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RESIDENT PHYSICIAN: Alan L. Cowan, M.D

FACULTY PHYSICIAN: Francis B. Quinn, Jr, M.D.

SERIES EDITORS: Francis B. Quinn, Jr., MD and Matthew W. Ryan, MD

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Introduction

Endocrinology is the study of the regulatory mechanisms of the body including the role of hormones and their effect on cell function. The study of endocrinology is a broad discipline, and therefore is not amenable to summary within this context. The following is meant as an overview of two focused aspects of endocrinology, namely the thyroid and parathyroid glands, which are commonly encountered by the otolaryngologist.

Hypophyseal – Pituitary Axis

The hypophysis consists of the neural tissues which line the third ventricle, including the supraoptic and suprachiasmatic nuclei. These tissues are responsible for the interaction between central nervous system and hormonal cycles. Each of the nuclei within the hypothalamus regulates a specific group of cells within the pituitary gland. The posterior portion of the pituitary gland, known as the neurohypophysis, is derived from a direct outgrowth of the third ventricle during development. As a result, the stimulation of neurohypophyseal structures is by nerve axons which arise from the hypophyseal nuclei. The cell types within the posterior pituitary produce ADH (vasopressin) and Oxytocin. The cells of the anterior pituitary gland are derived from an outgrowth of Rathke's pouch, and do not have direct neural connections to the hypophysis. As a result, these cells must rely on hormones secreted from the hypothalamic nuclei to stimulate or inhibit their activity. The vascular system of the hypothalamic – pituitary system is well designed for this flow of hormones. The posterior pituitary has a direct arterial supply, while the anterior pituitary has a purely venous blood supply. The veins which supply the adenohypophysis drain the hypophyseal nuclei above, and thus carry the central control hormones directly to the target tissue without systemic dilution.

The particular anatomy of the HPA has several clinical applications. First, the large venous blood supply to the pituitary makes this gland sensitive to thrombogenic disorders, especially during times of pregnancy in which the gland and its blood supply enlarges dramatically. Thrombosis of these vessels is termed Sheehan's syndrome, and is a surgical emergency requiring surgical evacuation of the thrombosis to prevent panhypopituitarism and

rapidly progressive blindness. Second, the neurovascular stalk which connects the hypophyseal tissues to the pituitary is susceptible to compression by local tumors. Since the mechanism of most of the hypophyseal to pituitary control systems is stimulatory, the compression of this structure will lead to deficiency states of all subsequent hormones except one. The cells which control the production of prolactin work on a dopamine inhibitory system. Therefore, when the stalk is compressed, a “stalk effect” may be measured by a dramatic increase in the serum prolactin, while the remaining pituitary hormones will be reduced. Last, as the outpouching of the neurohypophysis occurs, the arachnoid tissues adhere to the stalk, resulting in the separation of the pituitary structures from CSF communication. Any CSF noted in the sella is pathologic, and can indicate an empty sella syndrome, or post-surgical changes.

Thyroid Gland

The thyroid gland is the largest endocrine gland in the body. It is responsible for the production of the hormones T_3 , T_4 , and calcitonin (discussed later). These iodinated tyrosine hormones are responsible for the basal metabolic rate of numerous body tissues. When these hormones are present in abnormally low concentrations, symptoms such as low voice, constipation, dry skin, cold intolerance, and fatigue develop. In the neonate, low levels of these hormones can result in failure of proper neural development and may result in retardation or cretinism in severe cases. When thyroid hormones are in excess, symptoms such as palpitations, nervousness, and heat intolerance may develop.

Thyroid Physiology

Thyroid hormone is formed by organification of iodine to the tyrosine residues of thyroglobulin. Several steps are required to perform this task, and each has a separate system of controls which limit or promote this activity. The first step is the uptake of serum iodine into the thyroid cell. This process is facilitated by an Na^+/I^- symport protein on the basal membrane of the thyroid cell. This transport is powered by the Na^+/K^+ pump, which can be found in all cells. The process can be stimulated by the introduction of TSH, but is always limited by the body's available supply of iodine or medications such as perchlorate. Once the iodine is in the thyroid cell, it is then organified and linked to a tyrosine residue attached to thyroglobulin. Depending on the number of iodine ions attached to the tyrosine, MIT (Monoiodotyrosine) or DIT (Diiodotyrosine) will be formed. This process is catalyzed by thyroid peroxidase, an apical membrane protein present in thyroid cells. TPO can be stimulated to produce MIT and DIT by TSH, or can be inhibited by propylthiouracil, methimazole, or large concentrations of iodine. The iodinated complexes are then secreted out of the apical membrane of the cell into the follicular space, which serves as a thyroid hormone precursor storage area. When the thyroid gland is stimulated to release its hormone, the pre-formed MIT & DIT molecules attached to thyroglobulin are endocytosed. TPO catalyzes the combination of MIT & DIT (T_3) or DIT & DIT (T_4). The endocytosed vesicle then attaches to a lysosome which digests the thyroglobulin and releases the bound T_3 and T_4 . The hormones then exit the thyroid cell.

Thyroid Hormone

Once the thyroid hormones are released from the thyroid gland they travel through the body as either bound or free hormones. For both T_3 and T_4 , 99% of the systemic hormones are

bound to serum proteins, thyroid binding globulin (70%), albumin (15%), and transthyretin (10%). Since these proteins hold the majority of serum thyroid hormone, alterations in binding protein concentrations can significantly effect the concentrations of thyroid hormone. Common conditions which increase the serum binding proteins and thus increase the total thyroid hormone concentration include high estrogen states (pregnancy, oral contraceptives, and hormone replacement therapy) and early liver disease. Common causes of binding protein and thyroid hormone decrease include androgen or anabolic steroid use and late liver disease. Another factor that can change the total hormone concentration is binding site competition. Several medicines such as NSAID's, Furosemide, Phenytoin, and Carbamazepine can displace thyroid hormone from its binding site, and can eventually result in a lower total serum hormone concentration. Although these conditions can result in change in the total amount of bound hormone, the body regulates only the free component, and thus will eventually equilibrate by increasing or decreasing the overall amount of hormone produced.

Regulation of Thyroid Hormone

The thyroid system works through a standard feedback inhibition cycle, with the final hormone product inhibiting hormonogenesis. The initiation of hormone production starts with a central nervous system component in the hypothalamus. Here, thyrotropin releasing hormone is secreted in a pulsatile fashion based on an underlying circadian rhythm. The amount of TRH secreted not only depends on this pulsatile rhythm, but is also influenced strongly by T_3 concentration. The CNS, like the remainder of the body, is stimulated by T_3 rather than T_4 . This seems contradictory since more than 98% of all circulating hormone is in the form of T_4 ; however, all cells have a mechanism for transforming T_4 into T_3 . Therefore, the free T_4 concentration does influence overall body function and thyroid regulation, but it does so when it is converted peripherally into T_3 .

Once the hypothalamus produces TRH, it travels via the portal venous system and is detected by the thyrotrophs of the anterior pituitary. The TRH has a stimulatory effect on the thyrotrophs, while the feedback inhibition is again provided by T_3 . These thyrotrophs will produce TSH in response to TRH, however, the physiologic "gain" of this production is governed by the T_3 concentration. This means for a set amount of TRH stimuli, the amount of TSH production varies dramatically by the concentration of T_3 . Once the TSH is produced, it is released into the systemic circulation via the cavernous sinuses, and eventually makes its way to the thyroid gland.

As previously discussed, TSH has several stimulatory effects. First, it increases the amount of serum iodine uptake by the thyroid gland. Second, it stimulates the formation of MIT and DIT by thyroid peroxidase. Third, it stimulates the endocytosis of MIT and DIT and the subsequent formation of T_3 and T_4 via thyroid peroxidase. There is no feedback inhibition at this peripheral level, although there are some environmental factors such as excess iodine and medications which can inhibit the actions of TSH on the thyroid gland.

Selected Thyroid Tests

Radioactive Iodine Uptake - This test is performed using intravenous administration of I^{123} followed by early and late scintillation counter measurements of emitted radiation. This

provides basic information regarding the general function of the thyroid gland as inferred from its uptake of iodine. In active thyroid tissue, the radioactive iodine isotope will be absorbed by the Na^+/I^- transport action. However, the amounts of hormone which are taken up can vary widely by the iodine status of the patient. If the patient is from an area with little iodine in the diet, a normal scan can show a 90% uptake; however, in developed countries like the U.S., normal uptake is considered from 5% to 15%. Other factors can also influence the amount of uptake, including medical therapy with Amiodarone, recent radiographic studies performed with iodinated contrast, or liberal use of topical betadine solution.

If the RAIU is determined to be diffusely elevated and the patient has symptoms of hyperthyroidism, this is generally indicative of Grave's disease or multinodular goiter. The findings on RAIU for Grave's generally show a more homogenous uptake, while multinodular goiter often appears patchy. Symptoms of hyperthyroidism with a focal area of uptake is usually indicative of a benign hyperfunctional nodule. If the RAIU is determined to be diffusely low and the patient has symptoms of hypothyroidism, this is most commonly a sign of Hashimoto's or DeQuervain's thyroiditis. If the RAIU was low with symptoms of hyperthyroidism, this could signal an acute episode of thyroiditis, an ectopic thyroid tumor (struma ovarii), or ingestion of thyroid hormone.

Wolff-Chiakoff effect - When the thyroid gland is presented with a large iodine load, the Na^+/I^- transport protein will respond by moving the serum iodine into the cell. However, in large quantities, iodine actually inhibits further formation of thyroid hormone. The normal functioning thyroid gland responds to this by allowing excess iodine to "leak" through the basal membrane back into the circulation, and can thus shortly resume its normal homonogenesis. This short period in which the thyroid is prevented from synthesizing hormone due to the iodine load is termed the Wolff-Chiakoff effect. Two important variations of this should be noted. First, in patients with deficits in organification of iodine, such as auto-antibodies to TPO, the inhibitory effect of the iodine load is harder to overcome, and may produce significant hypothyroidism. Second, in diseases where the thyroid is pathologically overactive (Grave's), a large iodine load can actually be converted rapidly into active hormone, and thus induce hyperthyroidism. This hyperthyroid effect is termed the Jod-Basedow phenomenon.

Perchlorate test - The perchlorate test is based on the RAIU and the principles of "thyroid leak" as described above. After a dose of I^{123} , the patient is given a dose of perchlorate, which inhibits the Na^+/I^- transport protein. In a normally functioning thyroid gland, the iodine within the cell is rapidly converted into MIT and DIT and stored in the follicle, thus no loss of iodine is observed on repeat scans. However, in conditions where there is an organification defect, the free iodine in the cell will begin to leak out into the serum, and thus the gland will show progressively less radioactive iodine on subsequent scans. This test can be useful in delineating deficits in iodine organification, and is also used in the diagnosis of Pendred syndrome, which is associated with thyroid enzyme deficits and congenital hearing loss.

Hypothyroidism

Hypothyroidism is diagnosed based on a constellation of signs, symptoms, and laboratory values. Symptoms can include fatigue, weight gain, constipation, low voice, and a persistent sensation of being cold. Clinical signs include dry skin, lethargy, slowing of reflexes, swelling

or myxedema of face/hands/legs. In the newborn or young child, retardation, swelling, short stature, and deafness may occur. Although indirect measurements such as decreased reflexes, elevated cholesterol, and skin changes were once the mainstay of diagnosis, current assays now allow the direct measurement of thyroid hormones. The most common causes of hypothyroidism demonstrate a low free T_4 and a high TSH, these include Hashimoto's thyroiditis, endemic goiter, and post-treatment of hyperthyroid conditions such as Grave's. Conditions that present with a low T_4 and a low TSH indicate a central source for the hypothyroidism, and a workup including MRI with pituitary protocol, and possible TRH stimulation test should be performed. The pathogenesis of the hypothyroid conditions are discussed below, however, the treatment generally includes oral supplementation of T_4 (Levothyroxine) due to its longer half-life relative to T_3 . Treatment with exogenous hormone prevents complications of hypothyroidism such as bone loss, cardiomyopathy, and myxedema.

Hashimoto's Thyroiditis

This condition is also referred to as chronic, lymphocytic, or auto-immune thyroiditis. It is the most common cause of hypothyroidism in developed countries. It results from auto-antibodies against TPO or thyroglobulin. This disease is more common in middle age females, and usually presents as an asymptomatic or mildly symptomatic elevation of TSH hormone. Clinical exam is usually non-contributory. TSH is usually elevated, free T_4 is low, and antibodies against TPO or TBG may be demonstrated. This disease is slowly progressive, and treatment with Levothyroxine is used to prevent symptoms of hypothyroidism as well as prevent bone loss or cardiomyopathy.

Goiter

This disease can be separated into endemic goiter, which is due to a dietary deficiency of iodine, and goiter in non-endemic areas which is commonly caused by auto-immune thyroid diseases. In both cases, low levels of T_4 result in increases in serum TSH. Since TSH is thyrotropic, a slowly progressive enlargement of the thyroid gland ensues. The growth of the gland is more pronounced in endemic areas since there is no subsequent tissue loss from immune mediated thyroid destruction. Other causes include excess iodide, thyroid adenoma or malignancy, or genetic thyroid hormone abnormalities. Excess iodide results in goiter by inhibiting the production of thyroid hormone, thus resulting in increasing TSH levels. Excess iodine may be dietary (kelp) or medicine related (Amiodarone or Lithium).

Hyperthyroidism

Presenting symptoms of hyperthyroidism may include palpitations, nervousness, fatigue, diarrhea, sweating, and heat intolerance. Physical signs may include thyroid enlargement, tremor, sweating, or agitation. The laboratory workup for hyperthyroidism may include a TSH, free T_4 , and a RAIU scan. The most common cause of hyperthyroidism, Grave's disease, may be diagnosed just by TSH, T_4 , and clinical signs of Grave's disease. The RAIU is generally used to differentiate the cause when no definitive clinical signs are present. Other common causes are hyperfunctional adenoma, and multinodular goiter, and DeQuervain's thyroiditis, although Hashimoto's may also present with thyroid lab values and symptoms consistent with hyperthyroidism. Other rare causes include thyrotoxicosis factitia, struma ovarii, thyroid

metastasis, TSH-secreting tumor, or hamburger thyrotoxicosis. Although treatment depends on the specific etiology, beta blockers can be used to treat symptoms, PTU or methimazole can be used to decrease hormone formation, and surgery or radiation may be used to debulk or remove the hyperfunctioning thyroid tissue.

Grave's disease

This is the most common cause of symptomatic hyperthyroidism in the U.S. However, in regions of the world with iodine deficiency, the disease may exist in an asymptomatic state due to the inability to form excess thyroid hormone. The underlying pathogenesis of the disease is a result of antibodies against the TSH receptor. This not only results in gland hyperplasia due to the thyrotropic effects of TSH, but it also promotes the formation of MIT, DIT, and the release of T_3 , T_4 . If overt clinical signs such as goiter and exophthalmos are present, then the diagnosis can be made with a simple TSH (low) and T_4 (high). If the diagnosis is in doubt, anti-TSH receptor antibodies may be sought, and a RAIU may be obtained to see if a homogeneous elevated uptake is found. Once the diagnosis is confirmed, treatment of the acute adrenergic symptoms may be done with beta blockers. Long term medical therapy may then be attempted with PTU or methimazole to decrease formation of thyroid hormone. If these are unsuccessful, surgical debulking or surgical excision with lifelong hormone therapy may be considered. Radioactive iodine ablation of the gland with lifelong therapy is also an option.

DeQuervain's thyroiditis

This disease is also referred to as subacute or granulomatous thyroiditis. It is generally accepted to be the result of a viral infection of the thyroid gland. A viral prodrome may precede the acute presentation, which may include thyroid tenderness, symptoms of hyperthyroidism, and lab values consistent with hyperthyroidism (high free T_4 , low TSH). Care must be taken when diagnosing the condition based on lab values, since the course of the disease ranges from hyperthyroid to euthyroid to hypothyroid and back to euthyroid upon resolution. No antibodies are found if a hyperthyroid workup is carried out, but an elevated ESR is common. Treatment is generally symptomatic like with most viral illnesses. NSAID's or acetaminophen can be used for pain control. Prednisone is occasionally used to decrease pain and inflammation. Levothyroxine may be used during the hypothyroid period to prevent symptoms. The illness is self-resolving and non-relapsing.

Euthyroid Sick Syndrome

This is an unusual illness which is due to the peripheral conversion of T_4 to T_3 . In times of extreme stress or illness, the usual 5' deiodinase enzyme is not produced in sufficient quantities in peripheral tissues. However, all tissues except the pituitary also produce the enzyme 5 deiodinase. This is important since 5' deiodinase changes T_4 to T_3 , whereas 5 deiodinase changes T_4 to *reverse* T_3 or r T_3 . This reverse form of T_3 is physiologically inactive, thus the body may sense that T_3 is present in adequate amounts while it is physiologically hypothyroid. The best treatment for this disorder is reversal of the underlying illness, allowing for normal 5' deiodinase production. Exogenous thyroid hormone has not been found to be beneficial.

Calcium Regulation

Calcium is utilized by tissues for numerous reasons including muscle contraction, cardiac repolarization, and a number of intracellular second messenger systems. Due to the importance of this ion, its concentration in the intracellular and extracellular spaces is tightly controlled. In the extracellular space, calcium exists in its free ionized form (iCa^{++}), and in a bound form where it is associated with albumin, phosphate, or citrate. A number of organs are involved in the regulation of this extracellular ionized calcium concentration, including the thyroid, parathyroid, kidney, liver, and bone.

The parathyroid gland produces parathyroid hormone (PTH) in response to low ionized calcium or elevated phosphate ion. PTH stimulates the kidney to convert circulating inactive vitamin D to its active form. In addition, PTH directly stimulates the kidney to reabsorb Ca^{++} and excrete PO_4^{3-} . In bone PTH acts on osteoclasts, where it stimulates the resorption of subperiosteal bone with release of Ca^{++} and PO_4^{3-} ions.

Calcitonin is produced by the parafollicular C cells of the thyroid. Its secretion is stimulated by a high iCa^{++} . Its actions include inhibition of osteoclastic bone resorption and renal excretion of Ca^{++} . Although calcitonin helps to balance the effects of parathyroid hormone, it is not essential [iCa^{++}], since patients who have undergone total thyroidectomy have no difficulty with hypercalcemia. It has several important medical roles however; it can be used to treat Paget's disease or osteoporosis, and it can also be used in the monitoring for recurrent Medullary thyroid carcinoma.

Vitamin D is also a major influence in the total body calcium load. In developed countries, the supply of Vitamin D is more than adequate in the diet. In non-developed countries, the availability of Vitamin D is dependent on exposure of the skin to UV light, which is required for the conversion of cholesterol to D_3 . Whether vitamin D is ingested or produced endogenously, it is initially inactive. Two steps are required for its activation. First, it undergoes hydroxylation by the liver to form 25 (OH)D. This process occurs continuously, and is not subject to regulation. The final conversion from 25 (OH)D to 1,25 (OH) $_2$ D is catalyzed by the kidney and stimulated by PTH. Patients with renal disease, deficiencies of PTH, or lack of vitamin D will lack this activated form. Once vitamin D has been activated, its major role is in the GI tract, where it increases the absorption of dietary calcium.

Hypocalcemia

Calcium is required by several tissues for proper function, most notably muscle and nerve. Therefore, many of the signs of hypocalcemia are related aberrant nerve and muscle function as the calcium concentration decreases. Chvostek's sign is a twitching of the facial muscles, most notably the orbicularis oculi, when a tapping stimulus is applied to the facial nerve near the external auditory meatus. Trousseau's sign is a spasm or tetany of forearm muscles when a blood pressure cuff is applied to the brachial area. Other findings such as a prolonged Q-T interval on EKG due to prolongation of repolarization can be found when the calcium concentration is low.

Causes of hypocalcemia can be classified as disorders of PTH, Vitamin D, Kidney, or

direct binding of the calcium ion in the serum. Common causes of decreased PTH include surgery of the thyroid or parathyroid gland where the parathyroid glands may have been removed or stunned. Resistance to normal levels PTH may be noted if the patient is under therapy for osteoporosis such as bisphosphonates. Vitamin D abnormalities can be from a simple dietary deficiency, a failure of conversion of inactive vitamin D to its active form, or a peripheral resistance to vitamin D due to a faulty vitamin D receptor (familial Rickets). In the acutely ill patient, the release of phosphate from a crush injury or the introduction of citrate from blood transfusions may result in a decrease in the ionized fraction of calcium. Depending on the etiology of the hypocalcemia, treatment may include calcium supplementation, vitamin D supplementation, or dialysis to remove excess phosphate/citrate.

Hypercalcemia

In recent years the use of routine laboratory studies has changed the presentation of hypercalcemia. Previously, many patients with this disorder presented with renal stones, or the frank bone loss of osteitis fibrosa cystica. The classic mantra of symptoms included bones (osteitis fibrosa cystica, osteoporosis), stones (renal), abdominal groans (constipation, peptic ulcers), and moans (lethargy, depression, confusion). Today, some patients still present with stones, but the majority of patients are discovered to be hypercalcemic on routine laboratory studies before hallmark symptoms develop.

The causes of hypercalcemia can be classified into overproduction of PTH, malignancy, granulomatous diseases, renal failure, or drugs. PTH excess is commonly from a parathyroid adenoma, but may be the result of ectopic PTHrP produced by lung cancer. Malignancy is another common cause of elevated calcium. Often, this is due to direct bony destruction by a myeloma or lymphoma. Granulomatous diseases produce hypercalcemia by ectopic conversion of inactive vitamin D to active vitamin D. Drugs that are associated with increased calcium are thiazide diuretics, which prevent Ca^{++} excretion, and direct ingestion of large quantities of vitamin D via supplements or milk. Renal disease is a common cause of hypercalcemia. When creatinine clearance decreases, the kidney has difficulty excreting calcium and phosphate. The result is an increase in the bound form of calcium due to its complex with phosphate. The low ionized calcium and high phosphate both stimulate PTH which causes the release of calcium and phosphate from bone, thus exacerbating the cycle.

Medical treatments for non-adenomatous hypercalcemia include the selective estrogen receptor modulators (Evista), and bisphosphonates which prevent resorption of bone, and thus decrease both the calcium and phosphate concentrations. Acute hypercalcemia can be treated with simple saline diuresis, avoiding diuretics, especially the thiazides, which prevent calcium excretion, and the use of glucocorticoids for malignant or granulomatous diseases. If the episode is severe or emergent, calcitonin and dialysis may also be used.

Surgical treatment is reserved for hypercalcemia due to parathyroid adenomas. The diagnosis only requires an elevated serum calcium and an elevated PTH (not PTHrP). Indications for parathyroidectomy were set down by the NIH in 1990, and include the following: 1) Serum calcium > 12mg/dl, 2) Hypercalciuria > 400 mg/day, 3) Classic presentation with renal stones, osteitis fibrosa, or neuromuscular disease, 4) Cortical bone loss greater than 2 standard deviations below the mean, 5) Reduced creatinine clearance, 6) age less than 50. Other possible

indications include vertebral osteopenia, vitamin D deficiency, or perimenopause.

While most cases of primary hyperthyroidism are caused by solitary adenomas, there is 10-30% incidence of multiple parathyroid gland involvement. Parathyroid adenoma, especially multiple gland involvement necessitates a workup for a multiple endocrine neoplasia syndrome (MEN). The most common MEN, MEN1, is associated with pancreatic and pituitary tumors, and is associated with 10% of all multiple parathyroid gland hyperplasia. MEN2a is less frequently associated with parathyroid adenomas, but is defined by medullary carcinoma of the thyroid and possible pheochromocytoma. MEN2b is not associated with parathyroid disease.

Intraoperative PTH assays

Due to the incidence of multiple gland disease and the morbidity associated with bilateral parathyroid exploration, several studies have been conducted to evaluate the efficacy of intraoperative hormone assays. The intent of these studies was to establish if intraoperative assays could predict presence or absence of remaining disease after adenoma removal, and thus help avoid bilateral exploration. In general, the studies have shown that when the underlying pathology is a solitary adenoma, then the assays are very effective in predicting a cure and alleviating a bilateral dissection. However, in cases of multiple gland disease, there is often a dominant adenoma, and the removal of this gland may result in a dramatic drop in intraoperative PTH similar to a solitary adenoma. Other studies have confirmed that the remaining adenomas, which are usually small, often escape detection by iPTH and preoperative localization studies. Therefore, many surgeons still recommend bilateral exploration and visualization of all glands, especially if the patient population historically contains a high percentage of multiple gland disease.

Bibliography

Bailey, Byron J. Head and Neck Surgery – Otolaryngology. Lippincott Williams & Wilkins. Baltimore, MD. 2001.

Greenspan, Francis S.; Strewler, Gordon J. Basic & Clinical Endocrinology. Appleton & Lange. Stamford, Connecticut. 1997.

Koos, W.T.; Spetzler, R.F. Color Atlas of Microneurosurgery. Thieme. New York, New York. 2000.

Netter, Frank H. The CIBA Collection of Medical Illustrations – Volume 4, Endocrine System and Selected Metabolic Diseases. Ciba Pharmaceutical Company. New York, New York. 1970.

Randolph, Gregory W. Surgery of the Thyroid and Parathyroid Glands. Saunders. Philadelphia, PA. 2003.

Goretzki, P. E. et. al. “Management of Primary Hyperparathyroidism Caused by Multiple Gland Disease”. *World Journal of Surgery*. 1991; 15: 693-7.

Pattou, Francois. et. al. “Correlation of parathyroid scanning and anatomy in 261 unselected patients with sporadic primary hyperparathyroidism”. *Surgery* 1999; 126: 1123-31.

Jones, J. Mark. et. al. “Pre-operative Sestamibi-Technetium Subtraction Scintigraphy in Primary Hyperparathyroidism: Experience with 156 Consecutive Patients”. *Clinical Radiology*. 2001; 56: 556-9.

Berger, A. et. al. “Heterogeneous Gland Size in Sporadic Multiple Gland Parathyroid Hyperplasia.” *Journal of the American College of Surgery*. 1999; 188: 382-9.

Garner, Sanford; Leight, George. “Initial experience with intraoperative PTH determinations in the surgical management of 130 consecutive cases of primary hyperparathyroidism”. *Surgery* 1999;126:1132-8.

Weber, Collin; Ritchie, James. “Retrospective analysis of sequential changes in serum intact parathyroid hormone levels during conventional parathyroid exploration”. *Surgery* 1999; 126: 1139-44.

Libutti, Steven. et. al. “Kinetic analysis of the rapid intraoperative parathyroid hormone assay in patients during operation for hyperparathyroidism.” *Surgery* 1999; 126: 1145-51.