Chapter 1
Embryology and Anatomy of the Parathyroid Glands

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Introduction

As with most surgical procedures, a surgeon's knowledge of the relevant anatomy is critical to the technical success of operations on the parathyroid glands. This knowledge must encompass more than just an understanding of the anatomy of the normal neck; it must also include an understanding of the variant anatomy and aberrant anatomic relationships that may be encountered. The process is reinforced by an appreciation and understanding of not only parathyroid anatomy but also parathyroid embryology. This chapter reviews the embryology and anatomy of the parathyroid glands in a clinically relevant manner. Furthermore, it details recent advances in our understanding of the molecular mechanisms of parathyroid development. Our aim is to reinforce the link between embryology and surgical anatomy in the context of parathyroid surgery such that parathyroid glands are successfully identified and operative morbidity is minimized. We also intend for this to serve as a reference and preface to the other chapters in this text.

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A Historical Perspective

The importance of a detailed understanding of parathyroid embryology and anatomy is perhaps best appreciated by reviewing what may well be the most challenging case of persistent hyperparathyroidism in the surgical literature. Seventy-one years after Felix Mandl first removed a parathyroid tumor from his patient Albert J., a Viennese streetcar conductor with osteitis fibrosa cystica, the management of parathyroid disease remained a dilemma. So much so that at the 67th Annual Session of the Pacific Coast Surgical Association, Dr. Claude Organ noted:

> "William Halsted remarked once that 'It seems hardly creditable that the loss of bodies so tiny as the parathyroid should be followed by results so disastrous.' The second hardest decision is when to operate; the hardest decision is when to reoperate. It was inevitable with the dramatic increase in identification of the hypercalcemic syndromes and the increase in parathyroid surgery that we would eventually have to deal with the failed operation" [1].

While Mandl and his Austro-German colleagues were describing the physiology of hyperparathyroidism and anatomy of the parathyroid glands in the early twentieth century, parallel work was taking place across the Atlantic in the United States. Sea Captain Charles Martell, a World War I veteran, would become the first American patient diagnosed with hyperparathyroidism in 1926. Born in 1896 in Somerville, Massachusetts, Martell attended the Massachusetts Nautical School and graduated at the top of his class. He joined the World War I effort and was stationed near Liverpool. Following the armistice in 1918, he returned home to Massachusetts. At that time, he began experiencing back and groin pain that he attributed to his physical duties on the ship and rheumatism. The captain returned to the US Merchant Marines where he traveled throughout the world. At that time, his fellow officers noted that his physical appearance was beginning to change. He slowly lost height and his chest developed a pigeon deformity. Over time, he was no longer the athletic, vigorous, six-foot-one-inch man of the past. Meanwhile, he began passing what was described as "urinary gravel." Over the next several years, he was in and out of domestic and foreign hospitals due to multiple extremity fractures. In 1926, Captain Martell came under the care of Dr. Eugene F. DuBois at Bellevue Hospital in New York City. Unaware of Dr. Mandl's investigations of the patient Albert J., (who was found to have a parathyroid tumor associated with von Recklinghausen's disease as the cause of his osteitis fibrosa cystica) several years earlier in Austria, DuBois obtained a sample of blood from Martell. This revealed hypercalcemia. DuBois went on to identify that more calcium was being excreted than consumed by Martell. This was the first tentative diagnosis of hyperparathyroidism in the United States. Martell was referred to Massachusetts General Hospital in Boston where the senior thyroid surgeon, Edward P. Richardson, explored Martell's neck. A parathyroid gland was removed, but ultimately the pathology was normal and his hypercalcemia persisted. Over the next five neck explorations Martell underwent, his remaining parathyroid glands were removed without improvement in his disease. Finally, on November 2, 1932, at the seventh operation, Dr. Edward A. Churchill, Chief of Surgery at the Massachusetts General Hospital,

performed an anterior mediastinotomy, which revealed a 2.5 cm parathyroid adenoma. Following this exploration and adenoma resection, Martell's serum calcium levels fell for the first time. Unfortunately, he developed hypocalcemia and tetany. Despite successful surgery, the years of chronic renal disease secondary to hypercalciuria and nephrocalcinosis caused his ultimate demise. Following a complicated postoperative course managing his fluids and electrolytes, he developed a left-sided kidney stone which became impacted and ultimately led to acute renal failure and subsequently his death. Despite the loss, Martell and his doctor's persistence in attempting to identify the underlying cause of his illness resulted in significant contributions to medical and surgical knowledge. In retrospect, over eight decades later, this ectopic parathyroid adenoma was in a seemingly likely location given our current knowledge of parathyroid embryology and anatomy. With this knowledge in mind and with the improved parathyroid imaging techniques we enjoy today, perhaps he would have been cured at his first operation [2, 3].

The unfortunate case of sea captain Charles Martell and his seven operations, before a mediastinal parathyroid adenoma was discovered, highlights the difficulty of treating this disease, as well as how current diagnostic modalities can help prevent nontherapeutic parathyroid surgery and the associated morbidity of such operations. As compared to over 80 years ago when Captain Martell presented with his ectopic parathyroid gland, improved knowledge of potential sites for ectopic and supernumerary glands along with superior imaging techniques provides surgeons the opportunity to avoid multiple unnecessary operations. In view of this, it cannot be overemphasized how critical knowledge of the embryologic development and anatomic distribution of the parathyroid glands is for the surgeon treating patients with recurrent or ectopic disease in striving to perform a low morbidity operation.

Embryology and Anatomy

Like the thyroid gland (an outpouching of pharyngeal endoderm), the epithelial origin of the parathyroids is also the pharyngeal endoderm. The parathyroid glands, however, develop from the third and fourth pharyngeal pouches beginning in the fifth week of gestation (Fig. 1.1). The inferior glands are derived from the dorsal tip of the third pharyngeal pouch, as is the thymus. This collection of tissue, often referred to as the "parathymus," descends anteroinferiorly until the parathyroids find their position at the lower border of the thyroid lobes; the thymus, however, continues inferiorly into the anterior mediastinum. The superior glands, on the other hand, arise from the fourth pharyngeal pouch. By the sixth week of gestation, these superior glands separate from their origin, migrate inferiorly, and come to rest just superior and medial to the inferior glands. Their usual location approximates the point at which the inferior thyroid artery enters the thyroid gland or at which the inferior thyroid artery crosses the recurrent laryngeal nerve. Therefore, while the inferior glands begin more superiorly, they pass the superior glands on their descent and are named "inferior" based on their mature location (Fig. 1.2).

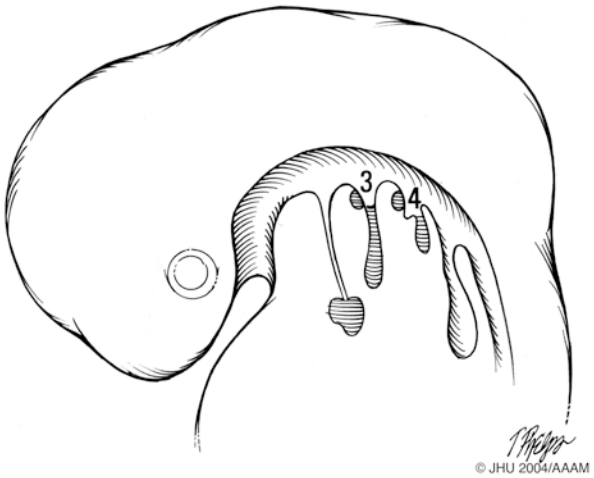

Fig. 1.1 Migration of the thyroid, parathyroids, and pharyngeal pouch derivatives. The thyroid, parathyroid glands, and ultimobranchial bodies migrate inferiorly from their origin in the embryo. Courtesy of Tim Phelps © JHU/AAAM 2004, Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine

To elaborate and consider this in further detail, the entire head and neck region is derived from ectoderm, mesoderm, endoderm, and neural crest-derived cells. During the fourth and fifth weeks of development, the pharyngeal, or branchial arches arise from a core of mesoderm that is lined internally by endoderm of the primitive foregut and externally by surface ectoderm. Bars of mesenchymal tissue become separated by deep grooves known as branchial clefts. Simultaneously, five pairs of outpockets develop along the lateral walls of the most cranial portion of the foregut, the pharyngeal gut. These outpockets are known as the pharyngeal pouches (Figs. 1.1 and 1.2). Unique to both the third and fourth pharyngeal pouches, dorsal and ventral wings develop bilaterally [4–7].

During the fifth week of embryogenesis, the endodermally derived epithelium of the third pouch differentiates. The dorsal wing becomes the right and left inferior parathyroid glands, respectively, while the ventral wing forms a portion of the thymus that will later coalesce. Bilaterally, the gland primordia lose their connection with the pharyngeal wall in order to allow migration in a caudal and medial direction. The rapid movement of the paired thymic counterparts toward the anterior mediastinum in the thorax draws the inferior parathyroid glands with them (Fig. 1.2). Upon arrival in the thorax, the thymic counterparts fuse to form the final gland. Occasionally, this fails to occur completely, and a tail of thymic remnant may persist in the thyroid gland (derived as noted from an outpouching of the pharyngeal endoderm; foramen cecum in the adult) or as an independent island of thymic tissue in the neck. As the thymus descends, the inferior parathyroid glands migrate to their final location most commonly along the inferoposterior aspect of the thyroid gland. However, the migration is highly variable and the glands can be found at any location

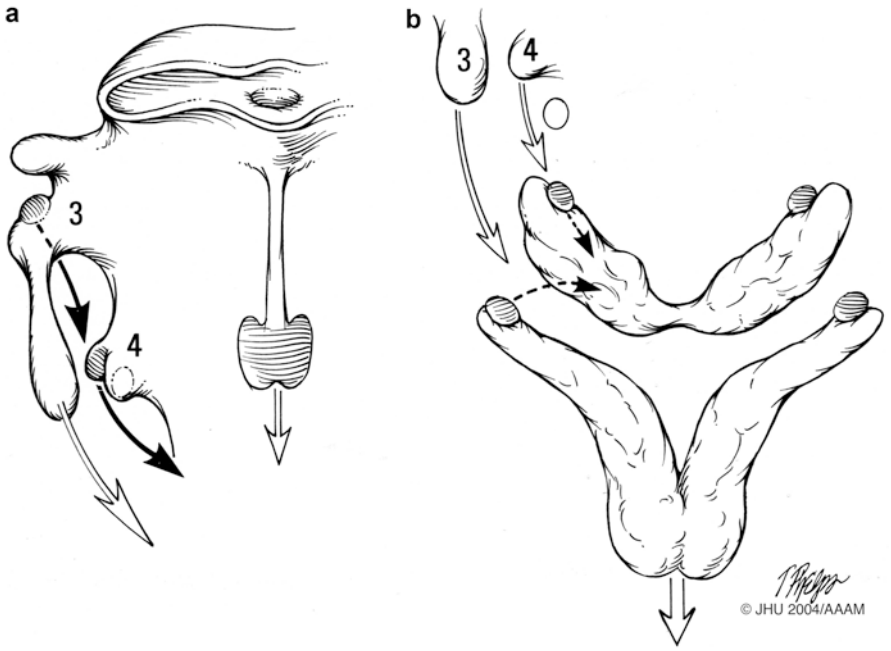

Fig. 1.2 (**a**) The upper (IV) and lower (III) parathyroids exchange position as they migrate; parathyroid III becomes the inferior parathyroid, whereas parathyroid IV becomes the superior parathyroid. (**b**) The inferior parathyroid has a more variable location due to its longer migration and may commonly be found in the thyrothymic ligament or the thymus itself. Courtesy of Tim Phelps © JHU/AAAM 2004, Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine

from intrathyroidally to along the thyrothymic ligament to within the thymus if the dorsal and ventral wings of the third pouch fail to separate. This variability of each parathyroid gland is independent of the migration of the contralateral gland, thereby resulting in significant variability in adults. Nonetheless, the lower parathyroid gland is typically located anterior to the recurrent laryngeal nerve.

Similar to the third pouch, the fourth pharyngeal pouch also divides into a dorsal and ventral wing. Again, the dorsal wing forms parathyroidal nests that give rise to the superior parathyroid glands bilaterally. The ventral wings develop into the ultimobranchial body, which will later become incorporated into the thyroid gland and become the parafollicular or C cells that secrete calcitonin. The superior parathyroid glands invaginate and attach themselves to the caudally migrating thyroid gland (Figs. 1.1 and 1.2). Ultimately, the bilateral superior parathyroid glands usually locate symmetrically, either in close association with the superior pole of the thyroid gland or occasionally within the thyroid gland itself. A majority of the superior glands are posterolateral in location and lie just above or just below the intersection of the inferior thyroid artery and the recurrent laryngeal nerve but posterior to the recurrent nerve.

It is the numerous variations in embryologic pharyngeal pouch development that result in the wide variability and the "predictable unpredictability" of parathyroid gland anatomy ranging from supernumerary glands and variable locations within the neck to intrathyroidal and, occasionally, ectopic sites such as those in the mediastinum. As a result of these substantial variations, the treatment of hyperparathyroidism may be complicated by recurrent or refractory disease.

Applied Anatomy and Embryology: Clinically Relevant Abnormalities

As a result of the embryologic development discussed above, parathyroid glands are often found in abnormal or ectopic locations or may be supernumerary (Fig. 1.3). The inferior parathyroids have the greatest irregularity in their position, based on their long path of descent. Ectopic inferior glands may be found in the lower pole of the thyroid lobes, or they may continue to descend with the thymus and continue into the mediastinal structures such as the thymus or thyrothymic ligament. Alternatively, the inferior parathyroid glands may fail to descend beyond the angle of the mandible or be along their proximal path of descent along or in the carotid sheath. Conversely, ectopic superior glands are usually within two centimeters of their expected location and usually found in a more dorsal position than the inferior

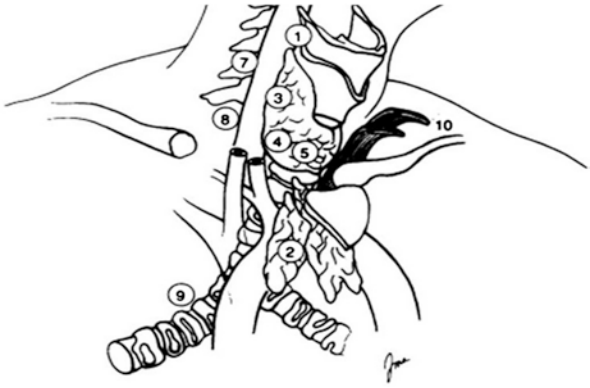

Fig. 1.3 Locations of normal, missed, and ectopic parathyroid glands. The single most common site of missed adenoma glands was in the tracheal esophageal groove in the posterior superior mediastinum (27%). The most common ectopic sites for parathyroid adenomas are thymus (17%), intrathyroidal (10%), undescended glands (8.6%), carotid sheath (3.6%), and the retroesophageal space (3.2%). Overall, the distribution of the 215 abnormal parathyroid adenomas resected in this series: (1) tracheoesophageal groove (n = 59; 27%); (2) anterior mediastinum/thymus (n = 38; 18%); (3) normal upper (n = 28; 13%); (4) normal lower (n = 26; 12%); (5) intrathyroid (n = 22; 10%); (6) undescended (n = 18; 8.4%); (7) carotid sheath (n = 8; 3.7%); (8) retroesophageal (n = 7; 3.3%); (9) other mediastinal (n = 3; 1.4%); (10) strap muscles (n = 3; 1.4%); (11) other (n = 3; 1.4%). Adapted from [8]

glands; the superior glands are often found in such positions as the retropharyngeal or retroesophageal spaces (Fig. 1.3). The single most common site of missed glands in a large series was in the tracheoesophageal groove in the posterior superior mediastinum (27%). The most common ectopic sites for parathyroid adenomas are also in the thymus (17%), intrathyroidal (10%), undescended glands (8.6%), carotid sheath (3.6%), and the retroesophageal space (3.2%) [8].

Supernumerary parathyroid glands may have an even wider variance in location. These glands are thought to develop from fragments of the pharyngeal pouches or primordial parathyroid tissue. These small clusters of cells migrate with surrounding structures and may develop in the lateral neck or lower mediastinum.

Molecular Biology of Parathyroid Development

The molecular mechanisms and biology of parathyroid development has been best described by the study of parathyroid developmental anomalies in humans. These anomalies, which result in hypoparathyroidism, may occur in up to one in 4000 live births and have been linked to defects in genes encoding putative transcription factors and/or enhancer proteins which impact parathyroid development. Several of the well-described syndromes are listed here, with the associated gene in parenthesis: DiGeorge syndrome (TBX1); hypothyroidism, deafness, and renal anomalies (HDR) syndrome (GATA3); isolated hypoparathyroidism (GCMB); X-linked recessive hypoparathyroidism (SOX3); and pluriglandular autoimmune hypoparathyroidism (AIRE1). These genes, as well as members of the homeobox (Hox) and paired box (Pax) families, have also been associated with parathyroid developmental abnormalities in mice [9]. This is not surprising, as the murine parathyroid glands have a similar embryologic development as human parathyroid glands. However, it should be noted that parathyroids in mice develop from only the endoderm of the third pharyngeal pouch and from neural crest cells arising from the embryonic mid- and hindbrain. As we have already reviewed, the parathyroids in humans develop from endoderm of the third and fourth pharyngeal pouches. In addition, recent studies have also demonstrated that fish express parathyroid hormone [10]. This is contrary to the long-held view that the earliest animals to possess parathyroid hormone were amphibians. In fact, two species of fish have been shown to express parathyroid hormone; however, the source and physiological function of this peptide in fish remains an area of ongoing investigation. As noted in the above murine and human studies, there is strong recent evidence that regulation and development of the parathyroid gland in mammals is controlled by a cascade of genes. A number of these regulatory factors that have been identified using genetically modified mouse models or as studying genes causing associated with human disease (including Gcm2/GCMB, Pax1/PAX1 and Pax9/PAX9, Hox3a/HOX3A, Tbx1/TBX1, Gata3/ATAGATA3, Tbce/TBCE, Sox3/SOX3, Eya1, and Six1/4) have also been found to be expressed in fish. While these parathyroid hormone expression genes are present in fish, their function remains unclear. Ongoing research promises to provide greater detail as to how this cascade of genes regulates parathyroid development.

Conclusion

In order that morbidity be reduced, and complications during parathyroid surgery (especially reoperative parathyroid surgery) be avoided in pursuit of achieving high rates of success in operations for hyperparathyroidism, the parathyroid surgeon must have an intimate understanding of the applied surgical embryology and anatomy of these endocrine glands. This current understanding of anatomy and embryology clearly would have benefitted Charles Martell, in helping to avoid most of his seven operations and his untimely death. Recent studies, as summarized above, have given us an even greater insight into the molecular factors important in parathyroid gland development and greater knowledge regarding gland migration, development, and morphogenesis. Ongoing and future work may provide even greater information regarding parathyroid anatomy and biology to further aid the parathyroid surgeon and patients afflicted with parathyroid disease.

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