HOWARD LEVITIN*
ANDRZEJ MANITIUS**
FRANKLIN H. EPSTEIN†

*Department of Internal Medicine, Yale University School of Medicine*

## URINARY DILUTION IN POTASSIUM DEFICIENCY‡

One of the earliest manifestations of potassium depletion is a reduction in the ability of the kidneys to elaborate a concentrated urine.[6] This defect has been shown to result at least in part from a decrease in the concentration of sodium in the interstitial fluids of the renal medulla and papilla.[9] The disturbance in renal concentrating ability may exist without impairment of glomerular filtration rate; renal extraction of para-aminohippurate[10] and the ability of the kidneys to excrete a highly acid urine, however, are frequently deficient.[3]

The present experiments have explored the ability of potassium-deficient animals to excrete a *dilute* urine in response to a water load. In contrast to certain other diseases of the kidney accompanied by hyposthenuria, the kidneys of potassium-depleted animals appear to dilute the urine normally. Studies of urinary dilution and concentration in two patients with severe potassium deficiency are also reported.

### METHODS

Twenty-one white male Sprague-Dawley rats weighing 170-220 grams were divided into experimental and control groups. Ten rats comprised the experimental group and were depleted of potassium by diet and desoxycorticosterone (DCA). Eleven rats served as controls and were fed a normal diet throughout the experiment. Both groups were studied concomitantly.

Following an initial seven days of normal diet, both groups were subjected to a water-loading test. Water equal to 5 per cent of body weight was given in a single dose by gastric intubation and the animal placed in a metabolic cage. During the next two to three hours, urine was collected in three consecutive aliquots of at least 2.5 ml. and the osmolality of each sample determined with the Fiske osmometer. Twelve hours later, drinking water was withdrawn. After 12 hours of water deprivation, 50 milliunits of vasopressin in oil were injected subcutaneously. The rats usually voided spontaneously

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* Advanced Research Fellow of the American Heart Association; Instructor in Medicine.
** Special Fellow of the Rockefeller Foundation.
† Established Investigator of the American Heart Association; Associate Professor of Medicine.
‡ Aided by grants from the American Heart Association, the National Heart Institute and the Lawrence M. Gelb Foundation.
*Received for publication February 10, 1960.*

while they were being injected. They were then placed in metabolic cages over funnels filled with mineral oil to minimize evaporation, and urine was collected during the next 12 hours for the determination of maximum urinary osmolality.

Thereafter the first group of rats was depleted of potassium by a diet containing normal amounts of sodium but low in potassium[9] and by daily subcutaneous injections of 0.2 mg. DCA for seven days. DCA was then discontinued and the low-potassium diet

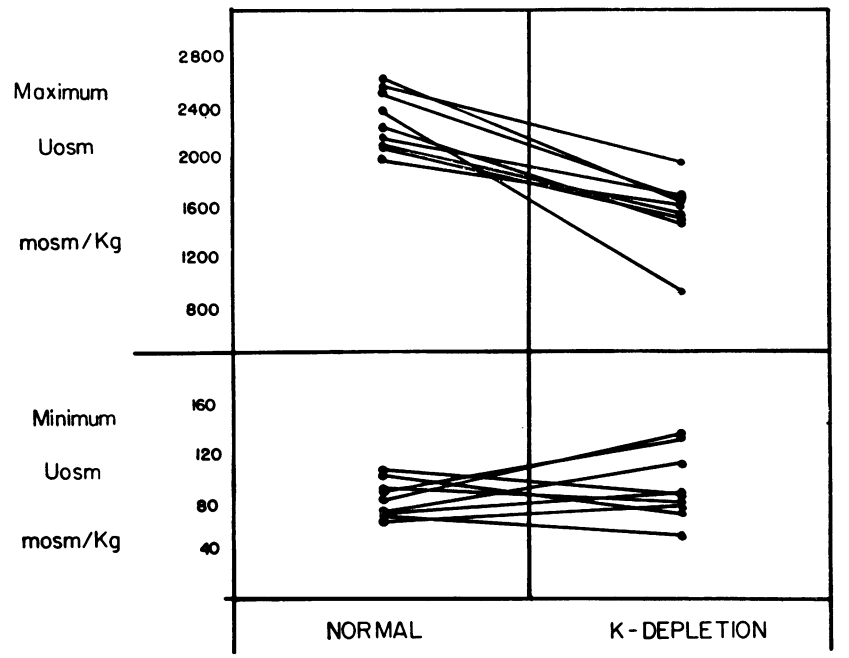


FIG. 1. Potassium deficiency did not alter *minimum* urinary osmolality, although *maximum* urinary concentration was greatly diminished.

maintained for the remainder of the experiment. Two days after stopping DCA both groups of animals were again gavaged with water to assess their diluting ability, and this was followed 36 hours later by a concentration test. At the conclusion of the experiment the rats were anesthetized with pentobarbital, exsanguinated via the abdominal aorta, and specimens of thigh muscle were obtained.

The chemical techniques employed for the analysis of tissue, urine and plasma were those previously detailed.[9]

## RESULTS

Potassium depletion resulted in the expected decrease in the content of potassium of serum and muscle and a slight increase in muscle sodium (Table 1). Maximum concentrating ability was greatly diminished, $U_{max}$ falling from an average of 2258 mosm/Kg. to 1570 mosm/Kg.

TABLE 1. THE EFFECT OF POTASSIUM DEPLETION ON URINARY CONCENTRATION AND DILUTION IN RATS

| | *Wt. gm.* | *Max. $U_{osm}$ mosm/Kg.* | *Min. $U_{osm}$ mosm/Kg.* | *$U_{Na}$ meq/L* | *Wt. gm.* | *Max. $U_{osm}$ mosm/Kg.* | *Min. $U_{osm}$ mosm/Kg.* | *$U_{Na}$ meq/L* | *Serum K meq/L* | *Muscle K meq/100 gm. FFDS** | *Muscle Na meq/100 gm. FFDS** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Experimental (10 rats)* | | | | | | | | | | |
| | *Initial* | | | | *Final* | | | | | | |
| Mean | 188 | 2258 | 85 | 5.5 | 211 | 1570 | 94 | 5.8 | 2.7 | 39.7 | 13.9 |
| s.d. | 14 | 266 | 31 | 3.0 | 23 | 266 | 27 | 2.4 | 0.6 | 2.1 | 1.2 |
| p (Initial vs. Final) | | | | | | $<0.01$ | $>0.4$ | $>0.7$ | | | |
| | *Control (11 rats)* | | | | | | | | | | |
| Mean | 191 | | 102 | 7.8 | 223 | 2048 | 104 | 7.1 | 4.0 | 44.9 | 8.9 |
| s.d. | 14 | | 27 | 4.5 | 14 | 249 | 52 | 5.4 | 0.4 | 1.7 | 1.7 |
| p (Exp. vs. Control) | | | $>0.2$ | $>0.2$ | | $<0.01$ | $>0.6$ | $>0.5$ | $<0.01$ | $<0.01$ | $<0.01$ |

* Fat-free dry solids.

Despite the evident loss of the ability of the kidneys to concentrate urine, diluting ability remained unimpaired (Fig. 1). Minimum urinary osmolality was essentially unchanged by potassium deficiency (Table 1), and the time required by depleted rats to excrete a water load was not significantly different from that of normal controls (Fig. 2). Although a tendency to waste sodium in the urine has been demonstrated in hydropenic potassium-

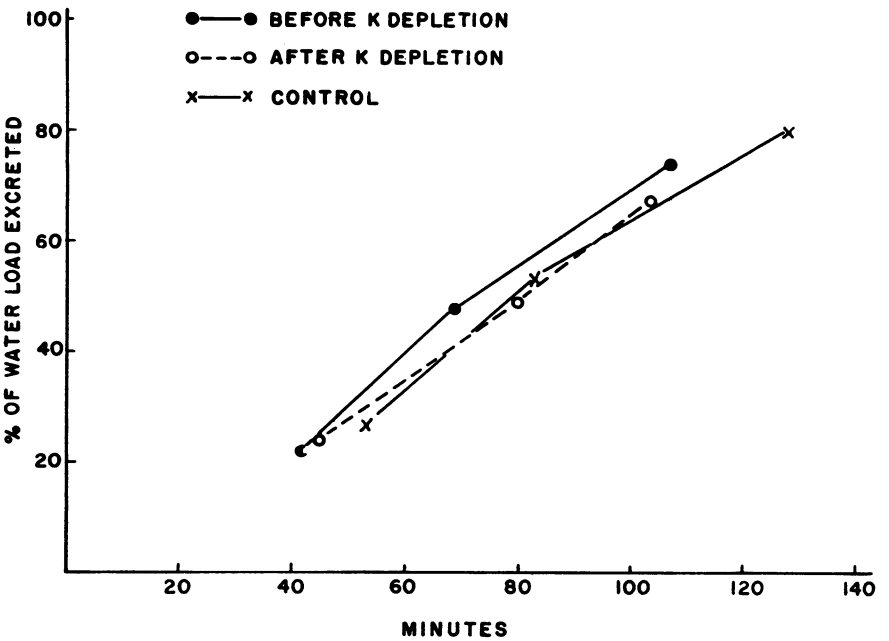


FIG. 2. Time required by rats to excrete a water load equal to 5 per cent of body weight. The ability to excrete water was unaffected by potassium depletion.

depleted rats on a low-sodium diet,[9] water-loaded animals in the present experiments, on a normal-sodium diet, excreted the same amount of sodium in the urine before and after potassium depletion.

Water-loading experiments were carried out on two patients severely depleted of potassium, as judged from subsequent balance studies carried out during repletion (Table 2). M.A., with nephrocalcinosis and renal potassium wasting, could concentrate the urine only to 325 mosm/Kg. after the intramuscular administration of vasopressin in oil. Creatinine clearance, blood nonprotein nitrogen and phenolsulfonphthalein excretion were all within the normal range. Although potassium-deficient and unable to concentrate the urine, she excreted 70 per cent of a liter of ingested water within

three hours and attained a minimum urinary osmolality of 45 mosm/Kg., a normal response. On the other hand, H.B., a middle-aged lady depleted of potassium by laxative addiction, initially exhibited much more severe impairment of renal function, with an NPN of 52 mg./100 ml. and a

TABLE 2

| *Patient* | *M.A. ♀ 46 yrs. 45 Kg.* | | *H.B. ♀ 53 yrs. 52 Kg.* |
|---|---|---|---|
| *Diagnosis* | *Renal tubular acidosis, nephrocalcinosis, renal K-wasting* | | *Laxative addiction* |
| Water load | Low-K | 1,000 ml. p.o. | 1,000 ml. i.v. |
| | After repletion | 1,000 ml. p.o. | 1,000 ml. p.o. |
| Excreted in 3 hrs. ml. | Low-K | 700 | 455 |
| | After repletion | | 455 |
| Min. $U_{osm}$ mosm/L | Low-K | 45 | 143 |
| | After repletion | | 135 |
| Max. $U_{osm}$ mosm/L | Low-K | 280 | 218 |
| | After repletion | 545 | 718 |
| NPN mg/100 ml. | Low-K | 32 | 52 |
| | After repletion | | 42 |
| $C_{cr}$ ml/min. | Low-K | 75 | |
| | After repletion | 88 | |
| PSP % in 2 hrs. | Low-K | 82 | 31 |
| | After repletion | | 77 |
| Serum K meq/L | Low-K | 2.1 | 2.5 |
| | After repletion | 4.5 | 4.6 |
| Estimated* deficit of K meq | | 540 | 700 |

* From balance studies during repletion.

phenolsulfonphthalein (PSP) excretion of only 31 per cent in two hours. Maximum urinary concentration after intramuscular injection of five units of vasopressin in oil was only 218 mosm/Kg. One liter of 5 per cent glucose in water given intravenously was excreted abnormally slowly, only 45 per cent appearing in the urine after three hours. The lowest urinary osmolality achieved was 143 mosm/Kg. Diluting ability did not improve appreciably even after potassium balance was restored. Impaired urinary dilution in this

potassium-depleted patient was probably associated with restriction of glomerular filtration rate and renal blood flow, perhaps as a result of more intense or prolonged generalized renal injury by potassium deficiency.

## DISCUSSION

These experiments demonstrate that potassium deficiency in rats, severe enough to produce marked impairment of renal concentrating ability, need not interfere with the capacity of the kidneys to dilute the urine in response to a water load. The results are consistent with the report of Brokaw that the time required for rats to excrete half of an oral water load consisting of 5 per cent of body weight was not prolonged by potassium depletion, although elimination of much larger doses of water was slowed.[1]

Urine is presumably diluted by active reabsorption of sodium in the thin loop of Henle and the distal convoluted tubule.[4, 12] The present experiments suggest that this process is not greatly disturbed by potassium depletion. This conclusion is reinforced by the finding of Gottschalk that fluid obtained by micropuncture of the distal convoluted tubule in potassium-deficient rats is as dilute as that obtained from the same site in normal animals.[5] These data are of interest in the light of the increased urinary sodium and decreased content of sodium of the renal medulla and papilla of hydropenic potassium-deficient animals.[9] Although they do not exclude the possibility that active reabsorption of sodium by medullary loops of Henle is diminished by potassium deficiency, they suggest that other mechanisms may be responsible for the lowered gradient of sodium concentration between cortex and papilla which characterizes this condition.

The ability to excrete a dilute urine depends not only upon the reabsorptive capacities for sodium of the ascending loop of Henle and the distal convoluted tubule, but also upon the quantity and composition of fluid delivered to these sites. The excretion of free water may be expected, therefore, to vary with the rate of glomerular filtration.[7] Thus, although moderate polyuria may characterize individuals with renal insufficiency and azotemia who have lost the ability to concentrate their urine, delayed excretion of water and decreased ability to dilute the urine is also generally the rule in such patients. Whether a particular patient with a deficit of potassium is able to excrete a normally dilute urine probably depends upon the degree to which glomerular filtration has been impaired as well as upon the extent of associated lesions of the renal parenchyma. It is interesting that patient M.A., with comparatively little restriction of endogenous creatinine clearance and a normal phenolsulfonphthalein excretion, was able to dilute her urine normally, while H.B., with considerably more severe impairment of renal

function, and a greater over-all deficit of body potassium, exhibited some restriction of water diuresis which persisted even after the body stores of potassium were repleted. Rubini has reported that normal human subjects in whom mild degrees of potassium depletion have been induced under controlled conditions retain the ability to dilute the urine at a time when concentrating power is distinctly diminished.[11]

Retention of the ability to excrete a dilute urine is probably responsible for the prominence of severe polyuria in some patients with potassium deficiency, especially those in whom disturbances of thirst or posterior pituitary secretion exist which lead to excessive drinking.[3,8]

## SUMMARY

1. Potassium depletion severe enough to lower the content of potassium in serum and muscle and to impair renal concentrating ability was induced in rats.

2. The capacity of the kidneys to excrete a dilute urine in response to an oral water load was unaltered by potassium deficiency.

3. Renal diluting ability was also normal in one patient with severe potassium deficiency but was found to be restricted in another.

## REFERENCES

1. Brokaw, A.: Renal hypertrophy and polydipsia in potassium-deficient rats. *Amer. J. Physiol.*, 1953, *172*, 333.
2. Clarke, E., Evans, B. M., MacIntyre, I., and Milne, M. D.: Acidosis in experimental electrolyte depletion. *Clin. Sci.*, 1955, *14*, 421.
3. Fourman, P. and Leeson, P. M.: Thirst and polyuria, with a note on the effects of potassium deficiency and calcium excess. *Lancet*, 1959, *1*, 268.
4. Gottschalk, C .W. and Mylle, M.: Micropuncture study of the mammalian urinary concentrating mechanism: evidence for the countercurrent hypothesis. *Amer. J. Physiol.*, 1959, *196*, 927.
5. Gottschalk, C. W., Mylle, M., Winters, R. W., and Welt, L. G.: Micropuncture study of the osmolality of renal tubular fluid in potassium-depleted rats. (abstract) *J. clin. Invest.*, 1958, *37*, 898.
6. Hollander, W., Jr., Winters, R. W., Williams, T. F., Bradley, J., Oliver, J., and Welt, L. G.: Defect in the renal tubular reabsorption of water associated with potassium depletion in rats. *Amer. J. Physiol.*, 1957, *189*, 557.
7. Kleeman, C. R., Epstein, F. H., and White, C.: The effect of variations in solute excretion and glomerular filtration on water diuresis. *J. clin. Invest.*, 1956, *36*, 749.
8. Kleeman, C. R. and Maxwell, M. H.: Contributory role of extrarenal factors in the polyuria of potassium depletion. *New Engl. J. Med.*, 1959, *260*, 268.
9. Manitius, A., Levitin, H., Beck, D., and Epstein, F. H.: On the mechanism of hyposthenuria in potassium deficiency. *J. clin. Invest.*, April, 1960.
10. Relman, A. S. and Schwartz, W. B.: The nephropathy of potassium depletion. *New Engl. J. Med.*, 1956, *255*, 195.
11. Rubini, M. E.: The conservation of water in potassium deficiency. *Clin. Res.*, 1960, *8*, 64.
12. Wirz, H.: The location of antidiuretic action in the mammalian kidney. Pp. 157-166 in *The neurohypophysis*. H. Heller, Ed. Proceedings of the VIII Symposium of the Colston Research Society. New York, Academic Press, 1957.