# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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**Supplemental Case Summaries**

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**Contents**

## Supplemental Case Summaries

***Introduction***. In this supplement, we illustrate the pathophysiological principles discussed in the main text with five brief clinical cases. To make the presentation as informative and as interesting as possible for the reader, we have chosen to provide synopses of previously described, classical cases from as long as six decades ago. We include a summary of the case and then comment on selected points from the perspective of today's knowledge (indicated by italics). We have chosen two cases describing patients with dilutional hyponatremia (SIADH) and three cases describing patients with polyuria/polydipsia .

Case 1. **Syndrome of inappropriate antidiuresis (SIADH) associated with oat-cell carcinoma of the lung**

(Condensed from: St Goar WT, Cohen RB. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 14-1966. Oat-cell carcinoma of lung, with extension to local lymph nodes, (associated with inappropriate secretion of antidiuretic hormone). ***N Engl J Med.*** 1966; 274: 678-86.)

A sixty-three year old man was admitted because of confusion. Throughout his life he and been a moderate smoker. He had been well until about 5 weeks prior to admission, when he began to feel 'vaguely unwell.' Subsequently, he developed generalized pruritus with a rash, which was initially treated with topical triamcinolone and subsequently with oral prednisone (30 mg daily). While taking prednisone, he developed a duodenal ulcer, after which the prednisone was tapered and withdrawn. The ulcer was treated with a bland diet and propantheline, a muscarinic antagonist. The patient developed blurred vision, paralytic ileus, confusion, and an atonic bladder, prompting the propantheline to be discontinued. However the obstipation and confusion persisted. Upon admission the patient was found to have the serum sodium of 107 millimoles per liter, a serum potassium of 2.3 millimoles per liter and a BUN of 10 mg per 100 ml. The urine had a pH of 7.5 and a specific gravity of 1.017 and was trace positive for protein. Large quantities of liquids were given by mouth and saline with supplemental potassium chloride was administered intravenously. On the following day the serum sodium was 115 millimoles per liter and the potassium was 2.7 millimoles per liter. The blood urea nitrogen was 9 mg per 100 mL. A 24-hour urine collection revealed the volume of 2050 mL with the sodium content of 191

millimoles and potassium content of 37 millimoles. On the seventh hospital day, he began to have seizures, treated with diphenylhydantoin and amobarbitol. On the 12th hospital day the patient's mental status had improved and the serum sodium had increased to 133 millimoles per liter, while the potassium had increased to 4.9 millimoles per liter. The calculated creatinine clearance was in the normal range. After developing a fever on the 19th hospital day, a repeat chest film now showed a mottled density on the left side behind the cardiac silhouette, not noted on the portable chest x-ray taken at the time of admission. The patient died after a downward course, 21 days after admission. On postmortem examination, a mass was identified in the right upper lobe near the hilus. Microscopic examination demonstrated that it was a typical oat cell carcinoma of the bronchus.

**Discussion**. The diagnosis was the syndrome of inappropriate antidiuresis (SIAD) associated with bronchogenic carcinoma. The chief discussant of this case (Dr. Walter St. Goar) pointed out that many neoplasms can make and secrete antidiuretic substances including vasopressin itself. *Modern studies summarized in the main text have demonstrated that vasopressin increases osmotic water reabsorption in the collecting duct through regulation of the aquaporin-2 water channel.* One commenter indicated surprise that the patient excreted more than 2 L per hour of water despite the presumed high levels of circulating antidiuretic hormones. Dr. Alexander Leaf pointed out that the kidney undergoes a process of "escape" from antidiuresis when antidiuretic hormone is persistently high. *Recent studies in a rat model of SIADH have demonstrated that this escape process occurs through the suppression of AQP2 gene expression in collecting duct cells.*[1]

Dr. Leaf commented that the observed hypokalemia is an atypical manifestation of SIADH and speculated that it could have been owing to the corticosteroids that the patient had received for pruritus. *We know now that agents that are nominally glucocorticoids can, at high very doses, bind the mineralocorticoid receptors present in the principal cells of the collecting duct and distal convoluted tubule, accelerating ion transport in these epithelia.*[2] *Isolated perfused tubule studies have demonstrated that mineralocorticoid receptor occupation accelerates potassium secretion into the urine by collecting duct principal cells.*[3] *Vasopressin works synergistically with corticosteroids to accelerate both sodium reabsorption and potassium secretion in the renal collecting duct.*[4] *The low serum potassium and high urinary potassium documented in this case is therefore consistent with the combined effects of the administered prednisone and the high level of vasopressin resulting from ectopic production by the tumor.*

Treatment of the hyponatremia was seemingly hindered by delayed recognition of the primary disease process and preoccupation with the resulting neurological symptoms. Despite lack of evidence of volume contraction, the patient was administered fluids both orally and intravenously (the latter apparently normal saline supplemented with potassium). As pointed out by the discussant, prior studies had shown that the hyponatremia seen in SIADH is chiefly the result of free water retention rather than a deficiency of total body NaCl. Thus, the first level of therapy in modern treatment of SIADH is fluid restriction.

Case 2**. Severe dilutional hyponatremia complicated by central pontine myelinolysis**

(Condensed from: Telfer RB, Miller EM. Central pontine myelinolysis following hyponatremia, demonstrated by computerized tomography. Ann Neurol. 1979; 6:455-6.)

A 51-year-old woman was admitted to hospital with a chief complaint of extreme weakness for one week prior to admission. She had recently been started on therapy for hypertension (propranolol [80 mg b.i.d.] and hydrochlorothiazide [50 mg b.i.d.] with supplemental potassium chloride. Her only other medication was an unknown sedative. On the day of admission, serum electrolyte values were: sodium, 92 millimoles per liter; potassium, 2.8 millimoles per liter; chloride, 45 millimoles per liter; total $CO_2$, 29 millimoles per liter. The serum osmolality was 197 milliosmoles per kilogram water and the urine osmolality was 348 milliosmoles per kilogram water. The antidiuretic hormone level was 8.1 μU per millilieter (normal range, 0.4 - 5.3 μU per millilieter). She was initially treated with 500 milliliters of 3% NaCl at a rate of 100 mL per hour. Intravenous fluids were restricted to 400 mL of 0.9% sodium chloride per day. By the third day, the serum sodium had increased to 124 millimoles per liter and, by the fifth day, to 137 mmol per liter. During the first week, the patient was lethargic but could talk and move all extremities. However during the second week she developed dysphasia, urinary incontinence and bilateral weakness of all extremities. A computerized tomography (CT) scan, performed 42 days after admission, revealed a circumscribed area of low density in the central portion of the pons anterior to the fourth ventricle. More rostrally, the lesion could be seen as too separate symmetrical lucent zones within rims of enhancement following injection of

contrast medium. Beyond the second week, her neurological symptoms gradually improved. Five weeks after her admission she was able to walk with assistance, but had severe weakness of both upper extremities. At discharge, seven weeks after admission, she could swallow well and could walk independently. Three months later the patient showed continued clinical improvement, but the repeat CT scan showed no change.

**Discussion**. The absence of underlying pulmonary or central nervous system disease, as well as the relatively favorable outcome, points to the likelihood that this case of dilutional hyponatremia was drug-induced. Dilutional hyponatremia is a well-known complication of thiazide diuretic use. The patient had recently begun treatment for hypertension with hydrochlorothiazide, and almost certainly this was the cause of her hyponatremia. *Thiazides directly inhibit sodium chloride transport via the SLC12A3 Na-Cl cotransporter of the distal convoluted tubule (Table 1 of main text). As discussed in the main text, the distal convoluted tubule lacks aquaporins and is the final site of constitutive urinary dilution. Therefore, the use of thiazides can limit urinary diluting ability, accounting in part for the observed SIADH. In addition, recent evidence from studies in humans suggests that thiazides can idiosyncratically stimulate thirst, resulting in primary polydipsia.[5] Polydipsia may be exacerbated by hypokalemia, a common side effect of thiazides that was also seen in this patient. Thus, it seems likely that this patient suffered from a mixed water-balance disorder, combining a loss of urinary diluting ability with primary polydipsia. Beyond this, the excretion of a slightly concentrated urine (urinary osmolality,348 milllisomoles per liter) is indicative of the inappropriate secretion of antidiuretic substances, i.e. true SIADH.*

In addition to thiazides, several other drugs have been associated with dilutional hyponatremia including anti-epileptics (carbamazepine, sodium valproate), antidiabetic drugs (chlorpropamide and metformin), non-seriodal anti-inflammatory drugs, antineoplastic drugs (cyclophosphamide, cisplatin, vinca alkaloids), antidepressants (tricyclics and SSRIs), loop diuretics, oxytocin, and the recreational drug ecstasy.[6] In addition, the vasopressin V2 receptor agonist desmopressin is often used to treat enuresis in children, posing an additional threat of dilutional hyponatremia.[7]

This case illustrates one of the key dangers that the clinician faces in the treatment of severe hyponatremia, namely central pontine myelinolysis. (CPM). Normally, CPM occurs when hyponatremia is corrected too rapidly, greater than 8 mmol per liter per day.[8] In this case, the patient presented with a profound degree of hyponatremia that was rapidly corrected, which undoubtedly contributed to the development of CPM. In cases of thiazide-induced hyponatremia, correction of serum sodium is frequently inadvertently more rapid than intended because the thiazide effects are rapidly reversible.[9] Thus, under similar circumstances, it may be wise to avoid the use of hypertonic saline. This case marks the advent of the use of advanced imaging techniques, here CT imaging and later MRI, in the diagnosis of central pontine myelinolysis. Prior to the late 1970's, the diagnosis could only be confirmed by autopsy.

*Osmotic regulation and cell volume regulation in the brain are important physiologically because of the need to maintain normal intracellular cerebral pressure within the rigid calvarium. The mechanism is believed to involve accumulation of various organic osmolytes, and CPM may occur in part because of slow dynamics of organic osmolyte*

*accumulation and release. Hypothetically, the oliogodendroglia, which are responsible for maintenance of the myelin sheath, are less able to respond to osmotic challenges than are other cell types in the brain.*

Case 3. **Polyuria Associated with Hypokalemia**.

(Condensed from: Kleeman CR, Maxwell MH. Contributory role of extrarenal factors in the polyuria of potassium depletion. **N Engl J Med**. 1959; 260:268-71.)

In April, 1957, a 68-year-old man was admitted to the hospital with a chief complaint of progressive fatigue, weakness, and drowsiness for six months. He reported polyuria and polydipsia of approximately 3 months duration. Four days prior to admission, he awoke with extreme weakness of the lower extremities. The family physician found him to be confused and dehydrated, and he was admitted to a hospital. On admission, he gave a history of eating poorly, weakness, and lack of memory.

Physical examination showed a thin, emaciated man with dryness of the skin and mucous membranes. Aside from dehydration, profound weakness, and hypoactive deep tendon reflexes, the examination was negative. An electrocardiogram taken on admission demonstrated a prolonged QT interval, broad flat T waves and first-degree heart block, consistent with hypokalemia. The serum potassium was 2.5 millimoles per liter and the total $CO_2$ was 36 millimoles per liter, indicative of metabolic alkalosis. He gave a history of taking 150 to 300 mL of milk of magnesia daily for 10 years. Because he had not felt well for the past 6 to 8 months, he added two enemas daily to the cathartic regimen.

Potassium replacement therapy given upon admission resulted in a marked clearing of the sensorium and improved muscle strength. Despite this, there was little early improvement in the abnormal water metabolism. Polyuria continued during the first eight days, the volume of urine ranging from 3 to 9 L per day. Urinary osmolality and specific grant gravity were always markedly hypotonic in spite of the negative water balance. His

sense of thirst seemed inappropriately poor and it was necessary to force the high levels of water intake required to maintain balance. A vasopressin concentration test was performed consisting of intravenous infusion of 200 milliunits of aqueous vasopressin per hour for a five-hour period. The urinary osmolality rose to 548 milliosmoles per kilogram of urinary water with a specific gravity of 1.016. Two hours after the infusion was stopped urinary osmolality fell to 200 milliosmoles per kilogram. These results were interpreted as being consistent with central diabetes insipidus secondary to hypokalemia. The patient was treated with therapeutic doses of aqueous vasopressin given intravenously, resulting in a moderate but distinct reduction in 24-hour urine volumes. The patient was discharged with instructions to take a regular varied diet and to refrain from taking cathartics and enemas.

He was readmitted to the hospital for study in March, 1958. During the interval, he stated that he had taken no enemas or cathartics and eaten quite well. He reported that his polyuria had progressively decreased. During water restriction for 16 hours, urinary osmolality rose to 600 milliosmoles per kilogram of urinary water, and the maximal urinary dilution after 1.5 L oral water load was 100 millimoles per kilogram water.

**Discussion**. The authors of this 1959 case report concluded that the patient had central diabetes insipidus associated with hypokalemia secondary to extrarenal potassium losses. Correction of the hypokalemia resulted in correction of the polyuria, indicating a causal relationship. Polyuria is a frequent accompaniment to hypokalemia. *Animal studies in a mouse model of Gitelman syndrome, which manifests hypokalemia in response to mild potassium restriction, also demonstrated polyuria of a central origin (central diabetes*

*insipidus).*[10] *It is worth noting that when the vasopressin levels in the blood are suppressed over a long period of time, e.g. in central diabetes insipidus or compulsive water drinking, the content of aquaporin-2 in the kidney can be expected to be suppressed.*[11] *Animal studies in rats manifesting central diabetes insipidus demonstrate total aquaporin-2 protein levels less than 10% that of vasopressin replete rats.*[12] *Several days of vasopressin infusion are required to restore aquaporin-2 levels.*[13] *The implication is that either central diabetes insipidus or compulsive water drinking can be expected to be accompanied by a form of physiological nephrogenic diabetes insipidus due to renal aquaporin-2 depletion.* As was seen in this case of hypokalemia-induced central diabetes insipidus, short-term administration of vasopressin does not completely restore concentrating ability. Animal models of chronic hypokalemia consistently manifest reduced levels of aquaporin-2,[14,15], despite the fact that polyuria is ultimately the consequence of central diabetes insipidus.

Case 4. ***Extreme polyuria associated with obstructive uropathy***.

(Condensed from: Earley LE. Extreme polyuria in obstructive uropathy; report of a case of water-losing nephritis in an infant, with a discussion of polyuria. **N Engl J Med**. 1956; 255: 600-5)

A six-month old black male was hospitalized for evaluation of persistent urinary tract infection and polyuria. At seven weeks of age he had been hospitalized with fever and pyuria. He was treated with antibiotics and discharged. However he continued to experience pyuria with concomitant polyuria and polydipsia. Upon admission, physical examination revealed a distended urinary bladder. Cystoscopy on the seventh hospital day showed hypertrophied musculature of the bladder neck. A suprapubic cystotomy was performed and the internal urethral orifice was found to be partially occluded by hypertrophic tissue. A wedge resection of the tissue established free drainage. At discharge on day 42, he was afebrile although he continued to display other manifestations of urinary tract infection as well as abnormally high daily intake of fluid and output of urine. By 14 months of age, the polyuria and polydipsia had resolved.

**Discussion**. Polyuria and polydipsia are common manifestations of neonatal obstructive uropathy. *Studies in animal models with either bilateral or unilateral ureteral obstruction have demonstrated that the resulting polyuria is due to a loss of aquaporin-2 protein in the obstructive kidney.*[16] In this case, the polyuria did not resolve immediately upon release of the obstruction, but did resolve within a few months. *Similarly, in animal models, reversal of ureteral obstruction is not accompanied by immediate recovery of renal aquaporin-2 levels, but requires days to weeks for recovery,*[17] *perhaps suggesting that*

*structural changes or inflammation may be involved in the pathophysiology of polyuria in this setting. Consistent with that view, anti-inflammatory agents such as cyclooxygenase-2 inhibitors[18] and $\alpha$-MSH[19] have been shown to abrogate the obstruction induced decrease in renal aquaporin-2 abundance . Interestingly, candesartan (an angiotensin receptor blocker) prevented the reduction in aquaporin-2 protein levels in obstructed kidneys, possibly through effects on cyclo-xygenase 2 activity.[20]*

Case 5. **Polyuria associated with hypercalcemia and a pelvic mass in a 22-year-old woman**.

(Condensed from: Young RH, Goodman A, Penson RT, Russell AH, Uppot RN, Tambouret RH. Case records of the Massachusetts General Hospital. Case 8-2010. A 22-year-old woman with hypercalcemia and a pelvic mass. **N Engl J Med.** 2010 Mar 18;362(11):1031-40.)

A 22-year-old woman was admitted to hospital because of hypercalcemia and a pelvic mass. The patient had been well one month before admission when she developed right lower quadrant pain that progressively increased in severity. During the same interval, she experienced increased thirst, polyuria, fatigue, anorexia, and nausea. Upon admission her serum calcium was 17.2 mg/dL. Serum parathyroid hormone level was suppressed while the parathyroid hormone-related protein level was markedly elevated, providing an explanation for her hypercalcemia. A large pelvic mass was readily palpable on pelvic examination. Furosemide, magnesium sulfate, potassium phosphate, and potassium chloride were administered intravenously. Serum calcium fell to 11.6 mg/dL 15 hours after admission. Surgical exploration revealed a large mass involving the left ovary. The mass was resected. Pathologic examination revealed and ovarian small cell carcinoma of the hypercalcemia type. The patient was treated with cisplatin and etoposide supplemented with paclitaxel. She was discharged after the first cycle of chemotherapy on the 12th hospital day and receive subsequent cycles as an outpatient. At the point of the case report she was in remission 24 months after the initial presentation.

**Discussion**. Hypercalcemia with polyuria and polydipsia are frequently seen in a variety of malignancies either due to bone metastases or ectopic secretion of hypercalcemia substances, most frequently parathyroid hormone-related protein. In this case, the hypercalcemia was apparently a result of the latter mechanism. In the absence of bone metastases, therefore, the serum calcium and urinary water excretion rate can be expected to normalize rapidly after tumor resection, as was apparently true in this case. Animal studies of hypercalcemia induced vitamin D administration demonstrated that the development of polyuria is associated with both suppression of aquaporin-2 trafficking to the plasma membrane and a marked decrease in the abundance of aquaporin-2 in collecting duct cells in rats.[21] Aquaporin-2 trafficking to the plasma membrane is dependent on calcium signaling in the collecting duct cell,[22] which is presumably disrupted with hypercalcemia. In addition, hypercalcemia can inhibit active Na-Cl reabsorption in the thick ascending limb of Henle's loop via actions mediated by an abundant G-protein coupled receptor termed the "calcium-sensing receptor" (*Casr*), the same receptor that senses calcium in the parathyroid glands.[23] The consequence is a decline in the osmotic gradient driving water absorption from the collecting ducts.

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