**Background:**

The parathyroid diseases are unique in several ways. They have subtle clinical characteristics that can be ignored, overlooked, or blamed on other clinical entities. They are usually curable if treated well (except for parathyroid cancer, which has a very poor prognosis.) And they are usually best treated by surgery. This is especially true in resource-limited settings. In resource-rich countries, less-severe cases of secondary hyperparathyroidism can be treated with medications. But the mainstay of parathyroid disease treatment remains surgery.

The cause of all of hyperparathyroidism’s symptoms is the inappropriate mobilization and elevation of calcium, stimulated by an inappropriately high level of serum parathyroid hormone (PTH.) This has several predictable effects, as described further below.

In resource-rich countries, routine serum calcium assessment as part of a combined blood test panel (“Basic Metabolic Panel”) has led to an increase in diagnosis and treatment of Primary Hyperparathyroidism. In some cases, patients diagnosed in this way had symptoms such as mild abdominal pain or subclinical depression, that they didn’t even realize were problematic until after their hypercalcemia had been successfully treated.

The usual clinical manifestations of hyperparathyroidism can be classified as follows:

**Kidney Stones:**

Elevated serum calcium leads to elevated levels of calcium in the urine, which leads to urinary tract calculus disease. Any patient presenting with an episode of urinary tract stones should be checked for serum hypercalcemia.

**Bone Pain and Bony Tumors:**

Parathyroid hormone stimulates the bone to release calcium. This leads to bone and joint pain and bone fragility. There is a characteristic x-ray finding of subperiosteal reabsorption which can best be seen on plain x-rays of the hand.

Subperiosteal resorption can be a subtle finding. In the image on the left, there is some erosion of the outer cortex on the first phalanx of the index finger (Red arrow.) The cortex of the first and second phalanges is also “lacy” in appearance, rather than solid as seen in the normal x-ray on the right. The tufts of the distal phalanges on the left also contain much less bone (Blue arrow) than the normal distal phalanges on the right. Case courtesy of Dr. Tom Ellswood, from the case [https://radiopaedia.org/cases/77849?lang=us](https://radiopaedia.org/cases/77849?lang=us) (Left) and Dr. Dai Roberts, from the case [https://radiopaedia.org/cases/80411?lang=us](https://radiopaedia.org/cases/80411?lang=us) (Right.)

Excessive forced bone release of calcium can also lead to bony tumors. These are called osteitis fibrosa cystica, or Brown tumors, and have a characteristic radiologic appearance. A patient’s initial presentation for hyperparathyroidism may be with a bony mass or a pathologic fracture of the tumor. These tumors resolve upon treatment of the hyperparathyroidism.

Characteristic radiolucent appearance of osteitis fibrosa cystica, seen here in the radius. Case courtesy of Dr Hani Makky Al Salam, from the case [https://radiopaedia.org/cases/12460?lang=us](https://radiopaedia.org/cases/12460?lang=us)
Abdominal Complaints
Patients will complain of dull constant abdominal pain that is not relieved or exacerbated by any factors. Other gastrointestinal complaints can include constipation, gastric ulcers and worsening acid reflux. In our limited-resource setting, when patients present with chronic abdominal pain and no apparent diagnosis, a serum Calcium level is part of our workup (as described further below.)

Neuropsychiatric Disturbances:
Patients will complain of symptoms such as extreme fatigue, lack of concentration, short-term memory loss, anxiety, insomnia and amotivation. Sometimes these may be subclinical; the patient only realizes they were present after the hypercalcemia has resolved.

Physiology and Anatomy
Parathyroid hormone is released in response to hypocalcemia or hyperphosphatemia by the parathyroid glands, which are so named because they are located adjacent to the thyroid gland. The hormone’s effect is to cause absorption of calcium and phosphorus from the intestine and release of calcium by osteolysis from the bones. In the kidney, parathyroid hormone’s effect is to increase reabsorption of calcium and increase release of phosphorus.

Hyperparathyroidism is due to excessive parathyroid hormone secretion by one or more parathyroid glands, leading to hypercalcemia. Causes include primary, secondary, or tertiary hyperparathyroidism as well as parathyroid cancer, as explained further below.

In patients presenting with hypercalcemia, secondary causes must be excluded, such as malignancy, multiple myeloma, parathyroid-related hormone related protein secreting tumors, Vitamin D deficiency, renal insufficiency, familial hypocalciuric hypercalcemia, granulomatous disease, use of thiazide diuretics or lithium, milk alkali syndrome, Paget’s disease, immobilization, and other endocrine disorders.

Primary Hyperparathyroidism
This disease is caused by one or more enlarged and independently functional, but not malignant parathyroid glands. In resource-rich settings, most patients are asymptomatic or with minimal symptoms. They present with hypercalcemia detected on routine blood work. They
are then found to have an inappropriately elevated parathyroid hormone during further work up. Nearly 15-20% of patients with primary hyperparathyroidism will present with multi-gland hyperplasia. Multi-gland hyperplasia will require subtotal parathyroidectomy (typically 3.5-gland resection), if indications for surgery have been met.

Secondary Hyperparathyroidism

This disease arises in patients with end-stage renal disease on dialysis, and results in global parathyroid hyperplasia and hyperfunction. Patients with this disease almost always present with normal or mildly elevated calcium with extremely high PTH levels. This PTH elevation is multifactorial. Persistent hyperphosphatemia due to renal failure is a stimulus for PTH secretion. Also, elevated phosphate levels complex with circulating calcium to make calcium phosphate, which deposits in the tissues and leads to lower calcium levels. Vitamin D deficiency also leads to increased PTH release. The end result of all of these processes is increased bone turnover, bone pain and fractures, increased calcification of all tissues (including coronary arteries,) and calcium phosphate deposits in soft tissues. Calciphylaxis, characteristic necrotic skin lesions caused by microvascular damage and calcium phosphate deposition, is another severe consequence of this process.

Typically, medical management of secondary hyperparathyroidism is undertaken first with vitamin D supplementation, active vitamin D or its analogs and the calcimimetic medication cinacalcet. Parathyroidectomy is indicated if medical management fails. In resource-rich countries, the availability of cinacalcet has led to decreased need for parathyroidectomy in dialysis dependent patients. As resource-poor countries develop economically and dialysis becomes more common, it is reasonable to think that surgical treatment of this disease will become more common as well, especially in patients who cannot afford cinacalcet in the long term.

Tertiary Hyperparathyroidism

This disease occurs when an excess of PTH is secreted by parathyroid glands, usually after longstanding secondary hyperparathyroidism, that persists after successful renal transplantation. The typical patient has been on dialysis for years before the transplant. After normal renal function has been restored, the hypertrophied parathyroid tissue fails to resolve; instead it continues to secrete PTH, despite serum calcium levels that are within normal range or even elevated. Hypertrophied parathyroid glands also may become resistant to calcimimetic treatment. The primary treatment of tertiary hyperparathyroidism is surgery. The main indication for surgical treatment is persistent hypercalcemia and/or an increased PTH levels.

Parathyroid Carcinoma

Parathyroid carcinoma is one of the rarest human malignancies and presents with unequivocal biochemical diagnosis of hyperparathyroidism, dramatic elevation in parathyroid hormone and serum Calcium levels and altered mental status. These patients need hospitalization for medical management of hypercalcemic crisis, followed by definitive surgical management of the tumor. Parathyroid carcinomas tend to be large, and may be locally invasive, requiring an en bloc resection of the mass. A dramatic presentation of hypercalcemia, such as a neck mass with very elevated calcium levels, should raise suspicion for this disease.
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Anatomic Considerations

The parathyroid glands usually consist of two pairs, the upper and lower parathyroid glands, although up to six glands can exist. They normally reside adjacent to the thyroid gland, adherent or adjacent to its posterior surface. Both the superior and inferior parathyroid glands’ blood supply is from the inferior thyroid vessels.

Normal parathyroid glands are 5-15mm in size, oval-shaped, and dark yellow or orange in color. They can be distinguished from surrounding fat by being darker in color than fat. They are usually found in the loose tissue that surrounds the capsule of the thyroid. Careful dissection of this capsule, removing the loose tissue from the thyroid without causing damage to this tissue, will usually help you preserve the parathyroid gland. When a parathyroid is identified during capsular dissection of the thyroid, be aware of its blood supply, which usually enters the gland from the dorsal and caudal side.

The normal location of the glands is highly related to the location of the recurrent laryngeal nerve. Another useful landmark for localizing the glands is the tubercle of Zuckerkandl, the posterior-most projection of the thyroid gland. The superior parathyroid glands will almost always be posterior to a line drawn through the recurrent laryngeal nerve; the inferior glands will normally be anterior to this line. Parathyroid adenomas are frequently found adjacent or adherent to the recurrent laryngeal nerve, which must be meticulously preserved during dissection.

An enlarged neck mass (Blue arrow) in a patient with parathyroid carcinoma. Source: http://www.endocrinesurgery.net.au, used with permission.

The location of the parathyroid glands relative to landmarks seen during neck exploration. The horizontal line goes through the tubercle of Zuckerkandl, the most posterolateral part of the thyroid gland. The vertical line is an imaginary line drawn along the course of recurrent laryngeal nerve. Note that the superior parathyroid glands can be cranial to the entrance of the nerve into the larynx, even though this anatomic relation is preserved. Source: http://www.endocrinesurgery.net.au, used with permission.

When a thorough search fails to show four glands adjacent to the thyroid gland in the above-described locations, you are dealing with one or more glands in an ectopic location. An understanding of the embryology of the parathyroid development is crucial in this situation. Parathyroid ectopic locations can range from high cervical position, inside the carotid sheath, intrathyroidal, within the tracheoesophageal groove, retroesophageal, mediastinal, or within the thymus gland in the chest. Identifying the parathyroid vascular stalk and where parathyroid blood supply is coming from in relation to the recurrent laryngeal nerve can be very helpful.

Parathyroid tumor (right) within the resected thymus gland shows the difference in color between parathyroid and fatty tissue. Source: http://www.endocrinesurgery.net.au, used with permission.
in identifying which gland, superior or inferior, is being resected. This dilemma is discussed further in the following chapters.

The superior parathyroid glands arise from the 4th pharyngeal pouch in the embryonic oropharynx. They do not travel far from this position to their final location in the neck. If you are having trouble finding an upper parathyroid, continue searching in the area of the upper thyroid lobe, especially along the superior thyroid vessels above the upper pole, within the tracheoesophageal groove, or in the retroesophageal position.

Conversely, the inferior parathyroid glands arise from the 3rd pharyngeal pouch and migrate farther before reaching their location in the neck. This process is more prone to disturbances in migration, leading to a more frequent ectopic location.

Therefore, the surgeon who is having trouble finding a lower parathyroid gland should expand the search to the following locations: retro-esophageal, within the carotid sheath, within the thymus gland in the upper mediastinum, and within the thyroid gland itself. More specific advice for dealing with ectopic parathyroid glands is given further below and in the individual chapters.

Principles:

Surgeons who do not have specific experience with parathyroid disease may nevertheless have considerable experience locating and preserving parathyroid glands from performing thyroid resections. As with thyroid surgery, the best results come from hands that are experienced operating in this area. Careful technique with meticulous attention to hemostasis is crucial: it is much harder to distinguish parathyroid tissue, and to tell it from the surrounding fat, in a blood-stained field.
The minimally invasive single-gland parathyroidectomy described in this Manual should be used when you have excellent preoperative imaging and the ability to assess PTH levels intraoperatively. If you have excellent imaging, you may consider a minimally invasive operation without intraoperative PTH, but you are placing the patient at risk for a second operation, a full neck exploration, if the hyperparathyroidism persists. Therefore, although it may be tempting to not perform a full neck exploration, we cannot recommend this strategy for low-resource settings.

The indications for neck exploration in hyperparathyroidism include:
1. Proven parathyroid disease and no intraoperative PTH assay
2. Failed single gland exploration
3. Secondary hyperparathyroidism: as mentioned, the availability of cinacalcet may influence your surgical decision-making, especially in patients with significant comorbidities.
4. Tertiary hyperparathyroidism

Imaging options for the parathyroid glands include:

**Ultrasound**

As in other areas in this Manual, we recommend that the surgeon become skilled at performing ultrasound. It is very helpful to be able to locate an enlarged gland using ultrasound in clinic, and then repeat it in the operating room immediately before surgery.

**Computed Tomography Scan**

On CT scan of the neck with IV contrast, parathyroid adenomas are visible as hyperlucent compared to surrounding structures. The scan typically is performed in three phases: non-contrast, arterial (30 seconds after contrast injection,) and delayed (60-90 seconds after contrast.) This is sometimes referred to as “4D CT,” with the 4th dimension being time. An adenoma will have low attenuation on non-contrast phase, light up promptly on arterial phase, and have decreased attenuation but still be visible on delayed phase.

4D CT is not used in every case of hyperparathyroidism, but it is very useful in identifying parathyroid gland(s) in the reoperative setting. It is more sensitive and specific than either ultrasound or Sestamibi in localizing parathyroid glands.

Parasagittal (left) and axial (right) views show the typical oval, hypodense ultrasound appearance of a parathyroid adenoma.

Three phases of CT scan of the neck showing a parathyroid adenoma in the right tracheoesophageal groove (Red arrow.)

Left, non-contrast phase: The tumor has low attenuation.

Center: arterial phase: The well-vascularized tumor has high attenuation.

Right, delayed contrast phase: The tumor has low attenuation, though more than surrounding tissues.

Case courtesy of Dr Jenny Hoang, from the case https://radiopaedia.org/cases/30418?lang=us
Sestamibi Scan

This radionuclide imaging technique will not be available in most low-resource settings. It consists of injection of Technetium-99 sestamibi (a shortening of “sesta-methoxyisobutylisonitrile,”) followed by measurement of radioactivity in the neck and upper chest. Scanning occurs at 15 minutes and 2 hours following administration. At 15 minutes, the thyroid gland and the largest parathyroid adenoma will be seen. At 2 hours, only the adenoma will be seen. This technique is best used in conjunction with an ultrasound, both to verify that a lesion seen at ultrasound is indeed a parathyroid adenoma, and to locate any adenomas not seen by ultrasound.

It is important to note that in the presence of two adenomas, only the larger one will be seen on Sestamibi scan. So the presence of only one tumor on the scan does not indicate that only one parathyroid adenoma is present: as stated above, 15-20% of patients with primary hyperparathyroidism have multi-gland disease.

Decision Making:

In patients with hypercalcemia, we perform a careful history and thorough physical examination with emphasis on masses in the neck. A palpable neck mass raises concern for parathyroid carcinoma, especially if the Calcium level is more than 12mg/dL.

A history of dialysis or renal transplantation raises the likelihood of secondary or tertiary hyperparathyroidism.

In all cases, an elevated parathyroid hormone level confirms the diagnosis. If it is normal or low, consider the other causes of hypercalcemia listed above under “Physiology and Anatomy.” In true primary hyperparathyroidism, both the serum calcium and the parathyroid hormone must be elevated. Isolated hypercalcemia with a low PTH is often due to occult malignancy.

For patients with chronic abdominal pain, if the history and physical does not yield any suspected diagnosis, we will check a serum Calcium level, Thyroid Stimulating Hormone level, Complete Blood Count and Erythrocyte Sedimentation Rate as part of our workup. This situation is discussed elsewhere in this Manual.

Once the diagnosis of hyperparathyroidism is confirmed, surgical planning begins. A meticulous neck exploration by an experienced surgeon is better than any imaging. If you do not have any of the
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advanced imaging mentioned in this chapter, you may still perform an ultrasound to help guide your exploration. Even if you are certain where the tumor is after ultrasound, we still recommend you perform a 4-gland exploration as described in the following chapter.

If you are faced with a patient who has persistent hyperparathyroidism after a neck exploration, be very cautious. Such patients are best treated by an expert in endocrine surgery. If you are the patient’s only option, try to get a well-performed “4D CT” scan. We refer the patient to a facility where we know the scan will be done well, and we discuss with the radiologist or radiographer beforehand. Search carefully in the areas described in this chapter.

For secondary and tertiary hyperparathyroidism, your main goal is to “debulk” the patient’s hypertrophic parathyroid glands. You will remove 3½ of the four glands. There are various options for the remaining parathyroid tissue, as described in the chapter.

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Resource-Rich Settings
- Preoperative imaging techniques such as $^{99}$Tc-SESTAMIBI, $^{99}$Tc-SESTAMIBI-SPECT, 4D CT neck with and without contrast (parathyroid protocol) can be employed for preoperative parathyroid localization and identification of the ectopic and mediastinal parathyroid gland(s).
- Parathyroid angiography can be used in cases of failed multiple parathyroid surgeries and require venous PTH sampling for localization.
- Intraoperative parathyroid hormone (IOPTH) monitoring is routinely utilized to confirm intraoperative biochemical cure following parathyroidectomy.
- Intraoperative nerve monitoring of the recurrent laryngeal nerve is prudent in re-operative setting and during resection of a parathyroid mass concerning for malignancy.
- Intraoperative use of near infrared parathyroid autofluorescence technology can aid in parathyroid identification and preservation.