The physiological basis of thirst has been a debatable subject for well over a century. Recent investigations have centered around the old controversy as to whether thirst is a general or localized sensation. The historical literature on this subject has been presented by Cannon (1918). Montgomery (1931) has briefly summarized the more recent contributions. Schiff in 1867 (cited by Cannon, 1918) was of the opinion that thirst was a generalized sensation which arose from a lessened water content of the body. The local reference of the sensation of thirst to the pharynx he placed in the same category as the local reference of hunger to the stomach, or of sleepiness to the heaviness of the eyelids. Recent investigations, however, have stressed the relationship of water intake to the local conditions of the mouth especially with reference to salivary flow (Montgomery, 1931).

The influence of general body hydration and the distribution of body fluids upon thirst has received scant attention. In the present study, observations on voluntary water intake were correlated with changes in blood osmotic pressure and the general distribution of the body fluids.

Procedure. Dogs were used as the experimental animals. A normal blood sample was taken from the femoral artery, after which the animals received, intravenously, 2.5 cc./kilo of either 20 per cent NaCl or 40 per cent urea. These concentrations are approximately isosmolar. Thirty minutes were allowed to elapse for the complete equilibration of the substances injected during which time the dogs were kept quietly on the table and were not given access to water. At the end of this period a second arterial blood sample was procured and the animals then returned to their cages where water was available ad libitum. Their fluid intake was recorded at fifteen minute intervals. Blood samples were obtained at intervals over six hours.

Measurements were made on the serum of total osmotic pressure by the vapor pressure method of Hill (1930) and specific gravity by the falling drop method of Barbour and Hamilton (1926).
Experimental results. Osmotic pressure. A marked increase in the blood osmotic pressure resulted from the injection of hypertonic urea and NaCl. Inasmuch as the solutions injected were approximately isosmolar and given in proportion to body weight, the increases in osmotic pressure in all experiments were almost identical (table 1). It is of interest in view of the constancy of the osmotic pressure rise to calculate the per cent of active body water from these figures. The normal osmotic pressure of the dogs receiving NaCl expressed in terms of the concentration of an isosmolar NaCl solution averaged 152.1 m. eq. per liter. After injection this rose to 164.6 m. eq. per liter, an increase of 12.5 m. eq. per liter. This resulted from an injection of 2.5 cc. per kilo of 20 per cent NaCl or 8.55 m. eq. per kilo. Thus for every kilo of body weight the animals received 8.55 m. eq. of NaCl and for every liter of body water they gained 12.5 m. eq. Despite the fact that the Na and Cl remain in the extracellular fluid, all of the body fluids contribute to the osmotic equilibration. Therefore we may say that the active water in the body may be considered 12 or 68 per cent. Using this same type of calculation for the urea experiments, a value of 65 per cent is obtained. This is in close agreement with the accepted figures obtained by other methods of calculation. It is subject to error due to the renal activity during the thirty minute equilibration period.

| DOG | INJECTION | SERUM O. P.* | | | SERUM S. G. |
|-----|-----------|-------------|---|---|
|     | Initial | 30 minutes after injection | Initial | 30 minutes after injection |
| A   | 20% NaCl | 0.902 | 0.980 | 1.0228 | 1.0197 |
|     | 40% Urea | 0.871 | 0.947 | 1.0201 | 1.0202 |
| B   | 20% NaCl | 0.897 | 0.966 | 1.0216 | 1.0188 |
|     | 40% Urea | 0.892 | 0.971 | 1.0209 | 1.0212 |
| C   | 20% NaCl | 0.873 | 0.942 | 1.0212 | 1.0196 |
|     | 40% Urea | 0.873 | 0.946 | 1.0217 | 1.0220 |
| D   | 20% NaCl | 0.880 | 0.955 | 1.0213 | 1.0190 |
|     | 40% Urea | 0.901 | 0.982 | 1.0210 | 1.0215 |

* Serum osmotic pressure is expressed as per cent concentration of an isosmolar NaCl solution.
Specific gravity. Although the blood osmotic changes in both the urea and NaCl series were identical, there were marked differences observed in the specific gravities. The injection of the hypertonic NaCl was accompanied by a reduction in serum specific gravity, whereas no demonstrable change followed the administration of urea. Inasmuch as serum specific gravity is essentially a reflection of the concentration of serum protein, this reduction after saline administration is evidence of a shift of water from the cells to the extracellular reservoir due to the impermeability of the cell membrane to the ions involved. After the injection of a permeable molecule such as urea, on the other hand, the specific gravity remained unchanged. Thus hypertonic urea contributed to the high total osmotic pressure of the blood without any shifts between intra and extracellular water. In short these injections resulted in two groups of animals, both characterized by abnormally high osmotic pressures of the same degree. In one group (NaCl) the increase in cellular osmotic pressure was accompanied by a loss of fluid, in the other (urea) the increase in cellular osmotic pressure resulted from the increased concentration of a freely permeable molecule with no fluid loss. It should be emphasized that the osmotic pressure within the cells of both groups of animals should be the same despite the difference in fluid distribution.

Water intake. Despite the identical rise in osmotic pressure, the water intake of these two groups differed markedly. The average voluntary consumption during the first fifteen minutes, of those animals receiving urea, was 12 cc. per kilo, whereas during the same period those dogs which had received NaCl drank 32 cc. per kilo. At the end of one hour the average intakes had risen to 20 cc. per kilo and 42 cc. per kilo respectively.

As would be expected from the different levels of voluntary fluid intake, there was a pronounced difference between the two groups in the return of the blood osmotic pressure to normal. Figure 1 depicts the complete protocol of a typical experiment in which dog B received injections of NaCl and urea seven days apart. Although the respective increases in osmotic pressure were identical, the fluid intake following NaCl was over twice that following urea. As a result the blood osmotic pressure after the administration of NaCl returned to its normal level within an hour. On the other hand, although there was some evidence of thirst after the urea administration, the voluntary water consumption was not sufficient to lower the osmotic pressure of the blood to its original level and the animal seemed comfortable, insofar as the sensation of thirst was concerned, with a blood osmotic pressure appreciably higher than normal. The responsibility of the return to a normal value was seemingly left to the kidney.

It is of interest to observe that the serum of the animal depicted in figure 1, before receiving NaCl was isosmolar with a 0.897 per cent NaCl solution. The dog received 28.5 cc. of 20 per cent NaCl. In order to render
this isotonic the animal would have to drink $28.5 \times \frac{20}{0.897}$ or 635 cc. of water. The animal actually consumed during the first hour 610 cc. which, plus the "osmotic work" of the kidney, was more than sufficient to dilute the blood to its original level.

Discussion. It can be seen from the above results that the sensation of thirst depends upon more than a mere increase in the total osmotic
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pressure of the body fluids. After the administration of hypertonic NaCl and urea the increases in blood osmotic pressure were the same. The essential difference between the two groups of experiments was in the water content of the cell. The logical conclusion to draw from the above results is that cellular dehydration rather than an increase in cellular osmotic pressure per se is the stimulus of true thirst.

It is of interest in this regard to cite some observations on dogs with abnormal water distribution characterized by anhydremia associated with a lowered blood osmotic pressure and cellular hydration. It has been shown by Darrow and Yannett (1935) that when large amounts of extracellular electrolyte, unaccompanied by H₂O are withdrawn from animals, the selective loss of extracellular ions results in a shift of fluid into the cells in order to maintain osmotic equilibrium. Such animals show anhydremia characterized by increased concentration of blood hemoglobin, specific gravity, hematocrit, and serum protein, accompanied by a cellular hydration. While utilizing dogs in this condition for other observations (Gilman, 1934) it was observed that in the acute stage of anhydremia such animals shunned water. Seemingly, despite the anhydremia and the striking dry appearance of the oral mucous membranes and the probable lack of salivary secretions, these dogs did not experience the sensation of thirst. It is tempting to attribute this to the low electrolyte and high water content of the cells.

The differences in voluntary water intake following the administration of NaCl and urea is of fundamental significance. Gamble and co-workers (1929, 1934) have emphasized “An economy of water in renal function referable to urea.” In their experiments the urinary excretion of urea and electrolytes was studied in rats receiving varying proportions of these substances in the diet. The animals were allowed water ad libitum. It was found that the water volume necessary for the excretion of varying proportions of salts and urea were not additive but that there was an economy of water in renal function referable to the excretion of urea. Reference to Gamble's data, however, shows that urine output varies with water consumption, and it is logical to assume that thirst was the primary mechanism involved in this economy. Thus the animals always drank sufficient fluid to compensate for the salt intake to the isotonic level. Urea added to the diet seemingly did not increase the thirst stimulus until its osmotic concentration was greater than that of the salt.

SUMMARY AND CONCLUSIONS

Voluntary water intake in dogs differed markedly following the intravenous injection of hypertonic solutions of isosmolar NaCl and urea despite identical increases in blood osmotic pressure. After the administration of hypertonic NaCl, animals immediately consumed sufficient
water to dilute their blood to its preinjection level, whereas after urea, in the absence of a thirst stimulus, the osmotic pressure of the blood remained elevated. This difference in water intake was attributed to the differences in the water content of the cell. Experiments were cited in which marked anhydremia accompanied by cellular hydration failed to stimulate thirst.

REFERENCES

Gilman, A. This Journal 108: 662, 1934.
Montgomery, M. F. This Journal 96: 221, 1931.