Unit 4

ENDOCRINOLOGY

Problem One: *Diabetes Mellitus A (type 1…)*

Summary of triggers:

A **12-year-old** boy named Ali was brought to the A&E with a chief complaint of **abdominal pain** and repeated **vomiting** for the past 2 days. He has also been drinking a lot of water (**polydipsia)** and would frequently urinate (**polyuria**); he **lost 4 kg** in the past two weeks. He looked **dehydrated**, and his heart rate was 140 bpm (high – **tachycardia**). His respiratory rate was high – **tachypnea**; 40/min (normal is 16 – 20/min). He had deep and rapid breathing patterns (***kussmaul breathing***), was **lethargic** and **confused**. Two of his brothers have diabetes mellitus type 1 – one of them developed kidney failure. Doctor now **suspected diabetes type 1**. Lab investigations on his blood revealed **high random blood glucose**, **high HbA1c**, **low bicarbonate (HCO^-_3)**, low sodium, **high urea** and **ketone bodies**. ABG revealed **low pH, low $PaCO_2$**. Urinalysis revealed **highly positive urinary ketones and glucose**. Diagnosis = **Diabetic Ketoacidosis** (DKA). He was **admitted** and started on **IV rehydration therapy** and **IV insulin**. He didn't really respond to therapy (blood glucose dropped, but not enough) + he still had polyuria and polydipsia. Insulin dose was changed and the doctor requested analysis of **HLA class II genotypes** and **diabetes-associated antibodies** (Ab). Three days later, his blood glucose stabilized and his acidosis resolved + urine output now normal. He was discharged with **subcutaneous insulin injections** (Glargine - daily and aspart – before meals) + asked to monitor his glucose levels (glucometer). 3 weeks later he came back for a checkup and he was fucking great! Doctor reminded him to take it FOREVER and stressed the importance of timing, amount and which type of insulin to use and also manage his diet.

EXPLANATION:

Based on the triggers, you know that:

- The boy had type 1 diabetes mellitus
- It is typically triggered or first diagnosed in childhood
- Differentiating between the signs and symptoms related to diabetes-induced ketoacidosis and that related to diabetes alone…
    - But since ketoacidosis is a symptom/consequence of diabetes type 1, we can say diabetes type 1 involves: abdominal pain, vomiting, polydipsia, polyuria, tachypnea (kussmaul breathing), tachycardia, weight loss, lethargy, confusion, hyperglycemia, etc.
- Kussmaul breathing is a deep and rapid breathing pattern that is commonly described in metabolic acidosis

- I didn't mention any specific values, but it's worthy to recall the normal range or values of the variables mentioned above and more:
    - Random blood glucose (we'll keep this for later)
    - Fasting blood glucose (also, later)
    - HbA1c (also later)
    - Bicarbonate (**22 – 28 mmol/L**… some books go up to 30 mmol/L)
    - Sodium (**135 – 147 mmol/L** or just 145 mmol/L)
    - Potassium (3.5 – 5 mmol/L or just 4 mmol/L)
    - Chloride (95 – 105 mmol/L or just 100 mmol/L)
    - pH (7.35 – 7.45 or just 7.4)
    - $PaCO_2$ (33 – 44 mm Hg or just 40 mm Hg)
    - We'll most probably get reference values in exams, but not for glucose or pH; they expect you to know those I think.
- He had low pH, low bicarbonate and low $PaCO_2$, which means he had metabolic acidosis with hyperventilation (Kussmaul breathing) as a compensation (lowering $PaCO_2$). He has positive ketone in blood and urine, so it is most likely "Diabetic Ketoacidosis" And btw, the vomiting is most probably also a compensatory mechanism to get rid of acid from the body (I'm not sure).
- You treat this condition (DKA) by IV rehydration therapy to compensate for the dehydration, and with IV insulin, because the lack of insulin led to hyperglycemia and increased ketone production by the liver. Insulin can reverse the effects.
- Now you can see that we need to know more about Diabetes, its inheritance (why do you think the doctor asked about HLA class II genotypes), its relation to autoimmunity ("antibodies"), and its management – especially with regards to insulin…

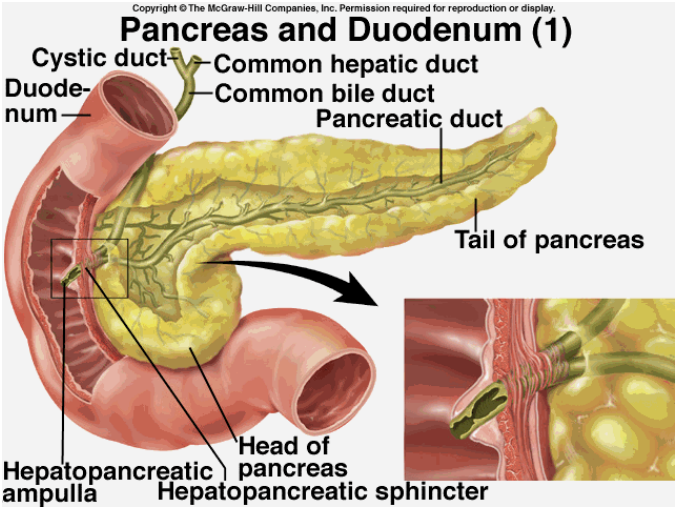
So let's start…

Anatomy: Don't focus on the unnecessary details ok?

<u>The Pancreas</u>

- It is an accessory digestive organ/gland
- Lies **posterior to the stomach** + duodenum on the right and spleen on the left
- It lies **anterior to the superior mesenteric vessels** (artery and vein)
- Conveniently divided into parts:
    - **Head** (near duodenum)
    - **Neck** (above superior mesenteric vessels)
    - **Body**
    - **Tail**
    - **Uncinate process** (part of head *behind* the superior mesenteric artery)
- Is **mostly** composed of exocrine "acinar" cells
- Its endocrine portion lies within small islands of cells scattered around in a sea of exocrine cells
    - This is called the ***<u>Islets of Langerhans</u>*** (***<u>not</u>*** Langhan's giant cells)
    - It's endocrine, so blood must pass through EACH islet
    - **Most abundant** portion with islets is the **TAIL**

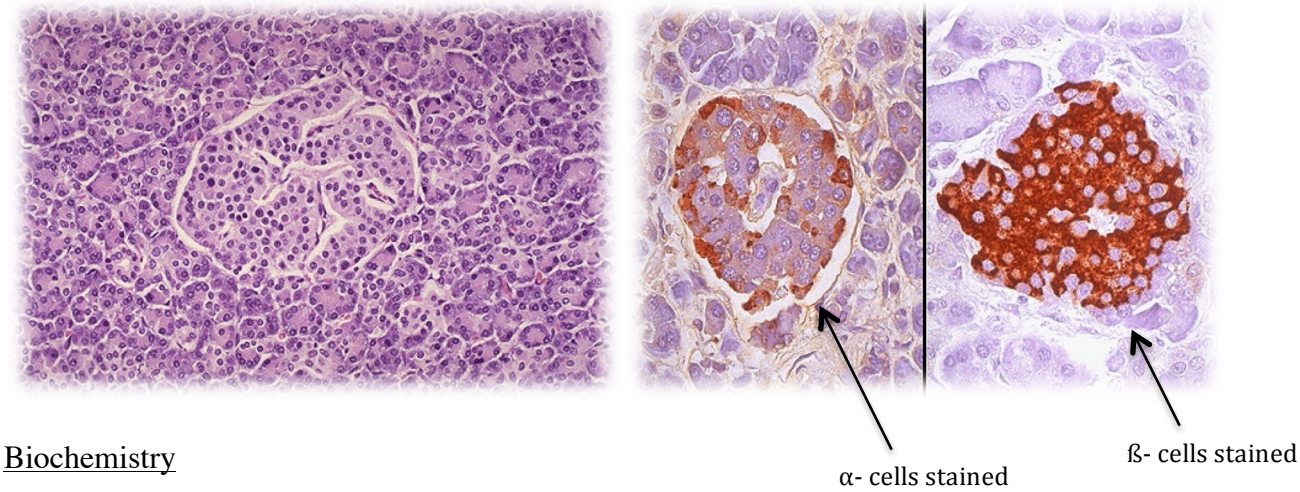
- For the exocrine portion, their secretions pass into the **main pancreatic duct**.
    - Pancreatic duct begins in the tail and runs to the head
    - The **bile duct** joins the **pancreatic duct** at the head to form the **Hepatopancreatic ampulla**
    - The ampulla opens into the **second part** of the **duodenum** as the **Major duodenal papilla**
    - The papilla is controlled by a sphincter known as the hepatopancreatic sphincter or **Sphincter of Oddi**
- **Accessory pancreatic duct**
    - Drains **uncinate process** and inferior head
    - The duct terminates at the **minor duodenal papilla**
    - Usually communicates with main pancreatic duct (not always)
- Arterial supply:
    - Pancreatic arteries (derived from branches of splenic artery)
    - Anterior and posterior **SUPERIOR pancreaticoduodenal arteries**
        - From gastroduodenal artery
    - Anterior and posteror **INFERIOR pancreaticoduodenal arteries**
        - From superior mesenteric artery
- Venous drainage:
    - Most drain into the **splenic vein**
    - Pancreatic veins (drains into hepatic portal vein)
- Lymph drainage (Don't even bother reading this):
    - They follow blood vessels
    - Most end in pancreaticosplenic nodes
- Innervation:
    - Vagus (X) and abdominopelvic splanchnic nerves
    - Parasympathetic NS = secremotor, but secretion is hormone-dependent



Look for more pictures from your books or whatever…

Histology

- Endocrine pancreas
    - Scattered among the exocrine acini
    - **Islets of Langerhans**
        - ISOLATED
        - PALE-STAINING
        - HIGHLY VASCULARIZED
        - Surrounded by reticular connective tissue
    - Islets consists of 4 cell types:
        - **α (alpha) cells** – **20%**, located **peripherally**, secretes **GLUCAGON**
        - **β (beta) cells** – **70%**, located **centrally**, secretes **INSULIN**
        - **δ (delta "D") cells** – scattered in between, secretes **somatostatin**
        - **PP cells** – secretes pancreatic polypeptide. Also called F cells.



Biochemistry

- Always remember: we describe effects of metabolism mainly on:
    - **Adipose tissue**
    - **Skeletal muscle**
- Other tissues involved include: liver, brain, kidneys
- **Insulin**
    - **Polypeptide** hormone
    - Produced by **ß cells** of **islets of Langerhans**
    - **ANABOLIC** effect (favors synthesis of glycogen, TAG, proteins)
    - Structure:
        - **51 amino acids**
        - Arranged in two polypeptide chains (α/A and β/b)
        - **A and B chains** are connected by **2 disulfide bridges**
        - **Chain A** has an **intra**molecular disulfide bridge

- Stored in vesicles as insulin after posttranslational modification, with zinc
- C-peptide = "central" peptide connecting A and B before complete posttranslational modification

- **Post-translational modification of insulin:**

In rER

Preproinsulin
(insulin + signal sequence + C-peptide)

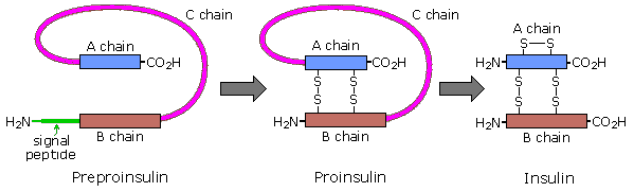
Signal sequence

In Golgi apparatus

Proinsulin
(insulin + C-peptide)

C-peptide

Insulin



- Insulin secretion is **stimulated** by:
  - **Hyperglycemia or raised blood glucose**
  - Amino acids
  - GI hormones like cholecystokinin (CCK) and incretins

- Insulin secretion is **inhibited** by:
  - **Low body fuels** (for example, **hypoglycemia**)
  - Body stresses (infection, fever, starvation)
  - **Epinephrine** (during fight or flight, you need to glucose in your blood)

- Effects on metabolism of:
  - Carbohydrates (you want to store glucose – get rid of it from blood)
    - Liver → **promotes glycogen synthesis**
    - Liver → **lower gluconeogenesis** and **glycogenolysis**
    - **Muscle and adipose tissue → increase glucose uptake… how?**

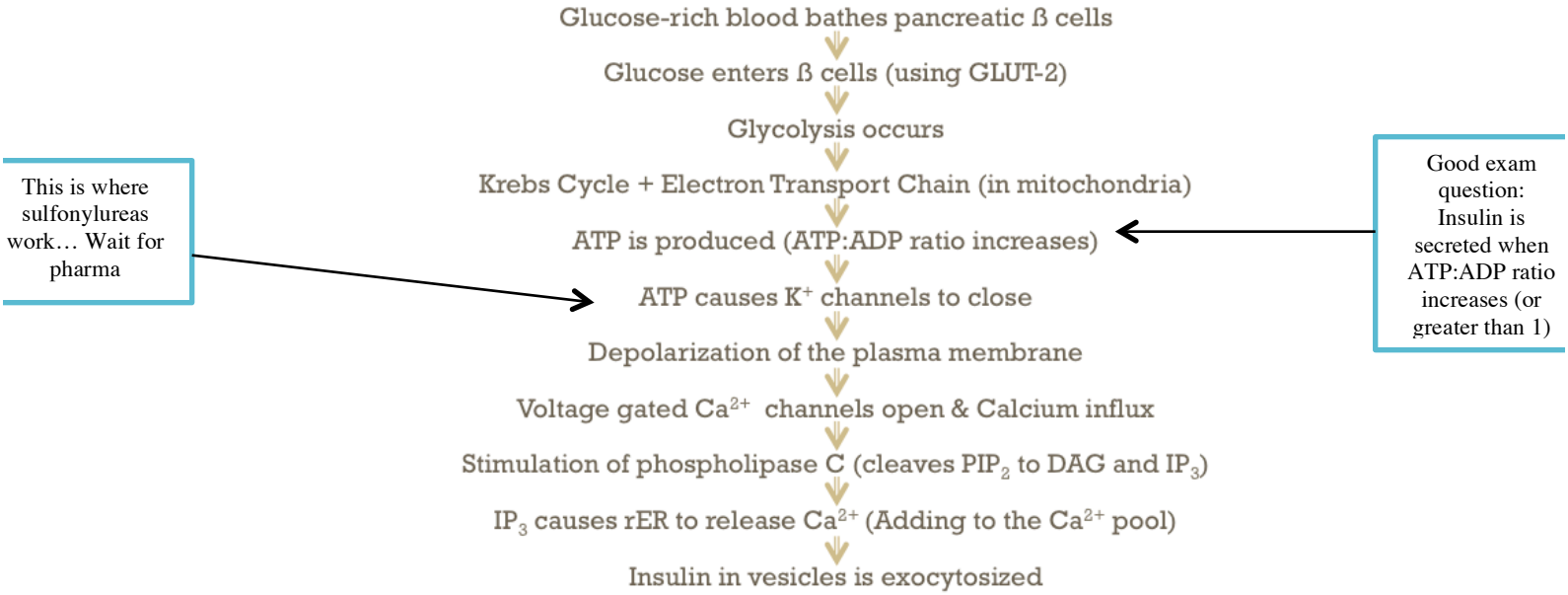
GLUT = Glucose transporter; MANY types. Insulin promotes GLUT-4. Remember, that a pool of GLUT-4 is stored in vesicles and only brought to the membrane after insulin stimulation…

Transporter	***Tissue***	***Function***
GLUT-1	RBCs, brain, kidney	Glucose uptake
GLUT-2	**Liver, pancreatic ß cells**, intestinal cells	Rapid uptake/release of glucose (high capacity)
GLUT-3	Brain, kidney	Glucose uptake
GLUT-4	**Skeletal muscle, adipose tissue** + heart	**INSULIN-STIMULATED Glucose uptake**
GLUT-5	Small intestines	Fructose and glucose absorption

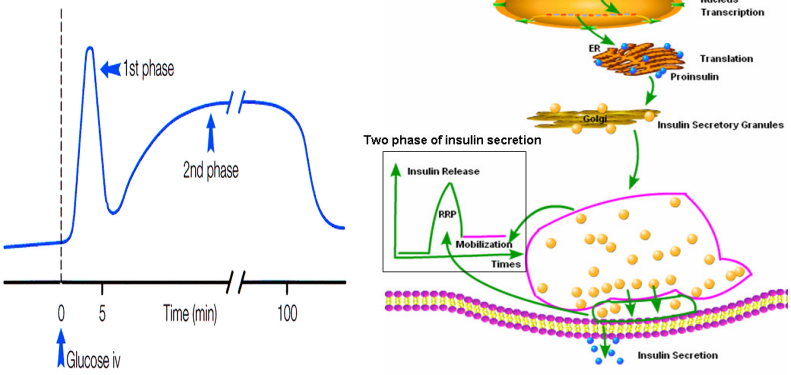
GLUT-2 is found in the pancreatic ß cells? Why? *Because insulin is stimulated by glucose*!

- Lipids
  - **Increased fatty acid (FA) production** (but decreased FA release)
  - Reduced TAG degradation
    - **Insulin inhibits hormone-sensitive lipase**
  - Promote TAG synthesis
    - **Insulin stimulates lipoprotein lipase (LPL) activity**
    - So, technically, it helps get rid of TAG from circulation
- Proteins
  - Increased amino acid (a.a.) uptake into cells
  - Promotes protein synthesis

Important: how does glucose stimulate insulin release? Big topic.



- **Amplification Pathway**
  - According to Dr. Deeba's lecture…
  - The vesicles containing insulin stores **take up Cl^-**
    - Subsequently, **H^+ is taken up** as compensation
    - This results in what is known as "**secretion competence**"
- **Insulin Pools**
  - In the beta cells, there are two pools of insulin:
    - **Rapid Release Pools (RRP):** less amount, quick secretion
    - **Reserve Pool (RP):** large amount, sustained release (second phase)
    - Leads to **oscillations** in insulin secretion; prevents **down regulation**

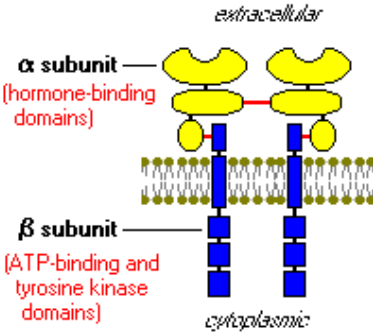


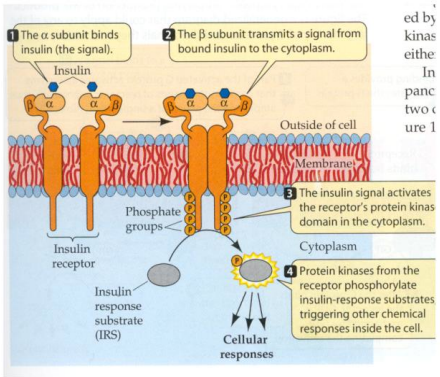
- **Insulin receptor and receptor action:**
  - **Pair of α and ß subunits**
  - **Tyrosine kinase** activity (the ß subunit)
  - Signal transduction pathway using **Insulin Receptor Substrate-1 (IRS-1)**

Insulin binds to insulin receptors on target tissues
↓
ß subunits undergo conformation change & autophosphorylates (specific tyrosine residues)
↓
Insulin Receptor Substrates phosphorylated (IRS-1, specifically)
↓
IRS interact with other signaling molecules (phosphorylation)
↓
Leads to gene expression, cell metabolism and growth (as we discussed)
↓
Vesicles with stored GLUT-4 join the cell membrane
↓
Increased glucose uptake
↓
METABOLISM and ANABOLISM!

Note: action of insulin terminated by dephosphorylation of receptor + serine phosphorylation "off-switch"

Note:
Insulin also has mitogenic effect! And can affect gene expression of enzymes like HMG-CoA Reductase (cholesterol synthesis) and ACC (FA synthesis)





GLUCAGON

- **Polypeptide hormone**
- Secreted by **α cells**
- **Epinephrine, glucagon, cortisol, GH**... All **oppose** the effects of insulin...
  - Counter-regulatory hormones

- Activates **hepatic glycogenolysis** and **gluconeogenesis**
- Synthesized as **preproglucagon** → posttranslational modification → glucagon
- Secretion **is stimulated** by:
  - **Hypoglycemia**
  - Low amino acids
  - **Epinephrine** (adrenal medulla, NE by sympathetic NS)
- **Inhibited** secretion by **hyperglycemia and insulin** (as what occurs after eating lunch)
- **Metabolic Effects of glucagon on:**
  - Carbohydrates
    - **Increased LIVER glycogenolysis** (*not muscle – no* glucose 6 phosphatase – muscle needs its own suga buddy!)
    - Increased liver gluconeogenesis
  - Lipids
    - **Increased lipolysis** (**activated hormone sensitive lipase** and lipoprotein lipase is less active)
    - **Increased lipolysis → FFA → if ß-oxidized → acetyl CoA → ketone bodies**
  - Proteins
    - Increased amino acid uptake by liver (used for gluconeogenesis)
- Glucagon uses **GPCRs (G_s)** → increased **cAMP** → PKA → phosphorylation of certain enzymes/water (LOOK AHEAD TO UNDERSTAND THIS)

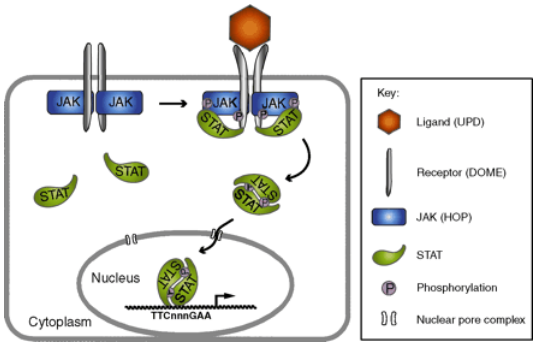
<u>HORMONE RECEPTOR ACTIONS (GENERAL TOPIC)</u>

- Before we move on, we need to talk about receptor actions.
  - Some hormones are **peptide hormones** and others are **steroid hormones**
  - **Steroid hormones** are **lipophilic** and can pass through the membrane and bind **cytosolic receptors** (form a **hormone-receptor complex**) with the help of heat-shock proteins. It can also form a heterodimer. The complex enters the nucleus and binds to **HRE (hormone-response elements) → genomic effect** leads to suppression and expression of certain genes and thus proteins
  - **Peptide hormone** binds to **membrane receptors** that usually lead to some sort of signal transduction
  - An example is **G-protein coupled receptors (GPCRs)**
    - **G_q** (Stimulates **phospholipase C**)
      - Phosphatidyl Inositol bisphophate (**PIP_2**) is cleaved by phospholipase C to Diacylglycerol (**DAG**) and inositol-triphosphate (**IP_3**)
      - **IP_3** stimulates the **endoplasmic reticulum** to release Ca^{2+} thus **increasing intracellular calcium** (can lead to secretion of certain substances out of the cell)
      - This is seen in pancreatic ß cell (to cause insulin release)
      - **DAG** activates **protein kinase C (PKC)** and so some enzymes are phosphorylated

- **G_s** (Stimulates **adenylyl cyclase**)
  - Upon stimulation, the receptor activates **adenylyl cyclase** and converts **ATP to cAMP**
  - cAMP acts as a **secondary messenger** that activates cAMP –dependent **protein kinase A (PKA)**
  - PKA then phosphorylates certain enzymes
  - This is seen with glucagon
- **G_i** (**<u>Inhibits</u> adenylyl cyclase**)

○ **"Intrinsic" Tyrosine kinase**
- Seen with **insulin** and we explained this
- In a later problem, you'll know IGF-1 also uses this

○ **"Receptor-associated" tyrosine kinase**
- I like to call it "fake" tyrosine kinase
- Using **JAK/STAT pathway** (**Janus Kinase**)
- A good picture will explain it to you… Basically it can have both genomic and non-genomic effects.



- Seen with **Growth Hormone** and **Prolactin** and cytokines (later problem)

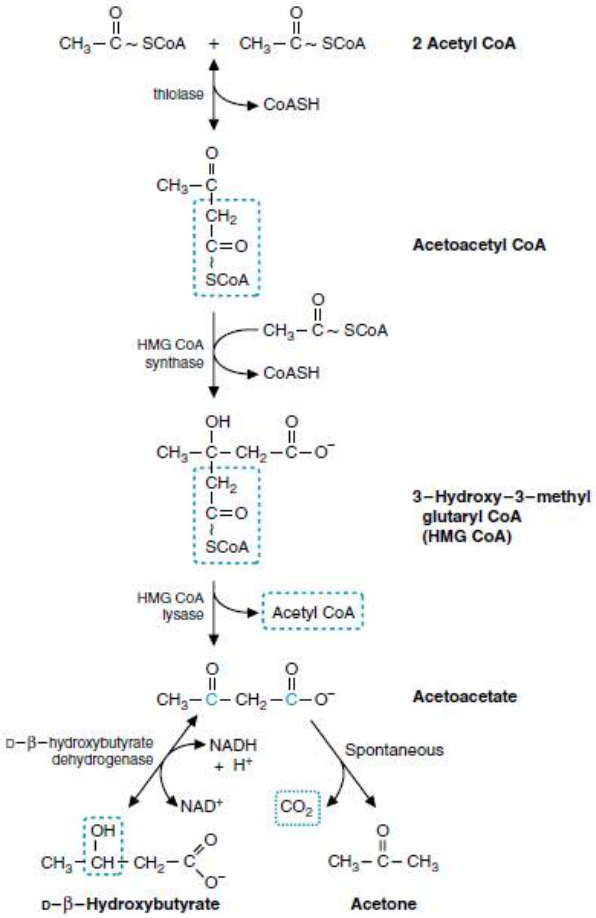
We always say, "Phosphorylates certain enzymes." But which ones? **<u>Why?</u>**

It's better you understand this now… Some enzymes are turned on when they are dephosphorylated. Others are turned on when they are phosphorylated. These enzymes affect metabolism. This is called "**covalent modification**."

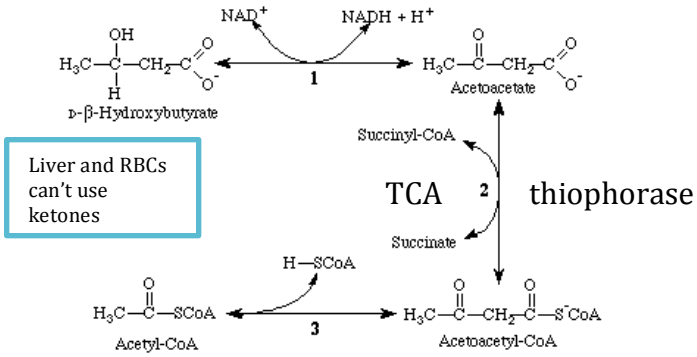
When you're in the fed state, most of the enzymes are dephosphorylated and active. Of course, there are some that are dephosphorylated and inactive – the exceptions (there are only 3).
Use your brain. When you're fed, you are raising insulin. Insulin promotes glycogenesis and glycolysis and stops gluconeogenesis and glycogenolysis. And as we said, insulin stimulates lipoprotein lipase and inhibits hormone-sensitive lipase (you don't want to break down fat for energy! You have energy!)….
So all enzymes are activated by dephosphorylation during fed state, **EXCEPT**:
Glycogen phosphorylase kinase, glycogen phosphorylase + hormone sensitive lipase

In the fasting state, most enzymes are phosphorylated and inactive, but these 3 enzymes are active when phosphorylated and *so… viola!*

- **Ketone bodies**
  - **Made in liver mitochondria *only*** (when acetyl CoA is very high)
  - They are:
    - **Acetoacetate**
    - **ß- hydroxybutyrate** or 3-hydroxybutyrate
    - **Acetone** (non-metabolized byproduct)
  - Soluble, transported in blood
  - Cannot be used by RBCs (RBCs lack mitochondria and rely only on glycolysis)
  - Used by brain, heart and skeletal muscle if no glucose is available
  - Acetone is highly volatile and is excreted in vapor thru exhaling (fruity smell)



  - Depends on NADH (so watch NADH/NAD+ ratio… if high = ketones can be made)
  - Liver can make ketones, but it is the only organ that CANNOT use ketones
    - Lacks thiophorase (enzyme that uses succinyl coA to convert acetoacetate to acetoacetyl CoA)



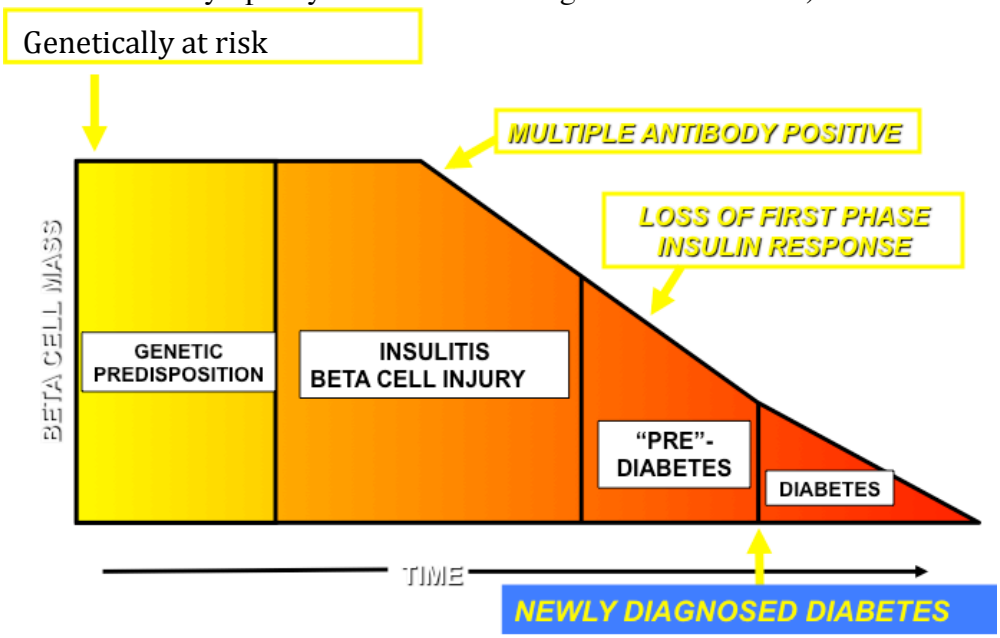
- Ketoacidosis → metabolic acidosis (**HIGH ANION GAP!**) → kaussmaul breathing (lower $PaCO_2$), vomiting (let go of HCl), excrete H^+ (leads to dehydration)… Treat with IV rehydration and IV insulin.
  - Hyperkalemia occurs (insulin promotes K^+ to enter cells) and acidosis moves K^+ out of cell to take in more H^+…
  - So signs of hyperkalemia are seen, but when ketoacidosis is corrected, patient gets HYPOKALEMIA (intracellular stores depleted)… So replace K^+ after ketoacidosis corrected…

- Hypoglycemia
  - Combat: high glucagon and epinephrine (acute), cortisol and GH (chronic)
  - **Medical emergency**
  - Characterized by:
    - **Adrenergic (Sympathetic) symptoms** (due to epinephrine release)
      - Anxiety, palpitations, tremors, sweating
      - Occurs when glucose falls abruptly
    - **Neuroglycopenic symptoms** (due to low glucose to brain)
      - Headache, confusion, slurred speech, seizures, coma, death
      - Occurs if glucose falls gradually
  - 3 main types:
    - **Insulin-induced** (most commonly in diabetics)
    - **Postprandial** (too much insulin secreted after meal!)
    - **Fasting** (adrenal insufficiency or hepatocellular damage – no gluconeogenesis when fasting!)
      Also: alcohol intoxication and fasting → gluconeogenesis not working (ethanol causes shunting of gluconeogenic intermediates to other pathways)
  - Management:
    - IV fluid replacement therapy + dextrose

Diabetes Mellitus

- Group of multifactorial, polygenic diseases/syndromes due to defects in insulin secretion, action or a combination of both
- Type 1 = "insulin-dependent diabetes" and type 2 = "insulin-independent"

- LADA (latent autoimmune diabetes of adults, "type 1.5"
- MODY (Maturity onset Diabetes of the Young) – single gene defect (glucokinase is an example)
- Actually it is divided into
    - Type 1A (immune mediated… there are auto-antibodies)
    - Type 1B (insulin deficient but no auto-antibodies)
    - Type 2 (no auto-Ab, low insulin – ß cell dysfunction and insulin resistance)
    - MODY
    - LADA
    - Gestational
- Type 1A
    - Autoimmune disorder
    - Occurs at an early age
    - ß cell destruction by activated leukocytes and their mediators
    - Initiated by activated cytotoxic T cells
    - Increased T cell activity leads to damage by macrophage recruitment and complements and auto-antibody production
    - Commenced by an environmental trigger and genetic predisposition
        - Environmental triggers: viral infection (coxsackie B virus, CMV) or pancreatic damage
        - Genetic predisposition: HLA-linked (HLA-2 DR)
    - Characterized by insulitis (infiltration and inflammation of islets with lymphocytes which leads to gradual destruction)



    - Even though genetic predisposition in HLA-DR3 is involved, type 2 diabetes has STRONGER inheritance and genetic background (family history)
    - Auto-antigens related to type 1 diabetes:
        - Insulin (IAA)
        - Glutamate decarboxylase (GAD)

        - Zinc transporter 8 (ZnT8)
        - IA-2 (Islet cell antigen)
    - Anti-Gad (autoantibodies)
        - Used especially for LADA diagnosis
        - Often seen in type 1 diabetics
    - Abrupt appearance of **polyuria, polydipsia** and sometimes polyphagia
        - Simple explanation = too much glucose (no insulin, more glucagon)
        - Surpasses renal threshold and begins to spill in urine (glycosuria)
        - Water will follow (osmotic diuresis)
        - Leads to hypovolemia and low ions in blood…
        - Along with the symptoms of ketoacidosis, it should make sense…
    - For diagnostic purposes:
        - **mmol/L = mg/dL ÷ 18**
        - **Fasting blood glucose (+8h) > 126 mg/dL or 7 mmol/L** (normal 3 – 6 mmol/L)
        - **Random blood glucose > 200 mg/dL or 11.1 mmol/L** (normal less than 6.6 mmol/L)
        - Check for auto-antibodies
        - HbA1C (Normal 6% or below)
    - Metabolic changes include **ketoacidosis** and **hyperglycemia** + **hypertriglyceridemia** (lipoprotein lipase inhibited → increasing VLDL and chylomicrons in blood!)
    - Clinical consequences and pathological findings in all body organs are the same for type 1 and type 2 diabetes EXCEPT in the pancreas;
        - **Type 1 → insulitis** (lymphocytic infiltration)
        - **Type 2 → amyloid deposits** in long standing type 2 diabetes
    - Can only be treated with lifestyle modification and insulin therapy

So… What I'm going to do is go straight to the pharmacology. The pathology of diabetes in most organs is the same, so I'll explain that in problem 2.

<u>Pharmacology</u>

- Insulin therapy is **necessary** for type 1 diabetics and late stage type 2 diabetics
- **Types of insulin**
    - **Rapid-acting** (**Very** rapid, **very** short duration)
    - **Short-acting** (rapid, short duration)
    - **Intermediate-acting** (slow onset + intermediate duration? Lol?)
    - **Long-acting** (very slow onset + very long duration… 24 hours)
- **Rapid-Acting:**
    - **First choice**
    - Taken **immediately before a meal**
    - 4 – 5 hours of action + approved for **insulin pumps**
    - **Aspart and Lispro**

- **Short-Acting:**
  - Taken 30 minutes before a meal
  - Unpredictable pharmacokinetics ("**glucose insulin mismatch**")
  - Only insulin **used for IV** in management of DKA
  - Example = **REGULAR INSULIN**
  - Technically obsolete (but used in poorer countries)
- **Intermediate-Acting:**
  - **Cloudy/turbid**
  - Unpredictable pharmacokinetics (mismatch)
  - Really obsolete
  - Works up to 16 hours
  - **NPH (Lispro protamine)**
- **Long-Acting:**
  - **Peakless (flat)**
  - **24 hours action** or longer
  - Given **once daily** at **BED TIME**
  - Long acting insulin of choice (**DOC for long acting**)
  - **Insulin Glargine and Detemir**
- Dispense methods: pens, standard injections, pumps
- Each ml = 100 units (insulin comes as 10 ml… or 1000 units)
- **Insulin of choice (Rapid and long acting)**
- Insulin regimens:
  - **Intensive Regimen**
    - **Check the food** and **blood glucose** + use ratio + bedtime long acting
    - Count carbs + glucometer
    - More effective!
  - **Conventional (less effective)**
    - **Only check blood glucose**
    - Take a fixed amount (before meal and at bedtime)
    - **"Rigid lifestyle"** because you don't get to modify how much insulin you want ☹
- Insulin injection sites (**SUBCUTANEOUS**): outer arm, **abdomen (Best place)**, thigh
- **Most common adverse effect = HYPOGLYCEMIA**
  - Lightheadedness, tremors, confusion, sweating, seizures, you KNOW!!!
  - **Treatment:**
    1. Give **sugar** in **liquid form** (easily absorbed by gut) – juice not chocolate (because it's FASTER!)
    2. If 1 doesn't work, give **IV dextrose**
    3. If 2 doesn't work, give **IM glucagon**
- Insulin toxicity → tissue hypertrophy at injection site or allergy (rare nowadays).

Note: type 1 diabetics present with weight loss because the loss of the anabolic effects of insulin and so on.

Problem 2: Diabetes Mellitus B (Gestational & Type 2 Diabetes)

Summary of triggers:

It's about a **42-year-old woman** who came in with a **chief complaint** of **increasing fatigability, polydipsia and polyuria** for 1 week. She went on a Hajj trip recently and blames that for her exhaustion, but she did have some polyuria and polydipsia before the trip. **Random blood glucose was high**. **Urine dip for ketones was negative**. 75 g **oral glucose tolerance test (OGTT)** was done the next day. OGTT showed high fasting blood glucose and still high 2 hours later. She was given **oral anti-diabetic medications**: **Sulfonyurea** (gliclazide) and **biguanide** (metformin). She was told to have **proper diet control**. She said her **mom has diabetes** and A LOT of other **maternal family members have diabetes** too! She was diagnosed many years ago with **gestational diabetes** on her first and second pregnancy. Blood test done 3 months later revealed high **FBG, HbA1c, LDL, cholesterol, TAG**. Renal function test and Liver function tests are alright. Doctor increased dose of gliclazide. She was told to recognize signs of hypoglycemia and keep candy/juice in her bag for use. She was given **rosuvastatin** (to treat her dyslipidemia). 3 years later, she came back with even higher blood glucose levels. She was given insulin glargine to take at bedtime (she was **reluctant to take the insulin** med + asked for alternatives!). She had right **foot problems** (cold, shiny, **diminished pulse**), **absent ankle jerk + diminished light touch sensation** in both feet. Eyes showed **microaneurysms** and **dot hemorrhages**. She didn't take the insulin and was given **sitagliptin** instead along with her old medication + diet. 3 months later, everything lowering (but still high), but **vitamin B12** and calcium **low**. She was given vitamin B and D supplements. Btw, she's obese.

The idea:

- She has type 2 diabetes, but had gestational diabetes
- One of the complications of gestational diabetes is type 2 diabetes
- Type 2 diabetes occurs in adults and frequently in obese people
- Negative ketones tell you that there's no ketoacidosis and it is not likely type 1 diabetes
    - In type 2 diabetes, enough insulin is secreted to prevent ketogenesis, but not enough to prevent hyperglycemia
- OGTT → what is this? We'll see
- Oral anti-diabetic medications → sitagliptin, biguandies, sulfonylureas
- Genetic background or family history is more prominent in type 2 diabetes than type 1
- Raised LDL, cholesterol and TAG… Why? Reduced LPL activity! A statin was given to combat this dyslipidemia.
- Pathological features of diabetes (microvascular and macrovascular manifestations of foot and eyes)
- She didn't want to take insulin… why? She'd gain weight! She doesn't want to gain weight!
- Vitamin B12 low… Why? One of the drugs lower B12 levels… METFORMIN!

Type 2 diabetes

- Occurs at an **older age** compared to type 1 diabetes
- Has a **strong genetic background** compared to type 1 diabetes
- Occurs in **obese** individuals
    - Obesity leads to lowering numbers of insulin receptors
- **Amyloid deposits** in islet cells seen in **long term** type 2 diabetes
- Usually discovered incidentally during routine checkup
- Symptoms of polyuria and polydipsia are not as prominent
- Enough insulin to prevent ketosis and ketoacidosis
- It involves **ß cell dysfunction** and **insulin resistance**
- Insulin resistance is the phenomena in which tissue responsiveness to insulin in the body is reduced
- Common feature: **Hyperosmolar hyperglycemic non-ketotic state/coma**
    - High glucose leads to glucosuria (passing renal threshold) → osmotic diuresis → hypotension and coma (but NO ketones)

- Comparing Type 1 and Type 2 diabetes:

Variable	Type 1	Type 2
Primary defect	Autoimmune destruction of ß cells (insulitis)	Insulin resistance Progressive ß cell failure
Insulin necessary in treatment	Always	sometimes
Age (exceptions occur)	< 30 years	> 40 years
Association with obesity	No	Yes (increases insulin resistance)
Genetic predisposition	Weak, polygenic	Strong, polygenic
Associated with HLA system	Yes (HLA-DR3 & 4)	No
Glucose intolerance	Severe	Mild to moderate
Insulin sensitivity	High	Low
Ketoacidosis	Common	Rare (hyperosmolar state)
ß – cell numbers in islets	Low (then almost gone)	Variable (amyloid deposits)
Serum insulin level	Low	Variable
Classic symptoms: polyuria, polydipsia, polyphagia, weight loss	Common	Sometimes
Histology	Islet lymphocytic infiltrate (insulitis)	Islet amyloid polypeptide (IAPP) deposits

Other types: **LADA, MODY**, **Gestational (most often 3rd trimester)**

Laboratory Investigations:

- Tests:
    - Random plasma (blood) glucose: ≥ 11.1 mmol/L or 200 mg/dL
    - Fasting plasma (blood) glucose: ≥ 7.0 mmol/L or 126 mg/dL
    - Oral Glucose Tolerance Test (OGTT) – look down
    - Glucose Tolerance Test Plasma (GTTP) – look down
- Blood for fasting blood glucose:
    - Overnight fasting (at least 8 hours)
    - Tube containing sodium fluoride
    - Measured using hexokinase/Glucose oxidase method
- Oral glucose tolerance test (OGTT)
    - Used only for gestation diabetes (GDM) diagnosis
    - OGTT also used if FPG is Impaired Fasting Glucose (IFG)
    - 3 days unrestricted diet before OGTT + overnight fasting (8 – 14 h)
    - Glucose load of 75g for adults is given
    - Normally, just check at 0 hours and after 2 hours
    - Other conditions, check at intervals (0, 1, 2, 3 etc)
    - Use a cannula to check blood (so you don't change site)

	Fasting	2 hours
IFG	≥ 5.8 to < 7.0 mmol/L	<7.8 mmol/L
IGT*	<7.0 mmol/L	≥ 7.8 to < 11 mmol/L
DM	≥ 7.0 mmol/L (126 mg/dL)	≥ 11.1 mmol/L (200 mg/dL)

*IGT = impaired glucose tolerance

- Gestational Diabetes
    - Average risk = if in the 3rd trimester
    - High risk = family history of diabetes, marked obesity, personal history of GDM, glycosuria
    - Use GTTP (glucose tolerance test – plasma)
        - Use 50 g glucose load and collect blood 1 h later
        - If more than 7.8 mmol/L, do OGTT
- Renal and alimentary glycosuria can be identified by OGTT alone with urine and glucose analysis (you can use the lag curve to identify!)
    - Renal glycosuria (urine positive + due to low renal threshold)
    - Alimentary glycosuria (1 h sample is greater than 11 mmol/L)
        - Due to delayed insulin release in response to glucose
- HOMA-IR
    - Homeostasis model assessment of insulin resistance
    - HOMA-IR = (Glucose mmol/L x insulin units)/22.5
    - HOMA-IR = (Glucose mg/dL x insulin units)/405
    - Remember mmol/L = mg/dL ÷ 18
    - Normal value is <2.4
    - High insulin resistance is >3.5

Biochemistry

- **Fed state**
  - **Fed state = absorptive state** (2 – 4 after eating a meal)
  - **Fed state → high insulin release; anabolic period**
  - Pathways controlled by 4 mechanisms:
    - Availability of substrates
    - Allosteric regulation of enzymes
    - Covalent modification of enzymes
    - Induction-repression of enzyme synthesis (transcription)
  - Increased glycolysis and inhibited gluconeogenesis
    - Increased fructose-2,6-bisphosphate
      - Allosteric activator of phosphofructokinase-1 (PFK-1)
      - Inhibits gluconeogenesis (inhibits fructose-1,6-bisphosphatase)
  - Covalent modification → example = dephosphorylation (explained!)
    - Dephosphorylation activates enzymes of anabolism
    - Exceptions: glycogen phosphorylase kinase, glycogen phosphorylase and hormone sensitive lipase
  - Induction-repression → insulin promotes gene expression of HMG-CoA reductase [cholesterol synthesis] and Acetyl CoA carboxylase (ACC) [fatty acid synthesis]
  - **In the liver:**
    - Has GLUT-2 (insulin independent)
    - **Increased glucose uptake** by increased **glucokinase** activity
      - Remember, glucokinase has low affinity, high K_m
      - Glucokinase is the first essential step in glycolysis
      - **Converts glucose to G6P** (negatively charged)
    - **Increased glycolysis**
      - Increased insulin:glucagon ratio
      - Activation of pyruvate dehydrogenase (PDH)
    - **Increased glycogen synthesis**
    - **Increased** activity of **pentose phosphate pathway (PPP)**
      - To increase NADPH formation (primary source)
      - You need NADPH for lipogenesis and cholesterol synth.
    - Lowered gluconeogenesis (first enzyme = pyruvate carboxylase)
    - Fat metabolism
      - Increased FA, TAG synthesis
      - Increased glycerol-3-phosphate (TAG backbone)
    - Amino acid metabolism
      - More degradation, so a.a. used for protein synthesis in other tissues
      - Branched Chain Amino Acids (BCAA) cannot be degraded in liver (Degraded and used by muscle)
      - Increased protein synthesis
  - Adipose tissue → more GLUT-4 (more glucose uptake), more glycolysis (DHAP instead of GAP), more PPP activity (more NADPH)

- Resting skeletal muscle → more GLUT-4, more hexokinase activity, more glycogen synthesis, more protein synthesis and uptake of BCAA.

- **Fasting state**
  - Between meals; **high glucagon**
  - 2 priorities:
    - Need to maintain blood glucose level for organs dependent on glucose (Brain, RBCs)
    - Need to metabolize FA from adipose and ketones from liver (to supply other tissue)
  - Muscle can't contribute glucose (no glucose-6-phosphatase)
  - Covalent modification: all phosphorylated, except 3 enzymes
    - Enzymes related to gluconeogenesis are activated
  - **In liver:**
    - First, **glycogenolysis**
    - Then **gluconeogenesis**
      - Enzymes activated → F1,6-bisphosphate, PEP carboxykinase, pyruvate carboxylase
    - **Increased FA oxidation** (ß-oxidation)
      - Low malonyl CoA because low ACC activity ☺
      - Malonyl CoA = rate-determining substrate
      - Provides NADH and ATP for gluconeogenesis
    - **Increased ketogenesis**
      - Liver can't use ketones (no thiophorase)
  - **Adipose tissue:**
    - Decreased GLUT-4 activity
    - **Increased TAG degradation** (thru **hormone-sensitive lipase**)
      - Activated by epinephrine, norepinephrine and glucagon
    - **Increased release of FA but reduced uptake of FA (low LPL)**
  - **Resting skeletal muscle:**
    - Decreased GLUT-4 activity
    - Uses FA and ketones as source of energy (mostly FA)
    - Protein degradation (a.a. used for gluconeogenesis in liver)
      - Most important gluconeogenic a.a. = alanine & glutamine
  - **Brain:**
    - No glycogen stores, so still depends on glucose
    - If over a week, then ketone bodies are used

. Preferred Fuels in the Well-Fed and Fasting States

Organ	Well-Fed	Fasting
Liver	Glucose and amino acids	Fatty acids
Resting skeletal muscle	Glucose	Fatty acids, ketones
Cardiac muscle	Fatty acids	Fatty acids, ketones
Adipose tissue	Glucose	Fatty acids
Brain	Glucose	Glucose (ketones in prolonged fast)
Red blood cells	Glucose	Glucose

- **Pentose phosphate pathway (PPP)**
    - Also called Hexose monophosphate shunt or 6-phosphogluconate pathway
    - Occurs in **cytosol**
    - **2 irreversible oxidation reactions producing NADPH** + series of reversible sugar-phosphate conversion
    - First oxidation reaction → uses **G6PD** (dehydrogenase)
    - Second oxidation reaction → uses 6-phosphogluconate dehydrogenase
    - **Ribulose 5-phosphate** (used for **nucleic acid biosynthesis**)
        - Converted using isomerase to ribose 5 phosphate
        - Converted using epimerase to xylulose 5 phosphate
    - Uses (many, but listed are some)
        - Reductive biosynthesis (NADPH for cholesterol and FA)
        - Hydrogen peroxidase reduction
        - Glutathione reduction (antioxidant)
        - Nucleic acid biosynthesis

Pathology (ALWAYS GO LOOK AT PICTURES IN SLIDES!!!)

- Remember the pathological changes seen in diabetes:
    - **Type I → Insulitis** with **progressive ß cell destruction** (**lymphocytic infiltration**)
    - **Type II → Reduction in islet cell mass** + fibrous tissue and late stage **amyloid deposits**
- Pathogenesis is multifactorial, but the hyperglycemia causes main pathology
- **Mechanism of pathogenesis:**
    1. Non-enzymatic glycosylation (NEG) with formation of irreversible **Advanced Glycosylation End Products (AGEs)**
    2. Activation of **protein kinase C (PKC)**
    3. Intracellular hyperglycemia and **disturbances in Polyol Pathway** (Sorbitol)
- **AGEs (Explaining number 1)**
    - AGE binds RAGE (receptor in inflammatory cells, endothelium, etc.)
    - AGE-RAGE complex formed
    - Causes release of proinflammatory cytokines and MØ factors
    - Generation of reactive oxygen species (ROS) from endothelial cells
    - Increased procoagulant activity
    - Increased proliferation of vascular smooth muscle cells (SMCs) and synthesis of extra cellular matrix (ECM)
        - AGEs can directly cross-link ECM proteins
    - Classification in terms of NEG
        - NEG of large and medium sized vessels
            - Trapping LDL and plasma proteins
            - Atherogenesis and eventual atherosclerosis
        - NEG of small vessels
            - Hyaline arteriolosclerosis (think of kidneys)

        - NEG of Hb → HbA1c (marker of glycemic control -120 days)
- **Activation of PKC**
    - Increased intracellular glucose → more DAG synthesis → PKC activity
    - PKC leads to formation of proangiogenic factors
        - Vascular endothelial growth factor (VEGF)
        - This leads to neovascularization (think of the eyes)
    - PKC leads to more endothelin and less NO (vasodilator)
    - PKC leads to more TGF-ß → increased ECM and BM
    - PKC leads to more PAI → lower fibrinolysis (dangerous)
- **Intracellular hyperglycemia and polyol disturbances**
    - Tissue with insulin independent GLUT get severely affected
        - Glucose flood the cytosol of the cell
        - Glucose converted by **Aldose Reductase** (using NADPH) to **SORBITOL (a polyol)**
        - Sorbitol can get converted to fructose
        - Increased intracellular osmolarity leads to **OSMOTIC CELL INJURY**
        - NADPH can be used up, and not enough left for glutathione! So there will be a build up of ROS!
        - Neurons → glucose neurotoxicity, schwann cells injured

Now, the actually pathology ☺ ☺ ☺ ☺ ☺

- VASCULAR SYSTEM:
    - **Macrovascular** → atherosclerosis (aorta, large and medium arteries)
    - **Microvascular** → microangiopathy (renal, retinal and peripheral arteries)
    - **Macrovascular:**
        - **Accelerated atherosclerosis** (LDL and plasma protein trapped)
        - Contributing factors: hyperlipidemia, low HDL, NEG, HTN
        - Common sites: large elastic and medium muscular arteries
            - Abdominal aorta, coronary, popliteal, internal carotid
        - Complications:
            - **Myocardial infarction (MI)** – equal in men and women
                - Normally, men at higher risk
            - **Gangrene** of lower extremities (advanced vascular disease)
            - Renal arteries atherosclerosis
            - **HYALINE ARTERIOLOSCLEROSIS (**look at kidneys)
                - Seen in HTN and diabetes (more severe)
                - Amorphous, pink, **hyaline thickening** of arteriolar walls
    - **Microvascular:**
        - **Diabetic microangiopathy (diffuse BM thickening)**
            - More leaky to plasma proteins
            - Causes many complications (retinopathy, nephropathy)

- **DIABETIC NEPHROPATHY**
  - Second most common cause of death in diabetics (no. 1 = MI)
  - 3 lesions are encountered:
    1. **Glomerular lesions (glomerulosclerosis)**
    2. **Renal vascular lesions (arteriolosclerosis)**
    3. **Pyelonephritis (necrotizing papillitis)**
  - Process:
    - **Hyaline arteriolosclerosis** affects kidney arterioles
    - **Afferent and efferent arterioles are both affected**
    - **Preferential involvement of efferent arteriole**

Afferent → entering
Efferent → exiting

[Can occur independently]

Afferent involvement
↓
Decreased blood supply to glomerulus
↓
Diffuse sclerosis of glomerulus (Diffuse glomerulosclerosis)
↓
Chronic renal failure

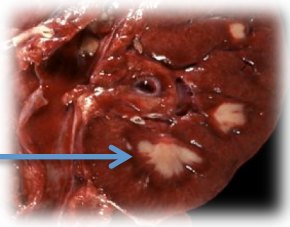
Can cause nephrotic syndrome

Efferent hyaline arteriolosclerosis
↓
Increased pressure in glomerulus
↓
Hyper-infiltration injury (microalbuminuria)
↓
Eventual sclerosis of mesangium (mesangiosclerosis)
↓
Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion/nodules)
↓
Nephrotic syndrome (Proteinuria, hypoalbuminemia, edema)

PAS + & trapped mesangial cells

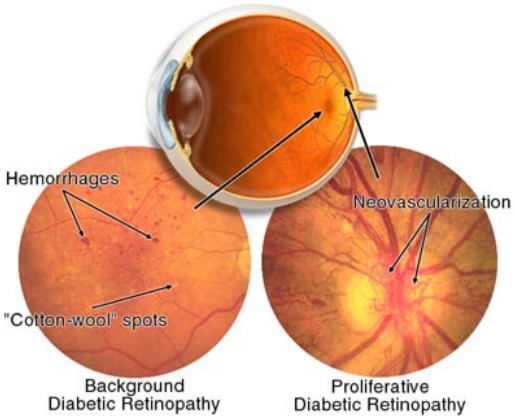
Granular Contracted Kidney (nephropathy)

Pyelonephritis:
- Acute/chronic inflammation of kidneys
- Begins in interstitial tissue and spreads
- Necrotizing papillitis (papillary necrosis)



- **DIABETIC OCULAR COMPLICATIONS**
  - 4th leading cause of blindness!
  - Involves:
    - Retinopathy (damage to pericytes of retinal vessels)
    - Cataracts (high intracellular osmolarity → osmolar damage)
    - Glaucoma

- **Retinopathy**
  - **Non-proliferative (BACKGROUND)**
    - **Hemorrhages** (starts off with dot)
    - **Exudates (cotton-wool?)**
    - **Microaneurysms**
    - Venous dilation
    - **Edema** (papilloedema?)
  - **Proliferative**
    - **Neovascularization (new vessels form!)**
    - Fibrosis
    - Vitreous hemorrhage and retinal detachment



- Pericytes retinal blood vessels die due to osmotic damage by sorbital and so the blood vessels' walls weaken and are more prone to aneurysm and hemorrhage
- Lens accumulate sorbitol and fluid → osmotic damage → cataracts

- **DIABETIC NEUROPATHY**
  - **Central neuropathy**
  - **Peripheral neuropathy**
    - Distal *symmetrical* sensory/ **sensorimotor neuropathy**
    - **Autonomic neuropathy**
    - **Focal**/multi-focal ***asymmetric*** **neuropathy**
  - **Diabetic mononeuropathy**
    - Single peripheral nerve (Foot drop)
    - Single cranial nerve (oculomotor nerve bells palsy)
    - Multiple individual nerves (mononeuropathy multiplex)
  - Occurs due to **glucose neurotoxicity**
    - **Schwann cell injury** (**osmotic damage** by **sorbitol**)
    - NEGs also can play a role here ☺
  - What happens?
    - Sensorimotor neuropathy:
      - Loss of pain sensation distally
      - Ulcer and poor healing
      - Infection and/or **gangrene**
      - **Amputation**
    - **Autonomic neuropathy symptoms:**
      - **Postural hypotension**
      - Poor bladder control (increased risk of UTI)
      - Poor defecation control (constipation/diarrhea)
      - **Sexual dysfunction**

Diabetics are more **susceptible to infections** such as TB, pneumonia, pyelonephritis… Due to low neutrophil functions, impaired cytokines, vascular compromise (thick BM!!!!)

EXTRA TOPICS OF DISCUSSION:

- Dawn phenomenon: surge of catabolic hormone at dawn
  - Dealt with by eating dinner early and light/moderate exercise
- Diabetes education: **SMBG (Self Monitoring of Blood Glucose)**
- Counseling patients: truth, age-appropriate, be positive, healthy lifestyle

Pharmacology

Note: Lifestyle modification (diet control and exercise) is required.

- **Oral anti-diabetic medications:**
    - **Insulin sensitizers (lowers insulin resistance)**
        - **Biguanides (Metformin)**
        - **Thiazolidinedione (Glitazones)**
    - **Insulin secretagogues (induces insulin secretion)**
        - **Sulfonylureas**
            - First-Generation (tolbutamide)
            - **Second-Generation (Glimepiride – *Amaryl*, Glipizide)**
        - Meglitinide analogues ("-glinides")
    - Other drugs:
        - **α-glucosidase inhibitors (acarbose)**
        - Amylin analogs (pramlintide)
        - **Incretin modulators**
            - Glucagon-like peptide (**GLP-1**) analog (exenatide)
            - **DPP-4 inhibitors** (Sitagliptin) ~ [DPP-4 inhibits GLP-1]

- **DOC is metformin (biguanide)**
    - "Euglycemic drug" doesn't involve insulin, **so no risk of hypoglycemia**
    - **Initial DOC for monotherapy** to treat **type 2 diabetes**
    - Not fully known; **Activates AMPK → inhibits gluconeogenesis**
    - May cause **LACTIC ACIDOSIS**
        - NOT FOR alcoholics, renal or liver failure patients
    - **Reduces vitamin B_{12}** absorption
        - Give supplements if needed
- Thiazolidinedione: **Glitazone** (**pioglitazone**)
    - **No hypoglycemia** (euglycemic)
    - 2nd line monotherapy or combination in type 2 diabetes
    - Ligands of **PPAR-γ** (Peroxisome proliferator-activated receptor gamma)
        - Nuclear receptors found in liver, fat, muscle
        - Increase glucose uptake in fat and muscle, adipogenesis, and lowers gluconeogenesis
    - Adverse effect = **EDEMA**
- **Sulfonylureas**
    - We use **second generation** (more potent, less dose needed, once daily)
    - Major risk is **hypoglycemia**
    - **Leads to closure of pancreatic ß islet cell ATP-K^+ channels → depolarization → more Ca^{2+} influx → more insulin secreted**
    - Adverse effects: hypoglycemia, **weight gain**, secondary failure (ß cell mass too low!)
- Meglitidines
    - Same as sulfonylureas, but not as effective and less severe side-effects
    - RAPID ONSET

- **α-glucosidase inhibitors**
    - **Acarbose…** Impair glucose absorption in gut by stopping breakdown
    - No hypoglycemia
    - ADR: **GIT distress** (flatulence, diarrhea, abdominal pain)
- Amylin analog (pramlintide) – suppress glucagon (not sure how!)
- GLP analogs & DPP4 inhibitors
    - Glucagon-like peptide 1 actually helps insulin when a meal ingested by suppressing glucagon release
    - **Exenatide is a GLP analog**
    - **GLP is degraded by DPP-4 (Dipeptidyl peptidase)**
    - So we can give a **DPP-4 inhibitor** (hence increasing GLP-1)
        - **Sitagliptin**

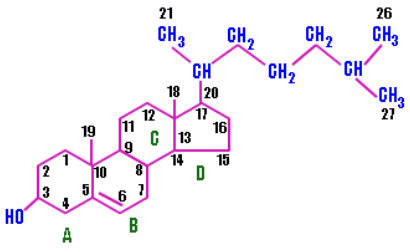
Problem 3: Dyslipidemia

Summary of triggers:

PART A:
A **16-year-old boy** presented with progressive number of multiple yellowish raised spots on his extremities, present since birth (**tendon xanthomas**). Lipid profile investigation shows **raised total cholesterol** and normal TAG. He was kept on **low cholesterol diet**, but 4 years later he returned with **angina pectoris** (chest pain when doing mild physical activity). He wasn't compliant with the diet management. His older brother died at the age of 20. Doctor suspected **familial hypercholesterolemia (FH).** ECG showed ischemic changes and blood sample was turbid. He was admitted and a culture of his skin biopsy (subcutaneous fibroblasts) revealed **deficiency of LDL receptors**. He underwent a double coronary artery bypass graft surgery. He was then kept on a special low CH diet + CH lowering drugs. It didn't do much and he then underwent a liver transplant surgery. His blood LDL lowered remarkably.
PART B:
A **35-year old diabetic man** is on anti-diabetic medication. He gets **epigastric pain** after having **fatty meals** and has a **history of cramps** in his calves when walking. He is a **heavy smoker**, **drinks alcohol** regularly, and **overweight**. He has **high BP** and a **large waist circumference + impaired peripheral pulses**. His **blood appeared milky**. High FBG, high total cholesterol, **very high TAG**, and urine analysis showed glycosuria. Younger brother and sister have asymptomatic abnormal lipid profile, but no other members have anything related to the man. He was diagnosed with **hyperlipoproteinemia IV**. He was told to **modify his lifestyle** (weight loss, stop smoking, eat better, exercise) and was prescribed **fibrate**.

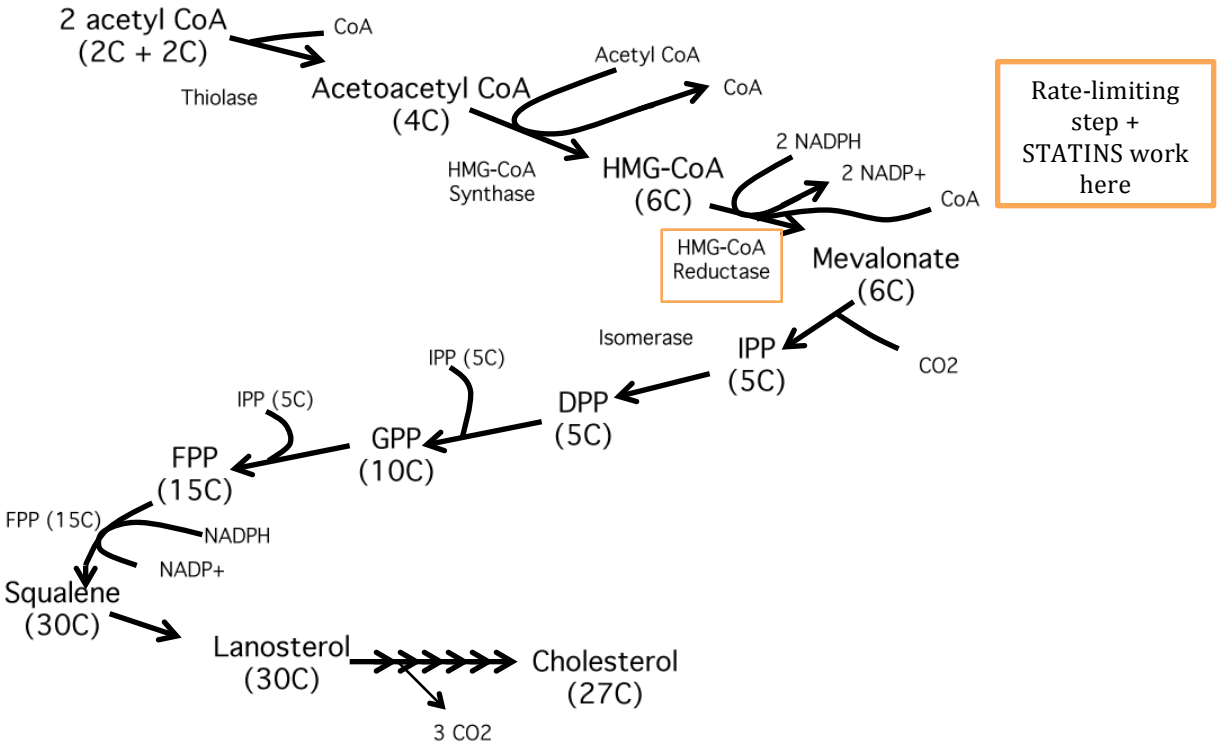
Biochemistry

- Cholesterol
    - Structural component of **plasma membranes** (**fluidity and rigidity**)
    - Precursors of **bile acids**, **steroid hormones** and **vitamin D**!
    - Elimination occurs only through **bile salt** in feces
    - Are components of **lipoproteins**
    - Increased blood levels contribute to atherosclerosis formation
    - **Atherosclerosis** increases the risk of:
        - **Cardiovascular disease (MI)**
        - **Cerebrovascular disease (stroke)**
        - **Peripheral vascular disease**
    - **Structure**
        - 4 fused CH rings (A, B, C, D) → "steroid nuclei"
        - Hydrophobic
        - Contains hydrocarbon chain attached at C17 of D
        - Ring A has OH group at C3
        - Ring B has a double bond



- Cholesteryl ester (FA chain instead of OH) ~ more hydrophobic

- **Synthesis**
  - Mainly by liver, intestines, adrenal cortex and reproductive organs
  - Needs acetyl CoA and NADPH (from PPP or Malic Enzyme)
  - Endothermic/endergonic/requires energy!
  - Enzymes involved are cytosolic (mostly) and rER bound



- Mevalonate formation → irreversible, committed step
- HMG-CoA reductase (ER membrane bound enzyme)
- Squalene to lanosterol is a cyclization reaction
- Regulation:
  - HMG-CoA reductase
    - Gene expression controlled by **SREBP-2**
    - SREBP = Sterol Regulatory Binding Protein
    - When cholesterol low, SREBP binds to SCAP (SREBP cleavage activating Protein)
    - **SREBP-SCAP complex** enters Golgi and gets modified
    - Then transported to **nucleus** where it binds to **SRE gene**
    - Acts like a **transcription factor** (promotes HMG-CoA reductase expression and thus synthesis)
    - When cholesterol high, it suppresses HMG-CoA expression

    - HMG-CoA reductase covalent modification by **AMPK (dephosphorylated = activated)**
    - HMG-CoA reductase also regulated by sterol amount DIRECTLY
        - **Sterol-accelerated enzyme degradation**
    - Insulin promotes HMG-CoA expression and activity (anabolic!)
- **Enterohepatic circulation**
    - Cholesterol is used to make bile acids, bile salts
    - Bile salts are secreted by liver through the gallbladder into the duodenum
    - Most bile salts (95%) are reabsorbed in the ileum
    - When reabsorbed, they are returned to the liver
    - Continuous recycling
    - The 5% not reabsorbed is excreted in feces

- Plasma lipoproteins
    - Macromolecular complexes of lipids and special proteins
    - Neutral core of lipids (TAG, CE) and shell of ampiphatic apolipoproteins, phospholipids and free cholesterol
    - The higher the density, the lower the size
    - Lipoprotein classes

apoA-I	HDL structural protein; LCAT activator;RCT
apoA-II	HL activation
apoA-IV	Tg metabolism; LCAT activator; diet response
apoB-100	Structural protein of all LP except HDL
apoB-48	Binding to LDL receptor
apoC-I	Inhibit Lp binding to LDL R; LCAT activator
apoC-II	LpL activator
apoC-III	LpL inhibitor; antagonizes apoE
apoE	B/E receptor ligand *E2:IDL; *E4: Diet Responsivity

    - Chylomicrons
        - Largest size
        - Assembled in intestinal mucosal cells
        - Carry dietary TAG, Cholesterol, fat-soluble vitamins (A,K,E,D)
        - TAG → 90%
        - Contains **Apoliprotein B48** (binds to LDL receptors)
        - Intestines → lymphatic system → blood
        - **Chylomicron + B48 = nascent chylomicron**
        - **Chylomicron + B48 + apoE & apoC2 (from HDL)** = **mature**
        - **ApoC2 activates lipoprotein lipase** (in adipose and muscles)
        - apoE needed for liver uptake
        - Chylomicron remnant after passing through tissues
    - **VLDL** (very low density lipoprotein)
        - **Made in liver**
        - **Composed mainly of ENDOGENOUS TAG (60%)**

- **Carry lipids from liver to peripheral tissues for use**
- Nascent VLDL = VLDL + apoB100
- Mature VLDL = VLDL + B100 + apoE & apoC2 (from HDL)
- Pass through tissue, activate LPL, take up TAG from VLDL
- Now you have **IDL (intermediate density lipoprotein)**
- Further metabolism and eventually becomes LDL (low-density lipoprotein)
- **LDL → mainly cholesterol** (all TAG is taken up already)
- HDL communication
  - HDL gives VLDL or IDLs Cholesteryl esters (CE) in exchange for TAG using the enzyme **CETP** (CE transport protein)
- IDLs and LDLs are taken up by tissue through **RECEPTOR-MEDIATED ENDOCYTOSIS** (needs apoE and apoB)
  - Dr. Wassim loves this diagram:

LCAT and ACAT:
- **LCAT** (lecithin cholesterol acyl transferase) converts Cholesterol to CE in HDL. This is what causes HDL to change shape & uptake lots of Cholesterol from tissues "Good cholesterol"

- **ACAT** (Acyl CoA acyl transferase) converts Cholesterol to CE in **hepatocytes**

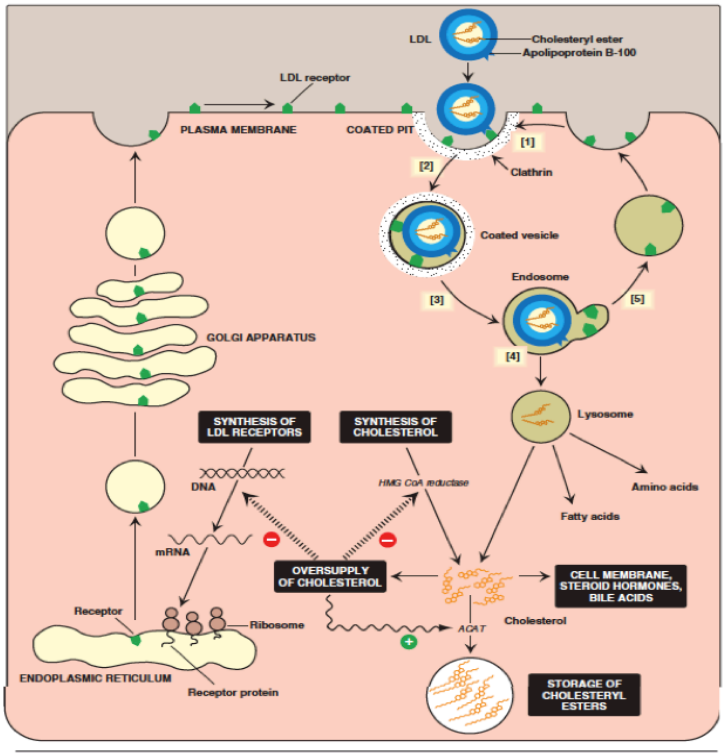


Figure 18.20
Cellular uptake and degradation of LDL. *ACAT = acyl CoA:cholesterol acyltransferase.*

LDL receptors recognize apoB and mediates endocytosis using clathrin-coated pits. The LDL receptors are recycled.

- **HDL**
  - Formed in blood by adding lipid to ApoA1
  - Reservoir of apolipoprotein apoE and apoC2
  - Reverse cholesterol transport
    - Efflux of cholesterol from peripheral tissue by ABCA1
    - HDL uptake + esterifies them with LCAT (HDL-2 spherical)
    - Gives Cholesterol to liver and steroidogenic tissue
    - Lipid-depleted HDL = HDL-3… (discoid)
  - CETP (said this already) activity

FYI:
Liver has **glycerol kinase**, adipose tissue doesn't; liver can make glycerol phosphate (TAG backbone) from glycerol. In adipose, it must come from DHAP by glycolysis only.

- **Lipoprotein(a) or Lp(a)**
    - Increases risk of coronary artery disease
    - Blocks plasminogen activation (slows fibrinolysis)

PATHOLOGY

- Classification of dyslipidemias (*POLYGENIC IS THE MOST COMMON*)
    - **Type I (Familial hyperchylomicronemia)**
        - Greatly **elevated TAG**
        - **Deficiency of LPL or apoC2**
        - **Autosomal recessive** inheritance
        - **Milky supranate** (upper layer)
        - **No** atherogenicity
        - **High chylomicron → pancreatitis → Emergency**
    - **Type IIA (Familial hypercholesterolemia)**
        - Also includes polygenic hypercholesterolemia
        - **Familial Hypercholesterolemia**
            - **Elevated LDL**
            - Normal TAG, but **high Cholesterol**
            - **Autosomal dominant** inheritance
            - **Deficiency of LDL receptors**
            - **Achilles tendon xathomas, xanthelasma**
            - Premature coronary artery disease and stroke
    - **Type IIB (Familial combined/mixed hyperlipidemia)**
        - **Autosomal dominant** inheritance
        - **VLDL and LDL raised**, **high TAG + Cholesterol**
        - Common (40% of dyslipidemias)
        - Associated with **metabolic syndrome**
            - Metabolic syndrome = combination of diabetes, HTN, obesity
            - Waist circumference > 102 cm in men and >88 cm in women
    - **Type III (Familial dysbetalipoproteinemia or Remnant Disease)**
        - **Autosomal recessive** inheritance
        - **Deficiency of apoE**
            - Reduced liver uptake of IDL and chylomicron remnant
        - Palmar & tuberous xanthomas (increased risk for CAD, PVD)
        - **High cholesterol and TAG**
        - You can identify apoE gene defect
    - **Type IV (Familial hypertriglyceridemia)**
        - Familial hypertriglyceridemia
            - Autosomal dominant inheritance
            - Most common (inherited?) dyslipidemia (45%)
            - Increased VLDL production
            - ERUPTIVE xanthomas
            - High TAG, normal to elevated cholesterol

        - Increased risk of CAD and PVD
        - Turbid infranate (throughout plasma)
    - Acquired causes
        - Excess alcohol (more VLDL made)
        - Oral contraceptives (estrogen increases VLDL)
        - Diabetes mellitus (more LDL, less active LPL)
        - Chronic renal failure
- **Type V (Familial mixed hypertriglyceridemia)**
    - **VLDL and chylomicrons elevated**
    - Increased VLDL production or decreased clearance
    - Usually seen as type 4 + disorder (alcoholism, obesity, diabetes)
    - Eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, acute pancreatitis (due to high chylomicrons)
    - **Turbid supranate AND infranate**

- Secondary causes of dyslipidemias:
    - Hypothyroidism, diabetes, alcoholism, blockage of bile flow, nephrotic syndrome, etc.
- **<u>Atherosclerosis:</u>**
    - Disease of large (elastic) and medium (muscular) sized arteries
    - Occurs in the middle-aged or elderly (takes years to manifest)
    - Characterized by intimal lesions & thickening called atheromas (plaques)
    - Atheromatous plaques consist of:
        - Necrotic lipid core
        - Fibromuscular cap (raised)
    - Risk factors:
        - Modifiable: HTN, diabetes, smoking, hyperlipidemias
        - Non-modifiable: age, gender, ethnicity and genetics
            - Increased risk at older age
            - Men and post-menopausal women more at risk… Estrogen lowers risk)
        - Lp(a), hyper-homocysteinemia, metabolic syndrome
        - Sedentary lifestyle + type A personality
    - Pathogenesis:
        - "Response to injury" hypothesis
            - Endothelial injury
            - Endothelial dysfunction and increased permeability
            - Adhesion of monocytes and platelets
            - Monocytes → MØ
            - MØ and platelets secrete cytokines and factors
            - Migration of SMCs from tunica media to intima
            - Accumulation of lipoproteins (LDL) & oxidize
            - SMCs and MØ engulf lipids → "FOAM CELLS"
            - Foam cells characteristic finding in FATTY STREAK
            - VEGF, TGF-ß, etc. → SMC proliferation, ECM deposition, plaque formation

    - Fatty streaks (yellow streaks)
        - Precursor lesion (whitish, yellowish)
        - Mainly in abdominal aorta or its ostia
        - Aggregates of foam cells
        - Found in teenagers and kids!
    - Atheromatous plaque then forms over the years
        - Soft necrotic lipid core, raised into lumen
        - **Intimal thickening** with **cholesterol clefts**
        - Fibromuscular cap (can be thick or thin)
    - Complications:
        - Atrophy of medial layer → aneurysm → rupture
        - Ulceration → thrombosis → thromboembolism
        - Embolization (with cholesterol clefts seen in emboli)
        - Calcification
        - Plaque hemorrhage → narrowing → occlusion
        - Progression of plaque → severe stenosis
            - If over 80% → symptoms appear
            - If near total occlusion → Infarction
        - Clinical manifestations include:
            - Infarction (MI, stroke, gangrene)
            - Ischemia (renal atrophy)
            - Aneurysm (dissection, rupture, hemorrhage)
            - Embolism (DVT and PE)

- Laboratory investigations:
    - Risk factors for CAD
        - Lipid Triad (High TAG, high LDLC, low HDLC)
        - HDLC is a NEGATIVE risk factor (more of it = good!)
        - Other risks
            - Lifestyle (old age, diabetes, obesity, HTN, smoking)
            - Family history of CAD
            - Lp(a), fibrinogen, homocystein, CRP
    - Plasma lipoproteins
        - Electrophoresis classification
            - Alpha (α) Lp → HDL → mostly phospholipids
            - Beta (ß) Lp → LDL → cholesterol
            - Pre (ß) Lp → VLDL → TAG
            - Omega (ω) Lp → Chylomicron → TAG (dietary)
    - Screening test recommended fasting
        - **12 – 14 h** is preferable
        - 12 – 14 h is essential when
            - CAD or PVD or diabetes or IGT present
            - Central obesity, HTN, chronic renal failure
            - Family history of CAD
    - LDLC estimated by: **FRIEDEWALD EQUATION**
        - **LDLC = total cholesterol – [HDLC + (TG/2.2)]**
        - **Non-HDLC = Total Cholesterol – HDLC)**

Waist circumference as a risk for dyslipidemia:
Men > 102 cm
Women > 91.5 cm

Pharmacology

- LDL Reducers
  - STATINS (HMG-CoA reductase inhibitors)
    - Rosuvastatin (Crestor), atorvastatin
    - Inhibit cholesterol synthesis and reduced LDL formation
    - This leads to increased need for circulating cholesterol
      - This is found where? LDL ☺
    - Liver increases no. of LDL receptors and increase cholesterol blood clearance
    - DOC for hypercholesterolemia (in which LDL is high)
    - DOC for mixed dyslipidemia
    - DOC for mild-moderate hypertriglyceridemia
    - Used in CAD to prevent MI
    - ADR: hepatotoxicity, myotoxicity
    - Contraindications (CI): pregnancy, lactation, hepatic disease
    - Interacts with CYP450
  - Bile Acid Binding Resins:
    - Colesevelam, choletyramine
    - Inhibit bile acid reabsorption at ILEUM (enterohepatic circulation)
    - Liver compensates by absorbing more cholesterol from blood
      - Increase LDL receptors
    - 2nd line (added to statins)
    - Safe for children, pregnancy and lactation
    - Slightly increases TAG
    - ADRs: GI distress, fat-soluble vitamins malabsorption, inhibits drug absorption (digitalis, statins)
    - CI: Mixed (combined) dyslipidemia (IIB)
      - Because it slightly increases TAG
  - Cholesterol absorption inhibitors (**Ezetimibe**)
    - Blocks sterol transporter **NPC1L1** in intestinal brush border
    - Cholesterol absorption inhibited (increased LDL to combat)
    - Used for high LDLC (2nd line, after statin, but better than resin)
    - ADRs: rare hepatotoxicity and myotoxicity
- **TG lowering agents**
  - **Fibrates** (fibric acid derivatives)
    - **Febofibrate** and gemfibrazil
    - Agonist of **PPAR-γ** (transcriptionally **upregulate LPL**)
    - Used in **SEVERE hypertriglyceridemia (DOC)**
    - ADRs: hepatotoxicity (rare) myotoxicity (especially with statins), gall stones
  - **Niacin (vitamin B_3/nicotinic acid)**
    - **HDL increasing agent**
    - Decreases efflux of FFA to liver (reduce VLDL synthesis)
    - **DOC for low HDL + Added to statins** in **mixed dyslipidemias**
    - ADR: hepatotoxicity, hyperuricemia (gout), flushing, GI distress
    - Second line for high TG, high LDL + used for high Lp(a) + MI

Problem 4: Thyrotoxicosis

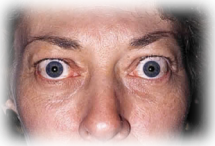
Summary of triggers:

A **35-year-old** married **woman** came in with complaints of **fatigue, nervousness, muscle aches, heat intolerance, palpitations, and weight loss** over 2 months duration. She had **irregular menstruation** (it was late) and a **swelling in her neck**. The swelling **moved upon swallowing**. Her **eyes** look prominent and **bulging**. Her **palms are sweaty**. She had **high systolic BP** (165/60) and **pulse** (110/min) – tachycardia. Eye exam revealed **staring gaze, lid lag and lid retraction**. **Diffuse enlargement of thyroid gland** (no nodules) was noted which was **smooth** and **not tender**. A **bruit** was heard over the thyroid. She had **fine tremors of the hands** and **decreased muscle strength** + thickening of the skin over the shins with **non-pitting edema** (**pretibial myxedema**). **Deep tendon reflexes** were **hyperactive**. Lab investigations were done; **pregnancy test negative**, **raised free T_4**, **free T_3** with **non-detectable TSH** and **TSI positive**. She was diagnosed as having **thyrotoxicosis** due to **Grave's disease** (upon exclusion of other causes of her hyperthyroidism such as **multi-nodular goiter**). She was given **carbimazole** once daily, with **propranolol** twice daily. She was told to **come to the clinic** if she ever feels like she has a **fever or a sore throat**. When she came back in a month, she had gain some weight and all her symptoms reduced. Pulse and BP were now normal. **Eye symptoms remained**. Her **WBC count lowered** (still normal range, but lower than previous test). She came back after 11 months for a checkup, but this time she had **very high TSH**! The doctor decreased the dose of carbimazole. On her next visit, she was fine and dandy; TSH normal now, TSI decreased.

What can we learn from the triggers?

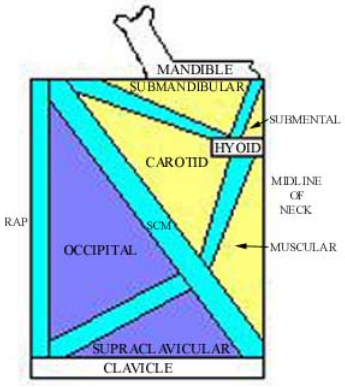
- The patient has Grave's disease (hyperthyroidism)
- Females are more likely to get thyroid pathologies
- The symptoms of hyperthyroidism are all stated above!
- Thyrotoxicosis = high thyroid hormones
    - Hyperthyroidism is a cause of thyrotoxicosis
        - Grave's disease
            - Diffuse enlargement
            - Smooth & not tender (not painful)
        - Multinodular goiter
        - Pregnancy induced hyperthyroidism (that's why a pregnancy test was done)
    - Intake of thyroxine drugs can lead to thyrotoxicosis too…
- Thyroid hormones increase the basal metabolic rate
    - Although we will explain later how, it is enough now to understand that bodily functions are hyperactive (Heart action, muscles, etc.)
- Recall that a bruit is a similar to a murmur but heard over blood vessels
    - It is heard when there is an occlusion (as in renal artery stenosis)
    - Thyroid enlarges (goiter) → more blood supply → heard as bruit
- Goiter = thyroid enlargement (irrelevant of the cause)

- TSH was low to near gone… Why?
    - Feedback inhibition; pituitary stimulated endocrine hormones, if increased in circulation (T_3 or T_4), inhibits further stimulatory hormone secretion by the anterior pituitary gland (TSH) and by the hypothalamus (TRH)
    - Greatly elevated T_3 and T_4 leads to almost diminished TSH secretion
- Carbimazole is an anti-thyroid medication and propranolol is a non-selective ß blocker
    - Although it will be explained later, anti-thyroid drugs take time to act and hyperthyroid patients need propranolol to reduce the sympathetic overstimulation symptoms that may be dangerous (HTN, arrhythmias, tremors, sweating)
- Why was the WBC count reduced and why did the doctor tell her to come if she feels sick?
    - Carbimazole can cause leukopenia and agranulocytosis and these can make the person vulnerable to infections (not be able to fight back)
- TSH was so high later… Why?
    - Overdose of the drug! It's iatrogenic! The doctor didn't carefully change the dose with time and so feedback inhibition comes in (less T_3 or T_4 being made, more TSH to stimulate!)
- Lid lag, lid retraction and staring gaze + exophthalmos
    - Exophthalmos is a condition in which the eyes of a hyperthyroid patient is bulging out (Seen from the side of the eye)
        - MANY causes (you'll see later)
    - Lid lag and lid retraction are caused by sympathetic-induced contraction of lid muscle
        - Lid lag = when you look down, lid doesn't move
        - Lid retraction = the upper lid is held too high up
    - Exophthalmos is harder to treat than the other eye symptoms



ANATOMY

- **TRIANGLES OF THE NECK (divided by sternocleidomastoid - SCM)**

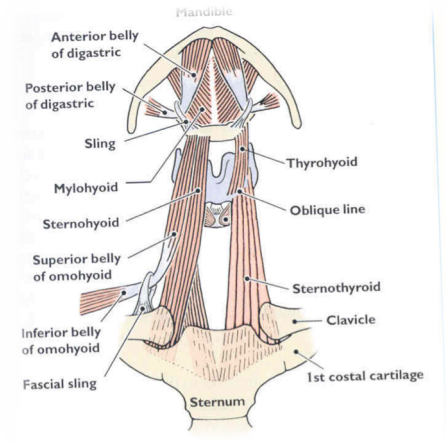


- **<u>Anterior Triangle</u> (neck midline anteriorly, SCM posteriorly)**
    - **Submental triangle**
        - Shared between anterior triangles from each side
        - Submental lymph nodes
    - **Submandibular/Digastric triangle**
        - Submandibular salivary gland (opens into tongue frenula)
    - **Muscular triangle**
    - **Carotid triangle**
        - **Carotid sheath**
            - **Common carotid artery (CCA)**
            - **Internal jugular vein (IJV)**
            - **Vagus nerve (CNX)**

These anatomy notes should NOT replace demo notes…

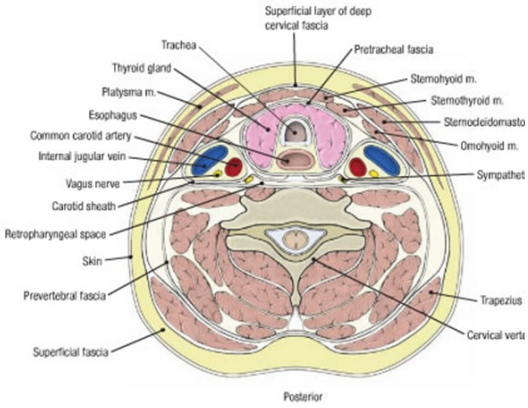
Ansa Cervicalis: Loop of nerves, part of cervical plexus, supply **infrahyoid muscles (Strap)** Found in **carotid triangle**…

- **<u>Posterior Triangle</u>** (SCM anteriorly, trapezius posteriorly)
    - Occipital triangle
        - Accessory nerve (XI)
    - Subclavian triangle
        - Subclavian artery and vein
    - Contains brachial plexus

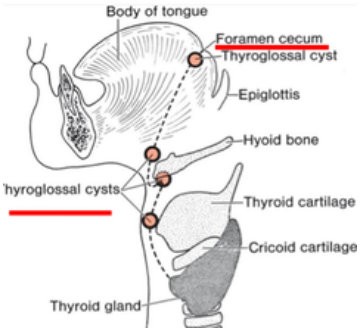


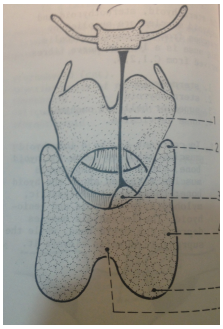
- **Strap Muscles (Infrahyoid Muscles)**
    - Sternothyroid (sternum to thyroid cartilage)
    - Thyrohyoid (thyroid cartilage to hyoid bone)
        - **Doesn't pass over the thyroid GLAND**
    - Sternohyoid (sternum to hyoid bone)
    - Omohyoid (has 2 bellies!)

- **Fascia of the Neck**
    - Fascia of the neck
        - Superficial fascia (underneath skin)
            - Platysmus muscle
        - Deep fascia (4 layers):
            - Investing layer (of deep fascia)
                - Contains SCM & trapezius
            - **Pretracheal fascia (look down)**
                - Contains **thyroid gland**
            - Prevertebral fascia
            - Carotid sheath

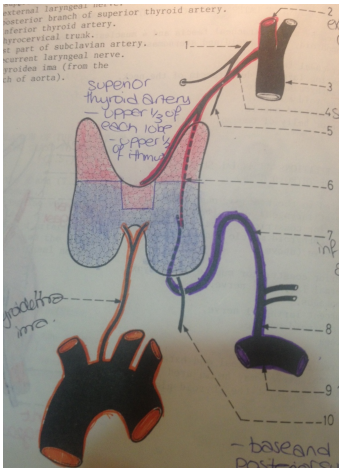


- **Thyroid Gland**
    - Anterior in the neck
    - Below and lateral to the thyroid cartilage
    - Consists of **2 lateral lobes**
        - Covering anterolateral sides of trachea & cricoid cartilage
        - **Superior poles reach oblique line of thyroid cartilage**
        - **Inferior poles** reach **6th tracheal ring**
    - **Isthmus**
        - Connects the two lateral lobes
        - **Covers the 2nd, 3rd and 4th tracheal rings**
    - Surrounded by **pretracheal fascia**
        - Attached to **hyoid bone (closed from up)**
        - **Blends with fibrous pericardium**
        - Causes **thyroid to move with swallowing**
        - **Retrosternal goiter** occurs because thyroid enlargement is limited upwards, but can grow downwards (because fascia is continuous)
    - Posterior relations
        - Esophagus, trachea, recurrent laryngeal nerves (RLN), carotid sheath





- **Embryology**
  - First endocrine organ to develop
  - Thyroid primordium forms as an pouch in the **floor of primordial pharynx** ("thyroid diverticulum")
  - Continues to develop while descending
  - **Descends down** past hyoid bone (still connected to tongue by thyroglossal duct)
  - Lumen of the thyroid diverticulum obliterates
  - By 7 weeks, the thyroid has assumed final destination
    - Thyroglossal duct degenerates
    - There may be a **pyramidal lobe** (remnant)
    - There may be fibromuscular band to hyoid (remnant)
  - Proximal opening of thyroglossal duct persists in the base of tongue as a pit = **FORAMEN CECUM**
  - Remnant of thyroglossal duct may persist
    - Thyroglossal duct cyst (moves with swallowing too!)
    - Think of this for differential diagnosis (cyst is soft!)
  - Failure of thyroid gland to fully descend
    - Lingual thyroid (most common type)
    - Or anywhere along route of descent



- **Arterial supply**
  - **Superior thyroid artery** ~ STA (at superior pole)
    - **First branch of external carotid artery**
    - Branches into **anterior** and **posterior glandular**
  - **Inferior thyroid artery** ~ ITA (at inferior pole)
    - From **thyrocervical trunk** (arises from **subclavian artery**)
  - Thyroidea ima (sometimes)
    - Arises directly from arch of aorta
  - **Ligation (for thyroidectomy)**
    - Ligate STA near thyroid gland (because superior laryngeal nerve follows STA but then follows superior laryngeal artery away from the thyroid gland)
    - Ligate ITA far from thyroid gland (because RLN comes close and begins to follow ITA near the thyroid gland)
- **Venous drainage**
  - Superior thyroid vein
    - Drains into IJV
  - Middle thyroid vein
    - Drains into IJV
  - Inferior thyroid vein
    - Drains into left brachiocephalic vein
- **Lymph drainage**
  - Prelaryngeal, pretracheal, paratracheal, lower deep cervical lymph nodes
- Innervation: recurrent laryngeal nerves

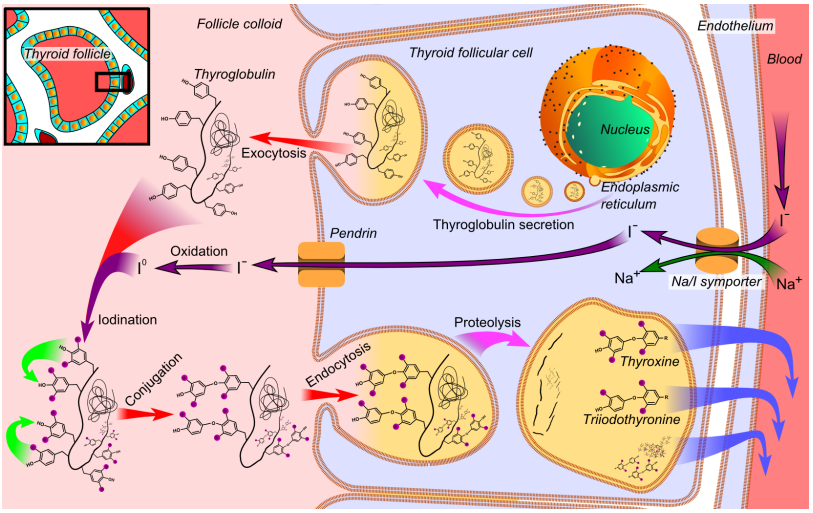
- **Histology**
  - Unique endocrine organ
  - Cells arranged in spherical structures called follicles
  - Single layer of follicular cells surround the follicular lumen:
    - Cells are usually single cuboidal to low-columnar cells
    - Increased activity turns them more columnar
    - Decreased activity turns them more squamous
    - Follicular lumen filled with "**COLLOID**"
      - Thyroglobulin deposit (precursor containing T_3 and T_4)
    - **Thyroglobulin**
      - Iodinated glycoprotein
      - Inactive storage form of thyroid hormones
    - Follicles surrounded by reticular fibers
    - Gland contains connective tissue septa (forming lobules)
    - Thyroid gland has scattered **parafollicular cells**
      - Large, pale-staining, peripherally located
      - Secrete **calcitonin** (**lowers** blood calcium)
  - **Parathyroid gland**
    - Embedded posteriorly in thyroid gland
    - **2 pairs (4 total)**
    - Secretes **PTH**, which **increases** blood calcium levels

PHYSIOLOGY

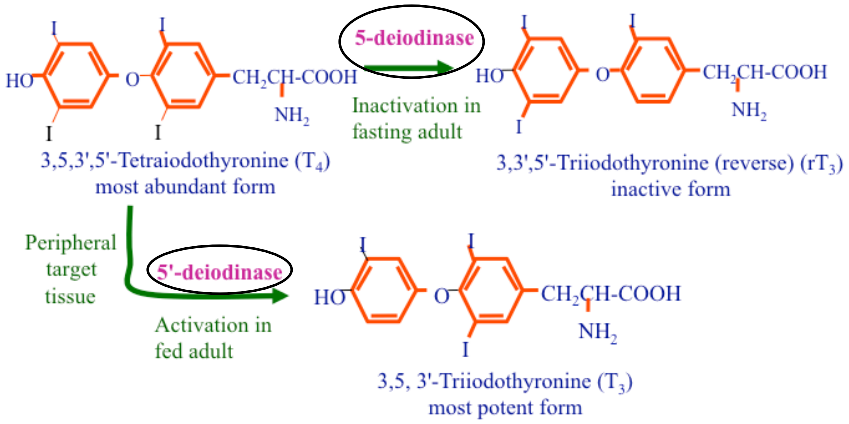
- Thyroid gland
  - Thyroid hormone synthesis
    - **93%** of circulating thyroid hormone → **T_4**
    - **7%** → **T_3** … but more potent and most T_4 is converted to T_3 in peripheral tissues
    - An essential component of thyroid hormone is iodine
      - Present in blood as iodide
      - Ingested iodide is major source
      - Table salt is iodinized to prevent deficiency
    - **Na^+-I^- symporter (NIS)**
      - First step involves **"iodide trapping"**
      - **Na^+-K^+ ATPase pump** provides the concentration gradient required to power NIS (takes Na^+ out)
      - Allows Na^+ and I^- to enter follicular cell
    - **Pendrin**
      - Cl^-/I^- counter-transporter
      - Iodide directly crosses to the other end of the cell
      - There, the iodide is pumped into the colloid (for Cl^-)
    - Follicular cells secrete thyroglobulin into the colloid
      - Glycoprotein (uniodinated when secreted)
      - Contains tyrosine residues

- When I^- is present in the lumen, it undergoes **OXIDATION**:
  - I^- becomes I^0
  - Done by **thyroperoxidase** (and hydrogen peroxidase)
- **ORGANIFICATION & COUPLING:**
  - I^0 is bound to **tyrosine residues** of **thyroglobulin**
  - Done by **thyroperoxidase**
  - Monoiodotyrosine /MIT (if one I^0 binds)
  - Diiodotyrosine / DIT (if two I^0 binds)
  - **MIT + DIT → Triiodothyronine (T_3)** } This is **coupling**!
  - **DIT + DIT → Thyroxine (T_4)**
  - NOTE: MIT, DIT, T_3 and T_4 are **still** bound to thyroglobulin!
  - RT_3 (reverse T_3) = inactive form

- Release of hormones
  - Thyroglobulin with MIT, DIT are **endocytocized** into follicular cells
  - Vesicles containing thyroglobulin interact with **lysosomal proteases**
  - T_3 and T_4 are liberated, while the remaining thyroglobulin is recycled
  - T_3 and T_4 diffuse out to capillaries and into the bloodstream



- Peripheral conversions (T_4 is mostly converted to T_3!)



Estrogen increases liver formation of plasma proteins, including TBG. That's why pregnancy may cause hyperthyroidism

- Transport in bloodstream
  - **99% of T_3 and T_4 are bound** to plasma proteins (liver-made!)
    - **Thyroxine-binding globulin (TBG) ~ mostly this**
    - Thyroxine-binding prealbumin & albumin
- **Hormone activity** (Genomic effect)
  - Binds to a **nuclear receptor** (thyroid-hormone receptor)
  - It forms a **heterodimer** with retinoid X receptor (RXR)
  - Binds to specific thyroid **hormone response element (HRE)** on t promoter region of genes:
    - Motifs recognized = zinc fingers
  - Initiates transcription of certain genes → translation → proteins
  - It does have some non-genomic effects

DNA structural Motifs (special recognized shape):
- Helix-loop-helix
- Helix-turn-helix
- Zinc fingers

- Metabolic Actions
  - Increased BMR
  - Increase no. and activity of mitochondria (for more ATP!)
  - Increases Na^+-K^+ ATPase pump activity
  - Increased O_2 consumption
  - Increased heat (as byproduct)
  - Necessary for brain and body growth in childhood
    - If fetus subjected to hypothyroidism → "Cretinism"
    - Cretinism → mental retardation and low physical growth
  - Stimulates all aspects of carbohydrate metabolism:
    - Increased glycolysis
    - Increased gluconeogenesis
    - Increased GI absorption
    - Increased insulin action
  - Stimulation of fat metabolism
    - Mobilization of lipid from adipose tissue (decrease fat stores)
    - Increased FFA concentration in blood
    - Increased ß-oxidation of FFA
    - Decreases cholesterol by increasing bile acid excretion
    - Increases LDL receptors in liver (lowers blood TAG)
  - Weight loss (but increased appetite)
  - Cardiovascular effects:
    - Increased blood flow
    - Increased cardiac output (COP) due to vasodilation (especially in the skin – for heat elimination)
    - Increased heart rate (sensitive sign for hyperthyroidism)
    - Increased heart strength (just as in exercise and fever)
    - NORMAL mean arterial pressure
      - Systolic BP raises, but diastolic BP drops
  - Increased respiration, increased GI motility
    - Hyperthyroidism → diarrhea / hypo → constipation
  - Stimulates sympathetic nervous system
    - Nervousness, psychoneurotic tendencies, anxiety, sweating
    - Increased ß-receptor actions

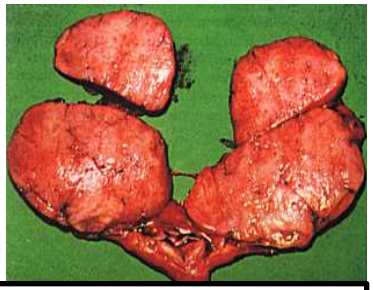
It also increases protein synthesis and catabolism

        - Fine muscle tremors, vigor muscle reactions (muscle weakness results if occurs too much)
    - More TIRED, but CAN'T SLEEP (insomnia)

- **Regulation**
    - **TSH (thyroid-stimulating hormone)**
        - Secreted by **anterior pituitary** in response to TRH stimulation
        - **TRH =** thyrotropin-releasing hormone (**hypothalamus**)
        - **TRH has G_q effect, while TSH has G_s effect**
        - TSH effects include:
            - **Increased proteolysis of thyroglobulin**
            - Increased organification
            - Increased activity of NIS
            - **Increased size and number of follicular cells** (change from cuboidal to low-columnar)
    - Feedback inhibition
        - High thyroid hormone in blood → inhibit TRH and TSH secretion

PATHOLOGY:

- Thyrotoxicosis
    - Hypermetabolic state
    - Can be caused by hyperthyroidism and extrathyroidal sources → **Factitious thyrotoxicosis** (patient takes too much TH medicatio OR **drug induced** thyrotoxicosis (amiodarione)
- Hyperthyroidism
    - Manifestations involve: over-activity of sympathetic NS and hypermetabolic state
    - Flushed skin, heat intolerance, excessive sweating, weight loss, increased appetite, diarrhea, palpitations, tachycardia, nervousness, tremors, irritability, proximal muscle weakness, staring gaze, lid lag, lid retraction, ophthalmology (proptosis and exophthalmos seen in Graves disease)
    - Thyroid storm = abrupt onset of severe hyperthyroidism
        - Seen in Graves disease (acute elevation of catecholamine)
        - Medical emergency (death from arrhythmia may occur)
    - Diagnosis → measure serum TSH (decrease even in subclinical!)
    - **GRAVES DISEASE**
        - **Most common** cause of endogenous hyperthyroidism
        - **Triad of manifestations:**
            - Thyrotoxicosis
            - Infiltrative ophthalmology (exophthalmos)
            - Localized infiltrative dermopathy (pretibial myxedema)
        - **More common in women** (20 – 40 year old)
        - Genetic factors involved: **HLA-DR3** (and CTLA-4)
        - **AUTOIMMUNE DISEASE**



Diffuse, symmetrical enlargement + BEEFY RED SURFACE

- **Auto-antibodies** formed against TSH receptor, but they occupy and over-stimulate the receptor
  - **Thyroid-Stimulating Immunoglobulin (TSI)**
  - Activates G_s (so cAMP raises)
  - Seen in Graves Disease
- Why does the volume of **retro-orbital connective tissue** and extra-ocular muscle increase?

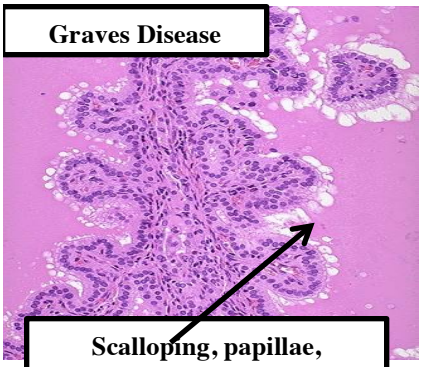
Displace eyeball forward (exophthalmos)

  - Marked infiltration by mononuclear cells (T cells) or "infiltrative ophthalmology"
  - Inflammatory edema and swelling of muscle
  - Accumulation of ECM components (more GAG)
  - Increase no. of adipocytes (fatty infiltration)

GAG = glycosaminoglyca

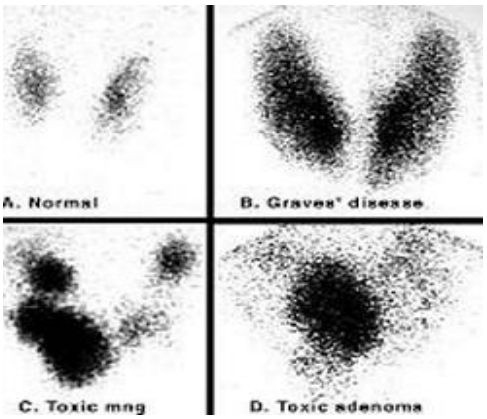
- Morphology:
  - **Diffuse symmetrical goiter**
  - Tall, columnar cells, with possible papillae
  - Pale colloid with **SCALLOPED MARGINS**
  - **Lymphocytic infiltration** (mostly T cell)
- Clinical (special) manifestations:
  - Audible bruit (more blood flow in hyperactive gland)
  - Sympathetic overactivity (staring gaze, lid lag)
  - Exophthalmos
  - Pretibial myxedema (non-pitting edema of shins due to accumulation of GAG [mucopolysaccharide] in tissue)
- High radioiodine uptake (diffuse uptake)

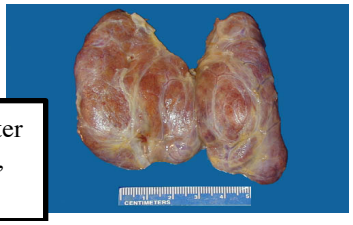
Graves Disease



Scalloping, papillae, columnar cells, lymphocytic infiltration

- Goiter
  - **Goiter is the enlargement of the thyroid gland**
  - May compress adjacent neck structures
  - **Diffuse and multi-nodular goiter**
    - **Iodide deficiency:**
      - Less T_3 and T_4 made (so more TSH and TRH)
      - TSH stimulates thyroid to hypertrophy and hyperplasia
      - **Results in diffuse symmetrical goiter to ensure euthyroid state** (so they have euthyroidism)
      - Can be **endemic goiter** (areas with low iodide in meals)
    - **Sporadic goiter**
      - Idiopathic, or with eating certain vegetables
    - **Most diffuse goiter become multi-nodular goiter**
      - Episodes of hyperplasia and involutions (ups and downs) lead to an irregular enlargement
    - **Toxic multi-nodular goiter (Plummer Syndrome)**
      - Multi-nodular goiter that produces autonomous TH
      - TH production without TSH stimulation
      - Multi-lobulated, asymmetrical enlargement
      - **Radioiodine uptake** shows **patchy uptake** (vs. diffuse uptake in Graves)



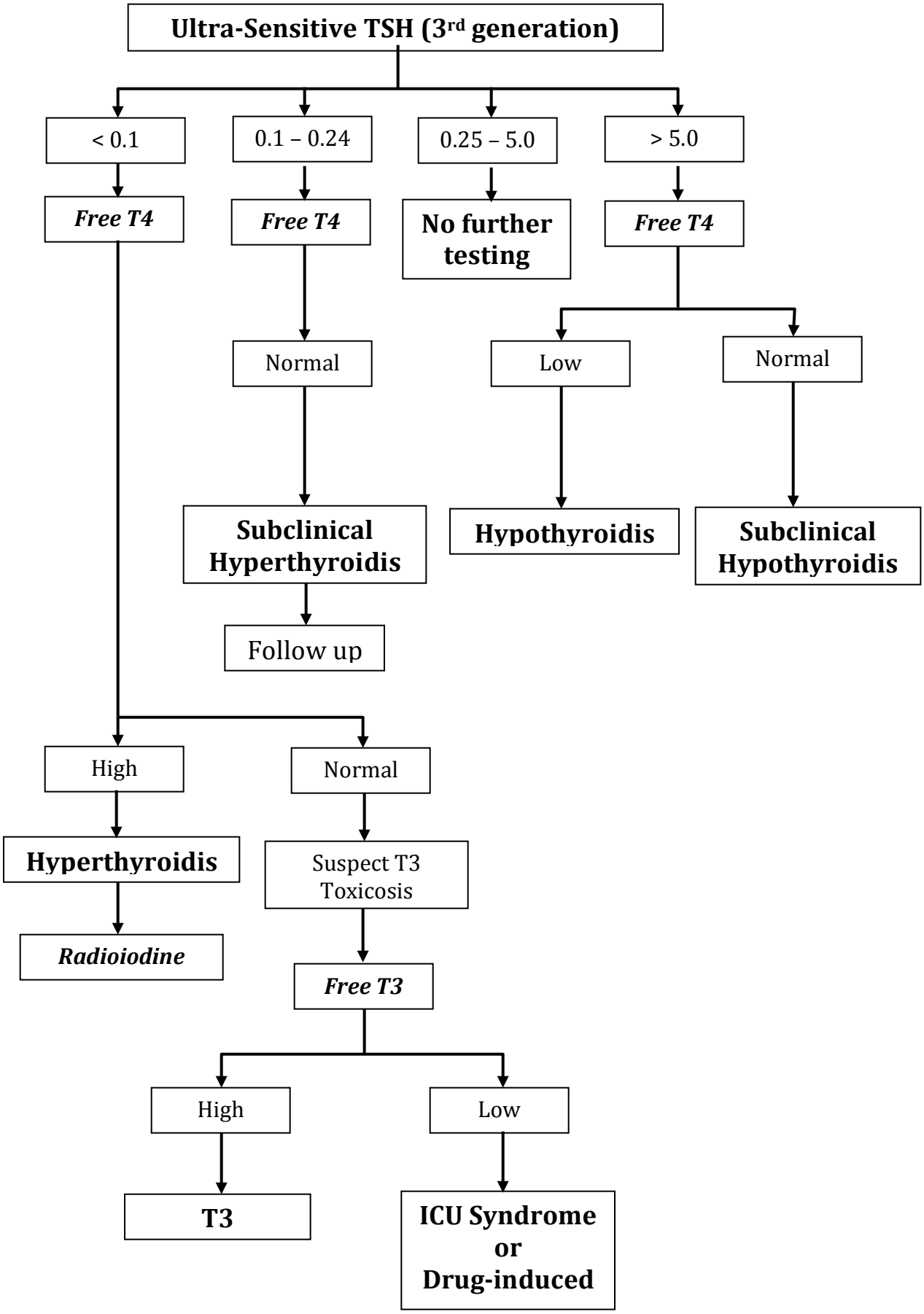


Multi-nodular goiter (multi-lobulated, asymmetric)

- Hypothyroidism (in case you really want to know)
    - Primary causes:
        - Genetic (dysgenesis or dyshormonogenetic goiter)
        - Postablative or after surgery or radioiodine therapy
        - Autoimmune (Hashimoto's thyroiditis)
        - Thyroiditis
        - Iodine deficiency
        - Drug-induced
    - Secondary & tertiary (central) causes:
        - Pituitary failure or hypothalamic failure
    - Thyroiditis
        - Inflammation of thyroid gland
        - Hashimoto's thyroiditis
            - Most common cause of hypothyroidism
            - Thyroid failure after autoimmune destruction
            - Auto-Ab are involved, but destroy gland
            - Mononuclear cell infiltration and fibrosis
            - Eosinophilic, granular follicular cells "Hurthle/oxyphil cells"
            - Possible hashitoxicosis (transient thyrotoxic.)
        - Subacute (de Quervain) Granulomatous Thyroiditis
            - Painful + viral infection involved
        - Subacute lymphocytic thyroiditis (postpartum)
        - Riedel fibrosing thyroiditis
            - Extensive fibrosis affecting adjacent structures

Lab investigations:

- Conditions involved:
    - Hypothyroidism (primary, secondary, tertiary, clinical, subclinical)
    - Hyperthyroidism (primary, clinical, subclinical)
    - Isolated T3 thyrotoxicosis, factitious thyrotoxicosis, drug-induced, iatrogenic (amiodarone, rifampicin, lithium)
    - Pregnancy (can be hyper or hypo)
- Check TSH levels (diagnostic tool)
    - 3^{rd} generation assay sensitivity (0.01 – 0.02 μU/ml) = ULTRASENSITIVE
- Auto-antibodies
    - TPOAb (thyroperoxidase Ab)
    - TgAb (thyroglobulin Ab)
    - TRAb (TSH receptor Ab)
        - LATS, TSI (Thyroid-stimulating IG), TBII (inhibiting)
        - TSI seen in Graves + TPOAb in Graves and Hashimoto's


Ultra-Sensitive TSH (3rd generation)
< 0.1
0.1 – 0.24
0.25 – 5.0
> 5.0
Free T4
Free T4
No further testing
Free T4
Normal
Low
Normal
Subclinical Hyperthyroidis
Hypothyroidis
Subclinical Hypothyroidis
Follow up
High
Normal
Hyperthyroidis
Suspect T3 Toxicosis
Radioiodine
Free T3
High
Low
T3
ICU Syndrome or Drug-induced

PHARMACOLOGY

- Drugs used to treat hyperthyroidism:
  - Thioamides
  - Iodide
  - Radioactive iodine
- Drugs to treat hypothyroidism:
  - Thyroid hormone replacement (thyroxin)
- **Thioamides**
  - **Methimazole (DOC)**
    - Carbimazole is converted to methimazole in vivo
  - **Propylthiouracil (PTU)**
  - Prevent T_3 and T_4 production by inhibiting **thyroperoxidase**
    - **Inhibits oxidation and organification**
  - PTU (and to a lesser extent, methimazole) inhibit peripheral conversion of T_4 to T_3
  - Slow-acting agents (3 – 4 weeks to make a difference)
    - Because they prevent synthesis NOT release
    - This is why we give ß-blockers
  - ß-blockers are given to alleviate pain and symptoms caused by sympathetic overstimulation (tachycardia, sweating, tremors)
  - Why is methimazole DOC?
    - More potent
    - Administered once daily (PTU is given 3 times a day)
    - Less toxic (PTU has black box warning for hepatitis)
  - When to use PTU?
    - Reserved for FIRST TRIMESTER of pregnancy
      - More protein bound, so less readily crosses placenta
    - Thyroid storm (because it is faster acting)
    - Toxicity caused with methimazole
  - ADR:
    - methimazole → Skin allergy (common), agranulocytosis (fatal effect) – call doctor if you feel sick or have sore throat
    - PTU → Hepatotoxic
- **ß – blockers**
  - Reduce symptoms (cardiac manifestations especially)
  - Started immediately with thioamides ("bridge therapy")
  - Possibly inhibits peripheral T_4 to T_3 conversion
- **Iodides** (too much of it can inhibit TH production – **Wolf-Chaikoff effect**)
  - Inhibit peroxidase step, thyroglobulin proteolysis
  - Rarely used now, but used with PTU in thyroid storm
- **Radioiodine therapy** (destruction of gland over course of weeks to months)
  - Used in the U.S.A.!!!!!!!!
  - Contraindicated in pregnancy

Managing Thyroid Storm:
1. PTU
2. Iodide

Managing Graves:
Thioamides + beta blockers
OR
Radioiodine therapy
OR
Surgery (thyroidectomy)

Hyperthyroidism in pregnancy:
PTU first trimester
THEN
Methimazole

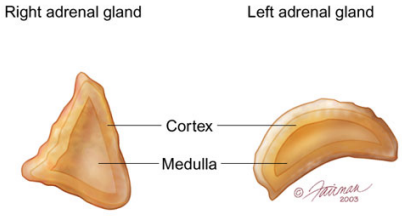
Problem 5: Cushing's Syndrome

Summary of triggers:

PROBLEM A:
A **35-year-old** married woman (she has 3 children) came in feeling depressed because she **gained weight** recently. She looked **obese** with **abnormal facial hair** (hirsutism). Over the last few months she also complained of **absent periods** (amenorrhea), backache, headache and **generalized weakness**. Family history was not significant. BMI was 31.25 kg/m^2 (obese). **BP was raised** (160/100 mm Hg) and she had the following features: **plethoric moon face, acne-like rash, buffalo hump, supraclavicular fat pads, protuberant abdomen, purple striae and bruises + thin extremities with proximal muscle weakness**. **Cushing's syndrome** was suspected. Investigation revealed **raised Hb, total leukocyte count**, PMNs, low lymphocyte count + **raised FBG**. **Hypokalemia** was noted as well as very **high urinary free cortisol (24 hours)…** Plasma cortisol was raised at night and in the morning. **Midnight salivary cortisol** was **raised** too! **Overnight dexamethasone suppression test** and 48 h low dose dexamethasone both showed no suppression of plasma cortisol! Plasma ACTH was undetectable… Abdominal CT scan showed a small mass in the right adrenal gland! She had generalized **reduced bone density**. She was treated by resection (surgical removal) of her **adrenal tumor**… It was an adenoma. She was put on **replacement therapy** with 0.5 mg of dexamethasone and her cortisol was monitored until her **hypothalamo-pituitary-adrenal axis** recovered.

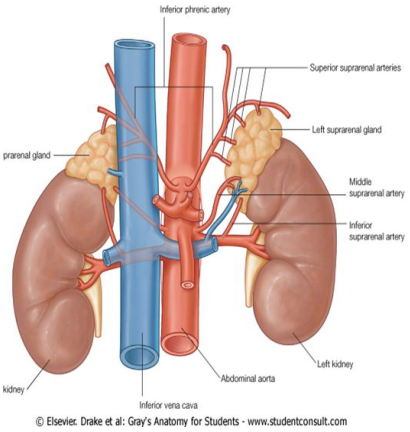
PROBLEM B:
55-year-old woman presented with **weakness, abdominal pain, fever, nausea, vomiting and diarrhea** one day after undergoing an emergency surgery for her auto-immune inflammatory disorder. She had been taking **prednisone** and **stopped it abruptly** without asking her doctor. She looked confused and **dehydrated** + cold extremities. **Raised body temp. and raised pulse with a drop in BP**! Hb was super low and so was her total leukocyte count… Eosinophils were raised! Hyponatremia, hyperkalemia, low bicarbonate (metabolic acidosis?), raised blood urea and **low blood glucose**. ACTH was undetectable and a **synthetic ACTH test (Synacthen test)** revealed low plasma cortisol (no stimulation)… She was diagnosed with **acute adrenal insufficiency** and managed with IV dextrose saline and **IV hydrocortisone**. She recovered and was warned to never stop her prednisone suddenly and she was told to take care if she gets infection, surgery or trauma.

ANATOMY

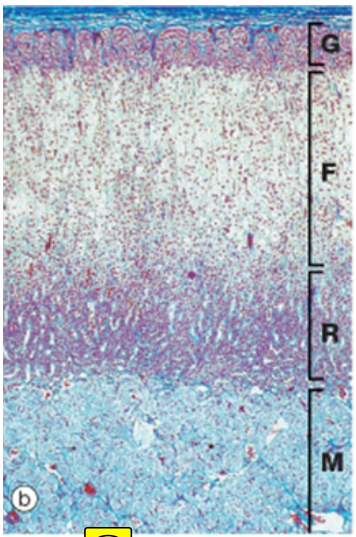


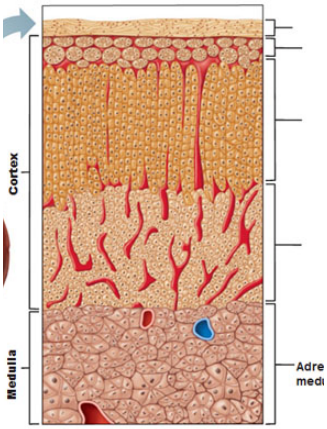
- Suprarenal (adrenal) glands
  - On superior poles of each kidney
  - Capsule + Outer cortex + inner medulla
  - Right adrenal gland → pyramidal in shape
  - Left adrenal gland → semi-lunar (LARGER)
  - Anterior to RIGHT adrenal → part of right lobe of liver + IVC

- Anterior to the LEFT adrenal → part of stomach, pancreas +/- spleen
- Surrounded by perinephric fat and enclosed in renal fascia
    - Thin septum separates each gland from its kidney
- Vasculature:
    - Extensive
    - 3 primary arterial sources:
        - Superior suprarenal arteries (arises from inferior phrenic arteries… Goes from abdominal aorta to diaphragm)
        - Middle suprarenal arteries (arises directly from abdominal aorta)
        - Inferior suprarenal arteries (from renal arteries)
    - Venous drainage:
        - Single vein leaving each gland
        - Right suprarenal vein → IVC
        - Left suprarenal vein → left renal vein → IVC
    - Rich nerve supply from:
        - Celiac plexus
        - Abdominopelvic splanchnic nerves (greater, lesser, least)



- Embryology of the adrenal glands
    - Develops from 2 components:
        - Mesoderm → cortex
        - Ectoderm (neuroectoderm) → medulla
    - 5th week of development:
        - mesothelial cells differentiate to form primitive cortex
        - Second wave of mesothelial cells penetrate to form definitive cortex
        - At the mean time, neural crest cells (originating from sympathetic NS) migrates and invades the medial aspect of the primitive cortex… This gives rise to the adrenal medulla
            - Stain yellow-brown with chrome salts → "CHROMAFFIN CELLS"
- Histology:
    - Outer cortex + inner medulla + thin C.T. capsule
    - There are fenestrated capillaries and large blood vessels in cortex and medulla
    - Adrenal cortex → 3 zonas
        - Zona Glomerulosa
            - Arranged in clumps + constitutes 15%
            - Stains pink (few lipid droplets present)
            - Synthesizes mineralocorticoids (Aldosterone)
        - Zona Fasciculata
            - Middle and WIDEST layer (75%)
            - Arranged in vertical columns or radial plates
            - Appear pale/vacuolated (filled with lipid droplets)
            - Secretes glucocorticoids (cortisol)



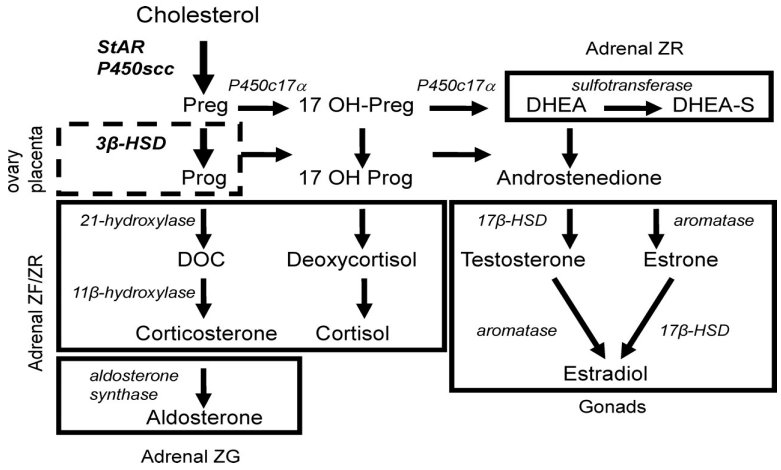


(a)Drawing of the histology of the adrenal cortex and a portion of the adrenal medulla

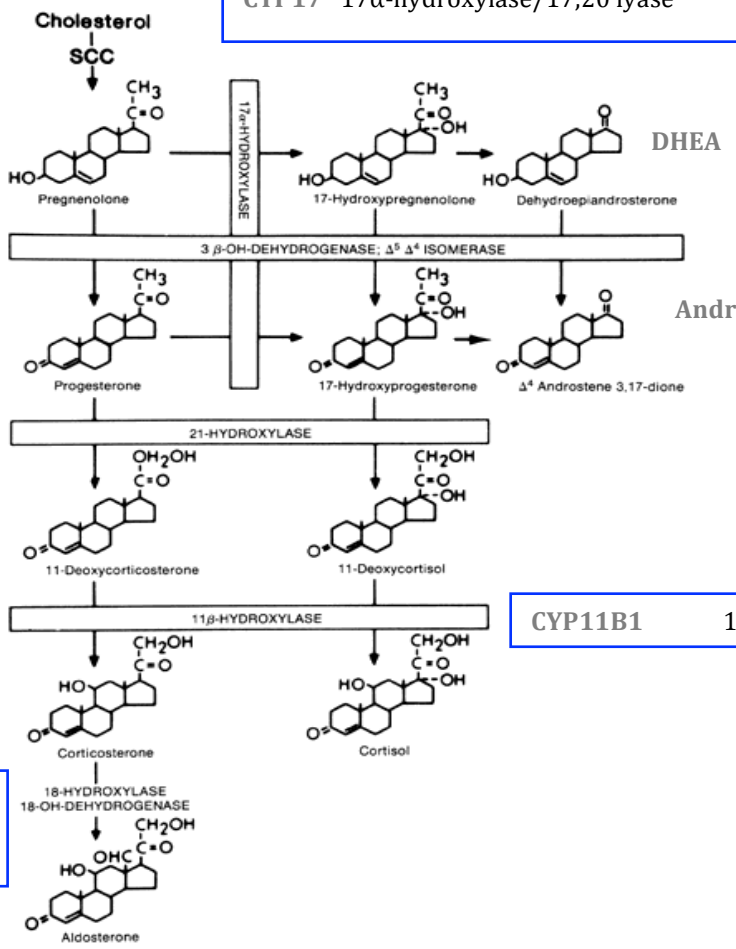
- Zona Reticularis
  - Innermost layer
  - Arranged in cords
  - Mostly produces androgens (DHEA and androstenedione)
  - Some glucocorticoid activity are mentioned
- Adrenal medulla
  - "Modified postganglionic sympathetic neurons"
  - Innervated by preganglionic sympathetic neurons (T10 – L1)
  - Clear cytoplasm and appear yellow-brown
  - Contains CHROMAFFIN CELLS
    - Using potassium bichromate
    - Brown staining of catecholamine granules (E and NE)
  - Secrete epinephrine (mostly) for fight-or-flight response (adrenergic/sympathetic activation)

PHYSIOLOGY

- Steroidogenesis:
  - Adrenocortical hormones → steroids derived from cholesterol
    - Cholesterol either made de novo (by acetate)
    - 80% of the cholesterol used is from LDL and taken up by LDL-receptor mediated endocytosis
    - Once cholesterol enters cortical cells (or other tissues such as the gonads, which produce sex hormones from steroids) → goes to mitochondria
    - To get to the cristae or to the inner membrane of the mitochondria, the required protein is StAR (Steroidogenic acute regulatory protein)
    - Mitochondria contains cytochrome oxidase enzyme system which provides many of its domains to form different steroids (CYP or P450)
    - Rate-limiting step = P450scc or cholesterol side chain cleaving enzyme or *cholesterol desmolase*… This converts cholesterol (27 C) to pregnenolone (21 C) by removing 6 carbons…
    - Reactions takes place in the **rER** and **the mitochondria**



CYP17 17α-hydroxylase/17,20 lyase



3βHSD 3β-hydroxysteroid dehydrogenase

CYP21A2 21-hydroxylase

CYP = Cytochrome oxidase P450
21 = hydroxylase at carbon 21

CYP11B1 11 β-hydroxylase

CYP11B2 Aldosterone synthase
(works on **carbon 18**)
(Hydroxylates 18, then aldehyde 18)

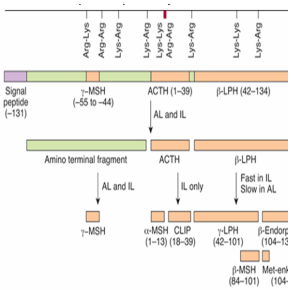
- Mineralocorticoids
  - Aldosterone (very potent, 90%)
  - Deoxycorticosterone (precursor)
  - Corticosterone (precursor)
  - Cortisol and cortisone (slight mineralocorticoid activity)
- Glucocorticoids
  - Cortisol (very potent, 95% of all glucocorticoids)
  - Corticosterone
  - Cortisone (almost at potent as cortisol)
  - Prednisone (synthetic, 4x as potent)
  - Methylprednisone (synthetic, 5x as potent)
  - Dexamethasone (synthetic, 30x as potent)
- 90 – 95% of cortisol is bound to plasma proteins:
  - Cortisol binding globulin (CBG/transcortin)
  - Albumin (lesser extent)
- Functions:
  - Aldosterone:
    - Responds to low blood volume

- Genomic effect (induce Na^+-K^+ ATPase activity in renal tubular cells) ~ slow
- Non-genomic effect (fast)
- Increases renal tubular reabsorption of Na^+ (followed by water) at the expense of K^+ (occurs in principal cells of collecting ducts) and H^+ excretion (occurs in intercalated cells)…
- Aldosterone excess → increase BP due to increased ECF volume and can be followed by pressure natriuresis and diuresis ("aldosterone escape"). [Na^+] not affected that much… since both water and Na^+ reabsorbed… and metabolic alkalosis
- Aldosterone excess → Hypokalemia → muscle weakness (altered electrical excitability of nerves and muscle fibers, prevents normal action potential)
- Aldosterone deficiency → hyperkalemia and metabolic acidosis… Hyperkalemia → arrhythmias and heart failure
- Stimulated by mainly:
    - Increased [K^+]
    - Increased angiotensin II in ECF
- Regulated by renin-angiotensin-aldosterone axis (Recall)

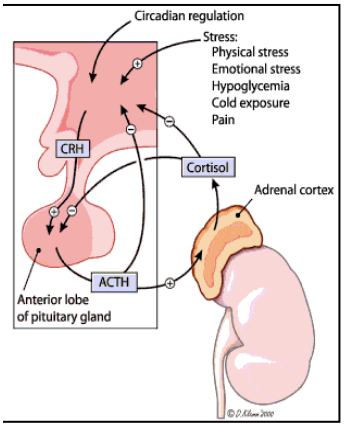
- Glucocorticoids:
    - Cortisol = hydrocortisone
    - Effects on carbohydrate metabolism
        - Stimulates gluconeogenesis
        - Decreased glucose utilization by cells
        - Increases blood glucose conc.
        - Lowers insulin sensitivity in muscles and adipose tissue
    - Effects on protein metabolism
        - Increased protein catabolism
        - Increases liver plasma proteins
        - Increased blood amino acids (enhanced transport into hepatocytes for gluconeo)
    - Effects on fat metabolism
        - Mobilization of FA (in adipose)
        - Enhanced FA oxidation
        - Promote FA utilization for energy (vs. glucose)
        - Redistribution of fat to chest, neck and head leading to buffalo-hump and moon face
        - So, generally, lipolysis and lipogenesis
    - Anti-inflammatory effects of high cortisol levels:
        - Blocks phospholipase A_2
        - Block early stages and causes resolution

Glucocorticoids promote lung maturation in the developing fetus by promoting surfactant production… No surfactant when born → neonatal respiratory distress syndrome. Premature delivery = give glucocorticoids if anticipated…

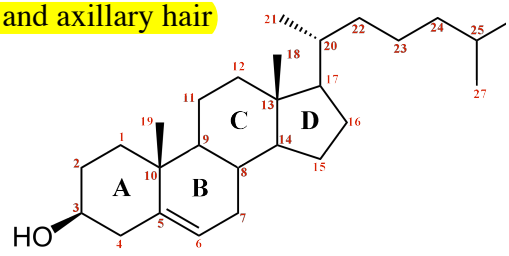
- Cortisol stabilizes lysosomal membranes
- Cortisol decreases capillary permeability
- Cortisol decreases WBC migration
- Cortisol decreases phagocytosis
- Cortisol suppresses T lymphocyte production
- Cortisol suppresses eosinophil count
- Cortisol increases RBC production
- Cortisol attenuates fever (reduces IL-1)



- Cortisol regulation:
  - ACTH (Adrencorticotropin hormone) stimulates secretion
    - Secreted by anterior pituitary in response to CRH
    - CRH = Corticotropin Releasing Hormone
    - ACTH → G_s (uses cAMP to activate protein kinase A, which promotes rate-limiting step of steroidogensis… Desmolase!)
    - ACTH is derived from Propriomelanocortin (POMC)
    - POMC also gives rise to ß-lipotropin and ß-endorphins and MSH
    - POMC → ACTH → α-MSH (melanocyte stimulating hormone)
    - MSH from ACTH is clinically relevant in Addison's Disease



  - Physiological and mental stresses stimulate ACTH release and hence cortisol secretion
  - There is FEEDBACK INHIBITION
  - CRH, ACTH, and CORTISOL show CIRCADIAN RHYTHM
    - High in early morning (logical; you were fasting while asleep)
    - Low at around midnight
- Adrenal androgens
  - DHEA and androstenedione are weak androgens (converted to testosterone, which is strong and found in men)
  - DHEA and androstenedione are important for pubic and axillary hair development in females



BIOCHEMISTRY

- Cholesterol
  - Remember that it contains 27 carbons + 4 rings
  - All steroids contain the same cyclopentanophenanthrene ring
  - Rate-limiting irreversible reaction = cholesterol → pregnenolone
    - Uses cholesterol desmolase (or CH side-chain cleaving enzyme)
    - Removes 6 carbons (from C27 to C21)
    - Byproduct = isocaproaldehyde (useless info, but meh!)
  - Remember: Pregnanes = C21, androgens = 19 C, estrogens = C18
  - Glomerulosa → aldosterone (aldosterone synthase: Hydroxylase at C18)
  - Fasciculata → cortisol and corticosterone
  - Reticularis → DHEA, Androstenedione
  - "As you go deeper, it gets sweeter" or "GFR"

- Mechanism of hormonal action:
  - Binds to intracellular receptors
  - Forms a hormone-receptor complex
  - Enters nucleus and binds to DNA promoter region known as HRE/SRE or hormone/steroid response elements
  - There are DNA structural motifs (ZINC FINGERS)
    - Recurrent DNA sequences recognized by binding proteins
  - Promotes certain gene expression while suppressing others
    - Good question to ask: which genes are suppressed, which are promoted?
    - Good answer: genes for gluconeogenesis and glycogenolysis are promoted, genes for glycolysis and glycogenesis are suppressed!

PATHOLOGY

- Adrenal cortex:
  - Paired endocrine organs consisting of a cortex (G, F, R) and medulla
  - Glucocorticoids (mostly cortisol) → F and kinda R
  - Mineralocorticoids (mostly aldosterone) → G
  - Sex steroids (androgens mainly) → R
- Adrenal medulla:
  - Chromaffin cells (secrete catecholamines, mainly epinephrine)

- Adrenocortical hyperfunction (hyperadrenalism):
  - Cushing's syndrome, hyperaldosteronism, adrenogenital/virilizing syndromes

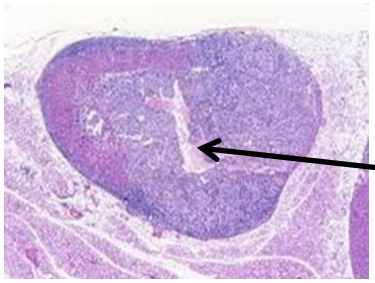
  - Cushing's Syndrome:
    - Any condition causing elevated glucocorticoids in the body
    - Causes can be iatrogenic, endogenous or exogenous
    - Most common cause is iatrogenic (by doctors!)
    - 3 common causes:
      - Primary hypothalamic-pituitary disease → High ACTH
      - Secretion of ectopic ACTH by non-pituitary neoplasms (think small cell carcinoma of the lung)
      - Primary adrenocortical neoplasms (adenoma or carcinoma) and rarely primary cortical hyperplasia
    - VERY IMPORTANT: The first of the 3 causes stated up is called CUSHING DISEASE and is very common.
    - CUSHING DISEASE → HIGH ACTH (pituitary origin) and HIGH CORTISOL
    - CUSHING SYNDROME → HIGH CORTISOL (could be due to problem at the level of adrenal or ectopic secretion)
    - More prevalent in females and in young adulthood (20s and 30s)

- Clinically classified as:
  - ACTH-dependent (Cushing's disease or ectopic secretion)
  - ACTH-independent (iatrogenic or adrenal tumors/hyperplasia)
  - Pseudo-cushing's syndrome (alcoholism, obesity, depression)
- Clinical features:
  - Round face (moon face)
  - Plethora, acne, thinning of scalp hair
  - Hirsutism
  - Weight gain → truncal obesity (lemon-on-sticks appearance), buffalo-hump, supraclavicular fat pads
  - Purple abdominal striae, easy bruising
  - Proximal muscle wasting (protein breakdown) and weakness (think hypokalemia – cortisol is a [weak] mineralocorticoid!!!)
  - Mood disturbances (depression, insomnia, psychosis)
  - Menstrual disturbances (amenorrhea)
  - Hypertension, hyperglycemia, osteoporosis
  - Susceptible to infections, peptic ulcer disease

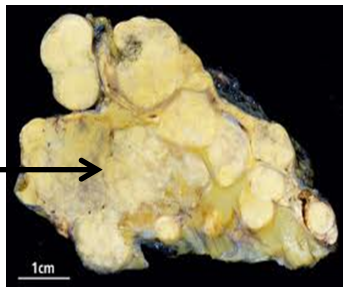
- Diagnosis:
  - Establish hypercortisolism (at least 2):
    - Urinary free (24 hr) cortisol
    - Low dose dexamethasone suppression test
    - Late night salivary cortisol
  - If not responsive to low dose dexamethasone test, perform a high dose dexamethasone test to distinguish between:
    - Cushing's disease (slight suppression of ACTH)
    - Ectopic (paraneoplastic) ACTH (no suppression)

- Primary adrenal neoplasms (ACTH-independent):
  - Adrenal adenoma and carcinoma
  - Primary cortical hyperplasia
  - Most cases = unilateral adrenocortical neoplasm (adenoma)
    - Adenoma = benign, carcinoma = malignant

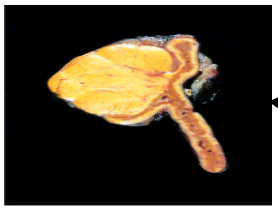
- MORPHOLOGY:
  - Possible changes in the adrenal glands:
    1. Cortical atrophy
    2. Diffuse hyperplasia
    3. Macronodular or micronodular hyperplasia
    4. Adenoma or carcinoma
  - Exogenous GC or iatrogenic → bilateral cortical atrophy
    - Think about it!
    - Basically, adrenal gland feels useless ☹
  - ACTH-dependent → diffuse bilateral hyperplasia
    - Yellowish color
    - Reticularis is thin, lipid poor, outer layer = lipid rich

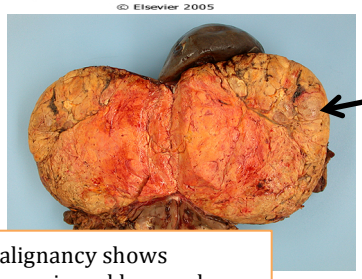


- Micronodular hyperplasia (picture on left)
  - 1 mm - 3 mm
  - Darkly pigmented micronodules
  - Atrophic areas (lipofuscin?)
- Macronodular hyperplasia (picture on right)
  - Prominent nodules, ≤3 cm



- **Adrenocortical tumors:**
  - **Adenomas**
    - ✓ Yellow
    - ✓ **Encapsulated**
    - ✓ Weigh less than 30 g
  - **Carcinomas:**
    - ✓ Large + yellow (≤3 cm)
    - ✓ **Not capsulated**
  - Tumors are **morphologically the same**!!!
  - **Contralateral adrenal gland is usually atrophic!**
  - **Metastasis** can differentiate malignancy





Malignancy shows necrosis and hemorrhage

- **Hyperaldosteronism**
  - **Primary Hyperaldosteronism (Conn Syndrome)**
    - Associated with overproduction + suppression of renin-angiotensin system **(At the level of adrenal gland)**
    - **So low plasma renin**
    - Associated causes:
      - Adrenocortical neoplasm
        - **Aldosterone-producing adenoma** (80%)
      - **Hyperplasia (bilateral nodular)**
  - **Secondary hyperaldosteronism**
    - Release occurs in response to **renin-angiotensin system activation**
    - **So high plasma renin**
    - Associated causes:
      - **low renal perfusion** (renal artery stenosis)
      - Arterial hypovolemia and edema (heart failure, cirrhosis, nephrotic syndrome)
      - Pregnancy (estrogen induced increase of renin-substrates)
  - Effect of aldosterone → Na^+ and water gain, H^+ and K^+ loss
    - Hypervolemia (High BP), metabolic alkalosis and hypokalemia
  - Morphology:
    - Adenomas
      - Solitary, small, well-circumscribed
      - More often in left adrenal gland
      - Lipid-laden cortical cells (G looks like F)
    - Bilateral nodular hyperplasia (explained… G still looks like G!)
  - Clinical hallmark = hypertension!

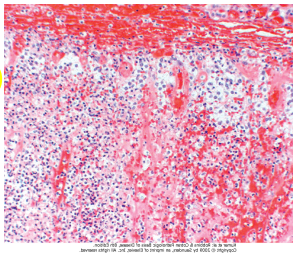
- **Adrenogenital syndromes:**
  - Gonadal androgens regulated by hypothalamo-pituitary-gonadal axis (by LH and FSH)
  - Adrenal androgens regulated by hypothalamo-pituitary-adrenal axis (by ACTH)
  - Adrenocortical neoplasms and Congenital Adrenal Hyperplasias (CAHs)
  - CAHs:
    - Autosomal recessive disorders → defect in enzyme system
    - In all cases, adrenals are producing less cortisol (so **high ACTH**)
    - Therefore, adrenals are **hyperplastic bilaterally** (hence the name!)
    - Most common cause = 21-hydroxylase deficiency (80%?)
    - **21-Hydroxylase deficiency**
      - No mineralocorticoids + no cortisol
      - More androgens → virilizing
        - Precocious puberty in males
        - Clitoral enlargement, hirsutism, oligomenorrhea in females
        - Life-threatening hypotension
        - Salt wasting + hyperkalemia + hypervolemia
    - 11-hydroxylase deficiency
      - Not as severe as 21-hydroxylase
      - You can make weak mineralocorticoids but no cortisol
      - No salt-wasting, no hyperkalemia or hypovolemia
      - But still has classic virilizing symptoms
    - 17 alpha hydroxylase deficiency
      - No cortisol, no sex steroids
      - Too much mineralocorticoids (high BP, etc.)

No cortisol (missing enzyme) → high ACTH → diffuse hyperplasia → Shifted to androgen production (enzyme still missing!)

In all 3 cases, **no cortisol** = **high ATCH** → bilateral **adrenal hyperplasia** (hence, "CAH")

- **Adrenal Insufficiency:**
  - Primary acute adrenal insufficiency
  - Primary chronic adrenal insufficiency (Addison's disease)
  - Secondary adrenal insufficiency
  - **PRIMARY** = problem at the **LEVEL OF ADRENAL GLAND**
  - **SECONDARY** = problem at any other level (pituitary, hypothalamus, exogenous therapy/iatrogenic, etc.)
  - **Inadequate secretion of cortisol +/- aldosterone**;
    - **Primary → whole cortex affected** → cortisol + aldosterone low
    - **Secondary → only F and R affected → only cortisol low**
  - **SECONDARY = MOST COMMON CAUSE**
    - **Rapid withdrawal of glucocorticoid therapy** (most common!!)
    - Pituitary/hypothalamus disease or surgery or removal?
  - PRIMARY ADRENAL INSUFFICIENCY
    - Acute (**Adrenal crisis**) ~ fatal!!!!
      - **Waterhouse-friderichsen syndrome**
        - Compromised, hemorrhagic adrenal gland due to sepsis especially by Neisseria meningitidis

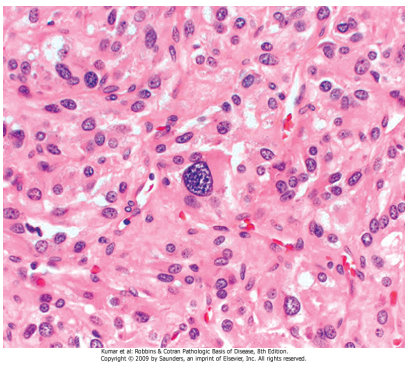
With prolonged glucocorticoid therapy, the adrenals become atrophic because it no longer depends on endogenous secretion. With rapid withdrawal, adrenal insufficiency is eminent!

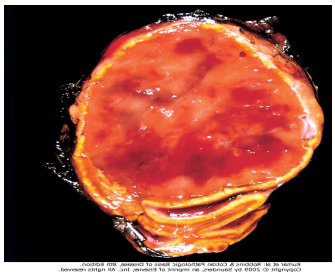


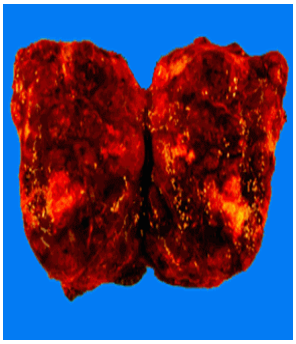
Caseating nodule of adrenal TB!

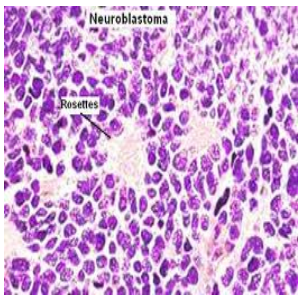
- **Chronic**
  - **Autoimmune adrenalitis** (60 – 70%)
  - Infections (AIDs, TB, fungal)
  - Metastatic neoplasm (breast and lungs)
  - Drugs (ketoconazole, metyrapone – see later)
- Clinical manifestations:
  - Clinical presentation not very specific
    - Nausea, fatigue, vomiting, anorexia, weight loss
    - Generalized weakness, decreased body hair (females)
    - Hyponatremia, hypoglycemia
  - SPECIFICS
    - **Addison's disease (or just primary)**
      - Whole cortex is compromised
      - Low cortisol and aldosterone
      - Hyperkalemia and hypovolemia (shock likely)
      - **Hyperpigmentation (high ACTH)**
  - Diagnostic test: **synthetic ACTH (synacthen) stimulation test**

- Adrenal Medulla:
  - Pathologies:
    - Pheochromocytoma
    - Neuroblastoma
    - Ganglioneuroma
  - **Pheochromocytoma**
    - **"10% tumor"**
      - 10% bilateral, 10% familial (MEN2), 10% malignant
    - Arises from chromaffin cells
    - **Correctable cause of hypertension**
    - Morphology: nests of chromaffin cells = **ZELLBALLEN**
    - Rest of gland suppressed! Necrotic and hemorrhagic.
    - **Urinary VMA** (metabolite of NE and E)
    - Symptoms:
      - **Episodic hypertension**
      - Perspiration (sweating)
      - Palpitations (tachycardia)
      - Pallor
    - **Treatment = surgery (tumor resection)**
      - It may seem intuitive to give a ß-blocker, but:
      - **α-blockade must be achieved** BEFORE giving ß-blocker to prevent hypertensive crisis by surge of catecholamines when taking out tumor!
  - **Neuroblastoma**
    - Most common childhood extracranial solid tumor
    - Small round blue cells and "rosettes"









LAB

- Diagnosis of Cushing's syndrome
  - Cortisol Rhythm
    - Measure plasma cortisol at 8:00 and 23:00
    - If 23:00 cortisol > 50% of 8:00, then positive
    - Interferences = STRESS!!!
  - 24 h Urinary Free Cortisol (UFC)
    - GOLD-STANDARD – high sensitivity and specificity
  - Overnight 1 mg dexamethasone suppression test
    - Give 1 mg orally at 23:00
    - Measure cortisol at 8:00 next morning
    - Normally, cortisol should be depressed
    - Interferences:
      - False +ve: poor absorption, elevated CBG, rapid metabolism
      - False –ve: slow metabolism
  - Liddle I (Low dose dexamethasone suppression test)
    - 0.5 mg qid (4 times a day) for 2 days
    - Collect urine for 24 h on day 2, and check plasma day 3…
    - Differentiate ACTH-dependent from ACTH-independent
    - If cortisol lowers and ACTH lowers = normal
    - ACTH-dependent = ACTH still high (no feedback inhibition)
    - ACTH-independent = ACTH lowers, but cortisol still high
    - If ACTH-independent → do an MRI or CT scan of adrenals
    - If ACTH-dependent, do Liddle II or high dose dexamethasone
  - Liddle II (high dose dexamethasone suppression test)
    - Determine basal cortisol + 2 mg qid for 2 days
    - Check plasma on day 3
    - Used to distinguish Cushing DISEASE and ectopic ACTH secretion
    - If ACTH slightly lowers, then Cushing Disease
    - If not → ectopic (think small cell carcinoma)
  - Synthetic ACTH (synacthen) suppression test
    - Used for adrenal insufficiency
    - Inject ACTH and see if cortisol will raise or not
    - Primary adrenal insufficiency → doesn't really raise
    - Secondary adrenal insufficiency → raises
  - CRH stimulation test (can be used instead of high dose dexameth.)
    - Differentiate Cushing's disease from ectopic ACTH
    - Ectopic ACTH not affected by CRH

PHARMACOLOGY

- Steroid classes (potency comparison relative to cortisol)

Look on next page for the table

Steroid	Potency relative to cortisol
SHORT-ACTING MILD STEROIDS (half life 8 – 12 h)	
Hydrocortisone (DOC) Note: it is cortisol	1
Cortisone	0.8
INTERMEDIATE-ACTING STEROIDS (12 – 18 hours)	
Prednisone (DOC)	4
Prednisolone (DOC)	5
Methylprednisolone	5
Triamcinolone	5
Paramethasone	10
Fluprdnisolone	15
LONG-ACTING STEROIDS (Very potent.. 36 – 54 hours)	
Betamethasone Antenatal lung maturation (surfactant)	25 – 40 (no mineralocorticoid activity)
Dexamethasone	30 (no mineralocorticoid acitivty)
Mineralocorticoids	
Fludrocortisone	-
Desoxycorticosterone acetate	-

- Steroid therapy is indicated in many conditions:
  - SLE, multiple sclerosis, vasculitis
  - Autoimmune disorders (nephrotic syndrome, Crohn's)
  - Blood disorders (leukemia and lymphoma)
    - Due to their lymphocytic suppressive effect
  - Eye disorders (uveitis, conjunctivitis, optic neuritis)
  - **Bronchial asthma (inhaled steroids – beclomethasone)**
  - Allergic rhinitis, eczema, allergy from bee and drugs
  - Adrenal insufficiency
  - **Lung maturation in pre-term babies (betamethasone)**
  - CAHs, organ transplantation, sarcoidosis, SO MANY THINGS!!!
- Remember, people on therapy need a higher dose when stress has been encountered… You need more cortisol when you're failing your exam.
- Steroid toxicity = osteoporosis, growth retardation in children (affects GH) + muscle wasting + striae + hirsutism and so on (CUSHING!!)

- **DOSE-TAPERING** (NOT rapid withdrawal!)
  - Negative feedback altered with exogenous steroids (adrenals are not working properly)… Tapering is **needed to recover the hypothalamo-pituitary-adrenal axis** or else **SHOCK** is eminent.
  - Required if steroid therapy **EXCEEDS TWO WEEKS**!!
- **Alternate-day therapy** is good too (one day yes one day no)

- **Steroid inhibitors:**
  - **Ketoconazole (DOC):** antifungal drug, inhibitor of P450 enzyme
  - **Metyrapone:** selective 11 hydroxylase inhibitor (treat cushing and diagnosis of adrenal insufficiency)
  - **Mifepristone** (RU-486): anti-progesterone (induces abortion), glucocorticoid receptor antagonist
- For adrenal insufficiency:
  - Start with hydrocortisone, then while it's being tapered, give fludrocortisone
- For cushing's disease:
  - trans-sphenoidal surgery (remove tumor in pituitary)
  - Or radiotherapy
  - Steroid inhibitors
  - If all else fails, do adrenalectomy
    - May cause Nelson's syndrome:
      - Removing adrenal causes hyperplasia/adenoma of pituitary gland
      - Too much ACTH → hyperpigmentation
- For cushing's syndrome: Adrenalectomy (unilateral or bilateral) + medical therapy with glucocorticoids and mineralocorticoids

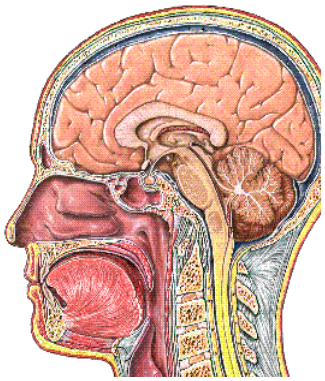
Problem 6: Pituitary Adenoma

Summary of triggers:

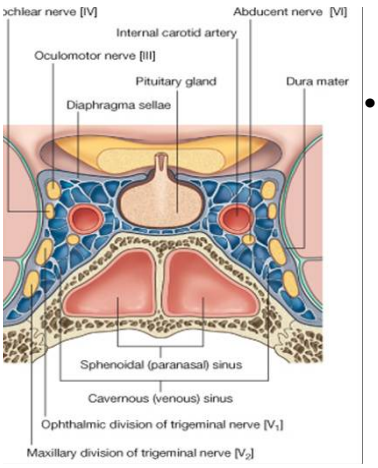
An 18-year-old boy complained of **recurrent headaches** and increased urination (**polyuria**) – about 10 times a day and 5 times a night – over the past two years. He was also thirsty (**polydipsia**) and drinks a lot of water. He **hasn't developed facial hair or a deep voice** like all of his friends. He does bodybuilding but his muscle didn't really grow. He had no interest in sex (**loss of libido**) and isn't able to get an erection. At the age of 14, he describes that he felt he ***stopped growing*** (**he's short**!). He felt generally tired and depressed. His **skin was pale and cold**, with **a low pulse** (56/min), BP (110/70 mmHg), respiratory rate (10/min). Oral temperature was 36 C, height 145 cm and weight 60 kg. Thyroid gland not palpable and **genitalia Tanner stage III**. Urinalysis negative except for **low specific gravity**. **Hormonal assays** revealed **low TSH, fT_3, fT_4, FSH, LH, testosterone, GH (fasting), IGF-1, ACTH** and **cortisol + raised prolactin.** This all indicated multiple anterior pituitary hormone deficiencies. He was treated for his adrenal insufficiency and he did a **water deprivation test**. 8 hours water deprivation made his plasma osmolality increase and urine osmolality to decrease (ADH should work and prevent this dehydration). After **desmopressin** was given, his plasma osmolality decreased and urine osmolality increased phenomenally. Serum **arginine vasopressin** (AVP or ADH!) at 8 hours was undetectable… **MRI scan** revealed a large **sellar mass** with **supra-sellar extension**, consistent with pituitary tumor. It was a **craniopharyngioma.**

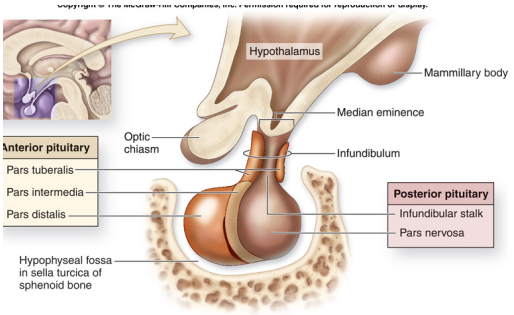
ANATOMY:

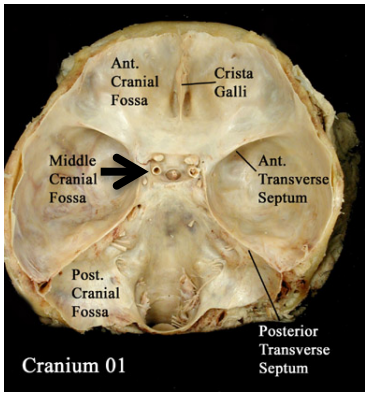
- Pituitary Gland



- Pituitary gland = **hypophysis cerebri**
- **Anterior pituitary gland = adenohypophysis**
- **Posterior pituitary gland = neurohypophysis**
- 500 – 900 grams
- Clearly seen on sagittal section or head
- Lies within depression of the **sphenoid bone** known as the **sella turcica** or **hypophyseal fossa**
    - This can be seen on a lateral X-Ray
- **Posterior relation = mammillary body**
- **Anterior-superior relation = optic chiasma**
    - Optic nerves from the eyes cross each other here
    - Any abnormal growth of pituitary can compress this causing disturbances on the lateral visual fields (bitemporal hemanopia)
- **Lateral relations = cavernous sinuses**
    - Contains the **internal carotid arteries** on either side
    - With **cranial nerves 3, 4, 5 (V_1, V_2) and 6…**
        - Cranial nerve III = oculomotor
        - Cranial nerve IV = trochlear nerve

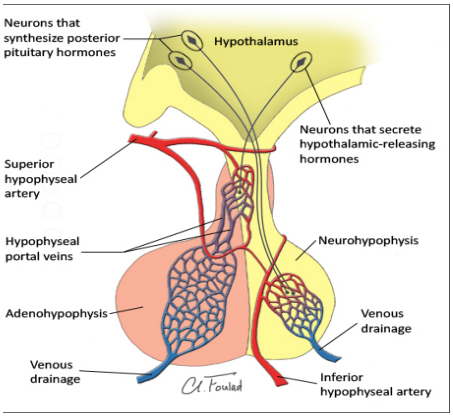




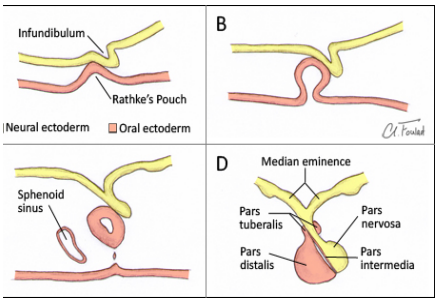


- Cranial nerve V = trigeminal
  - V_1 = ophthalmic
  - V_2 = maxillary
- Cranial nerve VI = abducent
  - **Lies next to internal carotid**

- **Inferior relation = sphenoidal air sinuses**
- It lies within the **MIDDLE CRANIAL FOSSA**
- **Diaphragm sellae**
  - Fold of Dura matter
  - Separates brain and meninges from sphenoid bone
  - **Has an opening to allow the infundibular stalk to pass**
  - Some say it surrounds the sella turcica (in the demo, it was said that "*Dura mater*"does this)
- **Adenohypophysis:**
  - **Pars distalis** (biggest part)
  - **Pars tuberalis** (on stalk)
  - **Pars intermedia** (middle)
- Neurohypophysis:
  - **Median eminence** (lowest point of hypothalamus)
  - **Infundibulum** (infundibular stalk)
  - **Pars nervosa** (biggest part)
- The **neurohypophysis** is connected to the hypothalamus by the **hypothalamo-hypophyseal tract**
- **Neuronal axons** from the **paraventricular** and **supraoptic nuclei** of the **hypothalamus** travel in the tract and terminate in the **neurohypophysis** as dilated terminals known as **HERRING BODIES**
- **Arterial supply:**



  - **Superior hypophyseal artery**
    - Branches of the **internal carotid artery**
    - Supply infundibulum and adenohypophysis
    - Forms **primary capillary plexus** near the hypothalamus and stalk (**fenestrated**)
    - Forms a **secondary capillary plexus** in pars distalis of adenohypophysis (**fenestrated**)
    - Both plexuses are connected by venules ("**Hypophyseal portal system"**)
      - Hypothalamus communicates with adenohypophysis thru this portal system
  - **Inferior hypophyseal artery**
    - Branches of the **internal carotid artery**
    - Supplies neurohypophysis
- **Venous drainage:**
  - **Hypophyseal veins**
    - Drains into **cavernous sinuses**



- **Embryology:**
  - Both adeno and neurohypophysis **arise from ectoderm**
  - **Neurohypophysis**
    - Derived from **neuroectoderm**
    - Neuronal tissue
    - Develops from **down-growth** of **floor of diencephalon**
    - Contains glial-like cells called **pituicytes**
    - Axons and their terminals are found here
    - The dilated terminal endings storing hormones produced by the hypothalamus are called herring bodies
  - **Adenohypophysis**
    - Derives from **oral ectoderm** (surface epithelium)
    - Develops from **up-growth** of **roof of stomodeum**
    - Developing up-growth becomes **Rathke's pouch**
    - Detaches from floor of mouth and meets with down-growth
    - Surrounds down-growth and becomes adenohypophysis
    - **Remnants** of Rathke's pouch → **craniopharyngioma**
    - Pars intermedia → rudimentary remnant of rathke's pouch
- Histology:
  - Using immunocytochemical techniques
  - **ADENOHYPOPHYSIS**:
    - No direct neuronal communication with brain
    - Contains hormone-producing cells
    - Hypothalamus synthesizes activating and inhibiting factors
    - These "factors" travel through the portal system to adenohypophysis to stimulate/inhibit their cells
    - **Chromophobes**
      - Pale
      - Not very defined
    - **Chromophils**
      - **Acidophils** (reddish staining)
        - ✓ Somatotrophs (GH)
        - ✓ Mammotrophs (Prolactin)
      - **Basophils (bluish staining)**
        - ✓ Gonadotrophs (FSH, LH)
        - ✓ Thyrotrophs (TSH)
        - ✓ Corticotrophs (ACTH, ß-lipotropin, MSH)
  - NEUROHYPOPHYSIS:
    - Direct connection to the brain
    - Contains **NO hormone-producing cells**
    - Magnocellular neuronal nuclei **produce hormones in the hypothalamus:**
      - **Supraoptic nuclei** (mostly gives ADH)
      - **Paraventricular nuclei** (mostly gives oxytocin)
    - The hormones bind to glycoprotein **NEUROPHYSIN**

        - These hormones are then transported in the neuron's unmyelinated axons down the infundibular stalk (through the "**hypothalamo-hypophyseal tract**")
        - They are stored in **herring bodies** in the neurohypophysis until needed
        - **Pituicytes**: glial-like supportive cells
    - Extra info:
        - Pars intermedia contains colloid-filled vesicles 😐

PHYSIOLOGY

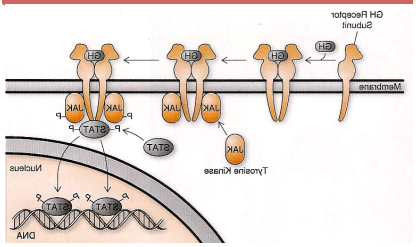
- The **hormones** secreted by the pituitary gland:
    - **Anterior Pituitary** (adenohypophysis):
        - Growth Hormone (GH)
        - Adrenocorticotropic Hormone (ACTH)
        - Thyroid-Stimulating Hormone (TSH)
        - Prolactin (PRL)
        - Follicle Stimulating Hormone (FSH)
        - Luteinizing Hormone (LH)
    - **Posterior Pituitary** (neurohypophysis):
        - Antidiuretic Hormone (ADH) or Arginine Vasopressin (AVP)
        - Oxytocin
- **Cells of the adenohypophysis:**
    - **Acidophils**:
        - **Somatotropes** (hGH – human growth hormone)
        - **Lactotropes**/mammotropes (PRL)
    - **Basophils:**
        - **Corticotropes** (ACTH)
        - **Thyrotropes** (TSH)
        - **Gonadotropes** (LH and FSH)
    - **30 – 40% = Somatotropes** (most abundant)
    - 20% = ACTH
    - Activating & inhibiting factors produced in hypothalamus
    - Transported to anterior pituitary through portal system
    - Example: pulsatile GnRH release (by arcuate nuclei of hypothalamus) → increased LH and FSH production & release from anterior pituitary
- **Neurohypophysis:**
    - Contains pituicytes and neuronal terminal endings
    - Storage of ADH and Oxytocin in these terminal endings
    - Secreted only when needed
    - Magnocellular neuron nuclei produce ADH and oxytocin:
        - **Paraventricular nuclei (mostly oxytocin)**
        - **Supraoptic nuclei (mostly ADH)**
    - Axons reach down to neurohypophysis thru **hypothalamo-hypophyseal tract**

To remember which nuclei produces which hormone mostly, think **"an O for each"**:
SupraOptic → ADH
Paraventricular → Oxytocin

TRH stimulates lactotropes;
(TRH stimulates prolactin)
So, hypothyroidism may cause hyperprolactinemia
Other factors: serotonin,

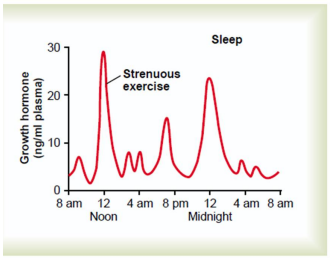
- Releasing and inhibitory hormones/factors:
  - Thyrotropin-releasing hormone (TRH)
  - Corticotropin-releasing hormone (CRH)
  - Growth hormone-releasing hormone (GHRH)
  - Growth hormone-inhibiting hormone (***Somatostatin***)
  - Gonadotropin-releasing hormone (GnRH)
  - Prolactin-inhibitory hormone (PIH) or ***Dopamine***
    - Prolactin is naturally suppressed
    - So without suppression, it'd be made in abundance

GH (and PRL) receptors:
They are **Receptor-associated tyrosine kinases** (**JAK/STAT pathway**)… "Janus Kinase"
GH binds to receptor, and another receptor joins and dimerize. JAK comes in and phosphorylates STAT. STAT-P has genomic activity.



- **Physiological functions of Growth Hormone**
  - Exerts its effect directly on almost all body tissue
  - Small protein molecule (single chain)
  - **Increases rate of protein synthesis in most body cells**
    - Enhances a.a. transport thru into cells
    - Enhanced RNA translation → proteins
    - Increased nuclear transcription of DNA
    - Decreased catabolism of protein and a.a.
  - **Increases FA mobilization from adipose tissue**
    - **Promoting FA use for energy**, not glucose
    - Enhances FA conversion to acetyl CoA (Krebs!)
    - Protein anabolic effect + fat utilization → INCREASED LEAN BODY MASS!
    - Ketogenic effect (high FA = high acetyl CoA = high ketogenesis)
  - **Reduces rate of glucose utilization:**
    - Reduced glucose uptake in skeletal muscle and adipose
    - Increased glucose production by liver (gluconeogenesis)
    - Increases insulin secretion
    - **INSULIN RESISTANCE!** (basically, a lot of insulin, but insulin carbohydrate-anabolic effect is lost!)
    - **GH = "DIABETOGENIC"**
    - But btw, without a pancreas, GH doesn't work 😐
      - ➢ So insulin is important… -_-
  - **GH stimulates cartilage and bone growth**
    - Increased deposition of protein in bone
    - Increased rate of reproduction of chondrocytes and osteogenic cells
    - Specific effect of converting chondrocytes into osteogenic cells
    - 2 principal mechanism of bone growth:
      - ➢ GH stimulates epiphyseal plate bone formation
      - ➢ GH stimulates osteoblasts activity vs. osteoclasts
  - Most of the effect of GH is done through **SOMATOMEDINS**
    - **Insulin-like growth factor** (**IGF-1**, especially)
    - Produced and released by **liver** in response to GH
    - Very potent substance that also has great effect on bone growth
    - Prolonged action and long half-life!

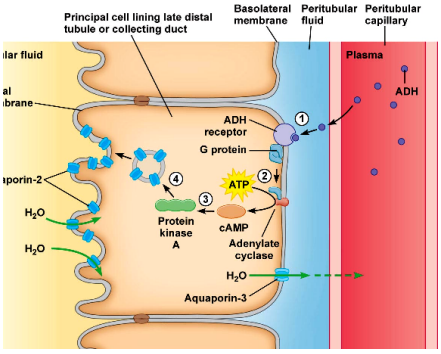
cAMP (G_s)	FSH, LH, ACTH, TSH, **CRH**, **ADH(V_2)**, **GHRH**, glucagon
IP_3 (G_q)	**GnRH**, **oxytocin**, ADH (V_1), **TRH**, Angiotensin II
Tyrosine Kinase	Insulin, IGF-1
Receptor-associated tyrosine kinase	**PRL**, **GH**, cytokines (JAK-STAT!)
Steroid receptor	Estrogen, testosterone, T_3/T_4, cortisol, aldosterone, progesterone



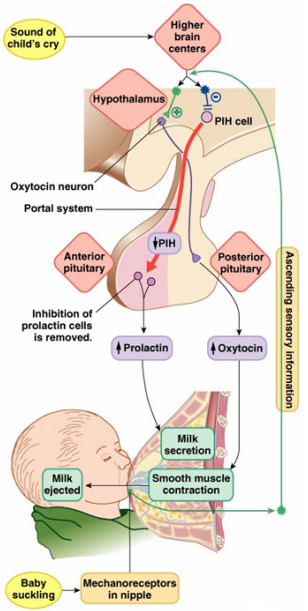
- **Regulation of GH secretion:**
  - High in childhood and during adolescence then drops in adulthood
  - GH secretion is **PULSATILE**
  - **Increases in** the first two hours of **DEEP SLEEP** (NOT REM!)
  - Several factors **stimulate secretion**:
    - **Starvation** (especially protein deficiency)
    - **Hypoglycemia** (or low FFA)
    - **Exercise**
    - Excitement
    - Trauma
    - **Ghrelin** (stomach secretion before meals… HUNGER)
  - **Somatostatin** inhibits GH release by adenohypophysis
  - GHRH stimulates release of GH
    - Uses G_s (cAMP) NOT G_q
  - GH can stimulate prolactin receptors (opposite is not true)
  - GH binds to **GH binding protein (GHBP)** – which is a **fragment of the GH receptor**

- **Neurohypophysis and physiology of oxytocin and ADH:**
  - Oxytocin and ADH produced by hypothalamus (We discussed this)
  - Transported down axon and binds to **NEUROPHYSIN**
  - ADH and Oxytocin differ from each other by just 2 amino acids
  - **ADH/AVP:**

Remember:
Aldosterone → responds to **low ECF volume**
ADH → responds to **high ECF osmolarity**



    - **Responds to high ECF osmolarity**
    - Causes **water reabsorption** in collecting ducts
    - This leads to a **concentrated urine**
    - In high amounts → **vasoconstriction** (hence, VASOpressin)
    - Receptors = V_1 (V_{1A} and V_{1B}) and V_2
      - V_1 is found in arterioles and arteries (vasoconstrictive)
      - **V_2** is found in **principal cells** of **collecting duct**
    - ADH action on V_2 receptor = G_s (cAMP → PKA)
      - **Increases AQUAPORINS**
      - Aquaporins selective allow water reabsorption
  - **Oxytocin:**
    - 1 known role: **milk ejection**
    - 1 semi-known role: labor **contractions**
    - Milk-let down/ milk ejection method:
      - Suckling of nipple stimulates sensory neurons
      - Hypothalamus promotes oxytocin release by posterior pituitary
      - Oxytocin stimulates **contraction of myoepithelial cells**
      - Myoepithelial cells of breast surround alveoli of mammary gland → contraction → milk into duct
      - NOTE: PRL causes milk production
      - MILK FOR DA BABY!



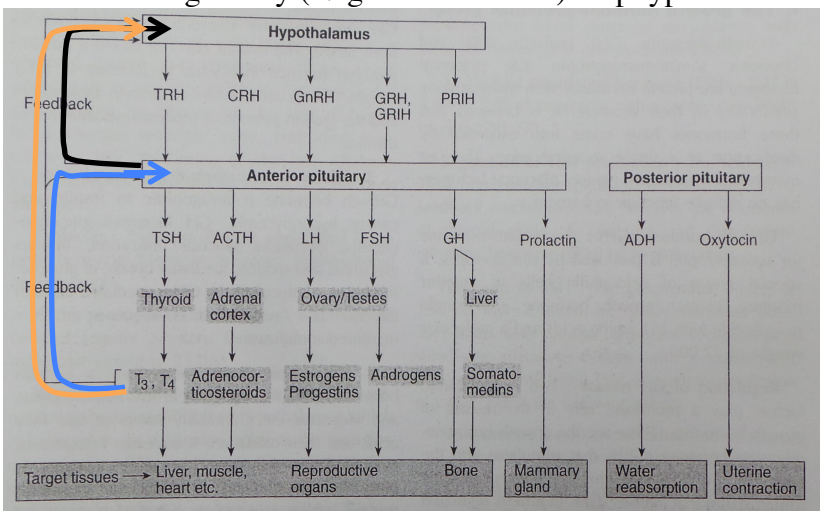
BIOCHEMISTRY

- Already discussed throughout
- Extra info: Regulatory (Negative Feedback) loop types

Ultra-short loop

Short loop

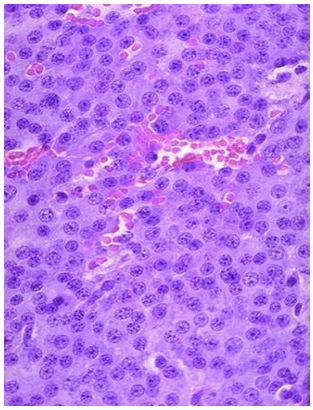
Long loop



PATHOLOGY

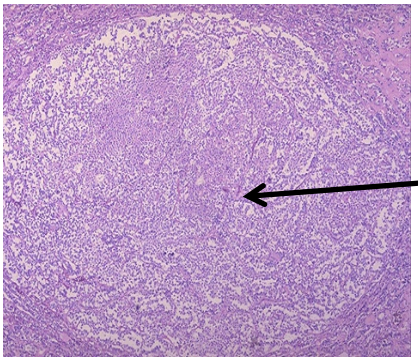
Pituitary gland disorders

- **Hyperpituitarism**
  - Need I say increased secretion of pituitary hormones is expected?
  - Causes:
    - Functional adenoma
    - Hyperplasia
    - Carcinomas
    - Ectopic hormone production (think small cell lung carcinoma)
  - **Pituitary adenomas**
    - Common features:
      - **Almost always benign**
      - Functional or non-functional (Based on clinical manifestations)
      - **Mass effect (pressure effect)**
        - Optic chiasm affected → bitemporal hemianopia
        - Adjacent pituitary cells → hyposecretion (or hypersecretion of prolactin)
      - 5% inherited
      - 25% incidental
      - 3% MEN1 and GNAS-I mutation (unopposed cAMP)
    - Morphology:
      - Gross:
        - **Well circumscribed**
        - Sparse reticulin and cellular monomorphism (hallmarks)
        - Hemorrhage and necrosis
        - Monomorphism, uniform homogenous cells



- Arranged in cords, sheets or papillae (NOT ACINAR)
- **Pituitary apoplexy**
  - Acute hemorrhage into adenoma
  - Rapid enlargement
  - Depressed consciousness and seizures → fatal
- **Sheehan Syndrome**
  - During pregnancy, pituitary gland grows
  - Blood supply to the gland does not
  - **Postpartum hemorrhaging** can lower blood supply to pituitary
  - **Postpartum ischemic necrosis** of pituitary gland

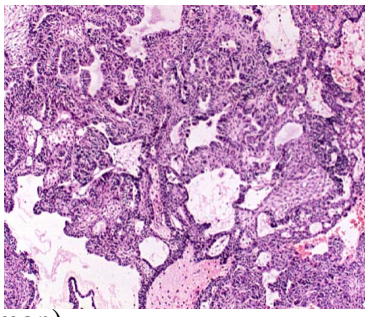
- Clinical features of pituitary adenoma:
  - Symptoms of hormones overproduced
    - Prolactin in women: galactorrhea and amenorrhea
    - Prolactin in men: loss of libido and infertility
  - **Visual field abnormality** (due to **optic chiasm** compression)
    - **Bitemporal hemianopia**
  - Increased cranial pressure symptoms (headaches, vomiting)
  - Seizures and obstructive hydrocephalus
  - Cranial nerve palsy
  - Hypopituitarism (due to mass effect destroying cells)
- **Classifications:**
  - **Based on CELL STAINING:**
    - Chromophobe
    - Chromophil (acidophil, basophilic)
  - **Based on SIZE:**
    - Microadenoma (< 1 cm)
    - Macroadenoma (> 1 cm)
  - **Based on FUNCTIONALITY:**
    - Functional (hormone symptoms)
    - Non-functional (mass effect, no hormone symptoms)

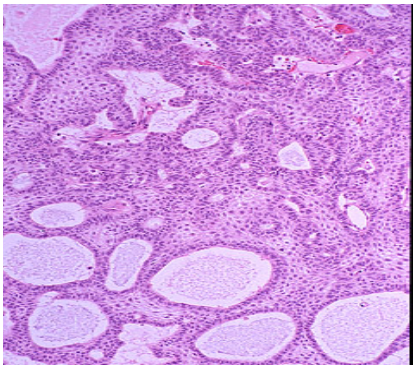


- TYPES:
  - **Prolactinoma** (**MOST COMMON** – 30%)
  - GH adenoma (second most common)
  - Corticotroph cell adenoma (think Nelson's syndrome)
  - Other cell types: gonadotropes, TSH, carcinoma (all rare)
  - **Null cell adenoma** (just mass effect)
  - **MIXED: usually GH and PRL** ("acidophilic adenoma")

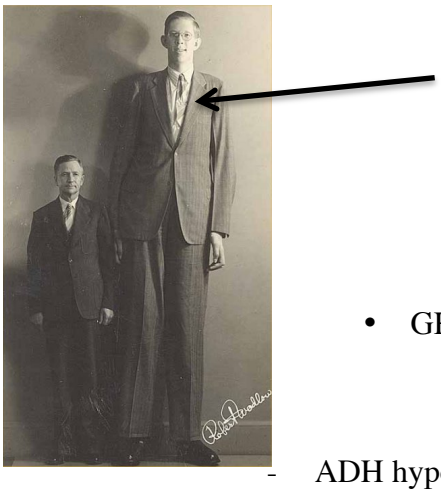
- **Hypopituitarism:**
  - Symptoms if > 75% of gland destroyed
  - **Ischemic necrosis** → seen in Sheehan syndrome
  - **Hemorrhagic necrosis** → pituitary apoplexy
  - **Ablation** (surgery or radiation)
  - **Pressure/mass effect** (by non-functional or null tumors)

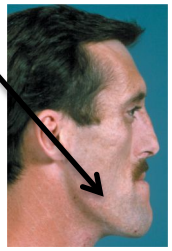
- Stalk effect (mass affect on infundibulum, preventing dopamine from reaching pituitary → hyperprolactinemia)
- **Empty Sella syndrome** (no pituitary gland develops)
- Inflammation (sarcoidosis or infection by TB)
- **Craniopharyngioma**
    - **Remnants of Rathke's pouch**
    - Mass effect and hypopituitarism results
    - Expect visual disturbances, compression symptoms
    - Benign and slow-growing
    - Affects neurohypophysis (*diabetes insipidus* is common)
    - **Sellar or Supra-sellar masses**
    - Cyst (contains **cholesterol crystals** and clefts)
    - **Sqamous epithelium** in **nests** or cords (keratin layers)
    - Oily fluid surrounded by squamoid and columnar cells
    - GROSS APPEARANCE: "**Motor oil**"
    - Arranged in sheets, papillae or cords





- GH hypersecretion and hyposecretion:
    - GH excess
        - Before closure of epiphyseal plates during puberty (so during **childhood**) → **GIGANTISM**
            - **Diabetic + giant** (very tall)
        - After closure of epiphyseal plates during puberty (so during **adulthood**) → **ACROMEGALY**
            - Only soft tissue grow + protruding jaw bone (prognathism), protruding supraorbital ridges, large hands, feet, nose
            - Have kyphosis and enlarged organs
    - GH deficiency
        - Dwarfism (there are many types)
            - Short stature and proportionate





- ADH hypersecretion and hyposecretion:
    - **Syndrome of Inappropriate ADH (SIADH) – (HIGH ADH)**
        - Can be **ectopic** (think small cell lung carcinoma) – **most common**
        - Or can be caused by hypothalamic/pituitary injury
        - Hyponatremia, neurological dysfunction and cerebral edema
        - Blood volume is maintained through other mechanisms
    - **Central Diabetes Insipidus (LOW ADH)**
        - Central → hypothalamic/pituitary hyposecretion
        - Nephrogenic diabetes insipidus → kidney doesn't respond to ADH
        - Polyuria, thirst, dilute urine with low specific gravity
        - Seen with craniopharyngioma or head trauma, neoplasms, surgery..

PHARMACOLOGY

- MRI should be done when suspecting pituitary pathology
- Surgery can be done (trans-sphenoidal surgery)
- *Hypopituitarism*
    - Replace cortisol (very important, essential for life)
        - Remember, cortisol stimulates gluconeogenesis during fasting
        - Remember, without cortisol → shock!
    - Replace other hormones if low (T_4, GH, ADH, testosterone [male], estrogen [female], and LH/FSH if fertility is desired)
    - GH deficiency → give somatotropin (DOC)
    - **ADH deficiency** → ADH agonist **(Desmopressin = DOC)**
        - Desmopressin is like vasopressin without vascular effects
        - Desmopressin can be given IV, oral, subcutaneous and nasally
        - Vasopressin is 2nd line, but has vascular effect + only IM, IV
        - Vasopressin is contraindicated in HTN and CAD
- *Hyperpituitarism*
    - Highly specific depending on tumor:
    - **Prolactinomas:**
        - **Dopamine agonists** are DOC (**Bromocriptine and Cabergoline**)
            - Digital vasospasms and hallucinations
    - **Acromegaly:**
        - **Somatostatin analogs** are DOC **(Octreotide)**
            - Major ADR = GIT distress
        - **GH receptor antagonists** 2nd line **(Pegvisomant)**
        - **Dopamine agonists** 3rd line **(Bromocriptine)**

ADDITIONAL INFORMATION:

Miniproblem of problem 3 mentions Tangier disease

- Tangier's disease (HDL deficiency)
    - Mutation in ATP binding cassette-1 gene
    - Hypoalphalipoproteinemia (alphalipoprotein = HDL)
    - Familial HDL deficiency = tangier's disease
    - Large orange tonsils (characteristic)
    - Hepatosplenomegaly
- Anterior pituitary hormones have alpha and beta subunits
    - It is the beta subunit that differentiates one from the other (mostly)