The Endocrine System

Dr. Emanuela Veras-Rentz, M.D.
Assistant Professor of Pathology
Duke University Medical Center
Copyright Statement

• This presentation is the property of Duke University School of Medicine and may not be used without express permission of the Duke University School of Medicine. Do not distribute this to other students, faculty, or health care practitioners who are not part of Duke or the Duke-NUS Graduate Medical School program. Do not post any portion of this material on a Web or Intranet site.

• In developing this presentation, faculty may have included copyrighted materials from other sources. Any use beyond this presentation may require permission from the copyright holder. No individual slides or images may be used from this presentation without express permission from Duke University School of Medicine.
The Endocrine System

- Pituitary gland
- Thyroid gland
- Parathyroid glands
- Endocrine Pancreas
- Adrenal glands
- Pineal gland
The anterior pituitary is the main producer of hormones in the pituitary gland. The table lists the types of cells located in it and their properties.

**Pituitary gland**

- **Two components:**
- **Anterior (adenohypophysis); 80%**

<table>
<thead>
<tr>
<th>Pituitary cell type</th>
<th>Hormone</th>
<th>Cytoplasm characteristics</th>
<th>Associated syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatotrophs</td>
<td>GH</td>
<td>acidophilic cells (eosinophilic cytoplasm)</td>
<td>Gigantism (children)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acromegaly (adults)</td>
</tr>
<tr>
<td>Lactotrophs (mammosomatotrophs)</td>
<td>Prolactin, GH</td>
<td>acidophilic cells</td>
<td>Galactorrhea and amenorrhea (females)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sexual dysfunction, infertility (males)</td>
</tr>
<tr>
<td>Corticotrophs</td>
<td>ACTH, MSH, POMC</td>
<td>basophilic cells (basophil cytoplasm)</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nelson syndrome</td>
</tr>
<tr>
<td>Thyrotrophs</td>
<td>TSH</td>
<td>pale basophilic cells</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Gonadotrophs</td>
<td>FSH, LH</td>
<td>basophilic cells</td>
<td>Hypogonadism, mass effects, hypopituitarism</td>
</tr>
</tbody>
</table>

From what germ layer does the adenohypophysis arise? What embryological structure formed from this germ layer is the precursor to the adenohypophysis?

Associated syndrome due to hyperproduction of the hormone
The posterior pituitary doesn't produce hormones. It stores and secretes oxytocin and ADH, which are produced by the hypothalamus.

**Pituitary gland**

- Posterior (neurohypophysis); modified glial cells extending from hypothalamus (*axon terminals*):
  - **Oxytocin**
    (contraction of uterine and lactiferous ducts smooth muscle)
  - **Antidiuretic hormone (ADH) (vasopressin)**
    (water conservation)

Note that the hypothalamus, through dopamine, has an inhibitory effect on prolactin secretion from the adenohypophysis. Thus, hyperprolactinemia results from anything that blocks dopamine from inhibiting the adenohypophysis; such things include infarction of the stalk and tumors.
Clinical manifestations of pituitary gland disease

- **Hyperpituitarism** (excess secretion of trophic hormones)
  - Adenomas, hyperplasia, carcinoma of anterior pituitary, etc
- **Hypopituitarism** (deficiency of trophic hormones)
  - Ischemic injury, surgery, radiation, inflammation
- **Local mass effects**
  - sella turcica abnormalities

Pituitary gland diseases of various etiologies can either present as too much trophic hormone (hyper-) or too little (hypo-).
Case 1

• 35 year old female presents with amenorrhea, galactorrhea, visual complaints and headache. CT scan discloses a 2 cm mass in the anterior pituitary.
• What’s the most likely cause?
• What could explain the “visual disturbances”?
The anatomy of the brain shows how mass effect from a pituitary adenoma can cause visual field deficits. Visual information coming from the part of the visual field where this text box is located would not be relayed if a pituitary adenoma impinged upon the decussating fibers of the optic chiasm.

Notice the proximity of the pituitary to the optic chiasm. It should be no surprise that a pituitary adenoma could push on the optic chiasm and cause bitemporal hemianopsia.

The pituitary would be right about there.
Pituitary Adenomas

- Most common cause of hyperpituitarism
- Functional or non-functional
- Affects adults (35-60)
- Microadenomas: < 1 cm
- Macroadenomas: > 1 cm
- Gross appearance: soft, well-circumscribed, and confined to sella turcica
- Microscopically: monotonous population of polygonal cells lacking significant reticulin framework.

The non-functional adenomas (i.e. no hypersecretory symptoms like galactorrhea) tend to get caught when big and cause compressive symptoms, like the bitemporal hemianopsia previously described. The functional adenomas tend to get caught when they are small since their hypersecretory symptoms are pronounced even when the tumor is not very large.

To understand what this means, go to slides 11, 12, and 13 to see the explanation of what the normal microanatomy should look like. framework
A nonfunctional adenoma, which are characteristically large. This sucker was so big it grew out of the sella turcica; Dr. Veras said that outgrowing the sella turcica is usually not the case.

FIGURE 24–4 Pituitary adenoma. This massive, nonfunctional adenoma has grown far beyond the confines of the sella turcica and has distorted the overlying brain. Nonfunctional adenomas tend to be larger at the time of diagnosis than those that secrete a hormone.
This is the microscopic appearance of a pituitary adenoma.

Note that the sheets of cells all look the same (in her words: "monotonous population of polygonal cells").

Sometimes, a pathologist must differentiate between a pituitary adenoma and a normal or hyperplastic pituitary tissue. This can be done by examining aforementioned reticulin fiber framework using a special reticulin fiber stain (not shown here). Normal or hyperplastic pituitary tissue should have cells arranged in acini that are surrounded by a well-developed reticulin network. Pituitary adenomas would show a breakdown of the reticulin fiber network as demonstrated by a loss of reticulin fiber staining.
This is normal pituitary tissue noted for its diverse cells, well-demarcated acini, and a robust reticulin network (which would be best seen with a special reticulin fiber stain).

Note the diversity of cells in normal pituitary. You have acidophils and basophils of various staining intensity.

Look at how the acini seem to be separated. A reticulin stain would show a very nice intact reticulin network surrounding each acinus.
I inserted this slide to show you what a reticulin stain would look like in a normal pituitary vs an adenoma.

**A**
Normal pituitary
w/ intact reticulin
network surrounding
the acini

**B**
Pituitary adenoma
w/ the breakdown of
the reticulin network
around the acini

What is the size of a microadenoma? What is the size of a macroadenoma?
Starting to go into some specific pituitary adenomas.
Prolactinoma ----> hyperprolactinemia

Few words about specific adenomas

• **Prolactinomas:**
  - Most common pituitary adenoma
  - Tendency for calcification ("pituitary stone")

• **Causes of hyperprolactinemia:**
  • Prolactinoma, pregnancy, lactotroph hyperplasia (inhibition of dopamine secretion)

  Dopamine(inhibitory) ➔ prolactin

  Tx: dopamine receptor agonists

Any time you have inhibition of dopamine secretion (e.g. stalk damage or apoplexy) you get hyperprolactinemia.

Simulate dopaminergic inhibition of the adenohypophysis to decrease prolactin secretion.
Few words about specific adenomas

- **Growth hormone cell adenomas:**
  - Second most common
  - Elevated GH → hepatic secretion of insulin-like growth factor (IGF-1)
  - Dx: failure to suppress GH after oral glucose dose
  - Tx: somatostatin analogs

**Clinical Presentation:**
Adults: acromegaly
Children: gigantism

Remember that GH is stimulated during hypoglycemia because it causes hepatic gluconeogenesis and reduced hepatic glucose uptake. On the other hand, hyperglycemia suppresses GH secretion because we already have enough blood glucose. In a pituitary adenoma, these feedback loops are lost so an oral glucose challenge would not yield the expected decrease in GH.

Somatostatin secreted by the periventricular nucleus inhibits GH secretion and acts as a counter to GHRH.
Acromegaly due to growth hormone cell adenoma. Before and after.

Mrs. A. B., aged twenty years, showing normal appearance of the patient.  
(Pershing.)

Same patient, aged forty-two years, affected with acromegaly.
Few words about specific adenomas

- ACTH cell adenomas:
  - ACTH → cortisol (adrenal) → Cushing’s dz
  - Removal of adrenals in Cushing’s sd → large adenomas → Nelson syndrome

- Pituitary carcinomas:
  - rare
  - functional (ACTH or prolactin)

**Cushing's disease** is pituitary in origin, and is defined as excess ACTH secretion from the pituitary.

**Cushing's syndrome** is simply a result of excess glucocorticoid whether it is pituitary or adrenal in origin. Thus, Cushing's disease is one cause of Cushing's syndrome but not vice versa.

**Nelson syndrome:** Removal of the adrenal glands leads to no more cortisol to inhibit ACTH production by negative feedback. Thus, ACTH cell adenomas grow unchecked. This presents as muscle weakness due to excess ACTH and skin hyperpigmentation due to excess melanocyte stimulating hormone, which is also increased because it is one of the products of POMC, a precursor to ACTH.
Hypopituitarism

• Causes:
  - Tumors, mass lesions, brain injury, subarachnoid hemorrhage
  - Pituitary surgery or radiation
  - Pituitary apoplexy (neurosurgical emergency)
  - Ischemic necrosis of pituitary and Sheehan sd: postpartum necrosis of anterior pituitary
  - Rathke cleft cyst
  - Empty sella syndrome (primary vs. secondary)
  - Hypothalamic lesions
  - Inflammatory disorders

These are some causes of hypopituitarism. She just mentioned the two highlighted ones and didn't say much more.

This is usually a postpartum complication after extensive bleeding. It results in necrosis of the anterior pituitary and deficiency of all the hormones secreted by the adenohypophysis.

What is the most common pituitary adenoma? What is the second most common?
Posterior Pituitary syndromes

- **Diabetes insipidus:** ADH deficiency
  - Central (hypothalamic) vs. Nephrogenic (renal tubular unresponsiveness to ADH)
  - Polyuria and increased thirst
  - Dilute urine with low specific gravity
  - High serum sodium and osmolality

- **Syndrome of inappropriate secretion of ADH (SIADH)**
  - Hyponatremia
  - Small cell carcinoma of lung (ectopic ADH secretion)

Problems in the posterior pituitary concern ADH (either deficiency or excess)

Problem with inadequate ADH production or secretion

Nothing wrong with secretion of ADH, the pituitary, or hypothalamus. The kidney is the problem in that it has tubular damage, nonfunctional ADH receptors, or nonfunctional

You retain too much water! This essentially dilutes your sodium concentration.

What other endocrine paraneoplastic syndrome is associated with small cell carcinoma of the lung?
The thyroid gland is under control of the pituitary and regulatory feedback loops.

Will exogenous ADH correct the hyponatremia in nephrogenic diabetes mellitus?

Blue arrows indicate induction of secretion. Red arrows indicate inhibition of secretion as a means of negative feedback regulation.
Thyroid gland

- **Thyroid follicular cells**: convert thyroglobulin into T4 (thyroxine) and triiodothyronine (T3)
- **Parafollicular cells (C cells)**: calcitonin (absorption of calcium by skeletal system and prevent resorption of bone by osteoclasts)

T3 is much more metabolically active than T4. The main effect of T3 is to raise the basal metabolic rate of the body.

Calcitonin conserves calcium in bone. It has the opposite effect of parathyroid hormone.

The thyroid's primary metabolically active hormonal secretions are T3 and calcitonin.
Hyperthyroidism (thyrotoxicosis)

• Elevated free T3 and T4

• Causes:
  - Diffuse hyperplasia of thyroid due to Graves dz (85%)
  - Hyperfunctional multinodular goiter
  - Hyperfunctional adenoma

**Hyperthyroidism:** Too much T3, the metabolically active thyroid hormone.

Grave’s disease is an autoimmune disease in which autoantibodies against the thyroid stimulating hormone receptor (TSHR) of the thyroid follicular cells activate the receptor. This causes an increase in the production and secretion of T3 and T4 independent of TSH. In fact, the high levels T3 and T4 would downregulate TRH and TSH secretion. Thus, Grave’s disease is noted for paradoxically high T3 and T4 with low TRH and TSH.

**Long story short...**
Grave’s Disease: T3 and T4: high
TRH: Low
TSH: Low

Multinodular goiter doesn’t always produce hyperthyroidism. It can produce a euthyroid state or hypothyroidism.
Hyperthyroidism's symptomology, especially increased basal metabolic rate, is due to elevated T3 and T4.

Clinical symptoms and lab diagnosis

- **Increased basal metabolic rate**
- Warm and flushed skin
- Heat intolerance, sweating
- Weight loss, increased apetite
- Cardiac manifestations (tachycardia, arrhythemias, heart failure)
- Ocular changes (thyroid ophthalmopathy)
- Decreased TSH; increased free T4 or T3
- Radioiodine uptake (etiology)

Most of the subsequent symptoms are due to the increase in basal metabolic rate and adrenergic stimulation (one of the initial treatments for Grave's is beta blockers).

This helps differentiate between factitious hyperthyroidism, which is due to exogenous thyroid hormone medication and does not cause increase uptake of radioiodine for T3 and T4 synthesis, and true hyperthyroidism, which would cause increased uptake of radioiodine due to increase endogenous production of T3 and T4.
Hyperthyroidism is noted for very protuberant and wide eyes.

What are the concentrations of T3 and T4, TRH, and TSH in Grave’s disease relative to physiologic levels?

The increased basal metabolic rate and subsequent sympathetic overdrive causes the wide-eyed staring gaze. Remember, that sympathetic drive is fight-or-flight, in which you'd want your eyes to be wide open to get a handle on your surroundings.

Buildup of glycosaminoglycans (GAG) in retro-ocular muscles and connective tissue cause the protuberant eyeballs.

FIGURE 24–9 A person with hyperthyroidism. A wide-eyed, staring gaze, caused by overactivity of the sympathetic nervous system, is one of the features of this disorder. In Graves disease, one of the most important causes of hyperthyroidism, accumulation of loose connective tissue behind the eyeballs, also adds to the protuberant appearance of the eyes.

Copyright © 2010 by Saunders, an imprint of Elsevier Inc.
More ophthalmopathy due to hyperthyroidism.

Panels A and B: pre treatment
Panels C and D: post treatment
Dissected eye and retro-ocular muscles with ophthalmopathy due to hyperthyroidism.

hyperthyroidism

edematous and engorged due to GAG deposition

Normal
Hypothyroidism

- Decreased levels of thyroid hormone
- **Common in the population** (0.3%)
- F:M = 10:1
- Primary:
  - Autoimmune thyroiditis (Hashimoto)
  - Iodine deficiency
  - Drugs (lithium, etc)
  - Dyshormonogenetic goiter
- Secondary:
  - TSH or TRH deficiency
Cretinism:
- Hypothyroidism that develops in early childhood
- Impaired development of skeletal and CNS, severe mental retardation, short stature, coarse facial features, protruding tongue and umbilical hernia

Myxedema:
- Hypothyroidism that develops in older child or adult

Presentations of hypothyroidism: Cretinism = children. Myxedema = older children and adults

Reversibility is dependent on timing of treatment. She did not specify the timing.

Myxedema:
- A specific form of cutaneous and dermal edema due to deposition of connective tissue components like GAGs

NOTE: Pretibial myxedema is different and occurs in Grave's disease, which is a hyperthyroid disease.
An extreme example of goiter, which is a swelling of the thyroid gland most commonly due to iodine deficiency. Goiter can be a presentation of both hypo- and hyperthyroidism.

What does hypothyroidism in children present as?
Infantile hypothyroidism

Infantile hypothyroidism 17 months of age
West. 1894. In Gould and Pyle, Anomalies and Curiosities of Medicine, 1896, p. 806

6 months after thyroid extract therapy

One year after treatment

Note the skeletal deformities, short stature
Hashimoto thyroiditis

- Most common cause of hypothyroidism (normal iodine level areas)
- Autoimmune destruction of gland
- **Painless symmetric enlargement** of gland
- **Older women** are more affected (10:1 to 20:1 / F:M)
- Genetic predisposition
- Increased risk for other autoimmune disorders and B-cell non-Hodgkin lymphomas
- Pathogenesis: progressive depletion of thyroid epithelial cells and replacement by mononuclear cells.
Hashimoto thyroiditis

FIGURE 24–10 Pathogenesis of Hashimoto thyroiditis. Breakdown of peripheral tolerance to thyroid auto-antigens, results in progressive autoimmune destruction of thyrocytes by infiltrating cytotoxic T cells, locally released cytokines, or by antibody-dependent cytotoxicity.
Gross appearance of a thyroid with Hashimoto's thyroiditis.

Very fleshy and whitish because it is completely infiltrated by mononuclear cells.

It actually looks like the cut surface of a lymph node, which makes sense given that there is infiltration by mononuclear inflammatory cells that are forming germinal centers.

Gross appearance of a thyroid with Hashimoto's thyroiditis (mimicks lymphoma)
Normal thyroid for reference.

Normal Thyroid

Note that the normal thyroid has a "fleshy, beefy" appearance.
Pathology

- Mononuclear inflammatory infiltrate
- Germinal centers
- Hurthle cells (epithelial cells with abundant eosinophilic, granular cytoplasm)

Note that the follicles have been destroyed and replaced by germinal centers.

These three things are used to diagnose Hashimoto's.
FIGURE 24–11 Hashimoto thyroiditis. The thyroid parenchyma contains a dense lymphocytic infiltrate with germinal centers. Residual thyroid follicles lined by deeply eosinophilic Hürthle cells are also seen.
Subacute (granulomatous) thyroiditis

De Quervain thyroiditis

- Much less frequent than HT
- F:M 3:1 to 5:1
- Post-viral inflammatory process (seasonal)
- Neck pain, fever
- Transient hyperthyroidism > transient hypothyroidism > full recovery

Pathology:
- Follicles destroyed by neutrophilic microabscesses
- Multinucleate giant cells enclosing pools of colloid

What three microscopic observations are used to diagnose Hashimoto’s thyroiditis?
FIGURE 24–12 Granulomatous thyroiditis. The thyroid parenchyma contains a chronic inflammatory infiltrate with a multinucleate giant cell (above left) and a colloid follicle (bottom right).
Subacute lymphocytic (painless) thyroiditis

- Uncommon cause of hypothyroidism
- Commonly “postpartum thyroiditis”
- **Mild gland enlargement** and hyperthyroidism
- Pathology:
  - Lymphocytic infiltration and germinal centers
  - No Hurthle cells or fibrosis

It goes through the same transient hyperthyroidism by the same mechanism as in De Quervain’s thyroiditis.

tends to be transient
Graves Disease

- Most common cause of endogenous hyperthyroidism (85-90%)
- Triad: hyperthyroidism; infiltrative ophthalmopathy (exophthalmos); localized, infiltrative dermopathy (pretibial myxedema)
- F:M > 7:1
- Genetic susceptibility (HLA-B8 and DR3)
- Autoimmune disorder:
  - Autoantibodies to TSH receptor:
    - LATS (long-acting thyroid stimulator); IgG Ab
    - Thyroid growth-stimulating Ig (TGI)
    - TSH-binding inhibitor Igs (TBII)

Memorize LATS! It is the IgG Ab that targets the TSH-R to cause the gland to grow and secrete thyroid hormones.

This is different from the myxedema associated with adult hypothyroidism.

Very high genetic susceptibility.

Instead of destroying the gland like in Hashimoto’s thyroiditis, the autoantibodies stimulate the TSH receptor. This causes the gland to grow and keep secreting thyroid hormones.
Gross appearance of a Grave's Disease thyroid

FIGURE 24–13A Graves disease. A, There is diffuse symmetric enlargement of the gland and a beefy deep red parenchyma. Compare with gross photograph of multinodular goiter in Figure 24–15. B, Diffusely hyperplastic thyroid in a case of Graves' disease. The follicles are lined by tall, columnar epithelium. The crowded, enlarged epithelial cells project into the lumens of the follicles. These cells actively resorb the colloid in the centers of the follicles, resulting in the scalloped appearance of the edges of the colloid.

(Reproduced with permission from Lloyd RV et al. (eds): Atlas of Nontumor Pathology: Endocrine Diseases. Washington, DC, American Registry of Pathology, 2002.)
**Graves Disease**

- Symmetric enlargement of gland
- Diffuse hypertrophy and hyperplasia
- **Crowded and tall follicular cells; small papillae**
- Mononuclear infiltrates are common
- **Scalloped colloid**
- Elevated free T4 and T3; depressed TSH; increased RAIU

---

**Microscopic description of thyroid in Grave's Disease**

- Normal follicles would be nice and round.
- Scalloped colloid refers to the round, white circles on the edges of the colloid space. This indicates active uptake of stored colloid.

---

These refer to pseudopapillae since they lack the fibrovascular core that is characteristic of true papillae. Since papillary carcinomas contain real papillae, the presence of papillary structures place papillary carcinoma on your differential. Thus, it is important to distinguish between pseudopapillae and true papillae to distinguish between Grave's and papillary carcinoma.
Pseudopapillae and scalloping in Graves’ disease

- Note how tall those follicular cells are.
- Note the scalloped colloid (edges of the colloid look like they have round bites taken out of them).
- Note this pseudopapillae. It lacks the fibrovascular core of a true papillae.
**Diffuse and Multinodular Goiters**

- **Dietary iodine deficiency** $\rightarrow$ impaired synthesis of thyroid hormone (goiter)
- **Increased TSH** $\rightarrow$ compensatory in gland functional mass $\rightarrow$ **euthyroid state**
- **Diffuse nontoxic (simple) goiter**
- **Multinodular goiter**

*In Grave's disease, how do you describe the colloid?*
Gross appearance of a multinodular goiter.

She pointed out this round and encapsulated follicular adenoma. It is not uncommon to see multiple diseases in a thyroid.
Thyroid neoplasms

- **Follicular adenomas** (well-encapsulated; cold nodules; sometimes “toxic”)
  - 20% have point mutations in RAS
- **Carcinomas**:
  - 1.5% of all cancers  
    - Female predominance
  - Papillary (75-85%)
  - Follicular (10-20%)
  - Medullary (5%)
  - Anaplastic (<5%)

“cold” means nonfunctional

**Luckily, the papillary carcinomas have a good prognosis**
Gross appearance of a follicular adenoma with its characteristic capsule.

This emphasizes that follicular adenomas are encapsulated. It is important to find the capsule for diagnosis because under microscopy, the normal follicles and adenomatous follicles look the same.

FIGURE 24–16A Follicular adenoma of the thyroid. A, A solitary, well-circumscribed nodule is seen. B, The photomicrograph shows well-differentiated follicles resembling normal thyroid parenchyma.
FIGURE 24–16B Follicular adenoma of the thyroid. A, A solitary, well-circumscribed nodule is seen. B, The photomicrograph shows well-differentiated follicles resembling normal thyroid parenchyma.
Follicular carcinoma

- About half harbor RAS mutations
- NRAS is the most common
- PAX8-PPARγ1 fusion
- 2nd most common specifically, the second most common thyroid neoplasm
- Female predominance; older age
- Increased incidence in areas of iodine deficiency
- Cold nodules
- Tendency for vascular invasion (not lymphatic)
FIGURE 24–20A Follicular carcinoma. A, Cut surface of a follicular carcinoma with substantial replacement of the lobe of the thyroid. The tumor has a light-tan appearance and contains small foci of hemorrhage. B, A few of the glandular lumens contain recognizable colloid.
Microanatomy of a follicular carcinoma. It is bland looking in that it looks like a normal thyroid or follicular adenoma without the capsule in view.

**FIGURE 24–20B** Follicular carcinoma. A, Cut surface of a follicular carcinoma with substantial replacement of the lobe of the thyroid. The tumor has a light-tan appearance and contains small foci of hemorrhage. B, A few of the glandular lumens contain recognizable colloid.

Copyright © 2010 by Saunders, an imprint of Elsevier Inc.
Capsular differences between follicular adenoma and follicular carcinoma.

In follicular carcinoma, the neoplasm invades the capsule. To prevent further spread of the tumor, the capsule reactively thickens. This thickening of the capsule can be used to differentiate an adenoma from a carcinoma.

In follicular adenoma, the capsule is nice and thin, encircles the tumor, and is not infiltrated by neoplasm.

Look at this guy trying to invade the capsule.

FIGURE 24–21A Capsular integrity in follicular neoplasms. In adenomas (A), a fibrous capsule, usually thin but occasionally more prominent, circumferentially surrounds the neoplastic follicles and no capsular invasion is seen (arrows); compressed normal thyroid parenchyma is usually present external to the capsule (top of the panel). In contrast, follicular carcinomas demonstrate capsular invasion (B, arrows) that may be minimal, as in this case, or widespread. The presence of vascular invasion is another feature of follicular carcinomas.
Capsular invasion is diagnostic of follicular carcinoma.

Capsular invasion in follicular carcinoma.
Vascular invasion is another diagnostic feature of a carcinoma versus an adenoma.
Papillary carcinoma

- Rearrangement of tyrosine kinase receptors RET or NTRK1
- ret/PTC fusion gene (1/5); children and background of radiation
- Mutations in the BRAF oncogene (1/3 to 1/2)
- RAS mutations
- **Most common thyroid cancer; excellent prognosis**
- Morphology: papillae, optically clear nuclei (ground glass or “Orphan Annie” eye), nuclear pseudo-inclusions, intranuclear grooves, psammoma bodies

Cytology is important in the diagnosis of papillary carcinoma because many of its distinguishing features are nuclear.

The nuclei are so convoluted that the cytoplasm interlaces itself into these convolutions such that it looks like there inclusions within the nuclei.

In what brain tumor would you see psammoma bodies?
Papillary carcinoma

• Types:
  • Encapsulated variant
  • Follicular variant
  • Tall cell variant
  • Diffuse sclerosing variant
  • Hyalinizing trabecular tumors
Histology of papillary carcinoma. The nuclear and papillary features can help you distinguish it from Grave's disease.

True Papillae in Papillary Carcinoma of the Thyroid. Note the crowded nuclei with optically clear nuclei (so-called Orphan-Annie eyes)
This is a reminder of what Grave's disease looks like under microscopy.
Crowded, optically clear nuclei in papillary carcinoma of the thyroid

Another picture of papillary carcinoma under microscope. You can see the coffee-bean appearance of certain follicular cells really well on this slide.
Metastatic papillary carcinoma in a lymph node

Lymph node metastasis of papillary carcinoma

This is invasion of the lymph node with papillary carcinoma. Even with this metastasis, the prognosis is still good.
Follicular variant of papillary carcinoma of the thyroid. There is one abortive papilla in the center of the picture.
Psammoma body in papillary carcinoma

Psammoma body: concentric and laminated calcification found in various tumors in the body. However, it is diagnostic of papillary carcinoma in the thyroid.
Medullary Carcinoma

- Parafollicular C cells (neuroendocrine neoplasm) → calcitonin secretion
- Sporadic: 80% of cases
- Familial forms: MEN-2 (RET protooncogene point mutation)
- Solitary or multiple nodules
- Polygonal or spindle-shaped cells
- Nests, trabeculae or follicles
- Amyloid deposits
Gross appearances don't really help you diagnose medullary carcinoma.

**FIGURE 24–22A** Medullary carcinoma of thyroid. A, These tumors typically show a solid pattern of growth and do not have connective tissue capsules. B, Histology demonstrates abundant deposition of amyloid, visible here as homogeneous extracellular material, derived from calcitonin molecules secreted by the neoplastic cells.

(Courtesy of Dr. Joseph Corson, Brigham and Women’s Hospital, Boston, MA.)
Nests of cells surrounded by fibrovascular stroma is characteristic of neuroendocrine tumors.

This slide emphasizes the cell nests surrounded by fibrovascular stroma characteristic of medullary thyroid carcinomas.
This slide emphasizes the amyloid deposits characteristic of medullary thyroid carcinomas.

Spindle cell pattern and hyaline material

deposition of hyaline material = amyloid
This slide emphasizes the amyloid deposits characteristic of medullary thyroid carcinomas.

Hyaline deposits crowd the tumor cells
Apple-green color with Congo red stain and polarization = amyloid. Again, another slide emphasizing that medullary thyroid carcinomas have amyloid deposits.

"Apple green" staining with Congo red stain and polarization demonstrates the hyaline deposits to be amyloid.
FIGURE 24–23 Electron micrograph of medullary thyroid carcinoma. These cells contain membrane-bound secretory granules that are the sites of storage of calcitonin and other peptides.
Poorly-Differentiated Carcinoma

- 5-10% of thyroid carcinomas
- Definition is unsettled.
  - 1. Morphology is similar to medullary carcinoma but without amyloid or calcitonin
  - 2. Necrosis and more than 5 mitoses/hpf
- Less than 50% 5 year survival

She skipped this. It isn't in Robbins. Just know that it has a bad prognosis.
"Poorly-differentiated" or "insular" carcinoma

She skipped this. It isn't in Robbins. Just know that it has a bad prognosis.
Anaplastic carcinoma

- Highly aggressive, lethal tumors
- Inactivating point mutations of \( p53 \) tumor suppressor gene
- Older patients (65 yo)
- Hx: multinodular goiter, differentiated carcinoma
- Morphology: anaplastic cells (pleomorphic, giant cells, spindle cells, small cells)
Microscopic observation of anaplastic carcinoma reveals many pleomorphic cells and many mitotic figures.
Note the bizarre pleomorphism in anaplastic carcinoma.

Bizarre cells in anaplastic carcinoma of the thyroid
She breezed past this saying we could look at it on our own. The diagram just shows what molecular disruptions in follicular cell pathways can lead to a particular thyroid cancer.

Schematic picture of molecular alterations seen in thyroid carcinomas

FIGURE 24–18 Genetic alterations in follicular cell–derived malignancies of the thyroid gland.

Copyright © 2010 by Saunders, an imprint of Elsevier Inc.
Congenital anomalies

- **Thyroglossal duct or cyst:**
- Most common clinically significant congenital anomaly of thyroid
- Mucinous, clear fluids may collect (spherical masses)
- **Midline** of neck (anterior to trachea)
- Higher lesions: stratified squamous epithelium
- Lower lesions: thyroidal acinar epithelium
- Can give rise to cancer

Embryology connection: The thyroid initially develops in the fetal oropharynx and descends through the tongue (hence, thyroGLOSSAL duct) and neck to reach its final position. Along its migratory path, it forms a duct that normally atrophies and closes. When this duct fails to close, a persistent duct or cyst can form.
Infected thyroglossal cyst. Note that it is midline and anterior to the trachea. This contrasts branchial cleft cysts, which are located more laterally.
Histology of a thyroglossal cyst.

- Cystic space
- Cystic lining

Stratified squamous lining of the thyroglossal cyst

Given the stratified squamous lining of this cyst, is it a higher or lower lesion?
Adrenal medulla

- Distinct from adrenal cortex
- **Neural crest** (neuroendocrine or chromaffin cells)
- Sustentacular cells
- **Produce catecholamines** (epinephrine and norepinephrine)
- Adrenal medulla: part of **paraganglion system**

*These cells wrap around the chromaffin cells to provide structural support*
Pheochromocytoma

- Neoplasms composed of *chromaffin* cells
- Release catecholamines
- Surgically correctable HTN
- Rule of “10s”
- 10% are extra-adrenal (paragangliomas), bilateral, malignant and not associated with HTN
- 25% → germline SDHB mutation
- Dx: Urinary free catecholamines, vanillylmandelic acid, metanephrines
Normal Adrenal
Normal medullary cells. Note vascularity and trabecular arrangement of cells.
On low power, you can tell that in pheochromocytoma, the slide looks more eosinophilic than the normal medulla shown two slides ago.
Pheochromocytoma. Bizarre cells

Crazy looking nuclei and morphology. compare to the normal cells two slides ago.
Multiple Endocrine Neoplasia syndromes (MEN syndromes)

- **Genetically** inherited disorders with associated proliferations (hyperplasias, adenomas, carcinomas)
- **MEN 1 (Wermer syndrome) or “3Ps”**
- Rare; germline mutation of MEN1 TSG (menin)
- Primary hyperparathyroidism (hyperplasia or adenoma)
- Endocrine neoplasm of pancreas
- Pituitary adenomas (prolactinoma)

- **Pituitary**: adenomas
- **Parathyroid**: primary hyperthyroidism
- **Pancreas**: Islet cell tumors

Menin is a tumor suppressor gene product of MEN1. Thus, loss-of-function mutation of this gene would predispose one to cancer.
• MEN 2
• MEN 2A (Sipple syndrome)
• Germline mutation of RET protooncogene
  • Pheochromocytoma
  • Medullary Carcinoma of thyroid
• Parathyroid hyperplasia
• MEN 2B
• Medullary Carcinoma of thyroid
• Pheochromocytoma
• Mucosal neuromas or ganglioneuromas
• Marfanoid habitus

*shared; then remember what is different to differentiate between MEN2A and MEN2B*