

continued lithium treatment, remitting and recurring when lithium is stopped and restarted. The parathyroid adenomas reported in some hypercalcemic patients with lithium therapy may reflect the presence of an independently occurring parathyroid tumor; a permanent effect of lithium on parathyroid gland growth need not be implicated as most patients have complete reversal of hypercalcemia when lithium is stopped. However, long-standing stimulation of parathyroid cell replication by lithium may predispose to development of adenomas (as is documented in secondary hyperparathyroidism and renal failure).

At the levels achieved in blood in treated patients, lithium can be shown in vitro to shift the PTH secretion curve to the right in response to calcium; i.e., higher calcium levels are required to lower PTH secretion, probably acting at the calcium sensor (see below). This effect can cause elevated PTH levels and consequent hypercalcemia in otherwise normal individuals. Fortunately, there are usually alternative medications for the underlying psychiatric illness. Parathyroid surgery should not be recommended unless hypercalcemia and elevated PTH levels persist after lithium is discontinued.

■ GENETIC DISORDERS CAUSING HYPERPARATHYROIDISM-LIKE SYNDROMES

Familial Hypocalciuric Hypercalcemia FHH (also called *familial benign hypercalcemia*) is inherited as an autosomal dominant trait. Affected individuals are discovered because of asymptomatic hypercalcemia. Most cases of FHH (FHH1) are caused by an inactivating mutation in a single allele of the CaSR (see below), leading to inappropriately normal or even increased secretion of PTH, whereas another hypercalcemic disorder, namely the exceedingly rare Jansen's disease, is caused by a constitutively active PTH/PTHrP receptor in target tissues. Neither FHH1 nor Jansen's disease, however, is a growth disorder of the parathyroids. Other forms of FHH are caused either by heterozygous mutations in *GNA11* (encoding Gα11), one of the signaling proteins at the CaSR (FHH2), or by heterozygous mutations in *AP1A1* (FHH3).