The Parathyroid Glands and Hyperparathyroidism: I

Series Editor and Author: Christopher R. McHenry, MD, FACS, FACE
Associate Professor of Surgery
Case Western Reserve University School of Medicine
Director, Division of General Surgery
MetroHealth Medical Center
Cleveland, OH

Table of Contents

Introduction .................................................. 2
Embryology, Anatomy, and Histology of the Parathyroid Glands ................. 2
Parathyroid Cell Physiology .......................... 6
Summary Points ........................................... 7
Board Review Questions ............................... 8
Detailed Answers ....................................... 9
References ................................................. 9

Cover Illustration by Scott M. Holladay

Copyright 2001, Turner White Communications, Inc., 125 Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications, Inc. The editors are solely responsible for selecting content. Although great care is taken to ensure accuracy, Turner White Communications, Inc. will not be liable for any errors of omission or inaccuracies in this publication. Opinions expressed are those of the authors and do not necessarily reflect those of Turner White Communications, Inc.
I.  INTRODUCTION

Hyperparathyroidism, the major disorder of the parathyroid glands, is a common endocrine disease characterized by excessive secretion of parathyroid hormone (PTH) and by hypercalcemia. Occurring in 0.2% of women and 0.05% of men in the United States, this condition most commonly occurs sporadically with an unknown cause but may occur as a long-term sequela of external-beam radiation to the head or neck, of iodine-131 treatment of Graves’ disease, or, rarely, as part of several inherited conditions (Table 1). Currently, the only definitive therapy for hyperparathyroidism is parathyroidectomy. To successfully treat this disorder, the surgeon must understand the anatomy, embryology, histology, and physiology of the parathyroid glands as well as have a comprehensive knowledge of clinical manifestations, diagnosis, methods of preoperative and intraoperative localization of abnormal parathyroid glands, and recent technological advances in the treatment of patients with hyperparathyroidism.

This manual is the first of a 2-part review on the parathyroid glands and hyperparathyroidism. The first part focuses on embryology, anatomy, histology, and cell physiology of the parathyroid glands. The second part focuses on diagnosis and surgical treatment of hyperparathyroidism. A case patient is presented to illustrate important principles in the management of patients with hyperparathyroidism.

II.  EMBRYOLOGY, ANATOMY, AND HISTOLOGY OF THE PARATHYROID GLANS

Inferior and superior parathyroid glands are formed through similar processes in the embryo. At the fourth week of embryonic development, 5 pairs of endodermally lined pouches arise from the lateral walls of the pharynx (Figure 1). The inferior parathyroid glands and the thymus develop from the third pharyngeal pouch (Figure 2). These glands then descend and undergo an extensive migration with the thymus primordia, eventually becoming positioned on the dorsolateral surface of the thyroid’s inferior pole. The superior parathyroid glands develop with the lateral anlage of the thyroid gland from the fourth branchial pouch (Figure 2). As they lose their connection with the pharynx, superior glands attach to the thyroid and ultimately lie adjacent
to the dorsomedial surface of the thyroid gland’s superior pole.

Both the number and location of parathyroid glands vary in normal individuals. From autopsy studies, it has been documented that 4 parathyroid glands are present in 84% of normal adults. Less than 4 parathyroid glands have been reported in 1% to 7% of normal adults and 5 or more parathyroid glands in 3% to 13%. Up to 8 parathyroid glands have been reported in an individual patient. The paired inferior and superior parathyroid glands tend to be bilaterally symmetrical and are usually surrounded by adipose tissue. Typically, these glands are ovoid, yellow-tan, and measure approximately 5 × 3 × 1 mm. When located within the capsule of the thyroid gland, parathyroid glands appear flattened and are adherent to the thyroid gland. When traumatized, parathyroid glands become mahogany-colored secondary to hemorrhage.

An average parathyroid gland weighs approximately 35 mg, although its weight can vary from 10 to 70 mg. Distinguishing a normal parathyroid gland from a fat lobule, thyroid nodule, or small lymph node can be difficult. A parathyroid gland is soft and highly vascular; a frozen-section sample will reveal diffuse bleeding from its cut edge. In contrast, a fat lobule has a brighter yellow color and a thyroid nodule is more firm and reddish in color. Nodal tissue is characteristically pale gray, firm, and adherent to surrounding tissue or other lymph nodes.

**LOCATION OF THE PARATHYROID GLANDS**

The superior parathyroid glands are found close to and often within the capsule of the posterior medial aspect of the thyroid gland’s superior pole. More specifically, these glands lie approximately 1 cm above the junction of the inferior thyroid artery and recurrent laryngeal nerve (usually positioned posterior and superior to the nerve), at the level of cricoid cartilage where the recurrent laryngeal nerve enters posterior to the cricothyroid muscle (Figures 3 and 4). Because they undergo less extensive migration during embryologic development, superior parathyroid glands have a more consistent location and are less likely to be in an ectopic

---

**Table 1. Familial Hyperparathyroidism and Associated Disorders**

<table>
<thead>
<tr>
<th>MEN I</th>
<th>Hyperparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary microadenoma (most commonly prolactinoma)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic islet cell tumors</td>
<td></td>
</tr>
<tr>
<td>Rarely, tumors of the thyroid or adrenal glands, carcinoid tumors, and multiple lipomas</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MEN IIA</th>
<th>Hyperparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td>Lichen planus amyloidosis</td>
<td></td>
</tr>
<tr>
<td>Hirschsprung’s disease</td>
<td></td>
</tr>
</tbody>
</table>

**Familial isolated hyperparathyroidism**

**Familial hyperparathyroidism—jaw tumor syndrome**

MEN = multiple endocrine neoplasia.

**Figure 1.** The 5 pairs of pharyngeal pouches that appear on the 26th day of embryologic development. The fifth pharyngeal pouch is the last to develop and is most often considered part of the fourth pouch as shown in this figure. (Adapted with permission from Gray SW, Skandalakis JE, McClusky DA: Atlas of Surgical Anatomy for General Surgeons. Baltimore, MD: Williams & Wilkins, 1985.5.)
location. When they do form, ectopic superior parathyroid glands are usually found in the tracheoesophageal groove or posterior superior mediastinum but may also be retropharyngeal, retroesophageal, or intrathyroidal (Figure 5).

The inferior parathyroid glands are commonly located on the posterior-lateral aspect of the lower thyroid gland pole, below the junction of the recurrent laryngeal nerve and the inferior thyroid artery (Figures 3 and 4). These glands tend to be anterior to the recurrent laryngeal nerve and are less often subcapsular. Because of their more extensive embryologic migration, inferior parathyroid glands are more likely to be found in ectopic locations, the most common of which is in or near the thymus. Ectopic inferior parathyroid glands may be in the anterior superior mediastinum or aortopulmonary window, within the thyroid gland, or undescended at the level of the carotid bulb within the carotid sheath (Figure 5).

Figure 2. Development of the superior (IV) parathyroid gland and lateral anlage of the thyroid gland from the fourth branchial pouch. Development of the inferior parathyroid gland (III) and thymus from the third branchial pouch. (Adapted with permission from Paloyan E, Lawrence AM: Anatomy of the parathyroid glands. In Mastery of Surgery. Nyhus LM, Baker RJ, eds. Boston: Little Brown, 1985:192.)

Figure 3. The parathyroid glands in their normal anatomic locations. a = artery; n = nerve; v = vein. (Adapted with permission from Gray S, Skandalakis JE, McClusky DA: Atlas of Surgical Anatomy for General Surgeons. Baltimore, MD: Williams and Wilkins, 1985:23.)
Typically, blood to each parathyroid gland (superior and inferior) is supplied by a single, small terminal artery, most often from a branch of the inferior thyroid artery. In approximately 15% to 20% of patients, this blood supply comes from the superior thyroid artery or from anastomoses between the inferior and superior arteries. Rarely, branches from the thyroid ima, tracheal, esophageal, or pharyngeal vessels may supply parathyroid glands.

**CELLULAR COMPOSITION AND FUNCTION**

Parathyroid glands are surrounded by a thin, fibrous capsule. Fibrous septae divide the parenchyma of the gland into lobules that consist of cell clusters separated by adipose tissue. The principal parenchymal cell of the parathyroid gland is the chief cell. Varying numbers of oxyphil and clear cells are also present in parathyroid glands, although all 3 types (chief, oxyphil, and clear) are believed to be morphologic and/or functional variants of the same parenchymal cell. Oxyphil cells (which are notable for their eosinophilic granular cytoplasm) appear at puberty, increase in number with age, and may form distinct oxyphil nodules. It is possible that clear cells may bechief cells with an excessive amount of glycogen in the cytoplasm. All of these parenchymal cells are believed to secrete PTH.

On average, adipose cells comprise about 50% of cells in a normal adult parathyroid gland. Abnormal parathyroid glands have less stromal fat; however, normal fat content can vary from 17% to 70% and is known to increase with age. Although the ratio of parenchymal cells to adipose cells does not definitely differentiate normal and hyperfunctioning parathyroid glands, intracellular fat is present in approximately 80% of parenchymal cells in a normal gland in contrast to less than 20% of cells from an abnormal, hyperfunctioning gland. Microscopic examination is useful only to confirm that an excised specimen is parathyroid tissue. Pathologists may have difficulty distinguishing between normal and hyperplastic or adenomatous parathyroid glands microscopically, primarily because of the varying levels of stromal fat content seen in parathyroid tissue. Reduced cytoplasmic fat content in the parathyroid cells, demonstrated by using intracellular lipid stains, is suggestive of hyperfunctioning parathyroid tissue. There are no absolutely reliable microscopic features that distinguish adenomatous and hyperplastic parathyroid glands.

The surgeon is the best judge of whether a parathyroid gland is normal, adenomatous, or hyperplastic. A gland that exceeds 7 mm in greatest dimension or weighs more than 70 mg is abnormal. An adenoma is diagnosed when a single enlarged gland is present with 3 normally appearing glands, whereas the presence of 4 enlarged parathyroid glands is indicative of parathyroid hyperplasia. In most patients with hyperplasia, the abnormal glands vary in size.
III. PARATHYROID CELL PHYSIOLOGY

GENERAL PRINCIPLES

The principal function of the parathyroid glands is to maintain normal systemic calcium homeostasis. The parathyroid cell senses changes in ambient levels of extracellular calcium and responds by altering secretion of PTH, an 84–amino acid peptide hormone with a half-life of 3 to 5 minutes. PTH increases calcium resorption from bone and kidney and indirectly increases intestinal calcium absorption by stimulating the 1-hydroxylase enzyme in the kidney, leading to an increase in 1,25-dihydroxyvitamin D3 levels. All of these actions increase serum calcium, which then acts by a negative feedback loop to reduce PTH secretion (Figure 6). This feedback loop is the primary mechanism regulating calcium homeostasis in humans.

The calcium-sensing function of the parathyroid cell is mediated by a calcium receptor (Figure 7), with extracellular calcium as the principle ligand. The first inorganic ion receptor described by scientists, the calcium receptor is a G protein–coupled receptor, which activates phospholipase C and inhibits adenylate cyclase (Figure 7). Phospholipase C activation leads to the rapid formation of inositol 1,4,5-trisphosphate (IP3) and the mobilization of intracellular calcium. Also, an increase in the transmembrane influx of calcium occurs through voltage-insensitive ion channels in the cell membrane. Unlike other endocrine cells where hormone secretion is stimulated by increases in cytoplasmic calcium, parathyroid cells decrease release of PTH in response to increased levels of cytoplasmic calcium.

Extracellular calcium is the principal physiologic stimulus regulating PTH secretion. An inverse sigmoidal relationship exists between PTH secretion and extracellular calcium concentration (Figure 8). A parathyroid...
cell’s calcium receptor is responsible for maintaining serum calcium levels within a narrow range. In humans, free or ionized serum calcium levels are maintained between 1.12 and 1.23 mM. The set point refers to the calcium concentration at which PTH levels are 50% of maximum (Figure 8). The calcium receptor determines the set point for the serum calcium level that the parathyroid cell maintains. Parathyroid cells are capable of sensing very small changes in serum calcium and of responding with large changes in PTH secretion. This response is depicted by the large slope of the PTH curve around the calcium set point in Figure 8. This impressive sensitivity to changes in calcium concentration is further demonstrated by maximal and minimal PTH secretory rates, which are regulated within a range of extracellular calcium concentration of only 0.5 mM (from 1.0 to 1.5 mM).

**PARATHYROID CELL FUNCTION IN HYPERPARATHYROIDISM**

In patients with hyperparathyroidism, the regulation of PTH secretion is abnormal. Sensitivity to changes in extracellular calcium is reduced in patients with adenomatous or hyperplastic parathyroid glands. Abnormal glands have also been shown to have an increased calcium set point and a PTH response curve that is shifted to the right when compared with normal glands (Figure 9). Thus, any extracellular calcium concentration will result in higher PTH levels in patients with hyperparathyroidism. Changes in the calcium receptor may play a role in increasing the calcium set point; multiple studies have demonstrated a reduced expression of the calcium receptor mRNA and protein in pathologic parathyroid glands. Hyperparathyroidism develops from DNA mutations in the parathyroid cell. Genetic mutations are believed to be responsible for the reduced parathyroid cell sensitivity to changes in extracellular calcium and to the increased parathyroid cell proliferation. Regardless of whether hyperparathyroidism is caused by single or multiglandular disease, the abnormal parathyroid glands are monoclonal in origin.

**IV. SUMMARY POINTS**

- The most common location for an ectopic superior parathyroid gland is in the tracheoesophageal groove or the posterior mediastinum.
- The most common location for an ectopic inferior parathyroid gland is in the thymus.
- Microscopic examination of an excised parathyroid gland is only useful for confirming that the specimen is parathyroid tissue and is not definitive for distinguishing normal, hyperplastic, or adenomatous parathyroid glands.
Reduced expression of calcium receptor mRNA and protein are observed in pathologic parathyroid glands.

**BOARD REVIEW QUESTIONS**

Choose the single best answer for each question.

1. A patient with primary hyperparathyroidism undergoes neck exploration, and 3 normal parathyroid glands are found. A right superior gland is not found in its normal anatomic position. Where is this gland most likely to be located?
   A) In or near the thymus
   B) Within the thyroid gland
   C) Undescended, high in the neck
   D) In a retropharyngeal position
   E) In the tracheoesophageal groove

2. Which of the following is most helpful in differentiating between a normal and hyperfunctioning parathyroid gland?
   A) The ratio of parenchymal cells to adipose cells
   B) Microscopic examination of the parathyroid tissue
   C) Staining for intracellular fat
   D) Size and weight of the parathyroid gland

3. Pathologic parathyroid glands in patients with primary hyperparathyroidism are characterized by:
   A) Reduced expression of calcium receptor mRNA and protein
   B) A reduced calcium set point
   C) Increased stromal and intracellular fat
   D) A shift in the PTH response curve to the left

4. The inferior parathyroid glands develop from the third pharyngeal pouch along with the:
   A) Lateral anlage of the thyroid glands
   B) Larynx
   C) Thymus
   D) Ultimobranchial bodies

5. The blood supply to the superior parathyroid gland most commonly came from the:
   A) Superior thyroid artery
   B) Inferior thyroid artery
   C) Anastomoses between the inferior and superior thyroid arteries
   D) Thyroid ima artery
DETAILED ANSWERS

1. (E) In the tracheoesophageal groove. An ectopic superior parathyroid gland is most commonly found in the tracheoesophageal groove or in the posterior superior mediastinum. It may also be in a retropharyngeal, retrosophageal, or intrathyroidal position. The most common location for an ectopic inferior parathyroid gland is in or near the thymus.

2. (D) Size and weight of the parathyroid gland. The surgeon is the best judge of whether a parathyroid gland is normal or abnormal. A gland that exceeds 7 mm in greatest dimension or weighs more than 70 mg is abnormal. Microscopic examination of excised parathyroid tissue is useful only for confirming that the specimen is parathyroid tissue. Pathologists may have difficulty in microscopically distinguishing a normal gland from a hyperplastic or adenomatous gland. Reduced cytoplasmic fat content in parathyroid cells suggests hyperfunctioning parathyroid tissue but often is not definitive. Because the fat content of normal parathyroid glands can vary from 17% to 70%, the parenchymal-to-adipose cell ratio also is not a definitive measure.

3. (A) Reduced expression of calcium receptor mRNA and protein. In patients with hyperparathyroidism, the regulation of PTH secretion is abnormal. Sensitivity to changes in extracellular calcium is reduced in patients with adenomatous or hyperplastic parathyroid glands. Abnormal glands have been shown to have an increased calcium set point and a PTH response curve that is shifted to the right when compared with normal glands. Thus, any extracellular calcium concentration results in higher PTH levels in patients with hyperparathyroidism. Changes in the calcium receptor may play a role in decreasing expression of the calcium receptor mRNA and protein in pathologic parathyroid glands.

4. (C) Thymus. The inferior parathyroid glands and the thymus develop from the third pharyngeal pouch. The inferior parathyroid glands undergo an extensive migration with the thymus, eventually becoming positioned on the dorsolateral surface of the thyroid’s inferior pole. As a result of their more extensive embryologic migration, the inferior parathyroid glands are more likely to be found in ectopic locations, the most common of which is on or near the thymus.

5. (B) Inferior thyroid artery. The blood supply to the parathyroid glands comes from a single terminal artery, which is a branch of the inferior thyroid artery in 80% to 85% of patients. In approximately 15% to 20% of patients, the blood supply to all 4 parathyroid glands comes from the superior thyroid artery or from anastomoses between the inferior and superior thyroid arteries. Rarely, branches from the thyroid ima artery may supply the parathyroid glands.

REFERENCES


