Hyperparathyroidism and Cancer

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Hyperparathyroidism is not uncommon. Recently available multichannel autoanalyzers (SMA-12) for routine biochemical scanning, combined with progressively accurate radioimmune assays of parathyroid hormone now reveal that the incidence of parathyroid tumors may be as high as one in two thousand adults.\(^1\)\(^-\)\(^5\)

Disease presentations are protean, producing a wide range of clinical and biochemical abnormalities. Renal lithiasis, hypertension, gout, peptic ulcer, pancreatitis, osteoporosis, psychiatric disorders, myopathy, neonatal tetany, familial and multiple endocrinopathy, pheochromocytoma, thyroid carcinoma especially medullary carcinoma, acute hypercalcemic crisis and, rarely, normocalcemic occult hyperparathyroidism are gradually being recognized as complications or manifestations of the disease.\(^6\)\(^-\)\(^17\)

The coincidence of hyperparathyroidism and cancer poses a critical problem in the differential diagnosis of hypercalcemia. Interest in this association is more than academic. Although hypercalcemia commonly results from metastases eroding bone, it may also be produced by those rare cancers elaborating parathyroid hormone, without demonstrable bone metastases; in the latter case, hypercalcemia can be reversed by treatment of the cancer. The differentiation of "cancer" hypercalcemia, ectopic hyperparathyroidism and primary hyperparathyroidism can be difficult but the sequelae of an incorrect diagnosis, grave. Moreover, primary hyperparathyroidism may co-exist with or mimic cancer. That a potentially curable disease may simulate a disseminated cancer has obvious therapeutic and prognostic significance.\(^18\)\(^-\)\(^23\)

Clinical Material

From 1937 through 1973, 100 patients with pathologically proven parathyroid tumors were detected at Memorial Sloan-Kettering Cancer Center, New York. (Fig. 1.) Three-fourths of these patients were female. The median age at diagnosis was 55 years, an age associated with the development of cancer, as well as postmenopausal osteoporosis. (Fig. 2.) The sharply increased incidence of parathyroid tumors in recent years is related to both clinical interest and the use of routine SMA-12 determinations on all out-patients and hospital admissions. Over 100 new instances of hypercalcemia are now recorded each year, and about 50 patients are presently under study for hyperparathyroidism. One adenoma has been discovered by an

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electrocardiogram, which was indicative of hypercalcemia.

In 34 patients, one-third of the series, cancer was found before, during, or after the removal of a benign parathyroid tumor. Five patients had coincidental thyroid carcinoma of the mixed papillary type; none were medullary. (Table 1.) Thirty-eight patients had benign tumors at various sites. (Table 2.) Thirty-three had benign giant cell tumors or osteoclastomas, giant cell epulis, and pathological fractures due to the hyperparathyroidism. (Table 3.) With such a spectrum of conditions, often of formidable appearance, it is fortunate that so many patients were eventually proven not to have a fatal disseminated disease.

**Symptoms and Signs**

In the early years of the study, when diagnostic methods were not as sophisticated as today, parathyroid tumors were three to five centimeters in average size at diagnosis and were often palpable...
prior to surgery. Extensive bone and renal disease were common. In recent years, adenomas are one to two centimeters in average size, and symptoms are minimal, if present at all. The discovery of a lump in the neck is now uncommon. (Table 4.) Serum calcium levels cannot be correlated with tumor size, but the extent and severity of systems involved and the level of parathyroid hormone appear to be related. Younger patients tend to have more aggressive disease.

**Laboratory Findings**

Ninety-one patients had proven hypercalcemia, 64 had hypophosphatemia, and 65 had hypercalcuria. Elevated alkaline phosphatase was present in 36 patients, one-third of these had transient tetany postoperatively due to the "hungry bones" of extensive osteoporosis. Elevated uric acid was noted in 17 patients. Several isolated examples of normal and near-normal serum and urinary calcium in some of these patients were reported. Not every patient, particularly during the earlier years, underwent all of these laboratory procedures.

The current minimal investigation for hypercalcemia at Memorial Hospital includes serial calcium, phosphorus, alkaline phosphatase and urinary calcium determinations on a three-day, low-calcium diet. Serum calcium levels should be drawn in a fasting state and, most importantly, corrected for any abnormality of serum protein level. Urinary phosphorus and creatinine excretion are helpful. Serum creatinine, blood urea nitrogen and uric acid are important in gauging renal function. Hyperchloremic acidosis is common. A skeletal survey for osteoporosis should be done, but this is frequently negative; only 13 patients had a positive study.

A reliable, provocative test to enhance parathyroid activity in marginal and masked cases of hyperparathyroidism is much to be desired. Calcium infusion, tubular reabsorption of phosphorus, and 10-day prednisone suppression tests are of historic and academic interest. Patients with hyperparathyroidism are very intolerant of vitamin D therapy, which raises the serum calcium level and may provoke a florid hypercalcemia. Thiazide diuretics lower urinary calcium excretion and they may also initiate or aggravate the hypercalcemia.

The isolation of purified human parathyroid hormone (PTH) from parathyroid adenomas and the very recent synthesis of the active portion of this 84 amino acid peptide are major advances toward a precise and reliable radioimmune hormone assay. At present any patient with hypercalcemia and ele-
vated PTH should be considered to have primary hyperparathyroidism until proven otherwise. The ratio between serum calcium and PTH levels distinguishes primary hyperparathyroidism from ectopic hyperparathyroidism and the far more common hypercalcemia resulting from bone metastases.\textsuperscript{25-27}

Ectopic hyperparathyroidism is rare. Over 60 percent of patients with this condition have epidermoid carcinoma of the lung or renal cell carcinoma; the remainder have isolated gastrointestinal, ovarian and advanced epidermoid carci-

Table 2.
Parathyroid Tumors and Benign Tumors

| Benign Tumors                  | Number |
|--------------------------------|--------|
| Thyroid nodules                | 16     |
| Benign breast tumors           | 12     |
| Rectal polyps                  | 4      |
| Uterine fibroids               | 3      |
| Parotid gland tumors           | 2      |
| Lipomas, multiple              | 1      |

Table 3.
Systems Involved, Skeletal

| Condition                              | Number |
|----------------------------------------|--------|
| Osteoporosis                           | 36     |
| Benign giant cell tumors (Epulis)      | 23     |
| Fractures, pathologic                  | (6)    |
| Extraosseous calcification             | 10     |
| X-ray films indicating hyperparathyroidism | 5      |

Table 4.
Chief Complaint

| Complaint                  | First 40 Patients | Last 40 Patients |
|----------------------------|-------------------|------------------|
| Bone pain or tumor         | 20                | 1                |
| Renal stone                | 10                | 5                |
| Lump in the neck           | 6                 | 7                |
| Gastrointestinal symptoms  | 2                 | 5                |
| Mental change              | 2                 | 5                |
| None: hypercalcemia        | 0                 | 17               |

The history is typically brief, two to six months, with fulminating symptoms, weight loss of 20 to 50 pounds, a variable response to prednisone suppression and hypercalcemia above 14 mgm. percent in 75 percent of patients. There is no evidence of renal calculi or bone changes, peptic ulcer or hypertension. The PTH level is lower than in primary hyperparathyroidism, particularly in relation to the high serum calcium. These cancers often secrete fragments of hormone with diminished

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physiological activity, rather than complete parathyroid hormone.

Hypercalcemia above 15 mgm. percent, particularly associated with confusion, lethargy or coma must be considered a combined medical-surgical emergency. Vomiting, aspiration secondary to gastric and esophageal atony and fatal arrhythmia may ensue. Essential laboratory studies should be completed rapidly and the serum calcium level quickly lowered by hydration and phosphate feeding, as the patient may require removal of a parathyroid tumor within 48 hours.

Sophisticated diagnostic localizing procedures are time-consuming and costly and should be reserved for the patient presenting serious problems in diagnosis, particularly those with negative cervical exploration and persistent hyperparathyroidism. The use of radioactive selenomethionine scanning has been discarded, since it has a 60 percent accuracy rate and can demonstrate only larger tumors, which are obvious at surgery. Selective jugular vein PTH assay combined with aortic arch and thyroid arteriography are precision determinations with up to 80 percent accuracy in expert hands.28–34

**Surgery**

In the nearly 40 years of this study, more than 90 operations for parathyroid tumors were performed at Memorial Hospital, with one postoperative death due to pulmonary embolism. In three patients, a temporary tracheostomy was required for vocal cord palsy or hematoma. Only two sternotomies were done, and one was unnecessary since the adenoma was located behind the sternoclavicular joint, clearly accessible from the neck. As preoperative diagnosis became more certain over the years, surgical confidence and precision were gained, so that a 95 percent success rate is now reported at this institution and elsewhere.1,35

Cervical exploration requires general anesthesia and meticulous dry dissection using an electrocoagulation unit and binocular loupes.36 Both thyroid lobes must be fully elevated by division of the middle thyroid veins, with complete exposure and preservation of the superior and inferior thyroid vessels and recurrent laryngeal nerves. All four parathyroid glands must be identified. Several delicate biopsies and frozen sections are necessary, since 10 percent of patients have multiple abnormalities, either hyperplasia or adenomata. The thymus gland, trachea and esophagus should be carefully palpated and explored down to the aortic arch, if possible. The typical adenoma is soft or cystic,
difficult to palpate, yellowish-brown in appearance (similar to liver tissue) and surprisingly small, considering the symptomatology. The extreme posterior regions of the visceral compartment of the neck and lower thyroid poles are favored locations; 10 tumors were found in the superior mediastinum and 10 were intrathyroid. Twenty-nine thyroid lobectomies were performed. (Fig. 3.)

Toluidine blue infusion was not employed in this series because of reported cardiac arrhythmia; methylene blue infusion, on the other hand, has been helpful. Since the classical primary clue to the presence of an adenoma is abnormal vascularization, the major thyroid vessels must be carefully preserved and traced throughout their course.

Recent emphasis on the polyglandular nature of hyperparathyroidism, hyperplasia and familial endocrinopathy, has led to some recommendations for routine biopsy of all parathyroid glands. The risk of such a policy is clearly illustrated by the four patients in this series who developed permanent postoperative hypoparathyroidism. Pathologic diagnosis requires only the adenoma and one normal gland for contrast. If hyperplasia is present in all glands, three and one-half glands should be removed. Temporary postoperative tetany was seen in 10 patients with extensive bone changes and elevated alkaline phosphatase.

Over the past 70 years, many surgeons, including William Halsted, have attempted transplantation of the parathyroid glands, but no convincing histologic evidence of graft survival, sufficient follow-up or adequate control studies have been presented. The crucial problem is to transplant tissue across a histocompatibility barrier and avoid rejection. This has recently been achieved in immunosuppressed dogs and in man. Isogenic parathyroid tissue can be maintained in culture up to six weeks, or stored in a frozen state for longer periods, and successfully transplanted into highly inbred, parathyroidectomized rats. Fresh and cultured allografts and xenografts were universally rejected.

The timing of parathyroid surgery is important. Renal stones should be removed later, unless obstructing or infected. In patients with multiple endocrinopathy, the islet cell tumor and pheochromocytoma take precedence. Hyperparathyroidism of pregnancy must be surgically corrected before delivery to prevent neonatal tetany. During acute parathyroid crisis, exploration should be briefly delayed until hydration and phosphates have had full effect.

The results of surgical treatment warrant emphasis. Renal calculi formation ceases, but stones already formed persist. Hypertension is usually unchanged, but no longer progresses. Bones heal, but deformities remain. Psychiatric disorders tend to improve, but are not cured. Muscular weakness and myopathy may improve dramatically.

Re-exploration after previous surgical failure is a very difficult procedure, which carries an appreciable morbidity and mortality due to disturbed anatomy and the need for prolonged dissection. The most common original surgical error is the failure to identify all four parathyroid glands, while the most frequent pathological error is unrecognized hyperplasia of all parathyroid glands. Selective angiography and jugular vein PTH assay are, therefore, mandatory prior to any cervical re-exploration or mediastinotomy.

Pathology
A close relationship must exist between clinician, surgeon and pathologist. Histopathology requires: clinical data, including a prior history of prolonged renal or gastrointestinal malabsorption disease; a description of the size and appearance of all parathyroid glands; the intact parathyroid tumor with its capsule; and a specimen from another parathyroid gland for contrast. Transfor-
mation into an adenoma is recognized by uninodularity, absence of normal interstitial fat and encapsulation by a rim of normal parathyroid tissue. However, the differential diagnosis of primary, secondary and tertiary hyperparathyroidism is difficult based on routine microscopic examination of the parathyroid glands alone.\textsuperscript{47,48}

Memorial Hospital Series
The rarity of hyperplasia in this series is unique. Even the one patient with four grossly hyperplastic glands up to five cm. in diameter is considered by several pathologists to have multiple adenomata. Four patients had multiple adenomata, one simultaneous and three sequential; two additional patients are presently under study for suspected recurrent adenoma. (Table 5.)

Three patients had parathyroid carcinomas with regional and distant metastases. One non-functioning carcinoma was difficult to distinguish from thyroid carcinoma. (Table 5.) Characteristically, all of these carcinomas were palpable prior to surgery, hard, nodular, adherent to surrounding structures and accompanied by marked hypercalcemia on admission and at recurrence.\textsuperscript{49}

Several examples of non-functioning, primarily oxyphilic, adenomas were included in this series. Since none were suspected clinically or before death from other causes, serum calcium values were determined infrequently and urinary calcium studies were not obtained.

New York Hospital Series
A parallel survey was conducted at New York Hospital, a general hospital in which 400 charts were reviewed for possible hyperparathyroidism. Primary hyperparathyroidism was proven in 180 patients. (Table 6.) Seventeen patients or 10 percent had cancer either synchronously or asynchronously.

Sixty patients had clinical and laboratory evidence of primary hyperparathyroidism, but never underwent surgery. In another 30 patients with multiple renal stones and hypercalcuria, the disease was suspected, but ruled out for lack of laboratory confirmation. The major clue to diagnosis was renal calculi in over 90 percent of patients, recurrent pancreatitis in three patients, and chronic peptic ulcer in two. One patient with multiple endocrinopathy and one with medullary carcinoma of the thyroid were seen. Secondary and tertiary hyperparathyroidism is well represented in this series, due to an active renal dialysis and transplant program.\textsuperscript{50,51}

Five patients had multiple adenomas. Three additional patients with late recurrent hypercalcemia are under suspicion. There were 14 negative cervical explo-
rations and, in three instances, two explorations were required to find the tumor. One sternotomy was performed, but was unnecessary as the adenoma was located low in the neck. There were no postoperative deaths. Complications were limited to two cases of vocal cord palsy and one tracheostomy. Two patients died of parathyroid crisis before surgical intervention was possible.

Summary
The diagnosis of primary hyperparathyroidism is rapidly increasing in frequency due to better methods of detection. Laboratory studies have been simplified and made more accurate. Cervical exploration should now be considered an integral part of the diagnostic workup, as it is safe and 95 percent successful in correcting the disorder.

One-third of patients were found to have cancer, one-third a benign unrelated tumor and one-third a benign tumor of hyperparathyroidism itself. Differential diagnosis may be difficult, but the rewards are gratifying.

While delay in confirming a diagnosis of primary hyperparathyroidism has been reduced from years to weeks, the clinical investigation of these patients continues to be unduly prolonged and treatment postponed. Progressive renal damage and shortened life span associated with this disorder have been well documented. 52

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