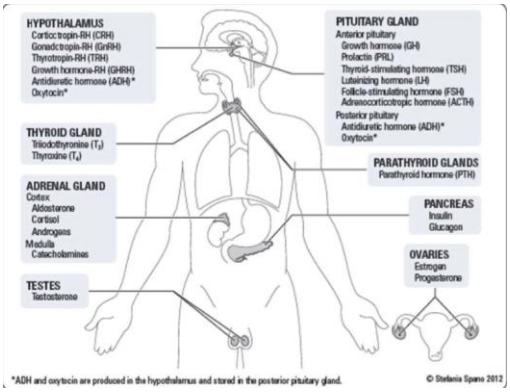
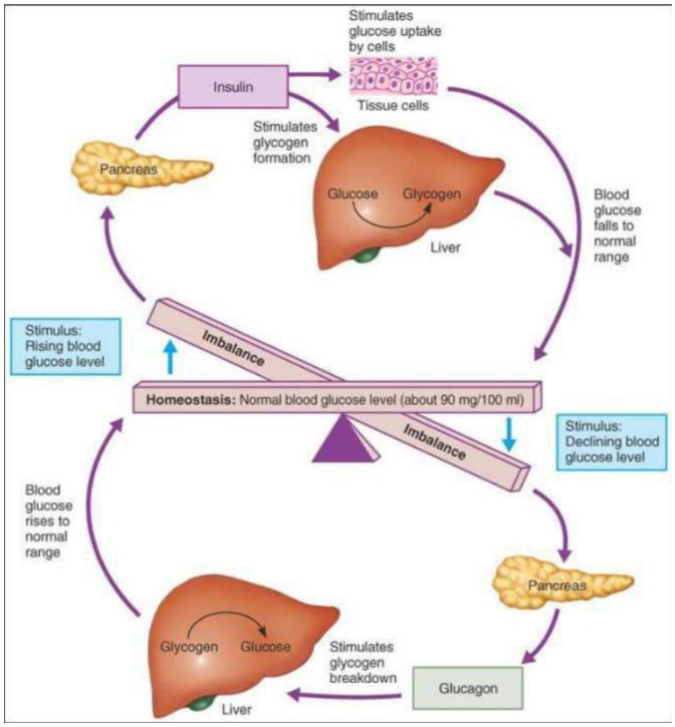
Endocrine Pathophysiology



Diabetes

Glucose Homeostasis

Gluconeogenesis	Occurs in the Liver Produces Glucose from carbohydrate precursors Stimulated with ↓ blood glucose
Glycogenolysis	Proteolysis of Glycogen (storage form of glucose) to form glucose and release into blood
Glucagon	Produced in Pancreas (α cells) Releases Glucose from tissues into blood when blood concentration ↓ Stimulates gluconeogenesis and glycogenolysis ↑ *Proteolysis* - Breakdown proteins from muscle into amino acids ↑ *Lipolysis* - Breakdown triglycerides from adipose tissue into glycerol and free fatty acids ↑ *Glycogenolysis* - Breaks down glycerol in liver/muscle into glucose monomers **End products of proteolysis, Lipolysis, and glycolysis shipped to Liver where gluconeogenesis can make glucose**
Insulin	Produced in Pancreas (β Cells) Uptake glucose from the blood to be utilised in tissues, and skeletal muscle
During Fasting	↓ Insulin, ↑ Glucagon to prevent hypoglycemia
After meal	↑ Insulin, ↓ Glucagon to prevent hyperglycemia



Insufficient Insulin secretion or action:

- Glucose no longer accessible for cells for energy -> Body enters starvation state despite patient eating and gaining nutrients
- Abnormalities in carbohydrate, fat and protein metabolism (↑ breakdown of proteins, carbs, and fats when don't need to)
  - ↑ Gluconeogenesis precursors
- Glucose accumulates in fluid from: Cellular underutilization, and Overproduction -> **Hyperglycemia**

Hyperglycemia	Polydipsia - Glucose exceeds renal threshold of reabsorption -> Excess is excreted in urine - Causes osmotic diuresis and dehydration as water follows glucose Microangiopathy (small blood vessel lumen ↓) Macroangiopathy (Large vessel lumen ↓) Neuropathy (Nerves affected) ** Heart disease = most common cause of death in diabetic patients**

Type 1 Diabetes Mellitus	
Things	**Insulin-dependent Diabetes Mellitus** (IDDM) or Juvenile Diabetes - Begins at childhood Characterized as β-cell destruction -> leads to lack of insulin production
Etiology	*Genetics* - Genetic loci have been associated with DM 1 (particularly MHC Class II) *Autoimmune* - Autoimmune destruction of β-cells within pancreatic islets - Trigger unknown but have 2 theories: 1. Molecular mimicry (Immune system mistakes β-cell proteins for foreign antigen like Rubella) 2. Activation of β-cell specific T-cells (viral infection = islet inflammation = β-cell specific T-cell) *Environmental* - Identical twins only have 50-70% concordance -> suggests environmental factors - Viral infection can kick off autoimmune reaction - Infants fed cow milk instead of breast milk ↑ risk of DM 1 *Idiopathic* (10-15% of patients)
Type 2 Diabetes Mellitus	
Things	AKA: **Non-insulin-dependent Diabetes Mellitus (NIDDM)** - 90-95% of diabetes cases Combination of: 1. Peripheral resistance to insulin (like a desensitization) 2. Inadequate secretion of insulin
Pathogenesis	Initially resistance induces compensatory response - Pancreatic islet hyperplasia w/ ↑ β-cells and insulin secretion Failure to compensate for insulin resistance cause by: 1. β-cell exhaustion -> overworked from the ↑ insulin resistance 2. Glucotoxicity -> Prolonged hyperglycemia = oxidative stress -> toxic to β-cells (↓ insulin gene expression) 3. Lipotoxicity -> Prolonged ↑ of fatty acids = toxic to β-cells
Etiology	*Genetics* - EXTREMELY STRONG GENETIC ASSOCIATION (more so than Type 1) - 38% ↑ risk if 1 parent affected, 60% chance if both parents *Environmental* - Obesity, Physical inactivity, high fat diet = primary environmental risk factors - Obesity is #1
Gestational Diabetes Mellitus	
Etiology	= Abnormal glucose tolerance at onset of pregnancy -> Kinda similar to type II - Thought is that pregnancy hormones interfere with insulin and its binding to insulin receptor Glycemic control returns to normal after giving birth -> But now living with ↑ risk of developing Type II Can lead to Spontaneous abortion, or a large fetus
Risk Factors	- Obesity - Family Hx of DM - Previous Hx of GDM - Previous child w/birthweight >4kg - Current glucocorticoid use (↑ blood glucose levels)
Treatment	**Non Pharma 1st** - Diet Mods and meal plans - Exercise and weight loss - Quit Smoking **Pharma if lifestyle change doesn't work** - Oral hyperglycemic (see pharma slides) - Insulin injections

This is more than just a foot….Its a hyperglycemic foot in an uncontrolled diabetic!

<table>
<tr><th colspan="3">Diabetes</th></tr>
<tr><td>Definition</td><td colspan="2">Metabolic disorder characterised by hyperglycemia from:
- Defective insulin secretion
- Defective insulin action
- Both
Associated with:
- Microangiopathy
- Macroangiopathy
- Neuropathy
- Retinopathy
- Polydipsia
- Polyphagia</td></tr>
<tr><td>Diagnosis</td><td>Diabetes
Fasting Plasma Glucose: >7mmol/L
2-hour Plasma Glucose: >11.1mmol/L
Random Plasma Glucose: >11.0mmol/L
Glycated Hemoglobin (A1c): >6.5%
- Glucose sticks to RBC for their entire life (120 days), gives a good long-term idea of plasma glucose levels</td><td>Pre-Diabetes
Fasting Plasma Glucose: 6.1-6.9mmol/L
2 hour PG: 7.8-11.0mmol/L

A1c: 6.0-6.4%</td></tr>
<tr><td>Long Term Complications</td><td colspan="2">Microvascular
- Peripheral neuropathy
- Nephropathy
- Eye complications
(retinopathy, cataracts, blurry vision, glaucoma, blindness)
- Foot Complications
(Ulcers, Gangrene, Arthritis, Paresthesia, Ischemia, ↓ wound healing)
Macrovascular
- Cardiovascular
(Myocardial Ischemia, Infarction, ↑ atherosclerosis, Hypertension)
- Cerebral
(TIA, CVA)
- Peripheral circulation
(Ischemia, claudication)
↑ Risk of Infection
- Compromised wound healing, ↓ chemotaxis, ↓ phagocytosis, ↓ bactericidal activity, ↓ cell-mediated immunity</td></tr>
<tr><td>Signs and Symptoms</td><td>Cardinals
- Polyuria
- Polydipsia
- Polyphagia
- Weight Loss (cells not getting glucose)
- Loss of strength (protein breakdown)

Orally -> None are diagnostic, but are early cues
- Gingivitis and Periodontal disease
(↑ risk of Perio refractory to treatment)
- Xerostomia, Sialosis
- Infection/↓ wound healing
(↓ neutrophil adherence, ↓ chemotaxis, ↓ phagocytosis, ↓ bactericidal action, ↓ cell-mediated immunity)
- Neuropathy
- Oral Candida infection
- Burning Mouth
- Dysgeusia
- Altered tooth eruption</td><td>Others
- Irritability
- Headaches
- Malaise
- Xerostomia
- Ketoacidosis (Sweet smelling urine or breathe)
- GI upset/Nausea
- Cataracts, Blurred or ↓ vision (changes in lens)
- Impotence
- Hypertension</td></tr>
<tr><td>Dental Considerations</td><td colspan="2">Bidirectional relationship between DM and periodontal disease -> Presence of 1 ↑ risk of developing or worsening the other
- Perio infections adversely affect metabolic control and other health outcomes in DM
- Controlling diabetes improves periodontal status

Morning appointments best
- Cortisol levels are highest = best blood glucose level
- DO NOT schedule immediately after an insulin injection -> hypoglycemic episode if they accidentally injected too early
Before Appointment
- Ensure patient takes all their meds on schedule
- Bring glucometer to their appointment
During Appointment
- Ask about medication or related complications
- Ensure they have eaten before the appointment and haven't just had insulin -> avoid hypoglycemic episode
After Appointment
- Ensure proper diet (soft foods after surgery etc)
- Rx antibiotics if major procedure is done (periodontal surgery, multiple extractions) -> DM has ↓ immunity
If uncontrolled or brittle
- No Epi in LA
- Rx Antibiotics and monitor patient carefully for sensitivity and efficacy</td></tr>
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Hypoglycemia

- Most common emergency in diabetics -> Hypoglycemic shock, insulin shock or diabetic shock
  - Excessive insulin, sulfonylurea, metformin etc administration
- Can occur after alcohol use -> While liver is busy processing alcohol, ↓ glucose is produced
- Can also occur spontaneously after-> Fasting, ↓ calories, intense exercise, moderate-severe infection, sepsis, insulinoma
  - Insulinoma = insulin secreting tumor of β cells in pancreas (usually benign) -> Its like opposite Diabetes! Bizzaro World Diabetes

Signs and Symptoms	**Neurologic** -> ↓ glucose to brain - ↓ concentration - Light Headed, and dizziness - Confusion - Fatigue, Weakness - Drowsiness - Blurred vision, Double Vision - Slurred Speech - Headache - ↓ memory	**Neurogenic (Autonomic)** -> Effects from regulatory hormones ↑ during hypoglycemia (Glucagon, Cortisol, Epi, Growth Hormone) -Tachycardia -Sweating - Hunger - Nausea - Heart Palpitations - Anxiety - Trembling - Pallor, Coldness, Clamminess - Dilated pupils
Dental Management	1. If unconscious STOP, initiate basic life support (CAB) - Put patient in comfy position - Monitor pulse (begin CPR if needed) - Confirm airway is open -> give O_2 (6L/min, non-rebreather mask) - If not breathing use bag-valve mask to ventilate - Activate EMS - Administer Glucagon 1mg (IM or IV) 2. If conscious = Confirm Hypoglycemia - Check blood glucose with glucometer - If less than 4mmol/L and patient responsive -> Give fast glucose (glucose tabs, candies, ¾ cup juice) - Wait 15mins and retest glucose 3. Don't let patient leave for 1hr	

Stage 1 – Mild	**Stage 2 – Moderate**	**Stage 3 – Severe**
- Most common, no EMS needed - Neurogenic symptoms but pt can self-treat	- Neurogenic and neuroglycopenic symptoms, pt can self-treat - No EMS needed	- Medical Emergency - Leads to: Seizure, Coma, Death - Associated with: Hypotension, hypothermia as well

Nocturnal Hypoglycemia: Issue mostly with kids who have Type I DM. Don't take a long acting basal insulin regime = ↓ blood glucose at night. Cortisol levels are at a minimum during the night -> Body can't cope with the hypoglycemic stress.

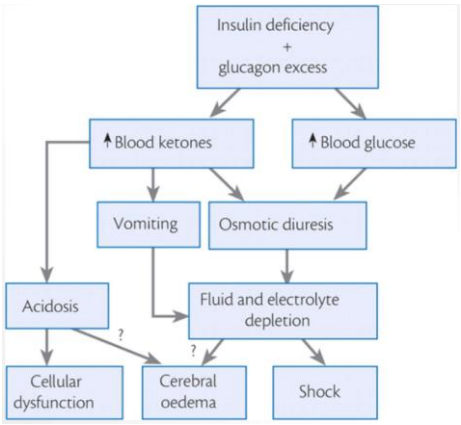
Glucose Homeostasis

	Glycogenolysis	Gluconeogenesis	Ketone Bodies	Lipolysis	Insulin
Glucagon	↑	↑	↑	↑	-
Insulin	↓	↓	↓	↓	-
Cortisol	-	↑	-	↑	-
Growth Hormone	-	-	-	↑	↓
Epinephrine	↑	↑	-	↑	-

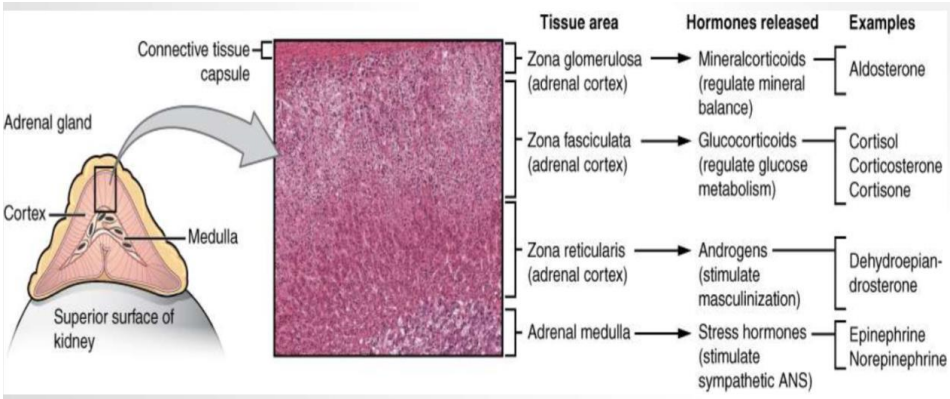
Hyperglycemia

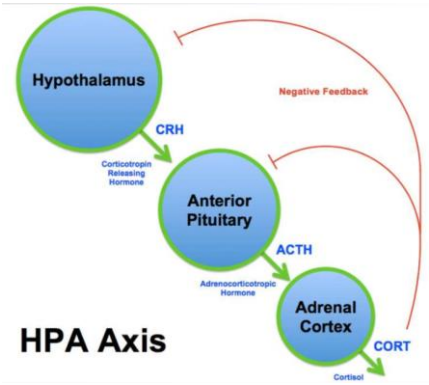
2 life threatening metabolic derangements that can occur in DM

1. Hyperosmolar Hyperglycemic State (HHS) -> Looks like ketoacidosis but without the acidosis
2. Diabetic Ketoacidosis

Hyperosmolar Hyperglycemic State (HHS)	
Preceding Complications	**Often an elderly institutionalized patient w/ ↓ thirst perception and ↓ ability to drink water** Infection (most common) - ↓ fluid intake Cardiovascular Accident Myocardial Infarction
Characterizations	Hyperglycemia w/o ketoacidosis Hyperosmolarity -> leading to Osmotic diuresis - Dehydration - Hypovolemia - Hypotension - Impaired tissue perfusion ➔ All of these can lead to hypovolemic shock
Diabetic Ketoacidosis	
Whats happening here?	Brain can only use 2 energy sources: Glucose and Ketones - Without insulin (or functioning insulin) glucose is not accessible for cells -> Brain must rely on ketones only for energy - Lipoprotein lipase breaks down adipose tissue = ↑ free fatty acids -> Liver breaks FFA down into ketone bodies via β-Oxidation
Definition	Metabolic state from ↑ concentrations of ketone bodies: Acetoacetic Acid, and β-Hydroxybutyrate - Causes a build up of ketoacids in the blood = ↓ pH
Signs and Symptoms	Hyperglycemia Dehydration (ECFV contraction) - From Osmotic diuresis mainly - Vomiting - ↓ consumption of fluids from abdominal pain and nausea - Can lead to hypovolemia, tachycardia, hypovolemic shock Fatigue Nausea and vomiting - ↓ pH in GI b/c ketoacids - Inflammatory mediators produced during β oxidation irritate GI Severe abdominal pain - Inflammatory mediators can cause pain in GI Fruity odor (acetone) breath and urine - Pretty characteristic Kussmaul Breathing (Deep and laboured) - Body trying to blow off excess CO_2 to ↑ blood pH ↓ consciousness - From cerebral edema and acidosis 
Precipitating Events	Inadequate insulin administration Infection - Pneumonia, UTI, Gastroenteritis, Sepsis Infarction - Cerebral, Coronary, Peripheral, Pulmonary Drugs - Cocaine Pregnancy
Management (in ER)	- Restore normal ECFV and tissue perfusion, and electrolyte imbalance -> Give IV fluids - Correction of Acid-Base balance -> Bicarbonate therapy (only for extreme cases, pH <7) - Hyperglycemia fix -> Insulin Progress through PCABD before EMS arrives - Position -> Keep patient in comfy position - Circulation -> Check pulse - Airway -> Ensure open airway - Breathing -> Ensure breathing, give O_2 through non-rebreather mask - Drugs -> IV infusion of 5% dextrose and H_2O or normal saline

HPA Axis and Its Issues



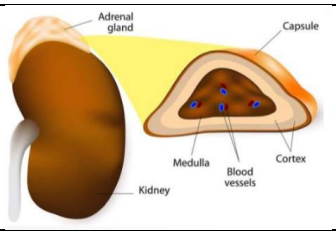


Conn's Syndrome (Primary Hyperaldosteronism)

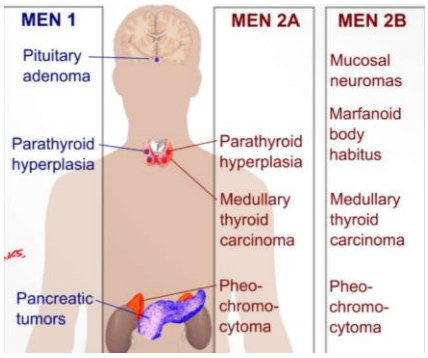
One of the most common causes of secondary Hypertension

Definition	Characterized by excessive secretion of Aldosterone from adrenal cortex - Affects Blood Volume, Blood pressure, and Electrolyte Balance - Autonomous secretion -> doesn't ↓ w/ ↓ renin
Aldosterone	Regulated by Renin (↑ with an ↑ renin) in response to: - Low blood pressure - ↓ renal blood flow - Na^+ deficiency Function: - ↑ Na^+ reabsorption and K^+ secretion in late distal convoluted tubule and medullary collecting ducts of nephron -> Cl^- follows Na^+ back into blood, and H_2O follows both = ↑ BP and volume - Acts on intercalated cells -> stimulates ATPase to induce H^+ secretion = acidifies urine and alkalizes extracellular fluid
Signs and Symptoms	High Blood Pressure - Often this is the only sign! Hypernatremia Hypokalemia Alkalosis
Causes	Bilateral Disease (both adrenal glands affected) - *Bilateral or idiopathic adrenal hyperplasia (BAH)* -> Most common - *Glucocorticoid-Remediable Aldosteronism* -> Genetic condition where gene stimulated by ACTH to produce Cortisol is inserted near Aldosterone gene. When ACTH ↑ Cortisol levels, it also ↑ Aldosterone. -> Treated with glucocorticoids to ↓ ACTH. Unilateral Disease (only 1 adrenal gland affected) - *Adrenal adenoma* (benign tumor - *Adrenocortical Carcinoma* (aldosterone producing) -> Pretty rare 
Treatment	Pharma - Calcium channel blockers - Mineralocorticoid antagonists - Glucocorticoids -> Turns off Hypothalamus and Pituitary via –'ve feedback (unless have adenoma) Surgery - Tx of choice for Adenoma or Carcinoma - Unilateral adrenalectomy is Tx of choice for 1° adrenal hyperplasia

Pheochromocytoma

Definition	Characterized by presence of catecholamine producing tumors -> Usually in Adrenal Medulla - Norepinephrine is mostly produced, less epinephrine -> Causes ↑ HR, ↑ Contractility, ↑ Vasoconstriction -> **2º Hypertension** 
Signs and Symptoms	Nervous System hyperactivity: - Headaches (most common) - Hypertension - Palpitations - ↓ Weight - ↑ Blood Glucose (↑ glycogenolysis, ↑ Gluconeogenesis, ↑ Lipolysis) - Tachycardia - Diaphoresis - Orthostatic Hypotension **Can lead to Diabetes Type 2 with chronic ↑ blood glucose** ****Vasoconstrictors ↑ ↑ ↑ risk of cardiac or cerebrovascular accident** -> Fully contraindicated**
Differential Dx	- Anxiety Disorder - Thyrotoxicosis (Hyperthyroidism) - Amphetamine or Cocaine abuse - Carcinoid -> slow growing neuroendocrine tumor typically in GI and lungs
Treatment	- Surgery (most frequent Tx) - Chemotherapy / Radiotherapy - α-adrenergic blockers and β-blockers to control symptoms

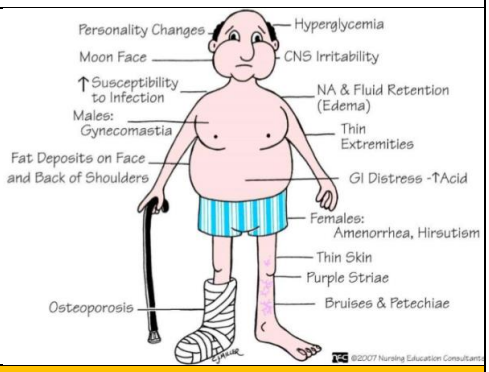
Multiple Endocrine Neoplasia (MEN)



MEN 1 3P's	Pituitary Parathyroid Pancreatic
MEN 2A 2P's, 1M	Medullary Thyroid Carcinoma Parathyroid Pheochromocytoma
MEN 2B 1P 2M	Medullary Thyroid Carcinoma Marfanoid Habitubs/Mucosal Neuroma Pheochromocytoma

MEN 1	Includes: - 1º Hyperparathyroidism - Develops during teenage years - Stones, Bones, Groans, Psychiatric overtones (Kidney stone, Hypercalcemia, Constipation, Peptic ulcers, Depression - Pancreatic tumors (gastrinomas, Insulinomas) - Gastrinomas = ↑ gastrin -> ↑ HCL from parietal cells = cause stomach ulcers and diarrhea - Insulinomas lead to chronic hypoglycemia - Pituitary Adenoma
MEN 2A	Tumors in 2 or 3 of the following: - Medullary Thyroid Carcinoma -> >80% develop thyroid cancer - Adrenal Gland -> 50% develop Pheochromocytoma - Parathyroid Gland Hyperplasia
MEN 2B	- Medullary Thyroid Cancer - Marfanoid Habitus -> Like Marfan's but w/o Cardio involvement - Pheochromocytoma Mucosal Neuroma -> Benign oral and submucosal tumors (1st presenting symptom)  Yellow-ish-white, sessile, painless nodules on lips or tongue

Paraneoplastic Syndromes

What are they?	Sets of signs and symptoms that are caused by a hormone secreting ectopic tumor (S/S occur remotely from the tumor site) Common Tumour locations: - Lungs - Breast - Ovaries - Lymphatics The cancers themselves are not of endocrine origin, and 50% of cases has small-cell lung carcinoma Most common: Cushing's Syndrome and SIADH
Cushing Syndrome - **↑ ↑ Cortisol**	
Ectopic Sites	↑ ACTH and ACTH-like substances from: - Small-cell lung cancer - Pancreatic carcinoma - Neural tumors
Presentation	- Hyperglycemia - Hypokalemia - Hypertension - Central Obesity - Moon Face - ↓ Libido - Weakness/Clumsy - ↑ Acne - Easy bruising - Depression/Irritability 
Syndrome of Inappropriate ADH Secretion (SIADH)	
Ectopic Sites	↑ ADH/Vasopressin from: - Small-cell lung cancer - Non-small cell lung cancer - CNS Malignancies
ADH Function	↑ Reabsorption of H_2O in the distal nephron and collecting ducts - Determines is hypoosmotic fluid in nephron is excreted or reabsorbed Regulated by: - Plasma osmolarity sensed by osmoreceptors in Hypothalamus and Circumventricular organs - <280 mOsm/L will ↓ ADH levels; >280 mOsm/L will ↑ ADH in order to ↓ plasma volume
MOA	**Excessive ADH -> Hypervolemia and Hyponatremia** - ↑ volume in blood dilutes the Na^+ leading to hyponatremia (despite Na^+ not actually being deficient) - ↑ H_2O creates hypotonic plasma relative to brain -> H_2O will move into cerebral cells = neurologic issues
Etiology	Dysregulation of ADH in CNS - Overproduction of ADH in hypothalamus Neoplasms - Tumors (sometimes ectopic) that produce ADH Drugs - ↑ effects of ADH form some meds Nephrogenic Syndrome of SIADH - Genetic disorder -> ADH receptor in collecting ducts stimulates H_2O absorption even in absence of ADH
Signs and Symptoms	- Fatigue - ↓ Appetite - Headache - Nausea and vomiting - Muscle cramps - Delirium, Hallucinations - Seizures - Coma
Differential Dx	- Acute Kidney Injury - Cerebral Salt Wasting - Addison's Disease - Chronic Kidney Disease - Exercise induced hyponatremia - Hypothyroidism and Myxedema Coma - Psychogenic Polydipsia

Diabetes Insipidus - ↓ ADH

What is it?	Not related to Diabetes meilitis at all! = Congenital or acquired condition where there is ↓ levels/Activity of ADH leading to dilute and odorless urine (insipid) - ↓ Reabsorption of water in the kidneys = Polydipsia and Polyuria - Pee 3-20 liters a day (normal is only 1-2) -> Leads to dehydration issues
Etiology and Subtypes	***Central*** - Damage to pituitary gland or hypothalamus -> Affects production, storage and release of ADH (Produced in Hypothal. Stored in posterior pit.) - Caused by: Surgery, Cancer, Meningitis infection, Inflammation, Head Trauma, genetic defect ***Nephrogenic*** - Defective ADH receptor in Distal convoluted tubule and Collecting ducts -> Acquired or congenital - Caused by: Chronic kidney disease, Meds (lithium, Cidofovir antiviral), ↓ K^+ in blood, ↑ Ca^{++} in blood, urinary tract blockage - Hypercalcemia = Polyuria by interfering with Na absorption and inhibiting ADH action ***Dipsogenic*** - Defective hypothalamic thirst mechanism (abnormal ↑ in thirst and liquid intake inhibits ADH) - Caused by: Hypothalamus or pituitary damage, medications, Mental health disorder ***Gestational*** - Rare, occurs when placental enzyme destroys maternal ADH - ↑ prostaglandin production during pregnancy ↓ renal sensitivity to ADH - Goes away after giving birth
Signs and Symptoms	**Dehydration** - Xerostomia - ↓ skin elasticity - Hypotension - Fever - Headache - Tacchycardia **Hypernatremia** - Fatigue/lethargy - Nausea - ↓ Appetite - Muscle Cramps - Confusion
Treatment	**Desmopressin** - Nasal spray, oral tabs, or injection - Also used to help ↑ clotting in vWD

Pre-Eclampsia

What is it?	Disorder of pregnancy and postpartum (20 weeks after gestation – 6 weeks postpartum) - Affects both mother and fetus Characterized by: - Hypertension - Proteinuria - Target organ damage -> **Heart, Kidneys, Brain, Eyes** ↑ risk of heart disease and stroke later in life
Symptoms	- Edema - Sudden weight ↑ - Headaches - Vision changes
Risk Factors	- Chronic Hypertension - High BMI - Chronic Kidney Disease - Age >40yr or < 18yr - Diabetes Melitus - Previous Pre-Eclampsia
Eclampsia	New onset of seizure or coma in a pregnant woman with untreated pre-eclampsia - Not related to an existing neurological condition

Calcium Homeostasis

Calcium

Ca^{++} is most abundant mineral in the body

- >98% is stored in bone -> Total serum calcium is only 0.1%-0.2% extracellular calcium. Of this serum Ca, only 40% is active
  - Moral of the story: There is SUCH a small amount just floating around, because its super important.

Functions:

- Neuromuscular excitability and synaptic transmission
- Excitation/Contraction in cardiac and skeletal muscle
- Blood Clotting (Coagulation Factor IV)
- Hydroxyapatite formation

Homeostasis

- Controlled by: **PTH, Calcitriol, Calcitonin**
- Very tightly regulated because it stabilizes Voltage gated ion channels … and those are pretty important

Hypocalcemia	Hypercalcemia
Voltage gated ion channels open spontaneously - Involuntary muscle spasms (Hypocalcemic tetany)	Voltage gated ion channels don't open as easily ↓ nervous system function ↑ Stones and calcium phosphate deposits in blood and kidneys

Phosphate

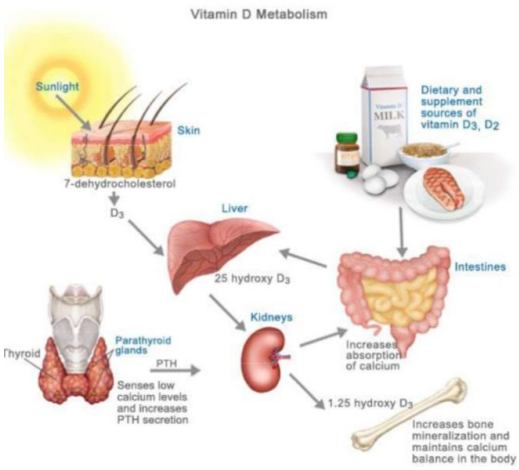
- 2^{nd} most abundant mineral

Function

- Component of RNA, and DNA (vital for growth and repair of cells and tissues)
- Vital for energy production + metabolism (part of ATP)
- Component of cell membranes (phospholipids)
- pH regulation
- Hydroxyapatite formation (85% found in bones)

Vitamin D

- No significant activity in body until its altered by the liver -> then PCT in kidneys
  - Biotransform Vit. D into active form -> Calcitriol



Functions

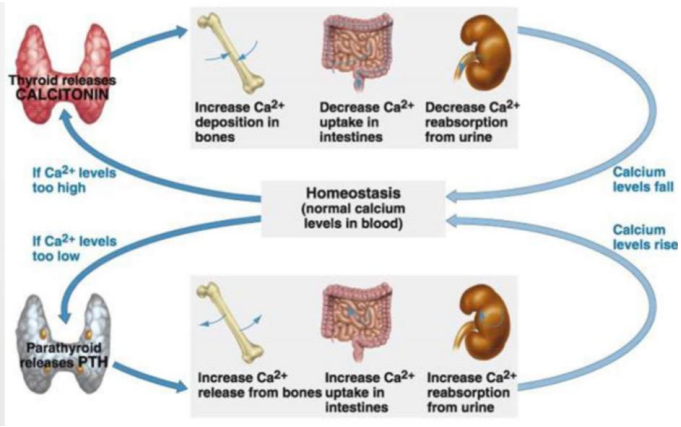
- Bone- promoting hormone
- Stimulate absorption of Ca^{++} (and a little PO_4 in the duodenum
- Stimulates renal tubular reabsorption of both Ca and PO_4

Calcitriol Deficiency	= ↓ Ca absorption = ↓ Ca in bone - Rickets, Osteomalacia, Osteoporosis
Rickets (Kids)	Defective mineralization of bones before epiphyseal closure - ↑ risk of pathologic fracture - Largest cause is calcitriol deficiency 
Osteomalacia (Adults)	Impaired mineralization of bones (↓ Ca, ↓ PO_4) and ↑ resorption of Ca from bone - ↓ Quality of bone - ↓ mineral matrix ratio Signs/Symptoms - Diffuse body pains - Muscle weakness - Pathologic fracture
Osteoporosis	Quality of bone is ok, it's the quantity of the bone that ↓ - Improper regulation of bone remodelling (↑ resorption, ↓ building)

Parathyroid Glands

- 4x Pea sized nodules of tissue embedded within the thyroid gland
  - Secrete PTH to control GI tract, Kidneys, and Bone

Parathyroid Hormone (PTH)	
Effects	**↑ Serum Ca** - Shorter term (minutes) stimulates osteoblasts to pump Ca out of the fluid surrounding bone into ECF -> Stimulates osteoblasts to express RANKL = Activates RANK receptor on osteoclast precursors to ↑ Osteoclasts - Longer term ↑ Osteoclasts = ↑ Ca and PO_4 released from bone - ↑ renal Ca resorption in DCT - ↑ Renal conversion inactive Vit D into active Calcitriol -> ↑ GI absorption of Ca - ↑ Renal elimination of PO_4 -> ↓ Serum PO_4 -'ve Feedback - Acts back on parathyroid gland to prevent hypercalcemia
Regulation	Glands - Sense the ECF bathing the gland to monitor Ca levels - ↓ plasma Ca = ↑ PTH secretion - ↑ plasma Ca = ↓ PTH - ↑ Plasma PO_4 = ↑ PTH - ↑ Calcitriol = ↓ PTH - ↑ PTH = stimulates Calcitriol production in kidneys Renal - PTH ↑ renal reabsorption of Ca in DCT and ↓ PO_4 reabsorption (↓ extracellular PO_4)
Calcitonin - Produced in Thyroid by parafollicular cells (C cells)	
Effects	**↓ serum Ca levels** - Opposes PTH Inhibits osteoclast activity (↑ Ca deposition in bone) ↓ Ca reabsorption in kidneys (↑ excretion)
Regulation	Regulated by plasma Ca levels - ↑ Ca = ↑ Calcitonin to try and ↓ Ca



Hypocalcemia	
Causes	Renal Failure Vit. D deficiency - ↓ sunlight, renal disease, liver disease, ↓ GI absorption Hypomagnesemia - ↓ PTH release (chronic use of diuretics or PPI's) - Mg = co factor for PTH synth and secretion Pancreatitis - Fat malabsorption syndromes Hypoparathyroidism - Autoimmune disorder - Surgery
Clinical Signs	↑ Neuromuscular excitability Muscle Spasms Tetany Cardiac Dysfunction

Hypercalcemia **Life-threatening Emergency. ↑ risk of Coma and Cardiac Arrest**	
Causes	Mostly Primary hyperparathyroidism and malignancy (>90% of hypercalcemia's) Primary - Parathyroid Adenoma - Autosomal Dominant Diseases (MEN 1, MEN 2A) Secondary -> Treat with Ca and Vit. D supps, or Cinacalcet (binds Ca receptors on PT gland to ↓ PTH secretion) - Chronic Kidney disease - Vit. D deficiency Malignancy
Clinical issues	Normally Ca and PO_4 in the blood are close to their saturation point - Any ↑ can lead to diffuse precipitation of $Ca(PO_4)$ -> Widespread organ dysfunction and damage ***"Stones, Groans, Bones, Thrones with Psychic Overtones"*** - Kidney Stones - GI Pain - Nausea and Vomiting - Bone Pain - Polyuria - Frequent Headaches - Confusion - Fatigue - Depression - Hypertension - Coma - Cardiac Arrest

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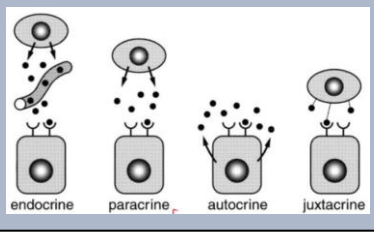
Endocrine Pharmacology

Definitions:

Exocrine = Secretion outside of the body (sweat glands)

Endocrine = Internal secretion of biologically active substance (hormones or enzymes)
- *Paracrine*: Locally acting hormone acting on cells other than the producing cell (neighbours)
- *Juxtacrine*: Hormone WITHIN the membrane of one cell interacts with receptor on another cell. Direct cell-cell contact
- *Autocrine*: Hormone can act upon the cell that produced it



Hormones (Generally)

Hormones	
Polypeptide and Protein Hormones	- Stored in secretory vesicles - Synthesized as longer proteins -> cleaved to form smaller prohormones in ER -> Cleaved again to form active hormone and packed into Secretory vesicles -> Exocytosis into blood **Glands:** - Pituitary (Anterior and Posterior) - Pancreas (Insulin, Glucagon) - Parathyroid gland (PTH)
Steroid Hormones	- Synthesized from Cholesterol - Not stored as a hormone - Steroid Producing cells have large storage of cholesterol esters to be able to quickly produce hormones - Lipid soluble -> Diffuses through cell membrane to be released, or to bind intracellular receptors **Glands:** - Adrenal Cortex (Cortisol, Aldosterone) - Ovaries (Estrogen, Progesterone) - Testes (Testosterone) - Placenta

Amine Hormones (from Tyrosine)	2 groups: Thyroid Hormone, Adrenal Medullary Hormones **Glands:** - Thyroid Gland (Thyroxine T_4, Triidothryonine T_3) - Adrenal Medulla (Epinephrine, Norepinephrine)
Receptors	
In/On Cell Membrane	Protein, Peptide or Catecholamine Receptors
In Cytoplasm	Steroid Hormone receptors
In Nucleus	Thyroid Hormone Receptors

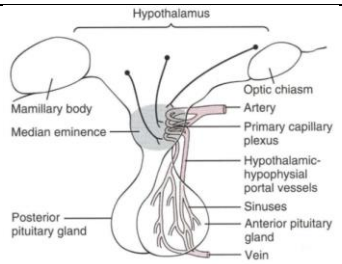
Feedback Control

Negative Feedback	Positive Feedback	Cyclical Variation
- Prevents over-secretion or activity of hormones at target tissue	- Biological action of hormone causes additional secretion of that same hormone Ex: LH surge from ↑ Estrogen -> Stimulates ovaries to secrete ↑ Estrogen = ↑ LH - Eventually at certain level LH turns to –'ve feedback	Superimposition of –'ve and +'ve feedback - Periodic variation in hormone release. Ex: ↑ Growth Hormone during sleep but not during waking hours -> Circadian rhythm

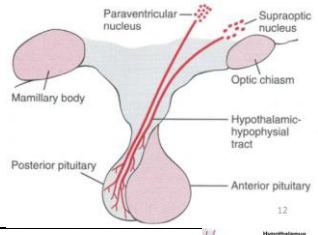
Hypothalamic – Pituitary System

Hypothalamic Hormones

Regulation of Anterior Pituitary -> *Hypothalamic-Hypophysial Portal System*
- Growth Hormone Releasing Hormone (GHRH)
- Somatostatin
- Dopamine
- Thyrotropin Releasing Hormone (TRH)
- Corticotropin Releasing Hormone (CRH)
- Gonadotropin Releasing Hormone (GnRH)



Regulation of Posterior Pituitary
- Regulated by Nerves running between Hypo and Post. Pit. (Supraoptic and Paraventricular Nuclei)



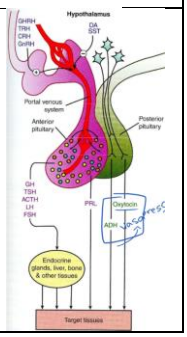
Pituitary Hormones

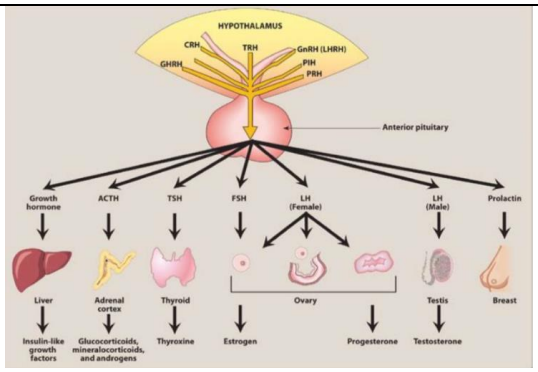
F – Follicular Stimulating Hormone (FSH)
L – Luteinizing Hormone (LH)
A – Adrenocorticotropic Hormone (ACTH)
T – Thyroid Stimulating Hormone (TSH)
G – Growth Hormone (GH)
P – Prolactin (PRL)

Anterior Pituitary Gland

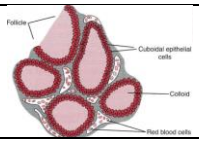
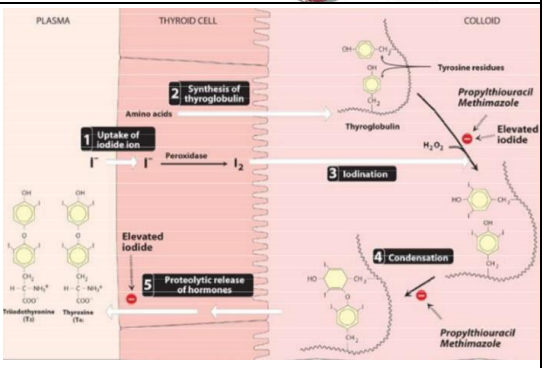
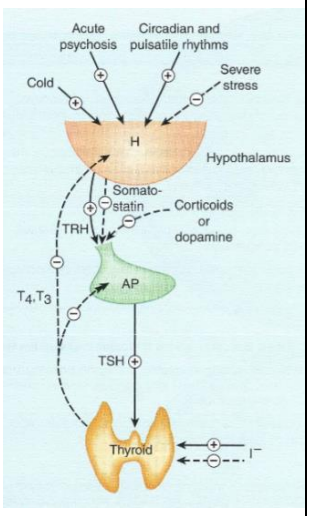
A - Antidiuretic Hormone/Vasopressin
O – Oxytocin

Posterior Pituitary Hormones





Thyroid Gland/Thyroid Hormone

Products	T_4 – Thyroxine T_3 – Triiodothyronine Calcitonin
Functions	Promote normal growth and development Regulate energy and heat production Help regulate calcium metabolism and blood concentration (Calcitonin) -> Puts Ca back in bone
Histology:	Follicles are lined with cuboidal epithelial cells, and filled with colloid fluid - Colloid: Thyroglobin glycoprotein (major constituent) -> contains Thyroid hormone within its molecule 
Synthesis of Thyroid Hormone	1. Iodide Ion from plasma is taken into the Thyroid cell -> Thyroidal Peroxidase converts Iodide (I^-) to Iodine (I_2) 2. Thyroid cell produces Thyroglobin (TG) -> Tyrosine Residues are important to the structure 3. Iodination of Thyroglobin -> Iodinase catalyses Iodine binding to tyrosine residues of thyroglobin. - Monoiodotyrosine (MIT) - Diiodotyrosine (DIT) 4. Condensation of Iodinated Tyrosine: - 2 x DIT -> T_4 - 1 x MIT + 1 x DIT -> T_3 - > Each thyroglobin molecule will contain up to 30 Thyroxine (T_4) and a few Triiodothyronine molecules (T_3). Stored in follicles this way in amounts that will be able to last 2-3 months without replenishment  5. Proteolytic release of hormones -> T_3 and T_4 cleaved off thyroglobin (TG) and released into blood as needed - < 20% of T_3 is produced this way. Very little 6. Iodine Recycling -> 75% of iodinated Tyrosine in TG will never become a thyroid hormone (remains MIT or DIT) - TG is digested to release iodinated tyrosine -> iodine freed by deiodinase enzyme to be recycled
Transport of T_4 and T_3	- Binds plasma carrier proteins (>99% are bound -> VERY few are freely active in plasma) - 0.04% T_4 and 0.4% T_3 are free and responsible for function *Transport Proteins:* 1. Thyroxine Binding Globulin (TBG) 2. Thyroxine-Binding prealbumin 3. Albumin
Receptors	Within the cell, T_4 converted to T_3 (by 5'- monodeiodinase) -> T_4 is a pro-hormone, ***T_3 is the active hormone*** - 90% of receptor binding is from T_3 2 Receptors: -> Located on or near DNA strands. When bound initiated T^c of thyroid hormone responsive genes - TRα (1 and 2) -> from chromosome 17 - TRβ (1 and 2) -> from chromosome 3
Physiologic Functions	*↑ Cellular Metabolic Functions* - ↑ basal metabolic rate - ↑ # and activity of mitochondria - ↑ Active transport of ions through cell membranes (Na/K ATPases -> Needed for nerve function) *↑ Growth and Development* - Regulate growth in children - Affects brain development and skeletal maturation in fetus and 1st few years of life after birth *Stimulates Carb and Fat metabolism -> ↑ Blood Glucose* - ↑ hepatic gluconeogenesis and glycogenolysis - ↑ Intestinal glucose absorption *↑ Blood Flow and Cardiac Output* - ↑ HR, Contractility and BP *↑ Respiration and GI motility* *↑ Cellular demand for O_2* - ↑ EPO and RBC production *↑ Secretion of most other endocrine glands* *Effects Sexual Function* - Women: Hypo/Hyperthyroidism can impair ovulation, ↓ TH can cause irregular periods - Men: ↓ TH = ↓ Libido, ↑ TH = Impotence 
Regulation	1. TRH from Hypothalamus acts on Anterior Pituitary to ↑ TSH 2. TSH from Ant. Pit acts on Thyroid Gland to ↑ TH Negative Feedback: - Free TH in plasma ↓ TSH release from Ant. Pit. *AND* TRH from Hypo.

Disorders of the Thyroid

Hypothyroidism		
Pathophysiology	***Primary***: -> Most have thyroid inflammation (thyroiditis) –> deterioration and fibrosis = ↓ TH - Most often chronic autoimmune thyroiditis (Hashimoto's Disease) -> Autoimmune against gland (destroying) - Iatrogenic - Iodine Deficiency - Enzymatic defects in the thyroid - Thyroid hypoplasia - Goitrogen Drugs	***Secondary:*** - Pituitary failure - Tumor (hypothalamus, or pituitary) - Surgery - External Pituitary radiation - Postpartum pituitary necrosis - Trauma - Metastatic tumor - TB infection - ↓ TSH production
Clinical Presentation	- Dry Skin - Cold Intolerance - Weight Gain - Constipation - Weakness - Lethargy - Fatigue - Muscle Cramps - Myalgia - Stiffness - ↓ Energy/Ambition - Psychological changes associated with depression Children: - Growth and intellectual retardation	
Treatment	*Replacement therapy* - Levothyroxine/Synthroid -> T_4 Replacement -> 1x/day until steady state achieved in 6-8 weeks - Liothyronine -> Synthetic T_3 -> ↑ $$, ↑ Cardiac adverse effects - Liotrix -> Synthetic T_4:T_3 in **4:1 ratio** -> Chemically stable -> Predictable potency -> $$$ Though	
Contraindications	P450 Inducers -> ↑ Metabolism of thyroid hormone ↓ effectiveness of Replacement therapy - Phenytoin - Rifampin - Phenobarbital	
Dental Implications	Affects women 7-10x more than men (with sharp ↑ after 40yrs old) - 5-6x more common than hyperthyroidism S/S may be similar to depression Kids -> Cretinism - Delayed eruption (sequence is right, but 1-2 years delayed) - Malocclusion - Skeletal Growth Retardation Exaggerated response to CNS depressants (Sedatives and opioids) **Myxedema** - Dull expression, puffy eyelids, alopecia of outer 1/3rd of eyebrow, dry/brittle hair ↑ tongue size, lethargy, anemia, cold - Stressors (drugs, surgery, trauma, infection) may precipitate myxedema coma (Severe presentation of hypothyroidism) Oral Manifestations - Tongue enlargement - Scalloping of tongue ****Barbituates ↓ thyroid hormone levels -> Use cautiously in patients on TH replacement therapy**** -> don't really use Barbs anymore	

Hyperthyroidism (Thyrotoxicosis)		
Pathophysiology	*TSH-secreting pituitary tumors* - Causes excessive TH release, but unresponsive to –'ve feedback *Graves Disease (#1)* - Thyroid-Stimulating antibodies -> Bind TSH receptors and stimulate TH production/release - Most common cause -> more in females *Autonomous Thyroid Nodules* - Thyroid mass functions independently of pituitary control *Multinodular Goiter* - Follicles with autonomous functions (out of control) coexist along side normal or non-functioning follicles *Painful Subacute Thyroiditis* - Etiology unknown, possibly related to autoimmunity *Excess Ingestion of thyroid hormone (Exogenous)* *Drugs* - Amiodarone (can induce hypo or hyperthyroidism)	
Presentation	- Palpitations and Tachycardia at rest - High Excitability - Intolerant to heat - ↑ sweating - Hand Tremor - Diarrhea - Weight Loss - Muscle weakness- Nervousness/Psychiatric disorders - Extreme fatigue, but can't sleep	

Treatment	*Surgical Removal* of some of the thyroid - Pre-treatment with Propylthiouracil (PTU) or Methimazole given until thyroid function is normal first *Thioamines* - Methimazole and Propylthiouracil (PTU) - Blocks peroxidase-catalyzed reactions (↓ iodide oxidation, ↓ tyrosine iodination, ↓ coupling of DIT and MIT) - PTU inhibits peripheral conversion of T_4 to T_3 as well *Iodide Salts* (Potassium Iodide, Lugol Solution) - Inhibit iodination of Tyrosine and TH release - Rapid onset (2-7 days) - Adverse Effects: Rash, drug fever, salivary gland swelling, metallic taste, bleeding disorder *Radioactive Iodine (^{131}I)* - 8 day ½ life -> Taken up and concentrated in thyroid gland - Emits gamma radiation of beta particles -> Beta particles destroys gland - Best option for Graves Disease, Toxic autonomous nodules and toxic multinodular goiter - **CONTRAINDIATATED IN PREGNANCY** *Anion Inhibitors (rarely used)* - Thiocyanate (SCN^-), Perchlorate (CLO_4^+) - Block uptake of iodide by thyroid -> Competitive inhibition of iodide transporter - Adverse Effects: Aplastic anemia *ß-Blockers* - Metoprolol, Propanolol, Atenolol - Block sympathetic symptoms (Adjunct Tx for thyrotoxicosis) - Propanolol inhibits T_4 to T_3 conversion
Dental Implications	Nervousness Always moving ↑ Bone loss *Cardiovascular:* - ↑ Stroke volume - ↑ HR - Supraventricular arrhythmias *Oral*: - Osteoporosis of alveolar bone - ↑ Caries and ↑ Periodontal disease risk *Kids* - Teeth and jaws develop earlier - Early eruption (sometimes even before birth if mother is hyperthyroid)

Thyroid Storm

= Acute exacerbation of all symptoms of hyperthyroidism

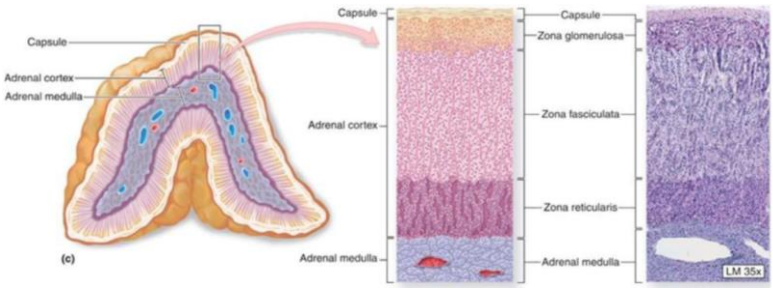
- Life Threatening Medical Emergency

Precipitating Factors	- Infection - Trauma - Surgery - Radioactive Iodine Tx (RAI) - Withdrawal form antithyroid drugs
Clinical Presentation	- High Fever (Often >40.4°C) - Coma - Tachycardia - Nausea - Tachypnea - Vomiting - Dehydration - Diarrhea - Delirium
Treatment	*Iodides* - Rapidly block release of preformed thyroid hormone *Antiadrenergic drugs (ß-blockers)* -> Esmolol, metoprolol, Propanolol - Controls cardiac symptoms *Corticosteroids* - Its recommended, but there is no evidence that it does anything really *Supportive Measures* - Acetaminophen - Fluid replacement - Sedatives - Digoxin and other antiarrhythmics ****Aspirin/NSAIDs displace bound thyroid hormone -> Makes it worse!** -> Contraindicated**

Adrenal Hormones

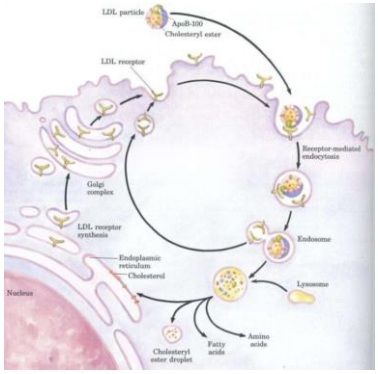
Adrenal Glands

- Found on top of each kidney, composed of 3 zones



Zone	Characteristics	Products	Control
Zona Glomerulosa	Most superficial layer (just under the capsule)	Aldosterone - Produced by Aldosterone Synthase	Fluid concentrations of Angiotensin II and Potassium
Zona Fasciculata	Thickest layer, middle layer	Glucocorticoids - Cortisol, Cortisone Some Androgens and Estrogens	HPA Axis - Adrenocorticotropic Hormone (ACTH)
Zona Reticularis	Deepest layer of the cortex	Adrenal androgens - Dehydroepiandrosterone (DHEA) - Androstenedione Some Estrogens and glucocorticoids	HPA Axis Adrenocorticotropic Hormone (ACTH)

Hormone Production



- Adrenal hormone synthesis begins with cholesterol
  - LDL is main cholesterol delivery system to the adrenal gland -> LDL receptors on the surface of adrenocortical cells endocytose LDL molecules

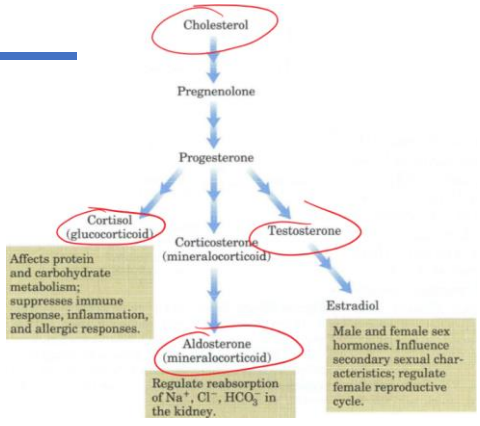
ACTH effects:

1. Stimulates adrenal synthesis
2. ↑ LDL receptors on adrenocortical cells
   - ↑ enzymatic release of Cholesterol from LDL

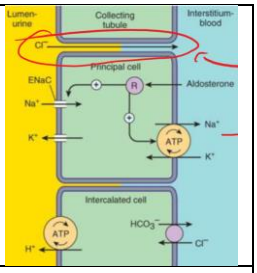
****The backbone for all Adrenocortical hormones is *cholesterol* -> There can be some cross-reactivity between the hormone receptors and different hormones (Ex: Mineralocorticoids can cause low level stimulation of Glucocorticoid receptors)****

Transportation:

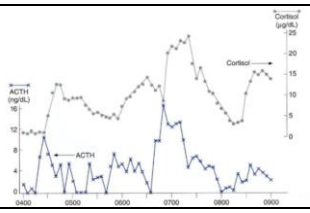
Cortisol	Aldosterone
90-95% bound to plasma protein - Cortisol-binding protein or transcortin (little bit to albumin) Longer Half-Life -> 60-90mins - Because they are so sequestered, the few that are active at a time need to last long to have affective function	60% protein bound Shorter Half-Life -> 20mins - More are active at a time so half life is ↓ to ↓ over reaction



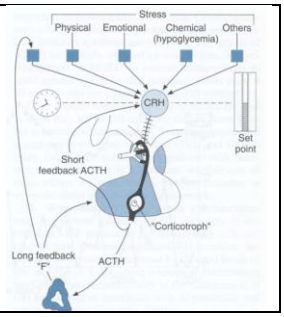
Aldosterone

Functions	*Maintain NaCl plasma concentrations* (Na moves, Cl and H_2O follow) - ↑ renal resorption of Na and secretion of K (principle cells of the collecting tubules, DCT) - ↑ Synthesis of Na/K ATPase in basolateral membrane and Na channels in luminal membrane - ↑ Na reabsorption from sweat glands, salivary glands, and GI Mucosa Maintains total extracellular fluid volume and blood volume/pressure	
Release	↑ Aldosterone Release - ↑ K in ECF - ↑ RAAS system - ACTH -> Necessary for secretion, but has little effect on rate ↓ Release - ↑ Na in ECF	
Dysregulation	**Excess – Conn's Syndrome** ↑ ECF Volume ↑ Arterial pressure (Hypertension) Hypokalemia Muscle weakness Mild Alkalosis - ↑ H^+ secretion in collecting tubules	**Deficiency** ↓ ECF Volume ↓ Arterial pressure Electrolyte Imbalance (Excessive Na, Cl loss, ↑ K in blood)
Pharmacology		
Agonists	**Used if there is ↓ BP, and ↓ Aldosterone in system** ***Deoxycorticosterone*** *(DOC)* - Precursor molecule to Aldosterone **Fludrocortisone** - Used as a mineralocorticoid, but has glucocorticoid function also.	
Antagonists	**Used if there is ↑ BP or volume** ***Spironolactone*** - Competitive inhibition of aldosterone cytoplasmic receptor = ↑ excretion of Na (and subsequently Cl and H_2O), ↓ K Secretion - Androgen antagonist effect also ***Eplerenone*** - Selective aldosterone receptor inhibition -> No cross reactivity with androgen receptors ***Drospirenone*** - Oral contraceptive -> Aldosterone antagonist also	

Glucocorticoids/Cortisol

Functions	*Carbohydrates* - ↑ Gluconeogenesis - ↓ glucose utilization by cells - ↑ blood glucose levels -> Adrenal diabetes *Protein* - ↓ storage of cellular proteins - ↑ plasma and liver a.a and proteins -> so they can be broken down and converted to glucose *Fat* - ↑ metabolism of fats -> Lipolysis *Immune cells* - ↓ capillary permeability - ↓ WBC migration into inflamed areas - ↓ phagocytosis of damaged cells by WBC - ↓ fever - ↓ inflammatory mediators - ↓ NF-κB gene -> ↓ cytokines, ↓ chemokines, ↑ Apoptosis, ↓ cell adhesion
Regulation	Corticotropin Releasing Hormone (CRH) from Hypothalamus stimulates ACTH release from Anterior Pituitary in a pulsatile diurnal (daily) rhythm -> Follows the circadian rhythm - ACTH levels peak before waking in the morning and ↓ progressively during the day (lowest at midnight) -> Cortisol will follow same trend as stimulated by ACTH, but ACTH follows this rhythm independent of Cortisol negative feedback 

	Physical or mental stress stimulates the entire system to cause rapid release of cortisol (minutes) - Pain -> Brainstem -> Median Eminence of hypothalamus -> CRH release -> ACTH release -> Cortisol release



Adrenocortical Disorders

Insufficiency (Addison's Disease)

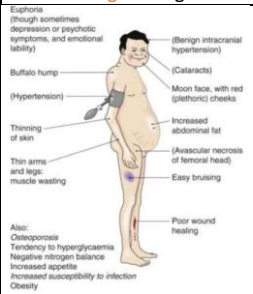
Primary (Addison's Disease)	**Secondary**
- Destruction in all zones of the cortex (↓ cortisol, aldosterone, various androgens) - CRH and ACTH ↑ to try and compensate *Etiology:* - 80-90% is autoimmune (Developed Countries) - Tuberculosis is a leading cause (Developing countries) - Cancer invasion - Drug Induced -> Ketoconazole (↓ Cortisol synthesis) -> Phenytoin, Rifampin, Phenobarbitol (↑ Metabolism of cortisol by inducing P450…you may recall they also ↓ effectiveness of TH therapy)	- Excess exogenous cortisol -> ↓ HPA axis via negative feedback - ↓ ACTH release = ↓ cortisol and androgen production ***Mineralocorticoids are usually unaffected in secondary diseases***

Presentation	- Weakness, Fatigue - Weight Loss - Hypotension - Hyperpigmentation - Inability to regulate blood glucose during fasting ↓ Mineralocorticoids -> ↓ Na resorption, ↓ ECF volume, Hyponatremia, Hyperkalemia, mild acidosis ↓ Glucocorticoid -> inability to maintain blood glucose between meals, impaired gluconeogenesis
Treatment	Replace glucocorticoids: Hydrocortisone, Cortisone, Prednisone Replace Mineralocorticoids: Fludrocortisone (or Deoxycorticosterone DOC)

Adrenal Crisis

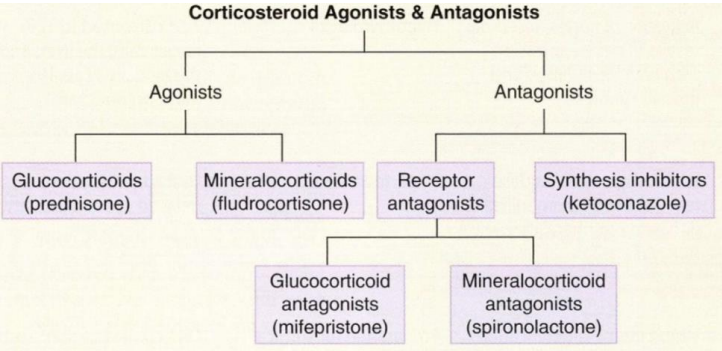
Triggers	Sudden ↑ in adrenal requirement (Stressful situations – infection, surgery, trauma) -> Body needs Cortisol to respond to stress. - Usually a complication of adrenal insufficiency
Causes	Surgery Trauma Infection Abrupt withdrawal of exogenous glucocorticoids (physician caused)
Tx	Hydrocortisone or Dexamethosone Fluid Replacement (IV Dextrose 5% in normal saline) Fludrocortisone Acetate (if hyperkalemia develops)

Adrenal Hyperfunction (Cushing's)

Causes	Overproduction of Endogenous glucocorticoids - *ACTH Dependent (Pituitary Issue)*: ↑ ACTH production by pituitary gland (pituitary adenoma, ectopic ACTH secreting tumors etc) - *ACTH Independent (Adrenal Issue)*: Adrenal adenomas and carcinomas Excess exogenous glucocorticoids
Clinical Presentation	 - Central Obesity and facial rounding - Myopathy/weakness - Hypertension - Psychiatric Changes - Osteoporosis with back pain - Fat accumulation in dorsocervical area (Buffalo hump) - Abdominal Striae (stretch marks) - Glucose Intolerance/Diabetes - Gonadal Dysfunction

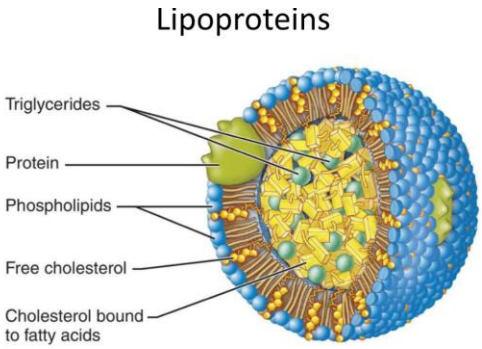
Treatment (pharma) ***Just need to recognize, don't memorize list***	*Synthesis Inhibitors* - Metyrapone - Ketoconazole - Etomidate - Aminoglutethimide - Trilostane - Abiraterons	*Neuromodulator of ACTH release* - Cyproheptadine (↓ ACTH release) - Pasireotide (Somatostatin analogue, ↓ ACTH) *Glucocorticoid antagonist* - Mifepristone *Adrenolytic Agents* - Mitotane

Therapeutic uses for Corticosteroids	Replacement therapy for: - 1° or 2° adrenocortical insufficiency - Congenital Adrenal hyperplasia Diagnosis for Cushing syndrome (Dexamethasone Suppression test) Inflammatory relief Allergy treatment Autoimmune conditions
Dental Considerations	Adrenal crisis is pretty rare in dentistry, pay attention to: - Undiagnosed adrenal insufficiency - Poor health status at time of treatment - Pain - Infection - Surgery - General Anesthesia with Barbiturates -> Sedation can add stress Assume some level of adrenal suppression if patient has had: - 30mg hydrocortisone/equivalence > 4 weeks - 80mg hydrocortisone/equivalence > 2weeks **Management:** - Give corticosteroids pre-op for high risk patients for Adrenal Crisis -> Rule of Two! - Schedule appointments early in morning (with corticosteroids 2hrs before procedure) **3 Approaches:** 1. Add 1 additional dose of steroid, no taper - Dexamethasone 6-10mg 2. ↑ Pre-op steroid (1-3 fold), taper back over several days back to baseline 3. Don't change the dose and focus on pain control -> Only really for minor surgery or routine treatment.



Lipid Metabolism

Lipid Transport



Atherosclerosis really quickly:

Risk Factors	- Hyperlipidemia - Arterial Hypertension - Smoking - Diabetes - ↓ Physical activity - ↓ HDL - Hyper-homocysteinemia - Hypercoagulable status

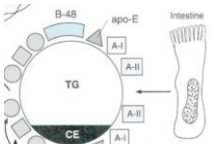
- Coronary atheromas contain cellular elements, collagens, and lipids

Atherogenic lipoproteins: LDL, IDL, VLDL, Lp(a) -> all contain Apolipoprotein B-100

- ApoB100 subject to oxidation -> bad for atherosclerotic plaques

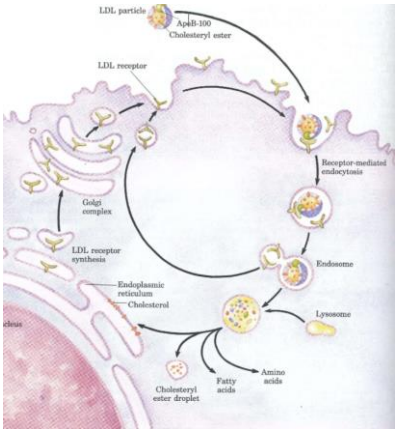
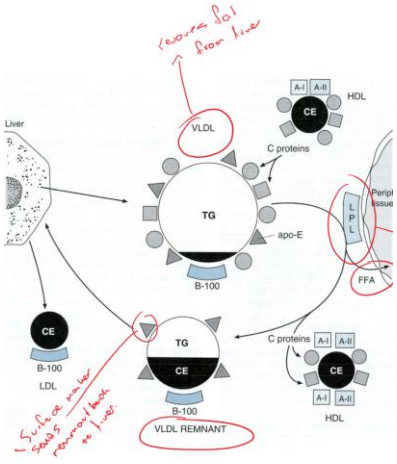
All lipids in the plasma are insoluble in H_2O -> they must be transported in association with proteins

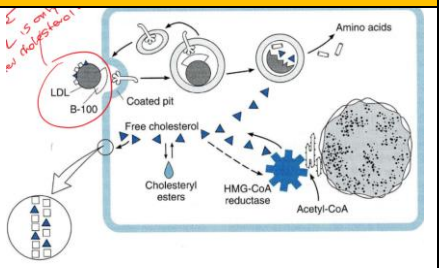
Formation of Chylomicrons



Lipid transport Mechanisms		
Albumin	Carries un-esterified cholesterol or FFA's from peripheral adipocytes to other tissues	
Lipoprotein Complexes	*Core region contains hydrophobic lipids* - Cholesteryl esters and triglycerides *Surrounding the core* - Amphiphilic lipids - Phospholipids - Free unesterified cholesterol *Apolipoproteins* - Non-covalently bound to the lipids - Located on surface of monolayer	Chylomicrons HDL (good cholesterol) LDL (bad) VLDL (bad) IDL (bad)
Apolipoproteins	B-Apolipoprotein - Behaves like intrinsic protein of cell membrane (but on the surface of a lipoprotein) - Found in VLDL (B-100 protein) -> retained as LDL is formed from the remnants of VLDL in liver - NOT in HDL - Has binding domain that forms upon conversion of VLDL to LDL -> Binds LDL receptors A-Apolipoproteins - A-I: Major apolipoproteins of HDL and chylomicrons - A-II: Important for HDL -> cysteine residues for disulpfide bridge between apo A and apo E - A-IV: mostly just in chylomicrons Lp(a) - Very similar to plasminogen - Forms disulfide bridge dimer with apo B-100 in LDL	

Lipoproteins

TG-Rich Lipoproteins (VLDL + LDL)	
Formation	1. Liver exports Triglycerides (synthesized from FFA) to the peripheral tissues within the core of VLDL - Augmented by anything resulting in ↑ flux of FFA to the liver in the absence of compensating ketogenesis 2. VLDL release is stimulated by: - Obesity/↑ caloric intake - Drinking alcohol - Administration of estrogens 3. Hydrolysis by Lipoprotein Lipase (LPL) -> ↓ TG in the cores of VLDL and ↓ diameter) - Apo C-II = necessary cofactor for activating LPL system - LPL found on capillary endothelium in heart, skeletal muscles, adipose tissue, mammary glands etc - LPL activity in adipose tissue ↑ with insulin release (elevated glucose) -> FFA stored - LPL activity in adipose ↓ during fasting -> Prevents storage of FFA and encourages immediate use 4. Lipoprotein Remnants are formed - 70% of TG's are lost and cholesterol is the main carried components - Remnants removed from blood by high-affinity receptor mediated endocytosis in the liver 5. LDL formation - Residual TG are removed from VLDL by hepatic lipase on the surface of the liver -> Forms LDL  
HDL	
	Source: Liver and Intestine -> Excess cholesterol and phospholipids are transferred to HDL by phospholipid transfer protein (PLTP) *Function*: Transport surplus cholesterol AWAY from peripheral tissues back to Liver -> Along with LDL, will deliver cholesterol to adrenal cortex and gonads for steroidogenesis

Cholesterol	
	Essential for: - Plasma membranes - Adrenal and gonadal steroidogenesis - Production of bile acids *Synthesis*: - All nucleated cells can make cholesterol from Acetyl-CoA - HMG-CoA is the first step -> HMG-CoA reductase is ↓ by ↑ cholesterol -> This is what is targeted by statin drugs *Diet*: - 1/3 of amount of cholesterol ingested reaches blood (transported to liver by chylomicron remnants) - Leads to hepatic cholesterogenesis suppression : ↑ Ingestion = ↓ Endogenous production 

Dyslipidemia Drugs

Family	Drugs	MOA	Effects	Side Effects
HMG-CoA Reductase Inhibitors **(-Statins)**	Lovastatin Simvastatin Pravastatin Atorvastatin Rosuvastatin	Specific, reversible, competitive inhibitors of rate limiting enzyme involved in endogenous cholesterol synthesis in Liver -> ↓ intracellular cholesterol = ↑ LDL receptor synth. Liver takes in more LDL to produce more cholesterol -> LDL clearance from periphery	↓ Serum LDL Levels ↑ Endothelial function ↓ Platelet aggregation ↑ fibrinolysis Stabilize atherosclerotic plaque	May be toxic if liver disease present
Bile Acid Binding Resins	Cholestyramine Colestipol	Bind bile acids (and similar steroids) in intestine - Prevents reabsorption and recirculation of bile - Excreted in feces Liver absorbs more LDL to produce more cholesterol for Bile	↓ absorption of exogenous cholesterol ↑ Metabolism of endogenous cholesterol into Bile Acids ↑ LDL receptors on liver cells -> to ↑ cholesterol and ↑ bile acids	Steatorrhea Bloating Constipation Impaired vitamin and drug absorption (Vit. K, Folates, Thiazide diuretics, warfarin)
Cholesterol Transport Inhibitor	Ezetimibe	Prevents absorption of dietary cholesterol and cholesterol excreted in bile Inhibits GI mediated transport of cholesterol	↑ LDL receptors on liver cells -> to ↑ cholesterol and ↑ bile acids	
Fibrates	Gemfibrozil Fenofibrate Clofibrate	Stimulate lipoprotein lipase (↑ LPL gene transcription) - ↑ clearance of triglyceride rich lipoproteins	↓ VLDL ↓ Triglyceride ↑ HDL	
VLDL Synthesis inhibitor	Niacin	Unknown	↓ VLDL Secretion from liver ↑ VLDL clearance ↓ Plasma triglycerides	Flushing - Limited with aspirin 30 mins prior to dose
Apo-B100 synthesis inhibition	Mipomersen	Apo B 20-mer antisense oligonucleotide -> targets mRNA for apo-B100 in the liver	↓ cholesterol ↓ LDL	
PCSK9 Inhibition	Evolocumab Alirocumab	Normally PCSK9 -> Causes degradation of LDL receptor Monoclonal Antibodies - ↑ recycling of LDL-receptors on hepatocytes	↑ removal of LDL from circulation ↓ TG ↓ apo B-100 ↓ Lp(a)	

Glucose Metabolism

- Pancreas is the main controller for glucose regulating hormones

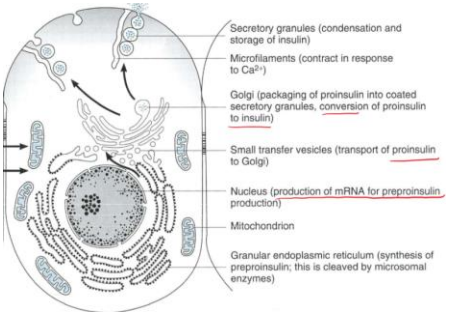
Cell Types	Products
α-Cells	Glucagon Proglucagon
β-Cells	Insulin C-Peptide Proinsulin Amylin
δ-Cells	Somatostatin
ε-Cells	Ghrelin

Hormonal Control of Blood Glucose

Hormone	Action	Stimuli	Inhibition	Effect
Insulin	↑ cellular glucose uptake ↑ Glycogen synthesis (storage glucose) ↓ Glycogenolysis ↓ Gluconeogenesis	*Humoral* ↑ blood sugars ↑ blood amino acids ↑ blood fatty Acids *Hormonal* Glucagon Glucose-dependent insulinotropic polypeptide *Neuronal* β-Adrenergic stimulation Vagal Stimulation *Drugs* Sulfonylureases Acetylcholine Meglitinide	*Hormonal:* Somatostatin Insulin Leptin *Neural:* α-sympathetic effects of catecholamines *Drugs:* Diazoxide Phenytoin Colchicine	↓ Blood Glucose
Glucagon	↑ Glycogenolysis	Hypoglycemia (Blood Glucose <3mmol/L) - Post exercise, Stress, high protein meals etc		↑ Blood Glucose
Epinephrine (Adrenaline)	↑ Glycogenolysis			
Glucocorticoids	↓ cellular Glucose uptake ↑ Gluconeogenesis			
Growth Hormone	↓ Glucose uptake			

Insulin

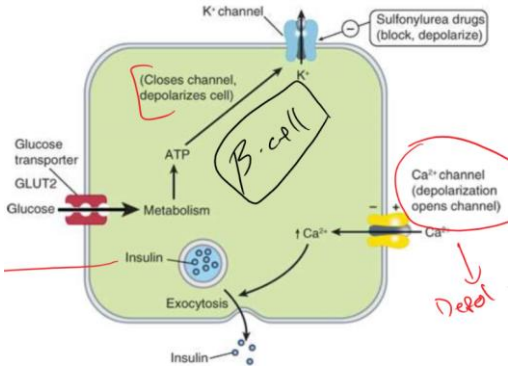
Insulin Production



1. Nucleus produces the mRNA for Preproinsulin
2. Preproinsulin is produced in the rough ER
3. Golgi cleaves Preproinsulin into proinsulin -> proinsulin into secretory vesicles and convert again it to Insulin
4. Secretory vesicles store Insulin in the β cells and release in response to ↑ Ca^{++} (like neurotransmitter release)

Insulin Release

1. Glucose from the blood is brought into the cell and metabolised to form ATP
2. ATP causes closure of the K^+ channels that are usually pumping K^+ out of the cell -> leads to ↑ of +'ve chare inside the cell = Depolarization
3. Upon depolarization the Voltage gated Ca^{++} channels are opened and Ca rushes into the cell
4. ↑ Ca^{++} in the cell stimulates microtubule contraction and exocytosis of the insulin containing granules
5. ↑ Blood insulin to ↑ Glucose uptake by the cells



Insulin effects

Type of Metabolism	Liver Cells	Fat Cells	Muscle Cells
Carbohydrate	↓ Gluconeogenesis ↓ Glycogenolysis ↑ Glycolysis ↑ Glycogenesis	↑ Glucose uptake ↑ Glycerol synthesis	↑ Glucose uptake ↑ Glycolysis ↑ Glycogenesis
Fat	↑ Lipogenesis ↓ Lipolysis	↑ Synthesis of Triglycerides ↑ Fatty Acid synthesis ↓ Lipolysis	-
Protein	↓ Protein Breakdown	-	↑ Amino Acid uptake ↑ Protein synthesis

Insulin Preparations

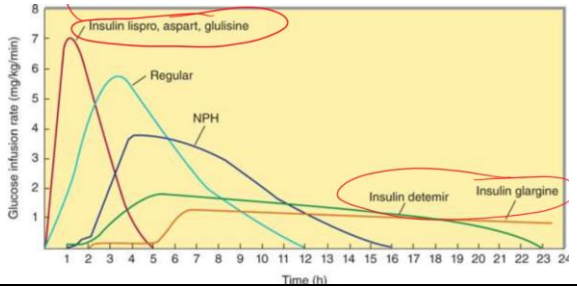
- Variables: Onset, Peak Time and Duration

Type of Preparation	Drugs	Use
Rapid – Acting (5-15min onset, 0.5-2hr peak, 2-4hr duration)	Insulin Lispro (Humalog) Insulin Aspart (Novolog) Insulin Glulisine (Apidra)	Injected immediately before a meal Preferred type for continuous subcutaneous infusion (pumps) Used also in emergency treatment of uncomplicated diabetic ketoacidosis
Regular/Short-Acting (30-60min onset, 2-4hr peak, 3-6hr duration)	Regular Insulin (Humulin R, Novolin R)	IV in emergencies or subcutaneous in regular dosage regiments - Administer 1 hr before meal - Bolus dose
Intermediate Acting (1-2hr onset, 4-12hr peak, 12-18hr duration)	NPH Insulin (Humulin N, Novolin N)	Combination of regular insulin and protamine - Has a delayed onset and peak of action - Combined with regular or rapid-acting insulins
Long- Acting (1-2hr onset, no peak, 24 hr duration)	Insulin glargine (Latus) Insulin Detemir (Levemir) Insulin degludec (Tresiba)	Provides a peak-less, base insulin dose lasting 20+hrs - Can get Nocturnal Hypoglycemia if don't take this - Especially a problem because ↓ cortisol can't help regulate blood glucose - Background/Basal insulin replacement

Site of injection affect blood glucose
- Fastest when given in abdomen
- Slower action from upper arm
- Slowest from thighs and buttocks

Pens:
- Disposable or cartridge loading -> set dosage and inject

Pumps:
- Delivers insulin like your body does. Big bolus on meals, and constant base level
- 1 pump Nic…



Glucagon

Synthesis	α-cells of islets of Langerhans in pancreas - Stimulated when blood glucose is low
Effects	Fuel mobilization - ↑ Gluconeogenesis, ↑ Glycogenolysis, ↑ Lipolysis, ↑ Proteolysis - ↓ Storage of triglycerides in the liver and prevents liver removal of FA from the blood (so they can be available in other parts of the body ↑ Blood Sugar ↑ HR and contractility ↑ blood flow to kidneys ↑ bile secretion ↓ Gastric acid secretion
Mechanism of Action	G-protein coupled receptors in Heart, Smooth muscle, Liver
Clinical Uses	Tx of hypoglycemia in the *unconscious* patient Tx Acute cardiac failure caused by β antagonist - ↑ cAMP in cardiac muscles without the use of β receptors.

Somatostatin

Synthesis	δ-cells of the islets of Langerhans in the pancreas - Only a short half life Secreted in response to: - ↑ Blood glucose - ↑ amino acids - ↑ Fatty Acids - ↑ GI hormones (released b/c of food intake)
Effects	↓ Secretion of insulin AND glucagon ↓ Mobility of Stomach, Duodenum, Gall Bladder (↓ secretion and absorption within the GI) ↓ Growth Hormone secretion by Ant. Pit.
Drugs	Octreotide (Sandostatin) - Long acting Somatostatin analogue - Tx of acromegaly (↓ GH) - ↓ symptoms of gastro-entero-pancreatic tumors

Diabetes

…We know about the complications and what it is by now…

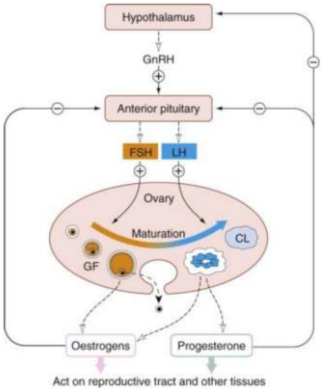
Antidiabetic Agents

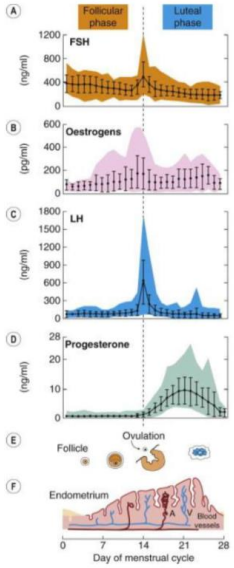
Drug	Action	Mechanism	Considerations
Sulfonylureases - Glyburide - Glipizide - Glimepride - Gliclazide **Secretagogues** - ***"-glinides"*** Meglitinide Analogues - Repaglinide - Mitiglinide D-phenylalanine Derivative - Nateglinide	↑ Insulin release from pancreas	Blocks efflux K^+ channel in β-cells = Depolarization - Depol opens Ca channels = Ca influx -> Insulin release - **Only works if β cells are function (Type II DM only)	Do not combine secretagogues with Sulfonylureases - Can induce hypoglycemic event
Biguanides - Metformin	↓ Hepatic Gluconeogenesis (No effect on insulin release) ↑ Glucose uptake from skeletal muscle ↓ glucose absorption from GI ↑ FA oxidation ↓ plasma glucagon ↓ LDL and VLDL	Unknown	Do not cause hypoglycemia (safer) ☺ Can cause GI distress though and lactic acidosis
Thiazolidinediones **"-Glitazone"** - Rosiglitazone - Pioglitazone	↑ Glucose uptake in muscles and adipose ↓ hepatic gluconeogenesis	Binds PPAR – gamma (mostly in adipose, muscle and liver) - Activated receptor ↑ T^c of genes to ↑ sensitivity to insulin	Possible fluid retention and heart failure -> Rosiglitazone ↑ risk of MI
α-Glucosidase Inhibitors - Acarbose - Miglitol	↓ post meal glucose ↑ by delaying digestion of starch and disaccharides	Carbohydrate analogue - Competitive inhibition of α-glucosidase enzyme (normally aids in the digestion of starches to be absorbed in SI)	Flatulence Diarrhea Abdominal Pain
Incretin Analogues Glucagon-like peptide (GLP-1) receptor agonists - Exenatide, - Liraglutide	↑ glucose induced insulin secretion ↓ hepatic glucagon production	G-protein coupled R -> ↑ cAMP -> ↑ intracellular Ca -> insulin release - Oral glucose - ↑ insulin release than glucose IV	
Dipetidyl Peptidase-4-Inhibitor Sitagliptin Saxagliptin Linigliptin	↑ activity of Incretin hormones ↑ Insulin release in response to meals	DPP-4 responsible for inactivating Incretin - These inhibit that inactivation	
Amylin Analogues Pramitide	↓ Gastric emptying ↓ postprandial glucagon secretion ↓ appetite	Amylin co-secreted with insulin from β-cells after meal	
Na^+-glucose Co-Transporter 2 inhibitor Canagliflozin Dapagliflozin	↓ resorption of glucose ↑ urinary glucose excretion ↓ blood glucose levels	SGLT2 - Responsible for resorbing filtered glucose in the kidney	

Gonadal Homeostasis

Female Reproductive System

1. Hypothalamus releases GnRH -> stimulates ant. Pit. To release LH and FSH
    - FSH -> Stimulates estrogen production
    - LH -> Stimulates mid-cycle ovulation
2. Progesterone is released from the corpus luteum
    - Maintains endometrium for fertilized ovum implantation





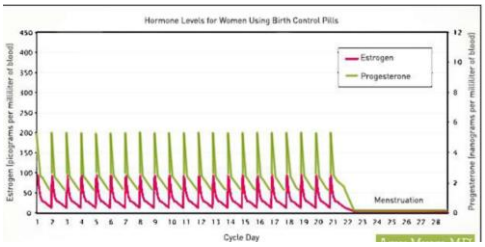
Estrogen	
Synthesis	Made in the ovaries and placenta mostly In males, made in a small amount by the testis and adrenal cortex *3 Types*: - Estradiol - Estrone - Estriol
Effects	***Metabolism*** - Salt + H_2O retention (like mineralocorticoids) - Mild anabolic action - ↑ Plasma HDL ***Sexual Development*** - 2º sexual characteristics - Induce artificial menstrual cycle (contraception) - ↓ menopausal symptoms and protect against osteoporosis ***Uterus***: - Myometrial cells in fundus act as pacemaker in response to E for rhythmic contraction - E ↓ uterine movements in early pregnancy (hyperpolarizes myometrial cells) -> Protects fetus from spontaneous abortion ***Bone Metabolism*** - ↓ resorption rate (antagonizes effects of PTH) - Promotes apoptosis of osteoclasts ***Coagulation*** - ↑ blood coagulation - ↑ factor II, VII, IX, X - ↓ antithrombin III - ↑ plasminogen and ↓ platelet adhesiveness
Progesterone	
Whats it's deal	***Follicular phase*** - Progesterone is low - Participates in the pre-ovulatory LH surge to cause maturation and secretory changes in the endometrium (*Luteal* Phase) ***Secretory Phase*** - Progesterone controls this phase - -'ve feedback on the hypothalamus and ant. Pit. ***Luteal Phase*** - In mid luteal, progesterone plateau's and starts to decline -> Menstruation
Effects	- Stimulates Lipoprotein lipase (↑ fat deposition) - ↑ basal insulin levels, ↓ insulin response to glucose -> Result is glucose remaining high in the blood - ↑ glycogen storage in the liver - Competes with aldosterone in kidneys for mineralocorticoid receptors -> ↓ Na reabsorption = ↑ aldosterone secretion and ↑ peeing during pregnancy

Effects of ovarian steroids (E and P) and Peptides on Gonadotropin secretion

Negative Feedback	Positive Feedback
Ovarian Steroids: - Estrogen ↓ secretion of FSH and LH (see an ↑ in FSH and LH after ovariectomy or menopause)	**Estradiol and Progesterone** - Can ↑ release of LH and FSH - During *menstrual cycle*, ↑ Estradiol at the end of follicular phase initiates the pre-ovulatory surge of LH via +'ve feedback - ↑ Progesterone initiates mid cycle FSH surge **GnRH** - Pulsatile release of GnRH in patients without GnRH induced menstrual cycles -> shows there is a cyclical release at play possibly not controlled by feedback mechanisms

Oral Contraceptives

- Act primarily though selective inhibition of pituitary function to inhibit ovulation
- Combination contraceptives (Estrogen + Progestogen) -> changes the cervical mucus in the endometrium and in the motility and secretion within the uterine tubules to ↓ the survival of sperm

	Combined Pill	Progestogen-only Pill
Mode of action	Estrogen inhibits FSH release and follicle development Progestogen: Inhibits LH release and ovulation + Makes cervical mucus inhospitable for sperm Together, E + P makes endometrium unsuitable for implantation Used for 21 consecutive days on a 28 day cycle  Different Preparations: - Monophasic -> Fixed dose of E and P over 21 days - Biphasic -> E is fixed, P ↑ over 21 days - Triphasic -> E and P vary every 7 days (3x) over 21 days - Quadrephasic -> E and P change 4 times over 21 days	Inhibits LH release and ovulation + Makes cervical mucus inhospitable for sperm - Less reliable than combined pill - Used when E is contraindicated (usually BP ↑ too much during E treatment) Used every day (no break)
Dental Considerations		
Antibiotic Use	*****No interference between E metabolism and commonly prescribed antibiotics***** - Thought that antibiotics causing diarrhea and vomiting will "wash" out contraceptives faster (↓ effectiveness), OR that antibiotics affect on gut flora ↓ the bacterial hydrolysis of conjugated E = ↓ reabsorption of E in enterohepatic circulation) -> These are only theories though, there is no evidence proving them either way **** Rifampin is the only antibiotic SHOWN to cause oral contraceptive failure**** - CYP450 inducer -> ↑ metabolism of E	
Other implicated drugs	Anticonvulsants Antidepressants Antihistamines Thyroid H Diuretics Vitamins Antiulcer Meds	
Periodontal Health	Early studies have indicated contraceptives to ↑ inflammatory status = ↑ erythema and tendency towards bleeding ……. Not sure what current studies are saying though?	

Hormonal Therapy

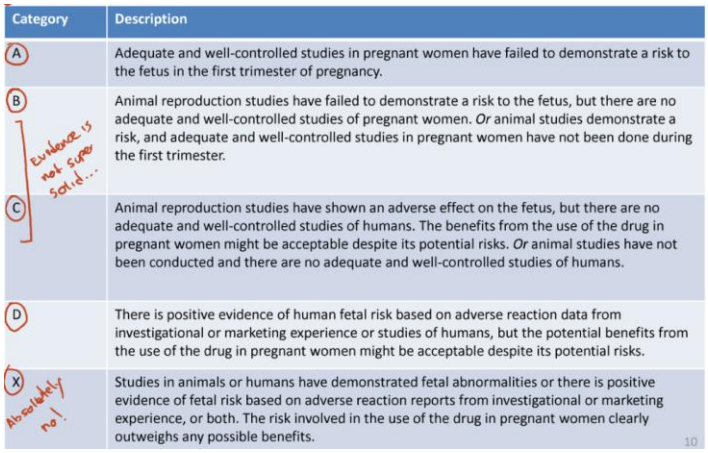
Estrogen Drugs - Non-steroidal compounds - Agonists in some tissues, antagonists in others	
Raloxifene	Antagonistic Anti-E effects *on breast and uterus* Agonistic Estrogenic effects on *bone, lipid metabolism and blood coagulaton*
Tamoxifen	Antagonistic Used for E dependent breast cancer Agonistic Estrogenic effects on plasma lipids, Endometrium and bone
Clomiphene	Antagonistic - Inhibits the –'ve feedback E has on Hypothalamus and ant. Pit. (Normally to ↓ levels of LH and TSH) - Induces ovulation, LH surge (↑ fertility)
Oxytocin	
Effects	*Uterus* - Stim. Uterine contraction (dose dependent effect on amplitude and frequency) - High Doses = sustained contraction -> ↓ blood flow to placenta and fetal death Cervical dilation and suckling stimulates release -> +'ve feedback during labour - Estrogen induces Oxytocin receptor synthesis (uterus at term is ↑ sensitive to oxytocin) Others: - Contracts myoepithelial cells in mammary gland (helps with milk letdown) - Vasodilation - ↑ Water retention
Prostaglandins	
Effects	Uterine smooth muscle contraction - Related to painful menstruation (dysmenorrhea) and excessive blood loss (menorrhagia) -> Tx with NSAIDs Misoprostol (PGE_1 analogue) - Promotes contraction of uterus to induce labor - When combined with other drugs can be used as an abortion medication
Androgens	
Effects	Testosterone works most through active metabolite -> **Dihydrotestosterone** - Modifies gene T^c Develops male 2^o sex characteristics and masculinization in women Sperm production in males ↑ muscle protein and hemoglobin synthesis ↓ bone resorption *Therapeutics* - Males with 1^o hypogonadism or 2^o hypogonadism
Agonistic drugs - Nandrolone - Oxandrolone - Danazol	Effects: - ↑ protein synthesis and muscle development Clinical uses: - Aplastic anemia - Hypogonadism - Cornea healing - Used in catabolic states (burns, cancer, AIDS)
Antagonists	*Receptor Inhibitors* - Flutamide (competitive inhibition of androgen receptors) - Apironolactone (K^+ sparing diuretic, also inhibits androgen receptors) *5a-Reductase Inhibitors* (Finasteride, Dutasteride) - Normally converts T into DHT -> stimulates prostate cells and hair follicles *Synthesis inhibitors* (Ketoconazole) - Inhibits CYP450 involved in androgen synthesis

Pregnancy

Pharmacokinetic and Dynamic Considerations

Pharmacokinetics	
Lipid Solubility	- Lipophilic drugs = ↑ crossing the placenta - Polar drugs = ↓ placenta crossing
Molecular Weight	<500 Da = Easily crosses placenta 600-1000 Da = slowly crosses placenta (but still crosses) >1000 Da = No significant placental crossing
pH	- Fetal blood is more acidic -> Basic drugs (pKa > 7.4) will be ionized in the fetal circulation = ion trapping and ↑ concentrations circulating for longer
Protein Binding	Differential protein binding (preferring to bind maternal plasma proteins vs fetal) - Affects poor lipid soluble drugs
Placental and Fetal drug metabolism	Placenta has metabolic activities -> Does the drug get detoxified in the placenta? 40-60% of umbilical venous blood goes to fetal liver (after the 1st trimester)
Pharmacodynamics	
Toxic drugs to fetus	Chronic maternal opioid use -> Dependence in fetus/newborn ACE inhibitors -> Fetal renal damage
Therapeutic drugs to fetus	Corticosteroids -> Stimulate fetal lung maturation Phenobarbital -> Induce fetal liver enzymes

Teratogenicity

Old System	New System (PLLR)
	 Lists the risks of the drugs for DURING pregnancy, post pregnancy for BREAST FEEDING, and for REPRODUCTION in Males and females **Pregnancy**: - Pregnancy Exposure Registry - Risk Summary - Clinical Considerations - Data **Lactation (Nursing Mothers)** - Risk Summary - Clinical Considerations - Data **Reproductive Potential (Males and Females)** - Pregnancy Testing - Contraception - Infertility

Drug Selection

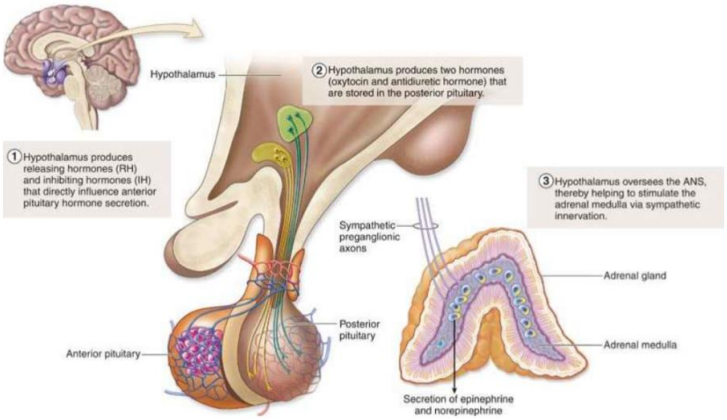
Use drugs that have been safe for a long time, prescribe at the lower end of the therapeutic range, eliminate nonessential and self-medications/supplements

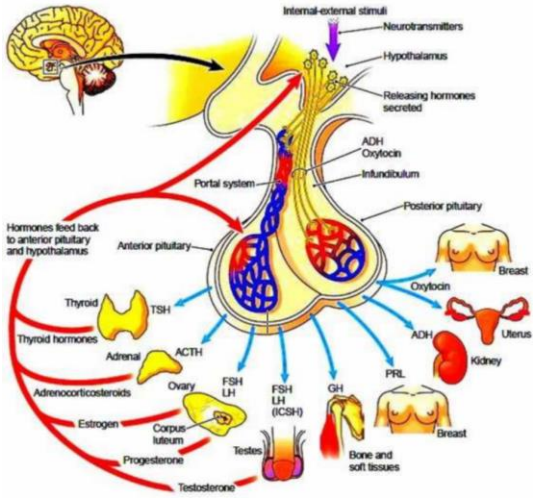
- If giving meds, the 2nd trimester is the safest time. Fetal organogenesis has finished by that time and it can handle some drugs

Analgesics Prostaglandins have oxytocic actions (Uterine contraction) - NSAIDs and Aspirin can block Thromboxane and Prostaglandin synthesis -> Avoid in 3rd trimester, may delay labor	
Aspirin	Irreversible inhibition of COX -> ↓ thromboxane A2 synthesis - ↑ risk of bleeding during labor if given close to delivery ↓ Vasoconstriction and Platelet aggregation - Low doses can prevent pregnancy induced hypertension and preeclampsia Do not use during breast feeding **Avoid in 3rd trimester: Prolongs gestation, complicates delivery and ↓ placental function**
NSAIDs	**Do not use after 28th week of pregnancy** - Similar effect on mother and fetus -> See Aspirin - Selective COX-2 should be avoided, there is no data
Opioids	**Only prescribe with compelling indications** - Can develop dependence in the fetus - Respiratory depression in fetus and withdrawal when given close to delivery - Codeine associated with organ malformations (congenital heart defect, clefting etc) Codeine (Class C Risk) -> Don't do it! - 1st trimester use associated with birth defects (while organogenesis is happening) - Found in breastmilk (codeine + metabolites) in small amounts -> avoid chronic therapy (1-2 days max) - After 1st trimester can be used if acetaminophen isn't strong enough
Acetaminophen (Tylenol)	This is the 1st line option - Can be used in any trimester - No considerations for breast feeding
General Anaesthetics	
Halogenated Inhaled GA	Can be used at anytime -> the standard anesthetic used in obstetrics - During labor = uterine relaxation and risk of hemorrhage and depressive effects on newborn Ex: (Desflurane, Enflurane, Halothane etc)
Nitrous Oxide	80% crosses placenta -> Half life of 3 mins and quickly eliminated from neonatal lungs when starts breathing - Can cause spontaneous abortion and congenital abnormalities following prolonged occupational exposure - Single dose is usually fine **Avoid in 1st and 2nd Trimesters if at risk of Vitamin B12 deficiency or undergoes in vitro fertilization** - Otherwise fine in dental treatments that cannot be postponed
Injectable GA	**Monitor respiratory depressant effects on the newborn** - Ketamine contraindicated if hypertensive or have preeclampsia - Use Propofol and Thiopental if needed Ex: Propofol, Thiopental, Ketamine, Etomidate
Sedatives	
Benzodiazepines	**Avoid in 1st trimester -> Associated with clefts and heart malformations** - For the most part they are ok though for treating acute anxiety during pregnancy - Keep duration as short as possible
Local Anaesthetic	
In General	**Well tolerated in all trimesters** - No lasting effects on newborn - Avoid Prilocaine b/c risk of methemoglobinemoa Ex: Lidocaine, Bupivacaine, Articaine, Prilocaine
Anti-infectives	
Penicillin	**The Antibiotic of choice during pregnancy if there is no allergy** - Crosses placenta and is detectable in amniotic fluid
Cephalosporins	**OK during pregnancy** - Crosses placenta and is detectable in amniotic fluid Ex: Cefaclor, Cefalexin, Cefuroxin
Erythromycin and Macrolides	**OK during pregnancy and breastfeeding** - Use only if need a broad spectrum **NO Erythromycin Estolate during 2nd or 3rd trimesters** -> Hepatotoxic
Clindamycin	**OK during pregnancy** - Use when Penicillin, Cephalosporin and macrolides have all failed - Caution with use (causes C. Diff)
Tetracyclines	***CONTRAINDICATED after 15th week of pregnancy**** - Crosses placenta and binds calcium ions in developing bones and teeth - Prior to 15th week use only as a 2nd line drug. Doxycycline is the preferred choice (↓ affinity to Ca^{++})
Metronidazole	**CONTRAINDICATED during 1st trimester** - Causes clefting in some cases (but no other abnormality risks) - OK during breastfeeding
Systemic -azole antifungals	**Only use after 1st trimester if possible** - Teratogenic in animal studies - Fluconazole and itraconazole are preferred if indicated
Nystatin	**OK with pregnancy** - Just a swish and spit solution, not absorbed systemically -> should be fine

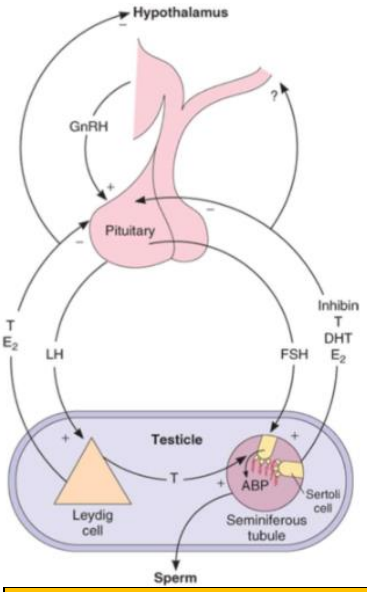
PBL 1 – Forthwind Bigge

Hypothalamus and the Hypothalamus Pituitary -Testicular Axis





Control of Testicular Function



Legend:	
ABP: Androgen Binding Protein	GnRH: Gonadotropin-releasing hormone
DHT: Dihydrotestosterone	LH: Luteinizing Hormone
E_2: Estradiol	T: Testosterone

In Words:

1. Hypothalamus produces GnRH -> Stimulates Anterior Pituitary to release LH and FSH
2. LH acts on Leydig cells in the Testes to produce Testosterone and Estradiol; FSH and Testosterone act on Sertoli cells in the seminiferous tubules to produce sperm and Androgen Binding Protein.
3. Negative feed back occurs on the pituitary gland by Estradiol, Testosterone, Inhibin, -Dihydrotestosterone; Estradiol and Testosterone act on the Hypothalamus for negative inhibition

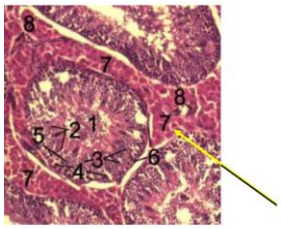
Releasing Hormones - ↑ intracellular Ca^{2+} -> vesicle fusion to release the respective hormone		
Hypothalamic hormone	**Primary Action**	**Effect**
Thyrotropin-Releasing Hormone (TRH)	Stim. Pituitary release of Thyroid stimulating Hormone (TSH) and Prolactin (PL)	Stim. Thyroid hormone synthesis and release
Gonadotropin Releasing Hormone (GnRH)	Stim Pituitary release of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH)	**LH:** - Stim follicle to secrete Estrogen in 1st ½ of menstrual cycle - Triggers completion of Meiosis and ovulation in mid cycle - Stimulates empty follicle to develop into corpus luteum (secretes Progesterone) in late cycle - Stim Interstitial cells of testes to produce and release Testosterone **FSH:** - Acts on Follicle to stimulate release of Estrogen - Acts on Sertoli cells with testosterone to stimulate sperm production
Growth Hormone Releasing Hormone (GHRH)	Stim Pituitary release of Growth Hormone (GH)	Growth
Corticotropin-Releasing Hormone (CRH)	Stim. Pituitary release of Adrenocorticotropic Hormone (ACTH)	Stimulates glucocorticoid synthesis and release

Somatostatin	Inhibits Pituitary release of TSH and GH	Pituitary control
Antidiuretic Hormone (ADH)	Produced in Hypothalamus, stored in Posterior Pit. - Promotes water absorption in renal tubules	Water Control
Oxytocin	Produced in Hypothalamus, stored in Posterior Pit. - Stimulates uterine contraction and breast milk ejection	Lactation and child-birth
Inhibiting Hormones - ↑ intracellular Ca^{2+} -> vesicle fusion to release the respective hormone		
Somatostatin	Tells pituitary to ↓ somatotropin (eventually ↓ GH) and GI tract to inhibit GI hormones	
Dopamine	Tells pituitary to ↓ prolactin Also acts as a neurotransmitter to affect other systems	
Follistatin	Tells Pit. To ↓ FSH	
Myostatin	Tells Myocytes to inhibit myogenesis	
Melanocyte-Inhibiting Factor (Melanostatin)	Inhibits release of other neuropeptides (α-MSH)	
Cortistatin	Inhibits the release of Cortisol	

Testes and Testosterone

Testes main function -> Production of Testosterone and Spermatozoa

- Spermatozoa produced within the seminiferous tubules
- Testosterone produced in Leydig cells adjacent to the Seminiferous tubules



Testis control

1. Hypothalamus sends **pulses** (90 mins) of GnRH to Anterior Pituitary cells
   -> Secrete FSH and LH
2. LH targets Leydig cells -> Testosterone production via cAMP messenger system
3. FSH target Sertoli cells to stimulate spermatogenesis (with help of T)
   - w/Prolactin, FSH ↑ LH Receptors as well
4. Inhibin (produced by testes) inhibits FSH release -> -'ve feedback

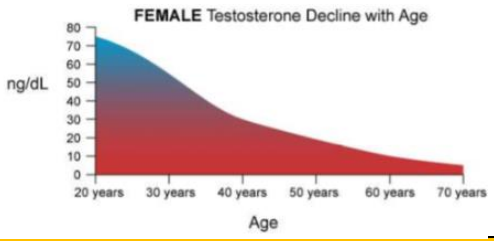
Leydig Cells	Release Androgens when stimulated by LH - Testosterone - Androstenedione - Dehydroepiandrosterone (DHEA) LH ↑ cholesterol demolase activity (Converts cholesterol to pregnanolone) -> Testosterone Synth Prolactin (PL) ↑ response of Leydig cells to LH by ↑ # of LH Receptors	**Potencies**
Testosterone	Produced by testicles (mostly) and the adrenal gland (<5%) - Driven by ACTH on adrenal gland and LH on Leydig cells Responsible for development of male sexual characteristics Establish and maintain Male functioning and Female libido **No relationship between plasma levels of T and sexual or aggressive behaviour, rather behavior has an influence on T production (↓T with stress, depression and being threatened) **	100%
5α-Dihydrotestosterone (DHT)	Androgen implicated in male pattern baldness, prostatic hyperplasia, prostate cancer Used as performance-enhancing drug -> Promotes muscle growth	90%
3 α-Androstanediol	Inhibitory androstane neurosteroid + weak androgen - Major metabolite of DHT - Potent positive allosteric modulator of GABA-A receptor -> Rewarding, anxiolytic, prosexual and anticonvulsant effects	60%
Androstenedione	4-Androstenedione -> Weak androgen and Estrogen intermediate 5-Androstenedione -> Prohormone of T 1-Androstenedione -> Prohormone of 1-Testosterone	20%
Dehydroepiandrosterone (DHEA)	Important precursor -> ***most abundant circulating steroid*** - Little function on its own, but is converted into other hormones (sex steroids) with strong function - Converted into 75% of Estrogens before menopause and 100% after menopause	10%
Androsterone	Steroid hormone, neurosteroid and Pheromone - Found in human axilla, skin and urine -> Mark your territory!	10%

Drugs that ↓ Sexual Desire

- Sedating drugs and Tranquilizers
- Antidepressants (via serotonin)
- Antipsychotics
  - **Prolactin ↑ = ↓ GnRH = ↓ LH and FSH -> ↓ T and ↓ Sperm production**
  - **Prolactin ↑ = ↓ Dopamine**

Women and Testosterone:

- Ovaries make T and A4
- Adrenal glands make prohormones DHEA, DHEAS, A4 -> Converted to T or Estrogen depending on which genes are switched on
- T levels ↓ with age, but there is no significant drop at menopause like in Estrogen



Low Testosterone	
Primary - **Testicular Failure**	- Idiopathic - Trauma - Synthesis Mutation - Chemo/Radiotherapy - Medications (Ketoconazole) - Mumps Infection - Klinefelter Syndrome - Alcoholism
Secondary - **↓ LH (Pituitary or Hypothalamic Dysfunction)**	- Exogenous steroid injections - Trauma - Infarction - Radiation - Stress - Infection - Neoplasm
Hypogonadotropic Hypogonadism - **↓ LH and ↓ FSH**	Found usually with pan-hypopituitarism (all Pit. Hormones ↓) - Can be caused by haemochromatosis -> ↑ Fe deposition = ↓ Gonadotropin release Hyperprolactinemia Glucocorticoids Neoplasm Infection
Signs and Symptoms	- ↓ Testicular Size with soft/mushy consistency = Primary dysfunction - ↓ size with rubbery consistency = Secondary dysfunction - ↓ Secondary Sexual characteristics -> (small genitalia, female pubic hairline, ↓ body hair, small larynx, upper abdomen obesity)
Testosterone Replacement Therapy	Risks: - ↑ Prostate cancer - CHF - ↓ Sperm Count - Sleep Apnea - Gynaecomastia (breast development in males) - ↑ RBC mass Buccal Patches - Bitter taste - Difficulty tasting food - Stinging or swelling of lips - Gingival pain and swelling

Hemochromatosis

Differential Dx of Oral pigmentation

Benign Lesions (Melanocytic)	- Racial Pigmentation - Smokers Melanosis - Melanotic Macule - Lentigo	**Syndromes/Disease**	- Addison's Disease - Hemochromatosis - Peutz-Jeghers Syndrome
Exogenous deposits	- Drug Induced (Contraceptives, Anti-malarial, minocycline) - Heavy Metals - Amalgam tattoo	**Neoplasms**	- Nevi - Melanoma

What is it even?	Excess iron stores become deposited in/on the internal organs Hyperpigmentation occurs on skin and mucous membranes (oral cavity is pretty rare though) ○ Oral lesions: Brown/Grey diffuse macules on the gingiva and palate Often affects the Pituitary gland -> common to find ↓ in LH and FSH = Sexual symptoms are early symptoms	
Iron Storage/Deposition	***Liver:*** - Enlargement -> cirrhosis and hepatocellular carcinoma ***Heart:*** - CHF and/or arrhythmia ***Pancreas*** - Type 2 Diabetes ***Skin*** - ↑ pigmentation	***Hair*** - Hair loss ***Joints*** - Arthritis (MCP and Proximal IP Joints of thumb, index and middle fingers ***Pituitary*** - Secondary Hypogonadism - Hypothyroidism ***Testes*** - Primary Hypogonadism
Diagnosis	**Genetics:** - Associated with HFE gene **Liver Biopsy** - When genetic testing is –'ve, but ↑ transferrin saturation, ↑ Ferritin points to hemochromatosis	
Treatment	Phlebotomy -> until ferritin is 50 µg/L - Every 2 weeks and monitor	

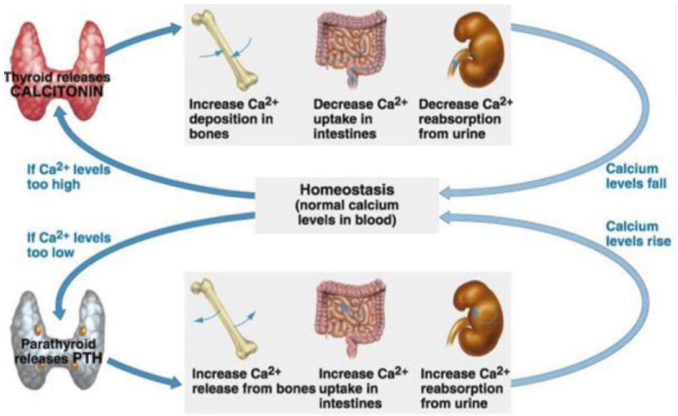
PBL 2 - Betty & Doc

Thyroid Hormones

- 2 Biologically active: T_4 and T_3 -> Effects on metabolism, growth, development
  - Affect function of almost every organ system by modifying gene transcription
  - Need to be constantly available -> 2-3 months worth of stores found in thyroid gland, and more bound to thyroxine binding globulin (TBG) and albumin in the blood

T_4 – Thyroxine	T_3 – Triiodothyronine
Biologically active prohormone - Major form in the blood (up to 20:1) - 0.03% is active in blood - 85% is converted into T_3	**Active hormone** (works on cellular level) - Far less found in blood, yet it is the most functional and active form with a longer ½ life. - 0.3% active in the flood
↑ Basal Metabolic Rate - ↑ Na/K ATPase - ↑ Respiration (O_2 consumption) - ↑ Mental alertness - ↑ GI motility and glucose absorption - ↑ Carbohydrate and fat metabolism (Gluconeogenesis, Lipolysis, glycogenolysis) - ↑ Heat generation - ↑ Cardiovascular activity (↑ HR, Contractility, and cardiac output)	

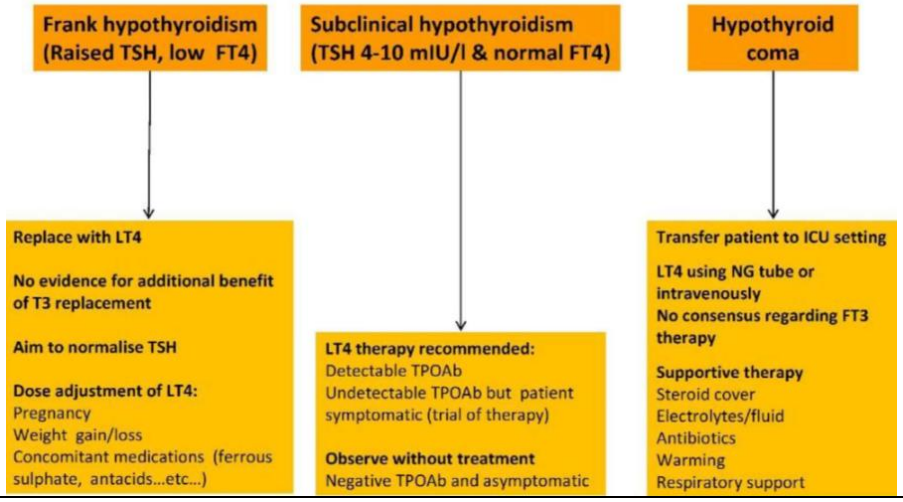
Calcitonin
Produced in thyroid by parafollicular cells (C cells) ***Function***: - ↓ blood calcium (Ca^{2+}) in response to high concentrations of Ca^{2+}-> opposite effect of PTH ***Effects***: - ↓ Blood Ca^{2+} - ↑ Ca deposition in bone - ↑ renal excretion of Ca



Hormone Disorders

Hypothyroidism	
Primary (more common)	**Secondary**
Autoimmune Thyroid Disease (Hashimoto's Thyroiditis) - Development of autoantibodies -> lymphoid infiltration of gland -> atrophy and fibrosis - More common in women in late middle age - Thyroid Peroxidase (TPO) antibodies present in high amounts *Iatrogenic* - Radioactive iodine therapy for hyperthyroid - Thyroidectomy - Radiation therapy to head and neck *Postpartum thyroiditis* - After birth, associated with postpartum depression *Thyroid infiltration* - Amyloidosis (build up of amyloid) - Sarcoidosis (granuloma formation in inflamed organs) - Hemochromatosis (Fe deposition) - Scleroderma (hardened CT and skin)	*Hypopituitarism* - Pituitary infarction - Pituitary tumors - Infiltrative disorders - Congenital TSH deficiency or receptor defect *Hypothalamic problems* - Tumor - Infarction - Infiltrative disorder

Clinical Presentation	- Dry skin - Weight Gain - Weakness - Muscle cramps/myalgia Children: Growth and mental deficits	- Cold Intolerance - Constipation - Lethargy/fatigue - *Myxedema* -> ↑ mucopolysaccharides in lips, tongue, eyes,

Differential Dx	- Anemia - Adrenocortical Insufficiency - Pregnancy - Liver Failure - Coronary artery disease - Congestive Heart Failure - Neoplasm Finding a nodule in the thyroid gland: - Cyst - Benign Tumor - Single nodules within a multinodular gland ***Hardness, rapid enlargement, cervical lymphadenopathy and fixation to surrounding tissues -> Malignancy!** **Diagnosing 1º hypothyroidism** - ↑ TSH - ↓ FT_4, FT_3, Total T_4 and Total T_3
Thyroid Findings	*Soft* - Graves Disease (1º hyperthyroidism) *Firm* - Hashimoto's Thyroiditis, Malignancy, Benign and malignant nodules *Tender* - Thyroiditis (inflammation) *Systolic or continuous bruit* - ↑ blood/turbulent flow. Heard over lateral lobes in hyperthyroid
Oral Manifestations	- Salivary gland ↑ - Xerostomia - Macroglossia - Dysgeusia (Hashimoto's specifically) - Periodontal Disease - Burning mouth syndrome - Delayed Wound Healing - Myxedema -> ↑ mucopolysaccharides (b/c ↓ breakdown of them) - Delayed tooth eruption
Myxedema Coma	Don't worry there is actually no coma…. or myxedema… = Chronic hypothyroidism with organ dysfunction and mental deterioration **Presentation**: - Stupor, Confusion, Coma - Hypothermia - Low T_4 and T_3 **Precipitating factors**: - CNS depression - Infection - Surgical Procedures
Treatment	

Hyperthyroidism	
Etiology	- Affects women more than men (6:1 ratio) -> risk ↑ with age - 99% of cases are cause by intrinsic thyroid disease (pituitary causes are very rare)
Definition	*Hyperthyroidism* -> High synthesis and secretion of TH. Hypermetabolic state with ↑ Sympathetic nervous activity *Thyrotoxicosis* -> clinical state resulting from ↑ TH action (same same but different than hyperthyroidism) *Sub-clinical hyperthyroidism* -> ↓ TSH, but normal T_3 and T_4 *Thyroid Storm* -> Medical emergency with involvement of: CV, Thermoregulatory, GI, Hepatic, and CNS systems

Presentations

Cardiac Manifestations:
- Earliest and most common symptoms
- ↑ Contractility and CO (response for ↑ peripheral O_2 requirements from ↑ metabolic rate)
- Tachycardia and Cardiomegaly (may lead to left ventricular hypertrophy -> CHF
- Palpitations

Sympathetic NS manifestations:
- Tremor
- Hyperactivity
- Emotionally unstable
- Anxiety
- Insomnia
- Weakness
- ↑ gut mobility (malabsorption, Diarrhea)

Others
- Intolerance to heat
- Diaphoresis (soft moist skin) -> Excessive sweating
- Weight loss
- Ophthalmopathy (bulging eyes)
- Hand tremor

Oral
- Periodontal disease
- Early tooth eruption
- Glossodynia (burning tongue)
- ↑ dental anxiety
- Macroglossia
- Dysphagia (from ↑ thyroid size)
- Maxillary and Mandibular osteoporosis
- Lingual thyroid tissue

↑ subcutaneous MPS

Hypothesis:
1. TSH receptor antibodies stimulate fibroblasts to ↑ MPS production
2. Fibroblasts activated indirectly via sensitised T-cells
3. Direct fibroblast stimulation by TSH receptor

Lab Tests
- Normal / ↑ TSH = NOT hyperthyroidism
- ↓ TSH – suggestive of hyperthyroidism
- ↑ T_4 and T_3 confirms hyperthyroidism
- Normal T_4 and T_3 with ↓ TSH = subclinical hyperthyroidism

Causes
- Graves Disease (50-80% of cases)
- Toxic thyroid adenoma -> Autonomous thyroid nodule, independent and unresponsive to pituitary
- Toxic multinodular goiter
- TSH producing pituitary adenoma
- Pituitary resistance to thyroid hormone (-'ve feedback malfunction)
- Thyroid cancer
- Gestational hyperthyroidism -> ↑ hCG from placenta cross reacts to stimulate TSH receptors (most in 1st trimester)
- Congenital
- Drug Induced
- Iodine Induced

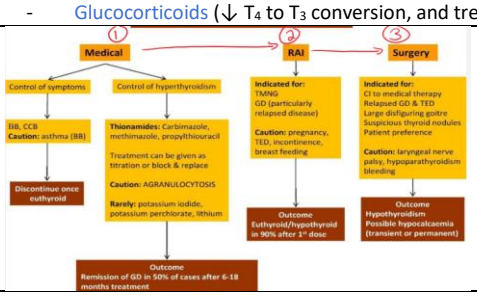
Graves Disease

Characterizations:
- Hyperthyroidism + Diffuse Goiter + Ophthalmopathy (bulging eyes)
- More common in females
- Bulging eyes from ↑ muscles enlargement and fat deposition within the orbit (from ↑ MPS)

Risk Factors:
- Family Hx of Graves or other autoimmune disorders
- Genetic mutations
- Smoking
- Infection with Yersinia eterocolitica

Tx:
- β-Blocker (Propanolol) -> blocks adrenergic activity (↓ tremor, HR, diaphoresis, and anxiety)
- Treatment to ↓ Thyroid synthesis (Drugs – Methimazole; Radioactive Iodine; Surgery)
- Iodinated radiocontrast agent (↓ peripheral conversion of T_4 to active T_3)
- Glucocorticoids (↓ T_4 to T_3 conversion, and treats autoimmune nature of disease)

Treatment



Thyroid Storm

Life Threatening Medical Emergency

Precipitating Factors:
- Surgery
- Infection
- Trauma
- Acute Iodine Load
- Extreme Stress
- Withdrawal of anti-thyroid drugs

Symptoms:
- Exaggerated symptoms of regular hyperthyroidism

Dental Management:
- Stop all proceudres -> Take vitals
- Place patient in comfortable pisition and activate EMS
- Monitor CAB
- Administer IM Hydrocortisone 100-300mg
- Cool patient down with Icepacks

Hospital Management:

- Immediate Tx to ↓ thyroid hormone levels -> Large doses of anti-thyroid drugs (PTU, Methimazole), Glucocorticoids, Dexamethazone (↓ release of hormones, and ↓ conversion ot T_4 to T_3)
- Cold Baths
- Rehydration with isotonic saline IV
- β-blockers
- Sodium Ipodate -> restores T_3 to normal levels
- Oral carbimazole -> inhibits synthesis of new TH

Lingual Thyroid

- Rare developmental issue -> Aberrant caudal migration of thyroid tissue during embryogenesis
- Most common ectopic location of thyroid gland though
- Usually asymptomatic, but if large enough can cause:
  - Dysphagia
  - Bleeding from mucosal ulceration
  - Airway obstruction

Test	Normal Range	Interpretation
Radioactive iodine uptake (RIU)	5-30%	*Elevated:* hyperthyroidism *Decreased:* hypothyroidism
Thyroid-stimulating hormone (TSH)	0.5-4.5 mIU/L	*Elevated:* hypothyroidism *Suppressed:* hyperthyroidism
Total serum T_4 (TT_4)	5-12 µg/dL 64-154 nmol/L	*High:* hyperthyroidism *Low:* hypothyroidism
Free T_4 (FT_4)	1.0-3.0 ng/dL 13-39 pmol/L	*Increased:* hyperthyroidism *Decreased:* hypothyroidism
Total serum T_3 (TT_3)	1.2-2.9 nmol/L 80-190 ng/dL	*High:* hyperthyroidism *Low:* hypothyroidism
Free T_3 (FT_3)	0.25-0.65 ng/dL 3.8-10 nmol/L	*Increased:* hyperthyroidism *Decreased:* hypothyroidism

Dental Management	
Generally	If either hypo-hyperthyroidism is well controlled -> No problems with routine dental care *If uncontrolled* consult physician to determine risks with: - LA use - Infection risk - Bleeding risk - ↓ wound healing - Medication interactions and altered metabolism
Hypothyroidism	Exaggerated response to CNS depressants (Sedatives, Narcotics) Can have respiratory depression -> Keep patient comfortable, in semi-upright position (possible O_2 supplementation) *Myxedematous Coma* -> Cause by CNS depressants, Infection, Surgery
Hyperthyroidism	Methimazole and Carbimazole: ↑ risk of infection PTU: ↑ Salivary stones and ↑ effects of warfarin ***Aspirin and NSAIDS ↑ free T_4 -> makes it worse**** Epinephrine caution if taking β-Blockers: - Epi causes vasoconstriction via α-adrenergic receptors, and dilation on β2 receptiors - Non-selective β blockers eliminate vasodilation effect of epi -> making the vasoconstriction action stronger (↑ BP)

Hypothyroidism	**Hyperthyroidism**
- Weight ↑	- Weight ↓
- Lethargy	- Nervousness and Tremor
- Cognitive Impairment	- Hypertension
- Depression	- Heart Palpitations and Tachycardia
- Constipation	- Atrial Fibrillation
- Goitre	- Muscle Weakness
- Dry Skin	- Goiter
- Cold Intolerance	- Diaphoresis and clammy hands
	- Heat Intolerance

Goiter

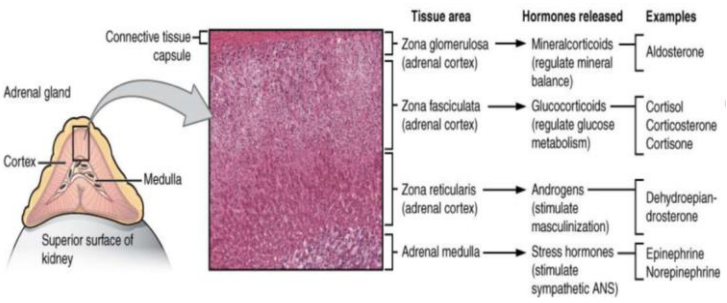
= Enlargement of Thyroid gland -> not always indicative of disease though

- If ↓ iodine in diet = ↓ TH produced. = ↑ TRH and TSH release. TSH causes growth of thyroid cells = Goiter

PBL 3 – Leslie Davis

ACTH Release from Anterior Pituitary:

- Cholesterol converted to pregnenolone within the adrenal cortex -> Precursor to progesterone, estrogen, glucocorticoids, and mineralocorticoids
  - -> ↑ Cortisol Production in Zona Fasciculata
  - -> ↑ Androgen production in Zona Reticularis
  - -> Helps ↑ Aldosterone production in Zona Glomerulosa (main mechanism is regulated by Renin though)

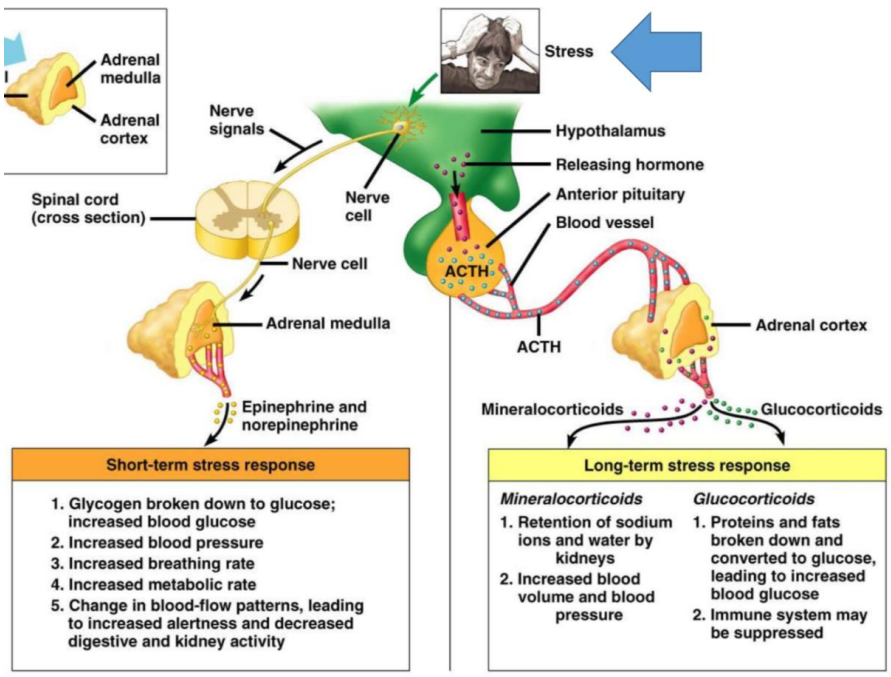


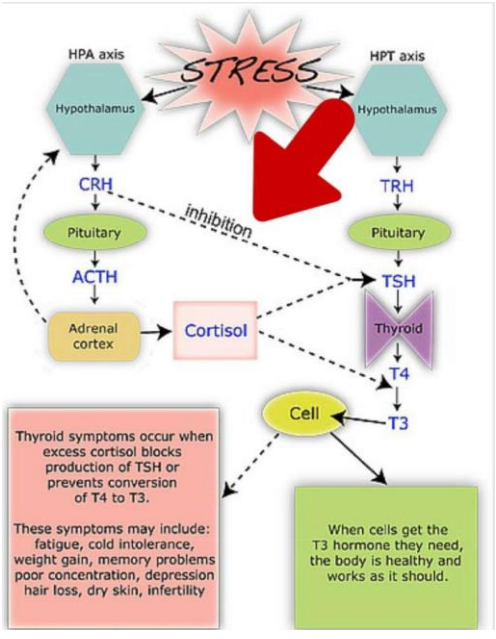
Adrenocortical Hormones

Hormone	Functions
Cortisol	Helps Body respond to Stress - ↑ Blood sugar (gluconeogenesis, glycogenolysis -> Anti- Insulin effects ->↑ metabolism of fat, protein, and carbs - ↓ Immune system (to ↓ inflammation) -> ↓ lymphocyte mitotic activity (↓ #'s) -> ↓ T-cell proliferation and eosinophil circulation -> ↓ NF-kB = ↓ cytokine production (IL-2, IFN-γ, IFN-α, and TNF-α -> ↑ Serum neutrophil # by ↓ adherence to vasculature - Maintains blood pressure Excess Cortisol -> ↓ bone density
Aldosterone	- Regulates salt and H_2O homeostasis
Androgens	- Maintain secondary sex characteristics (Testosterone, Androstenedione, 17 hydroxyprogesterone, Dehydroepiandrosterone sulphate (DHEAS))

Cortisol Regulation

1. Stress (as shown below)



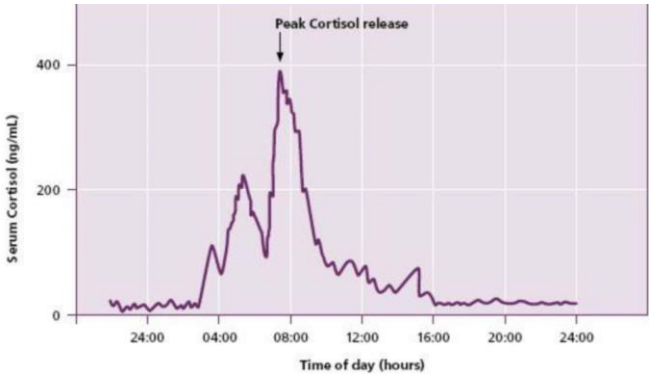


2. Circadian Rhythm

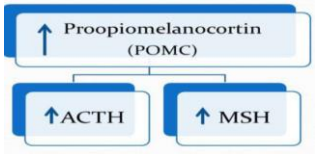
- Cortisol release is regulated in part by the central clock -> Suprachiasmatic nucleus within the nucleus

- Levels peak at 8am and gradually decrease throughout the day (with a total minimum around midnight) -> After midnight levels start to rise again until they peak (Cortisol Awake Response)

- This cycle has been shown to be reversed in people who work night shift



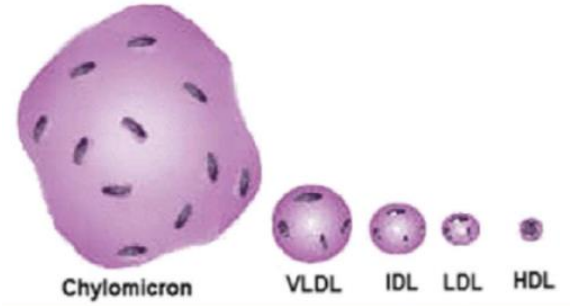
Addison's Disease (Adrenal Insufficiency)

Definition	↓ Production of Glucocorticoids, Mineralocorticoids or both	
Pathophysiology	*Primary* -> dysfunction/destruction of adrenal cortex - ↓ Production of adrenal hormones - Destruction of any of the 3 layers of the cortex	*Secondary* -> ↓ ACTH or ↓ CRH (upstream problem)
Causes	- Autoimmune Disease (80-90% of cases) - Often antibodies formed against steroidogenic enzymes - Neoplasm (Either of adrenal gland, pituitary, or hypothalamus) - Bilateral hemorrhage and/or Infarction - Infiltration (metastasis, amyloidosis, sarcoidosis, hemochromatosis, scleroderma)	Congenital ACTH deficiency Pituitary abnormality Hypothalamic abnormality
Signs and Symptoms	Mostly non-specific and vague symptoms: - Weakness and fatigue - ↓ appetite, Unexplained weight loss - Dehydration - Orthostatic hypotension - Hyperpigmentation -> POMC is gene precursor for both ACTH and Melanin secreting hormone. With ↑ ACTH already, POMC will ↑ MSH = ↑ pigmentation GI - Nausea, Vomit and Abdominal Pain Neurologic - Depression - Psychiatric and psychological disturbances Musculoskeletal - Arthralgias, and Myalgias Biochemical - Hyperkalemia (from ↓ aldosterone) - Hypoglycemia - Hyponatremia (from ↓ aldosterone)	
Dental Treatment	Routine Tx - Properly evaluate pt for risk of adrenal crisis - Normal dental care and minor surgical procedures -> do not ↑ stress to precipitate crisis - No corticosteroid supplementation is needed (pt just takes normal dose within 2hrs of the appointment) - LA is fine, and encouraged to ↓ pain and stress For major Surgery - 2-4x increased in regular dosage of steroids prior to appointment -> ***"Rule of Two"***	
Adrenal Crisis	*Symptoms* - ↓ consciousness, wet clammy hands, confusion, weakness, fatigue, headache, abdominal pain, nausea, vomit, hypotension - Precipitated by ↓ endogenous steroid production + not taking supplemental steroid prior to major surgery *Management* - Stop all treatments -> stop bleeding - Place patient semi-supine and activate EMS - Monitor CAB's + vitals - Administer IM or IV steroids -> Hydrocortisone 100mg or dexamethasone 4mg - Start IV line (if trained) 5% dextrose in Ringer's Lactate - Check blood glucose -> administer 1mg glucagon IM if needed - If cardiac arrest begins -> 0.5mL IM Epinephrine 1:1000	

PBL 4 – Mona Lisa

Types of Lipids:

- **Storage** Lipids (Triglycerides)
- **Structural** Lipids (Phospholipids)
- **Signalling** Lipids (Steroid Hormones)
- **Transporting** Lipids/Lipoproteins (Chylomicrons, VLDL, IDL, LDL, HDL)
  - Made of cholesterol + Triglycerides + Proteins
  - Single phospholipid + Cholesterol outer shell
  - Transports cholesterol, triglycerides and lipids around body



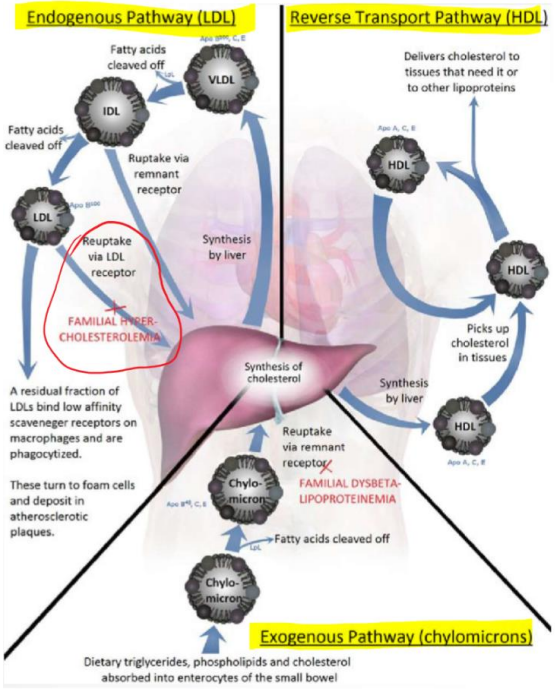
Relative sizes of lipoproteins[19]

Chylomicron	Carries triglycerides (TG) from intestines to: - Liver - Skeletal Muscle - Adipose Tissue
VLDL **(Very Low Density Lipoprotein)**	Synthesized in Liver - Carries TG from liver to adipose and muscle - Loses some TG to become IDL
IDL **(Intermediate Density Lipoprotein)**	Intermediate between VLDL and LDL - Loses some TG to become LDL
LDL **(Low Density Lipoprotein)**	Delivers cholesterol, TG and phospholipids to periphery - Most Cholesterol than all LP's -> Used for cell membrane and steroid hormone synthesis
HDL **(High Density Lipoprotein)**	Synthesized in Liver - Mobilize cholesterol from the periphery back to the liver - Reverse Cholesterol transport

Lipid Metabolism

3 pathways:

1. *Exogenous Pathway*
   - Dietary absorption through intestines
2. *Endogenous Pathway*
   - Hepatic-derived lipoproteins -> Circulate through blood until the lipids they contain are taken up by peripheral tissue or are cleared by liver
3. *Reverse Cholesterol Transport*
   - Unused cholesterol is brought back to liver with HDL



Lipoprotein Lipase: -> on Endothelial cells lining vessels

- Catalyses hydrolysis of lipids in chylomicrons and lipoproteins -> Release glycerol and fatty acids to be absorbed in adipose and muscles

Hormonal Control:

Hormone	Effect on Lipolysis
Insulin	↓ Lipolysis
Glucagon	↑ Lipolysis
Cortisol	
Growth Hormone	
Epinephrine	

Diabetic Dyslipidemia

= ↑ TG, ↑ LDL, ↓ HDL

- This lipid profile is a major link between diabetes and cardiovascular risk (Especially in obese type II patients with poor glycemic control)
- *Insulin resistance* leads to ↑ Lipolysis and ↑ Circulating FFA -> FFA is delivered to liver = ↑ VLDL production and release -> Deposits TG and cholesterol in adipose to become LDL (bad for arthrogenesis)
  - Worse because Type II pt's typically poor diet and ↓ exercise

Diabetics ↑ Rate of atherogenesis

- Hyperglycemia impairs endogenous antioxidant defences and induces free radicals = ↑ Advanced Glycation End products (AGE)
  - AGE = proteins/lipids that become glycated because of hyperglycemia -> ↑ production of proinflammatory cytokines = worse atherogenesis

HFH (Heterozygous Familial Hypercholesterolemia)

What is it?	Autosomal Dominant (has high penetrance) - If heterozygous = 1 defective allele -> Still affected though - If homozygous = both alleles defective -> Even worse (usually dead by 20) = Hepatic LDL Receptor Deficiency -> ↓ LDL receptor binding and ↑ LDL remaining in plasma to accumulate in plaques -> Chylomicron reuptake in the liver impaired as well
Atherosclerosis	Degree depends on: - Homo or Heterozygous - Serum LDL levels - Presence of other atherogenic lipoproteins (like Lp(a) -> more aggressive form of LDL, inhibits fibrinolysis = ↑ thrombus) - Presence of other risk factors (Smoking, Diet, ↓ Exercise etc) ***Smoking -> ↑ oxidation of LDL, ↓ HDL, ↑ LDL ↑ TG, ↑ Leukocytes*** 1. Damage of endothelial cells allows LDL to enter subendothelial space -> Oxidised LDL 2. Macrophages eat LDL and turn into foam cells -> Fatty Streak 3. Macrophages + T cells secrete proinflammatory cytokines -> Recruits smooth muscle cells from media into intima 4. SMC ↑ ECM production (collagen, elastin, Proteoglycans) -> Fibrous Cap 5. Apoptosis of SMC in deep layers creates necrotic core 6. Microvascular network forms and is susceptible to rupture -> Vasa Vasorum
Treatment	*Non-Pharma* - ↓ Risk factors - Lifestyle Modifications - Dietary Mods - ↑ Physical Activity *Pharma* - Antiplatelet drugs (Aspirin, Clopidogrel) - Anti-atherogenic drugs (Statins etc.)

Periodontal Health

Smoking	↑ expression of cytokines involved in perio. destruction Acrolein + Acetaldehyde = ↓ Gingival fibroblasts Abnormal phagocytosis by Polymorphonuclear leukocytes (PMN's) ↑ subgingival bacteria ↓ Mucosal blood flow **Heavy smokers have 6-7x ↑ alveolar bone loss, 90% of pt's with refractory periodontitis are smokers**
Cardiovascular Disease	Associations between Periodontal Disease and CVD (both effect each other) - Severity of perio disease correlates with risk of CVD - Educate patient! ***Direct Theory*** 1. Oral/Periodontal pathogens infiltrate into vasculature through ulcerated gingiva -> Inflammatory reactions detrimental to cardiovascular system - ↑ Hepatic acute-phase proteins -> Damages vasculature - ↑ Dyslipidemia - Activates Adaptive immune system -> Antibodies produced have cross reactivity with endothelium and LDL = ↑ infiltration into sub endothelium and ↑ Macrophage (turns into foam cells) ***Indirect Theory:*** 1. Bacterial endotoxins or pro-inflammatory cytokines leak into bloodstream -> Triggers inflammation - Liver ↑ acute-phase response (↑ CRP, Fibrinogen, Amyloid A protein etc) - ↑ Cholesterol synthesis - Chemokines cause ↑ in adaptive and innate immunity and initiate cell migration and activity
Calcified Carotid Atheroma	**MOA:** - Stenotic atheromatous plaque in carotid arteries -> Major contributor to cerebrovascular embolism - 1st develops at arterial bifurcation from ↑ endothelial damage and shear forces - May be visible in pan. Radiograph -> where carotid splits into external and internal carotids (adjacent C3 and C4) **Management:** - CAREFUL with extraoral exam -> don't want to dislodge it at sent it into brain - Refer to physician for dx **If have bypass surgery** - Wait 6 months until performing any dental surgery is there was ischemic damage - If no ischemia only need to wait 1 month

PBL 5 – Sharon

Scabies

What is it?	= Contagious skin condition/infestation of mites - Lay eggs in skin which hatch and grow into adult mites - Can last for months – years
Signs and Symptoms	Nocturnal Itching Rash Sores (often from scratching the itch) Thick crusts on skin -> typical of severe form "crusted scabies"
Tx	Scabicide creams

Glasgow Coma Scale

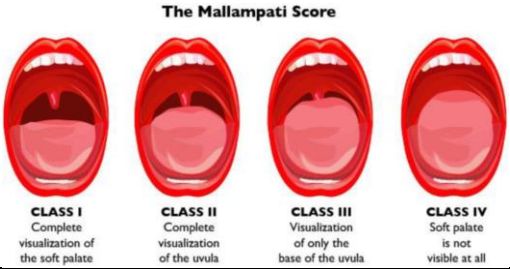
Eye Opening		Verbal Response		Motor Response	
Spontaneous	4	Normal and oriented	5	Normal	6
To Voice	3	Disoriented, confused	4	Localised to pain	5
To Pain	2	Incoherent words	3	Withdraws from pain	4
None	1	No words, just sounds	2	Arms, wrists, fingers curled in to chest (Flexion)	3
		None	1	Arms, Legs, Arms, Fingers extended out (Extension)	2
				None	1

Total from each category is tallied to quantify level of brain injury

- Severe = 3-8
- Moderate = 9-12
- Mild = 13-15

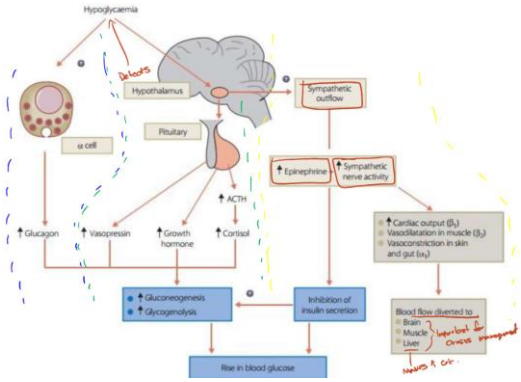
** Things affecting patient level of conscious (not related to brain injury) can confound the numbers: *Drugs, Alcohol, Shock, Hypoxia*****

More Random Things

Foot Ulcer Etiology	**Neuropathic** - ↓ Sensation common in diabetics, and chronic alcoholics **Arterial** - Diabetics have micro and macrovascular changes = ↓ blood flow (↓ wound healing)	**Venous** - Compromised veins with dysfunctional valves = lower extremity edema **Decubitus** - Excessive prolonged pressure on heals during bedrest -> ischemia = ↓ wound healing
C-Reactive Proteins	= Inflammation indicators from the liver - Triggered by IL-6 secretion from macrophages and T cells Levels rise in 4-6 hours (fast) and last 5-7 hours (also relatively fast) - Non-specific indication for inflammation somewhere in body - Levels of CRP indicative of severity of inflammation Mild Inflammation (Bacterial or viral): 10-40mg/L Moderate inflammation (Bacterial or viral): 40-100mg/L Marked Inflammation (Bacterial): 100-200mg/L Severe Inflammation (Bacterial, Vasculitis, arthritis): >200mg/L	
Mallampti Score		Dr. Matthew loves this. Just say the name and you will be his new favorite
High Anion Gap metabolic acidosis	Difference between cations and anions in the blood: $[Na^+] – ([Cl^-] + [HCO_3^-])$ = Anion gap - When Value is high -> Acidosis -> H^+ reacts with HCO_3^- = HCO_3 consumed as a buffer = [↓]	

Glucose Homeostasis

	Glycogenolysis	Gluconeogenesis	Ketone Bodies	Lipolysis
Glucagon	↑	↑	↑	
Insulin	↓	↓	↓	↓
Cortisol		↑		↑
Growth Hormone	↑	↑	↑	↑
Epinephrine	↑	↑		↑



Diabetes

= Metabolic disorder characterised by -> Defective Insulin secretion, action or both

Diagnostic Values	*Fasting Glucose*: ≥ 7mmol/L *2hr Plasma Glucose*: ≥ 11.1mmol/L *Glycated hemoglobin (A1c)*: ≥ 6.5% *Random Plasma Glucose*: ≥ 11.1mmol/L *Pre-diabetes:* - Impaired fasting glucose - Impaired Glucose tolerance - A1c: 6.0-6.4%
Classifications	***Type I*** - Autoimmune pancreatic β-cell destruction ***Type II*** - Begins as peripheral tissue insulin resistance (↓ insulin response) - Progresses to insufficient insulin production (β-cell dysfunction) ***Gestational*** - Abnormal glucose tolerance with onset during pregnancy
Long Term Complications	Associated with production of oxidative by-products -> oxidative stress damages vasculature and nerves - Glycosylated end products can also directly cause vascular damage ***Microvascular***: - Neuropathy - Nephropathy (CKD) -> Leads to renal failure - Eye Complications -> Retinopathy, Cararacts - Foot Complications -> Ulcers, gangrene, arthritis (Paresthesia, Ischemia, ↓ healing) ***Macrovascular*** - Coronary Circulation -> MI, Infarction, ↑ atherosclerosis, Hypertension - Cerebral Circulation -> TIA, CVA - Peripheral Circulation -> Ischemia, claudication - Foot Complications -> Ulcers, gangrene, arthritis ***Orally*** - Gingivitis and Periodontal disease -> accelerated bone loss - Salivary gland dysfunction -> Xerostomia - Sialosis - ↓ Healing, ↑ Infection - Oral Candida infection - Neuropathy - Burning mouth syndrome - Dysgeusia - Altered tooth eruption

↑ Risk of infection	↓ Neutrophil adherence (reversed with insulin injection) ↓ Chemotaxis ↓ phagocytosis ↓ Bactericidal activity ↓ ***Cell-mediated immunity*** (reversed with insulin injection) ****Because of this, acute oral infections can be a significant issue -> often leads to ↓ control over insulin levels**** - Treat Infections AGRESSIVELY: Open and Drain, Extraction, Pulpotomy, Antibiotics - Will usually need ↑ Insulin while infection is being managed Fasting Glucose: 206mg/100mL -> No ↑ infection risk 207-229mg/100mL -> 20% ↑ Infection risk 230mg/mL + -> 80% ↑ infection risk
Diabetic Ketoacidosis	
Whats going on?	With ↓ insulin, glucose isn't available for the brain (thinks it's starving) -> Needs to use ketones for energy - Lipoprotein lipase breaks down adipose tissue and ↑ FFA -> Liver converts FFA to ketone bodies - Ketone Bodies: Acetoacetic acid + β-hydroxybutyrate ***Build up of ketoacids = ↓ blood pH***
Precipitating Events	Inadequate Insulin administration Infection Infarction Drugs (cocaine) Pregnancy **Usually develops over 24hrs**
Manifestations	Abdominal Pain, Vomiting, Nausea - Inflammatory mediators from β oxidation irritate GI Dehydration - ↑ Vomiting = H_2O loss - Abdominal pain and nausea = ↓ H_2O intake - Osmotic diuresis ↓ Blood volume - Hypovolemia -> eventually hypovolemic shock - Tacchycardia ↓ Consciousness - Cerebral edema and acidosis Plasma Acidosis - Kussmaul Breathing in order to blow off the excess acid in the blood **Kussmaul** **K** – Ketones **U**- Uremia **S**- Sepsis **S**- Salicylates **M**- Methanol **A** – Aldehydes **U** = nothing **L** – Lactic Acid
Treatment	Progress through PCAD - Administer 5% dextrose and water IV or Normal saline before EMS if possible In the ER - Restore normal ECFV and electrolytes with IV fluids - Correct acid base balance -> Bicarbonate therapy if pH ≤7 - Correct Hyperglycemia with insulin injection

Doses of Oral Antibiotics for Odontogenic Infection

Antibiotic	Usual adult dosage	Usual pediatric dosage
Penicillin V	600 mg every 6 h	25–50 mg/kg/day divided into 4 doses
Amoxicillin	500 mg every 8 h	25–50 mg/kg/day divided into 4 doses
Cephalexin	500 mg every 6 h 2 g 1 h pre-op (joint prophylaxis)	25–50 mg/kg/day divided into 4 doses
Metronidazole	500 mg twice daily	15–30 mg/kg/day divided into 3 doses
Clindamycin	300–450 mg every 6 h	10–30 mg/kg/day divided into 3 or 4 doses
Moxifloxacin	400 mg daily	Not established
Erythromycin	500 mg enteric coated every 8 h 333 mg enteric coated every 6 h 250 mg (base) every 6 h	30–50 mg/kg/day divided into 2–4 doses

PBL 6 – Dr. Stan Dardman

Differential Dx for 2º Hypertension	
A – Apnea, Aldosteronism	**D** - Drugs
B – Bruits, Bad Kidneys	**R** – Renal Disease
D – Catecholamines, Cushings	**H** - Hyperaldosteronism
D – Drugs	**H** – Hyperthyroidism/Hypothyroidism
E - Endocrine	**C** – Coarctation of the Aorta
	C - Cushings
	P - Pregnancy
	P- Pheochromocytoma
	S – Sleep Apena

Metabolic Syndrome

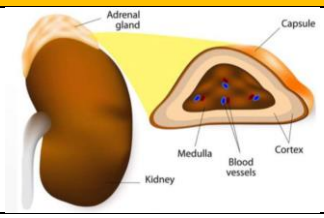
Dx when 3/5 present:

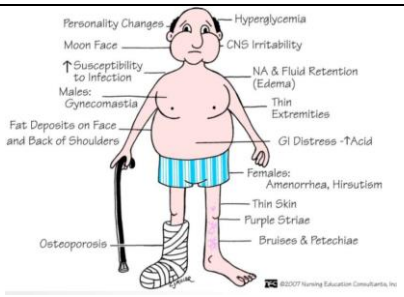
- **Abdominal Obesity**
- **↑ BP**
- **↑ Fasting Blood Glucose**
- **↑ Serum Triglycerides**
- **↓ HDL**

Problems:

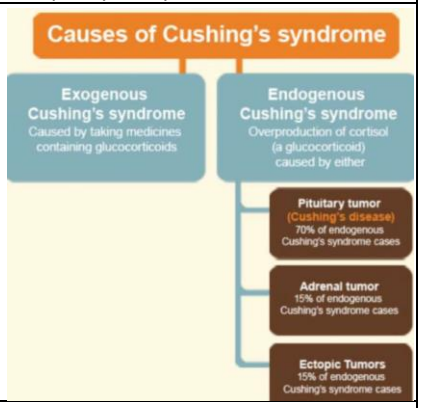
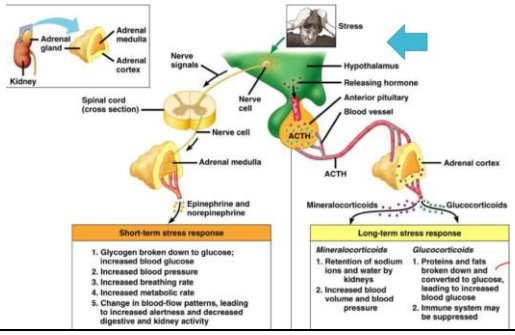
- ↑ Risk of CVD and Type II DM

Taking vitals on these patients is imperative

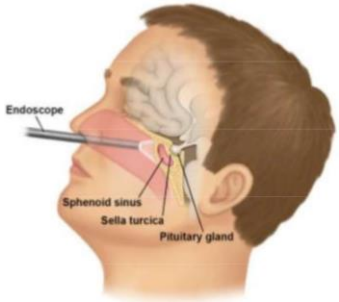
Primary Aldosteronism – Conns Syndrome	
Etiology	Bilateral Adrenal Hyperplasia -> 70% Aldosterone-Producing Adrenal Adenoma/ Carcinoma Unilateral Adrenal Hyperplasia Glucocorticoid-Remediable Aldosteronism -> No longer a transient ↑ with ACTH stimulation, but an actual ↑
Tx	Surgery (1st line for carcinoma's and adenoma's) - Unilateral adrenalectomy = 1st line for bilateral enlargement Calcium Channel Blockers Mineralocorticoid Antagonists Glucocorticoids (in the case of GRA)
Pheochromocytoma	
Definition-ology	= Catecholamine producing tumor (often located in adrenal medulla) - Norepinephrine is produced more than epinephrine Results: - ↑ HR, ↑ Contractility, ↑ Vasoconstriction (2º HT) 
Signs and Symptoms	Sympathetic Nervous System Hyperactivity - Hypertension - Headaches - Tachycardia - Palpitations - Diaphoresis - Weight Loss - Anxiety (Resembles panic attack) - Orthostatic Hypotension - ↑ Blood glucose - ↑ Risk of Type II DM ****VERY high risk of lethal cardiac/Cerebrovascular complications with Vasoconstrictors -> Contraindicated****
Tx	Surgery to remove tumor Chemotherapy Radiotherapy Meds to control symptoms: - α-Adrenergic Blockers - β-Blockers

<table>
<tr><th colspan="3">Hyper-Cortisol Secretion - Cushing's Syndrome
- The main ish for this case</th></tr>
<tr><td>Etiology</td><td><u>ACTH-Dependent</u>
- Cushing Disease (different from Cushings syndrome)
- Adrenal Hyperplasia
- Ectopic ACTH Syndrome
(Small cell Lung cancer, Non-small cell lung cancer, Panreatic tumor)</td><td><u>ACTH Independent</u>
- Iatrogenic
- Adrenal Adenoma/Carcinoma
- McCune-Albright syndrome</td></tr>
<tr><td>Clinical Presentations</td><td>- Weakness + Clumsy
- Central Obesity
- ↑ Acne
- ↑ Bruising
- Tachycardia
- Moon Face
- Hypokalemia
- Thin extremities
- ↑ Weight
- ↓ Libido
- Polyuria
- Depression
- Hypertension
- Hyperglycemia
- Buffalo Hump</td><td> 

This guy looks pretty cushy to me!</td></tr>
<tr><td>Cushings Disease Vs Syndrome</td><td colspan="2">Cushing's syndrome = collection of signs and symptoms from prolonged ↑ cortisol

Cushing's Disease = Specific to pituitary tumor secreting ↑ ACTH = ↑ cortisol
 
</td></tr>
<tr><td>Functions of Cortisol</td><td colspan="2">Necessary for body to deal with stress and low blood glucose
- ↓ Immune system, controls inflammation
- Inhibits NF-kB -> ↓ Production of IL2, IFN-γ, IFN, α, TNF-α
- ↓ Function of neutrophils, macrophages, APC's, NK cells, and B and T lymphocytes
- ↓ Histamine secretion
- ↓ Eosinophils
- ↓ Neutrophil adhesion = ↑ Neutrophil count in blood
- Maintain BP and cardiovascular function
- ↓ Bone Remodelling
- ↑ Metabolism of fat, protein and carbohydrates -> anti-insulin function in periphery (Brain and heart are spared, extra glucose used by heart and brain)
 
</td></tr>
<tr><td>Tests</td><td colspan="2"><u>Dexamethasone Suppression Tests **(Will be on test)**</u>
- Dexa is 30x more powerful than cortisol! Its power is over 9000!
- Synthetic steroids interact more with clucocorticoid receptor and are metabolised slowly = ↑ effect
<u>1. Low Dose Dex. Test</u>
- If HPA axis is normal, a supraphysiological (↓ than normal cortisol levels) dose will Inhibit ACTH secretion = ↓ cortisol
- If Cushing's -> No ACTH inhibition, still will have ↑ Cortisol

<u>2. High Dose Dex Test</u> -> When Cushings syndrome is confirmed and need to know etiology
- If Cushing's <u>Disease</u> (Pituitary tumor) -> Need high dose of of Dex. To supress ACTH secretion = ↓ Cortisol
- If there is no suppression of cortisol -> Means ↑ ACTH is coming from somewhere else = Ectopic Tumor</td></tr>
</table>

Tx	**Hypophysectomy** - Pituitary surgery to remove the tumor *Complications:* - Hypopituitarism (if remove all or most of pituitary) - Diabetes Insipidus - Meningitis - GH Deficiency - Hypogonadism - Hypothyroidism - Andrenal Insufficiency  **In the case of resulting hypopituitarism will need hormone replacement therapy for life** **Other Tx:** - Unilateral adrenalectomy (for carcinoma and adenomas) - Adrenolytic agents -> Mitotane, Ketoconazole, Metyrapone
Dental Considerations	Consider their other issues related to ↑ Cortisol: - Hypertension - Diabetes - Osteoporosis - ↓ Wound Healing - ↓ Immunity - Depression

The Rule of Two:

For Major Surgical Procedures:

- 2-4x ↑ in Corticosteroid dose 2hrs before treatment

For Minor Surgical Procedures/Routine Treatment:

- No Supplementary dose needed over their regular dose, provided they have taken it within 2hrs before appointment

Post Surgery Corticosteroid Tx (If patient is a healthy boi):

- If you want your patients to love you long time after a surgery, give 2mg Dexamethasone tabs BID to ↓ inflammation (and therefore pain) post surgery.
- Ensure it won't kill them though