In their studies of anatomy, early pathologists failed to immediately recognize the distinct entities of the parathyroid glands. It was not until 1850 that the organ was first described during the necropsy of an Indian rhinoceros at the London Zoo. Seventy-five years later, the first surgery for hyperparathyroidism was performed in Vienna by Dr. Felix Mandl on a trolley-car operator with severe osteitis fibrosa cystica known as "Albert." One enlarged gland was removed, and Albert had symptomatic improvement for about 6 years until his bone disease recurred. In 1926, a second parathyroid surgery was performed without any prior knowledge of Albert's case. This time, surgeons at the Massachusetts General Hospital explored the neck of Captain Charles Martell, a merchant marine who suffered severe back and leg pain, fractures of his arms and legs, kyphoscoliosis, urinary calculi, hypercalcemia, and hypophosphatemia. The initial exploration and five subsequent operations revealed only normal parathyroid glands. Only during a seventh surgery was a large parathyroid adenoma identified in Captain Martell's mediastinum. Ninety percent of this enlarged gland was resected while a small remnant was intentionally left behind. Captain Martell later died of chronic renal failure from his long-standing parathyroid disease. Despite much improvement in our ability to diagnose and treat parathyroid disease, current therapies are still challenged by similar issues such as the recurrent hyperparathyroidism that was seen with "Albert," and the ectopic parathyroid adenoma and the difficulties of reoperative surgery, which were the case with Captain Martell.

However, there has been a great evolution in the surgical management of primary hyperparathyroidism as our experience has grown. The past decade, in particular, has seen a marked change in opinion regarding the best approach to the diagnosis and treatment of this disease. Because we are currently in the midst of a technological revolution, many of the former standard surgical procedures are being challenged by minimally invasive approaches. Present strategies for the surgical management of parathyroid disease have been made possible by innovative ways to identify aberrant pathology both before and during surgery. The conventional practice of identifying and evaluating all four parathyroid glands at the time of surgery, which had been purposely performed without preoperative imaging results, has been largely replaced by the practice of obtaining preoperative localization studies as part of the initial workup for primary hyperparathyroidism, followed by a targeted minimally invasive surgical approach when appropriate. This highly localized procedure ultimately provides a better operation for the patient, with resolution of primary hyperparathyroidism, less pain, and a quicker recovery.

Basic Science of Parathyroid Disease

Calcium Physiology

A detailed understanding of the homeostatic mechanisms of calcium is required for the optimal management of hyperparathyroidism, including the proper selection of patients for surgical treatment. The average daily dietary intake of calcium may range between 500 and 1000 mg/day. However, despite marked dietary intake variations, the diurnal variation in the level of serum calcium is only 5% or less. This homeostasis is achieved by a careful balance between gastrointestinal absorption, bone deposition and release, and the urinary excretion of calcium. Absorption involves vitamin D metabolites, and occurs primarily in the duodenum and upper jejunum. In the kidney, approximately 99% of the filtered calcium is reabsorbed by the proximal tubule, but this amount varies inversely with the amount of dietary calcium intake. The absorption of calcium in the proximal tubule and loop of Henle is linked to sodium transport, whereas distal tubular absorption of calcium is influenced by parathyroid hormone and not sodium. Calcium losses approximate 100 mg/day and 800 mg/day in perspiration and feces, respectively. By far, the body's single greatest reservoir of calcium is skeletal bone, which contains approximately 1000 g (99% of the body's calcium). Extracellular fluid, osteoblasts, and cells usually contain 1 g, 500 mg, and 11 g calcium, respectively [Fig. 55.1].
Fecal Calcium (800 mg)

Bone and Teeth (1 kg)

~ 200 mg

FIGURE 55.1. Diagram of the average distribution of calcium in the body. The average daily dietary calcium intake is approximately 1 g. A net of 200 mg is absorbed from the dietary calcium intake, and the rest is loss through feces. The largest calcium reservoir is the skeleton, which contains approximately 1 kg. The kidney contributes to calcium homeostasis with a net daily excretion of 200 mg calcium.

Calcium is the body's most abundant mineral, yet only its ionized form is physiologically active. Ionized calcium plays critical roles in signal transduction, nerve excitability, skeletal and cardiac muscle contractility, and bone matrix formation. Additionally, cell structure, function, and metabolism are regulated by calcium-dependent processes. Approximately 47% of calcium is in the ionized form in plasma, 45% is protein bound, and 8% is complexed to organic anions. It is important to remember that in diseased states total serum calcium needs to be adjusted with plasma protein levels, particularly albumin. The following formula has been suggested to correct for adjustments in total serum calcium with respect to alterations in serum albumin levels:

\[
\text{Ca (adjusted)} = \text{Ca (total)} - 0.8 \times (\text{albumin} - 4.0)
\]

However, ionized calcium can now be rapidly measured, making it the method of choice to measure calcium in the serum.

Serum calcium is regulated by a closely integrated interplay of three hormones: parathyroid hormone (PTH), vitamin D₃ (1,25-dihydroxycholecalciferol), and calcitonin (Fig. 55.2). The key target organs include the parathyroids, skeletal muscle, kidneys, and intestine. PTH is synthesized in the parathyroid glands as a larger molecule, pre-pro-PTH, which is cleaved into its inactive form, pre-PTH. Pre-PTH is further cleaved into PTH, which is released into the circulation and rapidly broken down further into amino- and carboxyl-terminal fragments by the liver and kidney. Only the intact 84 amino acid long PTH molecule and the 1-34 amino-terminal fragment are physiologically active. The double-antibody immunoradiometric assay (IRMA) is the current method of intact PTH detection, it has greatly simplified the diagnosis of primary hyperparathyroidism.

PTH exerts its effect by activating membrane-bound adenylate cyclases, which in turn generate cyclic adenosine monophosphate (cAMP). PTH regulates serum calcium level by directly and indirectly affecting calcium exchange at the intestine, bone, and kidney. PTH directly increases serum calcium by inhibiting the synthetic function of osteoblasts and stimulating renal tubular calcium reabsorption. PTH indirectly contributes to calcium regulation by stimulating osteoclast maturation and inducing renal phosphate clearance and synthesis of calcitriol, which in turn promotes gastrointestinal absorption of calcium.

Vitamin D is another key regulator of bone mineral metabolism. Vitamin D synthesis begins with previtamin D₃ production via ultraviolet irradiation of 7-dihydroxycholesterol in the skin. Previtamin D₃ is then converted to vitamin D₃ (cholecalciferol), which is then 25-hydroxylated in the liver to produce 25-(OH)D₃ (calcifediol). Calcifediol undergoes 1a-hydroxylation in the kidneys to form calcitriol. Calcitriol is the major active form of vitamin D. It stimulates calcium-binding protein in the gut and enhances absorption of calcium and phosphorus; this in turn promotes deposition of hydroxyapatite in bone. On the other hand, calcitriol also inhibits pre-pro-PTH and induces calcium mobilization from bone.

Calcitonin is produced by the parafollicular C cells of the thyroid. Calcitonin decreases bone resorption by antagonizing the actions of PTH.

FIGURE 55.2. The interplay of parathyroid hormone (PTH), vitamin D, and calcitonin on calcium and phosphorus regulation at specific target organs. A decrease in serum calcium stimulates PTH secretion by the parathyroid glands. PTH directly and indirectly affects calcium exchange at the intestine, bone, and kidney to elevate the serum level of calcium. Calcitriol [1,25(OH)₂D₃], the major active form of vitamin D, enhances calcium and phosphorus absorption in the intestine while inhibiting PTH. There is a negative feedback loop between serum calcium and calcitonin levels. An increase in serum calcium results in calcitonin secretion, which regulates bone and kidney to decrease serum calcium.