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Denton D A. The study of sheep with permanent unilateral parotid fistulae. *Quart. J. Exp. Physiol.* 42:72-95, 1957.
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Successful preparation of a permanent parotid fistula in the sheep, despite earlier reports in Russian and German literature on its impracticability in ruminants, resulted in a 1-4 l alkaline salivary loss daily, a large sodium deficit, increased urinary chloride excretion, and an avid salt appetite. By substituting potassium for sodium in saliva, animals lived for weeks with large residual sodium deficits. This reveals how ruminant species adapt to the salt deficit areas of the planet. [The *SCI*® indicates that this paper has been cited in over 165 publications.]

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In the year following my graduation from medical school, I had under my care, at the Royal Melbourne Hospital, a young boy with a postgastrectomy duodenal fistula who lost 1-4 l of alkaline pancreatic juice each day. As the patient lost large volumes of alkaline pancreatic juice, his respiration rate rose, blood pressure fell, and urinary chloride excretion increased, despite a decrease in blood chloride. In those days, prior to flame photometry, the basis of clinical management of salt balance[1] was to use the amount of chloride in the urine, measured by the bedside Fantus test, as the criterion of adequacy of salt balance and status of circulation. However, subtraction of sodium in excess of chloride from the body, distorting acid base balance, caused a compensatory excess excretion of chloride by the kidney independently of the so-called "renal threshold" for chloride, and despite circulatory deterioration.[2]

An animal experimental model was necessary to validate the clinical findings. Despite earlier Russian and German reports of great difficulties, 37 sheep were prepared with a permanent unilateral parotid fistula. The papilla and duct were enclosed in a skin tube, as suggested by my colleague R. Douglas Wright. Thus saliva dripped from a dependent point of a teat on the cheek. The urinary chloride findings in man were confirmed.

This method placed a "tap" on the bloodstream that subtracted large amounts of alkaline sodium-rich fluid from the body. Homeostasis in the face of controlled distortion of body chemistry could be studied in a precisely controlled fashion.

The most dramatic finding was that, with a progressive sodium deficiency up to a negative balance of 500-800 mmol, the salivary Na decreased and the salivary K rose commensurately, the change being from Na/K = 170/5 when Na was replete to Na/K = 10/160 when sodium was severely deficient. Moreover, when depleted of, say, 400-500 mmol of Na, the animal could live for weeks in sodium equilibrium with a Na/K ratio of 60/120, the sodium intake in food just compensating for the Na loss from the fistula.

This showed how K, which is abundant in grass, was substituted for the Na in saliva. Thus the large sodium store in the rumen was drawn upon to counteract extracellular sodium depletion. This revealed a major mechanism in the phylogenetic development by ruminants of the capacity to adapt to the large sodium-deficient areas of the planet—alpine areas and the interiors of continents. The rumen sodium store could be drawn upon as needed. The hypothesis was confirmed by showing severe sodium deficiency with a reduced salivary Na/K ratio and low urine sodium in alpine cattle.[3]

D.B. Botkin et al. of Yale University[4] showed how moose on the Isle Royale in Canada survived and reproduced by eating large amounts of halophyte aquatic plants during a short three-month season of the year and drew on the rumen pool of sodium during the remainder of the year. Later, change in the salivary Na/K ratio was shown to reflect the current level of aldosterone in blood and used to study control of aldosterone secretion.[5,6]

The paper also recounted how with progressive sodium deficiency an avid appetite for salt developed. It pioneered the use of the parotid fistula to study specific sodium appetite in sheep and cattle. Studies by the Howard Florey Institute group over the past 20 years[7] have, inter alia, revealed that, in addition to cerebral receptors responsive to glucose, osmotic pressure, CO_2, pH, temperature, and sodium concentration in relation to thirst and ADH secretion, there are sodium-sensitive elements in the brains of ruminant species that generate a craving for salt in the face of a fall of Na in the extracellular fluids of the brain.

1. **Marriott H L.** *Water and salt depletion.* Springfield, IL: Thomas, 1950. 80 p.
2. **Denton D A.** Renal regulation of the extracellular fluid. *Nature* 162:618-9, 1948.
3. **Bott E, Denton D A, Goding J R & Sabine J R.** Sodium deficiency and corticosteroid secretion in cattle. *Nature* 202:461-3, 1964. (Cited 30 times.)
4. **Botkin D B, Jordan P A, Dominski A S, Lowendorf H S & Hutchinson G E.** Sodium dynamics in a northern ecosystem. *Proc. Nat. Acad. Sci. USA* 70:2745-8, 1973. (Cited 45 times.)
5. **Denton D A, Goding J R & Wright R D.** Control of adrenal secretion of electrolyte-active steroids. *Brit. Med. J.* 2:447-56, 1959. (Cited 85 times.)
6. ————. Control of adrenal secretion of electrolyte-active steroids. II. Adrenal stimulation by cross-circulation experiments in conscious sheep. *Brit. Med. J.* 2:522-30, 1959. (Cited 65 times.)
7. **Denton D.** *The hunger for salt: an anthropological, physiological and medical analysis.* Berlin: Springer-Verlag, 1982. 650 p. (Cited 50 times.)

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