In 1915, Bertram Welton Sippy introduced a Chicago cocktail to treat gastric and duodenal ulcers with hourly administration of milk, cream, eggs, and farina cereals, the Sippy diet, interrupted on the half-hour by a regimen of alkali comprising calcinated magnesia, sodium bicarbonate, and bismuth subcarbonate, which were known then as Sippy powders. As the Sippy method gained popularity, some patients developed toxic manifestations including a strong distaste for milk, headache, nausea, vomiting, mental clouding, and renal failure that eventually came to be known as the milk-alkali syndrome from the work of Burnett. The earlier milk-alkali syndrome using the Sippy diet often presented with hyperphosphatemia after prolonged ingestion of phosphorus-containing milk with cream. In contrast, the modern version of calcium-alkali syndrome associates with hypophosphatemia or low-normal serum phosphorus levels as a result of the phosphorus-binding properties of calcium carbonate. This hypophosphatemia is more pronounced in elderly patients or those with eating disorders, who tend to have relatively low consumption of protein and therefore phosphorus; low phosphate levels stimulate the renal metabolism of calcitriol and, consequently, absorption of calcium by the gut. Levels of 1,25-hydroxyvitamin D in patients with the calcium-alkali syndrome, of course, are generally low in the setting of hypercalcemia, although some are in the low-normal range and perhaps inappropri...
ately high.\textsuperscript{7,11,14} These latter levels may depend on previous exposure to vitamin D supplementation, because vitamin D is often added to some over-the-counter calcium preparations, but more epidemiology is needed to clarify this exposure.

Whereas the milk-alkali syndrome from the Sippy diet tended to affect men with peptic ulcer disease, the demographic risk today for the calcium-alkali syndrome has changed in favor of postmenopausal women, pregnant women, transplant recipients, patients with bulimia, and those who are on dialysis.\textsuperscript{7,11,14,17} Older patients with aging bone metabolism are susceptible to targeted advertising for their health care advice regarding the use of calcium supplements for the treatment of osteoporosis.\textsuperscript{18,19} Pregnant women have an increased susceptibility to developing calcium-alkali syndrome as a result of hyperemesis, causing volume depletion and enhanced calcium absorption through the gut, possibly aggravated by prolactin or placental lactogen signaling.\textsuperscript{20} Patients with anorexia nervosa occasionally have food fetishes rich in calcium,\textsuperscript{10,21} and cardiac transplant patients are sometimes given calcium carbonate.\textsuperscript{17} Dialysis patients who ingest large amounts of magnesium oxide and calcium carbonate also develop calcium-alkali syndrome,\textsuperscript{9} as can betel nut chewers in Asia because betel nuts are often blended with a lime paste made from ground oyster shells containing calcium oxide and calcium hydroxide.\textsuperscript{22} Several other medications, including aluminum hydroxide and magnesium hydroxide, provide a source of absorbable alkali in patients with calcium-alkali syndrome who also ingest large doses of calcium.\textsuperscript{23} Thiazide use predisposes to calcium-alkali syndrome by enhancing renal calcium absorption by causing volume depletion and thereby promoting alkalosis. Furthermore, angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs associate with calcium-alkali syndrome by reducing GFR, which reduces calcium excretion.\textsuperscript{14}

The pathogenesis of calcium-alkali syndrome is intricate and involves the interplay of multiple systems, including bone, intestine, and kidney.\textsuperscript{14,24} The average healthy adult contains approximately 1 kg of calcium (or 25,000 mmol), with >99% found in bone and <1% (20 mmol) in the extracellular fluid.\textsuperscript{24} Once calcium is absorbed through the gut and into the extracellular fluid space, the bone reservoir provides the principal site for buffering excess calcium. In elderly individuals, however, the net flux of calcium is out of bone, thereby making bone less functional as a reservoir; these patients are more susceptible to the syndrome when they begin taking supplemental calcium and alkali.\textsuperscript{14} Although the data are scant, levels of 1,25-hydroxyvitamin D tend to be suppressed but not in all patients.\textsuperscript{11,14} Factors affecting the amount of calcium absorption include dietary intake, levels of 1,25-hydroxyvitamin D, and gastric acidity.\textsuperscript{25} The amount of supplemental calcium generally considered to predispose to calcium-alkali syndrome is >4 g/d; however, there are reports that 1.0 to 1.5 g of calcium supplementation produce this syndrome.\textsuperscript{7,11} Nevertheless, when ingested levels of calcium are high, movement across the gut tends to be passive rather than regulated by 1,25-hydroxyvitamin D.\textsuperscript{26,27} Table 1 shows the amount of elemental calcium contained in various popular calcium supplements.

<table>
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<th>Type</th>
<th>Trade Name</th>
<th>Elemental Calcium (mg)</th>
<th>Vitamin D (IU)</th>
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<tr>
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<tr>
<td>Calcium acetate</td>
<td>Phosio</td>
<td>167</td>
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</table>

Table 1. Amount of elemental calcium in various supplements

Calcium-Alkali Syndrome
calcium influx. In the collecting duct system, luminal activation of CaSR as a result of excess luminal calcium concentration enhances both H+/H1001-ATPase pump activity and the downregulation of aquaporin 2 expression, leading to urinary acidification, systemic HCO3/H1002 generation, and polyuria. These latter effects have been proposed as a mechanism that normally protects the kidney from calcification induced by hypercalciuria but would tend to foster volume depletion and metabolic alkalosis. This latter hypothesis regarding hypercalciuria is controversial.

The main therapy for the calcium-alkali syndrome is volume expansion with saline to break the self-propagating reaction cycle induced by exposure to calcium alkali. Given that excess ingestion of calcium with or without vitamin D is an integral feature of this syndrome, the obvious preventive strategy is to limit intake of elemental calcium to no more than 1.2 to 1.5 g/d and to avoid ingesting alkali to reduce the risk that alkalemia will further predispose to calcium-alkali syndrome.

DISCLOSURES
None.

REFERENCES
1. Sippy BW: Gastric and duodenal ulcer: Medical cure by efficient removal of gastric juice corrosion. JAMA 64: 1625–1630, 1915

Figure 1. Mechanisms for renal calcium transport depend on the location of the CaSR and TRPV5 channel. (A) Thick ascending loop of Henle. (B) Distal convoluted tubule. NKCC, sodium-potassium-2-chloride co-transporter; ROM-K, renal outer medullary potassium channel; NaKATPase, sodium-potassium ATPase; +, stimulates; −, inhibits; NCC, sodium chloride co-transporter; NCX, sodium-calcium exchanger.