The introduction of multichannel serum biochemistry testing in the early 1970s uncovered a large number of patients with primary hyperparathyroidism who were asymptomatic, turning an extremely rare and severe disease into a fairly common and benign condition (1). The diagnosis of primary hyperparathyroidism—whether symptomatic or not—still requires hypercalcemia along with an elevated intact parathyroid hormone (PTH) level (2). Recently, endocrinologists have become aware of patients with normocalcemic primary hyperparathyroidism. This entity has not been characterized systematically, and it is not yet clear whether this is a “forme fruste” of the disease or a harbinger of the hypercalcemic type (3). The purpose of the present study was to define the characteristics of patients with this diagnosis in one endocrine outpatient clinic during the last 5 years.

METHODS

We reviewed medical records of patients with a diagnosis of primary hyperparathyroidism (International Classification of Diseases, Ninth Revision, code 252.0) seen in the endocrine clinic at Tel Aviv Sourasky Medical Center between January 1998 and October 2003. (Institutional review board approval was not required for this study.) The diagnosis of normocalcemic primary hyperparathyroidism was confirmed if a patient had never had documented hypercalcemia, and if all apparent causes of secondary hyperparathyroidism had been ruled out. Specifically, patients with impaired renal function, and those in whom vitamin D supplementation unmasked hypercalcemia, were excluded. Patients in whom elevated PTH levels decreased following treatment (vitamin D or calcium supplementation, or thiazides) were considered to have secondary hyperparathyroidism and thus were not eligible. We identified 32 patients who met these criteria.

Serum calcium levels were determined on a Hitachi 747 random-access analyzer (Roche Diagnostics Boehringer Mannheim, Mannheim, Germany) or a Bayer Advia 1650 analyzer (Leverkusen, Germany) with identical analytical performances; the normal range was 8.5 to 10.5 mg/dL. Plasma intact PTH level was measured with a solid-phase, two-site chemiluminescent enzyme-labeled immunometric assay (Immulite Intact PTH; Diagnostic Products Corporation, Los Angeles, California). Serum concentration of 25-OH-vitamin D was determined by an in-house competitive protein-binding radioassay (4). Concentrations of serum 1,25(OH)₂-vitamin D and urinary deoxypyridinoline were measured using commercially available immunoassays. Creatinine clearance was measured from a 24-hour urine collection.

Bone density was assessed by double-energy X-ray absorptiometry on a Hologic Elite QDR 4500 instrument (Bedford, Massachusetts). Parathyroid imaging was performed with high-resolution ultrasound (ATL HDI 5000 system; Philips Medical Systems, Eindhoven, The Netherlands); a single-isotope, dual-phase sestamibi planar scan with three-dimensional image acquisition (5); or both.

RESULTS

Of the 32 patients with normocalcemic hyperparathyroidism (Table), 1 presented with an abnormally low vitamin D level (7 ng/mL), and 2 others had borderline levels (14.4 and 14.6 ng/mL). However, correction of vitamin D deficiency and supplementation with calcium did not reduce the PTH concentrations in these 3 patients. Six patients presented with some degree of hypercalciuria (>300 mg/24 h); reduction of calcium excretion with thiazide diuretics, and ascertainment of positive calcium balance with appropriate supplementation, did not affect PTH levels. In 17 patients, the diagnosis of hyperparathyroidism was made after finding osteopenia or osteoporosis during routine bone densitometry. Altogether, 77% (20/26) of patients had osteopenia, including 46% (n = 12) with osteoporosis at the lumbar spine. The prevalence of osteopenia at the hip was 64% (16/25), including 36% (n = 9) with osteoporosis.

Three patients were evaluated because an ultrasound examination of the neck disclosed an incidental parathyroid abnormality. Two patients were evaluated because of a borderline serum calcium level (total calcium level of 10.6 and 10.4 mg/dL; corrected calcium level of 10.2 and 9.9 mg/dL; ionized calcium concentration of 4.94 and 4.66 mg/dL).

Other Abnormalities

Other manifestations of hyperparathyroidism were infrequent. Three patients had nephrolithiasis (assessed systematically by ultrasonography) and 2 had peptic ulcer disease. However, 20 patients had hypertension (blood pressure ≥140/90 mm Hg, or treated).

Seven patients had an associated endocrine neoplasm, including 5 with a pituitary adenoma, 1 with an adreno-
Plasminogen activator. The other 2 patients had parathyroid hyperplasia. Serum 1,25 (OH)2-vitamin D (pg/mL) 47.4
Serum 25(OH)-vitamin D (ng/mL)§ 22.7
Femoral neck T-score
Spine T-score

change appreciably (baseline, 9.8 ± 0.5 mg/dL; last
follow-up, 9.9 ± 0.4 mg/dL; P = 0.9) during the follow-up. None of these patients developed hypercalcemia, nor was there a significant change in mean urinary calcium excretion (initial, 201 ± 105 mg/24 h; last follow-up, 238 ± 149 mg/24 h; P = 0.9). Mean PTH levels were also similar (initial, 119 ± 60 pg/mL; last follow-up, 129 ± 28 pg/mL; P = 0.8). Follow-up of the 12 patients who underwent surgery (Figure) showed reductions in PTH levels, serum calcium levels, and urinary calcium excretion rates after surgery.

**DISCUSSION**

In a study of about 5000 postmenopausal women in Sweden who were screened with both serum calcium and PTH levels, Lundgren et al. identified 109 with primary hyperparathyroidism. Thirty (28%) of these were consistently normocalcemic and 40 (37%) had intermittent hyperparathyroidism. Although secondary causes of hyperparathyroidism were not excluded, there was pathological evidence of parathyroid disease in at least some of the normocalcemic patients (7). Of the patholog-
lich specimens obtained from the 57 patients who under- 
went surgery, 16 came from normocalcemic patients, 21 
came from patients with intermittent hypercalcemia, and 
20 came from patients with persistent hypercalcemia.
About 80% of all three groups of patients had parathyroid 
adenomas similar to what we observed. Based on the 
results of primary cell cultures from these tumors, 
the investigators predicted that normocalcemic primary 
hyperparathyroidism would eventually evolve into hy-
percalcemia. In another study (8), 3 of 22 patients with 
hyperparathyroidism who were normocalcemic became 
hypercalcemic during (at most) 1 year of follow-up, 
although it is possible that the 3 patients had intermittent 
hypercalcemia that was missed at baseline. In our series, 
patients who did not undergo surgery were followed for 
up to 13 years, and none became hypercalcemic. Thus, 
based on our experience, normocalcemic primary hyper-
parathyroidism does not appear to be a harbinger of hy-
percalcemic disease.

A majority of our patients were evaluated following the 
finding of decreased bone mass. Thus, the high preva-
ience of osteopenia and osteoporosis likely reflects sam-
ping bias. Indeed, a substantial fraction of patients may 
have normal bone mass, and thus escape attention.

We did not study how normocalcemia was maintained 
despite an elevated PTH level. A recent study by Maruani 
et al suggested that it may be due to generalized tissue 
resistance to PTH (9). However, the marked decrease in 
serum and urinary calcium level that we observed after 
surgery are not consistent with this hypothesis.

In summary, like their hypercalcemic counterparts, 
patients with normocalcemic primary hyperparathyroid-
ism are largely asymptomatic. They usually come to med-
tical in attention in the context of an evaluation for de-
creased bone mass. Nevertheless, they often have 
parathyroid adenomas as well as evidence of metabolic 
abnormalities and other endocrine conditions. Thus, we 
believe this is a bona fide disease. We cannot determine 
whether the patients in our series who underwent surgery 
would have eventually become hypercalcemic; however, 
none of the patients who were followed without surgery 
had any evidence of clinical worsening.

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Manuscript submitted November 12, 2003, and accepted in revised form 

Uncomplicated Alcohol Intoxication in the 
Emergency Department: 
An Analysis of the 
National Hospital 
Ambulatory Medical Care 
Survey

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Between 1992 and 2001, the number of active emer-
gency departments in the United States decreased by 
15% while the total number of emergency depart-
ment visits increased by 20% (1). The resulting 40% increase 
in average visit volume and concomitant increases in patient 
wait times and ambulance diversion rates has raised concern 
among emergency department physicians and hospital ad-
ministrators about potential declines in quality of care (2– 
4), and prompted attempts to identify patients who might 
not require emergency department services (5–8).

Persons who are acutely intoxicated by alcohol are 
commonly cared for in the emergency department. Because alcohol intoxication is usually not life threatening, 
some advocate triage of patients with uncomplicated al-
cohol intoxication to a “sobering center” designed to pro-