General

- Important Principle: (1) if High hormone then check suppression test vs (2) if Low hormone then check stimulation test
- Random single hormone levels are usually not helpful b/c pulsatile and diurnal except thyroid, hormones are bound to binding globulins except insulin
- 3° Hypothalamus → 2° Pituitary → 1° Endocrine Organ → End Organ Tissue (Positive Downward and Negative Feedback Mechanisms)
    - 3° Hypothalamus (stimulates hormone release from anterior pituitary by hormones and posterior pituitary by neurons NB except prolactin which is inhibited by dopamine)
    - 2° Pituitary aka Hypophysis in Sella Turcica of Sphenoid Bone is connected to hypothalamus thru diaphragmatic sella
        - Anterior aka Adenohypophysis = Pars Distalis/Intermedia/Tuberalis = FSH/LH, ACTH, TSH aka Thyrotropin, Prolactin, GH aka Somatotropin ("FLAT PiG")
        - Posterior aka Neurohypophysis = Pars Nervosa/Infundibulum = ADH aka AVP aka Vasopressin, Oxytocin
    - 1° Endocrine Organ
        - Gonads (refer)
        - Adrenal Gland: Zona Glomerulosa (ZG-Aldo) + Zona Fasciculate (ZF-Cortisol) + Zone Reticularis (ZR-DHEA-S) + Medulla (Epi) ("GFR")
        - Thyroid Gland: follicular cells forming a follicle w/ center filled w/ Thyroglobulin and surrounded by parafollicular cells which hold Calcitonin
        - NB NO endocrine organ for Prolactin, GH, ADP, Oxytocin
    - Other
        - Pineal Gland: diurnal melatonin secretion (also contains calcium crystal that appears on CT)
        - Parathyroid Gland: four separate glands w/ no follicular structure
        - Pancreas: Acinar Cells + Islet Cells of Langerhan

Syndromes (lifestyle-MS/autoimmune-PGA/genetic-MEN)

- **Metabolic Syndrome** (NB Syndrome X is a bad term b/c it is also used for the pts w/ nl coronaries but have ACS, can lead to atherosclerosis, need ≥3/5 but there are other problems including hyperuricemia, PCOS, OSA, NASH, thrombophilic, Tx: diet/exercise)
    - Abdominal Obesity >40/35 BMI in M/F or more importantly Waist Circumference >40/35in in M/F
    - TGL >150mg/dL or drug Tx for high TGL (NOT LDL)
    - HDL <40/50mg/dL M/F or drug Tx for low HDL (NOT LDL)
    - BP >130/>85mmHg or drug Tx for HTN
    - Insulin Resistance and Hyperinsulinemia w/ Fasting CBG 100-125mg/dL
- **PolyGlandular Autoimmune syndromes (PGAs)**
    - check anti-adrenal Abs aka 22-Hydroxylase Ab (if pt is + for Ab but doesn't have adrenal insufficiency but they do have other autoimmune problems like autoimmune thyroid dz, etc then very high likelihood pt will develop adrenal insufficiency in future)
    - if you have one autoimmune problem look for others

	Type I PGA	**Type II PGA Schmidt's/Carpenter's Syndrome**
Genetics	AR Less Common ~10yo M=F	Polygenic More Common ~30yo F>M
Adrenal Insufficiency	**85%**	**85%**
HypoPTH	**80%**	X
Mucocutaneous Candidiasis	**80%**	X
Ectodermal Dysplasia	20%	X
Alopecia	25%	X
Autoimmune Hepatitis	10%	X
Malabsorption	10%	X
Autoimmune Thyroid (H>G)	10%	**70%**
TIDM	10%	**50%**
Pernicious Anemia	15%	15%
Gonadal Failure	20%	5%
Vitiligo	10%	5%

- **Multiple Endocrine Neoplasia syndromes (MENs)**
    - The individual tumors that are associated with MEN have some distinctive features that differentiate them from their sporadic counterparts: occur at a younger age, multifocal/bilateral, preceded by hyperplasia, more aggressive, recur more often
    - Screen for cancer in family and pts
    - In order of incidence b/t and w/in MEN syndromes

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- Treat in order of incidence for I and opposite order of incidence for II

	MEN-1 (Werner's)	MEN-2A (Sipple's)	MEN-2B
			earlier onset more aggressive
Mutation	Menin gene	RET gene	RET gene
Surface			Marfinoid Habitus (long, lanky, etc) Pes Cavus(large arch) Planum (flat arch) Ganglioneuromas (thickened lips and small bumps on tip of tongue)
Thyroid		Medullary Carcinoma	Medullary Carcinoma
PT	PTH Hyperplasia	PTH Adenoma	
Adrenal		Pheochromocytoma	Pheochromocytoma
Pancreas	Pancreatic Islet 1° Gastrinoma, etc		
Pituitary	Pituitary 1° Prolactinoma, etc		

Thyroid

- Abnormal Sx so you check TFTs and they are abnormal
  - Decreased TSH
    - Decreased fT4: Secondary Hypo
    - Normal fT4: Subclinical Hyper but if really low TSH consider checking fT3 b/c it may be high while T4 normal
    - Increased fT4: **Primary Hyper then check RAUI/Scan**
      - **Hot**
        - **Homogenous: Grave's, Secondary**
        - **Heterogenous: Plummer's**
        - **Focal: Functioning Adenoma**
      - **Cold: Early Thyroiditis, Type I Amio, Iodine Excess, Exogenous, Ectopic**
  - Normal TSH
    - Decreased fT4: Euthyroid Hypothyroxemia?
    - Normal fT4: Normal
    - Increased fT4: Euthyroid Thyroxemia?
  - Increased TSH
    - Decreased fT4: **Primary Hypo then most just assume Hashimoto's and empirically Tx w/ HRT unless other Hx, S/S, RFs, etc makes one consider another diagnosis: Later Thyroiditis, Type II Amio, Iodine Deficiency, HyperTH meds, Infiltration, Trauma/Damage, Congenital Problem**
    - Normal fT4: Subclinical Hypo but if really high TSH consider checking fT3 b/c it may be low while T4 normal
    - Increased fT4: Secondary Hyper or Thyroid Hormone Resistance
- Goiters
  - Diffuse
    - Toxic (many different kinds refer to hypo/hyperthyroidism)
    - Non-Toxic aka nl TSH (2/2 iodine deficiency, goitrogen ingestion like brussels sprouts or cabbage)
  - Nodular
    - Toxic (refer to Plummer's)
    - Non-Toxic aka nl TSH (2/2 unknown, seen in women, very common, check US to r/u any dominant/suspicious nodules, Tx w/ bilateral subtotal thyroidectomy if compressive Sx)
- If Solitary Thyroid Nodule →check RFs/PEx/US → check TSH
  - DDx of a Thyroid Nodule/Mass (assure pt that in general 25% of population have nodules and only 5% are malignant)
    - Cyst: if (1) simple then aspirate if symptomatic otherwise watch or (2) complex then aspirate
    - NON-Toxic Multinodular Goiter
    - Toxic Multinodular Goiter (aka Plummer's Disease)
    - Adenoma, Carcinoma, Metastasis, Parathyroid Cancer
    - Aberrant Thyroid Tissue
    - Thyroglossal Duct Cyst (remnant of the diverticulum formed from the migration of thyroid tissue from foramen cecum to base of tongue thru hyoid to final position around the tracheal cartilage, presents as a midline non-infected mass at ~5yo, treated w/ surgical excision)
    - Brachial Cleft Cyst (remnant of the primitive branchial clefts in which epithelium forms a sinus tract between pharynx or external auditory canal to anterior neck, presents as a lateral infected mass at ~5yo, treated w/ surgical excision)
  - -RFs/-PEx/-US
    - Nl TSH then check size/number: (1) Multiple/Small (<1cm) then watch vs (2) Few/Large (>1cm) then FNA
    - Low TSH then likely functional adenoma therefore confirm w/ RAIU/scan

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- +RFs/+PEx/+US then concern for cancer esp if High TSH therefore confirm w/ RAUI/scan and do FNA (NB when you do an FNA don't use a >22G b/c it destroys histology therefore do a Core Bx w/ a <18G needle to see histologic changes in carcinoma (capsular/vascular invasion) that is not seen in adenoma, but since 75% of undetermined pathology is follicular carcinoma a Core / Large Needle Bx is obviated and surgery is done)
  - 70% Benign then f/u US in 6mo
  - 25% Undetermined (in general b/c pathologist cannot differentiate between follicular adenoma vs follicular carcinoma b/c cytologically they look the same w/ difference in histology alone) then repeat FNA or just surgery
  - 30% Suspicious/Malignant then (refer)

	Benign Adenoma	Malignant Carcinoma
RFs	Young Female No h/o Radiation Exposure	Old Male H/o Radiation Exposure
PEx	Slow Growth Soft and Regular Border Mobile NO LAD NO Recurrent Laryngeal Nerve Involvement NO Esophageal Involvement	Rapid Growth Firm and Irregular Border Fixed LAD Hoarse Dysphagia
US	Small (<10mm) Hyperechoic Cystic No Calcifications Hypo/Euvascular	Large (>10mm) Hypoechoic Solid Microcalcifications Hypervascular

- Sick Euthyroid Syndrome
  - Mech: NON-Thyroid illnesses (really any systemic illnesses) can affect the thyroid function in many different ways depending on how bad the illness is, adaptive responsive to illness so that the body does not catabolize itself down
  - Labs: (1) Decreased release of T4 along with (2) decreased conversion to T3 but rather to RT3 and as such (3) TSH goes up b/c RT3 does not act on pituitary
  - Tx: treatment is actually not beneficial therefore don't even check unless concerned about myxedema coma or thyrotoxic storm

	T4	T3	**RT3**	TSH
Mild	=	↓ (b/c ↓ conversion)	↑	↑ (b/c ↓ T3)
Moderate	↓ (b/c ↓ TSH)	↓↓	↑↑	↑↑
Severe	↓↓	↓↓↓	↑↑↑	↑↑↑

- Thyroid in Pregnancy
  - 0-12wks: ↑hCG non-specifically binds TSH receptor → ↑T4 and ↓TSH (very mild hence not clinically significant)
  - 12wks-Term: ↑estrogen → ↑TBG → Early On =TT4 but ↓fT4 (mod-severe hence this is when pts need to be monitored for worsening hypoTH) → Later On ↑TT4 w/ =fT4
  - NB often Grave's manifests during pregnancy and remember Tx w/ PTU NOT MM
- Labs/Studies
  - **TSH:** 0.5-5 mU/L, a small change in T4 results in a large change in TSH hence hard to manage and this is why you follow TSH instead of fT4
  - **Total (TT3/4)**: rarely measured b/c influenced by TBG thus order fT3/4
  - **Free (fT3/4)**: 20% of T3 from thyroid and 80% converted from T4 at liver/kidney, measure fT3 when TSH is undetectable (therefore you assume hyperTH) but fT4 is normal (therefore the hyperTH is 2/2 increased fT3 only), drugs that decrease T4 to T3 conversion (amio, corticosteroids, BB, PTU), drugs that displace TH from TBG (aspirin, AEDs, Lasix, Heparin)
  - **Thyroid Binding Globulin (TBG):** ↑TBG → initial ↓fT4 and =TT4 → after awhile the body adjusts to maintain normal fT4 by increasing production thus =fT4 and ↑TT4, Decrease (androgens/menopause, glucocorticoids, nephrotic syndrome) vs Increase (estrogens/pregnancy, opiates, liver dz)
  - **Reverse T3 (rT3):** order when you suspect sick euthyroid syndrome because it increases inactive hormone
  - **T3 Resin Uptake (T3RU):** %, Give pt ^{125}I-T4/3 and then allow ^{125}I-T4/3 and pt's own T4/3 "fight" for TBG, after the incubation period give pt resin that binds any free T4/3 around that has not bound TBG the measure the radioactivity of resin (↑ radioactive resin → ↓ TBG or HyperTH vs ↓ radioactive resin → ↑ TBG or HypoTH)
  - **Free Thyroxine Index (FTI):** tT4 x T3RU / 100 = FTI ≈ fT4
  - **Thyroglobulin (TG):** found in thyroid cells and thus is released and is detected in serum when cells breakdown as in inflammation, injury, cancer, etc, order when you suspect thyroiditis because it increases because as the thyroid gland becomes inflamed it breaks down releasing thyroglobulin. Order when you are following cancer.

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- **24hr RadioActive Iodine (I^{233}) Uptake (RAIU)**: <10% (low uptake), 10-30% (nl), >30% (high uptake), assesses **degree** of hyper/hyopfunctioning
- **Thyroid Scan Scintigraphy**: assess **location** of hyper/hypofunctioning
- **Thyroid US**: shows not only nodules/cysts but also blood flow if you use Doppler

Adrenal

	EXCESS	DEFICIENCY
Cortisol	• Immune (inhibits immune system w/ infection esp fungal, PCP, HepB/C reactivation, acute leukocytosis 2/2 demargination of WBC from endothelium into bloodstream) • CNS (range in mood from fatigue/apathy → depression → mania → psychosis and positive catecholamine effect w/ **HTN**) • Metabolism (anti-insulin/pro-glucagon w/ hyperglycemia, DL w/ atherosclerosis, change in fat distribution from extremities to weight gain, central/truncal obesity with thinning of extremities, supraclavicular fat pads, buffalo hump, moon facies, facial plethora) • MS (tissue breakdown w/ proximal muscle weakness, bone breakdown w/ hypocalcemia/osteoporosis/spontaneous fractures, aseptic necrosis of femoral/humeral head) • Derm (defective collagen synthesis w/ impaired wound healing, thin fragile skin, bruises, purple ab stria) • GI (**pancreatitis, PUD, fatty liver, anorexia, upper GIB**) • Renal (nephrolithiasis) • Eye (cataracts, glaucoma) • Heme (polycythemia, thrombocytosis) • General (increased r/o premature death)	• Immune (stimulate immune system w/ eosinophilia and lymphocytosis) • CNS (range in mood (same) and negative catecholamine effect w/ **HypoTN**) • Metabolism (pro-insulin/anti-glucagon w/ hypoglycemia) • Bone (hypercalcemia) • GI (anorexia, N/V, D, ab pain, weight loss) • Acute: hypoTN, N, ab pain, etc • Chronic: anorexia, weight loss, fatigue, etc
Aldo	• Renal (HTN, hypernatremia, hypokalemia, metabolic alkalosis, paradoxic polydipsia and polyuria due to hypokalemia)	• Renal (HypoTN, hyponatremia, hyperkalemia, metabolic acidosis)
DHEA-S	• Increase Male Characteristics (virilization, increased libido, amenorrhea, hirsutism)	• Increased Female Characteristics (feminization, decreased libido)

Systemic Steroids	Gluco Corticoid Effect	Mineralo Corticoid Effect	Hz?
dexamethasone (Decadron)	**25**	0	QD
fludrocortisone (Florinef)	**10**	125	
prednisone (Prednisone) w/ prednisolone (Prelone) slightly more active, main PO steroid • Low Dose: 0.1-0.25 mg/kg/d ~0-20mg • Med Dose: 0.25-0.5 mg/kg/d ~20-40mg • High Dose: 0.5-3 mg/kg/d ~40-200mg • Super High Dose = 250mg Q6hrs x3d • Pulse Dose = 1g Qd x3d	**5**	1	
methylprednisolone (Medrol) main injection steroid • (Solu-Medrol) IV, for acute inflammation • (Depo-Medrol) IM/IA, for chronic inflammation, get 40mg/mL Depo-Medrol and 10mg/mL 1% Lidocaine, Mix 1cc (40mg) of Depo-Medrol and 2cc (20mg) of Lidocaine into a syringe, spray topical anesthetic, inject straight lidocaine, then inject steroid/lidocaine mixture • (Medrol Dose Pack) PO, for acute inflammation, "Medrol Dose Pack - Take As Directed" (4mg tabs, take 6 tabs on day 1, 5 on 2, 4 on 3, etc) triamcinolone (Kenalog) main intra-articular steroid	**4**	0	BID
hydrocortisone aka cortisol (Cortef) w/ cortisone (Cortone) slightly less active • Adrenal gland makes cortisol aka hydrocortisone, all other steroids above do not interfere w/ "cortisol assay" • hydrocortisone ~10mg Qam and ~5mg Qpm approximates normal physiologic cortisol production with stress resulting in #x this amount based on how stressed the pt where # = 1 (mildly stressed) – 10 (almost dead)	**1**	2	TID

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- Adrenal Incidentaloma
  - Rule out clinically functional adrenal masses, non-adrenal masses (renal, pancreas, gastric) and most importantly metastatic malignancy (if pt has a primary cancer the lesion 50% of time is a met)

- 5% of pts who get CT-abdomen for non adrenal disorders and 10% of autopsies are found to have clinically silent adrenal masses aka incidentolomas and of these masses 80% are non-functional (produce no hormone usually met, myelipoma, hamartoma, granulomas, cysts, abscess, hemorrhage, etc) vs 20% are functional but clinically silent nevertheless still carry risk (5% cortisol adenomas/carcinomas, 5% pheo, 5% aldosterone adenomas/carcinomas, 5% infection w/ TB/fungus)
- Approach
    - Benign (<4cm Diameter, Homogenous, Non-Vascular, Smooth Border, Hypodense w/ <10 Hounsfield Units, Non-Enhancing w/ Contrast) follow with radiographic/endrocrinologic screening every 6-12mo, likely a myelolipoma
    - Malignant (change of previously thought benign, >4cm Diameter, Heterogenous, Vascular, Ragged Border, Hyperdense w/ >10 Hounsfield Units, Enhancing w/ Contrast) then FNA Bx or rather Surgical Removal

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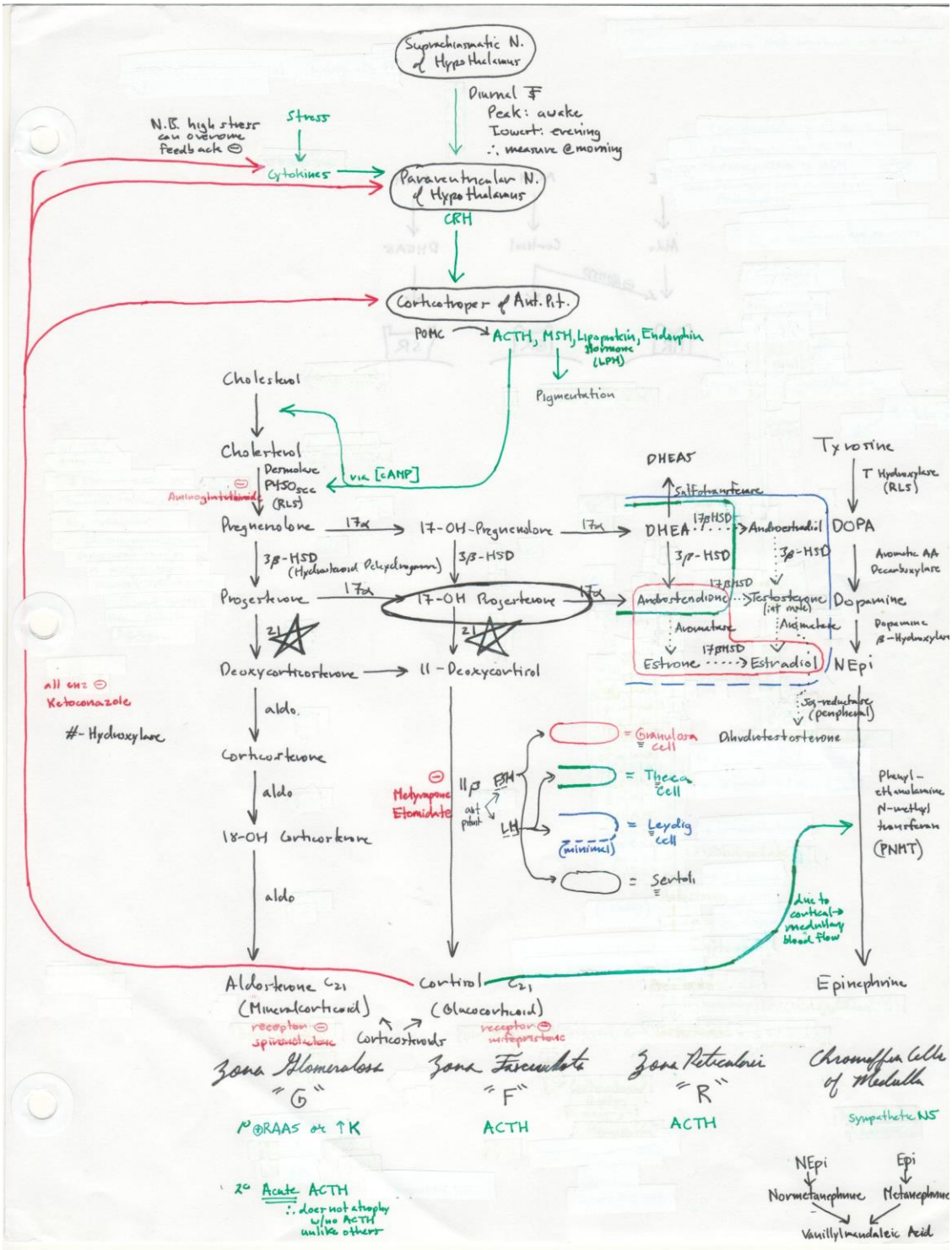
Suprachiasmatic N. of Hypothalamus
Diurnal ∓
Peak: awake
Lowest: evening
∴ measure @ morning
N.B. high stress can overcome Feedback ⊖
Stress
Cytokines
Paraventricular N. of Hypothalamus
CRH
Corticotroper of Ant. Pit.
POMC
ACTH, MSH, Lipomotrin, Endorphin
Pigmentation
Cholesterol
Cholesterol
Desmolase P450scc (RLS)
via [cAMP]
Aminoglutethimide ⊖
Pregnenolone
17α
17-OH-Pregnenolone
17α
DHEA
17βHSD
Androstadiol
DOPA
3β-HSD
3β-HSD (Hydroxysteroid Dehydrogenase)
3β-HSD
3β-HSD
Aromatic AA Decarboxylase
Progesterone
17α
17-OH Progesterone
17α
Androstenedione
17βHSD
Testosterone (at most)
Dopamine
21
21
Aromatase
Anastrozole
Dopamine β-Hydroxylase
Deoxycorticosterone
11-Deoxycortisol
17βHSD
Estrone
Estradiol
NEpi
all enz ⊖
Ketoconazole
#-Hydroxylase
aldo
Corticosterone
aldo
18-OH Corticosterone
aldo
Methyrapone
Etomidate
11β
cort
FSH
LH
= Granulosa cell
= Theca cell
= Leydig cell
(minimal)
= Sertoli
Dihydrotestosterone
Sig-reductase (peripheral)
Phenyl-ethanolamine N-methyl transferase (PNMT)
due to cortical→medullary blood flow
Aldosterone C21
(Mineralcorticoid)
receptor ⊖ spironolactone
Corticosteroids
Cortisol C21
(Glucocorticoid)
receptor ⊖ mifepristone
Epinephrine
Zona Glomerulosa
"G"
↑RAAS or ↑K
Zona Fasciculata
"F"
ACTH
Zona Reticularis
"R"
ACTH
Chromaffin Cells of Medulla
Sympathetic NS
2° Acute ACTH
∴ does not atrophy w/no ACTH unlike others
NEpi
Epi
Normetanephrine
Metanephrine
Vanillylmandaleic Acid