Clinical info (u can skip it…)
-steroids usage is very effective; patients love it! But the price is their health, cuz tolerance to it is very strong & quick. -excessive use of steroids leads to AGC dysfun, cuz the body now have an external source of steroids, so it doesn't have to waste energy & elements on the daily synthesis of its own steroids -hyperkalemia causes cardiac arrest -when taking a sample to measure Ca, don't let the patient move his muscles for that it alters ECF free Ca (Ca is used for muscles contraction) - when taking a sample to measure K, cuz RBCs will lysis and expel their inner concentrated K, and it will alter the results, cuz we're trying to measure ECF K -septicemia causes acute adrenal failure. In addition, the body fights it and forms millions of little clots in the blood, that will lead to clotting factors depletion, so its highly likely that the patient also have hemorrhage -addison's skin hyperpigmentation is due to ACTH acting on myelin -Essential Hypertension (idiopathic) is the most common cause of hypertension, 75& of all cases -GFR (is the order for AGC layers) -cholesterol is the precursor for all steroids -testosterone is formed eventually in peripheral tissue, never secreted as it is -frank hemorrhage is when the blood is so true, it has just came out of circulation with no effects on it at all -hypervolemia causes hypertension -surgeries are severe body physical stress

Cortisol	
Secretion	HT (CRH) → A. PG (ACTH) → AGC z. fasciculata (cortisol)
Regulation	-stress (physical and/or mental): inc CRH → ACTH → cortisol -diurnal rhythm: high in morning, less at night -negative FB: inc cortisol suppresses CRH & ACTH secretion
Pr bound	Strongly to CBG "cholesterol binding globulin"
CBG levels	-inc in: preg, & estrogen treatments (oral contraceptives) -dec in: hypoPremia (nephrotic syndrome)
Activ form	Free form only!
Lab	-ECF + CF = plasma (used for ACTH measurement) -ECF = serum (used for cortisol measurement) -samples must be collected early morning & late night -results are never accurate cuz of the tons of things that could alter them (stress…) (most of 24h-based measures are inaccurate)
Excretion	-by the liver -only after its inactivated by conjugation (forming glucuronides) -very small portion is excreted unconjugated (active), seen as UFC "urine free cortisol" we use it to measure things… -excreted in urine
Effects	**Over-all** -insulin antagonist -very weak MC effects -hyperglycemia (by inc production & inh its usage) **Liver** -Glugogenesis -Ketogenesis -AA uptake -AA break down (free Pr & lipids induce further Glucogenesis) **Lipid** **Muscles** Lipolysis Proteolysis

Cushing syndrome	
Is	AG hyperfun
Etiology	**ACTH-dependent** (high blood ACTH caused cushing) -PG hypersecretion of ACTH -Ectopic neoplasms 10% (tumors secreting ACTH - small lung carcinoma) -Ectopic therapy (the most common cause ever) **ACTH-independent** (blood ACTH is almost zero) -adrenal cortisol secreting tumor 20% (adenoma/carcinoma) -ectopic GC (cortisol) **Inc CBG** -cong. -preg -estrogen therapy **Other** -physio: stress, exercise, anxiety, depression… -obesity -chronic alcoholism -chronic renal failure
Symptoms	-weight gain (central obesity) -violet stria (trunk & legs) -buffalo hump -moon face -hirsutism (hair in abnormal locations) -excessive sweating -skin & muscles atrophy -proximal muscles weakness -dec lipido -amenorrhea (absence of menstruation) -infertility -psycho (euphoria…) (very first symptoms always seen is CR disturbance, if something else caused the disturbance than cushing, its called pseudocushing)
lab	-loss of ACTH rhythm -hypertension (aldosterone-like effect) “Na & H2o retention” -hyperglycemia (ass. With insulin resistance) -hypokalemia (causing alkalosis) -Pr hyper catabolism -weak immunity

<table>
<tr><td rowspan="3">diagnosis</td><td>Out-patients</td><td>-the ones visiting frequently following ups
-in for screenings (assess AG hyperfun & distinguish normal obesity from cushing obesity)
-<u>tests</u>: low dose dexamethasone suppression test
& 24h urine free cortisol measurement</td></tr>
<tr><td>In-patients</td><td>-ones staying in 24/7
-in for confirmation(mainly to rule out pseuodocushing)
-<u>tests</u>: insulin-induced hypoglycemia</td></tr>
<tr><td>Tumors</td><td>-we check its site & its nature
-<u>tests</u>: ACTH CR check
high dose dexamethasone suppression test
CRH stimulating test
Radiology</td></tr>
<tr><td>Diagnosis technique</td><td colspan="2">-screening to tell if he has cushing at all (using DXM & UFC)
If they indicate AG hyperfun
-confirming whether its pseudocushing or true cushing (using insulin-induced hypoglycemia) “when giving insulin in a non-cushing patient, it does its action & result in hypoglycemia, but insulin causes further hyperglycemia in cushing patients”
-if insulin caused hypoglycemia, diagnosis is: OH, stress, chronics…
-if insulin caused hyperglycemia, diagnosis is: true cushing
Then we diagnose the etiology of true cushing
-using the <u>tests</u> above to determine the etiology</td></tr>
</table>

Cushing syndrome tests	
(1) screening	
Note	Sensitive but not specific
low dose dexamethasone suppression test	-a low dose of DXM is given at night & sample is taken early morning -DXM suppresses CRH, so normally when taking the sample next day, cortisol should be much lessened -if the results were: <50 (indicating suppressed levels of cortisol, exclude cushing) -hepatic microsomal enzymes inducers are meds that causes the liver to strongly metabolize DXM & prevent it from reaching circulation, failing the results "phenobarbitone & phenytoin"
24h urine free cortisol measurement	-if cortisol <250 (exclude cushing - normal results) -disadv: very high risk of false negative -we can remove the risk by measuring morning-creatinine, from which we'll calculate free cortisol levels
(2) confirmatory	
insulin-induced hypoglycemia	-very high risk for death due to hypo/hyper glycemia (thus, its done only for in-patients) -contraind: in epilepsy history & heart patients -tests HT-PG-AGC axis -normally: hypoglycemia causes hypercortisolemia -steps: IV insulin → taking samples at 30, 45, 60, 90 m → normally glucose at 90m=2.2 (in cushing >200) -injected insulin amount (0.15) if the test didn't get glucose=2.2 but close, repeat it with additional 0.05 insulin -after doing the test in a non-cushing, 90m cortisol=400 (reference=150), in cushing patient, its normally already high without even doing the test, but at 90m cortisol= still very high & didn't respond to insulin -in a nutshell: True cushing: no response of hypoglycemia Pseudocushing: abnormal cortisol CR & inc CRH as response

(3) other	
Plasma ACTH	-if its undetectable: AG tumor (use radiology) -if its high: cushing -if its very high: ectopic (lung tumor) -in true cushing, high dose of DXM & CRH tests together are 100% specific & 100% sensitive
high dose dexamethasone suppression test	-used to distinguish cushing from ectopic ACTH hyperfun -suppresses to <50% of its normal values -almost all cushing patients show suppression -only 10% of ectopic hyperfun show suppression
CRH stimulating test	-measuring normal ACTH & cortisol, then measuring them 60m after CRH injection (100 unite) -normally CRH induces very high ACTH & cortisol secretion -in cushing, it shows a significant inc in ACTH & cortisol -in ectopic hyperfun, there is no response -this test very rarely fails the results (its good!)
Radiology	-AG tumors: CT -PG tumors: MRI