

Adrenal Cortex	Normal Hormone Production	Morphology	Reserve Capacity	Biosynthesis of Adrenal Cortical Hormones	
	<ul style="list-style-type: none"> •secretes many steroid hormones, but only 3 are physiologically important -hydrocortisone (cortisol) <ul style="list-style-type: none"> -1° glucocorticoid - approx. 7-13 mg/day in unstressed adult -aldosterone <ul style="list-style-type: none"> -major mineralcorticoid of adrenal cortex -approx. 50-150 µg/day -adrenal androgens <ul style="list-style-type: none"> -mild adrogenic potency -daily secretion equivalent to hydrocortisone •normally, other steroids produced in minor quantities -e.g. estradiol, testosterone, desoxytestosterone, corticosterone 	<ul style="list-style-type: none"> •normal adult gland weighs 3.5-4.5gm -total weight <ul style="list-style-type: none"> -in men = 8-9gm -in women =7-8gm •composed of 3 zones -glomerulosa <ul style="list-style-type: none"> -mineralcorticoid synthesis -fasciculata <ul style="list-style-type: none"> -glucocorticoid synthesis -sex steroids to a lesser degree -reticularis <ul style="list-style-type: none"> -adrenal androgen synthesis 	<ul style="list-style-type: none"> •acute stress <ul style="list-style-type: none"> -may → ↑hydrocortisone secretion = 200-300mg/day •some pts. lack this reserve capacity -pts. w/adrenal or pituitary disease -pts. treated chronically w/ pharmacologic doses of glucocorticoids → adrenocortical atrophy & suppressed HPA axis -these pts. may be asymptomatic until a stressful situation 	<ul style="list-style-type: none"> •cholesterol <ul style="list-style-type: none"> -major initial substrate •adrenal glands have small storage capacity for hormones •thus, circulating adrenal hormones represent newly synthesized steroids 	
ACTH	<ul style="list-style-type: none"> •component of a larger intrapituitary precursor (“pro-opiomelanocortin”) -structure includes β-lipotropin <ul style="list-style-type: none"> - β-lipotropin includes sequence of β-MSH, β-endorphin -β-endorphin includes sequence of metenkephalin -β-endorphin blood levels parallel ACTH secretion 	<p>ACTIONS</p> <ul style="list-style-type: none"> •directly controls hydrocortisone secretion •can briefly → aldosterone secretion •partially regulates adrenal androgen secretion 	<p>SECRETORY PATTERN</p> <ul style="list-style-type: none"> •ACTH secretion has diurnal variation -peaks in the morning -nadir in late evening -controlled by higher centers of CNS 	<p>REGULATION OF SECRETION</p> <ul style="list-style-type: none"> •CRH→ ↑ACTH secretion→ ↑hydrocortisone→ ↓CRH & ↓ACTH -feedback inhibition by free hydrocortisone at hypothalamus & pituitary •vasopressin → ↑ACTH •stress → ↑ACTH •inflammatory stress → cytokines from activated T-cells (TNF-α, IL-1β, IL-1α, IL-6) → ↑ACTH & ↑cortisol •HPA axis products (i.e. glucocorticoids) → ↓inflammatory response 	<p>NORMAL VALUES</p> <ul style="list-style-type: none"> •up to 80pg/ml -at A.M. in an unstressed pt.
	Etiology	Clinical			
Hyperadrenalism (Cushing’s Syndrome)	<p>2 main classifications</p> <p><u>ACTH-dependent</u></p> <ul style="list-style-type: none"> •ACTH hypersecretion by a tumor in anterior pituitary -most common etiology → excessive hydrocortisone production by both adrenal cortices -pituitary dependent ACTH hypersecretion is called Cushing’s Disease •ectopic ACTH secretion -benign or malignant tumors <ul style="list-style-type: none"> -most found in the chest -oat cell carcinoma of lung -bronchial carcinoid -thymic tumors <p><u>ACTH-independent</u></p> <ul style="list-style-type: none"> •benign or malignant tumor of adrenal cortex 	<ul style="list-style-type: none"> •abnormalities due to hypersecretion of glucocorticoids •in some pts., signs of excess androgens or mineralcorticoids are also present <p><u>Hydrocortisone excess</u></p> <ul style="list-style-type: none"> •abnormal fat distribution -moon face, central obesity, fat pad •↑protein catabolism -paper-like skin -easy bruisability→ ecchymoses -striae -osteoporosis w/hypercalciuria <ul style="list-style-type: none"> -↓bone formation, ↑↑↑bone resorption -impaired wound healing -muscle wasting <ul style="list-style-type: none"> -most marked in extremities -↓inflammatory response to infection •↑gluconeogenesis →Diabetes mellitus -hydrocortisone → ↓insulin activity •hyperexcitability→ psychiatric symptoms •↑periph. vasculature sensitivity to catecholamines→ HTN •leucopenia & eosinophilia •hyperpigmentation 2° to excess ACTH -not present in pts. w/ adrenal neoplasms <p><u>Androgen excess</u></p> <ul style="list-style-type: none"> •hair growth in women •deepened voice in women •acne •loss of scalp hair -temporal areas, crown of head •erythrocytosis •adnormal/absent menses •enlarged clitoris •anabolic effects -may mask catabolic effects of hydrocortisone <p><u>Mineralcorticoid excess</u></p> <ul style="list-style-type: none"> •hypokalemia → alkalosis -↑↑↑cortisol → activation of renal tubular/mineral-corticoid receptor -renin-AII-aldosterone is suppressed •usually occurs in Cushing’s syndrome due to Ectopic ACTH 			

<p>Hyperadrenalism (Cushing's Syndrome) [continued]</p>	<p>Diagnostic Tests</p> <p><u>Plasma ACTH</u></p> <ul style="list-style-type: none"> •no ACTH present -adrenal tumor •inappropriate ACTH levels -Cushing's disease -ectopic ACTH syndrome -substantial overlap between ACTH levels seen in both types of pts._ <p><u>Plasma adrenal hormones</u></p> <p><u>Hydrocortisone</u></p> <ul style="list-style-type: none"> •radioimmunoassay -measures total hydrocortisone -most circulates bound to corticosteroid-binding globulin (CBG) •normal pts: < 5% is free (biologically active) -range: 4-23µg/dl -↑levels in A.M. (> 10µg/dl) -diurnal variation •hyperadrenalism -diurnal variation disappears <p><u>Adrenal Androgens</u></p> <ul style="list-style-type: none"> •adrenal androgens directly measurable in the blood •DHEA levels ↑ and ↓ in a diurnal rhythm •DHEA-S is relatively stable -more often used in clinical eval._ <p><u>Urinary</u></p> <ul style="list-style-type: none"> •24hr free hydrocortisone -most precise measurement -normal pts.: ≤ 50µg/day -hyperadrenalism: >100µg/day <p><u>Salivary</u></p> <p>steroid molecules excreted in saliva in approx. proportion to plasma conc.</p>		<p><i>Dynamic tests</i></p> <p><u>Dexamethasone suppression</u></p> <ul style="list-style-type: none"> •Overnight (1mg) -taken PO at midnight -normal pts. → ↓plasma hydrocortisone to < 5µg/dl by 8am -Cushing's syndrome → levels usually > 10µg/dl by 8am •Low-dose (2mg) -0.5mg PO 4X daily for 2days -normal pts. → ↓urinary free cortisol to < 20µg/24hr -Cushing's syndrome → levels > 20µg/24hr •High-dose (8mg) -given to ACTH-dependent Cushing's -24hr baseline urine cortisol measured prior to dexamethasone -2mg PO 4X daily for 2days -urine measured on 2nd day -in 60% of pituitary-dependent ACTH pts. → urine cortisol 10% of baseline -almost NO pts. w/ectopic ACTH will suppress to 10% of baseline -but, failure to suppress can occur w/either <p><u>CRH stimulation test</u></p> <ul style="list-style-type: none"> •give ovine CRH (longer t½) IV -normal pts. → ↑ACTH and ↑cortisol conc. -pituitary-dependent Cushing's → ↑in ACTH is > normal response -ectopic ACTH → NO ↑ in ACTH -1° adrenal disease → ACTH level remains suppressed <p><u>Petrosal sinus sampling</u></p> <ul style="list-style-type: none"> •highly sensitive •determines presence of gradient between petrosal & periph. ACTH •give oCRH -pituitary-ACTH tumors → ↑gradient -also facilitates lateralization for neurosurgeon 			
<p>Diagnosis</p>	<p><u>Cushing's Disease</u></p> <ul style="list-style-type: none"> •most are women in 20s-40s •↑plasma ACTH -in absolute terms -in normal range, but inappropriate for cortisol level •8mg/day suppresses urinary & plasma steroids •oCRH → excessively ↑ACTH •↑in petrosal ACTH > ↑ in periph. venous ACTH •MRI or CT scan evidence of a tumor -≥ 50% of tumors are too small to see 	<p><u>Ectopic ACTH</u></p> <ul style="list-style-type: none"> •men = women •most in 50s-70s •often short duration of symptoms •↑↑↑plasma ACTH •8mg/day fails to suppress urinary & plasma •often hypokalemic •oCRH → NO ↑ in plasma ACTH •petrosal ACTH ≈ periph. venous ACTH •lung is most common site 	<p><u>ACTH-independent</u> (adrenal adenoma or carcinoma)</p> <ul style="list-style-type: none"> •plasma ACTH undetectable •oCRH → NO ↑ in plasma ACTH •adrenal tumor almost always seen w/abdominal CT -often contralateral adrenal is atrophied •Adenoma -most are endocrinologically silent -1° produce glucocorticoids -w/ low adrenal androgen levels -solitary, discrete, unencapsulated -bright yellow, non-necrotic, non-hemorrhagic -resemble adrenal cortical cells •Carcinoma -90% are functional -produce both glucocorticoids & androgens -usually unilateral -larger than adenomas -can be massive -areas of hemorrhage & necrosis -bizarre hyperchromatic nuclei & mitotic figures 			
<p>Treatment</p>	<p>Cushing's disease</p>	<ul style="list-style-type: none"> •transphenoidal surgery -80% remission rate -other pituitary functions usually remain -normal tissue recovers ACTH synthesis after 6-12 mo. -medical Tx: ketoconazole → inhibits steroid biosynthesis 	<p>Ectopic ACTH</p>	<ul style="list-style-type: none"> •tumor removal if possible •otherwise, bilateral adrenalectomy •medical Tx 	<p>ACTH independent</p>	<ul style="list-style-type: none"> •surgical removal of adrenal tumor if possible

	Etiology	Clinical	Diagnosis	Treatment
Hypoadrenalism	<p><u>Addison's disease</u> (1° adrenal disease)</p> <ul style="list-style-type: none"> •autoimmune adrenalitis -most common cause in U.S. & W. Europe <ul style="list-style-type: none"> -formerly tuberculous adrenalitis -cytotoxic lymphocytes slowly destroy adrenal cortex -pts. may have autoimmune thyroid disease •“polyglandular syndromes” -of which adrenal insufficiency is a part -Abs against 21-hydroxylase <ul style="list-style-type: none"> - steroidogenic enzyme •AIDS -assoc. w/abnormal adrenal function <ul style="list-style-type: none"> -↑cortisol -↓androgens -↓response to ACTH -↑freq. in AIDS pts. •adrenal amyloidosis •bilateral adrenal hemorrhage •metastatic disease -usually from 1° lung, breast or kidney cancer or lymphoma •fungal infection -histoplasmosis 	<p>1° and 2° adrenal insufficiency</p> <ul style="list-style-type: none"> •tiredness, weakness, depression •anorexia, ↓weight •dizziness, orthostasis •N/V, diarrhea •hyponatremia, hypoglycemia •mild normocytic anemia •lymphocytosis, eosinophilia •loss of sexual hair -in women <p>1° adrenal insufficiency only</p> <ul style="list-style-type: none"> •hyperpigmentation •hyperkalemia <p>-NOT present in 2° adrenal insufficiency b/c aldosterone remains under renin-AII control</p>	<p>ACTH stimulation test</p> <ul style="list-style-type: none"> •250µg cortrosyn IV or SubQ -normal pts. <ul style="list-style-type: none"> -plasma cortisol ↑ to >18µg/dl at 1hr. -cortisol ↑ by >7µg/dl over baseline -pt. w/ 1° adrenal insufficiency <ul style="list-style-type: none"> -NO cortisol response -pt. w/ 2° adrenal insufficiency <ul style="list-style-type: none"> -subnormal cortisol response -normalized after IM or IV ACTH adrenal insufficiency <ul style="list-style-type: none"> -may miss mild or recent onset 2° adrenal insufficiency <p>Plasma ACTH</p> <ul style="list-style-type: none"> •↑ in 1° adrenal insufficiency •↓ in 2° adrenal insufficiency <p>Auto-Antibody tests</p> <ul style="list-style-type: none"> •positive in ~70% of autoimmune adrenalitis cases -most likely to be positive during 1st few years after onset of symptoms <p>Adrenal Imaging</p> <ul style="list-style-type: none"> •easily visualizes -metastases -hemorrhage -atrophy -enlargement 	<ul style="list-style-type: none"> •lifelong -glucocorticoid -aldosterone •↑dose when under stress
	<p><u>ACTH deficiency</u> (2° adrenal insufficiency)</p> <ul style="list-style-type: none"> •all causes of hypopituitarism •withdrawal of long term glucocorticoid Rx → HPA axis suppression <p><u>Adrenal enzyme deficiency</u></p> <ul style="list-style-type: none"> •congenital adrenal hyperplasia (CAH) -↓enzymes → ↓neg. feedback by cortisol → ↑ACTH → excessive synthesis of steroid precursors -21-hydroxylase deficiency <ul style="list-style-type: none"> -most common form of CAH (90%) → adrenal androgen excess → virilization <ul style="list-style-type: none"> → premature virilization in male fetus → genital ambiguity in female fetus → mineralcorticoid deficiency → salt wasting -Tx. w/replacement glucocorticoids & mineral corticoids -“non-classical” 21-hydroxylase deficiency <ul style="list-style-type: none"> -does NOT present in infancy -androgen excess presents in young adulthood -11β-hydroxylase deficiency <ul style="list-style-type: none"> -assoc. w/virilization & HTN -17β-hydroxylase deficiency -3β-hydroxysteroid dehydrogenase deficiency 			
	<p><u>Acute adrenal insufficiency</u></p> <ul style="list-style-type: none"> •life threatening emergency 			<ul style="list-style-type: none"> •obtain steroid analysis prior to therapy

Adrenal Medulla	<ul style="list-style-type: none"> •derived from neural crest •10% of weight of adrenal •neoplasms are the only clinically important lesions 	<ul style="list-style-type: none"> •catecholamines -produced & released into circulation -small contribution to basal blood pressure 		
	Pathology	Clinical	Diagnostic tests	Treatment
Pheochromocytoma	<ul style="list-style-type: none"> •tumor arising from chromaffin cells •excess (nor)epinephrine secretion → HTN •weigh ~20gm •pink-gray color w/ a rim of yellow adrenal cortical tissue •areas of hemorrhage & cystic degeneration •cells resemble those of adrenal medulla -large amts. of basophilic cytoplasm -hyperchromatic nuclei -arranged in nests -surrounded on all sides by rich vasculature •invasion and/or metastasis is ONLY criteria for malignancy -cytology means NOTHING •10% bilateral •10% extra-adrenal •10% malignant •may occur -as part of multiple endocrine neoplasia type 2 -in assoc. w/ neurofibromatosis -in assoc. w/ Von Hippel Lindau Disease 	<ul style="list-style-type: none"> •HTN -most common manifestation -ranges from mild & labile to malignant -episodic in some pts. •episodic catecholamine secretion -sweating -headache -palpitations 	<ul style="list-style-type: none"> •24 hr urine measurement -catecholamines -metanephrine -vanillylmandelic acid •clonidine suppression test -in pts. w/essential HTN -↓plasma norepinephrine -in pts. w/pheochromocytoma -NO change in norepinephrine •CT or MRI -localizes most tumors -131-I-meta-iodobenzylguanidine is specifically taken up by chromaffin tissue -helps in localization -most neuroendocrine tumors express somatostatin receptors 	<ul style="list-style-type: none"> •surgery -pre-treatment w/ -catecholamine inhibitor -α-adrenergic blocker
Neuroblastoma	<ul style="list-style-type: none"> •poorly differentiated •derived from neural crest cells •usually unilateral •50-80% arise in adrenal •large, gray-tan mass •areas of hemorrhage, necrosis, & calcification •undifferentiated small cells -resemble lymphocytes w/elongated nucleus •arranged in rosettes •metastasize widely to -bone -liver -lung •> 90% produce catecholamines 	<ul style="list-style-type: none"> •occurs in infants and small children •prognosis better in pts. < 1y.o. 	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> •
Ganglioneuroma	<ul style="list-style-type: none"> •differentiated •neural crest origin •act benignly •comprised of neural elements & ganglion cells •encapsulated •white & firm 	<ul style="list-style-type: none"> •occur in older age group 	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> •