

# **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***

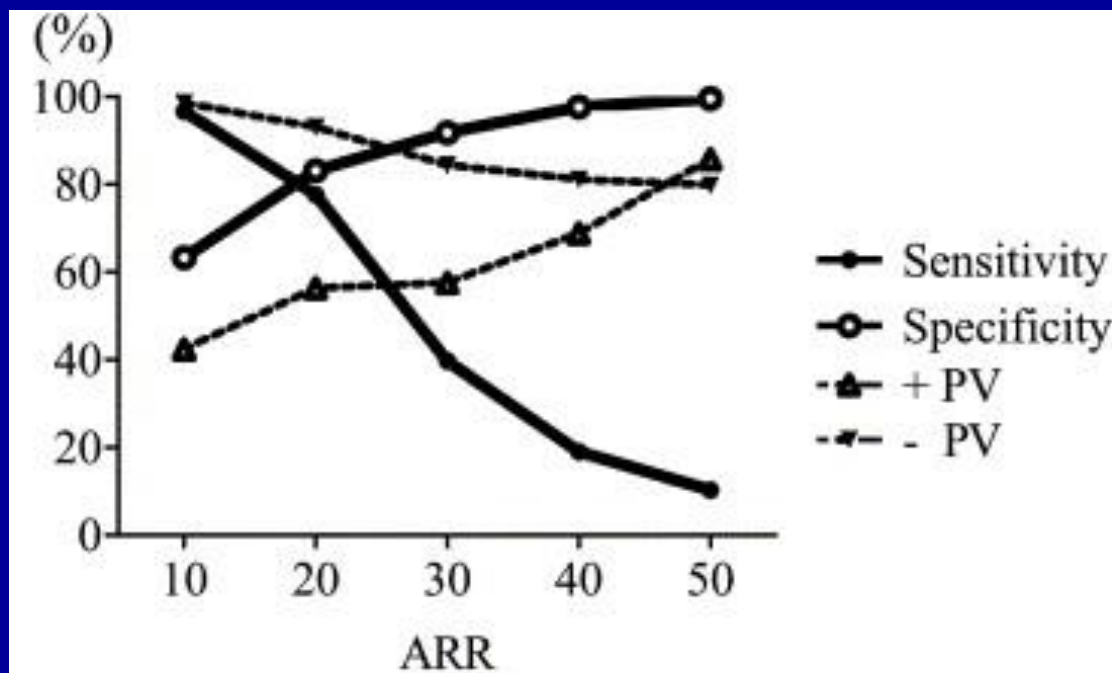
# Primary Aldosteronism

## 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

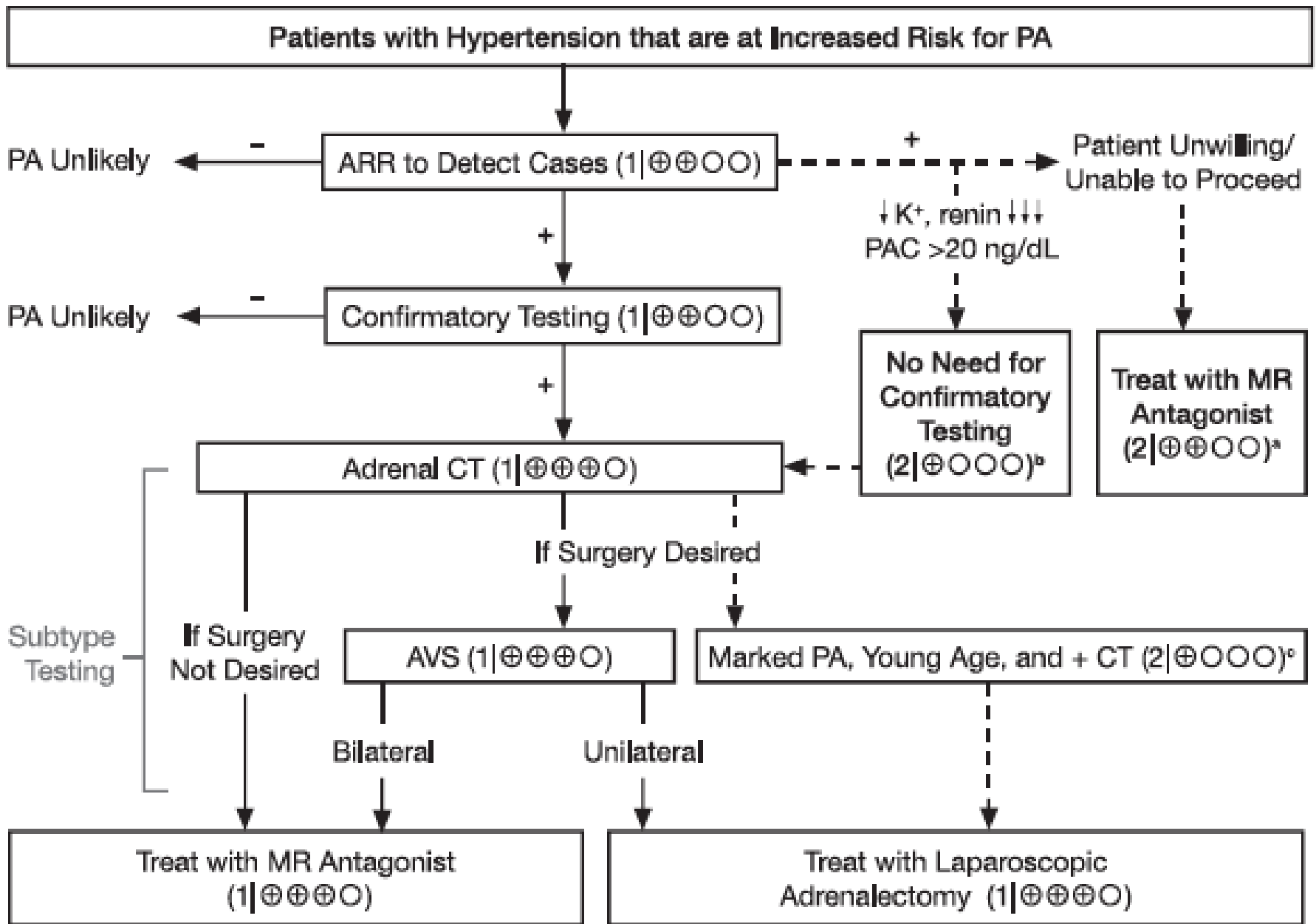


Cut-off	Sensitivity	Specificity	+PV	-PV
ARR >20	78	83	56	93
ARR >50	10	99	86	80
ARR >20 and PAC >15	57	88	57	88 (%)

# 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 aldo, 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**
- **Spironolactone 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 <sup>-3</sup> )	C <sub>RAV</sub> and C <sub>LAV</sub> ≥ 3C <sub>IVC</sub>	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 <sub>PV</sub> ≥ 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**

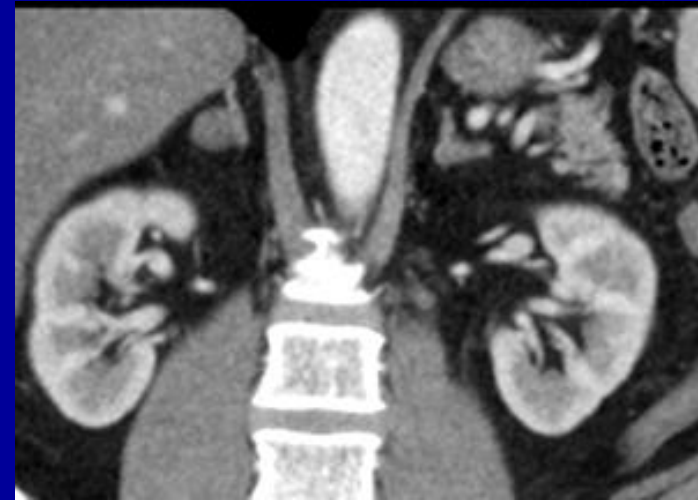
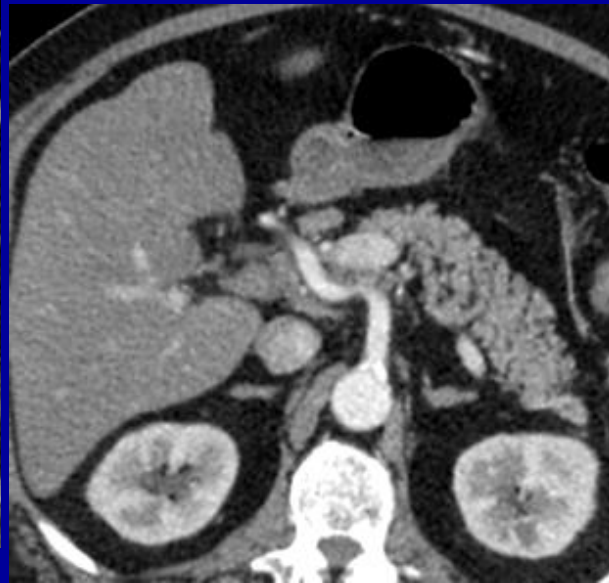
# Endocrine HTN

## 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



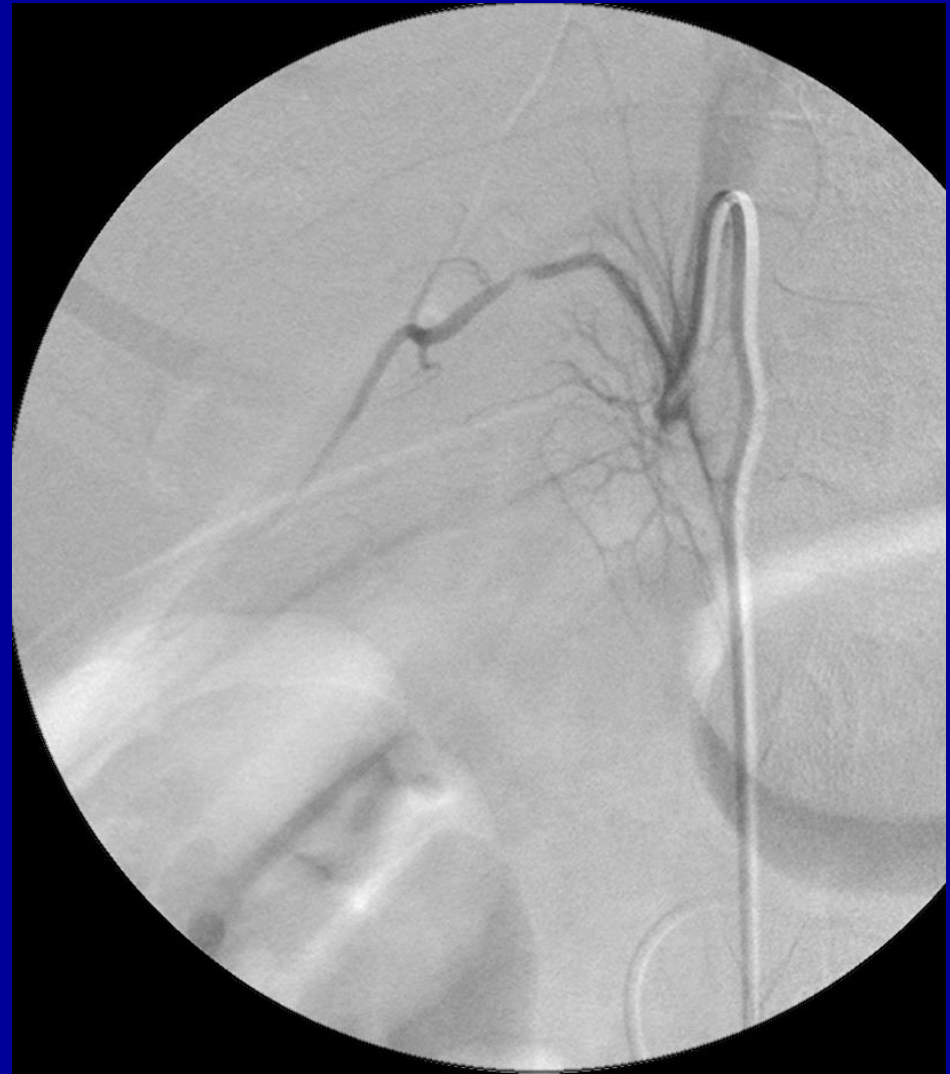
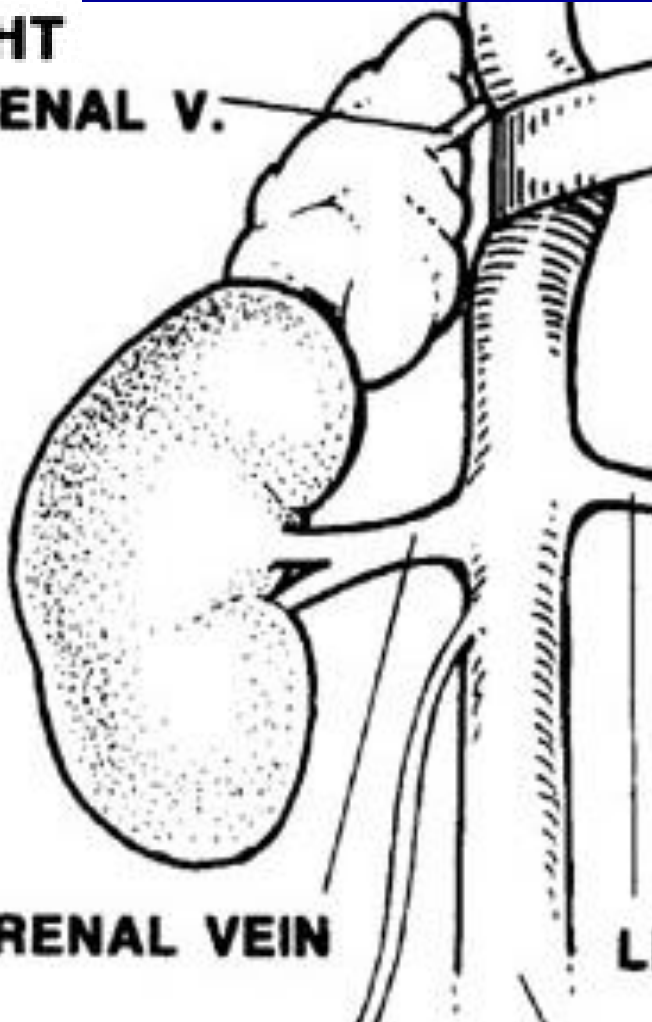


**Pearl #2: *Imaging* is not  
about whether an  
adenoma is present on  
one adrenal gland, it is  
about whether the *other*  
adrenal gland is  
*unequivocally normal***

# 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  $\mu$ 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/m<sup>2</sup>, +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  $\mu$ 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 $\beta$ HSD2, Licorice
- **11-DOC**
  - Tumor, Drugs, 17OHD, 11OHD
- **Liddle Syndrome**

# What the...???

3-yr girl:

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

Dexamethasone

ACTH

Spirolactone

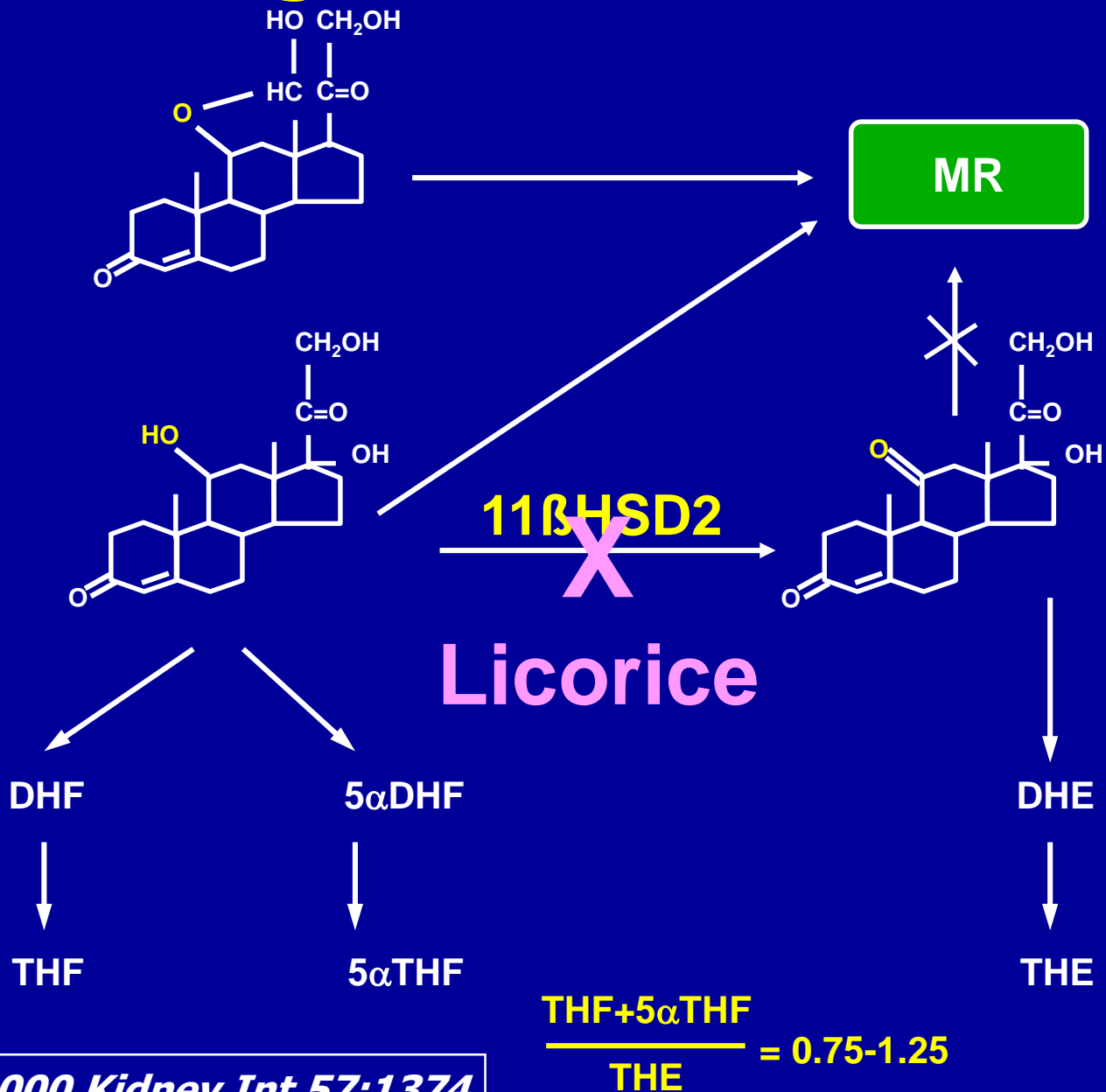


BD	160/100	140/90	100/60	155/90	100/55
Serum K	2.8	3.8	4.2	2.0	4.1
Urin Na	150	150	30	30	150
PRA	<0.3	<0.3	0.6	<0.3	1.1
Urin Aldo	<2.5	<2.5	<2.5	<2.5	3.5

**Dx: AME**

*Ulick et al 1979 JCEM 49:757*

# Protecting MR from Glucocorticoids



*Ferrari 2000 Kidney Int 57:1374*

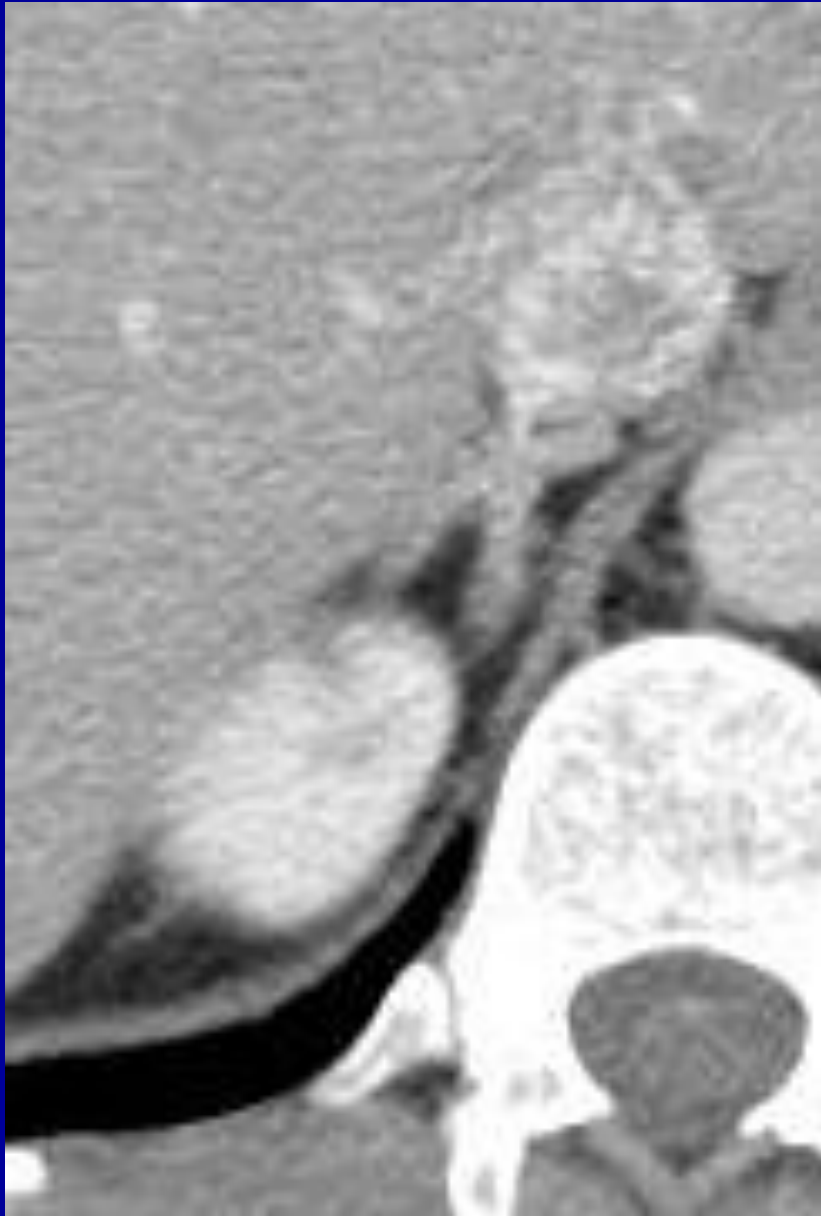
# Endocrine HTN

## 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

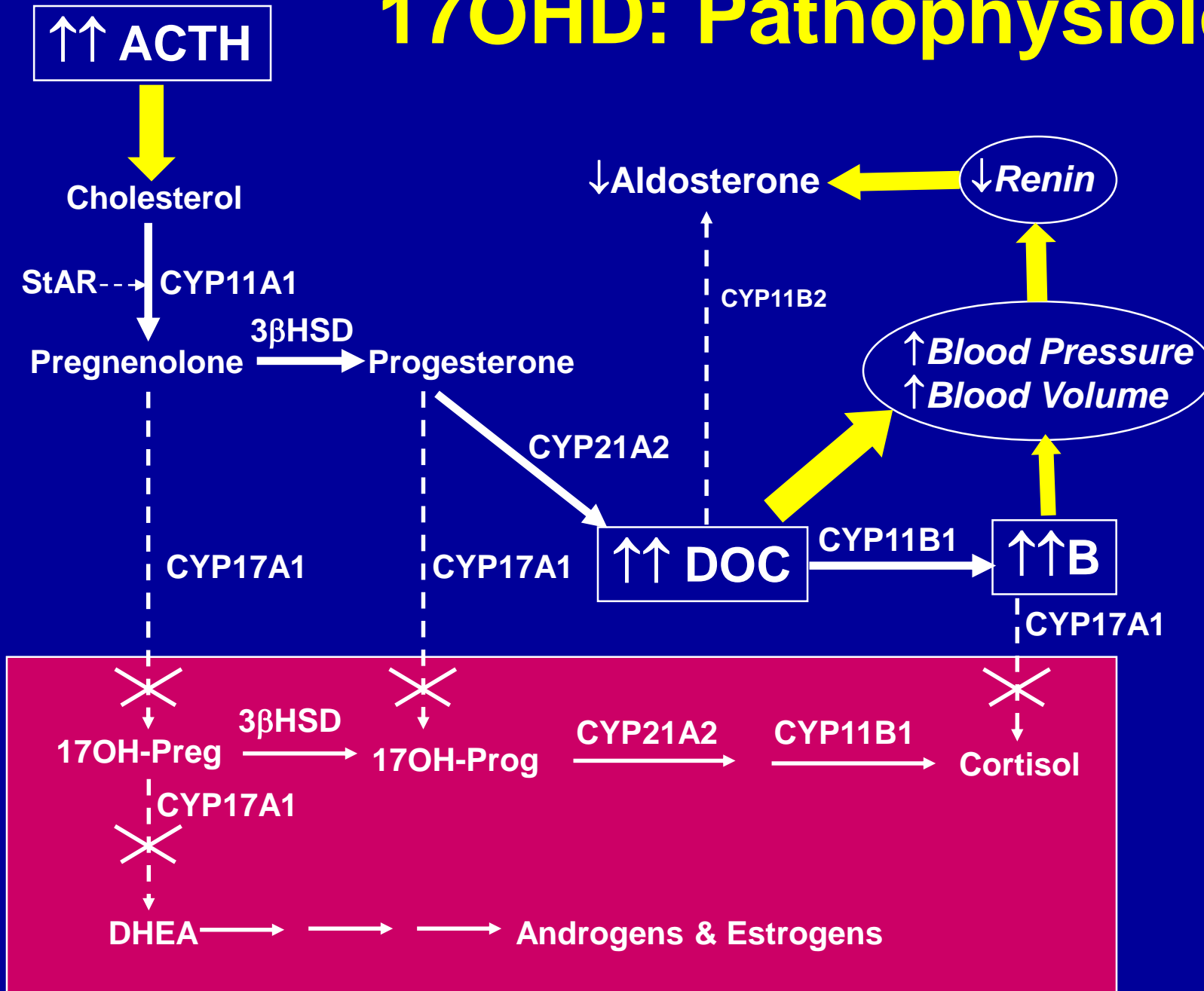


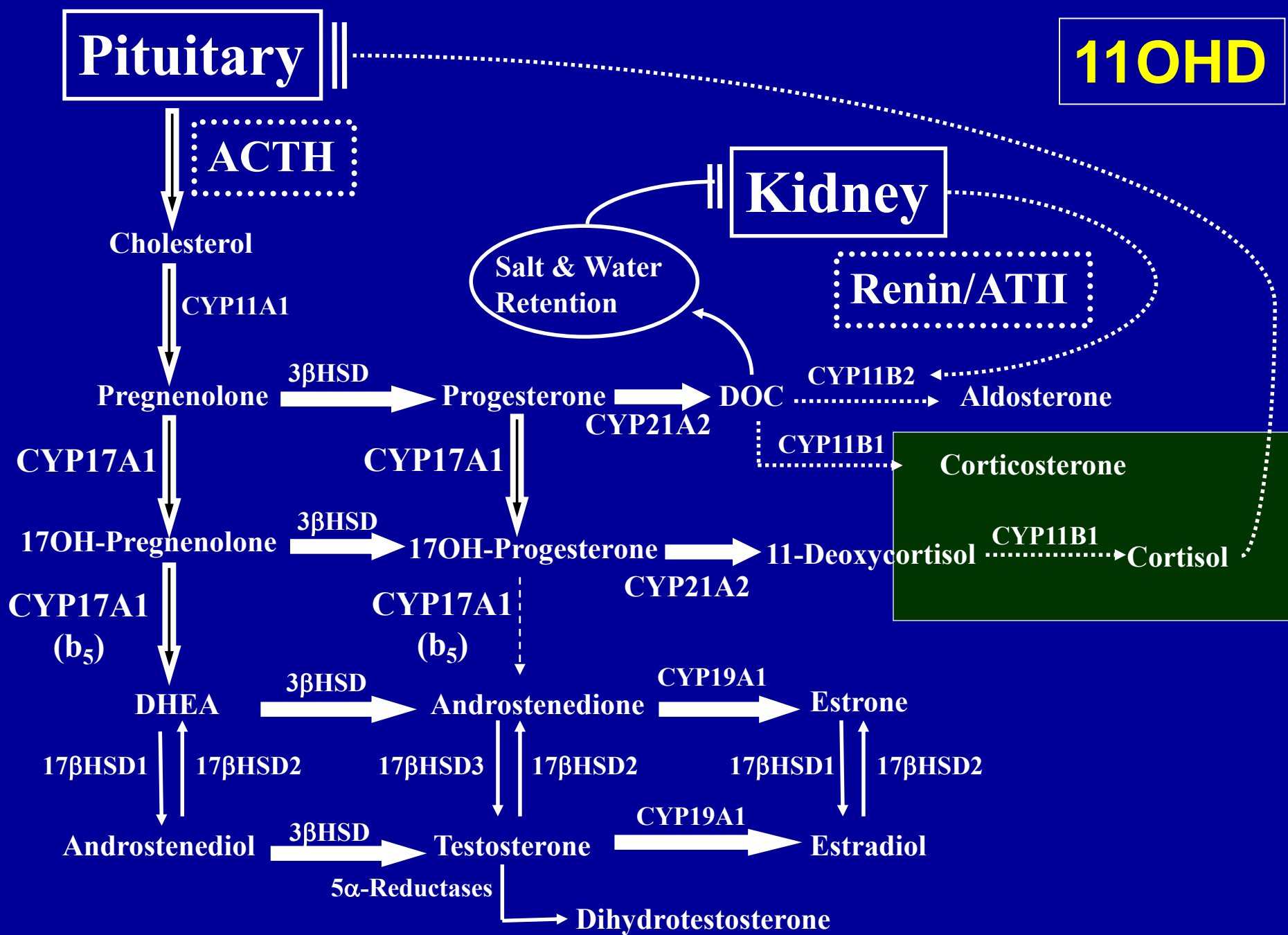
# Case 5: ACTH Stimulation Test

<u>Hormone (ng/dL)</u>	<u>Baseline</u>	<u>Post-ACTH</u>	<u>Normal</u>
ACTH (pg/mL)	31		<25
Direct Renin ( $\mu$ U/mL)	<8		8-15
DHEA-sulfate ( $\mu$ g/dL)	<15		45-380
Cortisol ( $\mu$ 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**

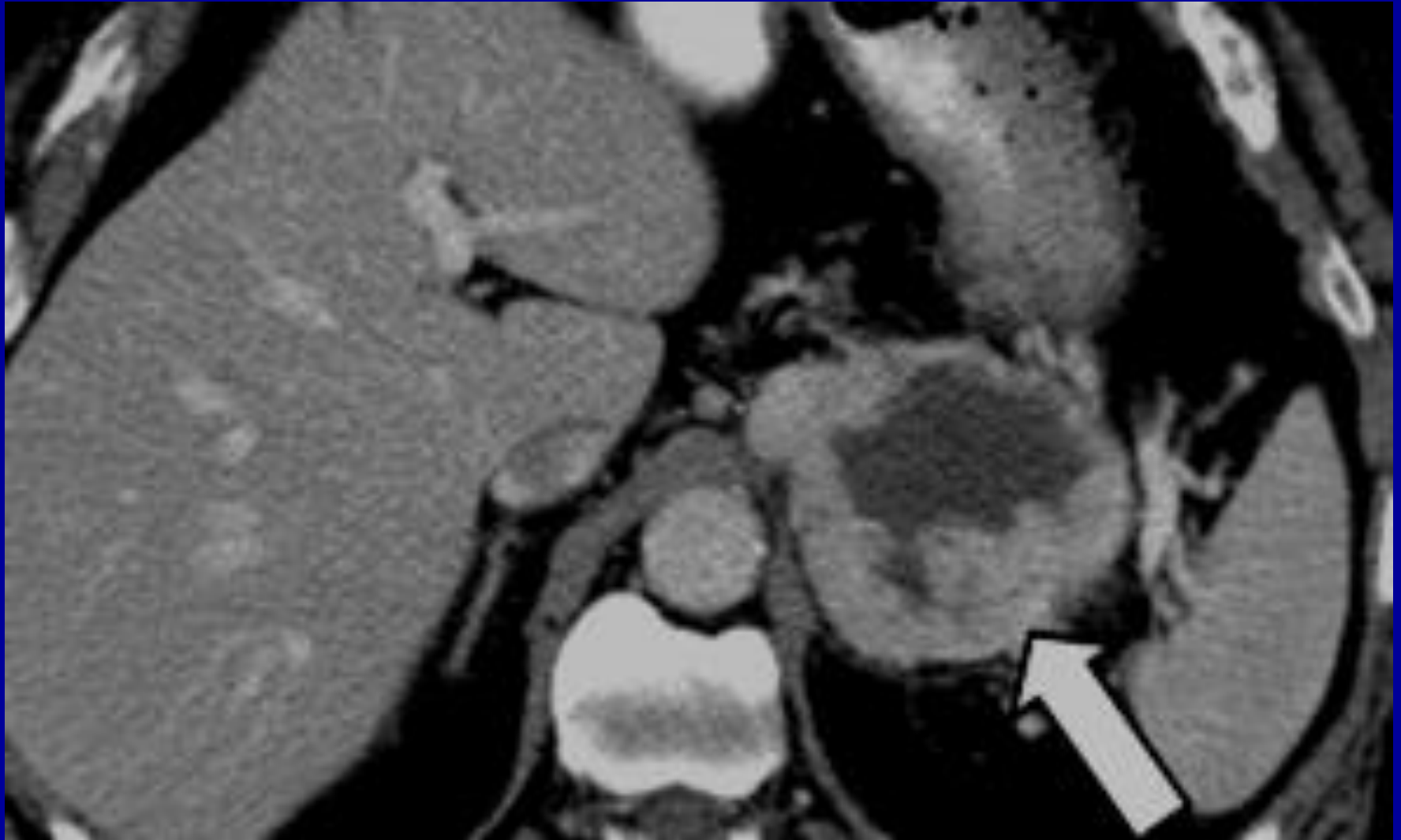
# Endocrine HTN

## 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**

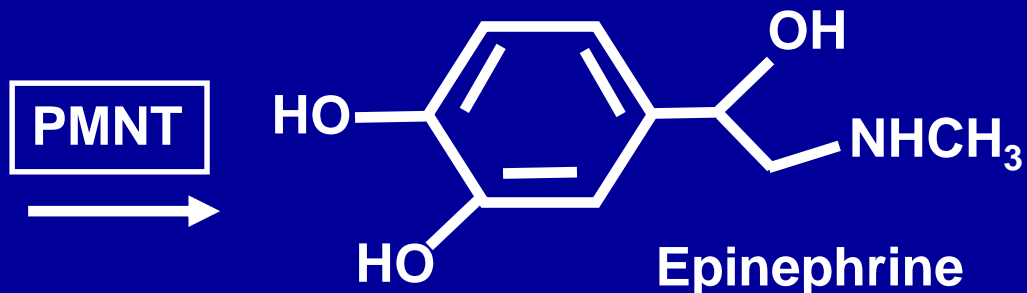
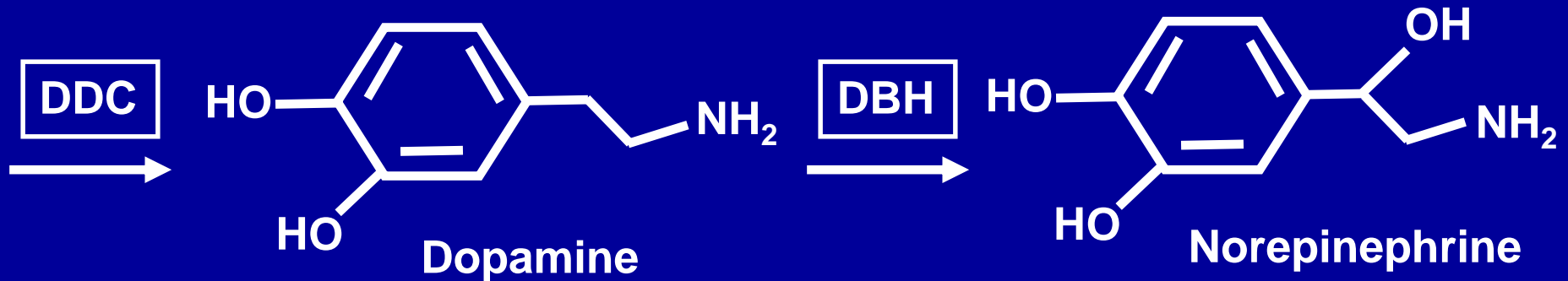
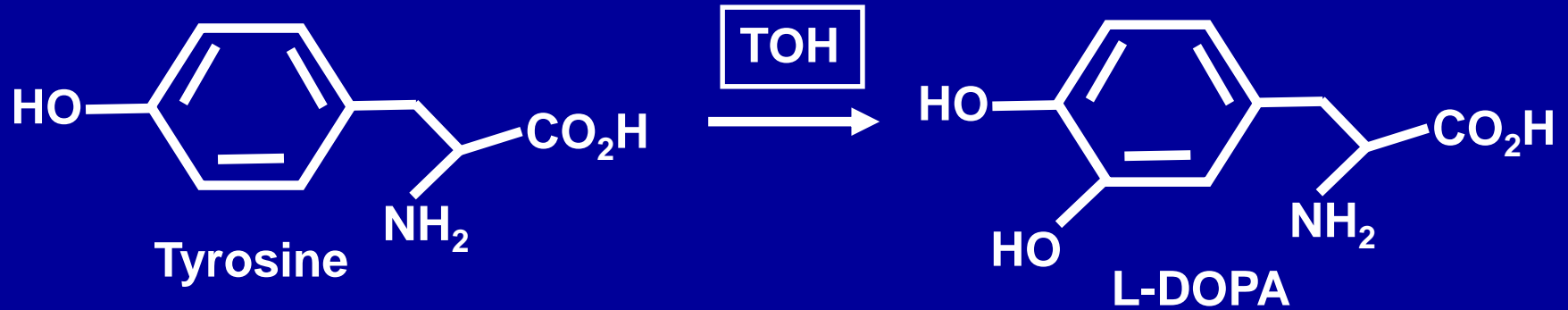
- **Pressure: Sustained HTN + Spikes**
- **Pain: Throbbing HA, Chest Pain**
- **Perspiration: Heavy, Generalized**
- **Palpitations**
- **Pallor**
- **Other: Hyperglycemia, Weight Loss, Tremor, Orthostasis, Hypercalcemia, Fatty Liver, Cardiomyopathy**
- **5-10% Asymptomatic(!!)**

# **Pheochromocytoma**

## **The Pheo Paroxysm (“Spell”)**

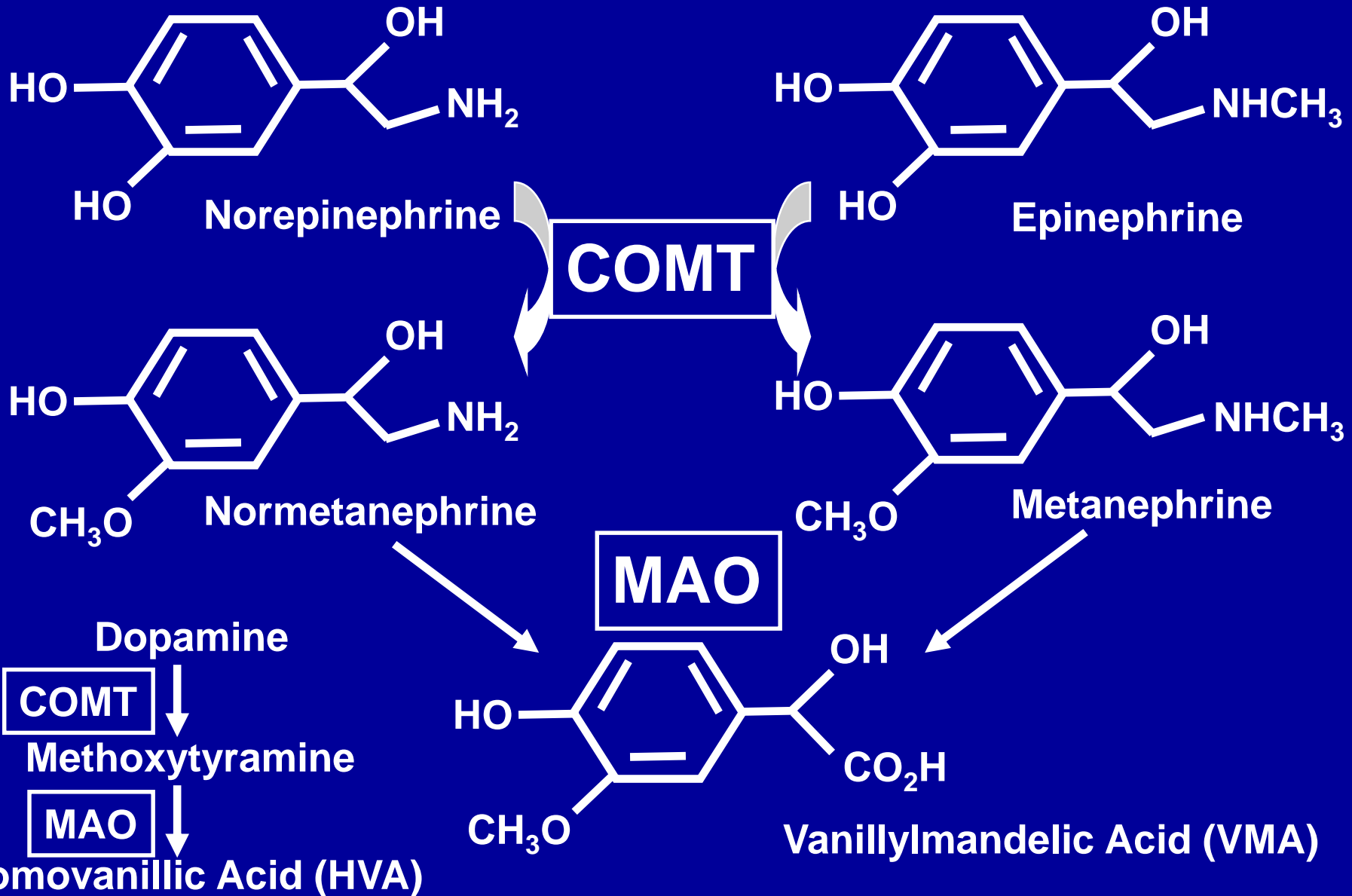
- **Throbbing HA & Chest Pain**
- **Drenching Sweat**
- **Pounding Tachycardia**
- **Extreme BP Elevation**
- **Pallor, All Lasting 10-60 Min**
- **NO Flush, Wheezing, Itching, Diarrhea, Syncope, Dermatographia**
- **DDx: Menopause & Clonidine Withdrawal**

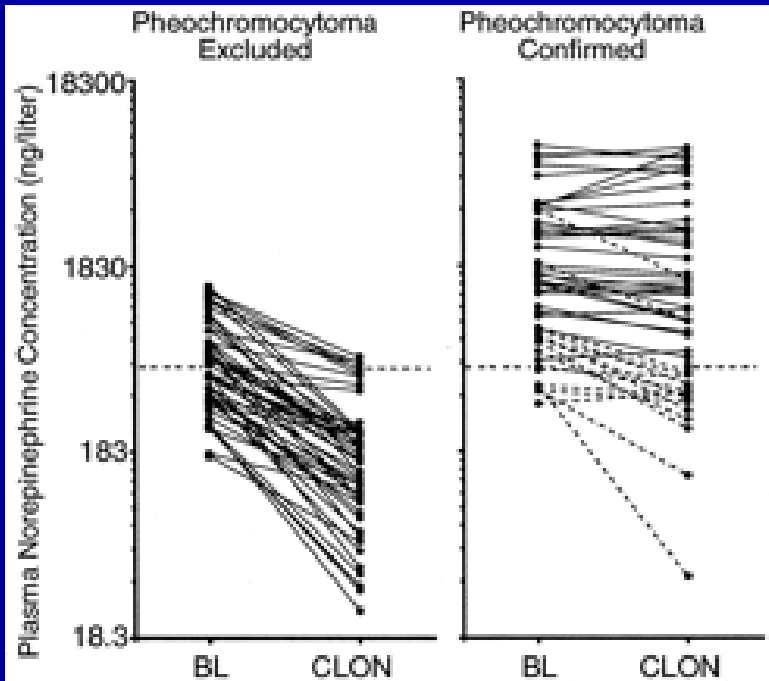
# Catecholamine Biosynthesis





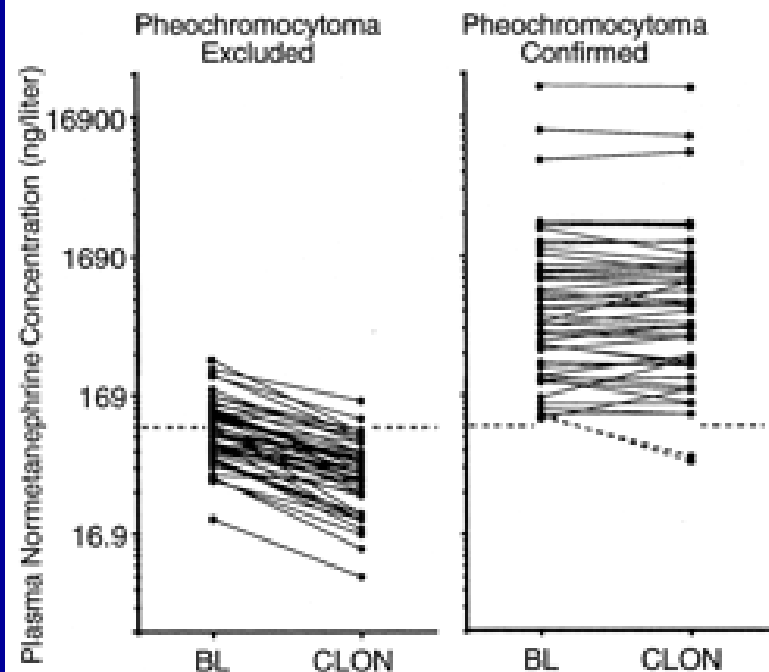
# Catecholamine Catabolism





--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  $\alpha$ -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