *ample water*. The type of experiment reported here, in which lack of water is the main limiting



FIG. 2. CONCENTRATION OF ELECTROLYTES IN URINE Columns represent concentration of electrolytes in urine for individual periods ending at the end of the day indicated, as follows: Cl, dotted; Na, solid black; K, blank columns. condition, may assume more significance in the present emergency, where not infrequently circumstances arise in which water is at a premium.

SUMMARY

In 4 dogs deprived of water and food for periods of 11 to 20 days, the exchanges of salt and water were studied.

The concentration of sodium in serum rose, indicating hypertonicity of body fluids.

The total water loss greatly exceeded the extracellular water loss, indicating a substantial intracellular water loss.

The intracellular water loss was differentiated into three processes: water lost on an osmotic basis, water lost with cell destruction in fasting, and water lost with potassium released in excess of nitrogen.

The concentration of sodium and chloride in urine diminished, whereas that of potassium increased.

The significance of these physiological responses to the conditions imposed has been discussed.

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BIBLIOGRAPHY

- Kerpel-Fronius, E., Über die beziehungen zwischen salz-und wasserhaushalt bei experimentellen wasserverlusten. Ztschr. f. Kinderheilk., 1935, 57, 489.
- Nadal, J. W., Pedersen, S., and Maddock, W. G., A comparison between dehydration from salt loss and from water deprivation. J. Clin. Invest., 1941, 20, 691.
- Darrow, D. C., and Yannet, H., Metabolic studies of the changes in body electrolyte and distribution of body water induced experimentally by deficit of extracellular electrolyte. J. Clin. Invest., 1936, 15, 419.
- Hastings, A. B., and Eichelberger, L., The exchange of salt and water between muscle and blood. I. The effect of an increase in total body water produced by the intravenous injection of isotonic salt solutions. J. Biol. Chem., 1937, 117, 73.
- Eichelberger, L., and Hastings, A. B., The exchange of salt and water between muscle and blood. III. The effect of dehydration. J. Biol. Chem., 1937, 118, 205.
- Heppel, L. A., The electrolytes of muscle and liver in potassium-depleted rats. Am. J. Physiol., 1939, 127, 385.
- 7. Ferrebee, J. W., Parker, D., Carnes, W. H., Gerity,

M. K., Atchley, D. W., and Loeb, R. F., Certain effects of desoxycorticosterone. The development of "diabetes insipidus" and the replacement of muscle potassium by sodium in normal dogs. Am. J. Physiol., 1941, 135, 230.

- Hald, P. M., in Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry, Vol. II, Methods, p. 838, Williams and Wilkins, Baltimore, 1932.
- 9. Hald P. M., The determination of the bases of serum and whole blood. J. Biol. Chem., 1933, 103, 471.
- Crandall, L. A., Jr., and Anderson, M. X., Estimation of the state of hydration of the body by the amount of water available for the solution of sodium thiocyanate. Am. J. Digest. Dis. and Nutrition, 1934, 1, 126.
- Elkinton, J. R., and Taffel, M., The apparent volume of distribution of sulfocyanate and of sulfanilamide in the dog. Am. J. Physiol. (In press.)
- 12. Harvey, S. C., The quantitative determination of the chlorids in the urine. Arch. Int. Med., 1910, 6, 12.
- Butler, A. M., and Tuthill, E., An application of the uranyl zinc acetate method for determination of sodium in biological material. J. Biol. Chem., 1931, 93, 171.
- Newburgh, L. H., Johnston, M. W., and Falcon-Lesses, M., Measurement of total water exchange. J. Clin. Invest., 1929-30, 8, 161.
- Peters, J. P., Kydd, D. M., and Lavietes, P. H., A note on the calculation of water exchange. J. Clin. Invest., 1933, 12, 689.
- Anderson, R. J., and Lusk, G., Animal calorimetry. The interrelation between diet and body condition and the energy production during mechanical work. Thirteenth paper. J. Biol. Chem., 1917, 32, 421.
- Lavietes, P. H., The metabolic measurement of the water exchange. J. Clin. Invest., 1935, 14, 57.
- Harrison, H. E., Darrow, D. C., and Yannet, H., The total electrolyte content of animals and its probable relation to the distribution of body water. J. Biol. Chem., 1936, 113, 515.
- Darrow, D. C., Harrison, H. E., and Taffel, M., Tissue electrolytes in adrenal insufficiency. J. Biol. Chem., 1939, 130, 487.
- 20. Painter, E. E., Total body water in the dog. Am. J. Physiol., 1940, 129, 744.
- Schwartz, B. M., Smith, P. K., and Winkler, A. W., The renal excretion of sulfate. Am. J. Physiol. (In press.)
- Stewart, J. D., and Rourke, G. M., Intracellular fluid loss in hemorrhage. J. Clin. Invest., 1936, 15, 697.
- Gamble, J. L., Chemical anatomy, physiology, and pathology of extracellular fluid. A lecture syllabus. Department of Pediatrics, Harvard Medical School, Boston, Mass., 3rd Ed., 1941, Chart 34.
- Stewart, J. D., and Rourke, G. M., The effects of large intravenous infusions on body fluid. J. Clin. Invest., 1942, 21, 197.
- 25. Elkinton, J. R., Unpublished data.
- Dill, D. B., Life, Heat, and Altitude. Harvard Univ. Press, Cambridge, Mass., 1938.