INTRODUCTION

Welcome to the Pituitary, Adrenal and Thyroid (PAT) week. To prepare for the week, please read through this page and complete the modules. The handout also has links to other supplemental material you might find useful. The goals of this week are:

- to familiarize you with the anatomy, embryology, normal function and control of these three endocrine glands,
- to describe what can go wrong with them (the basic disease processes are some combination of mass lesion(s), hyper-function and hypo-function).
- to provide you with the basic knowledge to be able to diagnose disorders of the glands, using the history, physical exam, laboratory tests and imaging.
- To describe the basic principles of endocrine therapeutics. We will emphasize the collaborative approach required to treat patients effectively, with contributions from the primary care physician, the endocrinologist, diagnostic imaging, pathologist and surgeon.

Overview of this week’s learning modalities:

1. This reading will provide the overview for learning for the week, we recommend that you complete at minimum the activities in bold prior to the week’s in-class activities, and complete the rest by the end of the week:
   a. This text-based primer of the physiology and clinical aspects of the three glands, for your reference
   b. Links to 4 short videos that provide “Just the basics” for an overview of disorders of the Pituitary (The Science and the Patient), the Thyroid and the Adrenal gland.
   c. Links to 3 short videos of patients with Hyperthyroidism, Acromegaly and Cushing’s disease.
   d. Link to a short video on mass effect cranial nerve exam for Pituitary lesions.
   e. Link to a short video on the physical exam of the Thyroid
   f. Links to two white board presentations (each is about 3 minutes in length) and PowerPoint presentations (15 minutes each) on breast discharge and polyuria on medskl.com (these are MCCQE presentations that you need to know about)

2. Monday morning lectures:
   a. Hour 1: Endocrinology Introduction:
      i. Endocrine overview (10 minutes)
      ii. “Dad isn’t the same”: the family practitioner’s perspective on common endocrine disorders in the geriatric population (20 min)
      iii. Endocrine Pathology Principles: the pathologist’s perspective (20 minutes)
   b. Hour 2: Pituitary diseases: A case-based interactive lecture
   c. Hour 3: Adrenal diseases: A case based interactive lecture

3. The CBL case – “The Anxious Accountant”

4. Self-directed Learning modules:
   #1 The patient with an Adrenal mass
   #2 The patient with a Prolactinoma
   #3 The patient with Adrenal insufficiency
PAT PRIMER – TABLE OF CONTENTS

I. HYPOTHALAMUS, PITUITARY, ADRENAL AND THYROID GLAND ANATOMY, EMBRYOLOGY AND FUNCTION, INCLUDING HORMONAL CONTROL AND HORMONAL ACTIONS

1. Overview of regulation

2. The Hypothalamus

3. The Pituitary gland
   Anatomy, Embryology, Histology, Physiology

4. The Thyroid gland
   Anatomy, Embryology, Histology, Physiology

5. The Adrenal gland
   Anatomy, Embryology, Histology, Physiology

II. APPROACH TO CLINICAL PROBLEMS OF THE PITUITARY, ADRENAL AND THYROID GLANDS

1. Key Concepts

2. Disorders of the Pituitary gland
   Presentations
   Mass effect
   Hyperfunction
   Prolactinoma
   Acromegaly
   Cushing’s syndrome
   Hypofunction
   Summary of diagnostic tests
   Summary of therapy

3. Disorders of the Thyroid gland
   Presentations
   Mass effect (solitary and multi-nodular)
   Hyperfunction
   Hypofunction
   Summary of diagnostic tests
   Summary of therapy

4. Disorders of the Adrenal gland
   Presentations
   Mass effect (solitary and multi-nodular)
   Hyperfunction
   Hypofunction
   Mixed hyper- and hypo-function
   Summary of diagnostic tests
   Summary of therapy
I. HYPOTHALAMUS, PITUITARY, ADRENAL AND THYROID GLAND: STRUCTURE, FUNCTION, HORMONAL CONTROL AND ACTIONS

1. An overview of the regulation of the endocrine system (see also Table 1 for summary)

As you learned last week, the endocrine systems of the body affect bodily functions through the production of hormones that circulate through the blood stream, and ultimately attach to receptors on or inside cells to have their final effect on cell function. These systems are tightly controlled through feedback loops.

There are several different ways in which the hormones of the endocrine system are regulated:

i. Some of them are controlled directly by the plasma level of ions or molecules that the hormone is regulating.

ii. Many hormones are controlled by the actions of other hormones.

iii. A few hormones involve a combination of these two. Finally, some hormones are directly under neural control.

(a) Hormones controlled by the plasma level of ions or molecules which they are regulating.

Examples of this first category are insulin, parathyroid hormone (PTH), and antidiuretic hormone (ADH).

- **Insulin.** Although there are other influences, the plasma level of insulin is mainly regulated by the plasma level of glucose: a high plasma glucose level stimulates the release of insulin from the pancreas, and a low plasma glucose level inhibits insulin release. When insulin is released, it acts to reduce the level of plasma glucose by reducing its production in the liver and increasing its utilization in the muscle (see Week 26).

- **PTH.** While PTH release is increased by several factors, the major stimulating factor is a low level of plasma calcium. PTH then acts to increase calcium release into the plasma from bone, and it acts on the kidney to reduce urinary excretion of calcium (see Week 29).

- **ADH.** ADH is produced mainly in response to the level of “free water” in the body, reflected by the plasma concentration of sodium. When the patient has a deficit of free water (manifested by hypernatremia, a high concentration of plasma sodium), this causes osmotic shrinkage of cells in the hypothalamus, which then triggers a signal that leads to the production of ADH from nearby cells in the hypothalamus. ADH then acts on the kidney to reduce the rate of excretion of water in the urine.

(b) Hormones whose level is controlled by other hormones

Many other hormones are regulated by the level of other hormones. Most are regulated through an “axis” involving coordinated actions at up to three levels: the hypothalamus, the pituitary gland, and in some cases a target gland.

The major hormonal axes are the following:

- **Growth hormone** (GH). This involves neurons of the hypothalamus (which produces growth hormone releasing hormone) and endocrine cells of the anterior pituitary gland (which produces GH). Growth hormone then acts on the liver to produce insulin-like growth factor; both growth hormone and IGF-1 have metabolic and growth-related actions.

- **Prolactin.** This is produced by endocrine cells of the anterior pituitary. Its rate of production is inhibited by the level of dopamine produced by the hypothalamus. Prolactin’s main physiologic function is to stimulate milk production in the female breast.

- **Thyroid axis.** The hypothalamic neurons produce thyrotropin-releasing hormone (TRH). This causes endocrine cells of the anterior pituitary gland to produce thyroid stimulating hormone (TSH), which acts on the thyroid gland to produce thyroid hormones (T4 and T3). The thyroid hormones then act on various organs to produce multiple effects.

- **Adrenal axis.** The hypothalamic neurons produce Corticotropin Releasing Hormone (CRH), which acts on endocrine cells in the anterior pituitary to produce POMC (Proopiomelanocortin. POMC, when cleaved, produces many compounds, including Adrenocorticotropic Hormone (ACTH). The main effect of ACTH is to act on the adrenal cortex to release the hormone cortisol. Cortisol then acts on many organs and tissues with various effects. Another POMC product is alpha-MSH (Melanocyte Stimulating Hormone) which attaches to its receptor on melanocytes, and it responsible for skin pigment production.

- **Sex hormone axis.** In the hypothalamus, neurons release Gonadotropin Releasing Hormone (GnRH) that acts on the endocrine cells of the anterior pituitary to release Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH). Then, LH and FSH via a complex series of influences, act on the gonads (ovaries in women, testes in men) to lead to the production of estrogen and progesterone in women, and testosterone in men, and these sex hormones then have various effects.
In each of these cases, there is also negative feedback, such that the level of the final hormone in the axis feeds back on the upper levels of the axis to (in most cases) reduce the production of the stimulating hormone.

(c) Hormones whose level is regulated both by other hormones and by molecules or ions whose level they control
Aldosterone is one hormone whose release from its source (the adrenal cortex) is regulated both by another hormone (angiotensin-2, released in states of body fluid volume depletion) and by the plasma level of an ion whose level the aldosterone regulates (potassium). Aldosterone increases urinary excretion of potassium, and reduces urinary excretion of sodium.

(d) Neural stimuli
The main hormones whose level is directly controlled by neural activity are adrenaline and noradrenaline. These are released from the adrenal medulla in response to neural stimuli originating in the hypothalamus and traveling via the sympathetic nervous system directly to the adrenal gland.

2. The Hypothalamus
The hypothalamus is a very small structure located in the very middle of the brain, just above the pituitary. It consists of multiple clusters of neurons called nuclei (nerve cell bodies), each of which has various functions in support of homeostasis (stable equilibrium) of the whole body. These functions include appetite and temperature regulation, among several others.

A very important function of the hypothalamus is its role in the endocrine system, as it produces several hormones.

(a) Oxytocin:
One group of paraventricular hypothalamic nuclei produces the hormone oxytocin. This hormone’s major function is to stimulate milk let-down in lactation. It may also facilitate the contraction of the uterus in the pregnant woman at the time of birth. Interesting results from research suggest oxytocin has a role in social bonding. Oxytocin is synthesized in the hypothalamus, within neurons whose axons extend down the pituitary stalk to the posterior lobe of the pituitary, from where it is released into the circulation.

(b) Antidiuretic hormone (ADH)
ADH is a nine-amino acid peptide hormone produced in the supraoptic and paraventricular nuclei of the hypothalamus. The major, usual stimulus for its release is a signal from a nearby set of neurons referred to as the osmoreceptor. When the person is “dehydrated” (lacking free water), this causes the concentration of substances in the plasma to rise, including the concentration of sodium; the increased concentration of sodium is called “hypernatremia”. This causes the cells throughout the body to shrink as water is osmotically dragged out of the cells, including the cells of the osmoreceptor. The shrunken osmoreceptor cells then send a neural signal to the ADH-producing cells to synthesize and release more ADH. As with oxytocin, ADH travels down the pituitary stalk by axonal transport and is released into the blood from the posterior part of the pituitary. It circulates in the plasma and exerts its main effects in the collecting ducts of the kidney, where it binds to a cell-surface receptor linked to the cAMP system. This enhances the reabsorption of free water from the urine, leading to the excretion of a small volume of highly concentrated urine. (There is a second set of influences which can also increase ADH release: patients who are volume-depleted, even if they are not hypernatremic, will stimulate ADH release via a baroreceptor response in the carotid sinus, similar to the activation of the sympathetic nervous system that occurs in patients who are hypotensive; see cardiovascular physiology section.)

(c) Other hormones:
The hypothalamus also produces a number of hormones whose principal effect is to act on certain sections of the pituitary gland and thereby to augment the release of hormones from these cells. The main hypothalamic hormones that work in this manner are: Thyrotropin-Releasing Hormone (TRH, which leads to increased released of TSH), Corticotropin-Releasing Hormone (CRH, which leads to the release of ACTH); Gonadotropin-Releasing Hormone (GnRH), which leads to the release of both LH and FSH; Growth Hormone-Releasing Hormone (GHRH, which leads to the release of growth hormone).

Other signals are inhibitory: the neuropeptide dopamine inhibits the release of prolactin, and the hypothalamic hormone somatostatin inhibits the release of GH.

Each of these hypothalamic hormones is released into capillaries that surround the hypothalamic nuclei, and travel via blood vessels through the pituitary stalk and then enter a second capillary network that surrounds the cells of the anterior pituitary.
3. The Pituitary Gland

(a) Anatomy
The pituitary gland is called the “Master gland” as many of its hormones regulate other peripheral glands in the body (see Figure 1 and Table 1). It is situated in the sella turcica, a small, box-like, boney enclosure located at the bottom of the brain. It is suspended from the hypothalamus by the pituitary stalk (as in “Jack and the beanstalk”).

(b) Embryology (Figure 1)

Figure 1- The anterior gland (adenohypophysis) arises from oral ectoderm (on the side of the hard palate in the mouth) and the posterior gland (neurohypophysis) arises from future brain (neural ectoderm). At day 24, Rathke’s pouch grows up from the oral ectoderm, and connects with the down-growing section of neural ectoderm. The pouch eventually breaks off from the main oral ectoderm and the two layers fuse to form the two-tissue pituitary gland.

Endocrine cells in the Adenohypophysis (anterior pituitary) can stain in three ways: as basophilic (blue), acidophilic (red) and chromophobic (no staining; pale appearance). Gonadotrophs that contain LH and/or FSH stain as chromophobic, somatotrophs that contain GH stain as acidophilic, lactotrophs that contain PRL and thyrotrophs that contain TSH both stain as lightly acidophilic to chromophobic, mammosomatotrophs that contain both GH and prolactin stain acidophilic, and corticotrophs that contain ACTH stain as basophils.

(c) Physiology
The pituitary is divided structurally and functionally into an anterior portion and a posterior portion. The posterior portion is really an extension of the hypothalamus, and it is here that ADH and oxytocin are released into the circulation.

The anterior pituitary consists of clusters of epithelial cells, which produce the various anterior pituitary hormones. The cell types are named in relation to the hormone they produce:

- **TSH** is produced by thyrotrophs
- **ACTH** is produced by corticotrophs
- **Prolactin** is mainly produced by lactotrophs but mammosomatotrophs also produce prolactin in addition to growth hormone.
- **Growth hormone** (GH) is mainly produced by somatotrophs but mammosomatotrophs (a more primitive cell) also produce growth hormone in addition to prolactin.
- **FSH** and **LH** are produced by gonadotrophs

Figure 2: Histology

Endocrine cells in the Adenohypophysis (anterior pituitary) can stain in three ways: as basophilic (blue), acidophilic (red) and chromophobic (no staining; pale appearance). Gonadotrophs that contain LH and/or FSH stain as chromophobic, somatotrophs that contain GH stain as acidophilic, lactotrophs that contain PRL and thyrotrophs that contain TSH both stain as lightly acidophilic to chromophobic, mammosomatotrophs that contain both GH and prolactin stain acidophilic, and corticotrophs that contain ACTH stain as basophils.
In general, the hypothalamus secretes hormones and neuropeptides (dopamine) that control the release of pituitary hormones by specific cells in the anterior pituitary that are each dedicated to the production of one type of hormone. These hormones in turn cause downstream effects in target peripheral glands or tissues, which often produce their own hormones, or react in other ways to the pituitary hormone. The target tissue hormones in turn feedback and inhibit the hypothalamic and pituitary hormone production, in what is called a negative feedback loop (similar to how a furnace turns off when a house has warmed up).

The pituitary hormones are either proteins (growth hormone, prolactin, ADH), or glycoproteins (LH, FSH, TSH). These glycoproteins are “dimers”, meaning they have two peptide chains, called alpha and beta. The alpha chain is the same for each hormone, but the beta chain varies, and it is the beta chain the gives each of the specific hormones its unique functional properties. Note that HCG is a non-pituitary glycoprotein hormone made during pregnancy by the corpus luteum of pregnancy, and then later by the placenta; its beta-chain level is measured in plasma during pregnancy testing as “beta-HCG”). Interestingly, it can act like TSH and cross react with the TSH receptor.

These peptide hormones bind to cell surface receptors. Most of their receptors on the target organs are 6-transmembrane domain G-protein coupled receptors.

Tables 1 A and B below summarize the effects of these pituitary hormones.

- ACTH regulates growth of the cells of the adrenal cortex and their cortisol and sex hormone production.
- TSH regulates growth of the follicular cells of the thyroid and their thyroid hormone production.
- LH and FSH, via complex feedback mechanisms, regulate the production of sex hormones in both women and men, and also regulate the production of gametes (sperm in men, ova in women)
- Prolactin regulates breast milk production, and suppresses the GnRH→FSH, LH→sex hormone, gamete pathway.
- Growth hormone regulates growth in childhood and adolescence.

(d) Growth hormone actions
As Growth hormone is the only anterior pituitary hormone to act directly on peripheral target cells (as well as through IGF-1 as an intermediary), we can review its specific hormone actions here. These include:

- Metabolic: Protein synthesis (nitrogen retention); IGF-1 antagonizes insulin, stimulates lipolysis
- Promotes Na, K and water retention
- Stimulates IGF-1 production in the liver and in other (“peripheral”) tissues
- Growth in childhood and adolescence: stimulates epiphyseal prechondrocyte differentiation→local IGF1 + GH = linear bone growth

The actions of ADH and oxytocin were reviewed above in the section on the hypothalamus.

These pathways can be depicted as feedback loops (Figure 4)

<table>
<thead>
<tr>
<th>Key concepts</th>
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</thead>
<tbody>
<tr>
<td>1. Understanding these negative feedback loops in hormone regulation allows us to interpret laboratory testing of pituitary and target organ hormones to determine, in a patient who has endocrine disease, at what level is the lesion. (Note that we are unable to measure hypothalamic hormones concentrations in plasma.)</td>
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<td>2. All pituitary hormones are under tonic stimulation from hypothalamic hormonal signals, except for prolactin, which is tonically (constantely) suppressed. This means that if there is a problem with the hypothalamus and/or the pituitary stalk caused by some kind of lesion or compression (e.g. due to a tumour), and this causes the hypothalamic signals to be lost, prolactin levels rise, and the levels of the other pituitary hormone levels fall.</td>
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<tr>
<td>Hypothalamic hormones that stimulate the pituitary hormone</td>
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<td>----------------------------------------------------------</td>
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<tr>
<td>GHRH</td>
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<td>Prolactin-releasing hormone (PRH) has very minor role</td>
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</tbody>
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*more about this axis in Week 28
Table 1- B - Overview of Posterior Pituitary Hormone Control and Actions

<table>
<thead>
<tr>
<th>Stimulus for Hormone release</th>
<th>Hypothalamic cell type and the hormone released</th>
<th>Factor that suppresses release of the hormone</th>
<th>Target Organ</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulated by: - - Hyperosmolar state - Nausea, pain, - Body fluid volume contraction</td>
<td>Antidiuretic hormone (ADH) is produced in the hypothalamus and released from the posterior pituitary</td>
<td>Hypo-osmolar state</td>
<td>Kidney</td>
<td>Water conservation</td>
</tr>
<tr>
<td>Stimulated by: -nipple stimulation in breastfeeding (-stretching of the cervix and uterus in labour probably does not occur in humans)</td>
<td>Oxytocin is produced in the hypothalamus and released from the posterior pituitary</td>
<td></td>
<td>Breast</td>
<td>Milk let-down</td>
</tr>
</tbody>
</table>

Figure 3: Pituitary and hypothalamus – Radiology and Pathology


Coronal (front) view of sella with pituitary adenoma (arrow)

Pathology
4. The Thyroid Gland

(a) Anatomy (Figure 6 – Part 1)
The thyroid gland typically has a mass of up to 20 g. It consists of two lobes each approximately 3 x 2 x 2 cm in size, connected to each other through a narrow isthmus. The thyroid gland sits in the anterior part of the neck, and wraps around the front of the trachea deep to the sternocleidomastoid muscles. The gland is adjacent to several critical structures, which can be injured at the time for surgery, including the parathyroid glands (loss of parathyroid hormone (PTH) causes hypocalcemia- See Week 29) and the recurrent laryngeal nerve (injury causes hoarseness).

(b) Embryology

Figure 5 - The thyroid gland starts to develop around day 24 from the primitive pharynx --- the thyroid diverticulum grows down into the future neck where it eventually divides and forms the two lobes of the thyroid gland. It is connected at first to the tongue by the thyroglossal duct. Remnants of the duct rarely persists into adulthood as a thyroglossal duct cyst, in the midline of the neck.
(c) Histology (Figure 6 – Part 2)
The key histological feature of the thyroid gland is the presence of hundreds of follicles. Each follicle is a roughly spherical structure whose outer surface consists of a layer of epithelial cells called follicular cells. The inside of the sphere consists of a jelly-like proteinaceous mass referred to as the colloid. Thyroid hormone is made by the follicular cells. There are also endocrine cells interspersed between the follicles called parafollicular cells (or C-cells) which make the hormone calcitonin, which regulates calcium levels in the blood (see Week 29). In addition to calcitonin, C-cells also release carcinoembryonic antigen (CEA).

(d) Physiology
(i) Production of thyroid hormone (see Figure 6 – Part 3)
The main function of the thyroid gland is to produce the thyroid hormones, T4 (thyroxine) and T3 (tri-iodothyronine). These thyroid hormones are synthesized from the building blocks of iodine and the amino acid tyrosine. The tyrosine molecule is attached to the protein thyroglobulin, which acts as a scaffolding for thyroid hormone production. Iodide is taken up from the blood into the follicular cell, oxidized and secreted into the colloid in the centre of the follicles, surrounded by follicular cells. In the colloid, either one or two iodine atoms bind to a tyrosine molecule, which is attached to a thyroglobulin molecule. Subsequently, two iodinized tyrosines are coupled to form T4 (containing 4 iodine molecules) (Figure 3 - Part 4) or T3 (containing 3 iodine molecules). The thyroid hormone is then endocytosed (taken up) into the follicular cells in a lysosome, then the lysosome is proteolyzed, releasing thyroid hormone into the bloodstream. About 80% of secreted thyroid hormone is released as T4, and 20% as T3. T4 has a half-life of approximately one week, T3 has a much shorter half-life.

(ii) Circulating forms of thyroid hormone:
The thyroid hormones circulate bound to three types of protein: thyroxine-binding globulin (TBG), transthyretin, and albumin. As well, a fraction of it circulates unbound in the bloodstream, and this is the “free T4” and “free T3” that the assays measure in blood tests of thyroid function. The free hormone is also the form of the hormone that interacts with cells in the tissues where the hormone acts. Note that thyroid hormone has effects on virtually all organs in the body.

(iii) Conversion of T4 to T3 and binding to nuclear receptor:
In the tissues, T4 is converted to T3 or reverse T3. T3 is the active hormone, which exerts its effect by binding to the T3 receptor inside cells. The activated receptor binds to the promoter region of specific genes and causes their up-regulation or down-regulation, with resultant high or low levels of RNA and ultimately of a protein product.

(iv) Thyroid hormone actions:
Specific thyroid hormone actions include:
- It increases oxygen consumption and heat production (i.e., increased basal metabolic rate)
- It increases cardiac output
- It potentiates the actions of GH, catecholamines (epinephrine, norepinephrine), glucagon and cortisol, resulting in increased glucose absorption, gluconeogenesis, ketogenesis and proteolysis. These actions mimic what happens in starvation.
- It increases sensitivity to catecholamines, by up-regulating their receptors, but does not alter their blood concentrations.
- Thyroid hormone is required for normal growth in the fetus and child, including the central nervous system.
Figure 6: The Thyroid gland: Anatomy, Histology, Thyroid hormone synthesis pathway, and Thyroxine

Part 1: Thyroid Anatomy
en.encyclopedia.org 372x348

Part 2: Thyroid Histology
Commons.wikimedia.org 4272 x 2848

Part 3: Thyroid Hormone Production
en.wikipedia.org 3195x2000

Part 4: Molecular Structure of Thyroxine (T4)
en.wikipedia.org 2000 × 838
5. The Adrenal Gland

(a) Anatomy (Figure 8 – Part 1)
There are two adrenal glands, each of which sits on top of one of the kidneys (hence its name: “ad-renal”). The adrenal gland is a pyramidal structure, and normally has a weight of about 4-5 g; one is shaped like a pyramid, the other is more crescent-shaped. It is composed of an outer cortex and an inner medulla.

(b) Embryology

(c) Histology
The adrenal cortex has three layers (from outer to inner: Glomerulosa, Fasciculata and Reticularis (note “GFR” mnemonic)). Different steroid hormones are synthesized in each layer:

- Glomerulosa layer: “mineralocorticoid” hormones are produced, the main one being aldosterone.
- Fasciculata layer: Cortisol (a “glucocorticoid”) is produced (Figure 4 – Part 2)
- Reticularis layer: Sex hormones are produced here and the zone also acts as a progenitor area, as the zona reticularis cells can differentiate into fasciculate and glomerulosa cells.

The central medulla is composed of chromaffin cell of the sympathetic nervous tissue also known as sympathetic paraganglia that produce catecholamines.

(d) Physiology

General features of adrenal hormone synthesis (Figure 8 – Part 3)
Steroid hormones are all synthesized starting with the cholesterol molecule. The synthesis proceeds through a variety of intermediates via the action of different enzymes. These enzymes cause different small and sequential modifications of the cholesterol backbone that eventually produce the specific hormones with their unique actions. The different layers of the adrenal cortex share some enzymes but also have enzymes that are found only found in a given layer. In some cases, an intermediate molecule in the steroid production pathway diffuses from one layer to another where it is further modified. ACTH drives the production of cortisol and the adrenal sex hormones, as described in the Pituitary section above.

Catecholamines in the adrenal medulla
In the inner medulla of the adrenal gland, the catecholamine hormones (epinephrine and norepinephrine) are produced from the amino acid tyrosine, through the intermediate step of dopamine. They are responsible for the “flight or fight” response to danger, released in response to activation of the sympathetic nervous system; norepinephrine is also produced by the neurons of the sympathetic nervous system. Dopamine, which is also another catecholamine, is not typically secreted by the adrenal medulla during normal physiological states.
Cortisol
Cortisol is the most critical hormone required for life. Its many actions are described below.
There is diurnal variation in its secretion: it peaks around 8:00 am and is lowest overnight, in people with a normal wake-sleep cycle. Cortisol has several actions:

- It has a catabolic role leading to glucose production from protein
- A further catabolic role is to facilitate fat breakdown (lipolysis)
- It supports vascular responsiveness, keeping arterioles appropriately vasoconstricted
- It modulates central nervous system function in general
- It also affects skeletal turnover, hematopoiesis, muscle function, immune response and renal function.

Cortisol circulates in the bloodstream bound to cortisol-binding protein. It diffuses across the cell membrane into cells, and binds to an intracellular cytosolic receptor. Like the T4 receptor, this receptor is a heterodimer that once activated (by binding to the hormone) then diffuses into the cell’s nucleus and binds to the promoter region of certain genes and acts to up-regulate or down-regulate the production of their messenger RNA and ultimately their protein product. All of the active adrenal cortical hormones act via their unique intracellular steroid hormone receptor.

Adrenal sex hormones
The main source of sex hormones in the body is of course the gonads (ovaries in women and testes in men). Sex hormones are also produced in the adrenal gland, and this happens under the control of ACTH (androgens are first produced, and may be converted to estrogens). Normal levels of sex hormones are both gender- and age-specific. The androgens are responsible for adrenarche (earliest stage in puberty when axillary and pubic hair start developing). Testosterone can be converted peripherally in adipose tissues to estrogen. Secretion of the androgen DHEAS is unique to the adrenal glands, so when its level is elevated, we know there is an adrenal disorder (as opposed to an ovarian or testicular disorder). DHEAS is not an important source of androgens in males.

Aldosterone
Aldosterone has two actions: (i) It acts to regulate body fluid volume and blood pressure by enhancing the reabsorption of filtered sodium in the collecting duct of the kidney; (ii) it increases the secretion and ultimate excretion of potassium and hydrogen ions in the collecting duct of the kidney. Its release is stimulated by (1) increased levels of potassium in the plasma (“hyperkalemia”); and (2) extracellular fluid volume contraction. Activation of the sympathetic nervous system and reduced perfusion to the renal afferent arterioles can each cause increased renin production by the juxtaglomerulus apparatus in the nephron. Renin stimulates the conversion of angiotensinogen (made in the liver) to angiotensin 1 (AT-1), and then the ACE (angiotensin converting enzyme) converts AT-I to AT-II. AT-II has many actions, including acting as a direct vasoconstrictor and also stimulating aldosterone secretion, both of which raise blood pressure.

Catecholamines
Adrenaline and noradrenaline are produced in response to neural stimuli that are integrated in the hypothalamus. The hypothalamus activates the sympathetic nervous system in response to various stimuli, such as any threat, a drop in blood pressure, a drop in plasma glucose levels, etc. The sympathetic nervous system then has various effects transmitted via sympathetic nerves throughout the body, leading to tachycardia, arteriolar and venous vascular constriction, pupillary dilatation, sweating, production of glucose in the liver, among other effects. These are all augmented by circulating catecholamines, most of which originate in the adrenal medulla. The biosynthetic pathway for catecholamines involves the following steps, starting with the amino acid L-Tyrosine: L-Tyrosine→L-DOPA→Dopamine→Norepinephrine→Epinephrine. Catecholamines have a short half-life of 2-3 minutes.
Figure 8: The Adrenal gland, Cortisol’s structure and the synthetic pathways for adrenal cortical and medullary hormones
II. APPROACH TO CLINICAL PROBLEMS OF THE PITUITARY, ADRENAL AND THYROID GLANDS

1. Key Concepts

2. Disorders of the Pituitary gland

   Presentations:
   a. Mass effect
   b. Hyperfunction
      - Prolactinoma
      - Acromegaly
      - Cushing’s syndrome
   c. Hypofunction
      - Adenoma
      - Other disorders

3. Disorders of the Thyroid gland

   Presentations:
   d. Mass effect (solitary and multi-nodular)
   e. Hyperfunction
      - Graves’ disease
      - Multi-nodular toxic goiter (there is also a non-toxic multinodular goiter where none of the nodules are hyperfunctional and the person has normal thyroid function tests)
      - Toxic adenoma (solitary or as part of a Toxic nodular goiter)
      - Subacute thyroiditis
      - Other
   f. Hypofunction
      - Hashimoto’s thyroiditis
      - Subacute thyroiditis
      - Iatrogenic
      - Other

4. Disorders of the Adrenal gland

   Presentations:
   a. Mass effect (solitary and multi-nodular)
   b. Hyperfunction
      - Cushing’s syndrome
      - Primary Aldosteronism (Conn’s syndrome., also called Primary Hyperaldosteronism)
      - Excess sex hormone production
      - Pheochromocytoma (Medulla)
   c. Hypofunction
      - Adrenal insufficiency
   d. Mixed hyper- and hypo-function
      - Congenital adrenal hyperplasia

Summary of diagnostic tests
Summary of therapy
II. APPROACH TO CLINICAL PROBLEMS OF THE PITUITARY, ADRENAL AND THYROID GLANDS

1. Key Concepts:

*Key Concept 1:* Endocrine gland problems can present in four ways (and combinations can occur):

i. Mass effect
   a) From tumour in gland compressing surrounding structures
   b) From the mass being detected during physical examination (for thyroid) and/or during “incidentally” during imaging for other reasons (for pituitary, thyroid or adrenal)

ii. Hyperfunction -- overproduction of a hormone

iii. Hypofunction -- underproduction of a hormone(s)

iv. Associated disease features (i.e., other manifestations of underlying disease process; e.g., disorders of the eye in patients with Graves’ disease of the thyroid gland)

*Key Concept 2:* We can use the patterns of pituitary and peripheral gland hormone levels to diagnose the level of the lesion.

E.g. for the hypothalamic-pituitary-thyroid axis, if someone has a thyroid disease causing overproduction of T4 and T3, these hormones will suppress TSH via the negative feedback loop. This pattern of hormone levels (T4 and T3 high, TSH low) tells us there is a primary thyroid problem (highlighted in yellow in the table below). The table shows what all the possible combinations of findings for these hormones would signify:

<table>
<thead>
<tr>
<th>Level of the lesion</th>
<th>TSH level compared to normal</th>
<th>T4 and T3 levels compared to normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid hyperfunction (primary- target gland disorder)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Thyroid hypofunction (primary- target gland disorder)</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Pituitary hyperfunction (secondary- pituitary disorder)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pituitary hypofunction (secondary- pituitary disorder)</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

*Key Concept 3:* “Primary” and “secondary” mean different things in different contexts:

1. Level of the lesion in the pathway: *primary* problem means “at the level of the target organ”; e.g. thyroid, adrenal, ovary, testes; *secondary* problem means at the level of the pituitary*. E.g., “primary hypothyroidism” means underfunction of the thyroid gland, due to a disease in the thyroid gland itself. “Secondary hypothyroidism” means underfunction of the thyroid gland due to a problem in the pituitary, with insufficient production of TSH.

2. Within a single organ, “primary” means an inherent defect, while “secondary” means the gland is influenced by an outside influence (for example, if the patient were taking the drug amiodarone and it induced hypothyroidism, one would say they had hypothyroidism secondary to amiodarone, i.e. secondary hypothyroidism)

3. When talking about prevention, “primary prevention” means preventing the person from ever getting the disease. In endocrinology, “secondary prevention” means stopping a second episode of the disease (usually refers to lipid lowering drugs used to reduce cardiovascular risk). In other contexts, somewhat confusingly, “secondary prevention” refers to detection of disease before it becomes symptomatic; e.g., a cervical Papanicolaou smear to detect early cervical cancer.

*Incidentally, “tertiary” meaning hypothalamic dysfunction can rarely occur, with resulting hypofunction of the whole axis Finally, when there is peripheral resistance to hormones, and the tissues do not respond to the hormone, then the hormone level will be elevated, yet the patient presents with hypofunction. We see this commonly with insulin resistance; the patient has a*
high level of insulin, yet it is not working effectively, and so despite the high level of the final hormone, the patient is still hyperglycemic. Other hormonal resistance syndromes are very rare.

**Key Concept 4:** “To determine the cause if a hormone’s level is high, try to suppress it; if a hormone’s level is low, try to stimulate it.”

Sometimes abnormal hormone patterns arise for physiological reasons (i.e., there is no disease). For example, in very stressful situations (e.g. a severe infection, an acute heart disease event), the H-P-A (Hypothalamic-Pituitary-Adrenal) axis will be stimulated by the brain. To assess if an abnormal hormone level is physiological or pathological (i.e., caused by a disorder) we check if the hormone is still under normal physiologic control.

In the example of the patient who is “stressed” in a “physiological” setting and whose cortisol level is high, one could attempt to suppress this by giving a single dose of exogenous synthetic glucocorticoid such as dexamethasone. This should lead via negative feedback to reduction in the levels of CRH (hypothalamus) and ACTH (pituitary), and therefore reduced endogenous cortisol production (from the patient’s adrenal glands). Conversely, if the patient has for instance a lung cancer producing ACTH as the cause of their elevated cortisol level, then administering extra exogenous glucocorticoid will not lead to suppression of CRH, ACTH or cortisol. This test (called “dexamethasone suppression test”), is done when we suspect a person has a disorder overproducing cortisol. We measure plasma cortisol after giving dexamethasone to see if the cortisol suppresses normally.

**Key Concept 5:** There are a broad range of disease processes that can affect the pituitary, adrenal and thyroid glands. Here are examples in each category, for your interest only. Don’t worry about them now, but if you return to the list in Table 3 at the end of the four weeks, you will recognize a lot of these!
Table 3 – Scholar’s corner: Types of disease processes affecting endocrine glands

<table>
<thead>
<tr>
<th>Disease process</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Congenital defect                     | Congenital hypothyroidism  
 Congenital adrenal hyperplasia  
 Turner’s syndrome (XO)  
 Kleinfelter’s syndrome (XXY)                                                                                                                                                                                  |
| Acquired defects                      | Autoimmune (co-exist commonly with each other and along with non-endocrine autoimmune disorders)  
 Type 1 Diabetes mellitus  
 Hashimoto’s thyroiditis (hypothyroidism), Addison’s disease (adrenal failure)  
 Less common:  
 Oophoritis (ovary), Hypophysitis (pituitary), Hypoparathyroidism  
 Vitamin B12 deficiency due to pernicious anemia (autoimmune destruction of gastric parietal epithelial cells)  
 Myasthenia gravis  
 Vitiligo  
 Neoplastic  
 Pituitary adenoma  
 Thyroid adenoma and carcinoma, Adrenal adenoma and carcinoma  
 (adrenal gland is a common site for metastases to spread)  
 Cysts in thyroid or pituitary  
 Vascular  
 Pituitary apoplexy (sudden loss of pituitary function and mass effect from bleeding, usually into a pre-existing tumour)  
 Drug-induced  
 Amiodarone (drug for cardiac arrhythmias) can cause thyroid dysfunction  
 Lithium (drug for bipolar disorder) can cause hypothyroidism, hypercalcemia, and nephrogenic diabetes insipidus  
 Anti-cancer immunotherapy related endocrine organ dysfunction  
 Nutritional  
 Hypothyroidism and goiter due to iodine deficiency  
 Trauma  
 Pituitary injury  
 (e.g., post-motor vehicle collision)  
 Ectopic production of hormone from tumour in another location  
 Ectopic ACTH production from small cell lung cancer  
 PTH-related peptide  
 ADH  
 beta-HCG from choriocarcinoma  
 Inflammatory/infection  
 Pituitary or adrenal involvement by: sarcoidosis, tuberculosis, fungi (these are very rare!) |
2. Disorders of the Pituitary gland

We will focus on benign pituitary growths called adenomas, which are the commonest lesion in the pituitary. These affect up to 15% of the general population. Most of these are very small, asymptomatic, and incidentally found on imaging of the head done for other reasons. Adenomas can be symptomatic because of hyperfunction (hormone secretion), and larger adenomas may present with either mass effect and/or hypofunction (or combinations of these presentations).

Scholar’s corner: The most common disorders of the pituitary gland are mass lesions, usually pituitary adenomas arising from endocrine cells of the anterior pituitary, but can also be developmental lesions (e.g. craniopharyngiomas), cystic lesions (a Rathke cleft cyst) and the pituitary can also be affected by both benign and malignant tumours arising from surrounding tissues, or by metastases from a malignancy originating elsewhere. The pituitary can be infarcted with acute hemorrhage, a rare but life-threatening condition referred to as pituitary apoplexy (acute hemorrhagic necrosis of the anterior pituitary). The pituitary can also rarely be affected by infiltrative diseases including autoimmune hypophysitis.

(a) Pituitary disease causing mass effect:

Pituitary lesions are particularly prone to “mass effect” (causing symptoms and signs due to their physical presence) because the pituitary is in the small box-like sella turcica, which is surrounded closely by critical nerves, Cranial nerve II (vision), Cranial nerves III, IV, and VI (eye movement), and the first and second branches of V: V1 and V2 (facial sensation). The patient may have a non-specific headache from the mass, or specific cranial nerve abnormalities, causing, respectively, loss of vision, double vision, or impaired facial sensation. Compression of the pituitary stalk may also result in reduced signals being transmitted from the hypothalamus, and therefore reductions in some or all of the pituitary hormones; the major is prolactin, whose level rises if its tonic suppression by hypothalamic dopamine is interrupted; this is a “double negative”: removing an inhibitor of prolactin causes its level to rise.

Click here for a video on how to examine the cranial nerves in a patient with a pituitary adenoma exhibiting mass effect

Figure 9 – Mass effect from pituitary lesions (highlights form the video)
(b). Hyperfunction from a pituitary adenoma
(see Table 4 for summary of presentation, diagnosis and treatment)

Most pituitary tumours are non-functional, meaning that they do not produce any hormones. When the tumour is functional, the most common hormone overproduced is prolactin. Much rarer is the overproduction of ACTH (leading to “Cushing’s disease”) or GH (leading to “acromegaly”). It is very rare to encounter a patient with a pituitary tumour which produces TSH, FSH or LH.

Prolactinoma
i. Clinical features
   Patients with a prolactinoma have a pituitary tumour that overproduces prolactin, which in turn stimulates the female breast (and rarely male breast) to produce milk (galactorrhea).

   Prolactin also inhibits the Hypothalamic-Pituitary-Gonadal axis which results in hypogonadism (low sex hormones and reduced fertility) in men and women. Complaints would include: menstrual irregularities or frank amenorrhea, low libido, erectile dysfunction, and, if severe in men, reduced shaving and loss of axillary and pubic hair, reduced muscle mass.

ii. Diagnosis
   The prolactin level in serum is elevated. There are no suppression tests for elevated prolactin levels. If an elevated prolactin level is encountered in a patient, it is important to appreciate that several other processes (apart from a prolactinoma) can cause this elevated prolactin level. These include:
   • Physiological reasons (pregnancy, breast feeding),
   • “Stalk effect” – this occurs when a non-secreting tumour of the pituitary, or sometimes another source (e.g. craniopharyngioma, metastasis) compresses the pituitary stalk, which reduces the dopamine inhibitory signal from the hypothalamus.
   • Hypothyroidism. This leads to elevated TRH, which directly stimulates prolactin release at high levels of TRH.
   • Medications which antagonize dopamine, including drug which enhance intestinal motility (e.g. domperidone, metoclopramide) and anti-psychotic agents
   • Decreased clearance of prolactin due to renal or liver failure.

iii. Treatment
   These tumours are usually effectively treated with dopamine agonists (drugs that act like dopamine), including Cabergoline and Bromocriptine. (Rarely, surgical resection or radiation may be required.)
Table 4 – Summary of Presentations of Hyperfunctioning Pituitary Adenomas

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Presentation*</th>
<th>Diagnosis: Confirmation of Hyperfunction**</th>
<th>Treatment</th>
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<td></td>
<td></td>
<td>Baseline Lab</td>
<td>Suppression testing</td>
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<td>Bone and tissue growth (face, hands, feet), Metabolic derangements: Diabetes mellitus, Dyslipidemia, Hypertension, Heart disease, Carpal tunnel syndrome, Sleep apnea, Colonic polyps, Osteoarthritis</td>
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</tr>
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<td>Abnormal fat distribution: Central obesity, Thin arms and legs, Round face, Supraclavicular and dorsal fat pads, Metabolic derangements: Diabetes mellitus, Dyslipidemia, Hypertension, Osteoporosis, Bruising, Purple striae on abdomen, Proximal weakness, Psychiatric illness: Depression, Psychosis, Mania, If high ACTH in women: Hirsutism, Acne, Male pattern hair loss</td>
<td>1. Rule out exogenous glucocorticoid 2. Confirm Cushing’s syndrome from endogenous source of cortisol: At least 2 of the following 3 tests should be abnormal: Overproduction: 24-hour urine collection for urine free cortisol, Lack of diurnal variation: increased midnight salivary cortisol level, 1 mg dexamethasone suppression test: Failure to suppress 8 AM cortisol after taking 1 mg of dexamethasone at midnight the night before 3. Check plasma ACTH: If ACTH level is high, do imaging to see if pituitary or ectopic source of ACTH, - If ACTH level is low, image the adrenal glands for tumour</td>
<td>1. Surgical removal of tumour 2. Medication (rarely used) 3. Radiation</td>
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*All can also present with mass effect and hypofunction of the other pituitary axes

**Once hypersecretion confirmed, imaging would also be done (MRI sella), and Ophthalmology consultation requested (with formal visual field testing)

***Not often available in Canadian laboratories

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***Not often available in Canadian laboratories
Acromegaly
Patients with acromegaly have a pituitary tumour that overproduces GH, which stimulates the liver to make IGF-1. Overproduction of GH and IGF-1 can result in the following clinical features.

i. Clinical features:
- Growth in the size of hands, feet, and altered facial features (orbital ridge, protrusion of jaw, enlarged nose and tongue)
- Carpal tunnel syndrome (compression of median nerve in the wrist due to growth of bone)
- Osteoarthritis
- Hyperhidrosis (increased sweating)
- Multinodular goitre
- Obstructive sleep apnea
- Enlarged heart
- Colonic polyps
- Metabolic derangements: (diabetes mellitus, dyslipidemia, hypertension)

A tumour overproducing GH in childhood or adolescence will cause gigantism if not treated, a condition in which the person may grow extremely tall.

ii. Diagnosis
1. ↑ serum level of IGF-1 (this is the screening test)
2. Persistently high GH serum level following the ingestion of a 75 g glucose drink (Oral glucose suppression test; GH normally suppresses to less than 1 ug/L)

iii. Treatment
- Generally, a pituitary tumour causing acromegaly is treated with transphenoidal surgical resection (Surgeons access the sella from below, through the nose and sphenoidal sinus)
- Medications can also be used to suppress the tumour size in patients who are poor candidates for surgery, or if surgical resection is incomplete. The most commonly used medication is an analogue of somatostatin called Octreotide LAR. Cabergoline (a dopamine agonist) can also be used. Occasionally, one uses a recently developed drug called Pegvisomant, which is a GH receptor antagonist.

A man with acromegaly: Mykolas required surgery and continued Somatostatin to treat his acromegaly. What are his ongoing symptoms and signs?

Cushing’s disease (Pituitary Cushing’s)
Patients with an excess of glucocorticoid present with Cushing’s syndrome. The commonest cause of this presentation is, in fact, the use of exogenous glucocorticoids, or “steroids” (most commonly due to prednisone or dexamethasone used as anti-inflammatory agents for many diseases such as rheumatoid arthritis, systemic lupus erythematosus, vasculitis and others). Sometimes patients consume supplements from a health food store that contains adrenal gland and they may develop Cushing’s syndrome as a result.

When this presentation is due to a disease process, i.e., “endogenous”, it is most commonly caused by the overproduction of ACTH from a pituitary adenoma (and this is called Cushing’s disease). Rarely, endogenous Cushing’s syndrome can result from an ectopic source of ACTH, such as a lung or gut tumour making ACTH (both of these conditions will cause both adrenal glands to make too much cortisol). Finally, benign or malignant tumours of the adrenal gland itself can produce cortisol; these patients will have suppressed ACTH from the negative feedback of the cortisol as it is produced independently of ACTH.

i. Clinical features: All causes of Cushing’s syndrome can present with:
- Abnormal fat distribution (central obesity, thin arms and legs, round face, supraclavicular and dorsal fat pads)
- Metabolic derangements (diabetes mellitus, dyslipidemia, hypertension)
- Osteoporosis, fractures
- Bruising, thin skin
- Purple striae on the abdominal wall
- Proximal muscle weakness
- Psychiatric illness (depression, psychosis, mania)
• If ACTH level is elevated in women, due to overproduction of adrenal androgens, they may develop hirsutism, acne, and male pattern hair loss on their head.

ii. Diagnosis:

The diagnosis of Cushing’s syndrome and disease involves the measurement of cortisol and ACTH. The cortisol can be measured in serum, in a 24-hour urine sample, and in the saliva.

Rule out exogenous glucocorticoids (which may be being used for asthma as an inhaled medication, as a skin cream for dermatitis, or as a joint injection to treat inflammatory arthritis, for example).

1. First step is to diagnose Cushing’s syndrome, which requires at least 2 of 3 of the following to be abnormal, to be diagnostic:
   a. Overproduction of cortisol
      Measured by increased cortisol excretion in a 24-hour urine sample
   b. Inability to normally suppress cortisol
      To test, give 1 mg of dexamethasone at midnight, and measure the 8:00 am cortisol. If it is not suppressed (i.e., if it is still over 50 nmol/L), this implies pathological overproduction of cortisol. Note that dexamethasone is a synthetic glucocorticoid that is not measured in the cortisol assay. A normal response to dexamethasone given at midnight is for it to feedback centrally and turn off CRH and ACTH, which causes endogenous cortisol production to fall to low levels, and the morning cortisol level to be low.
   c. Lack of diurnal variation
      Cortisol level is normally highest in the morning and lowest at night—check for midnight salivary or plasma cortisol levels that are high compared to controls.

2. If at least 2 of 3 of the above tests are abnormal, then one measures the serum level of ACTH. If the level is normal or high, then one concludes the cortisol overproduction is being driven by overproduction of ACTH in either the pituitary or in an ectopic site. If the ACTH level is low, then one searches for a primary adrenal gland source of cortisol overproduction such as an adenoma or rarely a carcinoma.

3. Imaging with elevated ACTH:
   If there is an inappropriately normal or elevated ACTH, then one looks for the source of overproduction. One starts with imaging: MRI of the sella would be the first test. A CT scan of chest and abdomen to look for a tumour ectopically producing ACTH is required if the MRI of the sella is normal. Additional testing may be required, including inferior petrosal sinus sampling to try to identify the precise source of ACTH in the pituitary. (The petrosal sinuses are the veins that drain the pituitary.)

   If ACTH is suppressed, then we look for an adrenal tumour.

iii. Treatment:

The preferred treatment is surgical for all three locations of tumour. There are some medications (like ketoconazole) that can be used to reduce adrenal gland overproduction of cortisol. Rarely, in ACTH-dependent Cushing’s, if the underlying tumour cannot be completely resected, both adrenal glands need to be removed to stop ACTH causing the overproduction of cortisol.

A man with Cushing’s disease: Dragan was 28 years old when we made this video. He had had 2 transphenoidal surgeries and still wasn’t cured, as you will see. Ultimately, he had a different kind of surgery. Now, ten years later, he no longer has Cushing’s, but is hyperpigmented from high ACTH levels, and has “Nelson’s syndrome” (see photo). What was the third surgery that cured him, at this price?

c. Pituitary Hypofunction (see Figure 6):

Causes

Pituitary hypofunction can be caused by inhibition of the signals from the pituitary stalk, or by destruction of the pituitary gland. In the setting of an enlarging pituitary tumour, the hormones are generally lost in this order: GH, LH, FSH, TSH, ACTH, Prolactin. (The mnemonic “Go-Look-For-The-Adenoma-Please” may help in recalling the sequence.). Because prolactin is under tonic suppression, it is often elevated with stalk compression, and requires destruction of the gland to be low,
as occurs in the case of “pituitary apoplexy” (hemorrhage into the gland). Figure 10 describes the symptoms that develop when each hormone is lost, and how to test for baseline pituitary function.

**Diagnosis**

Testing for serum levels of pituitary hormones when one suspects hypofunction is generally done at 8 AM, when cortisol levels are at their highest, to get its maximum level for that patient. It is important to measure both the pituitary hormone (e.g. TSH) and also the levels of the hormone in the target gland (e.g. T4 and T3). Baseline levels are obtained first. If they are definitely low for the pituitary hormone and for the target gland for that pituitary hormone, then the diagnosis of pituitary hypofunction for that hormone is confirmed. For instance, if both TSH and T4 are low, then the patient has hypofunction of the pituitary with respect to TSH production. Similarly, if both cortisol and ACTH levels are low, then the patient has hypofunction of the pituitary with respect to ACTH production.

If the levels of the pituitary hormones are not frankly low, then one may need to do stimulation testing:

- We stimulate release of GH and cortisol by inducing hypoglycemia. This is done by injecting insulin in a controlled setting, and seeing if both hormones rise appropriately. We do this when the levels of GH and/or ACTH are on the low side, but not so low as to be definitely deficient.

- We stimulate release of TSH and prolactin by administering synthetic TRH.

- We stimulate release of FSH and LH by administering synthetic GnRH.

**Treatment**

All of the deficient hormones can be replaced when required with synthetic target gland hormones (GH, Testosterone or Estrogen and progesterone, L-Thyroxine and Hydrocortisone).

ADH can also be replaced when deficient from stalk or hypothalamic damage to control polyuria and polydipsia. This occurs classically with suprasellar tumors like craniophayngiomas or after transphenoidal pituitary surgery.

There are many causes for hypopituitarism, in addition to an adenoma (see Figure 11 for a list of causes)

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**Hypofunction**

- **Assess clinically** for symptoms and signs of pituitary hormone deficiency:
  - GH: short stature in childhood onset of disease
  - LH + FSH: hypogonadism (erectile dysfunction, amenorrhea, loss of libido, decreased shaving)
  - TSH: hypothyroidism (weight gain, cold intolerance, constipation, decreased mentalation)
  - ACTH: hypocortisolism (weight loss, hypotension, nausea + vomiting, weakness, fatigue)

- **Measure baseline hormones:**
  - 8 AM cortisol, ACTH, sTSH, free T4, GH, IGF-1, LH, FSH, estradiol or bioavailable testosterone, prolactin

- If low-normal, try to stimulate it (insulin tolerance test for ACTH and GH deficiency)

**Lesions of the Pituitary and Hypothalamus**

- Pituitary adenoma (benign tumor)
- Other benign tumors
  - e.g. Craniopharyngioma, meningioma
- Malignant tumor:
  - 1st (starts in pituitary, including lymphoma) and 2nd (diffused elsewhere)
- Cyst (fluid-filled sac): e.g. Rathke’s cleft, arachnoid, other
- Inflammation: e.g. TB
- Infarction: e.g. sarcoidosis
- Infarction (dead tissue due to interrupted blood supply) + APOPLEXY (bleed into tumor)
- Aneurysm (dilation in blood vessel)

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Emergency #1: PITUITARY APOPLEXY: life-threatening emergency characterized with acute pituitary hemorrhage, usually into pre-existing pituitary macroadenoma. Patients typically complain of the worst headache of their life, may have vision loss, cranial nerve III, IV, V1, V2, VI involvement, hypotension, hypoglycemia, hyponatremia. This can also happen postpartum, if the setting of hypopitension (“Sheehan’s syndrome”).

Treatment: hemodynamic support; replace deficient hormones, at least i.v. Hydrocortisone acutely, treat hypoglycemia and hyponatremia. Surgery is done when there is visual loss (Cranial nerve II is affected).
2. Disorders of the Thyroid gland

A variety of disease processes can affect the thyroid gland, but a few of these diseases account for most of the patients who present with thyroid disease:

(a) Causes of thyroid disease

(i) Neoplasia. The various cells of the thyroid can proliferate uncontrollably in either a benign manner (leading to adenoma) or in a malignant pattern (leading to carcinoma). The follicular cells can proliferate in two distinct patterns, leading to either follicular carcinoma or papillary carcinoma. The parafollicular C-cells, which produce calcitonin, can lead to a rare form of thyroid carcinoma called medullary thyroid carcinoma. Since CEA is also produced by C-cells, both calcitonin and CEA serve as serum biomarkers of medullary thyroid carcinoma.

(ii) Autoimmune disease. Patients may form autoantibodies (antibodies that are directed against the patient’s tissues). Different consequences then result from different types of antibodies.
   a. Thyroid-stimulating immunoglobulin. This autoantibody is directed against the TSH receptor, and when the antibody binds to the receptor, it behaves just like TSH. This leads to enlargement of the gland and an increased rate of thyroid hormone production, and the associated disease is called Graves’ disease.

   b. Antibodies associated with injury to the gland.
      i. In a condition called Hashimoto’s thyroiditis, antibodies directed against either thyroglobulin and/or thyroid microsomes (intracellular organelles) lead to inflammatory injury and eventually hypofunction of the thyroid.
      ii. Some patients experience a viral infection of the thyroid, and subsequently immune injury leading at first to leak of pre-formed thyroid hormone from the gland (and elevated levels of thyroid hormone), and subsequently injury to the gland with thyroid hypofunction. Because the initial phase of the illness is often associated with pain over the thyroid, this is called painful thyroiditis.
      iii. Some patients experience autoimmune damage to the thyroid gland following pregnancy. This is called painless thyroiditis.

(iii) Nutritional. In some parts of the world, iodine deficiency is widespread, and can lead to hypothyroidism, causing high TSH levels which causes the thyroid gland to grow and form a “goitre” (enlarged thyroid gland).

(iv) Multinodular Goitre – Clonal growth of multiple nodules, some of which may have an activating TSH receptor somatic mutation

(v) Injury to thyroid caused by medications. The main culprits are lithium (a drug used for bipolar affective disorder) which can cause damage to the thyroid with hypothyroidism; and, amiodarone, a drug used for cardiac arrhythmias which also injures the thyroid, and can cause both hyperthyroidism and hypothyroidism.

These various processes lead to diseases via three major pathways: mass effect, hyperfunction, and hypofunction.

(b) Presentations of thyroid disease – Mass Effect (see Week 29)

Thyroid masses can be solitary and multi-nodular; see week 29 for more detailed information.

Clinical features
(1) symptomatic: due to compression of local structures – dysphagia (due to pressure on esophagus); dysphonia (due to pressure on the recurrent laryngeal nerve); or stridor, due to pressure on the trachea;
(2) incidentally, on physical examination;
(3) incidentally, on imaging such as an ultrasound done to investigate some other problem

Differential diagnosis: Types of masses:
Benign: solitary or multiple: colloid nodule, follicular adenoma
Malignant: Malignant tumors arising from follicular epithelial cells include Papillary thyroid cancer, follicular thyroid cancer, poorly differentiated thyroid cancer, and anaplastic thyroid cancer. Those arising from parafollicular C-cells are termed as medullary thyroid cancer. Primary thyroid lymphoma can also occur.
Risk factors for thyroid cancer include: family history of thyroid cancer (5-10%), personal history of head and neck irradiation, iodinated salt, and obesity
**Investigation for a patient with a thyroid nodule detected on examination or by ultrasound**

- check sTSH (the “sensitive TSH” or “sTSH” assay is the most accurate way to measure TSH in the laboratory); if level is normal or high: order ultrasound with fine needle aspiration (FNA) of any suspicious nodule(s)
- If sTSH level is low, the patient may have a “toxic nodule” overproducing thyroid hormone (either solitary or as part of a multinodular goitre). In such a case, the patient should be investigated with a “thyroid scan”. This involves injecting a radioactive pharmaceutical called technetium, which is taken up by an actively metabolizing thyroid nodule. If the nodule looks “hot” (overproducing thyroid hormone), one does not biopsy (since a biopsy of such a nodule may look like carcinoma, but almost never is). Instead, one should just treat the thyrotoxicosis, and only consider surgery to remove the nodule if its size is causing symptoms.

- If the patient has a low sTSH and then on the thyroid scan the lesion looks “cold” (i.e., not producing thyroid hormone) then it should be biopsied. (In such a case, the sTSH would be suppressed because of over-production of thyroid hormone for another reason, not related to the nodule, such as Graves’ disease (see below).) Patients with solitary functioning nodules are termed to have toxic adenomas. In the setting of multinodular toxic goiter, multiple functioning thyroid adenomas are typically identified. Unlike toxic nodular goiter (toxic adenoma) or multinodular toxic goiter, patients with Graves’ disease present with non-nodular diffuse uptake on thyroid scan.

---

**Thyroid Nodule**

- **Normal or hi sTSH**
  - Thyroid ultrasound with FNA
  - Investigate the hi TSH

- **Suppressed sTSH, N or hi free T4 and free T3**
  - RAI uptake and scan
  - Then IUS and FNA of any cold nodules on scan
  - Treat the thyrotoxicosis

*Figure 12 – Clinical Approach to Thyroid Nodules*

**Treatment**

If biopsy shows benign nodule
- If biopsy results indicate a benign nodule: monitor with serial ultrasounds (done approximately every 3 – 6 months), and re-investigate if nodule develops concerning ultrasonographic features (for example increasing growth or microcalcifications (which are somewhat indicative of malignant transformation).

If biopsy shows malignant or toxic nodules
- The nodule should be removed surgically (hemi- or total thyroidectomy), followed by L-thyroxine therapy.Suppressive doses of L-thyroxin (using a dose high enough to cause TSH to be low or undetectable) are used in high-risk tumours (tumours with pathological features that suggest a high risk of recurrence). Patients with higher risk tumours are also treated with radioactive iodine to ablate (kill) normal thyroid tissue and any tumour cells that may remain after surgery.

- Monitor: plasma thyroglobulin level (a rising thyroglobulin level suggests there is a risk of recurrent malignancy), thyroid bed ultrasound
Key concept:

The word “thyrotoxicosis” means the patient has elevated plasma free T4 and/or free T3 levels.

“Hyperthyroidism” means the thyrotoxicosis is due to ongoing over-production of thyroid hormone. Most cases of thyrotoxicosis are due to hyperthyroidism, and will have increased radioactive iodine uptake on nuclear testing, and will respond therapeutically to thionamide drugs. However, some patients with thyrotoxicosis have an underactive thyroid gland, due to either leakage of previously formed T4 and T3 from an injured/infamed gland, or due to exogenous intake of excessive T4.

Thyrotoxicosis

i. Clinical features:

Patients who have thyrotoxicosis may present with any of the following symptoms:

- Weight loss,
- Heat intolerance
- Tremor
- Palpitations
- Proximal muscle weakness
- Oligomenorrhea (reduced amount and/or frequency of menstrual blood loss)
- Shortness of breath
- Hyperdefecation (increased frequency of bowel movements)

Signs of thyrotoxicosis:

- General: anxious appearance, thin
- Vital signs:
  - Tachycardia (heart rate over 100/minute +/- irregularly irregular from atrial fibrillation)
  - Systolic hypertension,
  - If fever, consider thyroid storm (Hyperthyroidism that is severe enough be a medical emergency).
- Eyes: Lid lag, “Stare”, Proptosis (in patients with Graves’ orbitopathy),
- Thyroid: enlarged +/- nodular, may be tender (subacute thyroiditis), may have audible bruit (Graves’)
- Congestive heart failure (rarely)
- Neurologic: tremor, hyperreflexia, proximal muscle weakness

ii. Diagnosis of primary thyrotoxicosis requires: low TSH, elevated free T4 and free T3

The differential diagnosis can be divided into:

1. Diseases that cause overproduction of thyroid hormone (hyperthyroidism) or
2. Diseases that cause “leak” of endogenous thyroid hormone or where there is exogenous thyroid hormone consumption

The radioactive iodine uptake test is used to differentiate overproduction from leak or exogenous thyroid.

(1) Hyperthyroid disorders:

Graves’ disease (pathophysiology and distinguishing features)
Autoimmune, Thyroid-Stimulating Immunoglobulin (TSI) produced (acts like TSH, causing follicular cell hyperplasia and overproduction of thyroid hormone)
Graves’ disease is quite common
Distinguishing clinical features (in addition to the symptoms and signs of thyrotoxicosis):

- History: There may be personal or family history of other autoimmune disorders
- O/E (“On Examination”): There may be Graves’ orbitopathy
- Diffusely enlarged thyroid gland, with audible thyroid bruit
- +/- acropachy (clubbing)
**Foundations Year 1, Faculty of Medicine, University of Toronto**

+/- pretibial myxedema (thickened, waxy skin over the tibia)

*Special investigations:* Elevated TSI in blood

**Multi-nodular goiter (pathophysiology and distinguishing features)**

Clonal and polyclonal growth of multiple nodules

Those showing hyperfunction “multinodular toxic goiter” may have multiple clonal proliferations harboring activated TSH receptor (TSHR) mutations or G protein alpha-subunit mutations (GNAS).

(Common)

*History:* Patient may complain of dysphagia, dysphonia or stridor if very enlarged thyroid

*O/E:* enlarged thyroid with multiple nodules

*Special investigations:*

Thyroid ultrasound to document size and location of nodules

Thyroid scan to document if nodules are “hot” (overproducing thyroid hormone) or “cold”

Cold nodules may need Fine Needle Aspirate (FNA) to rule out cancer, depending on their size and ultrasound features

**Toxic adenoma (pathophysiology and distinguishing features)**

Clonal growth of nodule with activated TSH receptor; this is a rare condition

Similar to those of multinodular toxic goiter, toxic adenoma harbors activating mutations in the TSHR or GNAS.

With a solitary nodule, the rest of the gland is suppressed, so the rest of the gland is difficult to palpate

*Special investigations:*

Thyroid ultrasound to document size and location of nodule

Thyroid scan to document if nodule is “hot” (overproducing thyroid hormone)

No FNA if confirm it is a toxic “hot” nodule.

**Other causes of hyperthyroidism (pathophysiology and distinguishing features)**

*Beta-HCG at high level during pregnancy can cross react with the TSH receptor*

First trimester pregnancy: Common

Post-partum with choriocarcinoma: very rare

*TSHoma (also known as Thyrotroph adenoma or TSH-producing pituitary adenoma)*

Pituitary tumor producing TSH stimulates thyroid gland in an uncontrolled manner

Very rare (not discussed in the Pituitary section)

TSH is elevated in the setting of high free T4 and high free T3

(2) *Thyrotoxicosis without hyperthyroidism (i.e., without overproduction of thyroid hormone)*

(Radioactive iodine uptake is low due to lack of thyroid gland function)

*Subacute thyroiditis (pathophysiology and distinguishing features)*

Inflammation of the thyroid, causing “leak” of stored thyroid hormone

Painful: preceding upper respiratory tract infection, very painful and tender thyroid gland

Painless: may occur after pregnancy, or sporadically

Both types go through subsequent euthyroid, and then hypothyroid phases

Often get full recovery over time

**Exogenous thyroid hormone consumption**

This diagnosis should be obvious from the history, unless the patient is surreptitiously taking it.

Can be either:

- Exogenous thyroid hormone supplementation
  - Consuming L-thyroxine, Cytomel (T3) or dessicated thyroid hormone (in some foreign weight loss medications)
  - If taking L-thyroxine, they will have low thyroglobulin level
- Consuming meat contaminated with thyroid gland (improper butchering)

**Struma ovarii**

A very rare ovarian tumour that produces thyroid hormone.
Summary for diagnosis of thyrotoxicosis, and underlying cause:
After history and physical examination:
1. Confirm thyrotoxic: Check sTSH (“sensitive TSH” is the assay used to measure TSH), free T4 and free T3
   Expect: sTSH fully suppressed, free T4 elevated and free T3 elevated

2. Confirm etiology (will be directed by history and physical exam):
   a. Check TSI (in order to help diagnose Graves’ disease)
   b. Obtain radioactive iodine uptake (RAIU) to see if hyperthyroid (actively overproducing T4 and T3) versus “leak” in
      subacute thyroiditis or consumption of thyroid hormone. Must not be on anti-thyroid medications, and have had no
      iodine loads recently.

3. Do thyroid ultrasound and nuclear scan if suspect thyroid nodules (cold nodules need fine needle aspirate for cytology to
   address the possibility of malignancy)

ii. Treatment
Beta-blockers are drugs that block catecholamines from interacting with their beta-receptor). They may be used for all
symptomatic thyrotoxic patients to suppress the symptoms due to exaggerated catecholamine sensitivity (palpitations, tremor,
anxiety), if there are no contraindications (e.g, asthma).

There are three options for therapy of underlying hyperthyroidism (Graves’ disease, multinodular goiter, toxic adenoma)
   i. Anti-thyroid medications, called thionamides (methimazole and propylthiouracil (PTU)) block production of T4 and
      T3 in the thyroid gland
   ii. Radioactive iodine treatment. This is given orally as a tablet. The thyroid gland avidly takes up the radioactive
      iodine, and it causes severe injury to the thyroid cells and leads to destruction of most or all of the gland. A higher
      dose is used than that used for diagnostic testing, in order to ablate (destroy) the overproducing follicular cells
   iii. Surgery to remove either the whole gland (e.g. for Graves’ disease) or the diseased portion (e.g. a hemithyroidectomy
        for a toxic adenoma)

Monitor with sTSH, free T4 and free T3 (you need to follow all three because the TSH will remain suppressed for a while even
after the free T4 and free T3 drop into the normal (or low) range with therapy.

| Emergency #2: THYROID STORM: life-threatening emergency with severe thyrotoxicosis, typically with fever,
| congestive heart failure, vomiting |
| Can occur postoperatively when thyrotoxicosis isn’t controlled before surgery |
| Treatment: hemodynamic support; cooling; beta-blocker; PTU; iodine after PTU given, to block thyroid hormone release
| from follicular cells; glucocorticoids |

A young woman with Graves’ disease and a thyroid goitre: see the video to learn Jessie’s story.

c. Hypofunction (Hypothyroidism)

i. Clinical features
In general, patients with hypothyroidism may present with any of the following symptoms:
  • fatigue
  • weight gain
  • cold intolerance
  • difficulty with concentration, and with memory (can cause dementia in the elderly)
  • dry skin and dry hair
  • weakness
  • constipation
  • menorrhagia
Signs of hypothyroidism include:
- apathetic appearance
- orange skin
- dry skin and hair
- bradycardia, diastolic hypertension
- hyporeflexia, delayed relaxation phase of reflexes
- hoarse voice
- periorbital edema

ii. Diagnosis of primary hypothyroidism requires an elevated TSH, then confirmed by a low free T4

Differential diagnosis:

- **Congenital**
  Due to an anatomical defect in the gland, an inborn error of thyroid metabolism, or iodine deficiency
  *Special investigation:* Elevated sTSH on neonatal screening

- **Hashimoto’s thyroiditis**
  Autoimmune disease with thyroid cell destruction
  *History:* Personal or family history of other autoimmune disorders is common
  *O/E:* Enlarged thyroid gland on examination and ultrasound
  *Special investigations:* Elevated thyroid autoantibodies

- **Iatrogenic (due to prior or ongoing treatment with any of the following):**
  - Anti-thyroid medications (PTU, methimazole)
  - Other drugs: lithium, amiodarone
  - Prior therapeutic radioactive iodine
  - Prior thyroidectomy

- **Subacute thyroiditis**
  After thyrotoxic phase (see Thyrotoxicosis above)
  Often reversible

  *Special investigations:* Elevated thyroid autoantibodies

- **Secondary hypothyroidism: Pituitary or hypothalamic dysfunction**
  See Pituitary section
  Symptoms or signs of sellar mass effect
  *Special investigations:* TSH low or normal in the setting of low free T4, other pituitary hormones high or low

*Investigations in a patient with suspected hypothyroidism:*

- Screen for hypothyroidism by checking plasma sTSH (if high, confirm diagnosis with low free T4 level)
- Measure anti-thyroid antibodies (antimicrosomal, antithyroglobulin) if Hashimoto’s thyroiditis suspected.

*Treatment:*

Oral tablets of L-thyroxine are used, the dose is typically 1.6 microgram/kg/day (mcg/kg/d), once daily (e.g., if 60 kg, use 100 mcg). It is taken with water on an empty stomach; the patient should wait at least 30-60 minutes before eating, and take any iron and calcium supplements at a different time of day.

We start with a much lower dose if elderly, or if the patient has heart disease (typically, one would start with 25 mcg daily then slowly increase dose to level needed to achieve desired effect over several months).

Monitoring is with sTSH only, you should wait 6 weeks after each dose adjustment (half-life is ~ 1 week, so want to wait 5 – 6 half-lives), then annually once stabilized.

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**Emergency #3: MYXEDEMA COMA:**

Life-threatening emergency with severe hypothyroidism, typically patients have hypothermia, bradycardia and coma, may have heart failure

Can occur with severe longstanding hypothyroidism

*Treatment:* hemodynamic support; may need respiratory support, warming, high dose intravenous T4 and T3, glucocorticoid
3. Disorders of the Adrenal gland

A variety of disease processes can affect the adrenal gland, but a few of these disorders account for most of the patients who present with adrenal disease:

1) **Congenital enzyme abnormalities.** Patients may have an inherited deficiency or other abnormality of one of the several enzymes involved in adrenal steroid synthesis. This can lead to either elevated levels of glucocorticoids, mineralocorticoids and/or sex steroids (those that are proximal to the enzyme block), or it can lead to deficits of one of these categories of hormone (those that are distal to the block). Often there is a mixture of elevated and low adrenal hormones.

2) **Neoplasia.** The various cells of the adrenal can proliferate uncontrollably in either a benign manner (leading to adenoma or hyperplasia) or in a malignant pattern (leading to carcinoma). These include both adrenal cortical cells as well as the neurons of the adrenal medulla, which can also proliferate, leading to a disorder called pheochromocytoma.

3) **Autoimmune disease.** Patients may form autoantibodies directed against the epithelial cells of the adrenal gland, causing adrenalitis, and ultimately destruction of the normal tissue.

4) **Infection.** Rarely, various infections can cause adrenal gland failure (“adrenal insufficiency”). The main causes are HIV infection, cytomegalovirus infection, tuberculosis, and various fungal infections.

5) **Hemorrhage into adrenal gland.** This can occur as a complication of anticoagulation (which is a very rare complication), or a complication of systemic infection with meningococci.

6) **Metabolic: Adrenoleukodystrophy** is an X-linked metabolic disorder, characterized by progressive neurologic deterioration due to demyelination of the cerebral white matter, due to an abnormal accumulation of saturated very-long-chain fatty acids (VLCFA). The boys with this disorder often have adrenal insufficiency as well.

7) **Iatrogenic: surgical removal or drug effects**

---

Scholar’s corner:

Autoimmune diseases are common in endocrinology, and often goes in clusters, with other endocrine or non-endocrine autoimmune disease:

Autoimmune Polyglandular Syndromes are composed of the following clusters of disorders:
- **Type 1:** Hypoparathyroidism, Adrenal insufficiency, Alopecia, GI tract Candidiasis
- **Type 2:** Hashimoto’s thyroiditis, Graves’ disease, Adrenal insufficiency, type 1 DM, pernicious anemia, primary hypogonadism, vitiligo, coeliac disease, myasthenia gravis
- **Type 3:** very rare: X-linked polyendocrinopathy, immunodeficiency and diarrhea syndrome (XLAAD or IPEX), most have diabetes

Presentations: These various processes lead to diseases via three major pathways: incidentally discovered mass on abdominal imaging, hyperfunction, and hypofunction.

a. **Adrenal Mass:**
   i. **Differential diagnosis/clinical presentation:**
      Benign masses. These are either “functioning” (meaning they produce adrenal hormones – catecholamines, aldosterone, cortisol or sex hormones) or “non-functioning” (and most are non-functioning).
Malignant masses are either primary (i.e., they are adrenal carcinomas, which may be either functioning or non-functioning), or they are secondary (i.e., they are a metastasis from a cancer of the lung, breast, kidney, etc.) The adrenal glands are a fairly common site for metastatic spread from a primary malignancy originating somewhere else.

ii. Diagnosis
1. Look at image characteristics to see if the mass looks benign or malignant.
Benign lesions tend to be round, homogeneous, not calcified or hemorrhagic, small (less than 4 cm), with relatively low density as measured by Hounsfield units (less than 10) on CT scan done without intravenous contrast. The density is in between fat and liver, since the adrenal cortex produces cholesterol-based hormones and cholesterol is a type of fat.) The absence of one or more of these features raises concern that the mass may be malignant – i.e., if it is calcified and/or hemorrhagic and/or larger than 4 cm and/or has a CT scan density of more than 10 Hounsfield units.

2. Do history, physical examination and laboratory testing to rule out pheochromocytoma, Cushing’s syndrome, and (if the patient is hypertensive and/or hypokalemic, hyperaldosteronism. (See below for details.)

iii. Treatment
1. Surgical removal if:
   (1) the mass is over 4 cm in size (increased risk of malignancy);
   (2) it’s imaging characteristics are worrisome for cancer; or
   (3) if it is a functioning mass causing a clinical syndrome.
2. Other masses can be monitored.

b. Hyperfunction of the adrenal gland
Hyperfunction of the adrenal gland can be due to a functional nodule, due to bilateral adrenal hyperplasia or rarely due to a functional carcinoma (cancer). The presentation depends on the layer of the adrenal gland the hyperfunctioning cell originates in: if it is from the outer layer of the cortex (the glomerulosa), then aldosterone will be overproduced (Primary Aldosteronism); from the middle cortex layer (the fasciculata), cortisol is overproduced (Cushing’s syndrome), and from the inner layer (the reticularis), then sex hormones will be overproduced (DHEAS is specific for the adrenal gland; the adrenal gland can also over-produce estradiol or testosterone). Tumours that originate in the adrenal medulla (in the very centre of the gland) are of sympathetic nervous system origin, and are called pheochromocytomas.

Primary hyperaldosteronism:

i. Clinical features:
   • Hypertension which may be quite severe and difficult to treat
   • Hypokalemia is often but not always present

ii. Diagnosis:
   1. Elevated serum aldosterone: renin ratio
   2. Lack of suppression of aldosterone with NaCl loading (p.o. or i.v.)
   3. CT scan may show an adrenal adenoma. One may need to confirm localization with adrenal vein sampling which would show a very high level of aldosterone coming from one adrenal gland compared to the other side.

iii. Treatment:
   Adenoma: Surgical removal of the affected adrenal gland in most people (some can be treated medically as for hyperplasia, if they are at risk of having essential hypertension)
   Bilateral Hyperplasia: Medical treatment with diuretics which antagonize aldosterone or its effects
      - Spironolactone or Eplerenone block the aldosterone receptor, Amiloride blocks the ENaC sodium channel in the kidney

Cushing’s syndrome

i. Clinical features: Cushing’s syndrome
(see Pituitary section for details of presentation) ---adrenal Cushing’s syndrome does not result in hyperandrogenism since ACTH is suppressed (in contrast, high ACTH can cause the adrenal glands to overproduce androgens)

ii. Diagnosis:
   1. Elevated levels of cortisol
      • High 24-hour urine free cortisol
• High 8 am cortisol, measured after taking 1 mg dexamethasone the night before (dexamethasone suppression test). The 8 am cortisol would normally be suppressed by the dexamethasone taken the night before. In Cushing’s syndrome the suppression fails to occur; i.e., the 8 am cortisol remains high.
• Midnight saliva is collected, and the cortisol level is measured – in all types of Cushing’s syndrome this will be elevated

2. Suppressed ACTH

iii. Treatment: Surgical removal of affected adrenal (rarely, one can use medical treatment with the drug Ketoconazole, which is actually an antifungal medication, which as a side effect blocks adrenal hormone production)

Overproduction of sex hormones by the adrenal gland

i. Clinical features:
• Virilization of women due to androgenic hormones being produced: deepened voice, acne, hirsutism, frontal balding, increased musculature, decreased breast size, cliteromegaly
• Feminization of men due to estrogenic hormones being produced (erectile dysfunction, gynecomastia, decreased male-pattern hair growth
• Often malignant

i. Diagnosis: Markedly elevated DHEAS, testosterone or estradiol level
ii. Treatment: Surgical removal of affected adrenal gland

Pheochromocytoma

i. Clinical features: Pheochromocytoma can present with:
• Triad of 3 P’s: attacks with Pain (severe headache), Palpitations and Perspiration
• Severe and/or difficult to control hypertension
• Hypertensive “crises”
• Incidental imaging finding
• Genetic syndromes account for around 40% of clinical presentations (MEN2A, MEN2B-also known as MEN3, von Hippel Lindau syndrome, Neurofibromatosis 1, Succinate dehydrogenase subunit-driven familial paraganglioma syndromes (external to adrenal glands, in sympathetic nervous tissue)

ii. Diagnosis:
1. Elevated 24-hour urine levels of metanephrines (a breakdown product of catecholamines), epinephrine and norepinephrine and/or elevated plasma level of metanephrines
2. Once confirmed biochemically, then do imaging of adrenal glands (CT or MRI)

iii. Treatment: Surgical removal of affected adrenal: blood pressure must be very well controlled prior to surgery since there is a risk of triggering a massive release of previously synthesized catecholamines when the tumour is handled. Treatment usually involves an alpha-blocker like Doxazosin, prior to surgery to avoid a hypertensive crisis at the time of surgery.

EMERGENCY #4: Pheochromocytoma can present with a hypertensive crisis, especially if the tumour in manipulated intraoperatively without proper medical preparation.

c. Hypofunction of the adrenal gland (HYPOADRENALISM):

i. Clinical features:
Patients who have adrenal insufficiency (hypoadrenalism) may present with the following symptoms:
• Weight loss
• Weakness, fatigue
• Hyperpigmented skin (due to high levels of melanocyte stimulating hormone, co-secreted with ACTH)
• Dizziness (i.e., presyncope, due to low blood pressure)
• GI complaints: nausea, vomiting, diarrhea

Signs include:
• Wasted, ill appearance,
• Hyperpigmented skin,
• Low blood pressure, evidence of ECF volume depletion (postural tachycardia and postural hypotension, low JVP)
ii. Diagnosis:
   • Electrolytes:
     o Hyponatremia (due to cortisol deficiency, causing increased levels of ADH, which is normally inhibited by cortisol)
     o Hyperkalemia (Due to primary adrenal insufficiency with associated lack of aldosterone, and therefore reduced renal excretion of potassium)
   • Glucose: Glucose levels are often low due to lack of cortisol effect
   • Eosinophils are often mildly elevated due to lack of cortisol inhibition of eosinophil production

ACTH stimulation test: draw blood for levels of cortisol and ACTH, then give synthetic ACTH 250 mcg im or iv, with repeat cortisol level 1 hour later. Normal response is for the cortisol to rise over 500 nmol/L.

Primary adrenal insufficiency leads to low levels of cortisol, both unstimulated and stimulated and high ACTH levels. The next step is to determine the underlying etiology of the primary adrenal hypofunction (see Table 5)
Table 5 - Causes of Adrenal Hypofunction:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology</th>
<th>Distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease</td>
<td>Autoimmune, antibodies produced that destroy the adrenal gland</td>
<td>History: +/- personal or family history of other autoimmune disorders</td>
</tr>
<tr>
<td></td>
<td>Rare, but life-threatening</td>
<td>Extra investigations: auto-antibodies to thyroid and to adrenal</td>
</tr>
</tbody>
</table>
| Bilateral adrenal hemorrhage or infarction | • Anticoagulation therapy  
• Sepsis  
• Bleeding/thrombosis disorder | CT scan imaging                                                                       |
| Infections                            | TB, HIV, CMV, fungi (rare)                                                | TB skin test, Chest X-Ray, HIV testing, CMV serology                                     |
| Congenital adrenal hyperplasia        | Several forms, with each involving different enzymes in the steroid-hormone synthetic pathway.  
21-hydroxylase deficiency is the most common: leads to deficiencies in both cortisol and aldosterone, with excess adrenal androgens due to compensatory elevated ACTH level. | • Classic CAH (due to nearly complete 21-hydroxylase deficiency) presents at birth with very sick infant, hypotension, hyperkalemia, ambiguous genitalia in females; fatal if not diagnosed quickly  
• Universal screening now done for this  
• Non-classic CAH (due to less severe 21-hydroxylase deficiency) presents later in life (teens-twenties) with hyperandrogenism in women (acne, hirsutism, male-pattern balding)  
• Measure 17-hydroxyprogesterone (precursor on the pathway, so it will be elevated due to high ACTH levels in response to low cortisol) |
| Adrenoleukodystrophy                  | Due to accumulation of very long chain fatty acids                        | Measure VLCFA                                                                           |
| Secondary or tertiary adrenal hypofunction | Due to pituitary or hypothalamic defect                                  | • Not hyperpigmented (since ACTH levels are low)  
• Normal plasma potassium (since aldosterone levels are normal)                          |

iii. Treatment for adrenal crisis (acute insufficiency):
1. Supportive: intravenous normal saline, may need intravenous glucose
2. Intravenous hydrocortisone (glucocorticoid) 100 mg iv initially, then 50 mg every 8 hours
3. Once stabilized, switched to oral Hydrocortisone, 15-25 mg daily given in divided doses. A typical regimen is 10 mg in the morning, and 5 mg in the afternoon. If larger adult, one might give 15 mg in the AM and 10 mg in PM
4. Primary adrenal insufficiency requires aldosterone replacement. Fludrocortisone, usual dose is 0.1 mg daily p.o.
5. Sick day management instructions:
   a. If mild-moderately ill (e.g., upper respiratory tract infection, significant emotional stress), the patient should double the baseline dose of glucocorticoid, to mimic what the adrenal gland would be producing under stress
   b. If severely ill (e.g. sepsis, major trauma, major surgery) – give hydrocortisone 50 – 100 mg i.v. every eight hours until stabilized, then “taper” (gradually reduce over several days) back to baseline dose
   c. Get medic alert bracelet
   d. Take injectable glucocorticoid with you on remote trips

EMERGENCY #5: Addison’s disease (Hypoadrenalism above): While there is typically a long prodrome with the patient gradually getting worse with this condition, the patient can decompensate when a superimposed illness causes an increased demand for glucocorticoid action: the patient can die if the condition is not recognized and treated urgently.
Table 6 - OVERVIEW OF PITUITARY/ADRENAL/THYROID HYPER- AND HYPO-FUNCTION PRESENTATIONS

<table>
<thead>
<tr>
<th>Pituitary makes these Hormones→</th>
<th>ACTH ↓</th>
<th>TSH ↓</th>
<th>LH+FSH ↓</th>
<th>Growth Hormone (GH) ↓</th>
<th>Prolactin ↓</th>
<th>ADH ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target glands then make these Hormones→</td>
<td>Cortisol ↓</td>
<td>T4 and T3 ↓</td>
<td>Estrogen and progesterone/eggs OR Testosterone + sperm</td>
<td>IGF-1 ↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Normal effect of target gland hormone →**
- Maintains blood pressure
- Needed to survive stress
- Catabolic
- Sets basal metabolic rate (how fast one’s cells are working)
- Sexual function and reproduction
- Growth in children
- Maintains bones, muscle, fat balance in adults
- Anabolic for protein, growth
- Catabolic for carbohydrates and fat
- Milk production
- Allows the kidneys to conserve water

**If Pituitary and/or Target Gland hormone levels are too high (cortisol, T4 and T3, GH, prolactin, ADH)→**
- Cushing’s syndrome:
  - Weight gain
  - Bruising
  - Facial hair
  - Acne
  - Bone loss
  - Diabetes
  - Blood pressure
  - Weak muscles
  - Depression
- Overactive thyroid (hyperthyroid):
  - Almost always Primary disorder
  - Weight loss
  - Palpitations
  - Tremor
  - Diaphoresis
  - Heat intolerance
  - Hyperdefecation
  - Oligomenorrhea
- Acromegaly:
  - Growth of Face, hands and feet
  - Fatigue
  - Diabetes mellitus
  - Blood pressure
  - Colonic polyps
  - Ischemic heart disease
  - Osteoarthritis
  - Carpal tunnel syndrome
  - Obstructive sleep apnea

**If Pituitary and/or Target Gland hormone levels are too low→**
- Adrenal insufficiency:
  - Weak
  - Tired
  - Weight loss
  - Dizziness
  - Nausea
  - (when primary adrenal failure: hyperpigmented, hyperkalemia)
- Hypothyroid:
  - Weight gain
  - Fatigue
  - Cold intolerance
  - Constipation
  - Dry skin & hair
  - Difficulty concentrating
- Infertility
- ↓ libido
- Bone loss
- Men:
  - Amenorrhea
- Males:
  - Poor sexual function
  - Loss of muscle power
- Fatigue
- Bone loss
- Muscle loss
- Fat gain
- Can’t breastfeed

**Diabetes insipidus:**
- Polyuria,
  - polydipsia
  - If reduced access to water→
- Hyponatremia
Table 7 - Thyroid disease: Summary of diagnostic tests

<table>
<thead>
<tr>
<th>Condition</th>
<th>Lab test</th>
<th>Special lab tests</th>
<th>Radioactive iodine uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R/O pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cannot be on anti-thyroid drugs or iodine</td>
<td></td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>↓sTSH</td>
<td>TSI (present in Graves’ disease)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑free T4</td>
<td>Yes</td>
<td>Only do if also has palpable nodules</td>
</tr>
<tr>
<td></td>
<td>↑Free T3 (if ↓free T4, look for pituitary disease)</td>
<td></td>
<td>Only do if also has palpable nodules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ = Graves’, MNG, toxic adenoma, choriocarcinoma, TSHoma</td>
<td>Only for cold nodule (will be detected on scan)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 = subacute thyroiditis, exogenous thyroid hormone, struma ovarii</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>↑sTSH to screen</td>
<td>Anti-thyroid antibodies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- if high, confirm with ↓free T4</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Thyroid mass</td>
<td>sTSH</td>
<td>No</td>
<td>Only do if has low TSH</td>
</tr>
<tr>
<td>Known thyroid cancer</td>
<td>sTSH (for L-Thyroxine dose)</td>
<td>Anti-thyroglobulin antibody</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroglobulin (for recurrence)</td>
<td>Only do with cold nodule - TSH normal or high - if TSH low, do if nodule is cold on scan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes (for recurrence)</td>
<td>Only if recurrent neck mass</td>
</tr>
</tbody>
</table>

TSI = Thyroid stimulating immunoglobulin, RAI = radioactive iodine, MNG = multinodular goitre
Table 8 - Thyroid disease: Summary of therapy (*BOLD* means preferred first-line therapy)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Possible therapy for each disorder</th>
<th>Specific condition where the therapy is considered</th>
<th>Counselling and other follow-up issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid mass</td>
<td>Monitor only</td>
<td>Benign on FNA</td>
<td>- Monitor with ultrasound periodically</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>Malignant/ suspicious FNA</td>
<td>- Hypothyroidism if total thyroidectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Risk of hypocalcemia −2% (due to parathyroid injury)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Risk of hoarseness −2% (due to injury to recurrent laryngeal nerve)</td>
</tr>
<tr>
<td>Low or high dose radioactive iodine (RAI)</td>
<td></td>
<td>Thyroid cancer that has features of “high risk” (RAI given after total thyroidectomy)</td>
<td>- Make sure patient is not pregnant!</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- RAI precautions afterwards</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Very small risk of future haematological malignancy, earlier menopause, dry mouth</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Thionauracils:</td>
<td>Graves’ disease</td>
<td>- Need to monitor thyroid function tests closely</td>
</tr>
<tr>
<td></td>
<td>-Propylthiouracil (PTU)</td>
<td>Multinodular goitre</td>
<td>- Watch for:</td>
</tr>
<tr>
<td></td>
<td>-Methimazole</td>
<td>Toxic adenoma</td>
<td>- Agranulocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Increased liver enzymes (with PTU)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Rash/joint pains/fever</td>
</tr>
<tr>
<td>Low dose RAI</td>
<td>Graves’ disease</td>
<td>Multinodular goitre</td>
<td>- Make sure patient is not pregnant!</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic adenoma</td>
<td>- RAI precautions afterwards</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Significant risk of hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Very small risk of future haematological malignancy, earlier menopause, dry mouth</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>Graves’ disease</td>
<td>Multinodular goitre</td>
<td>See above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxic adenoma</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>All causes of thyrotoxicosis</td>
<td></td>
<td>- Avoid with asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Adjust dose to normal heart rate (goal pulse is 60 – 100)</td>
</tr>
<tr>
<td>NSAID (Non-Steroidal Anti-Inflammatory Drug) or Prednisone (glucocorticoid Rx)</td>
<td>Painful thyroiditis</td>
<td></td>
<td>- NSAID: Risk of gastric irritation, peptic ulcer, and renal dysfunction (NSAID)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Prednisone has many other potential side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(psychiatric, myopathy, bone loss, weight gain, HPA axis suppression, avascular necrosis of long bones, etc)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>L-Thyroxine</td>
<td>All causes of hypothyroidism</td>
<td>- Monitor TSH every 6 weeks after dose adjustment, then annually or with symptoms of hypo- or hyper-function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Take dose first thing in the morning with water on an empty stomach, nothing to eat for 30-60 minutes, take calcium and iron at a different time of day</td>
</tr>
</tbody>
</table>

FNA = fine needle aspirate, RAI = radioactive iodine, PTU = propylthiouracil, TFT= Thyroid function tests, MNG = multinodular goiter, LFT = liver function tests, NSAID = non-steroidal anti-inflammatory drug
<table>
<thead>
<tr>
<th>Condition</th>
<th>Lab test</th>
<th>Special lab tests</th>
<th>Imaging</th>
<th>Adrenal vein sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal mass</td>
<td>Rule out:</td>
<td></td>
<td>CT adrenals +/- contrast or MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Cushing’s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hyperaldosteronism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Pheochromocytoma (see below)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>- 24-hour urine free cortisol</td>
<td></td>
<td>CT adrenals +/- contrast or MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Give dexamethasone 1 mg at midnight, then check 8 am cortisol the next morning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 3x midnight salivary cortisol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACTH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>Serum potassium</td>
<td></td>
<td>CT adrenals +/- contrast or MRI</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Aldosterone/renin ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Saline-suppressed aldosterone level in serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma “Pheo”</td>
<td>24-hour urine for</td>
<td></td>
<td>CT adrenals +/- contrast or MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- metanephrine and normetanephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- catecholamine levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma free metanephrine and normetanephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>8 AM Cortisol 17-OH progesterone</td>
<td>ACTH stimulation test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>8 AM cortisol</td>
<td>ACTH stimulation test</td>
<td>CT adrenals +/- contrast or MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenal antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 10 - Adrenal disorders: Summary of therapy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Possible therapy for each disorder</th>
<th>Counselling and other follow-up issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal mass</td>
<td>Unilateral adrenalectomy for malignancy or hyperfunction</td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome due to adrenal adenoma or carcinoma</td>
<td>Unilateral adrenalectomy</td>
<td>Will have secondary adrenal insufficiency after surgery, because the endogenous cortisol had been suppressing the HPA axis. Taper off Cortef over 6 months or as tolerated.</td>
</tr>
<tr>
<td>Hyperaldosteronism due to adenoma</td>
<td>Unilateral adrenalectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug therapy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eplerinone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Unilateral adrenalectomy</td>
<td>Screen first degree family members for pheo</td>
</tr>
<tr>
<td></td>
<td>Prepare for surgery with alpha-blocker, then beta-blocker</td>
<td>Consider genetic testing depending on biochemical phenotype and pathology findings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifelong follow-up for recurrence (annual biochemical screening for recurrence)</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>Dexamethasone/ other glucocorticoid</td>
<td>See below</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Hydrocortisone</td>
<td>Sick day management</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone</td>
<td>a. If mild-moderately ill (e.g., upper respiratory tract infection, significant emotional stress), the patient should double the baseline dose of glucocorticoid.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. If severely ill (e.g. sepsis, major trauma, major surgery) – give hydrocortisone 50 – 100 mg i.v. every eight hours until stabilized, then “taper” (gradually reduce over several days) back to baseline dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. Get medic alert bracelet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>d. Take injectable glucocorticoid with you on remote trips</td>
</tr>
</tbody>
</table>

Thanks to:
Martin Schreiber for major editing and content suggestions
Elysia Adams for feedback on clarity