History of Presenting Illness
- Goiter
- Tachycardia
- widened pulse pressure
- warm, fine, moist skin
- tremor
- eye signs (!! EXOPHTHALMOS !!)
- atrial fibrillation
- nervousness and increased activity
- increased sweating
- hypersensitivity to heat
- palpitations
- fatigue
- more appetite
- weight loss
- insomnia
- weakness
- frequent bowel movements (occasionally diarrhea).

Differential Diagnoses

<table>
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<th>Anxiety Disorders</th>
<th>Pituitary Macroadenomas</th>
<th>Thyroiditis, Subacute</th>
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<td>Hashimoto Thyroiditis</td>
<td>Pituitary Microadenomas</td>
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<td>Pheochromocytoma</td>
<td>Thyroid, Papillary Carcinoma</td>
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Findings on History
Has there been an ABRUPT ONSET OF FLORID SYMPTOMS??
- Fever
- Marked weakness and muscle wasting
- extreme restlessness
- wide emotional swings
- confusion
- psychosis
- coma;
- hepatomegaly
- mild jaundice

~"THYROID STORM" ~
= life threatening !!

Findings on Examination

**LOOK**
- Weight loss
- Anxiety
- Frightened thyrotoxic stare
- Patient may be pacing and unable to sit still

**HANDS**
- Put arms out: fine resting tremor
- Onycholysis – rarely Graves
- Acropachy (clubbing)
- Palmar erythema
- Warmth
- Sweaty palms

**PULSE**
- Sinus tachy
- !! Could be in atrial fibrillation if elderly !!
- collapsing “bounding” pulse

**PROXIMAL MYOPATHY**
- test for weakness

**REFLEXES**
- Brisk but not hyper-reflexive

**HEART:**
- Systolic flow murmurs due to massive increase in cardiac output
- Atrial fibrillation in the elderly
- Congestive heart failure in the elderly

**EYES:**
- exophthalmos: !! bilateral = always Graves !!
- look from the side or from above
- complications thereof = scleral injection, oedema of the conjunctiva ("chemosis") + corneal ulceration, inferior rectus muscle weakness
- Lid retraction and lid lag
- ?? IS THERE PTOSIS as well ?? there shouldn't be!

**NECK:**
- Feel the thyroid from behind and from in front; Graves Dz may be enlarged all over and smoothly, while everything else will be nodular or unilateral.
- THYROIDECTOMY SCAR ➔ look for Trousseau’s sign (hypoparathyroid)

**ARMS:**
- Raise arms above head, keep em there: proximal myopathy means patient cant do that

**CHEST:**
- Gynacomastia, occasionally.

**LEGS:**
- Pretibial myxoedema: spongy swelling of anterior tibia, elevated dermal nodules and plaques ➔ ONLY GRAVES!
Thyroid Auto-Antibodies

The Antithyroid Microsomal Antibodies
- are usually elevated in patients with Autoimmune Thyroiditis (Hashimoto’s Thyroiditis)
- Antithyroglobulin antibodies may also be elevated in patients with autoimmune thyroiditis, but this is less frequent and to a lesser degree.
- Thyroid Stimulating Immunoglobulins are associated with Grave’s Disease and are the likely cause of the hyperthyroidism seen in this condition.

**Management**

- **Radioactive Iodine**: an outpatient treatment (6-8wks)
  - May end up destroying whole gland; → Thyroxine supplements ever since
  - NSW government is too poor to let us run all thyroid function tests; only TSH and T4 are allowed
  - Pituitary tumour, hypothalamus tumour...
  - Hashimoto’s atrophic thyroiditis
  - Sub-Acute hyperthyroid
  - Subacute hypothyroid
  - Graves disease
  - Early thyroiditis
  - Abuse of oral thyroxine
  - Ophthalmopathy: major issue: eyes will dry out, get infected and DIE
    - THUS: early Ophthalmopathy = artificial tears ointment, dark sunglasses, eye-patches at night
    - Late (fibrotic) Ophthalmopathy = orbital radiotherapy (~!! CAREFULLY !!-) + steroids
    - If that fails → surgery
  - Thyroid Storm will ensue due to massive sudden release of thyroid hormones.
  - MUST PREPARE FOR THIS POSSIBILITY: “beta-blockade” before getting on the table
  - Overall: surgery nowadays reserved for only the biggest most obstructive goitres

**I**

~A note on thyroid drugs~
- **Propylthiouracil** -- inhibits organification of iodine by thyroid gland. Blocks oxidation of iodine in thyroid gland, thereby inhibiting thyroid hormone synthesis; inhibits T4-to-T3 conversion by blocking type I deiodinase (advantage over other agents).
- **Methimazole (Tapazole)** -- Inhibits thyroid hormone by blocking oxidation of iodine in thyroid gland; however, not known to inhibit peripheral conversion of thyroid hormone.
Epidemiology
- Approx. 30 cases per 100,000 persons per year.
Commonly, patients have a family history involving a wide spectrum of autoimmune thyroid diseases such as Graves disease, Hashimoto thyroiditis, or postpartum thyroiditis, among others.

Thyroid storm (an exaggerated state of manifestation of thyrotoxicosis)
→ with aggressive therapy and early recognition, the mortality rate remains approximately 20%.

GENETICS:
Susceptibility is influenced by genes in the HLA region on chromosome 6 and CTLA-4 on chromosome 2q33. The gene focus CTLA-4 appears to be an important locus because it contains code for a negative regulator of T-cell activation and may play an important role in the pathogenesis of Graves disease.

Sex:
- As with most autoimmune diseases, susceptibility is increased in females. Hyperthyroidism due to Graves disease has a female-to-male ratio of 7-8 : 1
- The female-to-male ratio for pretibial myxedema is 3.5 : 1.

Age:
- Typically, it is a disease of young women, but it may occur at any age.
- The typical age range is 20-40 years.
- Most affected women are aged 30-60 years.

Behavioural science: MANIFESTATIONS OF ANXIETY

SOMATIC SYMPTOMS of anxiety: “fight or flight response”
→ mediated by CNS, ANS and hypothalamus-pituitary-adrenal axis
- shakiness/trembling
- flushes/chills
- sweating
- nausea/"stomach churning"
- palpitations.

The heightened alertness, quick reactions, enhanced muscle function = evolutionary advantage

WHAT INCREASES IN ANXIETY
- heart rate
- respiration rate
- blood glucose
- triglyceride concentrations
- corticotrophin releasing hormone (CRH)
- adrenocorticotropic hormone (ACTH)
- prolactin (from the anterior pituitary)
- vasopressin (from the posterior pituitary)
- cortisol and adrenalin

SEQUENCE OF EVENTS:
1. STRESSOR: charging bull, senior staff specialist, etc:
2. CNS: appreciates the level of danger according to limbic system (amygdala, hippocampus)
3. CNS: sends input to HYPOTHALAMUS
4. HYPOTHALAMUS: secretes CRH, activates sympathetic nervous system
   Prolactin and vasopressin release seems a collateral effect of central hypothalamic stimulation
5. PITUITARY: in response to CRH secretes ACTH
6. ADRENAL GLANDS: in response to ACTH, Secretes CORTISOL

ACTIVATES ADRENAL GLANDS:
ADRENALINE released, thus increases heart rate and blood pressure; vasoconstricts selectively to redistribute blood flow: FAVOURING MUSCLES, LUNGS, HEART and BRAIN

WHAT LOOKS LIKE ANXIETY:
Catecholamine secreting tumour (phaeochromocytoma)
OR
Thyrotoxicosis (catecholamine effects are potentiated but circulating titres are not increased)

BOTH COUNTERACT INSULIN:
- increase glycogenolysis (breakdown of glycogen)
- increase gluconeogenesis (formation of glucose from some amino acids)
- increase hepatic glucose output.
As a result, an increased supply of glucose is available for muscle action.
BMR Management and THERMOGENESIS

**Basal Metabolic Rate**
- **Definition:** The idling of the body engine
- **Description:** The energy expended when completely at rest but not asleep, in the absence of muscle movement and without any sympathetic nervous system arousal.

**Resting Metabolic Rate**
- **Note:** Unlike BMR, this is actually measurable.

**Resting Metabolic Rate**
- **Note:** About 10-15% over the BMR measured in Kilocalories / 24 hrs.

**BMR is primarily dependent on lean body mass (LBM).**
- The greater the LBM, the higher the BMR.

**Shivering thermogenesis**
- Involves muscle contraction and superficial circulatory vasoconstriction to reduce the loss of normally produced heat energy to the atmosphere.

**Non-shivering thermogenesis**
- Is the production of additional heat energy via biochemical reactions. In rodents, heat production occurs in brown adipose tissue whereas in humans, the main site of this energy production is the skeletal muscle.

**THERMOGENESIS**

- **Basic premises:**
  - HEAT is produced as the result of exothermic chemical reactions.
  - It also arises from molecular movement.
- **OBLIGATORY THERMOGENESIS**
  - Is the heat produced at BMR.
- **ADAPTIVE THERMOGENESIS**
  - Triggered by exposure to cold, intake of nutrients etc.
  - Is coordinated by the hypothalamus (increases SNS activity, triggers TSH release).

**Brown Adipose Tissue:**
- @ Neonate or small mammal.
- Brown because of all the mitochondria in it.
- Here, thermogenesis is dependent on "uncoupling" protein upregulation by T3 and T4.

**Skeletal Muscle:**
- Thermogenesis here is either shivering or non-shivering.
  - **Shivering:**
    - Muscle contraction relies on the breakdown of ATP, which is an exothermic reaction.
  - **Non-shivering:**
    - There is no contraction, but metabolic cycles run back and forth.
    - **Futile cycles:** Do nothing except convert a chemical back and forth.

**In the mitochondria:**
- **Varying nutrients**:
  - Acetyl CoA
  - Oxaloacetate
  - Citrate
  - 3 NADH = electron carriers
- **3 NADH = electron carriers**
  - With co-enzyme Q
  - With cytochrome C
  - With reduction of Oxygen to H2O
  - Uncoupling protein
  - ATP
- **Mitochondrial matrix (the inside bit):**
  - H+ cycles back into the matrix via Complex V, this drives the synthesis of ATP from ADP.

**Sites of adaptive thermogenesis:**
- Citrate
- Oxaloacetate
- Acetyl CoA
- GLUCOSE
- PYRUVATE
- 3 NADH
- NAD+ recycled
- ATP
- ADP
- H+
Control of thyroid hormone secretion:
HYPOTHALAMUS: commands the Anterior Pituitary via Thyroxin-Releasing Hormone (TRH); thus stimulated, the anterior pituitary produces Thyroid-Stimulating Hormone (TSH)

PATHOGENESIS OF GRAVE’S DISEASE:
LOSS OF SELF-TOLERANCE:
immature self-reactive T-helper cells somehow escape the thymus without being destroyed !!OK!!
CROSS-REACTIVITY with a microbial antigen that somehow happens to closely resemble the TSH receptor
...either way...
AUTOIMMUNE REACTION TAKES PLACE

The ANTIBODIES cause peripheral effects, specific to Graves disease only:
- Thyroid-stimulating antibody binds to the TSH receptor
- Graves’ ophthalmopathy
- The antibodies react with something in the retro-orbital space; NOBODY knows exactly what

The Antibodies cause peripheral effects, specific to Graves disease only:
- TRAVELLING IN BLOOD:
  - 75% bound to Thyroxine-binding globulin
  - the rest bound to Thyroxine-binding prealbumin
  - And normal simple Albumin

MECHANISM OF GRAVES DISEASE 7.01

Increased thermogenesis
-Due to T3-induced expression of an extra protein into the electron transport chain of the mitochondria: the “UNCOUPLING PROTEIN” which turns the oxidative phosphorylation reaction into a “futile cycle” where ATP is not produced, but rather repetitively turned back and forth into ADP. This generates HEAT.
- ALSO T3 induces a skeletal muscle protein “SERCA” to do something similar by pumping Ca++ ions back and forth out of the sarcoplasmic reticulum.
- Also a net gain of heat and nothing else.

BECAUSE the futile cycles don’t synthesise anything and the beta (3) receptors on adipose tissue are upregulated and potentiated, the poor thyrotoxic patient LOSES WEIGHT
(beta-3 receptors mediate lipolysis and the release of free fatty acids)
The thyroid gland is located in the neck, in close approximation to the first part of the trachea. In humans, the thyroid gland has a "butterfly" shape, with two lateral lobes that are connected by a narrow section called the isthmus. Most animals, however, have two separate glands on either side of the trachea. Thyroid glands are brownish-red in color.

Close examination of a thyroid gland will reveal one or more small, light-colored nodules on or protruding from its surface - these are parathyroid glands (meaning "beside the thyroid"). The image to the right shows a canine thyroid gland and one attached parathyroid gland. The microscopic structure of the thyroid is quite distinctive. Thyroid epithelial cells - the cells responsible for synthesis of thyroid hormones - are arranged in spheres called thyroid follicles. Follicles are filled with colloid, a proteinaceous depot of thyroid hormone precursor (more about that later). In the low (left) and high-magnification (right) images of a cat thyroid below, follicles are cut in cross section at different levels, appearing as roughly circular forms of varying size. In standard histologic preparations such as these, colloid stains pink.

The structure of a parathyroid gland is distinctly different from a thyroid gland. The cells that synthesize and secrete parathyroid hormone are arranged in rather dense cords or nests around abundant capillaries. The image below shows a section of a feline parathyroid gland on the left, associated with thyroid gland (note the follicles) on the right.

**Chemistry of Thyroid Hormones**

Thyroid hormones are derivatives of the the amino acid tyrosine bound covalently to iodine. The two principal thyroid hormones are:

- **thyroxine** (known affectionately as T4 or L-3,5,3',5'-tetraiodothyronine)
- **triiodothyronine** (T3 or L-3,5,3'-triiodothyronine).

As shown in the following diagram, the thyroid hormones are basically two tyrosines linked together with the critical addition of iodine at three or four positions on the aromatic rings. The number and position of the iodines is important. Several other iodinated molecules are generated that have little or no biological activity; so called "reverse T3" (3,3',5'-T3) is such an example.

A large majority of the thyroid hormone secreted from the thyroid gland is T4, but T3 is the considerably more active hormone. Although some T3 is also secreted, the bulk of the T3 is derived by deiodination of T4 in peripheral tissues, especially liver and kidney. Deiodination of T4 also yields reverse T3, a molecule with no known metabolic activity.

Thyroid hormones are poorly soluble in water, and more than 99% of the T3 and T4 circulating in blood is bound to carrier proteins. The principle carrier of thyroid hormones is thyroxine-binding globulin, a glycoprotein synthesized in the liver. Two other carriers of import are transthyrein and albumin. Carrier proteins allow maintenance of a stable pool of thyroid hormones from which the active, free hormones are released for uptake by target cells.
Fabrication of thyroid hormones is conducted by the enzyme **thyroid peroxidase**, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

1. Iodination of tyrosines on thyroglobulin (also known as "organification of iodide").
2. Synthesis of thyroxine (or triiodothyronine) from two iodotyrosines.

Through the action of thyroid peroxidase, thyroid hormones accumulate in colloid, on the surface of thyroid epithelial cells. **Remember that hormone is still tied up in molecules of thyroglobulin - the task remaining is to liberate it from the scaffold and secrete free hormone into blood.**

**Thyroid hormones are excised from their thyroglobulin scaffold by digestion in lysosomes of thyroid epithelial cells.** This final act in thyroid hormone synthesis proceeds in the following steps:

- Thyroid epithelial cells ingest colloid by endocytosis from their apical borders - that colloid contains thyroglobulin decorated with thyroid hormone.
- Colloid-laden endosomes fuse with lysosomes, which contain hydrolytic enzymes that digest thyroglobulin, thereby liberating free thyroid hormones.
- Finally, free thyroid hormones apparently diffuse out of lysosomes, through the basal plasma membrane of the cell, and into blood where they quickly bind to carrier proteins for transport to target cells.

**ANATOMY OF THE NECK and the structures thereof**

**Thyroid Gland**

- Curves across anterior surface of the trachea just inferior to the thyroid cartilage
- 2 Lobes of the thyroid gland are united by slender connection called the isthmus
Selected Arteries and Veins of the Upper Body

Anterior View, Right Arm

Arteries

Anterior View, Left Arm

Veins
CALCIUM HOMEOSTASIS: important but underexplained

The C cells of the Thyroid Gland: Calcitonin

- A 2nd population of endocrine cells lies between the cuboidal follicle cells and their basement membrane. These cells are larger than those of follicular epithelium.
- These C (clear) cells, or parafollicular cells produce the hormone calcitonin (CT). Calcitonin aids in the regulation of Ca\(^{2+}\) concentrations in body fluids. The net effect of calcitonin release is a drop in the Ca\(^{2+}\) concentrations in body fluids. This leads to the inhibition of osteoclasts (slows the rate of Ca\(^{2+}\) release from bones), and the stimulation of Ca\(^{2+}\) excretion at the kidneys.
- Control of calcitonin is an example of direct endocrine regulation, because the C cells respond directly to elevations of Ca\(^{2+}\) concentrations of the blood. ↑ Ca\(^{2+}\) levels → ↑ Calcitonin release.
- Calcitonin is most important during childhood, when it stimulates bone growth and mineral deposition in the skeleton. Also important in reducing the loss of bone mass 1) during prolonged starvation and 2) in the late stages of pregnancy (when maternal skeleton competes with developing foetus for calcium ions).

The Parathyroid Glands

- 2 pairs of parathyroid glands are embedded in the posterior surface of the thyroid gland (separated by the dense capsular fibres of the thyroid).
- At least 2 different cell populations in the parathyroid. The chief cells produce parathyroid hormone (PTH); the functions of the other cells, called oxyphils are unknown.
- The chief cells monitor the circulating concentration of Ca\(^{2+}\) (like the C cells) When the Ca\(^{2+}\) level ↓’s below normal, the chief cells secrete PTH → net result of ↑ Ca\(^{2+}\) concentration in body fluids.
- PTH has 4 major effects:
  - Stimulates osteoclasts → ↑’d mineral turnover and release of Ca\(^{2+}\) from bone
  - Inhibits osteoblasts → ↓’d rate of calcium deposition in the bone
  - ↓’s urinary excretion of Ca\(^{2+}\)
  - Stimulates the formation and secretion of calcitriol at the kidneys (the general effects of calcitriol enhance those of PTH but also enhances Ca\(^{2+}\) and PO\(_4^{3-}\) absorption by the digestive tract.
- PTH (aided by calcitriol) is likely the 1º regulator of circulating calcium ion concentrations in healthy adults.