MALE PATHOLOGY

Penis

Epispadias is the urethral opening is on the dorsal penis (on top when erect and standing up). Hypospadias is when the urethral opening is on the ventral penis (on the bottom when erect and standing up). This is more common than Epispadias, and is caused by the failure of the urethral folds to fuse.

Cryptorchidism is when the undescended testes remain in the abdomen or the inguinal canal. This can lead to hypotestosteronism and infertility. More importantly, there is an increased risk for testicular carcinoma.

Balanitis is inflammation of the glans penis. The risk factors are poor hygiene and the absence of circumcision. The patient will accumulate a substance called smegma (that’s a real thing, though I call it shmegma, like Dr. Evil’s Magma) which can lead to inflammation and subsequent infection.

Peyroni’s Disease. Fibroblast get activated and lay down collagen in the penis. This causes painful curved erections. There may or may not be a palpable nodule of fibrous tissue in the penis.

Chondylomas Accuminata. This is caused by HPV strains 6 and 11. These are genital warts which cause the same condition in female pathology. We learned about these there and in dermatopathology.

Squamous Cell Carcinoma. SCC of the penis occurs almost exclusively in uncircumcised males infected with HPV stains 16 and 18. Just like cervical cancer in female pathology, HPV can cause a cancer in males. There is squamous dysplasia, and the skin may be keratinized or not. Look for keratin pearls and cytoplasmic bridging (classic for any form of squamous cell carcinoma). Precursor lesions include Bowen’s Disease, Bowenoid Disease, and some (de Quervat) French-sounding name you need not worry about. These are simply different grades and basically represent carcinoma in situ. Be sure not to confuse the HPV strains. Remember that the E6 and E7 component of HPV 16 or 18 cause cancer. Interestingly, males are not inoculated for these strains, as women are with Gardisil.

Testes

Varicocele. Dilated, tortuous veins in the spermatic cord feels like a bag of worms. These will decompress when the patient lies down. Since there is so much blood flow going by the testes, they are warmed to a temperature which puts the patient at risk for male infertility.
Path Endocrine Paragraph Format

**Hydrocele.** This is too much fluid within the *tunica Vaginalis* that came down from the abdomen through the patent Processus Vaginalis.

**Spermatocele.** This is a dilate portion of the epididymitis that contains sperm

**Epididymitis.** For *acute* condition, there will be pain the posterior aspect of the testes. While not always caused by bacteria, for the exam, assume that it is. For sexually active individuals (<35 years of age) pick the STD like *gonorrhea* or Chlamydia. For inactive individuals (>35 years of age) choose the GI gut flora such as *E. Coli.* For the *chronic* condition, it will be caseating, since it is usually caused by TB

**Orchitis.** There is a *unilateral enlargement* of the testes, often caused by a *virus* such as Mumps.

**Testicular Torsion.** This is common in young males, associated with physical activity or trauma. Normally, the testes are tacked down to the wall by connective tissue. In some people, they are allowed to freely hang. This allows the testes to *twist around the spermatic cord,* causing *strangulation of the vasculature.* This puts the testes at risk for ischemia and infarction, which constitutes a medical emergency. With torsion of one testes comes risk for torsion of the other testes. Therefore, when they fix on, they fix both at the same time, prophylactically, surgically supporting the testes to the wall of the inguinal canal and scrotum.

**Testicular Carcinoma**

Testicular carcinomas are generally *painless masses within the testes.* Risk factors include testicular Dysgenesis (Kleinfelter’s), Testicular Feminization, and Undescended Testes. Carcinomas are divided into germ cell (most tumors) and nongerm cell tumors (rare). Germ cell tumors are again divided into Seminomas and Nonseminomas. *Seminoma* is a discrete type of tumor of the testes that is most common in almost all age groups. It is responsive to radiotherapy and chemotherapy and has the best prognosis. *Nonseminomas* are multiple tumors lumped together (embryonal, Choriocarcinoma, teratoma, and Endodermal sinus). These are rarer, usually occur as a mixed tumor, are *not* radiosensitive, and carry a worse prognosis. Non-Germ Cell tumors have no general characteristics. We will go through each tumor to describe a bit about each one.

*Seminoma* is a *germ cell tumor.* This is the most common tumor in the 15-35 age group. On gross it presents as a *large, white, bulky, painless mass* that generally is NOT hemorrhagic. Under the scope there are “polygonal tumor cells” (which doesn’t really mean anything to you). More pathognomically, they demonstrate a *chronic inflammatory infiltrate, delicate fibrosis* and the possible *giant cell / granuloma formation.* Placental Alkaline Phosphatase is elevated (differential: biliary obstruction, bone metastasis). Unfortunately, the test can trip you up with Seminoma. When giant cells are present, it is possible that Seminoma produces hCG (which usually means Chorio). So if you see elevated hCG look for choro. If it’s not present, then pick seminoma. This can be treated with *both radio* and *chemotherapy.* It has an excellent prognosis.

*Embryonal* is a *germ cell tumor.* It is not commonly tested, though it occurs in the 20s-30s presenting as a *large, white, bulky, painless mass* that generally IS hemorrhagic/necrotic (differential from Seminoma). It is strikingly different on Histo, demonstrating *primitive cells* resembling mesenchyme, making it more aggressive. Can have any serum marker since embryonal tissue can progress on to any of the other germ cell tumors.
**Choriocarcinoma.** This is a Board Favorite. This is the **fastest growing, most malignant** germ cell tumor. Remember that this one spreads **hematogenously** opposed to the lymph spread of all the other germ cell tumors. It is composed of **syncytiotrophoblasts** next to **cytotrophoblasts**. On gross, it is generally a **small mass** because it disseminates so quickly. The tumor marker of choice is **hCG**. It carries the worst prognosis.

**Endodermal Sinus/YolkSac.** You must learn both names of this **germ cell tumor.** This is the most common germ cell tumor in **children**. It can occur in adults, but it generally occurs as mixed. On histology, there are **Shiller-Duval Bodies**, which are basically the tumor trying to form yolk-sac elements. In the blood, look for **alpha-feto-protein**.

**Teratoma.** These are **germ cell tumors** consisting of **two or more germ layers** (endoderm, ectoderm, mesoderm). This is the same tumor that can occur in women. They form **cystic masses**, often possessing skin, hair, and teeth. In general, one must decide whether these tumors are mature (benign) or immature (malignant). In males, **all teratomas are assumed to be immature/malignant** (striking contrast to almost all benign in females). There is no serum marker for Teratomas.

**Mixed.** More than 60% of germ cell tumors are mixed.

**Leydig Cell Tumor.** This is a **stromal cell tumor**. Leydig cells make androgens and estrogen. Commonly occurring in adult life (20-50), patients will present with a **painless intratesticular mass**. The tumor is making androgens and estrogen. The androgen effect in males is hard to notice (more hair, deeper voice). The **estrogen effect** is more pronounced: **gynecomastia** + intratesticular mass = Leydig Cell. If the tumor occurs in a child before puberty (which is rare), the androgens can induce precocious puberty. The prognosis is good, most of the time these tumors are benign.

**Lymphoma.** This is a **tumor of the testes** that is not associated with the tissue of the testes. Occurring in the **elderly** (60+) it is most often a B cell lymphoma. It occurs as an insinuating mass, essentially taking over the testes, difficult to spot on gross. The tumor can be seen invading both stroma and parenchyma on histology. The prognosis is poor.

**Reminder on Prostate** (Dr. Crawford told us there might be a Bonus Question on it)

**BPH.** Benign Prostatic Hypertrophy is really a **Hyperplasia** of the central/Periurethral zone resulting from **DHT** stimulation. The prostate grows, palpable as a **nodular rubbery mass**. This is **NOT premalignant**, though incidence increases with age (as does Prostatic Cancer). As the prostate enlarges, it causes urinary outflow obstruction. This presents as **trouble starting and stopping urination**, nocturnal urination, dribbling, and the inability to control the bladder. Over time, the bladder may hypertrophy or **hydroureter/hydronephrosis** may result. The old treatment was a transurethral resection (which was barbaric). Now, the prostate can be shrunk by drugs that block DHT (**finasteride**) that requires years to shrink the prostate and **alpha-1 blockers** for immediate symptom relief.

**Prostatic Carcinoma.** This is a malignant lesion occurring in the **peripheral zone**, usually in the posterior area. This is described as a firm or multinodular prostate on digital rectal exam. The tumor can be resected. However, it often occurs as a result of **old age**, where surgery may be precluded. In this case, **orchietectomy or chemical castration** (flutamide) is required to terminate the growth of the tumor. Most often asymptomatic, it is detected by digital rectal exams and PSA screens (usually REALLY high).
Path Endocrine Paragraph Format

REVIEW YOUR PHYSIO ENDOCRINE! That section is incredibly high yield. There is so much to know, learn, and figure out here, that it would be impossible to do it all at once in this small section. It is critical you understand your physiology and even histology; I am not going to go into intense detail on these, even though there is some pretty specific stuff. I felt like each gland was a whole chapter!

Pituitary

The pituitary diseases are essentially “hyper” or “hypo” functioning. Those that are Hyperfunctioning are generally adenomas, such as Prolactin (Prl), Growth Hormone (GH), or Corticotropin (ACTH) adenomas. Other adenomas are rare. Hypofunctioning generally relates to the destruction of the pituitary for any reason. The anterior pituitary receives a chemical signal from the hypothalamus through the portal system. The cells in the anterior pituitary secrete TSH, ACTH, GH, Prolactin, FSH and LH. The posterior pituitary is actually an extension of the hypothalamus; neuron somas in the hypothalamus have axon tracts that store and secrete oxytocin and ADH/Vasopressin. All tumors of the pituitary may cause a bitemporal heminaopsia as a result of compression on the optic chiasm.

Prolactinoma. This is the most common anterior pituitary adenoma. This is a tumor of lactotrophs, which produce Prolactin, producing a prolactinemia. If they are female, they will come in with a bilateral clear or milky nipple discharge (“normal” lactation). Infertility, osteopenia, and amenorrhea is possible. In males, there is a simple loss of libido (obviously harder to spot in male).

Growth Hormone Adenoma. GH is being released by the tumor. It activates IGF-1 in the liver, which induces growth. If this adenoma occurs in children, before closure of the epiphyseal plates there will be gigantism, where the patient is abnormally tall, with really long long-bones. If this adenoma occurs in adults, after the closure of the epiphyseal plates, only the bones that grow without epiphyseal plates will grow (face, hands, feet) resulting in acromegaly.

Corticotropin Adenoma. ACTH is being released by the tumor. This is a specific cause of Cushing’s Syndrome (see adrenal cortex) called Cushing’s Disease. In this case, ACTH is produced by the pituitary, which activates cortisol production from the adrenal cortex. Because the source of cortisol is actually the source of ACTH (the pituitary) and even adenomas retain some semblance of regulation of hormone synthesis, this is the only Cushing’s Syndrome that can be suppressed with the Dexamethasone test. Please read on to the Adrenal Gland for a more in depth discussion of presentation of Cushing’s Disease.
Sheehan Syndrome. This is an ischemic necrosis of the pituitary secondary to postpartum hemorrhage and subsequent DIC. In order for the pituitary to lose function, about 75% of the gland must become infarcted. While other causes of DIC or hypotension can result in anterior pituitary deficiency, Sheehan syndrome is a postpartum infarction of the anterior pituitary.

Oxytocin. There is no defect in the absence of abundance of Oxytocin that we know of.

Diabetes Insipidus. This is a form of diabetes. There is usually a preceding trauma, such as a car accident, that causes destruction of the pituitary stalk. Since the axons of the hypothalamus run through the stalk to the posterior pituitary, with trauma, the axons die, as do their ability to secrete ADH. Without ADH, the kidneys cannot resorb water. This causes a massive diuresis, concentrating whatever is left in the body. This presents as dehydration with hypernatremia. The patient often will consume large amounts of water every day, urinating frequently with an unconcentrated urine. Two potential conditions exist involving ADH. Central Diabetes Insipidus is the inability to make ADH, described above, treated with desmopressin (ADH analog). Nephrogenic Diabetes Insipidus is the inability of the kidneys to respond to ADH, a much worse condition since there is almost no solution.

Syndrome of Inappropriate ADH. This is often caused by a tumor outside the hypothalamus-pituitary, usually a paraneoplastic syndrome of small cell lung carcinoma. The production of ADH causes too much water to be resorbed, resulting in a hyponatremia (diluting the blood), increased vascular fluid volume, and cerebral edema. You must kill the cancer to stop the production of ADH, but make sure you restrict fluids in these patients (consumption of water will exacerbate the cerebral edema).

Thyroid

Goiter. Goiters can have many forms. Simple goiter is an enlargement of the goiter. Eventually, continued simply goiter gives rise to multinodular goiter. These are usually nontoxic goiters (generally nonfunctioning enlargement of the thyroid that does NOT produce T3/T4). Occurs usually in females that are asymptomatic except for an enlarged neck mass. These patients remain euthyroid. Late in the course, which occurs rarely, they can develop hyperthyroidism, called Plummer Syndrome. The most common cause of goiter in the world is iodine deficiency (usually mountainous regions) called the endemic form. The low iodine results in low T3/T4, which feeds back to the hypothalamus and pituitary and signals the “we need more T3/T4” signal. This signal is TSH which activates the follicular cells to make T3/T4, but also induces them to grow, thus making the goiter. This continues until the patient reaches T3/T4 normal levels.

Hyperthyroid. Defined as an elevated T3/T4 resulting in a hypermetabolic state. In general, these patients have exophthalmos, heat intolerance, diarrhea with malabsorption, and warm flushed skin. Tachycardia, palpitations, and agitation can be dangerous if not fatal. A give away in a vignette would be something along the lines of always turning down the temperature in the apartment. In the laboratory we must check levels of TSH and T3/T4. If both are elevated, then the problem is in the anterior pituitary. If the TSH is low and the T3/T4 is elevated, there is a problem in the thyroid. The most common cause of hyperthyroidism is Graves Disease (see later).
**Hypothyroid.** This is the opposite of hyperthyroid. There is a decreased T3/T4 resulting in a hypometabolic state. They often have cold intolerance, constipation, and cold skin. They do not suffer cardiac dysrhythmias, though they are often lethargic or overweight. In adults, they suffer from myxedema (deposition of GAGs in the skin). In kids, they suffer from cretinism (a severe growth defect represented by severe mental retardation and growth retardation).

**Grave’s Disease.** This is an autoimmune disease that causes the most common form of hyperthyroidism. It occurs most often in females in their reproductive years (20-50), a product of the production of stimulating anti-TSH-receptor immunoglobulins. They bind to, and activate, the TSH-Receptors, activating follicular action. This causes an excess in T3/T4. The production of T3/T4 is accelerated, so the consumption of colloid is also accelerated. This causes colloid scalloping on histology. The activation of TSH-Receptor is also a growth signal resulting in follicular hypertrophy and hyperplasia, represented on gross as a diffuse (opposed to nodular) growth. There are the classic signs of thyrotoxicosis (hyperthyroidism) in addition to ophthalmopathy (exophthalmos, the “bug-eyed” appearance from deposition of myxedema behind the eyes) and dermatopathology (pretibial myxedema).

**THYROIDITIS**

**Hashimoto’s Thyroiditis.** This is the most common cause of hypothyroidism excluding iatrogenic causes (excision of the thyroid or radio-iodine destruction are the most common). It also occurs most often in females in their later reproductive years (40-50), but is a product of Anti-TSH-Receptors as well as Anti-T3/T4 and Anti-Thyroxine Peroxidase Antibodies. The net effect is a transient hyperthyroidism caused by release of T3/T4 from the colloid as it is destroyed (called Hashitoxosis) followed by a chronic hypothyroid (a product of thyroid destruction). The gland presents as a painless mass in the throat. Under the scope are some important things. First it is inflamed (lymphocytes) that often form germinal centers. The follicular cells get injured, swelling with abundant pink cytoplasm, called Hurtle Cells. Hashimoto’s may be associated with other automimmune diseases (either endocrine or not) and Non-Hodgkin’s Lymphomas.

**Subacute Thyroiditis, Granulomatous Thyroiditis, De Quervain Thyroiditis.** Quervain rhymes with Pain. This is the second most common cause of hypothyroidism after Hashimoto’s, again in females in their reproductive ages. It is preceded by a viral infection and genetic susceptibility. It presents as a painful mass in the thyroid, especially when swallowing. Under the scope you will see granuloma formation. You may think “TB can cause granulomas.” However, in the thyroid, granulomas are pathognomonic for Subacute Thyroiditis. This, like a viral infection, is self-limiting. At first, as thyroid is destroyed, T3/T4 is released, producing a transient hyperthyroid (like the acute phase of Hashimoto’s). It is then followed by a transient hypothyroid (the chronic part of Hashimoto’s). However, unlike Hashimoto’s, there is almost always complete recovery after several months to a euthyroid state.
Subacute Lymphocytic Thyroiditis. This form did not make it into Kaplan’s review, but is in Robbins. It is a special form of lymphocytic infiltrate, without the formation of granulomas or germinal centers (it isn’t Hashimoto’s and it isn’t Granulomatous). Just know that this exists, probably as a distractor

Reidel’s Thyroiditis. This is a very rare form of thyroiditis. It causes dense fibrosis of the thyroid and wraps around, causing fibrosis of the other structures in the neck. This presentation can be sometimes confused for anaplastic carcinoma of the thyroid, given its old age predominance and its infiltration to nearby neck structures. With a biopsy, we see dense fibrosis that destroys or replaces the gland, whereas cancer would have glandular structures.

TUMORS OF THE THYROID

While adenomas are far more common than carcinoma, the thing that is commonly tested is Carcinoma and its subtypes. You need to focus on the carcinomas.

Adenoma. The most common type is follicular adenoma, presenting as single, painless masses in only one lobe of thyroid. These tend to be nonfunctional, that is, “cold” on a radiiodine scan. Because they do not pick up iodine, they do not make T3/T4, they are nonfunctional, and are generally asymptomatic. A small subset may be “hot” on radiiodine scan, which means functional, and may produce hyperthyroidism (called toxic adenoma).

Papillary Carcinoma. This is the most common thyroid carcinoma, occurring usually in women in their 20s-40s. It is associated with exposure to radiation (radiotherapy technicians, treatment of non-hodgkins lymphoma). Under the microscope you will see characteristic, pathognomonic Orphan-Annie Nuclei (clear nuclei with nuclear grooves) of cells forming a papillary growth pattern. Psammoma Bodies may be present, which, in a thyroid tumor, is pathognomonic (you can see psammoma bodies in Meningioma, Papillary Carcinoma Thyroid, and Papillary Carcinoma Ovary). This carcinoma spreads through the lymphatics. There is a great prognosis, resection and radioactive iodine work great. This cancer is measured in 20 year survival rates, with 90% alive at 20 years.

Follicular Carcinoma. While it accounts for only 15% of the thyroid cancer, it is important to learn about because it is the only one that spreads hematogenously. It doesn’t get asked that much and neither Kaplan, BRS, nor Goljan had much on it.

Medullary Carcinoma. This is the most commonly board tested thyroid tumor even though it represents 5% of the thyroid carcinomas. It is a carcinoma of the C Cells of the thyroid, which came from neural crest cells that produce Calcitonin. Under the scope, these tumors form nests. As they produce lots of protein (the Calcitonin) a unique feature emerges. There will be heavy amyloid deposition between and around the nests of cells, pathognomonic for medullary carcinoma. It is associated with MEN syndromes (particularly MEN2A and MEN2B, see adrenal medulla section).

Anaplastic Carcinoma. This is the rarest carcinoma of the thyroid occurring usually in elderly females (60+). It presents as a firm, large bulky mass in the neck. This has a dismal prognosis (weeks-months survival). It permeates the capsule and invades local structures, literally strangling the patient.
Parathyroid

Primary Hyperparathyroidism. This is an **elevation of PTH**. The goal of PTH is to **increase blood calcium** and **decrease blood phosphate**. It increases absorption of both in the Gut, It increases absorption of both from the Bone, it upregulates Vitamin D (stimulates 1-α-Hydroxylase) which also increases absorption of both, and finally it **increases calcium resorption** while **increasing phosphate excretion** in the kidneys. The most common cause of Primary Hyperparathyroidism, that is, the cause of ↑PTH is from the parathyroid gland is **parathyroid adenoma (80%)** usually associated with the MEN1 syndrome. Another condition that mimics primary hyperparathyroidism is a condition in which some other tumor secretes a **PTH-rp** (PTH-related protein) that acts like PTH but does not suffer the regulation that PTH does. This is seen in paraneoplastic syndromes such as **squamous cell lung cancer**. The total effect of elevated PTH is **hypercalcemia**. Too much calcium (look back to the T1 Guide Calcium lecture in physio) is **nephrocalcinosis/renal stones** and a shortened QT interval. The effect on the bone is constant resorption leading to **osteoporosis** or the super ube form **osteitis fibrosa cystica** (see bone). In general, hypercalcemia can be remembered as the “renal stones, psychic moans, abdominal groans, and painful bones.”

Secondary Hyperparathyroidism. **Chronic renal failure** results in **vitamin D deficiency** (the final step of Vitamin D synthesis is in the kidney). Decreased calcium level constantly permits PTH secretion (remember that CaSR inhibit PTH when the calcium is high, and permits PTH secretion when Calcium is low). It is, in effect, a physiologic change to make up the calcium difference. This is important because it can form **autonomous nodules** in the parathyroid which are free of CaSR regulation.

Hypoparathyroidism. This is caused by a **depressed PTH**. The most common cause is malpractice ready iatrogenic removal of the parathyroid glands (Thyroidectomy gone wrong). Another reason you could be missing PTH is **DiGeorge Syndrome** (failure to develop 3rd and 4th pharyngeal pouch, where the parathyroid gland fails to develop). In any case, PTH falls, calcium falls with it, and phosphate is up. People will present with **tetany, tingling**, and **Trousseau’s Sign** (during BP you get carpal spasm). The QT interval gets prolonged. Treatment is calcium supplementation and vitamin D.

Familial Hypercalciuric Hyperparathyroidism. This is an **autosomal dominant** disease whereby the CaSR “Set point” is elevated, so that it requires a **higher calcium level** to inhibit PTH secretion. These patients have slightly elevated PTH, slightly elevated Calcium, but are generally **asymptomatic**. This disease causes more concern for the doctor than it does the patient.

Hypercalcemia of Malignancy. **Cancer** can cause high calcium in one of two ways. **Bone metastasis** can induce bone destruction (↑osteoclasts via RANK) which simply destroys the bone and releases the calcium. Alternatively, there can be the secretion of **PTH-related Protein (PTH-rp)** as a paraneoplastic syndrome. It does the same thing as PTH, but has no calcium regulation.

Granulomatous Disease. For some reasons, chronic diseases involving **granulomas** may produce a hypercalcemia. An **extra-renal 1-α-hydroxylase** from macrophages ↑Vitamin D, without regard to PTH.

Medications. Some medications, like Isoniazid for TB can cause HyperCa.
Adrenal Gland

It is important to review the anatomy and physiology of the Adrenal Gland before we start. The adrenal gland is divided into the Adrenal Cortex and the Adrenal Medulla. The adrenal cortex is divided into the zones Glomerulosa (Aldosterone secretion, Salt Regulation), Fasiculata (Cortisol secretion, sugar regulation), and Reticularis (Androgen secretion). This can be remembered by several clever quibbs. Since the Adrenals sit on top of the kidneys, “GFR” is a way to remember the order of the cortex. Salt, Sugar, Sex, are the order of the hormones, remembered by the fact that “it gets better as you go deeper.” The adrenal medulla produces catecholamines (Norepi, Epi). Continuing with the Salt, Sugar, Sex theme, if we go deeper into the medulla, I suppose we start doing cocaine.

Cushing’s Syndrome. This is a disease of cortisol overproduction. It has 4 causes. (1) Iatrogenic is the most common and is caused by exogenous administration of glucocorticoids for a variety of reasons including inflammation. Caution must be made in discontinuing glucocorticoids because exogenous administration inhibits both the pituitary secretion of ACTH and therefore the adrenal cortex production of Cortisol, causing atrophy. Rapid removal of the exogenous cortisol does not give the tissue sufficient time to recover, resulting in an acute cortisol insufficiency. (2) Pituitary Adenoma called Cushing’s disease, where the problem is a tumor of the pituitary. This is the only form that is responsive to the dexamethasone test. (3) Adrenal Cortex Adenoma where the problem is a tumor of the adrenal cortex directly producing cortisol. (4) Tumor somewhere else producing a paraneoplastic syndrome, either ACTH or Cortisol (cortisol more likely). Symptoms of Cushing’s Syndrome are multiple. The most noticeable are moon facies, Truncal obesity, and the buffalo hump. Glucose intolerance and potential insulin resistance, osteopenia, and impaired wound healing are actually more debilitating, but less noticeable. Finally, proximal weakness from peripheral neuropathy may develop. Of all laboratory diagnostic features, you must remember that only Cushing’s disease responds to high dose dexamethasone.

Addison Disease. This is a disease of cortisol underproduction. The most common cause of Addison’s is autoimmune adrenalitis though tuberculosis and metastatic cancer (particularly lung) can cause it. While it is often discussed in relation to its cortical insufficiency, it is actually the destruction of adrenal cortex, leading to a deficiency in androgens, cortisol, AND aldosterone. In this case, cortisol effects dominate. Firstly, cortisol is low, so cannot feedback on the hypothalamus. Both the hypothalamus and pituitary know there is not enough cortisol, so try to make more. To do that, more CRH is made in the hypothalamus, which stimulates ACTH production in the anterior pituitary. The gene for ACTH happens to also be the gene for melanin (the protein is split up to form both). Therefore, with ↑ACTH generation, there is ↑melanin, leading to hyperpigmentation of the skin. The other major finding is a hypotension because cortisol is required for epinephrine to exact its vasoconstrictive effects. Other symptoms include a gradual onset to weakness, hypoglycemia (no catabolic cortisol to offset epinephrine and insulin), loss of libido and a poor response to stress. The good news is that this can be treated with exogenous administration of the missing steroids.

Conn Syndrome. This is a disease of hyperaldosteronism. This is a cortical adenoma of the zone glomerulosa. Increased aldosterone will cause overactivity of its receptor in the collecting ducts of the
kids. Aldosterone causes hypernatremia and hypokalemia along with an expansion of the extracellular fluid volume, aka hypertension (where Na goes, H₂O will follow). Because the signal is coming from a primary adrena, and sodium levels are high, the signal that would generate more aldosterone (the renin-angiotensin-aldosterone axis) is suppressed (↓renin). If we then contrast that to hypoaldosteronism the exact opposite is true: hyponatremia, hyperkalemia, and hypotension which contributes to the hypotension seen in Addison’s disease

Adrenogenital Syndromes. The overproduction of androgens can be caused by two major mechanisms: (1) cortical adenoma or (2) congenital adrenal hyperplasia. The cortical adenoma follows the same pattern as other primary adenomas for the adrenal cortex and isn’t really interesting (hormone made, lots of it, downregulation of its signal, ↓FSH/LH). Congenital Adrenal Hyperplasia is caused by inborn errors of metabolism, namely, 21-β-Hydroxylase Deficiency. This is the enzyme that takes progesterone down the road towards aldosterone and cortisol. Well, if that enzyme is deficient, those two never get made. If they never get made, a whole lot of precursor is hanging around. Of course, that precursor can also be used to make androgens, especially since its enzyme is still working. So, any time the body wants cortisol or aldosterone, it gets androgen instead. Since the body still needs aldo and cortisol, it sends the signal to make more of them. The only one made, though, is testosterone. The cycle continues until there is hyperplasia of the adrenal cortex and a crap-load of androgens. Obviously, there are going to be severities of disease. In the complete absence of cortisol and aldo there is basically death worse than in Addison’s, requiring exogenous administration for life. In most cases there is a mild deficiency, resulting in mild hyperpigmentation, hypotension, and hyponatremia. The presentation is virilization of the genitalia in females (creating ambiguous genitalia) and precocious puberty in a male. Substituting the missing steroids (aldo and cortisol) is curative.

Waterhouse-Friderichsen Syndrome. This is a form of acute adrenal insufficiency. Remember the other form involved exogenous administration of compounds that were rapidly removed. This disease is a bacterial septicemia induced hemorrhagic infarction of the adrenal glands. Seen commonly in kids infected with Neisseria Meningococcus, it is caused by a widespread, disseminated, meningococcal septicemia. The exact mechanism remains unclear, but either a systemic DIC or simple bacterial seeding destroys the adrenal glands bilaterally. This is usually incompatible with life, presenting with hypotension, acute adrenal insufficiency, DIC, and death.

Adrenal Medulla

Pheochromocytoma. This is a tumor of the adrenal medulla. It is fairly rare in life but abundant on shelf and Board exams. A pheochromocytoma produces epinephrine. But it does it so in a Pulsatile, paroxysmal fashion. This means that the patient will suffer from attacks of tachycardia, palpitations and hypertension in an episodic fashion. There is a rule of 10 to help you remember the key features of the disease. This is usually a tumor of adults (10% are in kids), is usually unilateral (10% bilateral), is a tumor of the adrenal gland (10% external), are usually benign (10% malignant), and are usually sporadic (10% are familial). There is an elevated urinary VMA and urinary catecholamines. The tumor has to be cut out in order to fix the condition. However, blood pressure must be controlled before attempting resection. Generally, we use nonselective alpha antagonists to control BP.
**MEN1 Syndrome.** Also known as *Wermer Syndrome,* this is an *autosomal dominant* mutation of *MEN1 gene* that causes hyperplasia or adenomas of the “3 Ps:” Pituitary Adenomas, Parathyroid Adenomas, and Pancreatic Adenomas. There is a strong association with Gastric Ulcers (Zollinger-Ellison syndrome from the pancreatic adenomas), Hypoglycemia (Insulinoma), and Hypercalcemia (PTH).

**MEN2A and MEN2B.** These are essentially the same disease and are not clearly separated. They are both caused by a mutation in the *RET proto-oncogene.* These cause endocrine tumors everywhere except the 3ps. Look for *Pheochromocytomas* and thyroid adenomas. The parathyroid glands can also be involved, but is not classic. Really, the only difference between 2A and 2B is the presence of *neuronal tumors* found in MEN2B.

\[
\begin{align*}
\text{MEN1} &= \text{Pituitary + Pancreas + Parathyroid} \\
\text{MEN2A} &= \text{Pheochromocytomas + Thyroid + Parathyroid} \\
\text{MEN2B} &= \text{Pheochromocytomas + Thyroids + Neuronal}
\end{align*}
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**Pancreas**

<table>
<thead>
<tr>
<th>COMPARISON OF TYPE 1 AND TYPE 2 DIABETES</th>
<th>Type I</th>
<th>Type II</th>
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<tbody>
<tr>
<td><strong>Named</strong></td>
<td>Insulin Dependent Diabetes Mellitus (IDDM)</td>
<td>Non-Insulin Dependent Diabetes Mellitus (NIDDM)</td>
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<tr>
<td><strong>Age</strong></td>
<td>Childhood (&lt;20 years)</td>
<td>Adult (&gt;30 years)</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Rapid</td>
<td>Insidious</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Thin to Normal</td>
<td>Obese</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>HLA-DR3, HLA-DR4 Haplotype Family history uncommon</td>
<td>Family History Common, no HLA haplotype African American and Native American at risk</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Autoimmune destruction of ( \beta )-islets, target is glutamic acid carboxylase No insulin production at all after destruction Trigger suspected to be a viral mimicry</td>
<td>Initial glucose intolerance Insulin resistance followed by ( \beta )-Cell dysfunction Need more insulin, Pancreas meets it, then burns out ↓ Insulin Receptor, Insulin Pathway Alterations</td>
</tr>
<tr>
<td><strong>Clinical Findings</strong></td>
<td>Polyuria, Polydypsia, Polyphagia and Weight loss, usually in kids Nephropathy, Retinopathy, Neuropathy, Cardiovascular</td>
<td>Recurrent Blurry Vision (retinopathy) Recurrent Infections (Candida, Bacteria) Nephropathy, Retinopathy, Neuropathy, Cardiovascular</td>
</tr>
<tr>
<td><strong>Metabolic Derangement</strong></td>
<td>DKA – hyperglycemia, coma, ketone bodies (butyric and acetooacetic), sugar &gt; 600</td>
<td>HNKC – hyperglycemia, coma, without Ketoacidosis, sugars in the 400-600</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Insulin</td>
<td>Weight loss (upregulates Insulin receptor synthesis) Oral Hyperglycemic (See pharm)</td>
</tr>
</tbody>
</table>

**Type 1 diabetes** is a disease of children, caused by *autoimmune destruction* of the pancreatic \( \beta \)-islets by targeting glutamic acid carboxylase following a viral infection. The child will present with polyuria, polydypsia, and polyphagia with weight loss, despite eating. They have *no insulin* and can suffer *diabetic Ketoacidosis* with sugar above 600. The only treatment is *insulin* injected with meals.

**Type 2 Diabetes** is a disease of *obese adults* caused by *burn out* of the pancreatic \( \beta \)-islets. A crap diet and obesity cause *dysregulation* and *downregulation* of the insulin pathway, requiring more insulin to achieve the same goal. Pancreatic output can keep up for a while, but eventually, the increased amount is required with an insufficient production. These patients have *retinopathy* (Sorbitol pathway), increased risk of infections (Candida, Mucor), *nephropathy* (Kimmelstel-Wilson Nodules with sclerosis of glomeruli), *peripheral neuropathy* (loss of sensation, erectile dysfunction, impaired wound healing), and *accelerated atherosclerosis/macrovascular disease.*
Hereditary Diseases

**Achondrosis.** This is an *autosomal dominant* disease that is the most common form of *dwarfism*. It is caused by a mutation in the fibroblast growth factor receptor gene on chromosome 4. Basically, this is a gain-of-function mutation that leads to *overactive fibroblasts* and *premature ossification* of the epiphyseal plates. This means that any bone that grows by *enchondral growth* (the long bones) will be fused early, while any bone that grows by *intramembrinous growth* (hands, vertebra, head) will continue as normal. Thus, these patients have *short stature*, but normal *hands, feet, heads*, and *intelligence* with the ability to reproduce.

**Osteogenesis Imperfecta.** Known as *brittle bone disease*, this is a genetic defect in the *synthesis in type I collagen*. This results in the inability to form normal bone structure, leading to *generalized osteopenia* (brittle bones) resulting in *recurrent pathological fractures* (generally mistaken for abuse). Collagen Type 1 is also found in the sclera, without it, patients have a *blue sclera*. The bones in the ear are prone to fracture, causing *deafness*. Inheritance pattern is either autosomal dominant or recessive depending on which type. Type 1 is the only one that matters, and it is *autosomal dominant*.

**Osteopetrosis.** Also called *marble bone disease* this is a genetic disease that causes *decreased osteoclast function*. Without the bone clearing osteoclasts, the bone building osteoblasts win out. This causes *severely sclerotic bone*. On histology, despite increased bone density and thickening of the cortex, the bones are brittle and prone to fracture. The constant production of bone *crowds out* hematopoietic stem cells, leading to *pancytopenia* (anemia, infection, bleeding) and *organomegaly* (as extramedullary hematopoiesis in the spleen takes over). While the bone grows in, crowding out the stem cells, it also grows out, causing compression defects (*deafness, blindness*, other *cranial nerve palsies*). On CT, the bones have a *hyperdensity* and on X-ray the long bones have a *Erlenmeyer Flask Shaped deformity* (a flaring at the ends of the bones). Like Osteogenesis Imperfecta, there are multiple types.

**Paget’s Disease.** It is a localized bone abnormality, in that, for any given bone, the disease may be at varying stages of development. There are three stages. The first stage, *Osteolytic* is predominated by osteoclast activity, resorbing bone. In his stage, the bone is *hyperlucent* on X ray. The next phase is a *mixed phase*, predominated by Osteoblast activity, haphazardly laying down bone. It goes out of control until you reach the *sclerotic phase*, a quiescent stage where dense sclerosis has caused the cessation of any type of activity. This will present as *hyperdense, thick* bone on X ray. Histologically, there is the characteristic *mosaic pattern*, whereby the cement lines of bone are traveling in a variety of directions, where normally they would be traveling all parallel to one another. Ultimately, the bone is thick and...
remodeled improperly, leading to ↑risk of fracture. On gross, there are characteristic changes to the skull, which demonstrates abnormal growth (called “Frontal Bossing”) resulting in what is termed the lion-like facies. Once again, serum alkaline phosphatase can be elevated (always remember to ensure the source of elevated Alk Phos: Liver, Bone, or Testes).

**Bone Deficiency**

**Osteoporosis.** It is defined as an age-related decreased bone mass (osteopenia) resulting in thin, fragile bones that are susceptible to fracture. In life, dependent mainly on genes, we reach a maximum density. As we age, the only thing we can do is lose bone. The process is worse for women, who lose estrogen after menopause, a major risk factor for the development of osteoporosis. So what can we do to keep our bones? Exercise (trauma requires calcification) and nutrition (vitamin D and calcium) are all we can do to slow the process of osteoporosis. **Post-Menopausal Women** (absence of estrogen) and **Lack of Activity** (use it or lose it) significantly increase the risk of osteoporosis, as do the minor risk factors such as corticosteroids/Cushings, and genetics. Unfortunately, there is no way of knowing someone has osteoporosis because the bone is normal, its just weaker. They have no symptoms except for pathologic fractures usually of the hip, wrist, and vertebrae. When severe, there will be reduced bone size (thinned cortical and trabecular bone), leading to height shrinking, and a radiolucency on X-ray. But in the early stages of osteoporosis there is nothing to tip us off. In general, estrogen replacement is not recommended because of its increased risk of breast cancer.

**Osteomalacia** (adults) and **Rickets** (kids). This is a nutrition-related decreased bone mass caused by decreased mineralization of newly formed bone. It is commonly secondary to vitamin D deficiency, affecting children who see little sun AND get insufficient vitamin D in their diet. The disease is far worse in children, whose bones are growing. Essentially, with ↓vitamin D, there is ↓calcium, so there is reactively ↑PTH. This corrects the calcium levels in the blood but causes a major drawback of consuming the calcium from the mineralized bone; bone formed at the epiphysyal growth plate are undermineralized. This results in frontal bossing / skull deformities, overgrowth of the cartilage in the chest wall (rachitic rosary), an outward protrusion of the sternum (pigeon-breast deformity), a abnormal Lumbar curvature (Lordosis), and a characteristic bowing of the legs. In adults, their bone is already formed, so decreased mineralization simply causes osteopenia and ↑risk of fractures, much like osteoporosis. The difference being that in this case vitamin D supplementation reverses deformities.

**Hyperparathyroid.** Depending on how severe the PTH secretion is, the bone manifestation may range from osteopenia to osteitis fibrosa cystica. When largely elevated without feedback inhibition (as in a primary tumor), massive amounts of bone is resorbed. This stimulation of osteoclasts leaves giant holes in the bone, called cysts. The cysts may hemorrhage or fill with fibroblasts/osteoblasts, giving rise to an abnormal appearance called a brown tumor. Note that this is not a neoplasm, yet is in striking contrast to normal bone. This condition, called osteitis fibrosa cystica is essentially an uber-resorption problem, going beyond osteopenia.

**Renal Osteodystrophy.** With renal failure comes the inability to synthesize vitamin D or filter/resorb calcium. The end result is a secondary hyperparathyroidism similar in presentation to osteomalacia.
Osteomyelitis

Osteomyelitis. The bone can become infected either **hematogenously** or through **direct inoculation** (bone marrow biopsy, penetrating wound). The most common bacteria doing the infecting is dependent on the history. Overall, **Staph Aureus is most common.** In Sickle Cell, it is **Salmonella.** In patients who are overly sexually active, look for an STD like gonorrhea. Bone infections suck. There is **fever, Leukocytosis,** extreme pain, with swelling above the site of infection on the skin. There is often a suppurative, liquifactive necrosis. Blood cultures will show you which bug it is, and you treat the patient for systemic infection. The most important thing to remember in osteomyelitis is which bug affects which history.

**Pott’s Tumor.** A special form of bone infection, this is not a tumor at all. It is caused by **Tuberculosis,** presenting in all the same ways as TB does (fever, night sweats, weight loss) only with **caseating granulomatous necrosis** of the bones, most commonly the **lumbar vertebra.** This infection destroys the bone, predisposing for vertebral compression fractures and extension of the necrosis into the psoas muscle.

**Bone Cancer**

It wasn’t assigned. Really? Can you believe it? I even emailed Crawford, who said “it’s not on the exam.” He loves cancer though, so make sure you double check with him during your year.

I was behind when it came to this block. I just couldn’t get to it with studying for Tulane Stuff, the Shelf, and upcoming Boards. *Editor’s Note: I had hoped to fill in what was missed during the school year with information from my Boards Studying, but just didn’t have enough time to write it from scratch. If there is someone who wants to write this up, please do!*

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**Female Pathology**

<table>
<thead>
<tr>
<th>Vulva</th>
<th>Vagina</th>
<th>Cervix</th>
<th>Uterus</th>
<th>Ovary</th>
<th>Placenta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condyloma (Warts) Extramammary Paget’s</td>
<td>Vaginal Adenosis Rhabdomyosarcoma</td>
<td>PID</td>
<td>Endometritis Endometriosis Leiomyoma Endometrial Carcinoma</td>
<td>Polycystic Ovarian Disease Cystadenoma Cystadenocarcinoma Teratoma Dysgerminoma Other Tumors</td>
<td>Complete Mole Incomplete Mole Accreta Previa Abruption</td>
</tr>
</tbody>
</table>

**Breast**

- **Risk Factors / Prognosis**
  - Age, Estrogen, Progesterone, Genes
- **Inflammation**
  - Acute Mastitis Fat Necrosis Mammary Duct Ectasia Granulomatous
- **Benign**
  - Fibrocystic Change Phyllodes Tumor Intraductal Papilloma Adenoma
- **Carcinoma**
  - Ductal Carcinoma In Situ Invasive Ductal Invasive Ductal Subtypes Lobular Carcinoma in Situ Invasive Lobular Carcinoma
- **Male Breast**
  - Gynecomastia Carcinoma