

Clinical Cases of Endocrine Hypertension

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Disclosures

- **Contracted Research**
 - Novartis Pharmaceuticals
 - Strongbridge Biopharma
 - Millendo Pharmaceuticals
- **Consultant**
 - Quest Diagnostics
 - Corcept Therapeutics
 - Janssen Pharmaceuticals
 - Novartis Pharmaceuticals
 - Diurnal LTD
 - Alder BioPharmaceuticals
 - Spruce Biosciences
 - Strongbridge Biopharma

Endocrine HTN

Case 1

- 52 YO WM Difficult-to-control HTN for 25 Years
- Amlodipine, Benazepril, Carvedilol, HCTZ, KCl
- Question: What is your Differential Diagnosis for Resistant Hypertension?

Resistant HTN

Differential Dx

- **Medication Nonadherence**
- **Ethanol Consumption**
- **Sleep Apnea**
- **Renal Insufficiency**
- **Mineralocorticoid Excess**

Endocrine HTN

Case 1

- Preoperative Knee Surgery K = 1.9 meq/L
- Nephrology Evaluation
- Renal Artery Doppler Sono Normal
- High Urine K & Aldosterone, Normal PRA
- MRI Showed Possible 1 cm Nodule L Adrenal
- Spironolactone 100 mg QD Added
- BP & K Much Better
- Referred to Surgeon; Requested Endo Consult

Endocrine HTN

Case 1

- PRA 2.4 ng/mL/hr; Potassium 4.7 meq/L;
Serum Aldosterone 74.5 ng/dL
- 24 h Urine: Epinephrine 40 mcg,
Norepinephrine 286 mcg, Dopamine 697 mcg,
Aldosterone 149 mcg, Potassium 80 meq,
Creatinine 4.1 g

Questions:

- What is the likelihood that this man has
Primary Aldosteronism?
- Would you order any tests now?

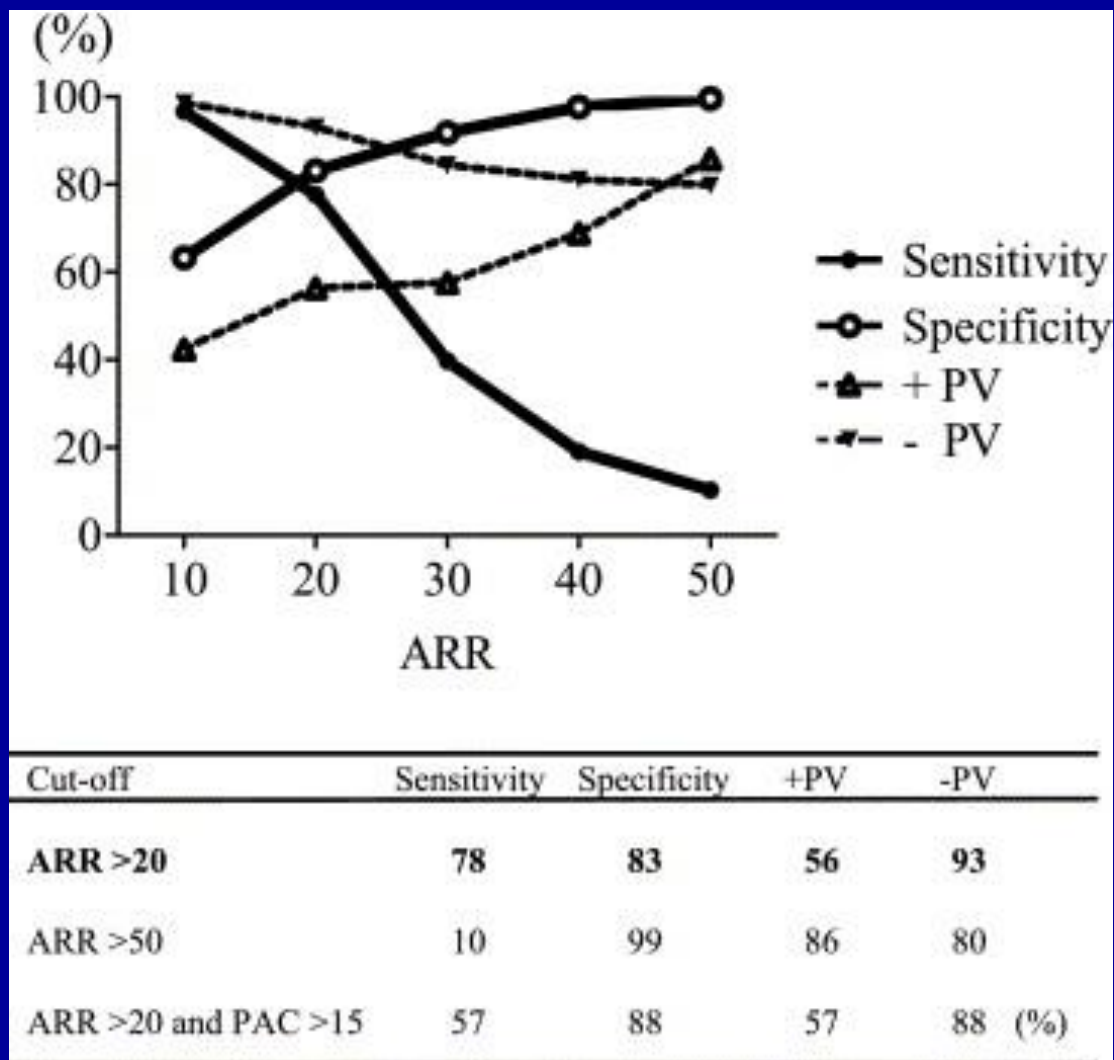
**Pearl #1: *Screening* is
about whether *renin*
is *suppressed*, not
whether *aldosterone*
is *high***

Primary Aldosteronism

Whom To Screen?

- HTN + Hypokalemia
- Patients With Resistant HTN
 - Or Controlled With 4 Drugs
- Patients With HTN At Age < 40
 - Or FH HTN or CVA Age < 40
- Considering Secondary Causes
- Sustained BP $> 150/100$
- HTN + Known Adrenal Mass or OSA
- HTN + First-Degree Relative With PA

ARR Sensitivity & Specificity

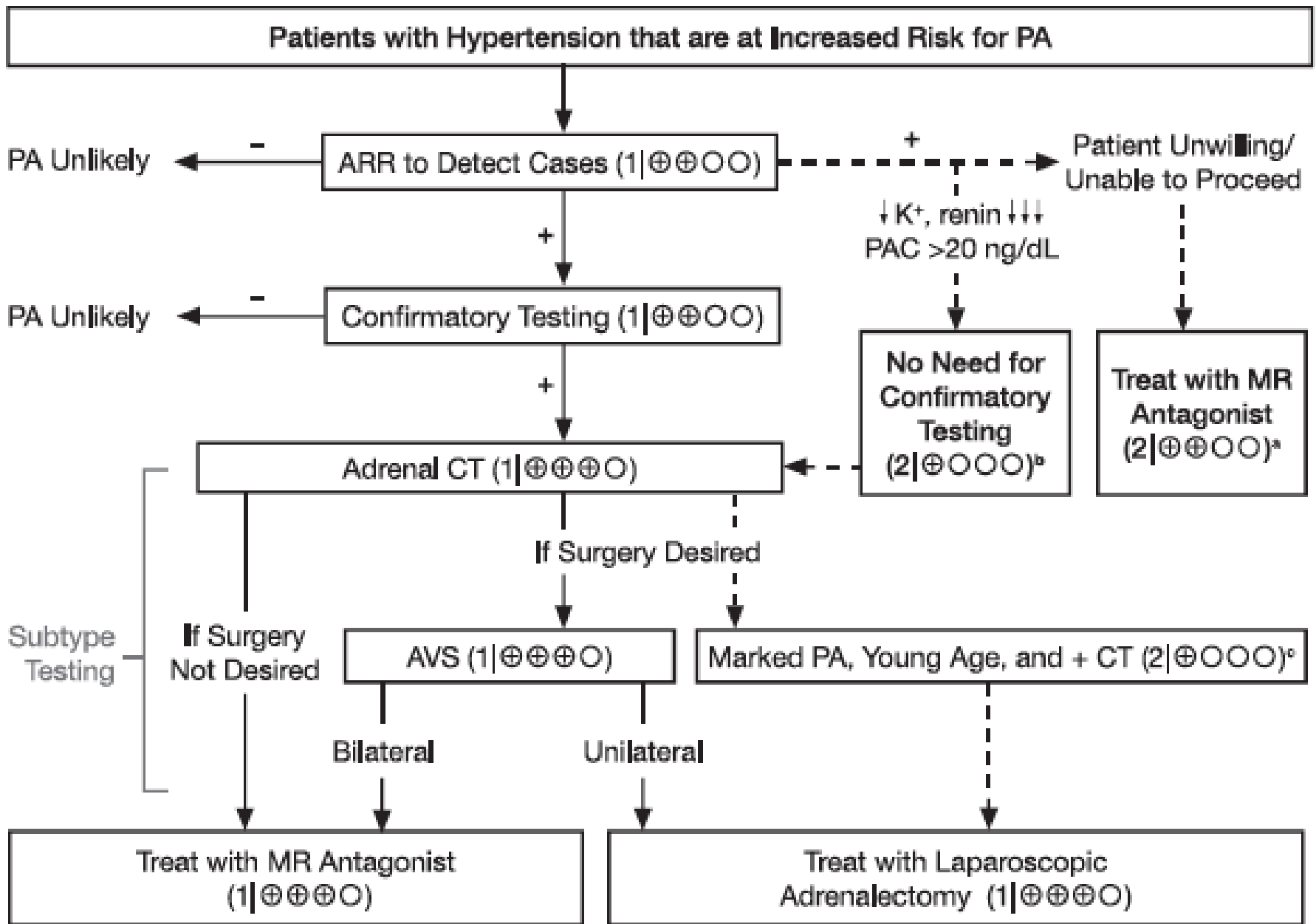


Nishizaka 2005 Am J Hypertens 18:805

Who Has Primary Aldo?

ARR Interpretation

<u>Aldo</u> (ng/dL)	<u>PRA</u> (ng/mL/hr)	<u>ARR</u>	<u>Serum</u> <u>Potassium</u> (meq/L)	<u>Interpretation</u>
6	3.2	2	4.4	Low ARR, not PA, stop
3	0.1	30	4.0	Low aldosterone, not PA, stop
18	0.6	30	3.5	Positive screen for PA, go to confirmatory testing
11	0.8	15	2.9	Probably PA, supplement K, rescreen
38	2.0	19	4.2	Probably PA, stop meds and rescreen



Endocrine HTN

Case 1

- **Labs Obtained: PRA 1.5 ng/mL/hr; Serum Aldosterone 55 ng/dL, Potassium 4.0 meq/L**
- **Spirolactone Discontinued, KCl Increased to 40 meq/d; 24 h Urine Collected 2 Weeks Later:**
 - **24 h urine: Aldosterone 41 mcg, Sodium 246 meq, Potassium 54 meq**
 - **PRA <0.6 ng/mL/hr; Serum Aldosterone 29 ng/dL, Potassium 3.8 meq/L**
- **BUT--Unable to Do AVS For Several Weeks**

Endocrine HTN

Case 1

- Potassium 3.2 meq/L; Amiloride 5 mg/d Added
- 3 Weeks Later/1 Week pre-AVS: Potassium 3.9 meq/L, PRA 0.64 ng/mL/hr; Amiloride Stopped 3 Days Prior to AVS (Potassium 2.9 meq/L!)

				R.J. Auchus	9-Sep-10	S.C.Josephs,MD			
Specimen Source	During Cosyntropin Infusion		A/C Ratio (x10 ⁻³)	C _{RAV} and C _{LAV} ≥ 3C _{IVC}	Adrenal Vein A/C Ratio				LI
	[Aldo], ng/dL	[Cortisol], mcg/dL			Dominant (D)	D/IVC	Non-dominant (ND)	ND/IVC	
RAV	610	630.5	0.97	Yes	13.96	5.39	0.97	0.37	14.43
LAV	8400	601.6	13.96	Yes					
IVC	72	27.8	2.59	Yes	◀ Overall AVS successful?				
PV	75	30.3	2.48	Yes	◀ C _{PV} ≥ 20 mcg/dL?				

Endocrine HTN

Case 1

- L ADX
- Remains on Amlodipine Monotherapy
- BP 115-130/80-85; Potassium 4.8 meq/L
- Everybody is Happy

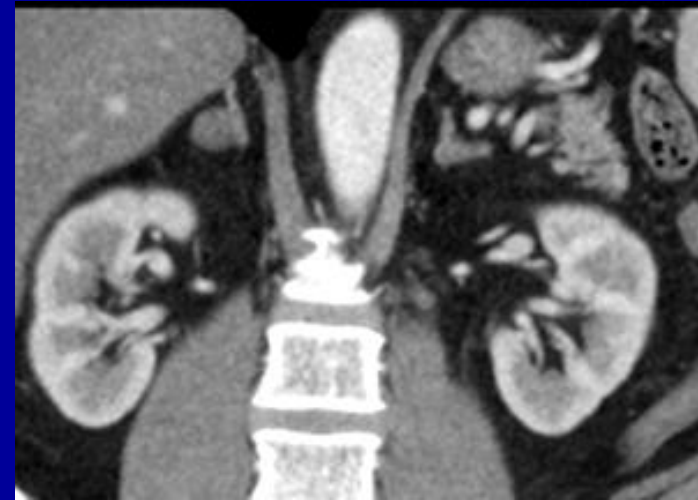
Endocrine HTN

Case 2

- 56 YO WM Referred for Evaluation of PA
- HTN, Low K, Elevated ARR
- PRA <0.15 ng/mL/hr; Potassium 3.1 meq/L; Serum Aldosterone 15.6 ng/dL
- CT: R Adrenal Mass of 1.2 cm
- AVS Outside: “Localized to the Left”
- Rx Spironolactone but Severe Gynecomastia
- Cannot Afford Eplerenone Chronically
- What Did the AVS Really Show??
- What Would You Do Now??

Endocrine HTN

Case 2: CT Scan

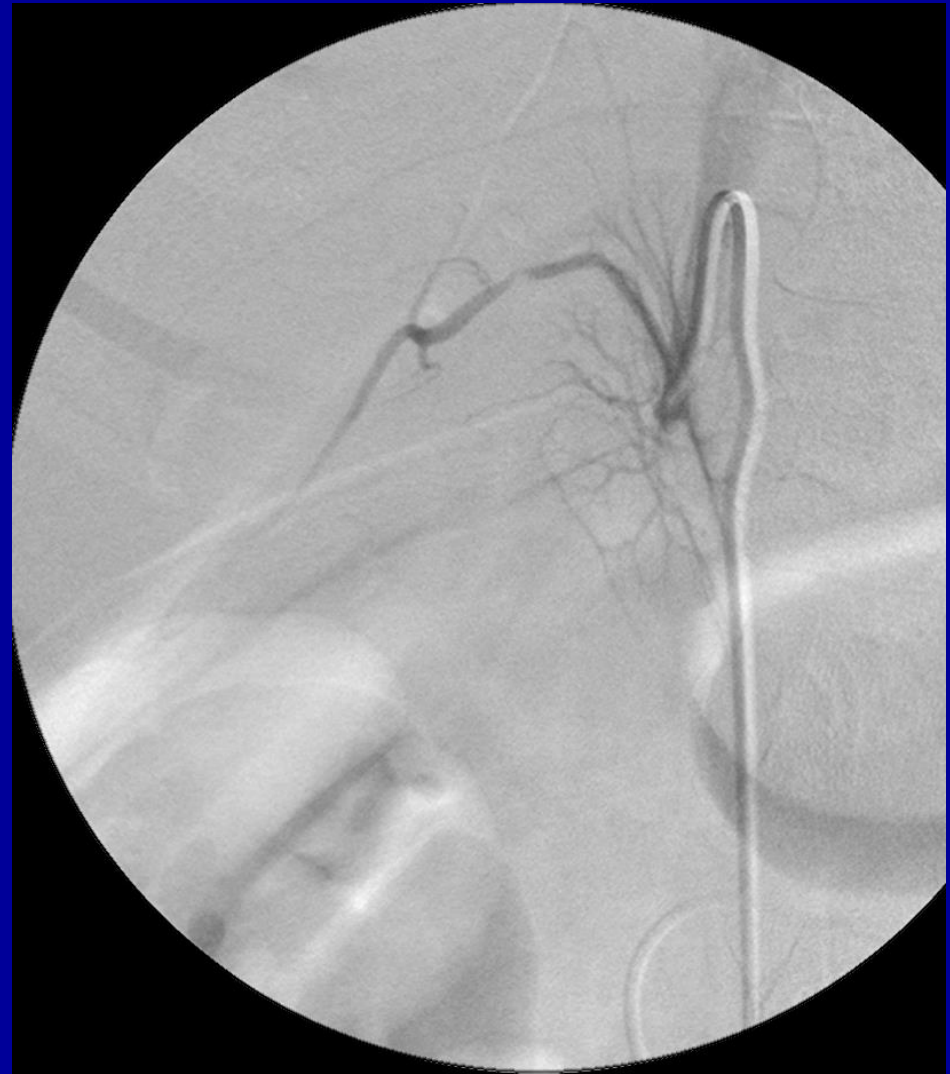
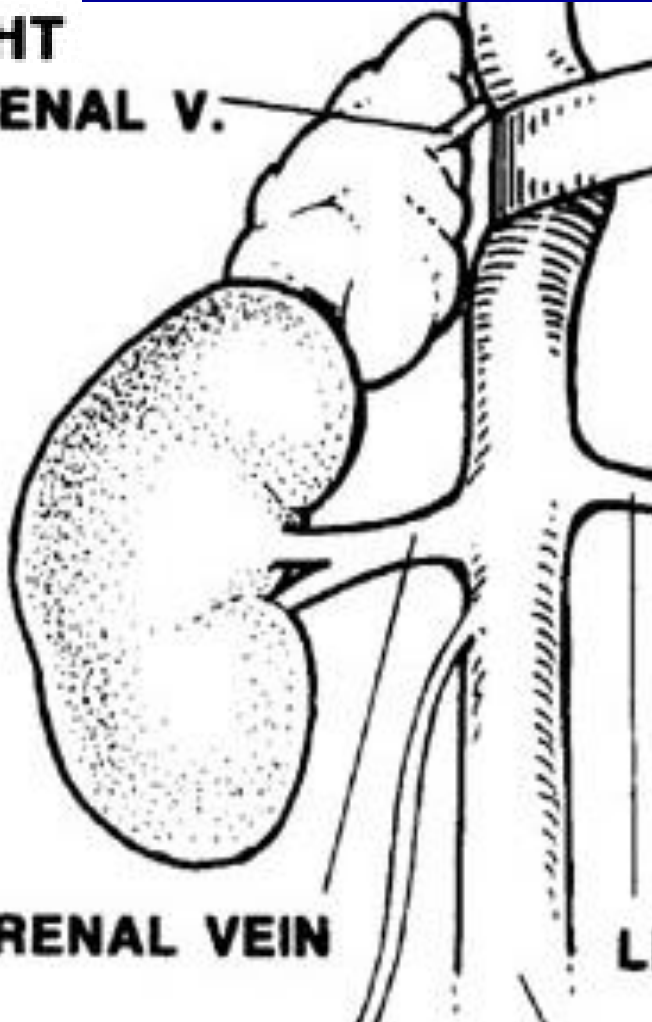


**Pearl #2: *Imaging* is not
about whether an
adenoma is present on
one adrenal gland, it is
about whether the *other*
adrenal gland is
*unequivocally normal***

Adrenal Vein Sampling

Right Adrenal Venogram

**RIGHT
ADRENAL V.**



AVS Interpretation

- ✓ Mixed Venous Cortisol & Aldosterone
- RAV, LAV Cortisol = Selectivity Index (SI)
 - $>2x$ IVC -Cosyntropin; $>4x$ IVC +Cosyntropin
- A/C Gradients = Lateralization Index (LI)
 - >2 -Cosyntropin; >4 +Cosyntropin
 - Low Side $<$ IVC = Contralateral Suppression
- Two Common Patterns (+Cosyntropin):

<u>High AV</u>	<u>Low AV</u>	<u>IVC</u>	<u>Interpretation</u>
4-50	0.5-1.5	1-5	Lateralized
2-4	2-4	1-2	Bilateral

Endocrine HTN

Case 2

- PRA <0.6 ng/mL/hr; Potassium 3.4 meq/L; Serum Aldosterone 42 ng/dL
- Switched to Amiloride 5 mg/d
- AVS Lateralized to R
- R ADX
- K Normal, BP Much Better

Primary Aldosteronism

Teaching Points Cases 1 & 2

- **Interpreting ARR on Medications**
- **Confirmatory Testing**
- **Managing Hypokalemia During Workup**
- **Healthy Skepticism for Reports of CT, MRI, and AVS**
 - **In God We Trust, All Others Show Us the Data**

Primary Aldosteronism

AVS Example

- 42 yo HM, HTN x 5 yr
- BP 155/95; 3 Drugs; Many Side Effects
- 24 h Urine K 106, Na 385, Aldo 217
- PRA 1, PAC 47, K 4.7, 18OHB 45
- CT: L 1.5 cm; 5 mm R

AVS Example

A 26,160
C 922
A/C 28.4

IVC:
A 39
C 19.3
A/C 2.02

A 2,131
C 1,264
A/C 1.79



Endocrine HTN

Case 3

- 36 YO Vietnamese F
- Recurrent Pregnancy Losses
- Resistant HTN, Hypokalemia
- Labetolol, Amlodipine, KCl
- PRA 1 ng/mL/h; Aldo 21 ng/dL, K 3.0
- 24h U Aldo 17 μ g Na 155 meq, K 197 meq
- CT: 3 cm R Adrenal Mass, L Poorly Seen

Endocrine HTN

Case 3: CT Scan



Endocrine HTN

Case 3: AVS

<u>Site</u>	<u>Aldo</u>	<u>Cortisol</u>	<u>Ratio</u>
RAV	6845	1382	5.0
LAV	2806	129	21
IVC	55	56	1.0
PV	49	37	1.3

What's Going On???

Endocrine HTN

Case 3

- Endo Referral
- ROS: Bruising, 10 lb Wt Gain, Depression
- Exam: Wt 103 lbs, BMI 24 kg/m², +Bruises, SC Fat Pads
- 24h UFC 260 µg
- ACTH <5 pg/mL
- DHEA-S 18 µg/dL
- AM Cortisol After 1 mg Dex 22.5 µg/dL

Endocrine HTN

Case 4

- 42 YO WF Sudden Onset HTN, Hirsutism
- PRA <0.4 ng/mL/h; Aldosterone 5 ng/dL, DST Cortisol 1 μ g/dL, K 2.8 meq/L, T 125 ng/dL
- Spironolactone 300 mg/d Normalized BP & K



Mineralocorticoid HTN

Differential Diagnosis

- **Primary Hyperaldosteronism**
 - APA, IHA, FHAs
- **Secondary Aldosteronism**
- **Cortisol**
 - Cushing Syndrome
 - AME: 11 β HSD2, Licorice
- **11-DOC**
 - Tumor, Drugs, 17OHD, 11OHD
- **Liddle Syndrome**

What the...???

3-yo girl:

Growth retardation, hypertension (180/140 mmHg),
Hypokalemia (2.7 mmol/l),
hyporeninemic hypoaldosteronism

Dexamethasone

ACTH

Spirolactone

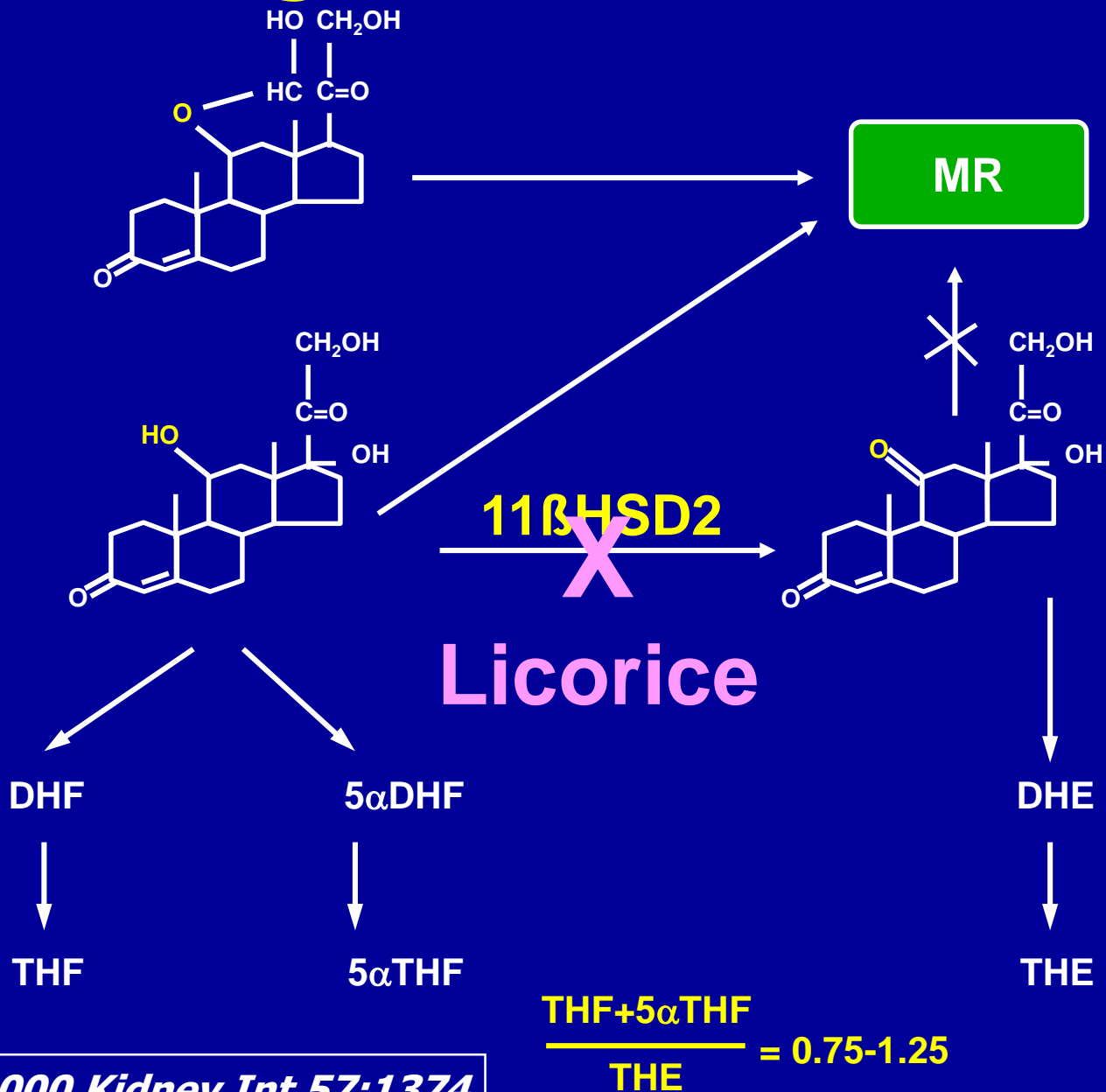


BD	160/100	140/90	100/60	155/90	100/55
Serum K	2.8	3.8	4.2	2.0	4.1
Urin Na	150	150	30	30	150
PRA	<0.3	<0.3	0.6	<0.3	1.1
Urin Aldo	<2.5	<2.5	<2.5	<2.5	3.5

Dx: AME

Ulick et al 1979 JCEM 49:757

Protecting MR from Glucocorticoids



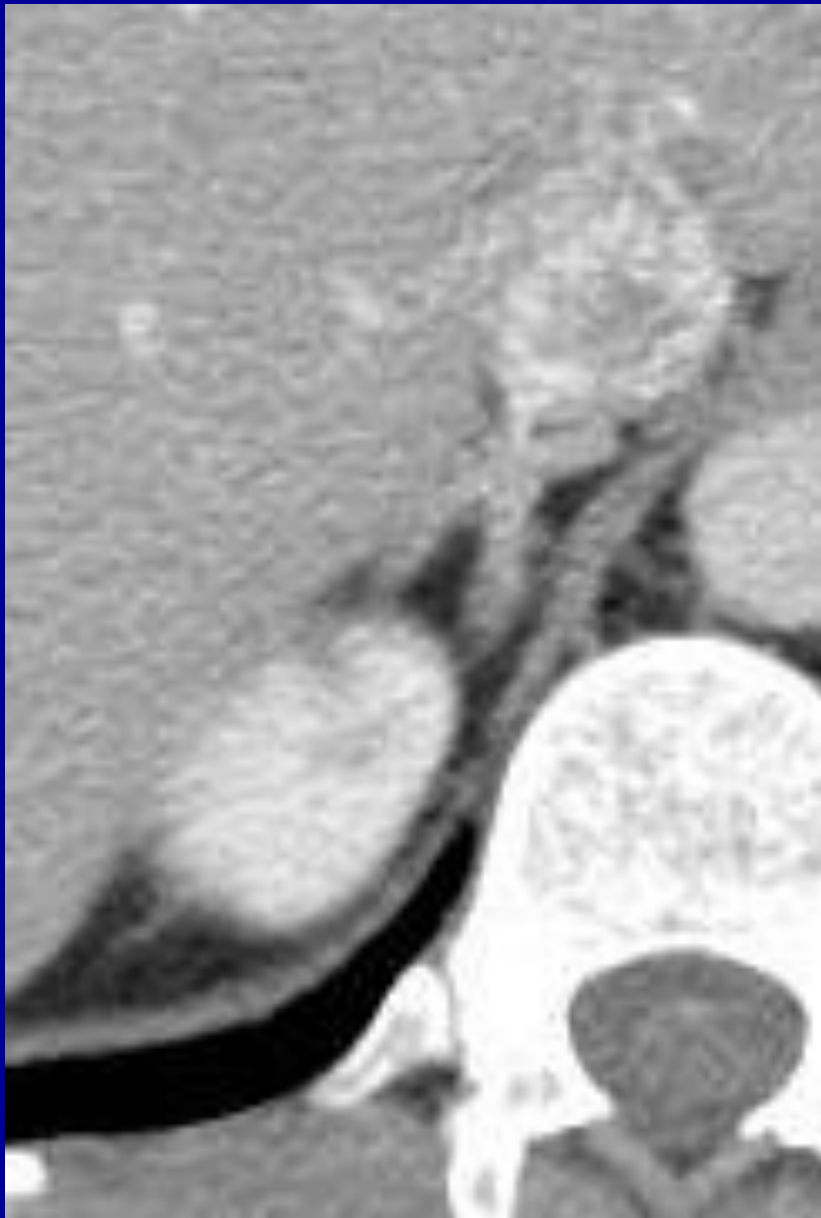
Ferrari 2000 Kidney Int 57:1374

Endocrine HTN

Case 5

- **35 YO WF, “Ovaries/Uterus Did Not Develop”**
 - Email: “I think I have Androgen Insensitivity”
- **PMH: HTN, Inguinal Hernia Repair**
- **Meds: Metoprolol, Irbesartan, Amlodipine
Hydralazine, KCl + Premarin**
- **BP 130/86 HR 73, Not Obese, 2/6 SEM**
- **No Cushingoid Stigmata**
- **Breasts Tanner V, Sparse Body Hair**
- **K 3.0, MR-Angio: NI Renal Arteries, But....**

CT Adrenals

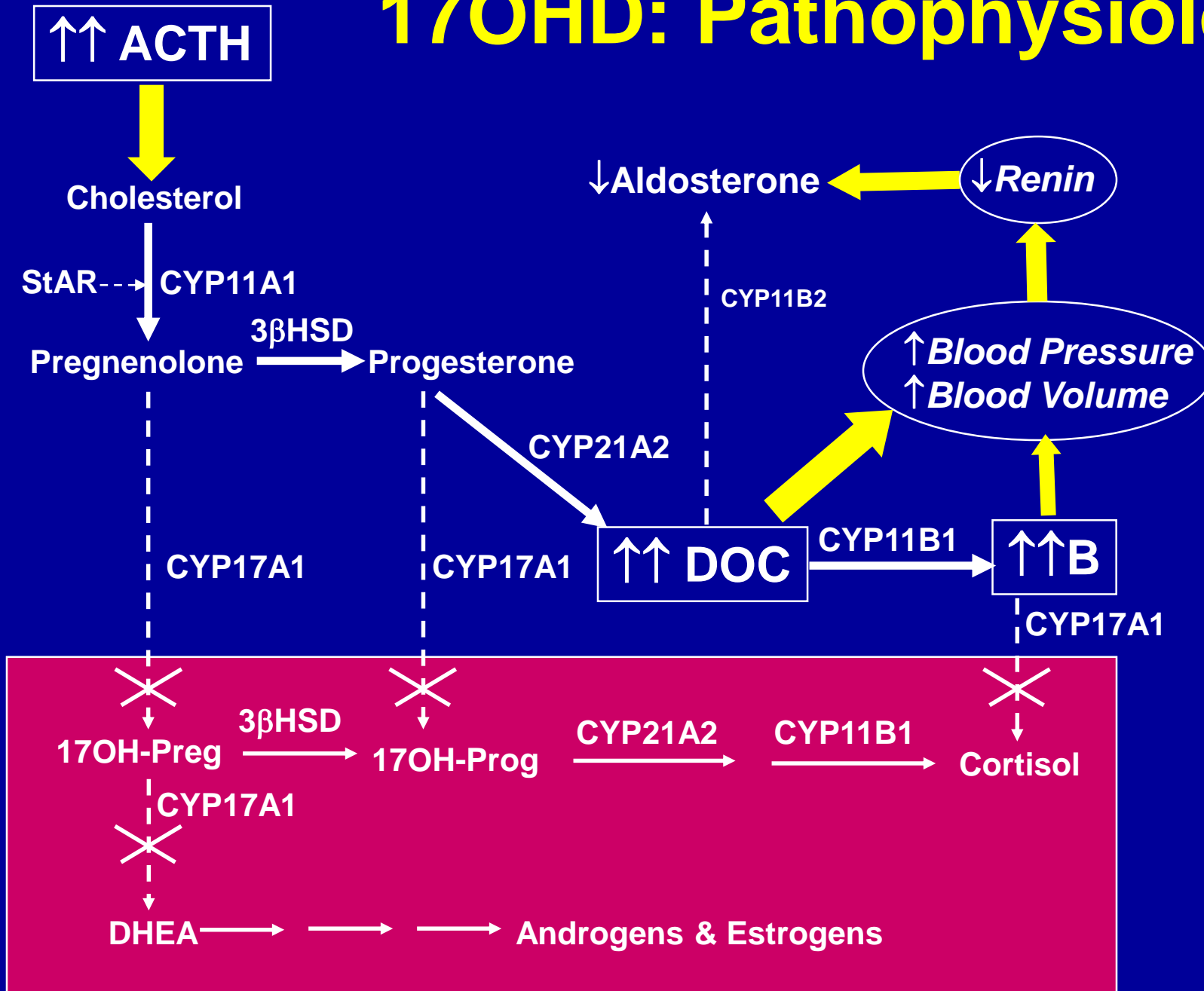


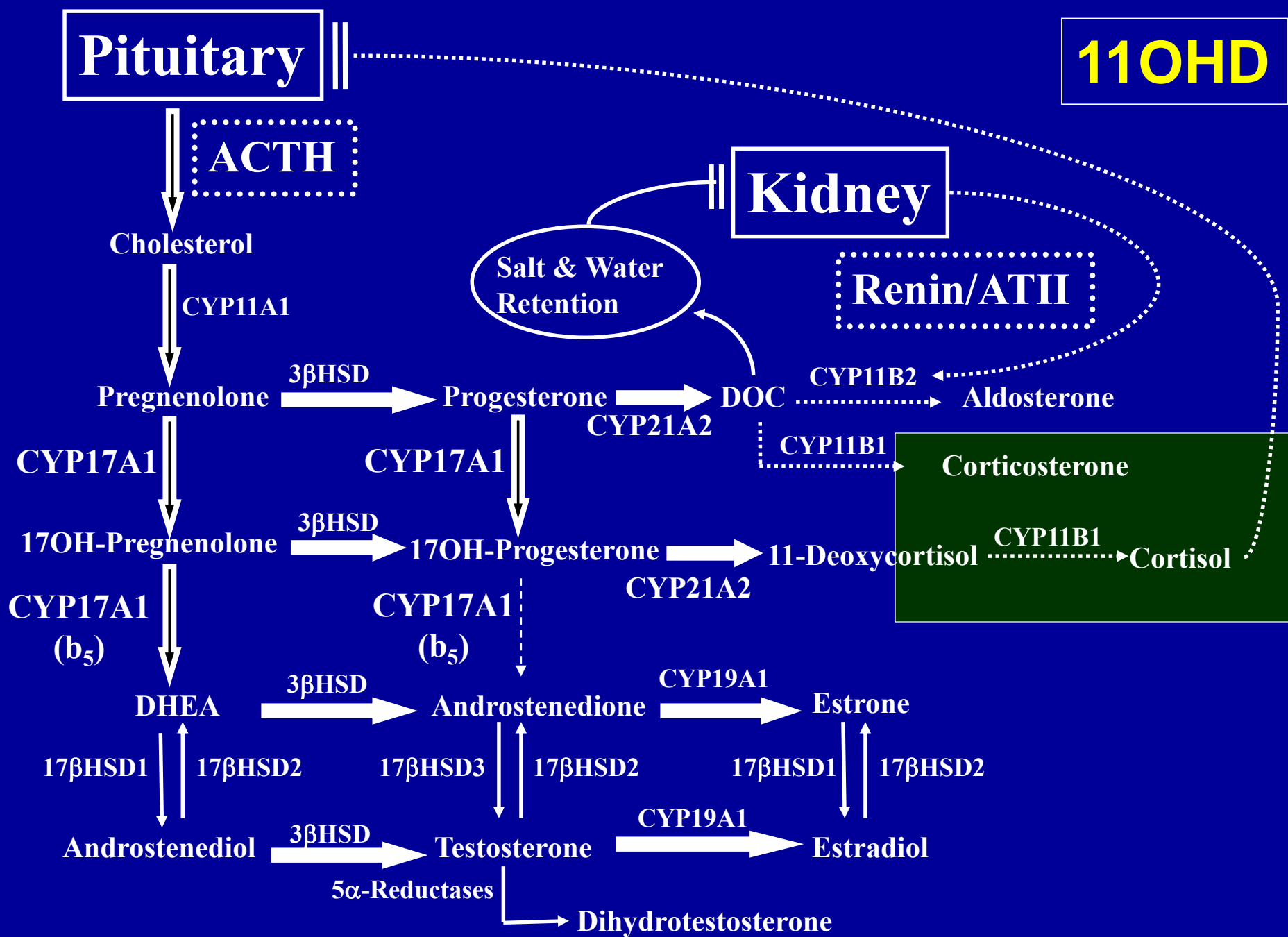
Case 5: ACTH Stimulation Test

<u>Hormone (ng/dL)</u>	<u>Baseline</u>	<u>Post-ACTH</u>	<u>Normal</u>
ACTH (pg/mL)	31		<25
Direct Renin (μ U/mL)	<8		8-15
DHEA-sulfate (μ g/dL)	<15		45-380
Cortisol (μ g/dL)	3.6	3.9	>20
Aldosterone	4	6	doubles
Corticosterone	14,544	21,981	<1,300
11-Deoxycorticosterone	121	368	14-33

Dx: 17-Hydroxylase Deficiency

17OHD: Pathophysiology





DOC Excess & AME in 2017

- **Abiraterone Acetate**
 - **CYP17A1 Inhibitor for CRPC**
 - **Co-Administer Prednis(ol)one 5 mg BID**
- **Osilodrostat (LCI-699)**
 - **CYP11B1/11B2 Inhibitor (“New Metyrapone”)**
 - **In Phase III Trials For Cushing Disease**
- **Licorice**
 - **Good & Plenty Contains Some Real Licorice**
 - **Chewing Tobacco + Licorice**
 - **Nutritional Supplements**

Management

ACTH-Dependent MC HTN

- **MR Antagonists**
 - Titrate to Normal Renin
- **Glucocorticoids Sparingly**
 - Cushingoid Side Effects Dex > Pred > HC
- **Amiloride, Triamterine for K; CCB for BP**
- **AME: MRA + Hydrocortisone**
- **17OHD: Spironolactone + Estrogen + HC**
- **11OHD: HC + Eplerenone (M) or Spiro (F)**

Endocrine HTN

Summary: Mineralocorticoids

- Know Who to Screen and When to Stop
- Must Confirm Non-suppressible Aldo
- Do Not Be Duped by CT Scans
- AVS for Most PA Cases Prior to Surgery
- Genetics of Mineralocorticoid Excess
- Do Not Forget Other Mineralocorticoids
- Spironolactone, Eplerenone Medical Rx

Endocrine HTN

Case 6

- 53 YO WM, Uncontrolled HTN
- Morbidly Obese, IGT, +Cigs +EtOH
- Fatigue, Snoring, Medication AE's
- Amlodipine, Losartan-HCT, Clonidine
- BP 148/96 HR 88, Spikes to 190/110
- K 4.0 meq/L, Cr 1.8 mg/dL, mAlb 110 mg/g
- PRA <0.4 ng/mL/h; Aldosterone 6 ng/dL
- Plasma NMN 1.3, MN <0.2 nmol/L

**Pearl #3:
Pheo Symptoms
Correlate With
Catecholamine
Elevations**

Endocrine HTN

Case 7

- 40 YO LAM With Abd Pain, Dyspnea
- ECG: HR 156, ST-Depression
- Echo: LVEF 20%, Normal Filling & Valves
- Cath: Global Hypokinesis, Normal Cors, BP <70
- TFTs Normal, LFTs Slight High, BNP 488 pg/mL
- CXR: Cardiomegaly, Bibasilar Infiltrates

Endocrine HTN

Case 7



**Pearl #4:
Pheos Do Not
Hide on CT
Scans**

Pheochromocytoma

Differential Diagnosis Of Spells

+ HTN &/Or Tachycardia

- Labile Essential HTN
 - Sleep Apnea
- Clonidine Withdrawal
- Neuroblastoma
- Arrhythmia
- Thyrotoxicosis
- Panic Attacks
- Hypoglycemia
- Drugs

Flushing, No HTN

- Menopause
- Mastocytosis
- Carcinoid
- Medullary Thy CA
- Diencephalic Sz
- Diabetes/Autonomic
- Drugs
- (Panic Attacks)

Pheochromocytoma

Clinical Features

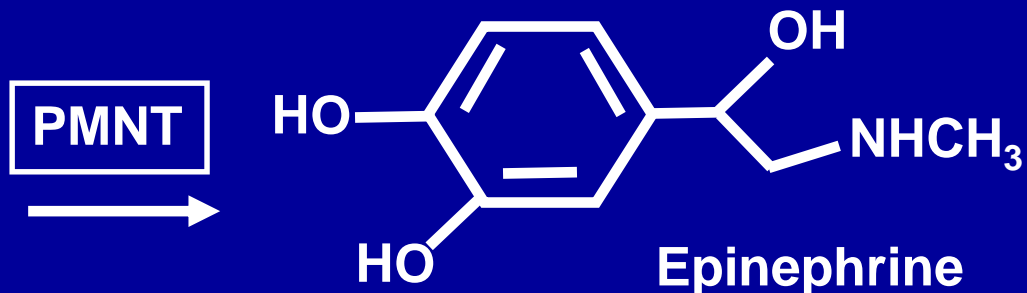
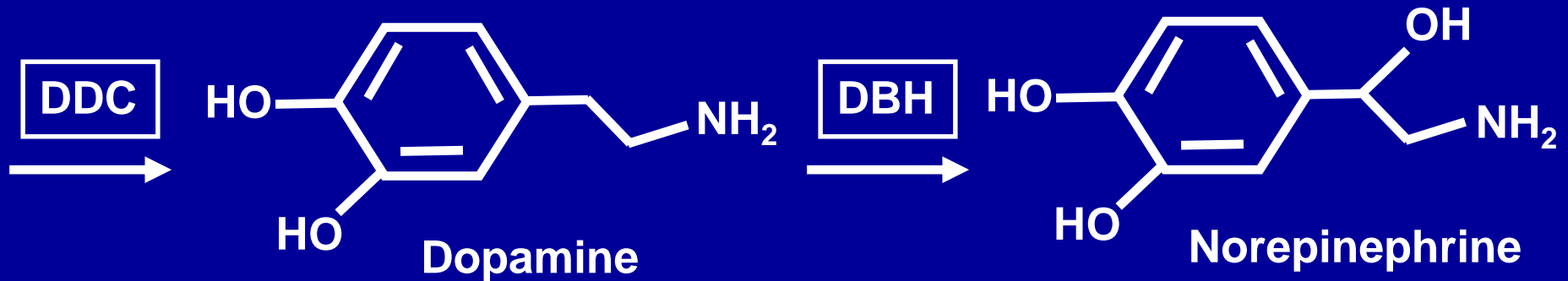
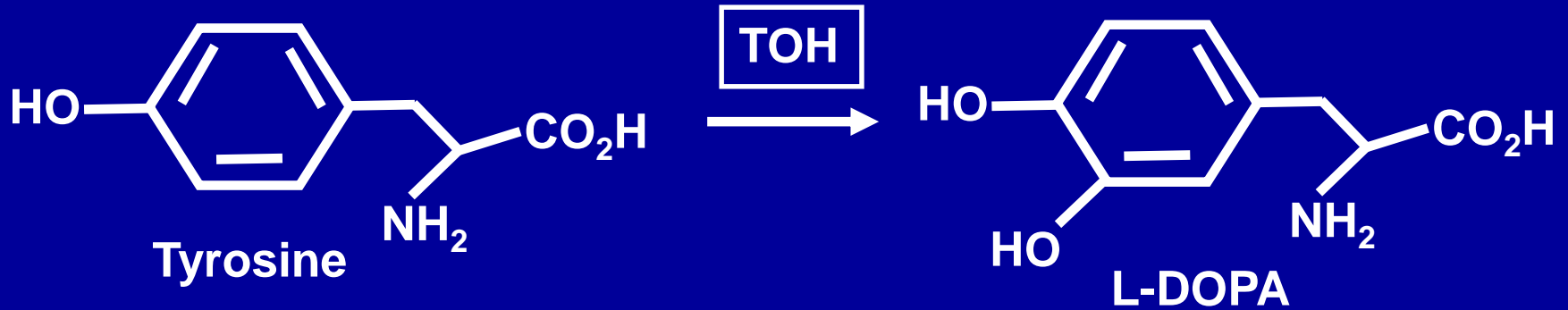
- **Pressure: Sustained HTN + Spikes**
- **Pain: Throbbing HA, Chest Pain**
- **Perspiration: Heavy, Generalized**
- **Palpitations**
- **Pallor**
- **Other: Hyperglycemia, Weight Loss, Tremor, Orthostasis, Hypercalcemia, Fatty Liver, Cardiomyopathy**
- **5-10% Asymptomatic(!!)**

Pheochromocytoma

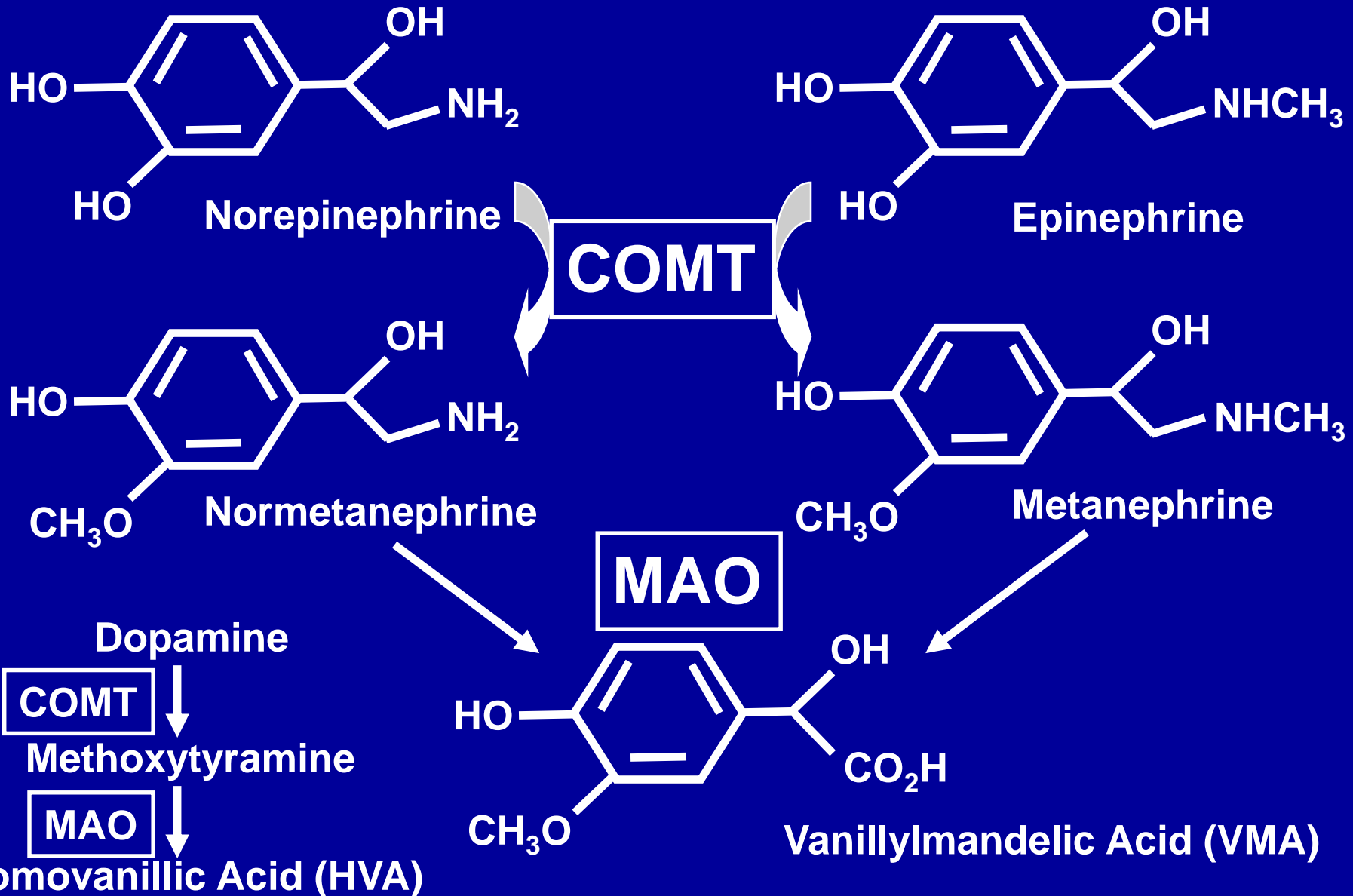
The Pheo Paroxysm (“Spell”)

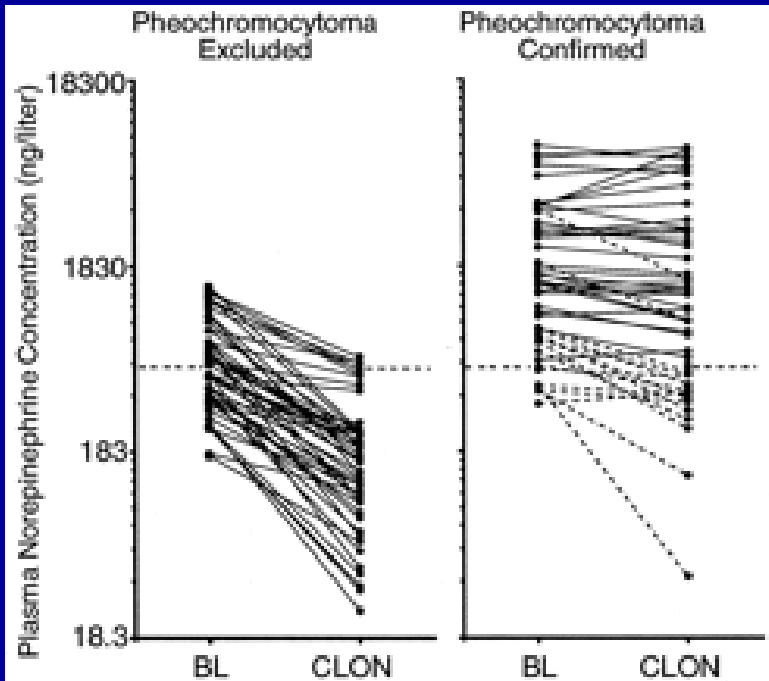
- **Throbbing HA & Chest Pain**
- **Drenching Sweat**
- **Pounding Tachycardia**
- **Extreme BP Elevation**
- **Pallor, All Lasting 10-60 Min**
- **NO Flush, Wheezing, Itching, Diarrhea, Syncope, Dermatographia**
- **DDx: Menopause & Clonidine Withdrawal**

Catecholamine Biosynthesis



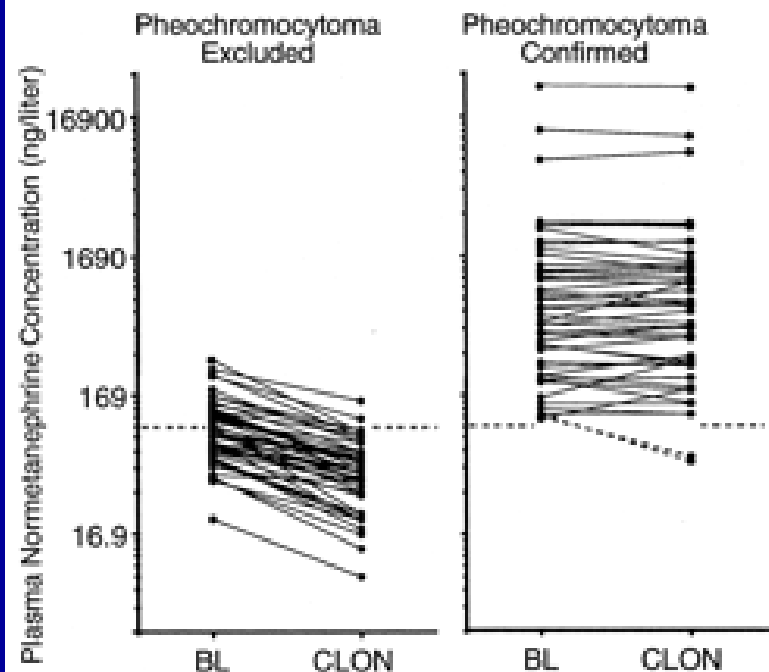
Catecholamine Catabolism





--500 pg/mL

Plasma Catecholamines & Metanephrines After 0.3 mg Clonidine



--1 nmol/L

Eisenhofer et al 2003
JCEM 88:2656

Pheochromocytoma

Associated Diseases & Genes

- Most Autosomal Dominant
- MEN2A: MTC, Pheo, HPTH, *RET*
- MEN2B: MTC, Pheo, Neuromas, *RET*
- VHL: Angiomas, Renal Cell CA, *VHL*
 - Isolated Familial Pheo Is *VHL* Type 2C
- NF-1: Café au Lait, Neurofibromas, *NF1*
- Paragangliomas: *SDHx = A, B, C, D, AF2*
- Phakomatoses: Tuberous Sclerosis, Ataxia-Telangectasia, Sturge-Weber
- Other Genes: *TMEM127, MAX, HRAS, HIF2A, PHD1, PHD2, FH, ATRX, MDH2*

Endocrine HTN

Case 8

- 58 YO WM, Single Episode Hematuria
- No Paroxysms, NI BP
- US: R Adrenal Mass
- 24 h Urine MN 233 mcg, NMN 2504 mcg
- MRI: 3.4 cm R adrenal mass
 - High, Heterogeneous Signal T2-weighted
 - No Signal Drop-out on Out-of-phase T1
- Plasma MN 0.45, NMN 7.65

Endocrine HTN

Case 7



Summary: Pheo/PGL

- Plasma & Urine Metanephrines Both OK
- Most Slightly Positive Screens Not Pheo
 - Sleep Apnea, Clonidine Withdrawal
- Reversible α -Blockers If Mild Disease
- Blockade Prior to CT Scans Not Needed
- Think Familial If Young, Weird Tumor(s)
- Think VHL In Isolated Familial Pheo
- Think *SDHx* for Paragangliomas