TABLE 63-1 CAUSES OF THE SYNDROME OF INAPPROPRIATE ANTIDIURESIS (SIAD)

Malignant Diseases	Pulmonary Disorders	Disorders of the Central Nervous System	Drugs	Other Causes
Carcinoma	Infections	Infection	Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Lung	Bacterial pneumonia	Encephalitis	Chlorpropamide	Idiopathic
Small cell	Viral pneumonia	Meningitis	SSRIs	Transient
Mesothelioma	Pulmonary abscess	Brain abscess	Tricyclic antidepressants	Endurance exercise
Oropharynx	Tuberculosis	Rocky Mountain spotted fever	Clofibrate	General anesthesia
Gastrointestinal tract	Aspergillosis	AIDS	Carbamazepine	Nausea
Stomach	Asthma	Bleeding and masses	Vincristine	Pain
Duodenum	Cystic fibrosis	Subdural hematoma	Nicotine	Stress
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage	Narcotics	
Genitourinary tract		Cerebrovascular accident	Antipsychotic drugs	
Ureter		Brain tumors	Ifosfamide	
Bladder		Head trauma	Cyclophosphamide	
Prostate		Hydrocephalus	Nonsteroidal anti-inflammatory drugs	
Endometrium		Cavernous sinus thrombosis	MDMA ("ecstasy")	
Endocrine thymoma		Other	AVP analogues	
Lymphomas		Multiple sclerosis	Desmopressin	
Sarcomas		Guillain-Barré syndrome	Oxytocin	
Ewing's sarcoma		Shy-Drager syndrome	Vasopressin	
		Delirium tremens		
		Acute intermittent porphyria		

Abbreviations: AVP, vasopressin; MDMA; 3,4-methylenedioxymethamphetamine; SSRI, selective serotonin reuptake inhibitor.

Source: From DH Ellison, T Berl: Syndrome of inappropriate antidiuresis. N Engl J Med 356:2064, 2007.

circulating AVP, suggesting either a gain in function in renal water reabsorption or a circulating antidiuretic substance that is distinct from AVP. Gain-in-function mutations of a single specific residue in the V_2 AVP receptor have been described in some of these patients, leading to constitutive activation of the receptor in the absence of AVP and "nephrogenic" SIAD.

Strictly speaking, patients with SIAD are not euvolemic but are subclinically volume-expanded, due to AVP-induced water and Na^+-Cl^- retention; "AVP escape" mechanisms invoked by sustained increases in AVP serve to limit distal renal tubular transport, preserving a modestly hypervolemic steady state. Serum uric acid is often low (<4 mg/dL) in patients with SIAD, consistent with suppressed proximal tubular transport in the setting of increased distal tubular Na^+-Cl^- and water transport; in contrast, patients with hypovolemic hyponatremia will often be hyperuricemic, due to a shared activation of proximal tubular Na^+-Cl^- and urate transport.

Common causes of SIAD include pulmonary disease (e.g., pneumonia, tuberculosis, pleural effusion) and central nervous system (CNS) diseases (e.g., tumor, subarachnoid hemorrhage, meningitis). SIAD also occurs with malignancies, most commonly with small-cell lung carcinoma (75% of malignancy-associated SIAD); ~10% of patients with this tumor will have a plasma Na^+ concentration of <130 m*M* at presentation. SIAD is also a frequent complication of certain drugs, most commonly the selective serotonin reuptake inhibitors (SSRIs). Other drugs can potentiate the renal effect of AVP, without exerting direct effects on circulating AVP levels (Table 63-1).

Low Solute Intake and Hyponatremia Hyponatremia can occasionally occur in patients with a very low intake of dietary solutes. Classically, this occurs in alcoholics whose sole nutrient is beer, hence the diagnostic label of *beer potomania*; beer is very low in protein and salt content, containing only 1–2 m*M* of Na^+. The syndrome has also been described in nonalcoholic patients with highly restricted solute intake due to nutrient-restricted diets, e.g., extreme vegetarian diets. Patients with hyponatremia due to low solute intake typically present with a very low urine osmolality (<100–200 mOsm/kg) with a urine Na^+ concentration that is <10–20 m*M*. The fundamental abnormality is the inadequate dietary intake of solutes; the reduced urinary solute excretion limits water excretion such that hyponatremia ensues after relatively modest polydipsia. AVP levels have not been reported in patients with beer potomania but are expected to be suppressed or rapidly suppressible with saline hydration; this fits with the overly rapid correction in plasma Na^+ concentration that can be seen with saline hydration. Resumption of a normal diet and/or saline hydration will also correct the causative deficit in urinary solute excretion, such that patients with beer potomania typically correct their plasma Na^+ concentration promptly after admission to the hospital.

Clinical Features of Hyponatremia Hyponatremia induces generalized cellular swelling, a consequence of water movement down the osmotic gradient from the hypotonic ECF to the ICF. The symptoms of hyponatremia are primarily neurologic, reflecting the development of cerebral edema within a rigid skull. The initial CNS response to acute hyponatremia is an increase in interstitial pressure, leading to shunting of ECF and solutes from the interstitial space into the cerebrospinal fluid and then on into the systemic circulation. This is accompanied by an efflux of the major intracellular ions, Na^+, K^+, and Cl^-, from brain cells. Acute hyponatremic encephalopathy ensues when these volume regulatory mechanisms are overwhelmed by a rapid decrease in tonicity, resulting in acute cerebral edema. Early symptoms can include nausea, headache, and vomiting. However, severe complications can rapidly evolve, including seizure activity, brainstem herniation, coma, and death. A key complication of acute hyponatremia is normocapneic or hypercapneic respiratory failure; the associated hypoxia may amplify the neurologic injury. Normocapneic respiratory failure in this setting is typically due to noncardiogenic, "neurogenic" pulmonary edema, with a normal pulmonary capillary wedge pressure.

Acute symptomatic hyponatremia is a medical emergency, occurring in a number of specific settings (Table 63-2). Women, particularly before menopause, are much more likely than men to develop encephalopathy and severe neurologic sequelae. Acute hyponatremia often has an iatrogenic component, e.g., when hypotonic intravenous fluids are given to postoperative patients with an increase in circulating AVP. Exercise-associated hyponatremia, an important clinical issue at