however, potassium excess and potassium restriction have opposing, aldosterone-independent effects on the density and activity of apical K^+ channels in the distal nephron, i.e., factors other than aldosterone modulate the renal capacity to secrete K^+. In addition, potassium restriction and hypokalemia activates aldosterone-independent distal *reabsorption* of filtered K^+, activating apical H^+/K^+-ATPase activity in intercalated cells within the outer medullary CD. Reflective perhaps of this physiology, changes in plasma K^+ concentration are not universal in disorders associated with changes in aldosterone activity.

HYPOKALEMIA

Hypokalemia, defined as a plasma K^+ concentration of <3.5 m*M*, occurs in up to 20% of hospitalized patients. Hypokalemia is associated with a 10-fold increase in in-hospital mortality, due to adverse effects on cardiac rhythm, blood pressure, and cardiovascular morbidity. Mechanistically, hypokalemia can be caused by redistribution of K^+ between tissues and the ECF or by renal and nonrenal loss of K^+ (Table 63-4). Systemic hypomagnesemia can also cause treatment-resistant hypokalemia, due to a combination of reduced cellular uptake of K^+ and exaggerated renal secretion. Spurious hypokalemia or "pseudohypokalemia" can occasionally result from in vitro cellular uptake of K^+ after venipuncture, for example, due to profound leukocytosis in acute leukemia.

Redistribution and Hypokalemia Insulin, β_2-adrenergic activity, thyroid hormone, and alkalosis promote Na^+/K^+-ATPase-mediated cellular uptake of K^+, leading to hypokalemia. Inhibition of the passive *efflux* of K^+ can also cause hypokalemia, albeit rarely; this typically occurs in the setting of systemic inhibition of K^+ channels by toxic barium ions. Exogenous insulin can cause iatrogenic hypokalemia, particularly during the management of K^+-deficient states such as diabetic ketoacidosis. Alternatively, the stimulation of *endogenous* insulin can provoke hypokalemia, hypomagnesemia, and/or hypophosphatemia in malnourished patients given a carbohydrate load. Alterations in the activity of the endogenous sympathetic nervous system can cause hypokalemia in several settings, including alcohol withdrawal, hyperthyroidism, acute myocardial infarction, and severe head injury. β_2 agonists, including both bronchodilators and tocolytics (ritodrine), are powerful activators of cellular K^+ uptake; "hidden" sympathomimetics, such as pseudoephedrine and ephedrine in cough syrup or dieting agents, may also cause unexpected hypokalemia. Finally, xanthine-dependent activation of cAMP-dependent signaling, downstream of the β_2 receptor, can lead to hypokalemia, usually in the setting of overdose (theophylline) or marked overingestion (dietary caffeine).

Redistributive hypokalemia can also occur in the setting of hyperthyroidism, with periodic attacks of hypokalemic paralysis (thyrotoxic periodic paralysis [TPP]). Similar episodes of hypokalemic weakness in the absence of thyroid abnormalities occur in *familial* hypokalemic periodic paralysis, usually caused by missense mutations of voltage sensor domains within the α_1 subunit of L-type calcium channels or the skeletal Na^+ channel; these mutations generate an abnormal gating pore current activated by hyperpolarization. TPP develops more frequently in patients of Asian or Hispanic origin; this shared predisposition has been linked to genetic variation in Kir2.6, a muscle-specific, thyroid hormone–responsive K^+ channel. Patients with TPP typically present with weakness of the extremities and limb girdles, with paralytic episodes that occur most frequently between 1 and 6 AM. Signs and symptoms of hyperthyroidism are not invariably present. Hypokalemia is usually profound and almost invariably accompanied by hypophosphatemia and hypomagnesemia. The hypokalemia in TPP is attributed to both direct and indirect activation of the Na^+/K^+-ATPase, resulting in increased uptake of K^+ by muscle and other tissues. Increases in β-adrenergic activity play an important role in that high-dose propranolol (3 mg/kg) rapidly reverses the associated hypokalemia, hypophosphatemia, and paralysis.

Nonrenal Loss of Potassium The loss of K^+ in sweat is typically low, except under extremes of physical exertion. Direct gastric losses of K^+ due to vomiting or nasogastric suctioning are also minimal; however, the ensuing hypochloremic alkalosis results in persistent kaliuresis due to secondary hyperaldosteronism and bicarbonaturia, i.e., a *renal* loss of K^+. Diarrhea is a globally important cause of hypokalemia, given the worldwide prevalence of infectious diarrheal disease. Noninfectious gastrointestinal processes such as celiac disease, ileostomy, villous adenomas, inflammatory bowel disease, colonic pseudo-obstruction (Ogilvie's syndrome), VIPomas, and chronic laxative abuse can also cause significant hypokalemia; an exaggerated intestinal secretion of potassium by upregulated colonic BK channels has been directly implicated in the pathogenesis of hypokalemia in many of these disorders.

Renal Loss of Potassium Drugs can increase renal K^+ excretion by a variety of different mechanisms. Diuretics are a particularly common cause, due to associated increases in distal tubular Na^+ delivery and

TABLE 63-4 CAUSES OF HYPOKALEMIA

- I. Decreased intake
  - A. Starvation
  - B. Clay ingestion
- II. Redistribution into cells
  - A. Acid-base
    - 1. Metabolic alkalosis
  - B. Hormonal
    - 1. Insulin
    - 2. Increased β_2-adrenergic sympathetic activity: post–myocardial infarction, head injury
    - 3. β_2-Adrenergic agonists – bronchodilators, tocolytics
    - 4. α-Adrenergic antagonists
    - 5. Thyrotoxic periodic paralysis
    - 6. Downstream stimulation of Na^+/K^+-ATPase: theophylline, caffeine
  - C. Anabolic state
    - 1. Vitamin B_{12} or folic acid administration (red blood cell production)
    - 2. Granulocyte-macrophage colony-stimulating factor (white blood cell production)
    - 3. Total parenteral nutrition
  - D. Other
    - 1. Pseudohypokalemia
    - 2. Hypothermia
    - 3. Familial hypokalemic periodic paralysis
    - 4. Barium toxicity: systemic inhibition of "leak" K^+ channels
- III. Increased loss
  - A. Nonrenal
    - 1. Gastrointestinal loss (diarrhea)
    - 2. Integumentary loss (sweat)
  - B. Renal
    - 1. Increased distal flow and distal Na^+ delivery: diuretics, osmotic diuresis, salt-wasting nephropathies
    - 2. Increased secretion of potassium
      - a. Mineralocorticoid excess: primary hyperaldosteronism (aldosterone-producing adenomas, primary or unilateral adrenal hyperplasia, idiopathic hyperaldosteronism due to bilateral adrenal hyperplasia, and adrenal carcinoma), genetic hyperaldosteronism (familial hyperaldosteronism types I/II/III, congenital adrenal hyperplasias), secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia), Cushing's syndrome, Bartter's syndrome, Gitelman's syndrome
      - b. Apparent mineralocorticoid excess: genetic deficiency of 11β-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess), inhibition of 11β-dehydrogenase-2 (glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone; licorice, food products, drugs), Liddle's syndrome (genetic activation of epithelial Na^+ channels)
      - c. Distal delivery of nonreabsorbed anions: vomiting, nasogastric suction, proximal renal tubular acidosis, diabetic ketoacidosis, glue-sniffing (toluene abuse), penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin)
    - 3. Magnesium deficiency