

# **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***

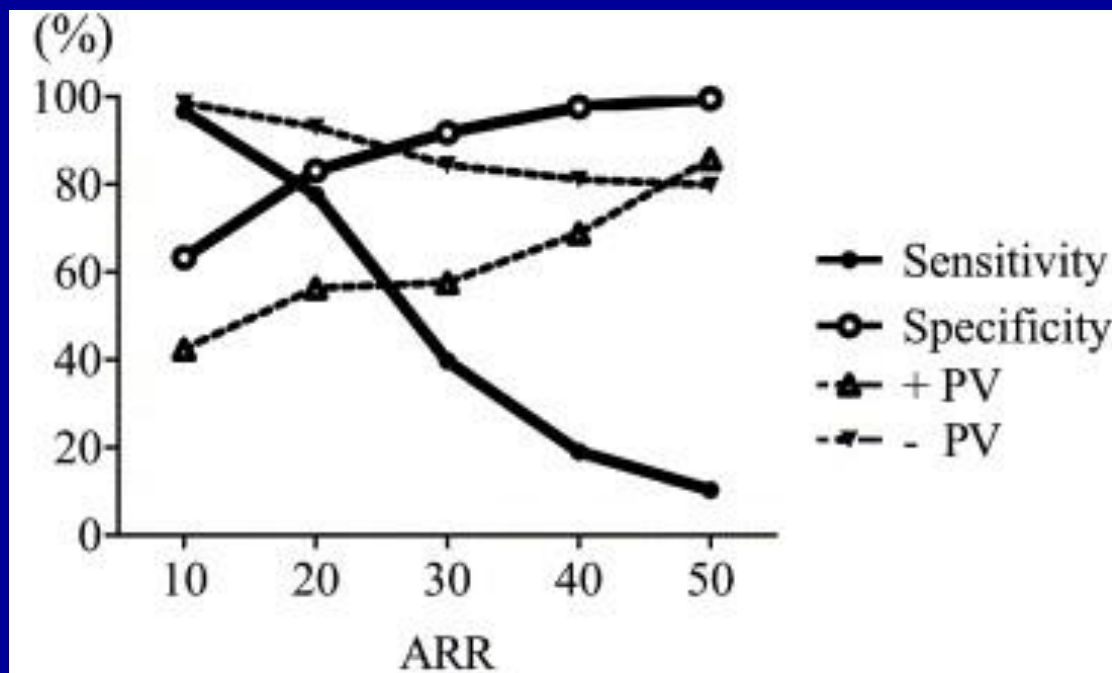
# Primary Aldosteronism

## 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><br>(ng/dL) | <u>PRA</u><br>(ng/mL/hr) | <u>ARR</u> | <u>Serum</u><br><u>Potassium</u><br>(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,<br>go to confirmatory testing |
| 11                     | 0.8                      | 15         | 2.9   | Probably PA,<br>supplement K, rescreen                |
| 38                     | 2.0                      | 19         | 4.2   | Probably PA,<br>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**

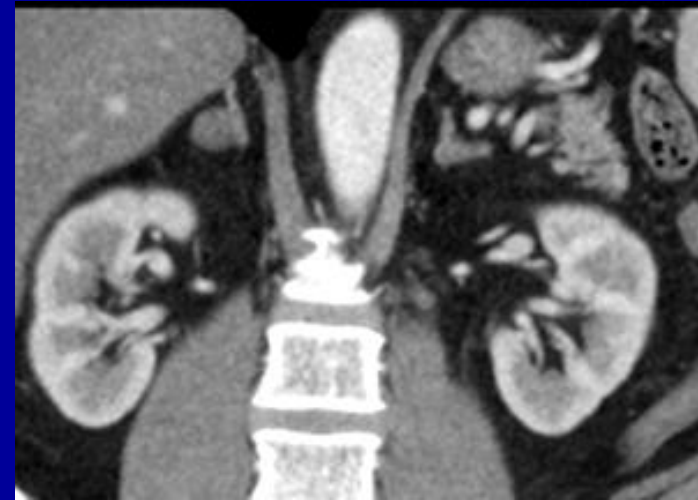
# Endocrine HTN

## 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



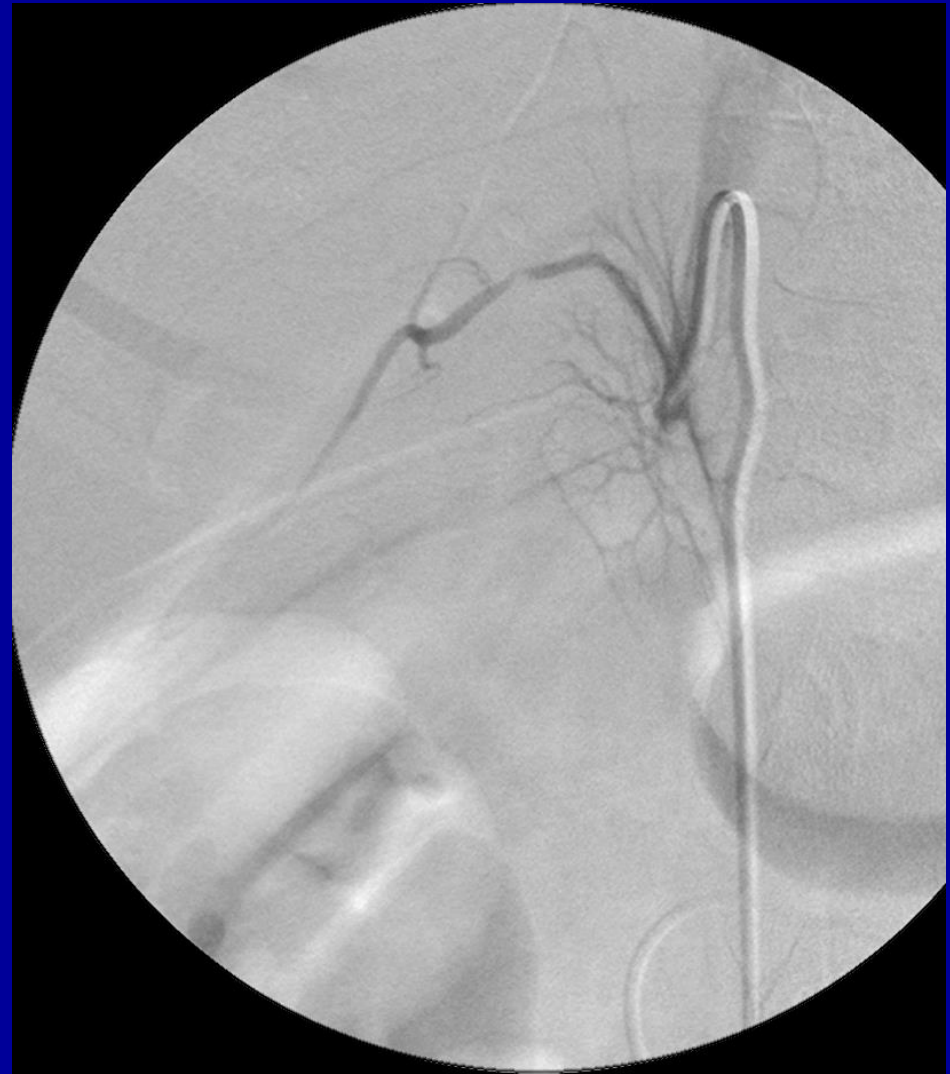
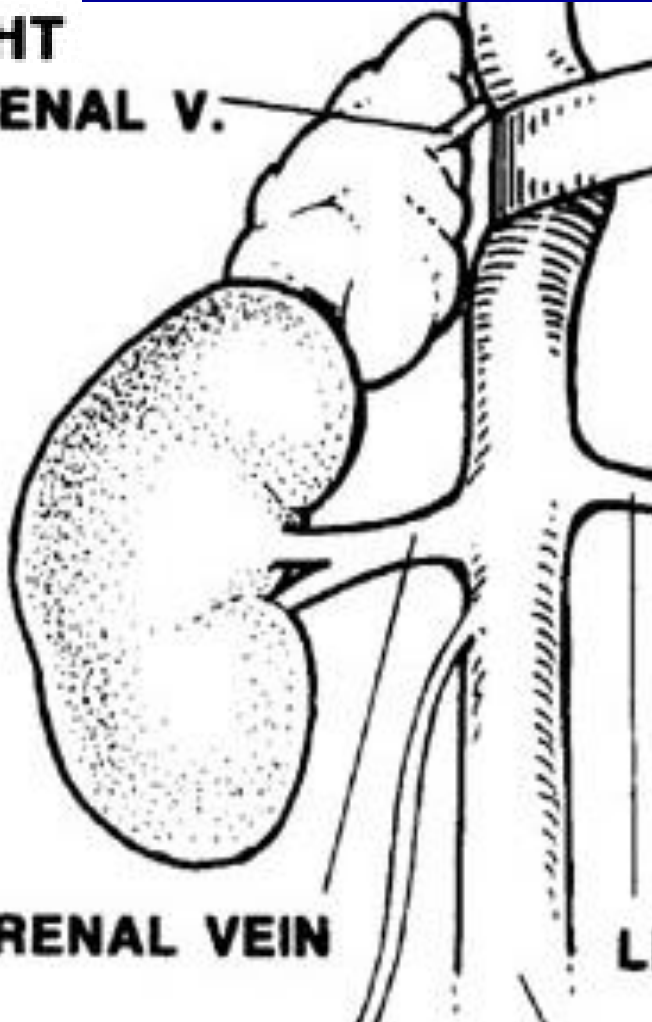


**Pearl #2: *Imaging* is not  
about whether an  
adenoma is present on  
one adrenal gland, it is  
about whether the *other*  
adrenal gland is  
*unequivocally normal***

# 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 Cortsol 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-yo girl:

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

Dexamethasone

ACTH

Spirolactone

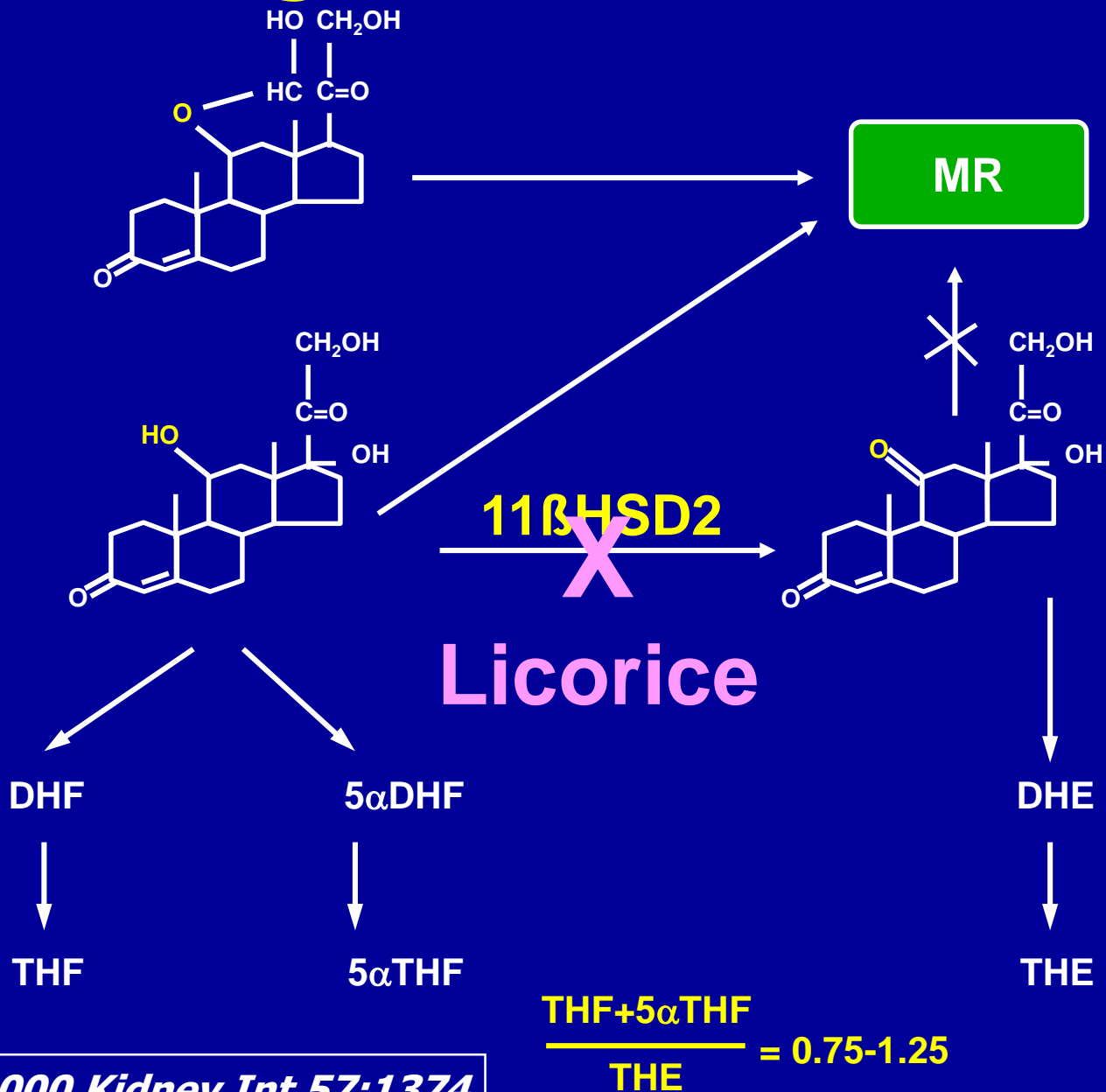


|           |         |        |        |        |        |
|-----------|---------|--------|--------|--------|--------|
| BD        | 160/100 | 140/90 | 100/60 | 155/90 | 100/55 |
| Serum K   | 2.8     | 3.8    | 4.2    | 2.0    | 4.1    |
| Urin Na   | 150     | 150    | 30     | 30     | 150    |
| 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*

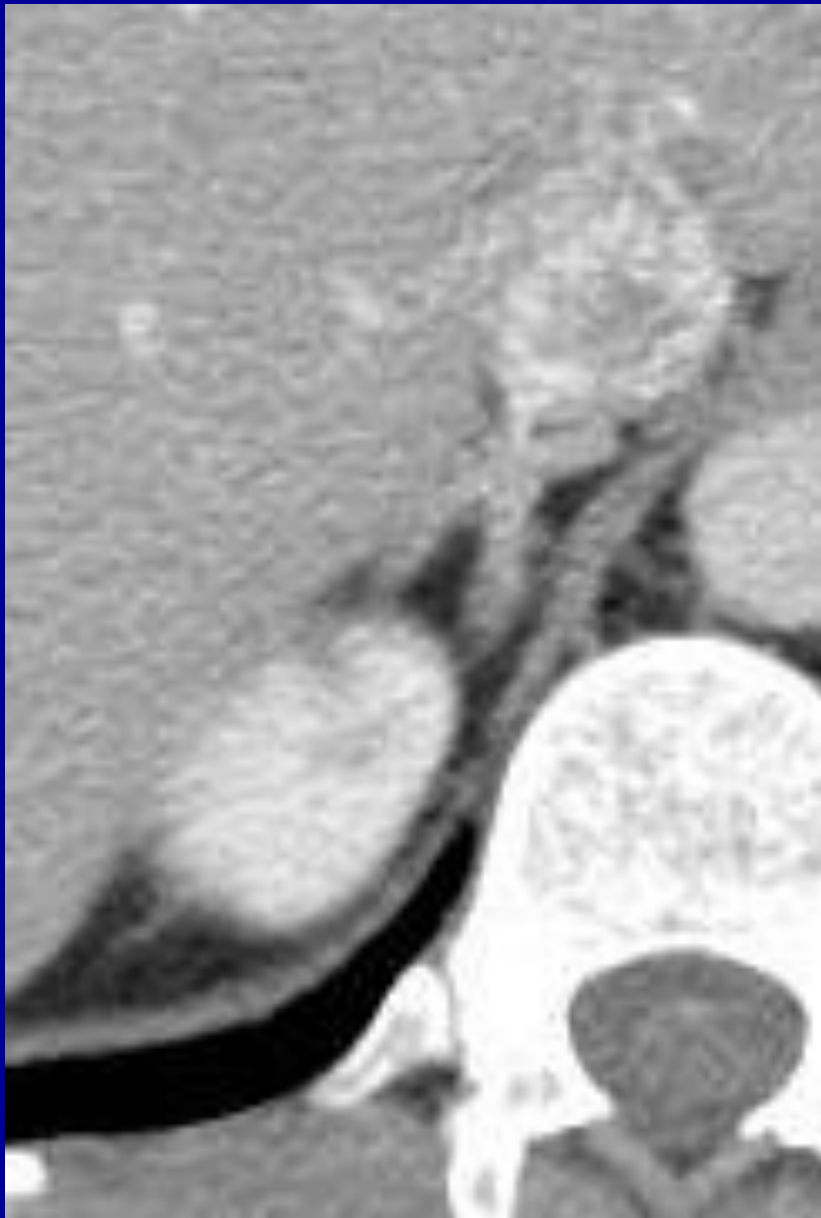
# Endocrine HTN

## 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

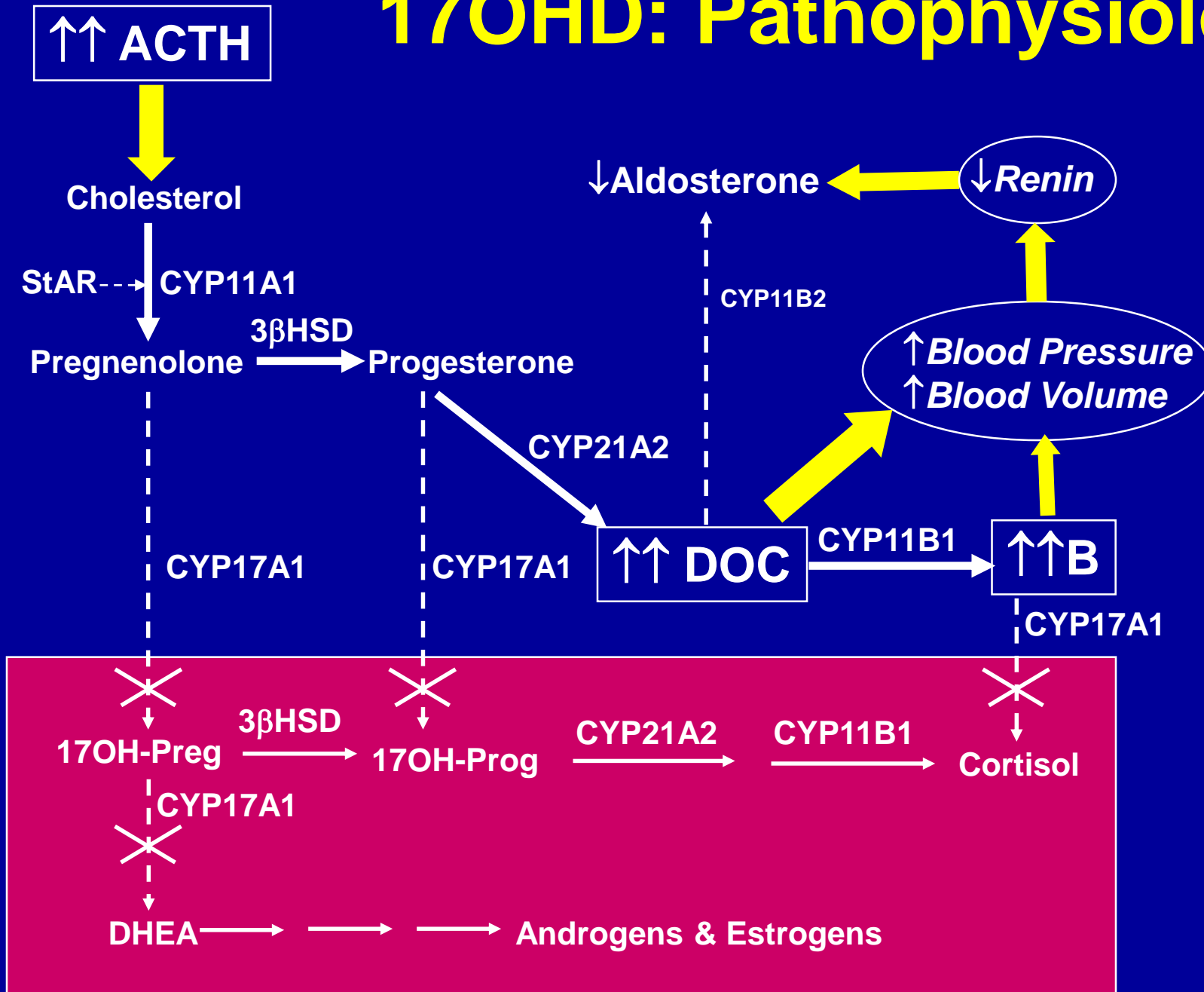


# Case 5: ACTH Stimulation Test

| <u>Hormone (ng/dL)</u>     | <u>Baseline</u> | <u>Post-ACTH</u> | <u>Normal</u> |
|----------------------------|-----------------|------------------|---------------|
| ACTH (pg/mL)               | 31              |                  | <25           |
| Direct Renin ( $\mu$ 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**

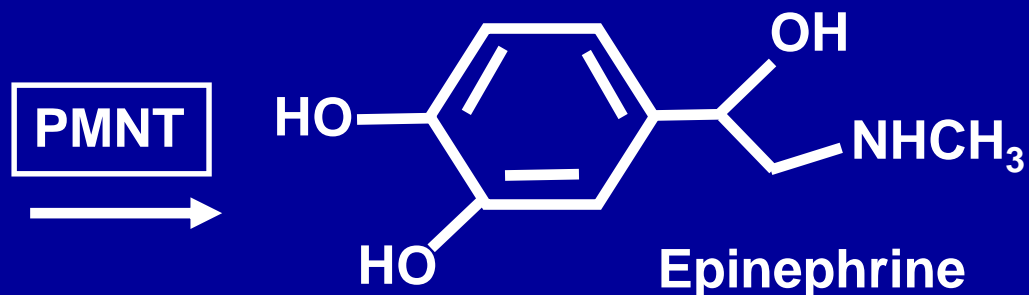
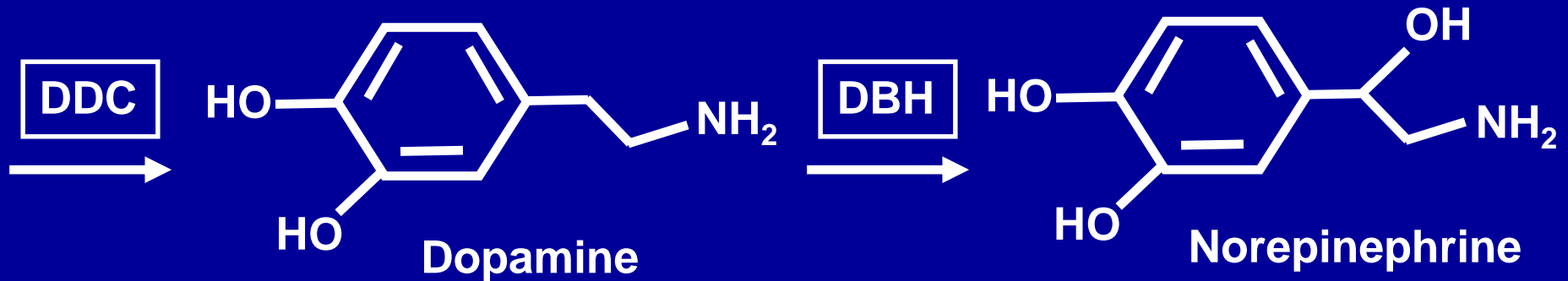
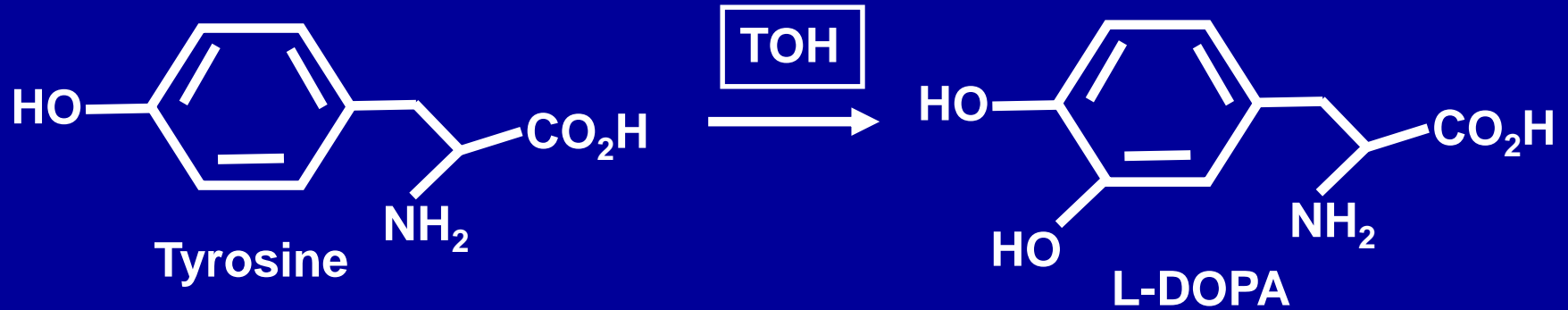
- **Pressure: Sustained HTN + Spikes**
- **Pain: Throbbing HA, Chest Pain**
- **Perspiration: Heavy, Generalized**
- **Palpitations**
- **Pallor**
- **Other: Hyperglycemia, Weight Loss, Tremor, Orthostasis, Hypercalcemia, Fatty Liver, Cardiomyopathy**
- **5-10% Asymptomatic(!!)**

# **Pheochromocytoma**

## **The Pheo Paroxysm (“Spell”)**

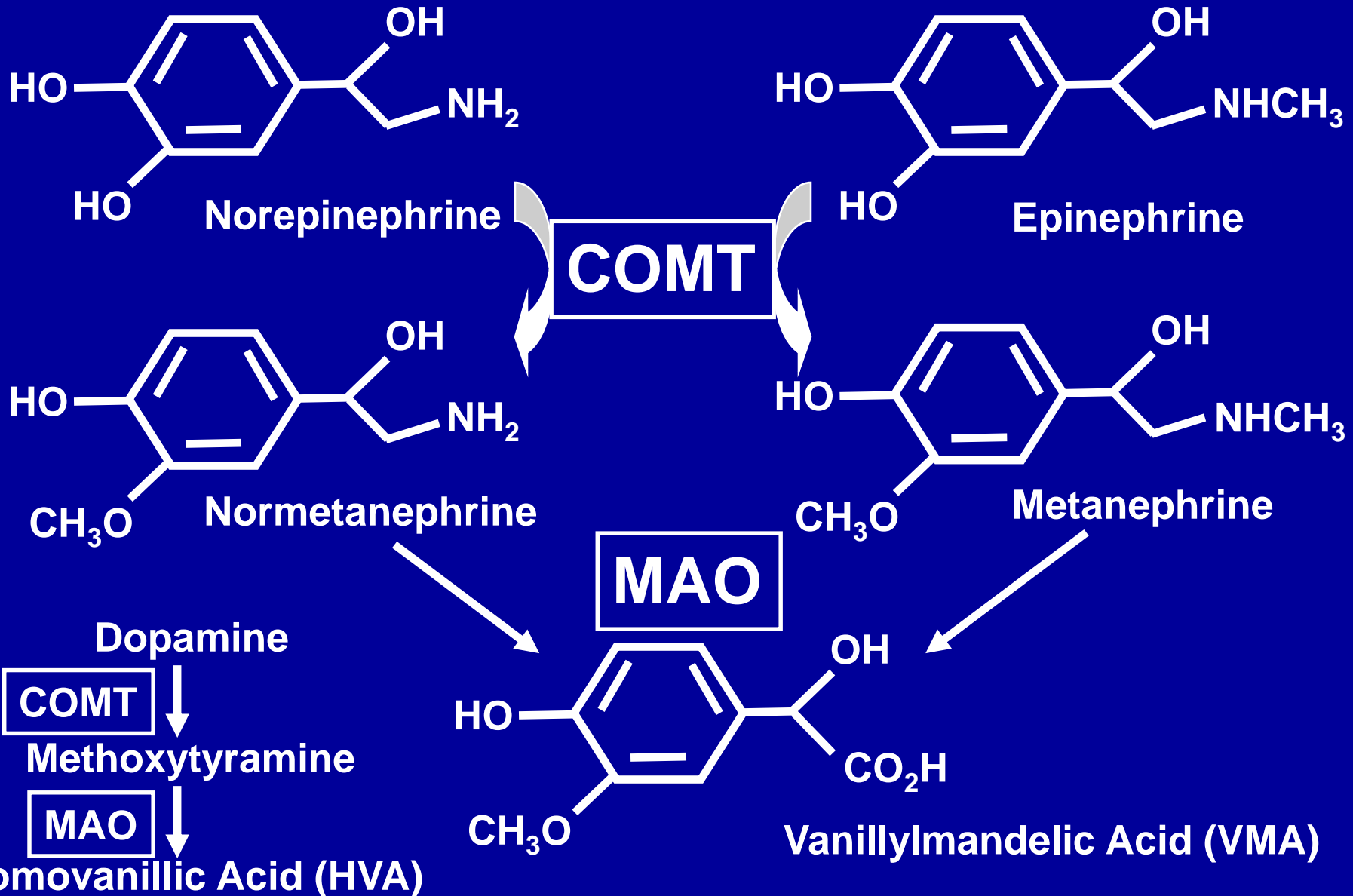
- **Throbbing HA & Chest Pain**
- **Drenching Sweat**
- **Pounding Tachycardia**
- **Extreme BP Elevation**
- **Pallor, All Lasting 10-60 Min**
- **NO Flush, Wheezing, Itching, Diarrhea, Syncope, Dermatographia**
- **DDx: Menopause & Clonidine Withdrawal**

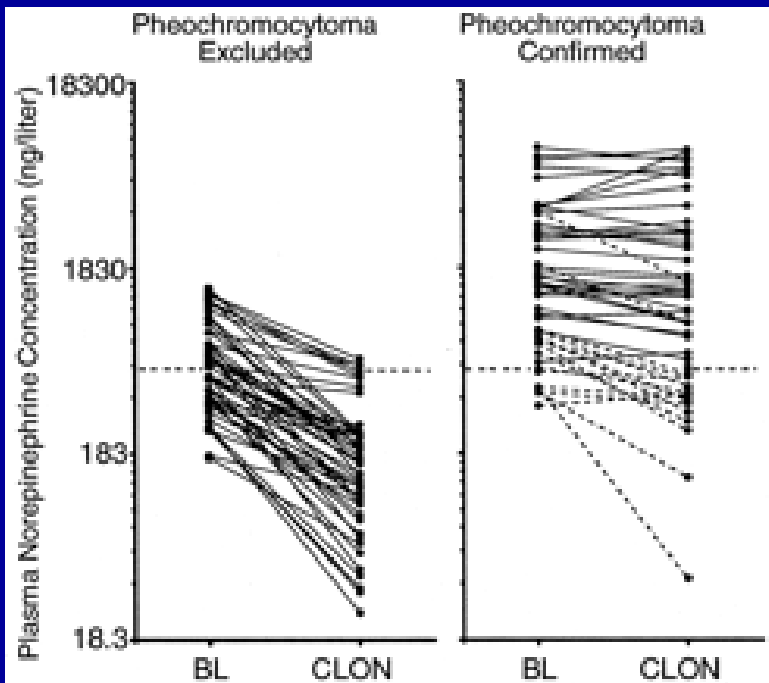
# Catecholamine Biosynthesis





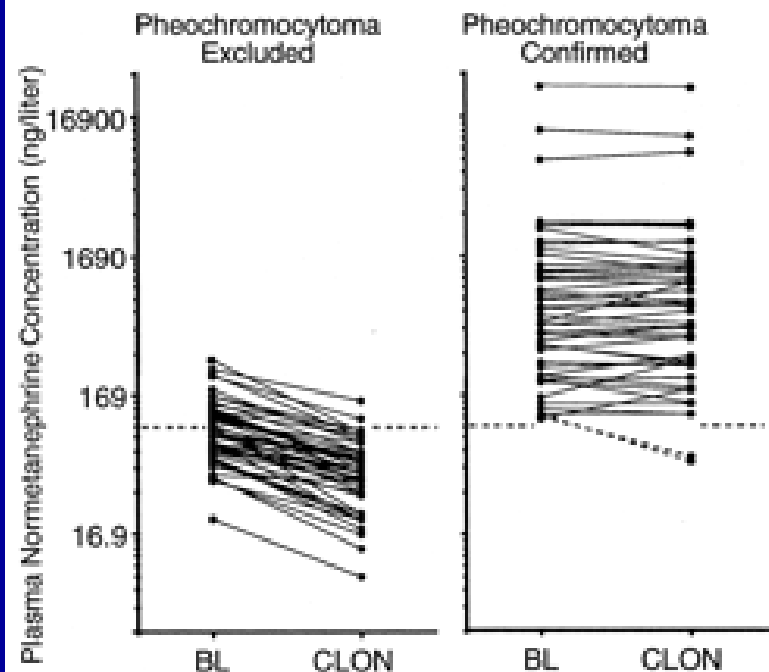
# Catecholamine Catabolism





--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