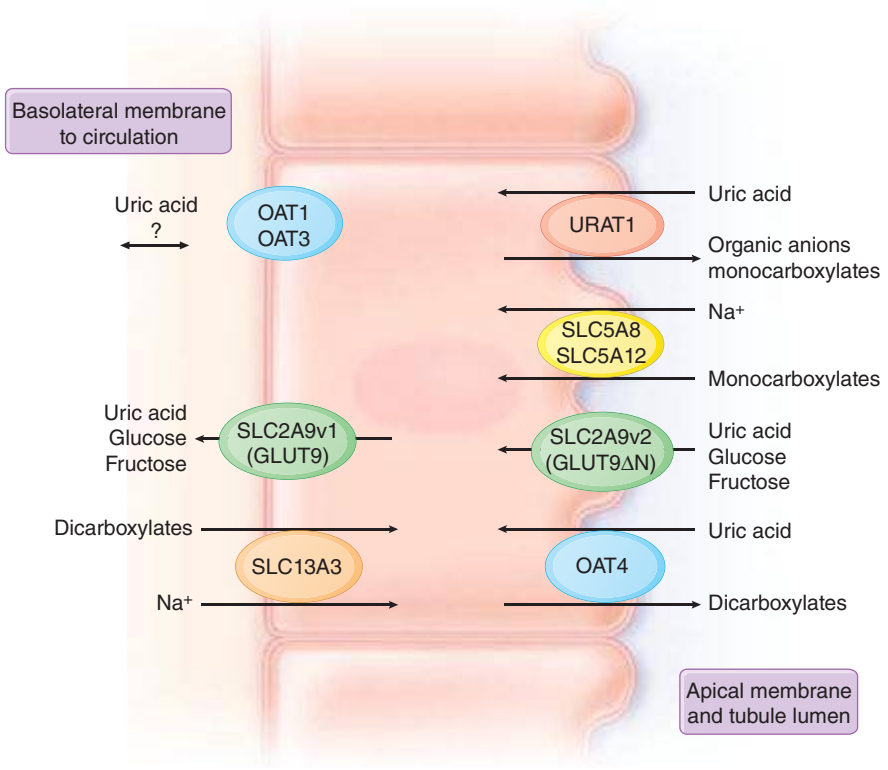

FIGURE 431e-2 Schematic for handling of uric acid by the kidney. A complex interplay of transporters on both the apical and basolateral aspects of the renal tubule epithelial cell is involved in the reabsorption of uric acid. See text for details. Most uricosuric compounds inhibit URAT1 on the apical side, as well as OAT1, OAT3, and GLUT9 on the basolateral side.

(~1 mg/dL) and urinary uric acid excretion by ~1.2 mmol/d (~200 mg/d). Foods high in nucleic acid content include liver, "sweetbreads" (i.e., thymus and pancreas), kidney, and anchovy.

Endogenous sources of purine production also influence the serum urate level (Fig. 431e-3). De novo purine biosynthesis is a multistep process that forms inosine monophosphate (IMP). The rates of purine biosynthesis and urate production are predominantly determined by amidophosphoribosyltransferase (amidoPRT), which combines phosphoribosylpyrophosphate (PRPP) and glutamine. A secondary regulatory pathway is the salvage of purine bases by hypoxanthine phosphoribosyltransferase (HPRT). HPRT catalyzes the combination of the purine bases hypoxanthine and guanine with PRPP to form the respective ribonucleotides IMP and guanosine monophosphate (GMP).

TABLE 431e-1 MEDICATIONS WITH URICOSURIC ACTIVITY

Acetohexamide	Glyceryl guaiacolate
Adrenocorticotropic hormone	Glycopyrrolate
Ascorbic acid	Halofenate
Azauridine	Losartan
Benzbromarone	Meclofenamate
Calcitonin	Phenolsulfonphthalein
Chlorprothixene	Phenylbutazone
Citrate	Probenecid
Dicumarol	Radiographic contrast agents
Diflunisal	Salicylates (>2 g/d)
Estrogens	Sulfinpyrazone
Fenofibrate	Tetracycline that is outdated
Glucocorticoids	Zoxazolamine

Serum urate levels are closely coupled to the rates of de novo purine biosynthesis, which is driven in part by the level of PRPP, as evidenced by two X-linked inborn errors of purine metabolism (Table 431e-3). Both increased PRPP synthetase activity and HPRT deficiency are associated with overproduction of purines, hyperuricemia, and hyperuricaciduria (see below for clinical descriptions).

Accelerated purine nucleotide degradation can also cause hyperuricemia—i.e., with conditions of rapid cell turnover, proliferation, or cell death, as in leukemic blast crises, cytotoxic therapy for malignancy, hemolysis, or rhabdomyolysis. Hyperuricemia can result from excessive degradation of skeletal muscle ATP after strenuous physical exercise or status epilepticus and in glycogen storage disease types III, V, and VII (Chap. 433e). The hyperuricemia of myocardial infarction, smoke inhalation, and acute respiratory failure may also be related to accelerated breakdown of ATP.

Decreased Uric Acid Excretion More than 90% of individuals with sustained hyperuricemia have a defect in the renal handling of uric acid. For any given plasma urate concentration, patients who have gout excrete ~40% less uric acid than those who do not. When plasma urate levels are raised by purine ingestion or infusion, uric acid excretion increases in patients with and without gout; however, in those with gout, plasma urate concentrations must be 60–120 μmol/L (1–2 mg/dL) higher than normal to achieve equivalent uric acid excretion rates.

Diminished uric acid excretion could theoretically result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption. Decreased urate filtration does not appear to cause primary hyperuricemia but does contribute to the hyperuricemia of renal insufficiency. Although hyperuricemia is invariably present in chronic renal disease, the correlation among

TABLE 431e-2 CLASSIFICATION OF HYPERURICEMIA BY PATHOPHYSIOLOGY

Urate Overproduction		
Primary idiopathic	Myeloproliferative diseases	Rhabdomyolysis
HPRT deficiency	Polycythemia vera	Exercise
PRPP synthetase overactivity	Psoriasis	Alcohol
Hemolytic processes	Paget's disease	Obesity
Lymphoproliferative diseases	Glycogenosis III, V, and VII	Purine-rich diet
Decreased Uric Acid Excretion		
Primary idiopathic	Starvation ketosis	Drug ingestion
Renal insufficiency	Berylliosis	Salicylates (<2 g/d)
Polycystic kidney disease	Sarcoidosis	Diuretics
Diabetes insipidus	Lead intoxication	Alcohol
Hypertension	Hyperparathyroidism	Levodopa
Acidosis	Hypothyroidism	Ethambutol
Lactic acidosis	Toxemia of pregnancy	Pyrazinamide
Diabetic ketoacidosis	Bartter's syndrome	Nicotinic acid
	Down syndrome	Cyclosporine
Combined Mechanism		
Glucose-6-phosphatase deficiency	Fructose-1-phosphate aldolase deficiency	Alcohol
		Shock

Abbreviations: HPRT, hypoxanthine phosphoribosyltransferase; PRPP, phosphoribosylpyrophosphate.