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- Speakers are also expected to openly disclose intent to discuss any off-label, experimental, or investigational use of drugs, devices, or equipment in their presentations.

- **This speaker has nothing to disclose.**

# Pheochromocytomas and Paragangliomas

Justin Caron, MD
Clinical Chemistry
2014-09-22

# Learning Objectives

1. Discuss the physiology, production, and metabolism of catecholamines.
2. Describe the clinical presentation of pheochromocytomas and paragangliomas.
3. Select appropriate laboratory tests for screening and diagnosis of pheochromocytomas and paragangliomas.
4. Recognize common analytical and physiologic interferences seen in laboratory testing of pheochromocytoma.

# 1. INTRODUCTION

**“…produce work worthy of your efforts.”**
**- *Dr. William J. Mayo***

# Historical Perspective


From: *De humani corporis fabrica libri septem, 1543*
Andreas Vesalius

- The adrenal glands went *unnoted* by early physicians and the great anatomists:
  - **Galen**
  - **Leonardo da Vinci**
  - **Andreas Vesalius**
- **Bartholomaeus Eustachius** (1563)
- **Thomas Addison** (1855)
  - The first physician on record to describe the importance of the adrenal glands

# Historical Perspective

| | | |
|---|---|---|
| 1886 | Paul Mannase | **Chromaffin reaction** |
| 1886 | Felix Fränkel | First to describe adrenal medulla tumor |
| **1912** | Ludgwig Pick | Coined the term **“pheochromocytoma”** |
| 1926 | Felix Roux | First surgical removal (Europe) |
| **1927** | **Charles H. Mayo** | **First surgical removal (United States)** |

**phaios (“dusky”)**
**chroma (“color”)**
**cytoma (“tumor”)**

# Historical Perspective


PAROXYSMAL HYPERTENSION WITH TUMOR OF RETROPERITONEAL NERVE

REPORT OF CASE *

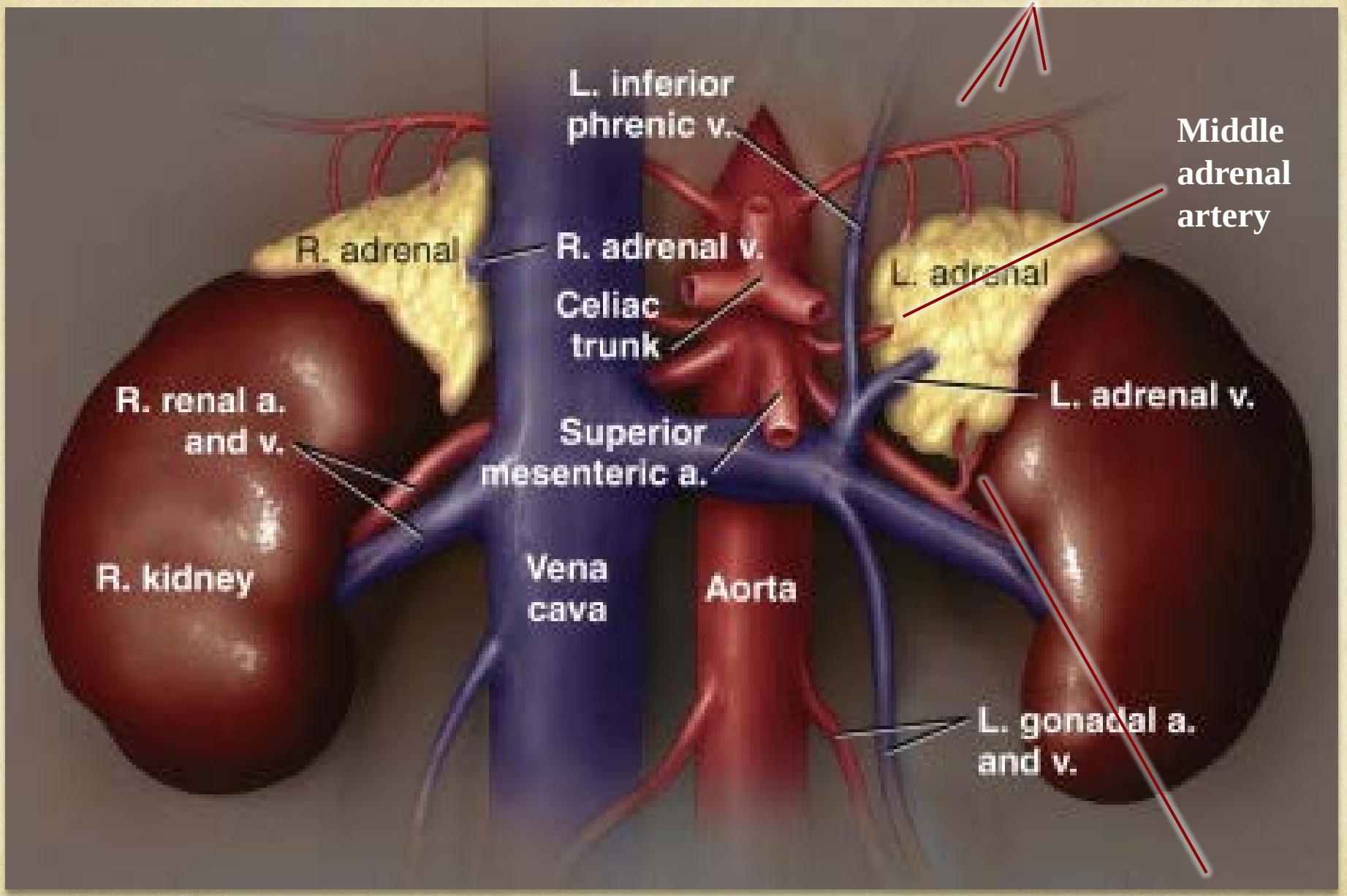
CHARLES H. MAYO, M.D.
ROCHESTER, MINN.

JAMA 1927;89(13):1047-1050

# 2. ADRENAL GLANDS

***"Begin your anatomy with a man fully grown; then show him elderly and less muscular; then go on to strip him stage by stage right down to the bones."***

- Leonardo da Vinci (1452-1519)



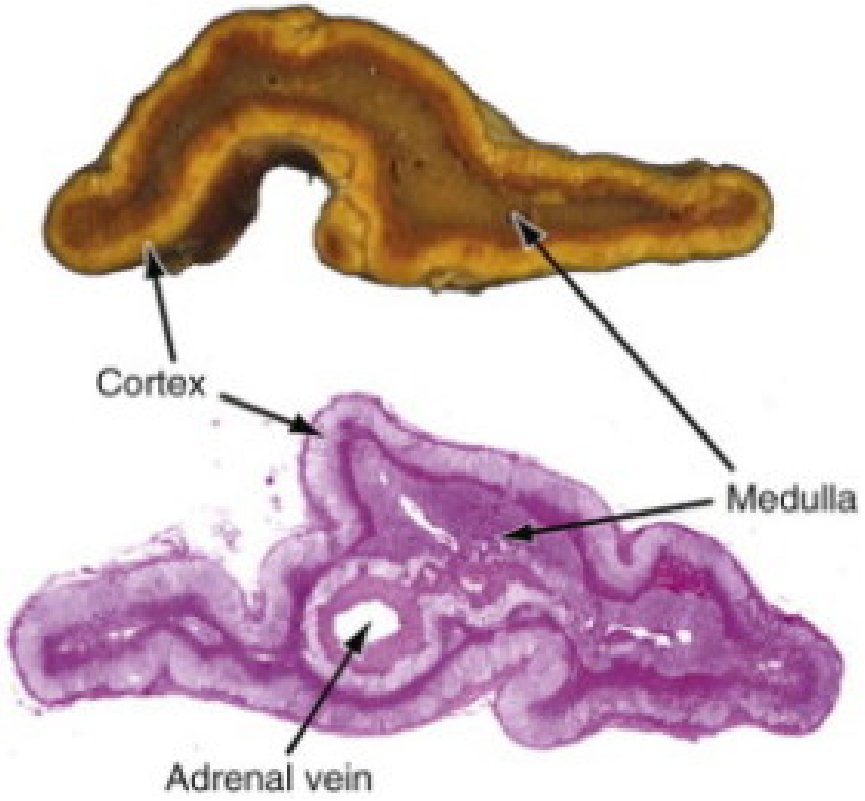

Campbell-Walsh Urology. 10th ed.

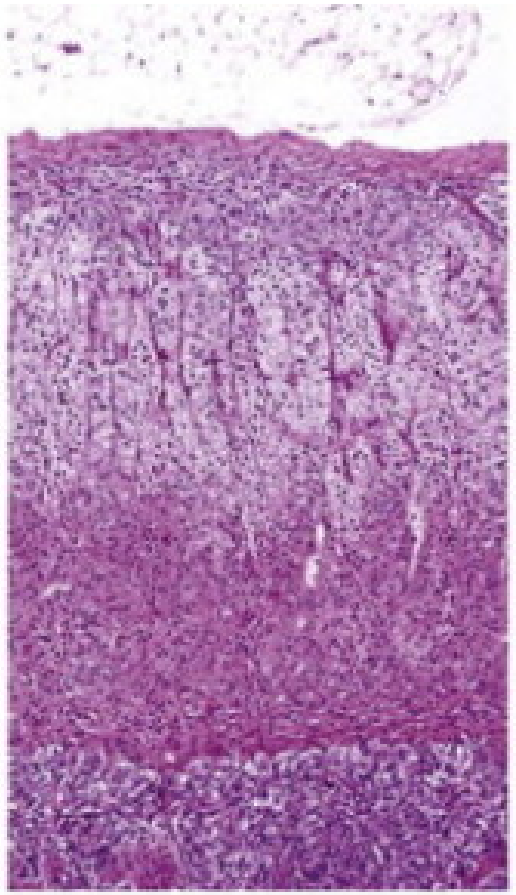
# Adrenal Gland Histology

**GFR: Salt, Sugar, Sex**

The deeper you go, the sweeter it gets

Campbell-Walsh Urology. 10th ed.



Capsule

Zona glomerulosa

**Aldosterone**

Zona fasciculata

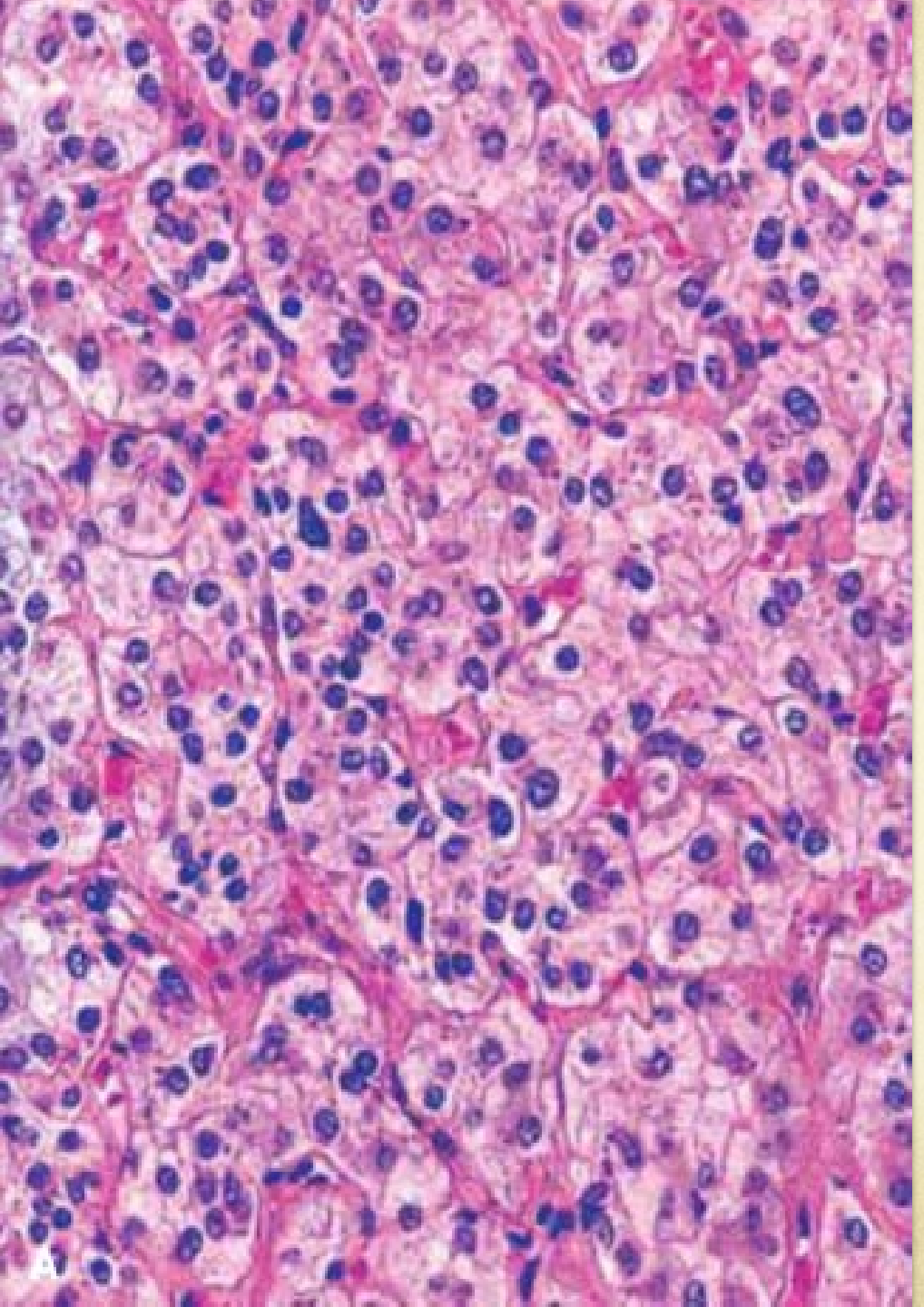
**Cortisol**

Zona reticularis

**Sex hormones**

Medulla

**Catecholamines (Epi, NE)**



# Histology

- **Chromaffin cells (pheochromocytes)** in tight clusters
- **Basophilic, finely granular cytoplasm**
- Delicate vascular supporting stroma

Histology for Pathologists. 4th ed.

# “Chromaffin Cell Reaction”

- Oxidizing agents polymerize the catecholamine-containing granules, turning them brown
  - Potassium bichromate
  - Ferric chloride
  - Ammoniacal silver nitrate
  - Osmium tetroxide

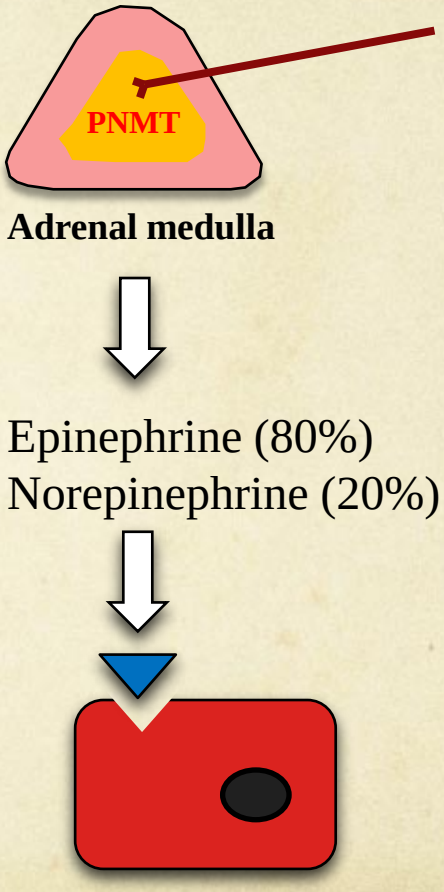

Rosai and Ackerman’s Surgical Pathology, 10th edition

This staining is called the **chromaffin reaction**

**We can use this type of electrical activity (oxidation) in our testing**

# Adrenal Medulla Overview

- **Phenylethanolamine-N-methyltransferase:**
  - Converts **norepinephrine** (NE) to **epinephrine** (E)
  - Cortisol enhances enzyme activity




**Epinephrine and norepinephrine belong to a class of molecules called catecholamines…**

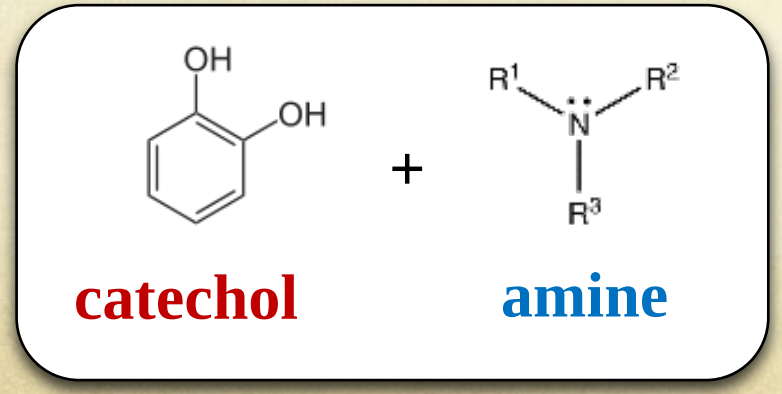
# 3. CATECHOLAMINES

***“That stuff makes pure mescaline seem like ginger beer, man. Pure adrenochrome.”***

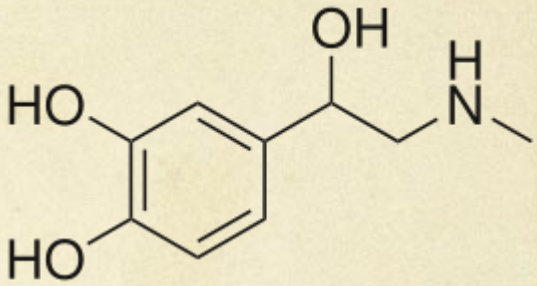
- Dr. Gonzo, Fear and Loathing in Las Vegas

# Catecholamines

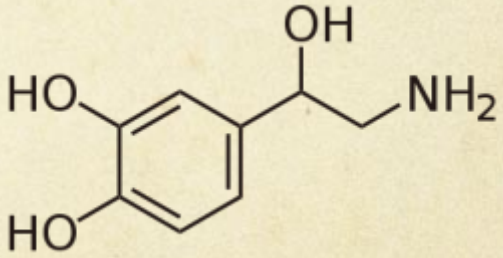
- Organic amines produced by the body to serve as chemical signals for the nervous system
- Consist of:
  - **Catechol…**
  - Attached to an **amine**




**catechol** **amine**




**epinephrine**




**norepinephrine**

# Catecholamines

- Organic amines produced by the body to serve as chemical signals for the nervous system
- Consist of:
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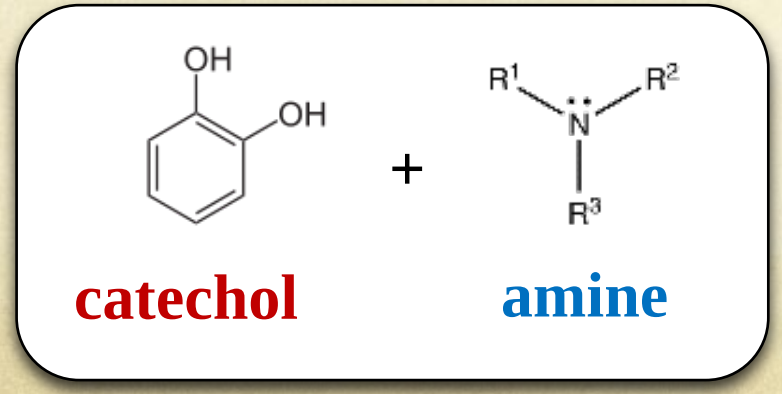
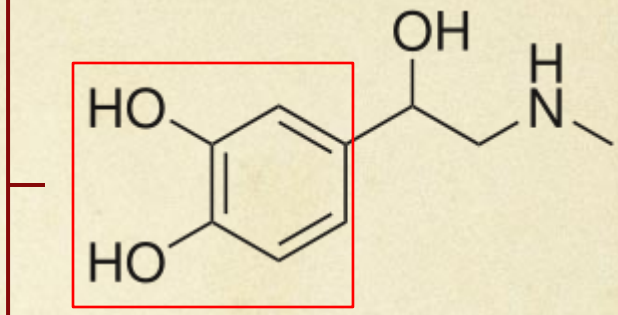
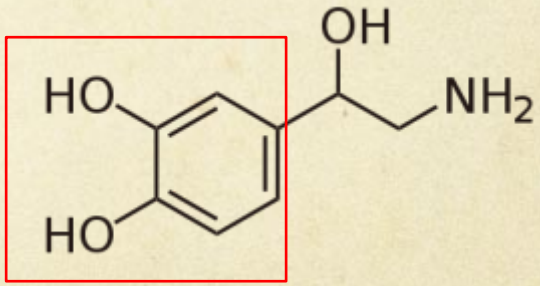



**3,4-dihydroxybenzene**

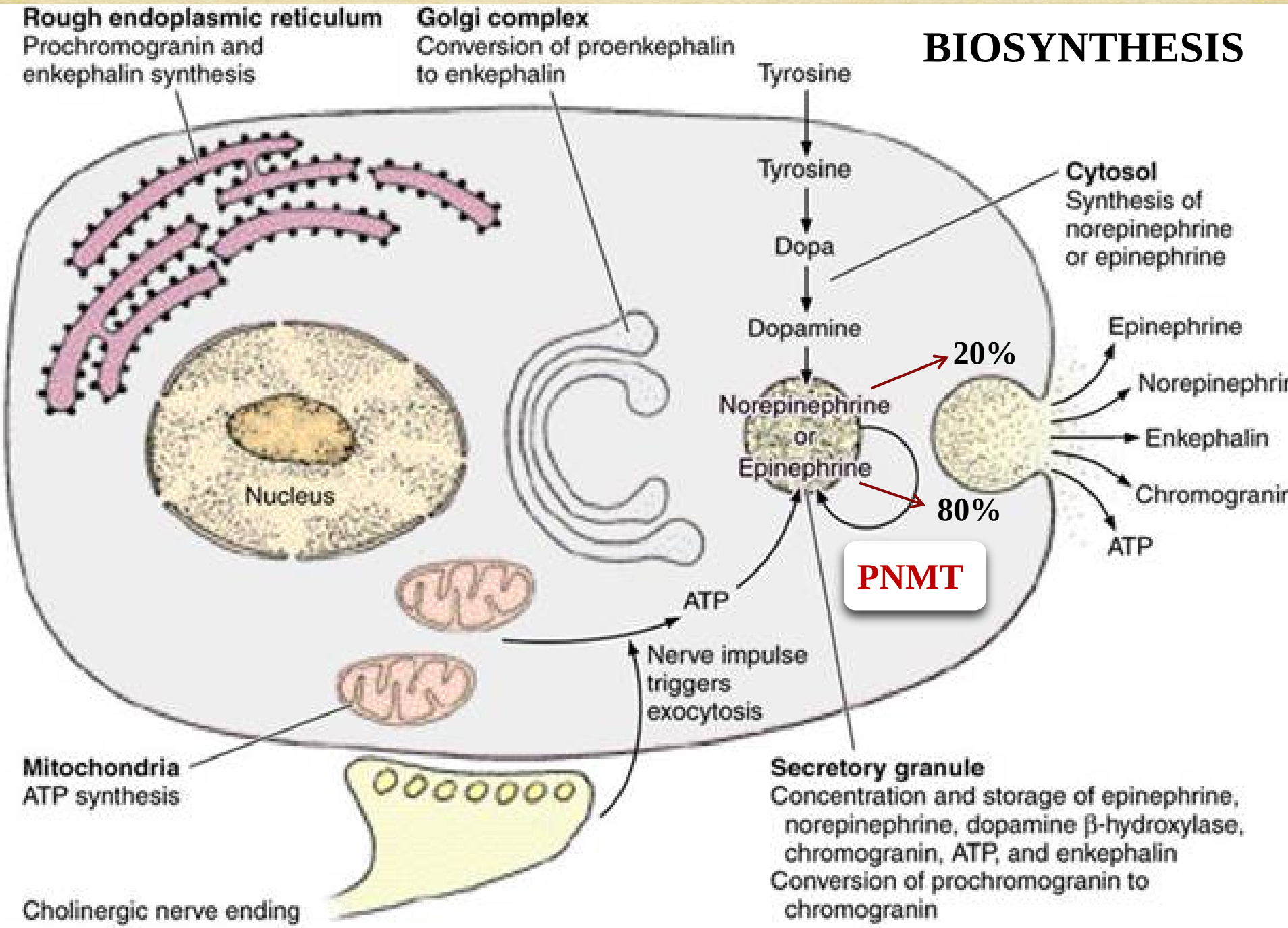



**epinephrine**




**norepinephrine**

# BIOSYNTHESIS




Basic Histology Text & Atlas, 11th ed.

# Sites of Biosynthesis

- **Epinephrine** is produced by the adrenal medulla
  - 90% of circulating epinephrine
  - **PNMT** is expressed mainly by adrenal chromaffin cells
- **Norepinephrine** is produced in the CNS and sympathetic nervous system
  - 90% of circulating norepinephrine

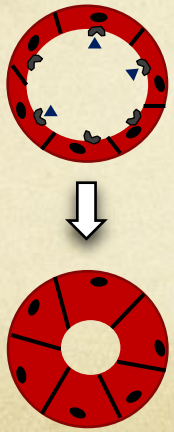
# “Fight or flight”

A **diffuse** systemic response; **due to catecholamines:**

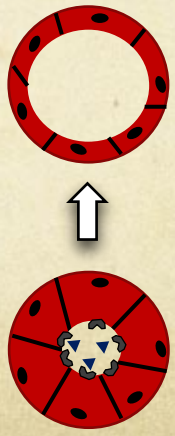
- Systemic vasoconstriction: **↑ BP**
- **↑ HR, contractility**
- Pupil dilation
- **Bronchodilation**
- Stimulation of **glucose** release
- Decrease in blood flow to nonessential organs
  - **Inhibition of digestion**

# Adrenoreceptors

- $\alpha_1$
  - **Smooth-muscle contraction**
    - -Vasoconstriction
    - -↑ BP
- $\alpha_2$
- $\beta_1$
  - **Cardiostimulation**
    - -↑ HR
    - -↑ myocardial contractility
- $\beta_2$
  - **Smooth-muscle relaxation**
    - -Vasodilation
    - -Bronchodilation
    - -↓ PVR



$t_{1/2}$ = 2 min.



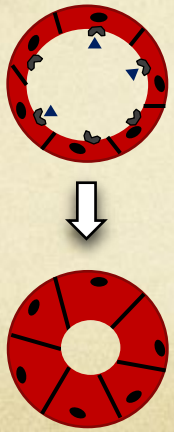
# Adrenoreceptors

- $\alpha_1$
- $\alpha_2$
- $\beta_1$
- $\beta_2$

**Smooth-muscle contraction**
- -Vasoconstriction
- -↑ BP

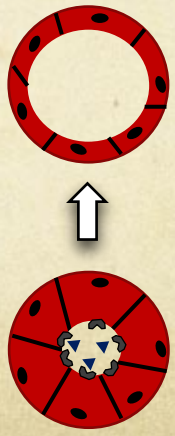
**Cardiostimulation**
- -↑ HR
- -↑ myocardial contractility

**Smooth-muscle relaxation**
- -Vasodilation
- -Bronchodilation
- -↓ PVR



Lots of catecholamines = lots of adrenergic stimulation!!

**↑↑ BP and HR**



**Adrenoreceptors**

**$\alpha_1$**

**Smooth-muscle contraction**

-Vasoconstriction

-↑ BP

**$\alpha_2$**

**$\beta_1$**

**Cardiostimulation**

-↑ HR

-↑ myocardial contractility

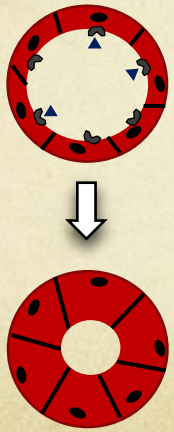
**$\beta_2$**

**Smooth-muscle relaxation**

-Vasodilation

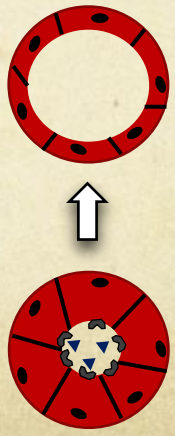
-Bronchodilation

-↓ PVR



**Pre-operative blood pressure management**:

1. **α-blockade** with **phenoxybenzamine**
2. **β-blockade** with **Labetalol**

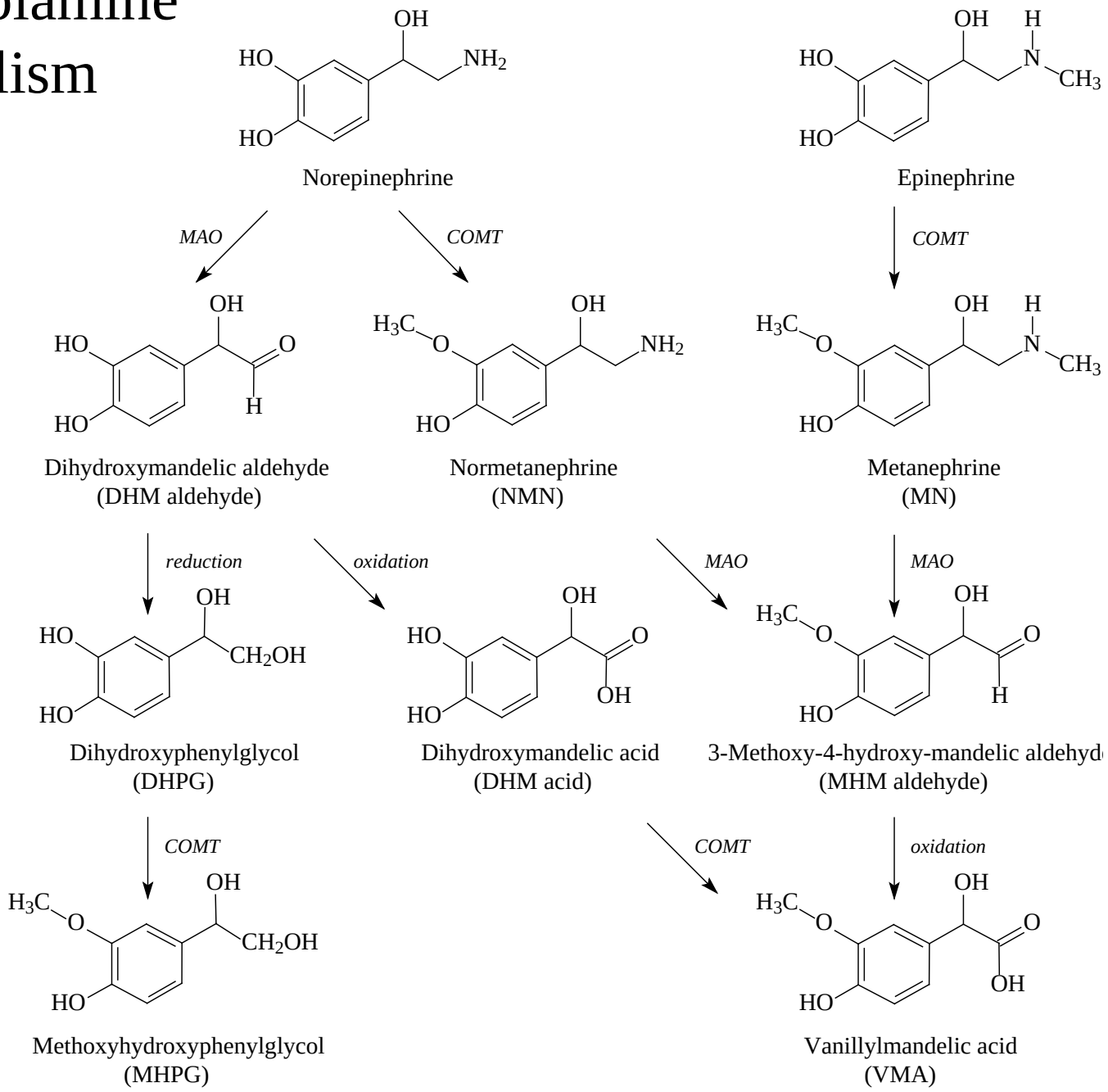


# Metabolism

Two major degradation pathways:

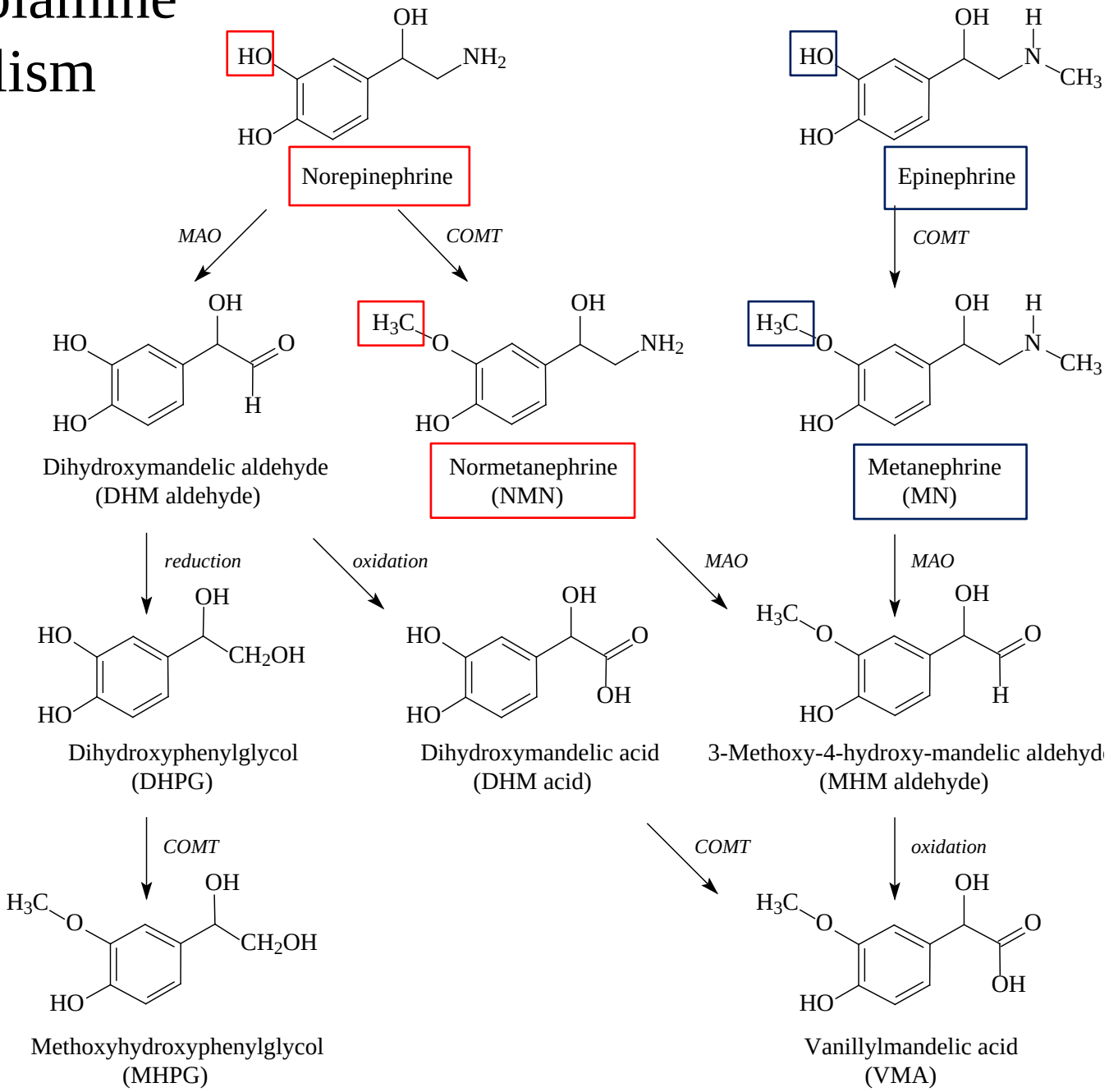
- **Monoamine oxidase (MAO)**
  - Responsible for the **oxidative deamination** of:
    - Norepinephrine and epinephrine to aldehydes
- **Catechol-*O*-methyl transferase (COMT)**
  - Responsible for ***O*-methylation** of:
    - Norepinephrine to normetanephrine
    - Epinephrine to metanephrine

# Catecholamine metabolism



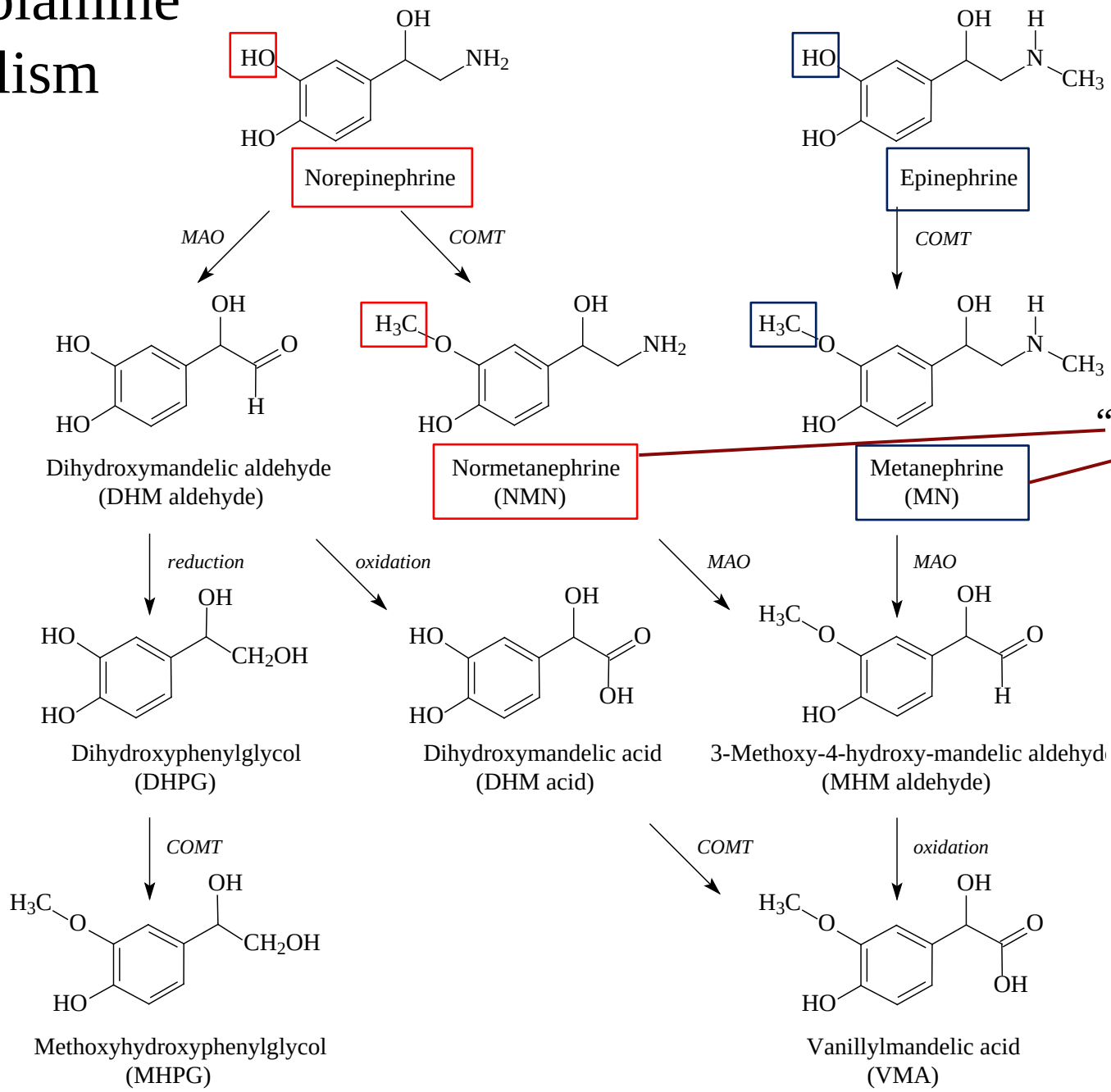

**Tietz Fundamentals of Clinical Chemistry, 5th edition**

# Catecholamine metabolism




**Tietz Fundamentals of Clinical Chemistry, 5th edition**

# Catecholamine metabolism

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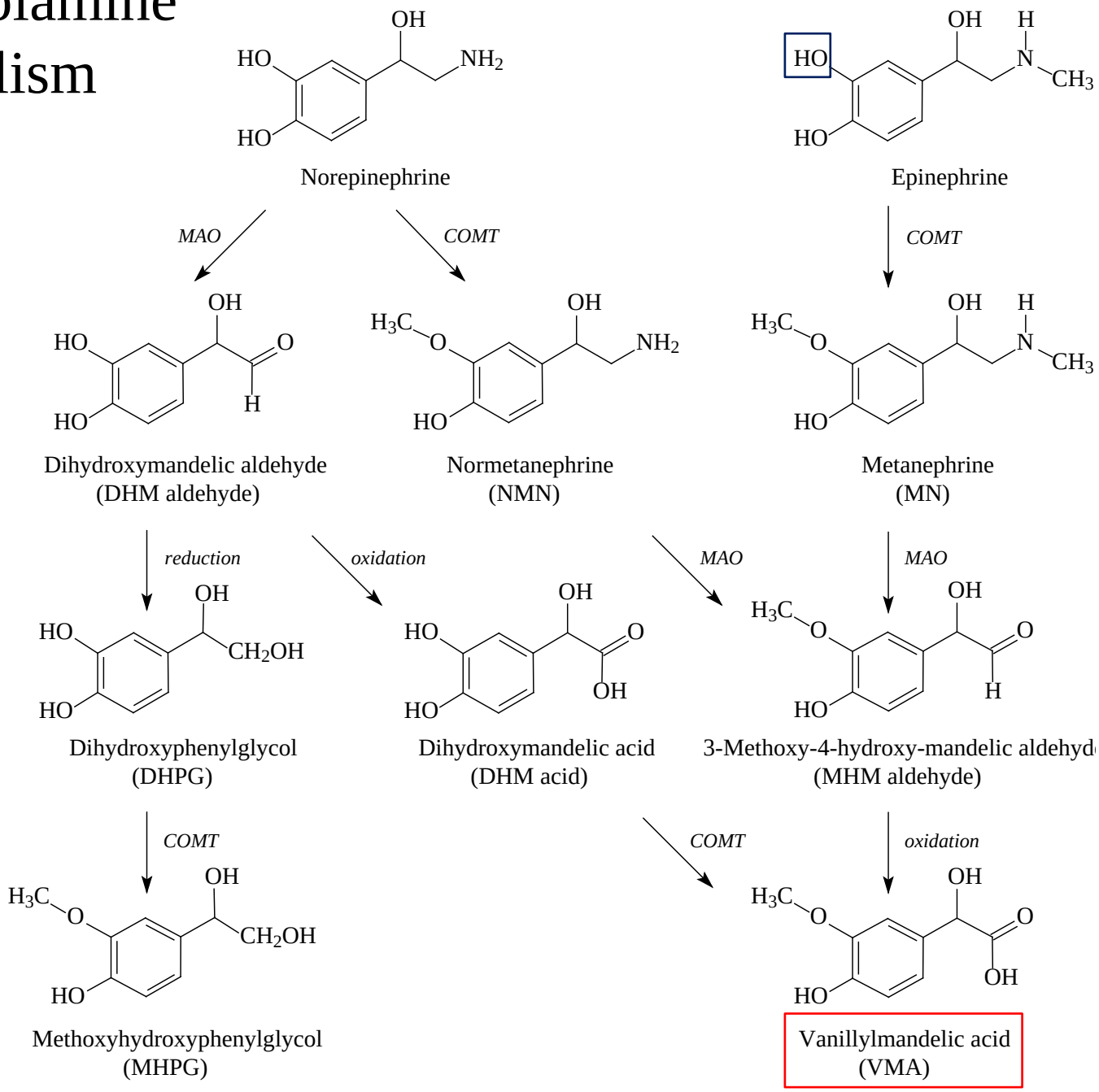
# Catecholamine metabolism




**Tietz Fundamentals of Clinical Chemistry, 5th edition**

# Case 1:
# The Music Teacher

History of present illness:

- A 30 year-old female music teacher presented to her physician complaining of attacks of dyspnea, headache, tachycardia, and vomiting
- These attacks are **paroxysmal** in nature and have been increasing in frequency and severity over the past year and a half
- During the attacks, she is prostrate with discomfort

Alphonse Mucha

# Case 1: The Music Teacher

- Upon admission to the hospital
  - Physical examination:
    - Reveals a **pale** and **undernourished** woman but the exam is otherwise unremarkable
    - Vitals: normal heart rate; blood pressure: 130/82
  - Labs: CBC is normal
  - Other studies: EKG, CXR, Abdominal x-ray are all normal

# Case 1: The Music Teacher

- Shortly after admission: the patient develops tachycardia; BP is measured at 280/180
- Symptoms: chest pain, headache, N&V, blurry vision, numb extremities
- EKG: tachycardia
- BP is repeated: 300/180
- Due to severe hypertension and intractable abdominal pain, an **exploratory laparotomy** was performed…

# Case 1: The Music Teacher

- **…This is the presentation from the original case published by Dr. Charles Mayo in 1927**
- The diagnosis of pheochromocytoma did not exist as such-
  - There were **no biochemical laboratory tests** for pheochromoctyoma!!
  - No **CT scans** or **MRI**
  - No understanding of how to control the blood pressure before and during surgery

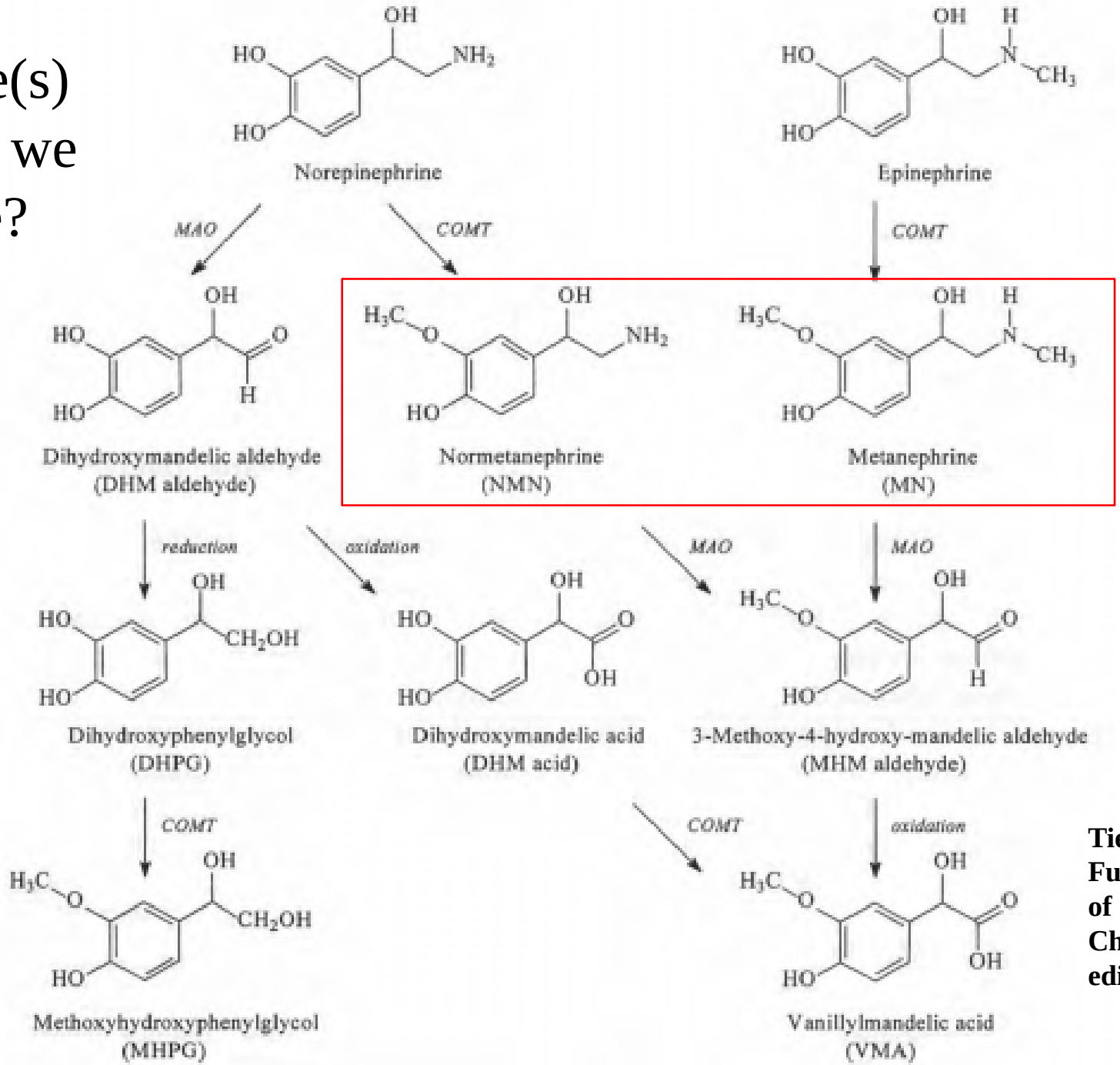
**Perioperative mortality rates were as high as 50%**

# 4. LABORATORY TESTING

*“You know, I am sorry for the poor fellows that haven't got labs to work in.”*

-Sir Ernest Rutherford (1871-1937)

Which analyte(s) should we choose?

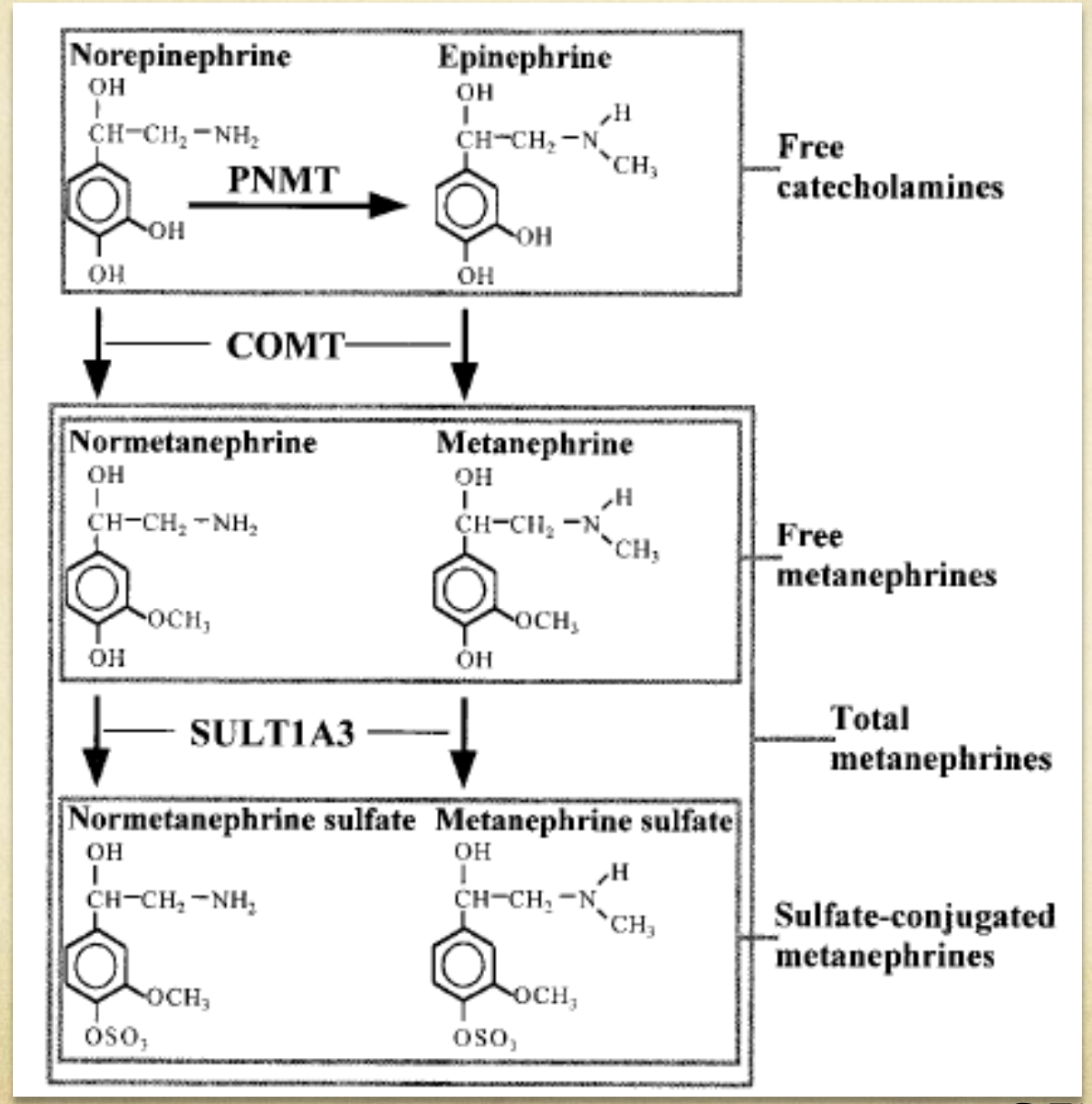



**Tietz Fundamentals of Clinical Chemistry, 5th edition**

# Too Many Options!!

- Biochemical testing options:
  - Plasma metanephrines (HPLC/ECD)
  - Urine metanephrines (GC-MS)
  - Plasma catecholamines (HPLC/ECD)
  - Urine catecholamines (LC-MS/MS)
  - Urine vanillylmandelic acid (HPLC/ECD)
  - Urine homovanillic acid (HPLC/ECD)
  - Serum chromogranin A (EIA)
  - Clonidine suppression test

# PLUS confusion over the terms free, total and fractionated!




Clin Chem 2001 June;47(6):988-989.

G Eisenhofer

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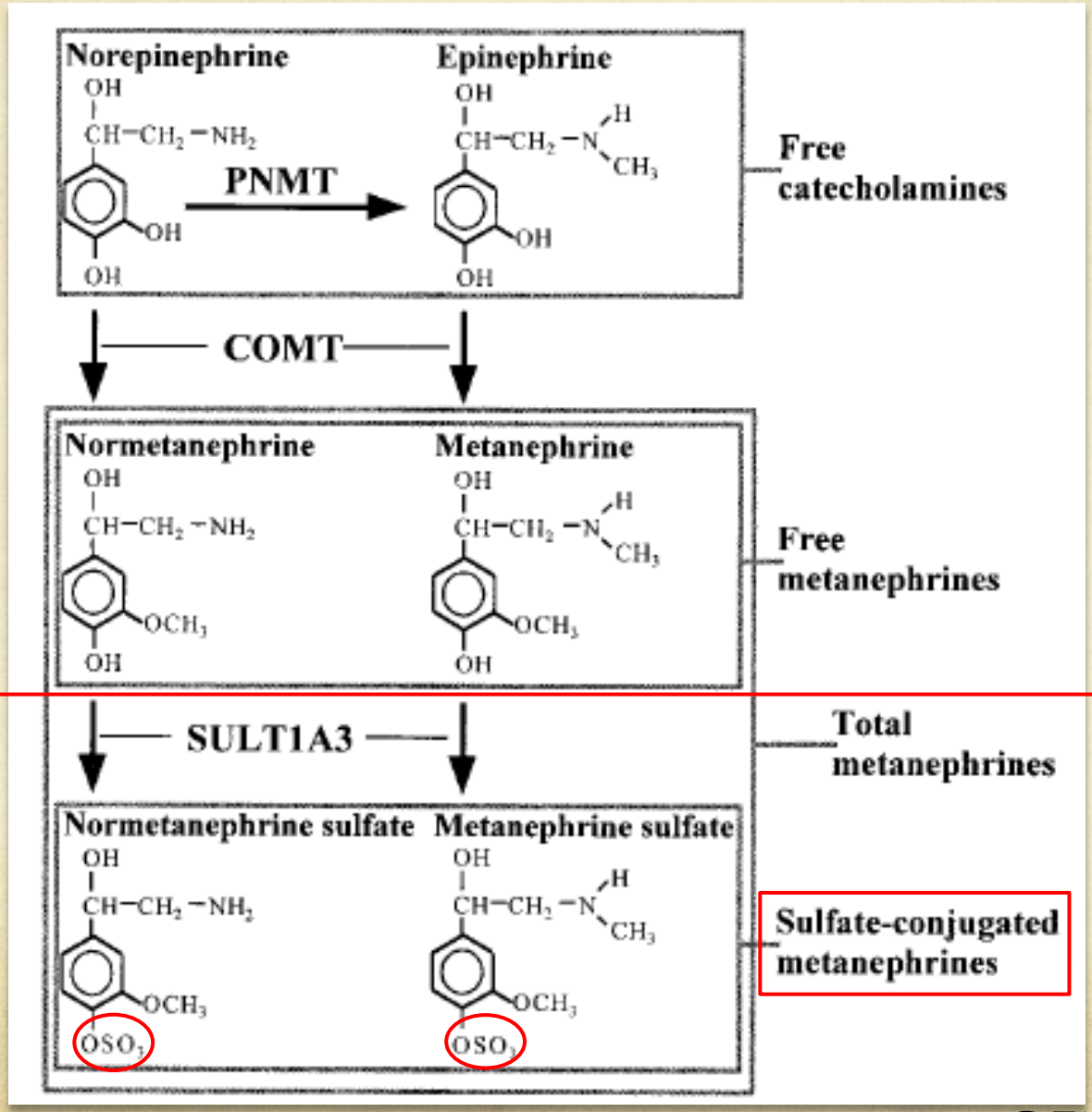


FREE = unconjugated

Conjugated forms

Clin Chem 2001 June;47(6):988-989.

G Eisenhofer

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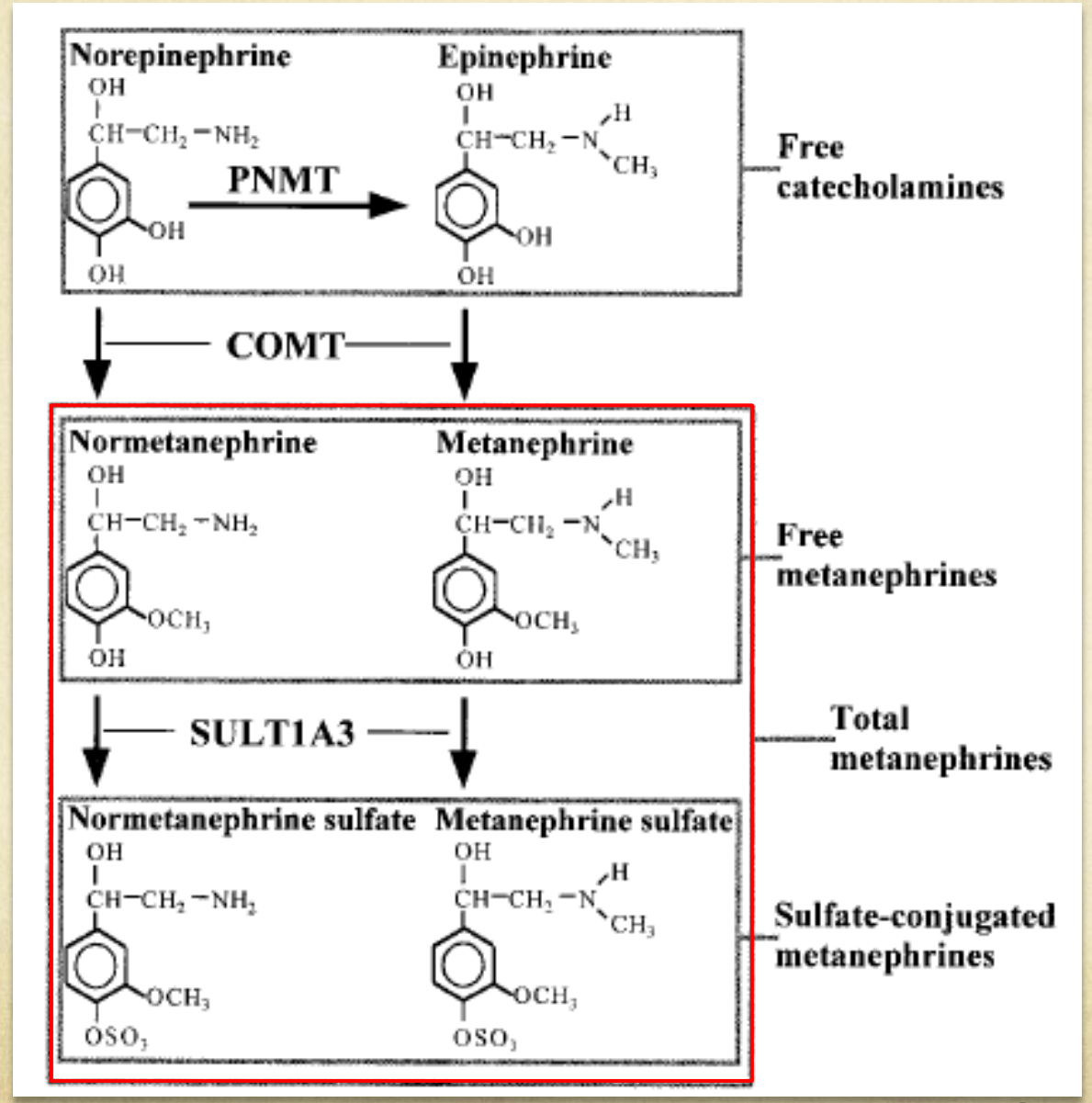
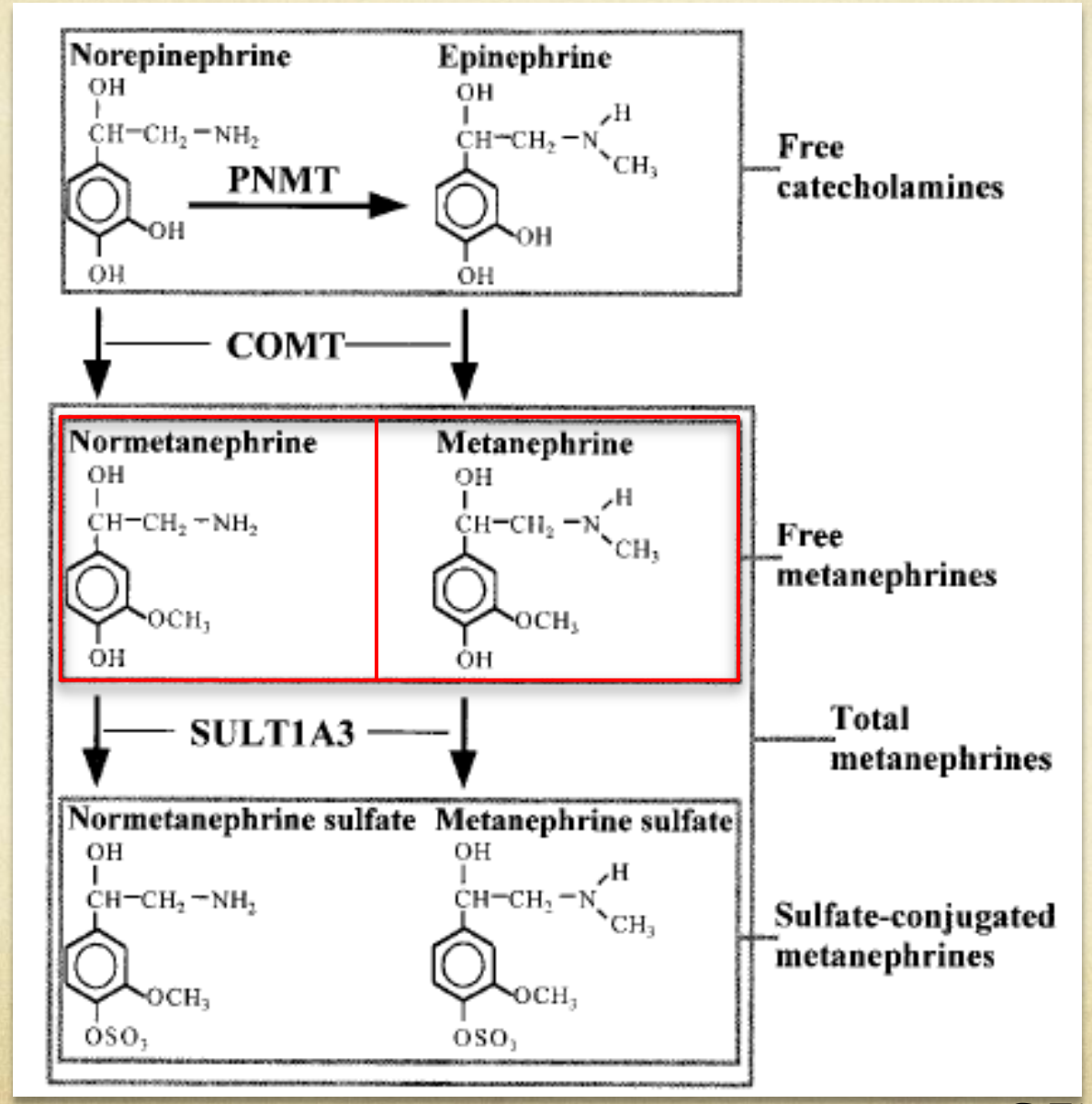



**Total = metanephrines plus conjugated metabolites**

Clin Chem 2001 June;47(6):988-989.

G Eisenhofer

# PLUS confusion over the terms free, total and fractionated!




Fractionated = separate out normetanephrine and metanephrine

Clin Chem 2001 June;47(6):988-989.

G Eisenhofer

# Current Recommendations

**Endocrine Society Clinical Practice Guidelines (2014)**

1. **Initial biochemical testing should include:**
   - **Plasma free metanephrines and/or**
   - **Urinary fractionated metanephrines**
2. Liquid chromatography using mass spectrometry or electrochemical detection is the preferred methods
3. For measurements of plasma metanephrines:
   - Draw samples with patient in supine position
   - Use reference intervals established in the same position

# Diagnostic Considerations

- The most important consideration is the potential harm of a **false negative**
  - Pheochromcytomas have a high rate of morbidity and mortality if undetected
- Therefore, **sensitivity is a primary consideration** for any testing strategy
  - If we have a negative test, can we trust the result to rule out the diagnosis?

**SNOUT** = **S**e**N**sitivity rules **OUT**

**SPIN** = **SP**ecificity rules **in**

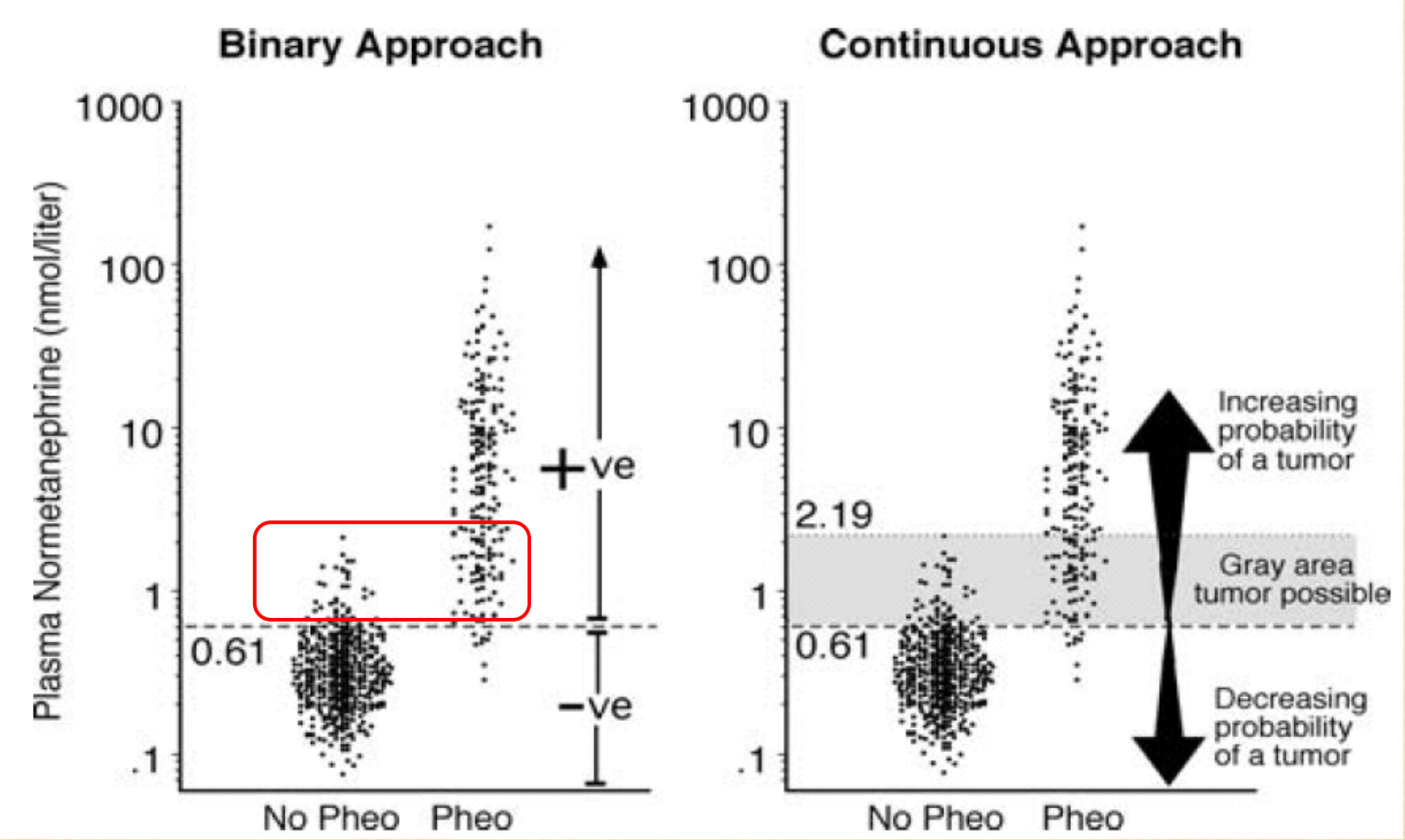
| | Sensitivity | Specificity |
|---|---|---|
| Plasma-free metanephrines | 99% | 89% |
| Plasma catecholamines | 84% | 81% |
| Urinary catecholamines | 86% | 88% |
| Urinary-fractionated metanephrines | 97% | 69% |
| Urinary total metanephrines | 77% | 93% |
| VMA | 64% | 95% |

Sensitivity values of all tests for familial phaeochromocytoma are lower than that for sporadic phaeochromocytomas; the reverse is the case for specificity values. Table adapted from reference 64.

***Table 3:*** **Sensitivity and specificity of biochemical tests for diagnosis of phaeochromocytoma**

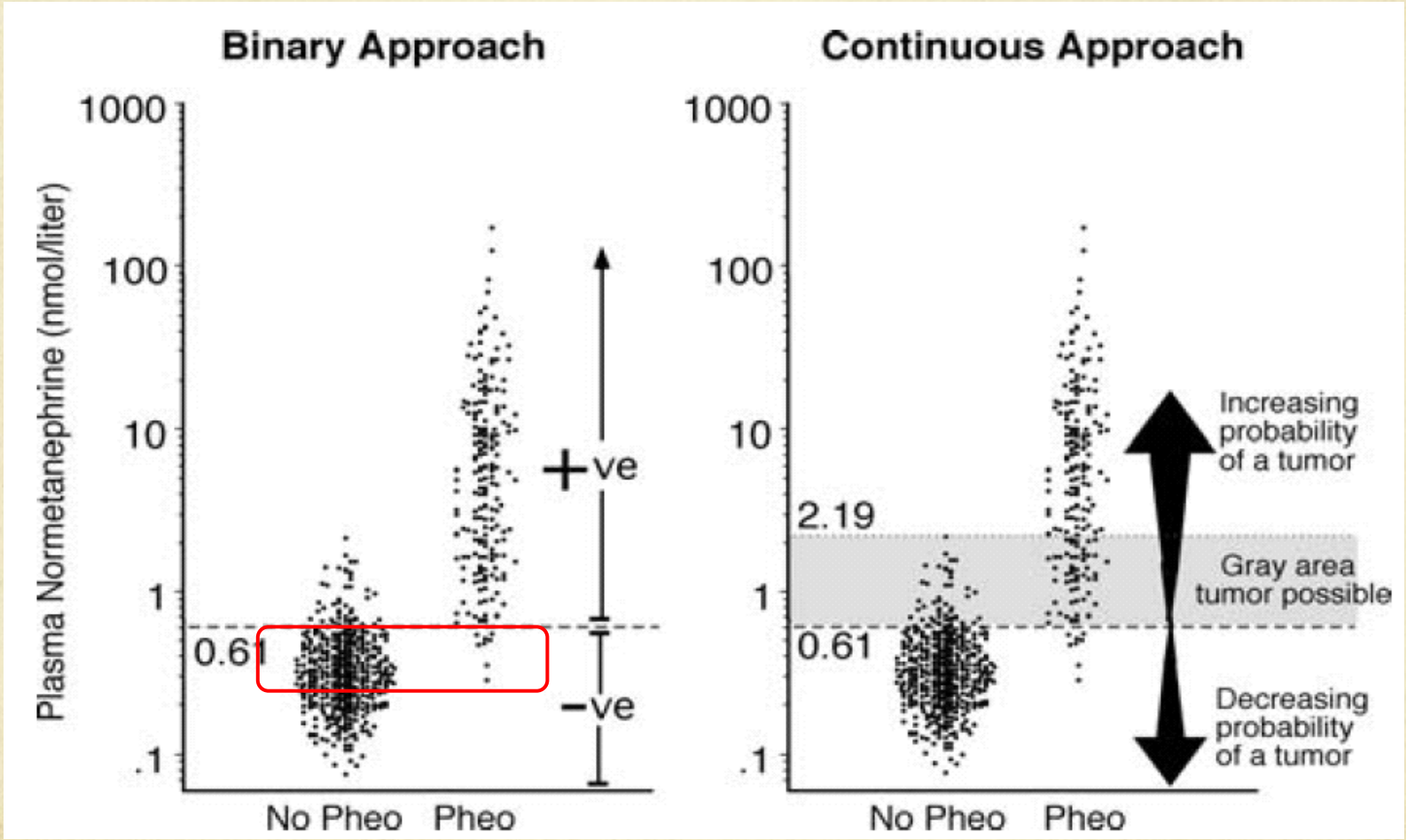
Lancet. 2005;365:665-675

# Binary vs. Continuous Approach




Grossman, Pacak, Sawka, et al. Biochemical diagnosis and localization of pheochromocytoma: Can we reach a consensus? Ann NY Acad Sci 2006;1073:332-347.

# Binary vs. Continuous Approach

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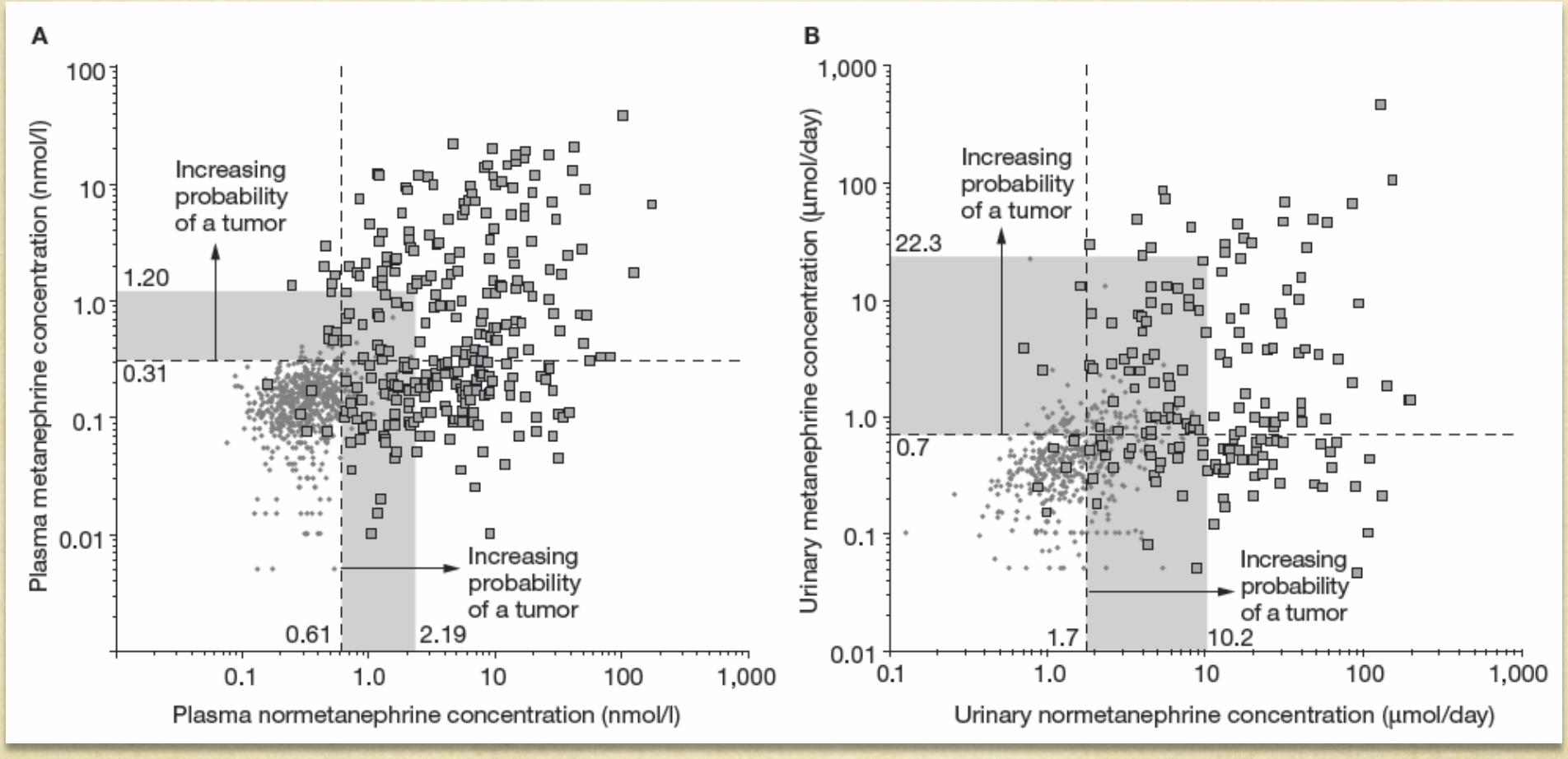



Nat Clin Pract Endocrinol Metab. 2007 Feb;3(2):92-102.

# Current Recommendations

**Endocrine Society Clinical Practice Guidelines (2014)**

1. Initial biochemical testing should include:
   - Plasma free metanephrines and/or
   - Urinary fractionated metanephrines
2. **Liquid chromatography using mass spectrometry or electrochemical detection is the preferred methods**
3. For measurements of plasma metanephrines:
   - Draw samples with patient in supine position
   - Use reference intervals established in the same position

**Table 4.** Summary Characteristics of 15 Diagnostic Studies Involving Measurements of Plasma Free Normetanephrine and Metanephrine for Diagnosis of PPGL

J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42

## Plasma Metanephrines

- LC-MS/MS
  - **Best performance**
  - Sensitivity 100%
  - Specificity 96%
- LC-ECD
  - Good performance
  - Sensitivity 96-100%
  - Specificity 85-100%

# Methods

- **Plasma and urinary fractionated metanephrines: LC-MS/MS**

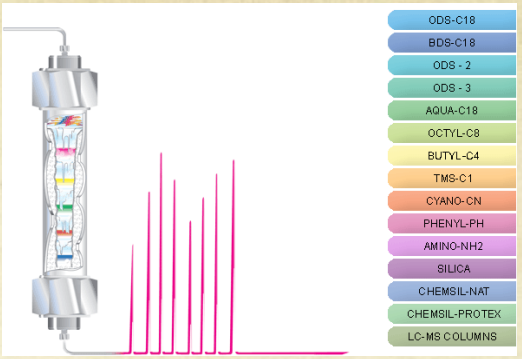
# Plasma Metanephrines

**Analytic Biochemistry Lab**

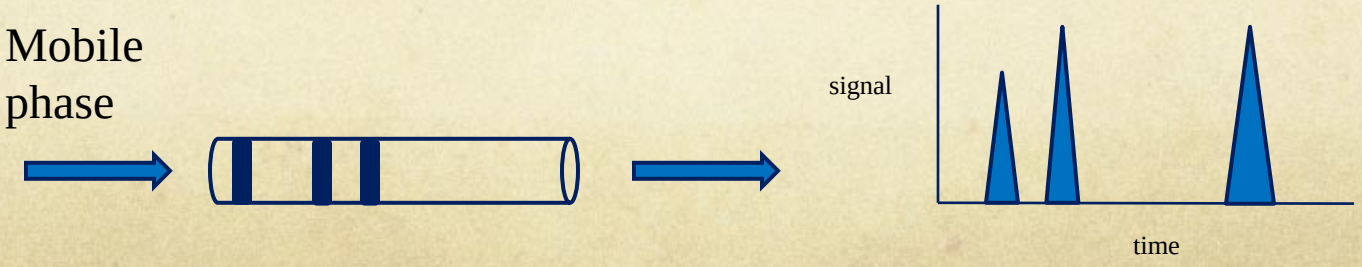
- Spike with IS
- Extraction:
  - **Weak cation exchange** (WCX) 96-well solid phase extraction plate
  - Prep: water and methanol
  - Add sample
  - Wash: water and methanol
- Elute: weak acid
  - Formic acid (2%) in acetonitrile


Ready for HPLC followed by TMS

# Liquid Chromatography




- Separation by LC is based on distribution of the solutes between a liquid mobile phase and a stationary phase
  - High pressure pump pushes mobile phase through the solid phase (in the column)
  - Separates analytes by time, charge, affinity
  - Each analyte will come off at a specific time



# HYDROPHILIC LIQUID INTERACTION CHROMATOGRAPHY (HILIC)

- **Atlantis Silica HILIC Column**
- Variation of normal phase chromatography
- The stationary phase is hydrophilic (likes water)
- High organic mobile phase
  - (>80% acetonitrile)
- Better retention of polar compounds

Tandem mass spectrometry

# Urinary Metanephrines

- Metanephrines in urine are conjugated to glucuronic acid or sulfate
- **Acid hydrolysis**
  - Spike with IS
  - Add acid (6 M HCl)
  - Heat in water bath
- Hydrolyzed samples are pH adjusted
- Solid phase extraction (SPE)

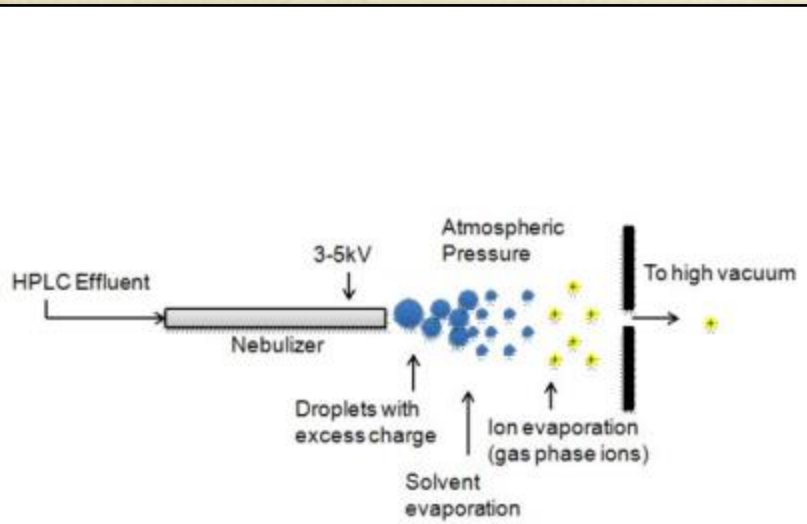
## Mass Spec II

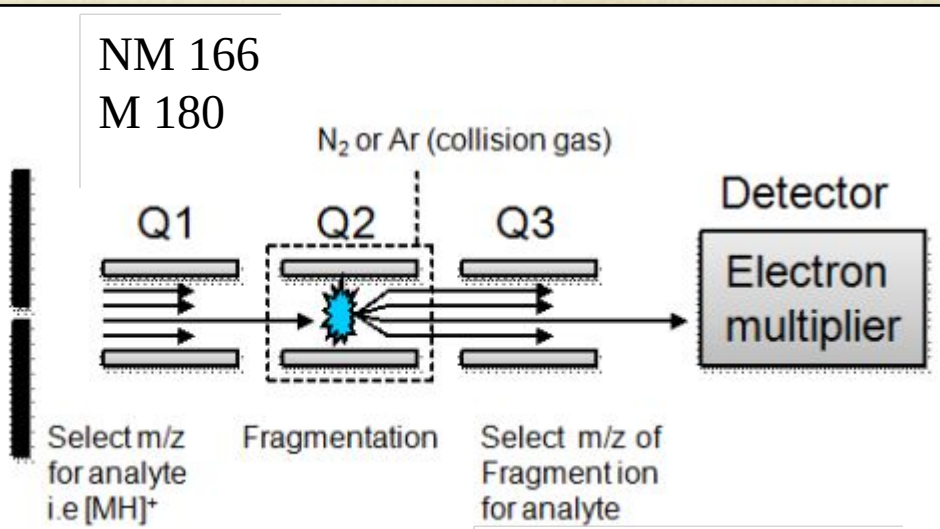

Ready for HPLC followed by TMS

# Tandem Mass Spectrometry

- Electrospray ionization -> Q1 (select m/z) -> Q2 = collision cell (inert gas) -> Q3 (look for fragments with specific m/z)

**m/z:**



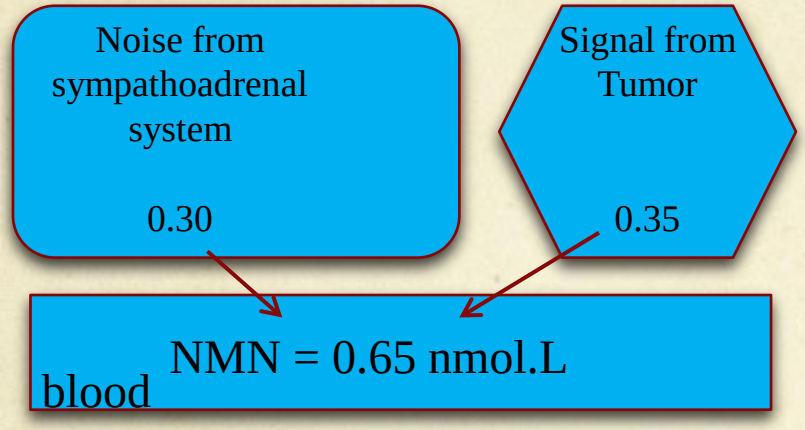



# Current Recommendations

**Endocrine Society Clinical Practice Guidelines (2014)**

1. Initial biochemical testing should include:
   - Plasma free metanephrines and/or
   - Urinary fractionated metanephrines
2. Liquid chromatography using mass spectrometry or electrochemical detection is the preferred methods
3. **For measurements of plasma metanephrines:**
   - **Draw samples with patient in supine position**
   - **Use reference intervals established in the same position**

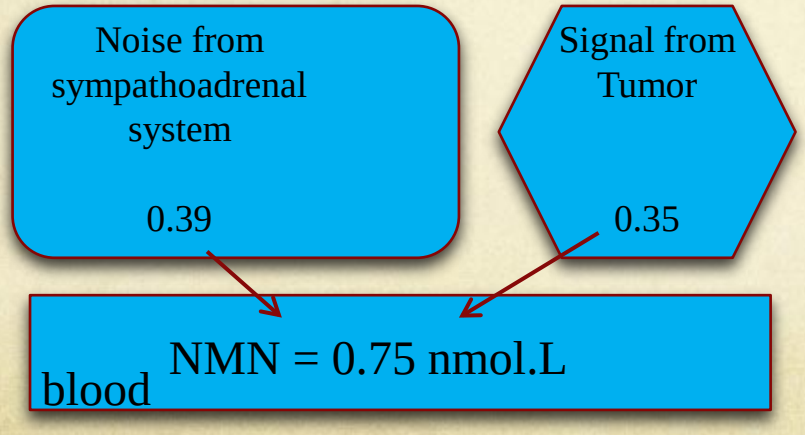
# Influence of Reference Intervals




Upper limit of reference intervals in supine position

**0.61 nmol/L**

Positive result tumor detected




Upper limit of reference intervals in seated position

**0.79 nmol/L**

Negative result tumor detected

Adapted from Tietz Textbook of Clinical Chemistry 5th ed.

# Analytical Interferences

| | |
|---|---|
| Coffee (including decaffeinated coffee) | HPLC assays: plasma catecholamines |
| Labetalol | Spectrophotometric and fluorometric assays: urinary catecholamines and metanephrines; |
| Sotalol | HPLC assays: plasma catecholamines |
| Buspirone | HPLC assays: urinary metanephrines |
| Paracetamol | HPLC assays: plasma-free metanephrines |
| Levodopa | HPLC assays: catecholamines and metabolites |
| α-methyldopa | HPLC assays: catecholamines |
| Sympathomimetics (eg, amfetamines, ephedrine) | Spectrophotometric and fluorometric assays: plasma and urinary catecholamines |

Lancet. 2005;365:665-675

# Drug Interferences

**Table 7.** Major Medications That May Cause Falsely Elevated Test Results for Plasma and Urinary Metanephrines

| | Plasma | | Urine | |
|---|---|---|---|---|
| | NMN | MN | NMN | MN |
| Acetaminophen[a] | ++ | − | ++ | − |
| Labetalol[a] | − | − | ++ | ++ |
| Sotalol[a] | − | − | ++ | ++ |
| α-Methyldopa[a] | ++ | − | ++ | − |
| Tricyclic antidepressants[b] | ++ | − | ++ | − |
| Buspirone[a] | − | ++ | − | ++ |
| Phenoxybenzamine[b] | ++ | − | ++ | − |
| MAO-inhibitors[b] | ++ | ++ | ++ | ++ |
| Sympathomimetics[b] | + | + | + | + |
| Cocaine[b] | ++ | + | ++ | + |
| Sulphasalazine[a] | ++ | − | ++ | − |
| Levodopa[c] | + | + | ++ | + |

J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42

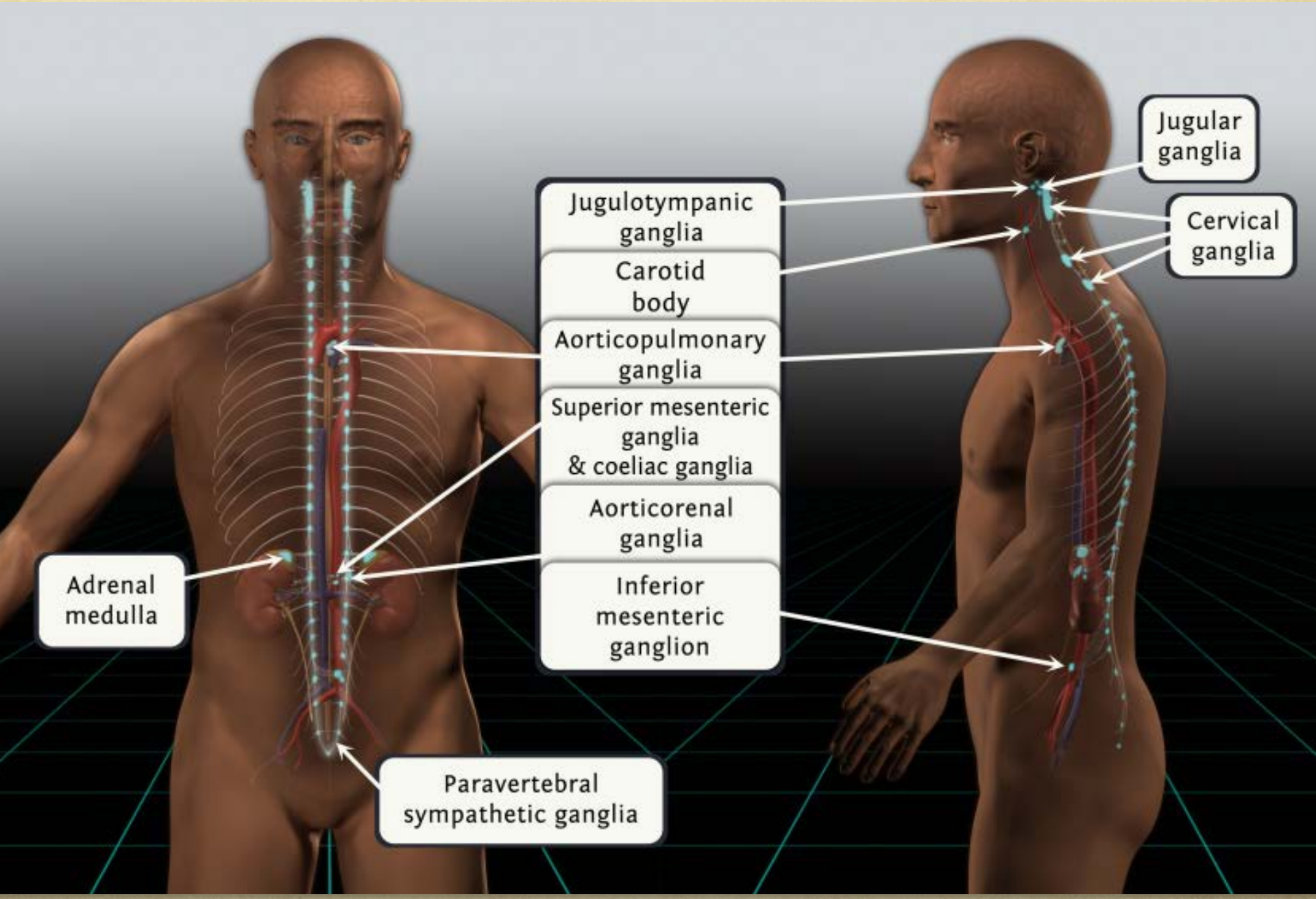
# 5. PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS

# Pheochromocytomas

- Tumors arising from **chromaffin** cells
  - Produce one or more **catecholamines**:
    - Epinephrine, norepinephrine
    - Rarely, these tumors are biochemically silent
- The majority are benign
- Distribution:
  - Adrenal medulla (80-85%)
  - Paragangliomas (15 to 20%)

# Paragangliomas

- Tumors derived from **extra-adrenal chromaffin** cells
  - **Sympathetic paravertebral ganglia** of thorax, abdomen, and pelvis
  - **Parasympathetic ganglia** located along nerves in the neck and at the base of the skull



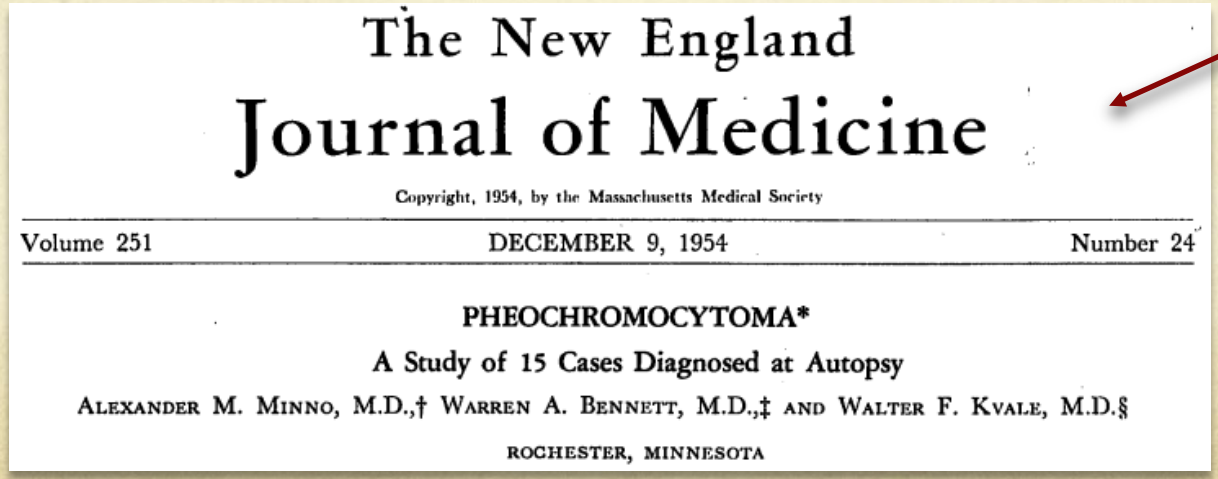

https://science.nichd.nih.gov/confluence/display/pheo/Home

# Clinical Presentation

- The dominant presentation is **paroxysmal hypertension**
- Classic triad:
  - Tachycardia/palpitations
  - Headache
  - Sweating
- Others: pallor, nausea, fatigue, weight loss, hyperglycemia

# Background Information

- Benign (~85%) or malignant (~15%)
- Sporadic or familial
- Can occur at any age (4th - 5th decade most common)
- Rare: 2-8 per 1 million persons per year
- 0.1% of hypertensive patients have pheochromocytoma



The New England

Journal of Medicine



Volume 251 DECEMBER 9, 1954 Number 24

PHEOCHROMOCYTOMA*

A Study of 15 Cases Diagnosed at Autopsy

ALEXANDER M. MINNO, M.D.,† WARREN A. BENNETT, M.D.,‡ AND WALTER F. KVALE, M.D.§

ROCHESTER, MINNESOTA

**Of 15,984 total autopsies**

# Inherited Syndromes

- von Hippel-Lindau syndrome (VHL)
- Multiple endocrine neoplasia (MEN) type 2A & 2B (RET)
- Neurofibromatosis type 1 (NF1)
- Paraganglioma syndromes (SDH)

# Clinical Importance

- **High mortality rate** if untreated or not recognized
  - Hypertensive crisis is a threat to life and/or organs
  - Enlarging masses can compress vital structures
  - ~15% of cases are malignant
- Surgical resection is **curative** in most cases

# Clinical Importance

- Elevated catecholamines may acutely precipitate:
  - Congestive heart failure
  - Pulmonary edema
  - Myocardial infarction
  - Ventricular fibrillation
  - Cerebrovascular accidents

# Case 2:
# An Inherited Syndrome

- A 45-year-old female with **neurofibromatosis type 1** and severe kyphoscoliosis
- HPI: palpitations, rapid heart rate (140s) and persistent headache
- Meds: **Ritalin** and **methadone**
- Symptoms attributed to Ritalin

# Case 2: An Inherited Syndrome

- PMH: remote history of a stroke 23 years ago
  - She has had dizziness and palpitations for years
  - Biopsy for a thyroid nodule (2009) - benign
  - A CT scan performed during that work up revealed a right adrenal mass thought to be a likely neurofibroma
- Family history: multiple first degree relatives who have died from complications of NF-1

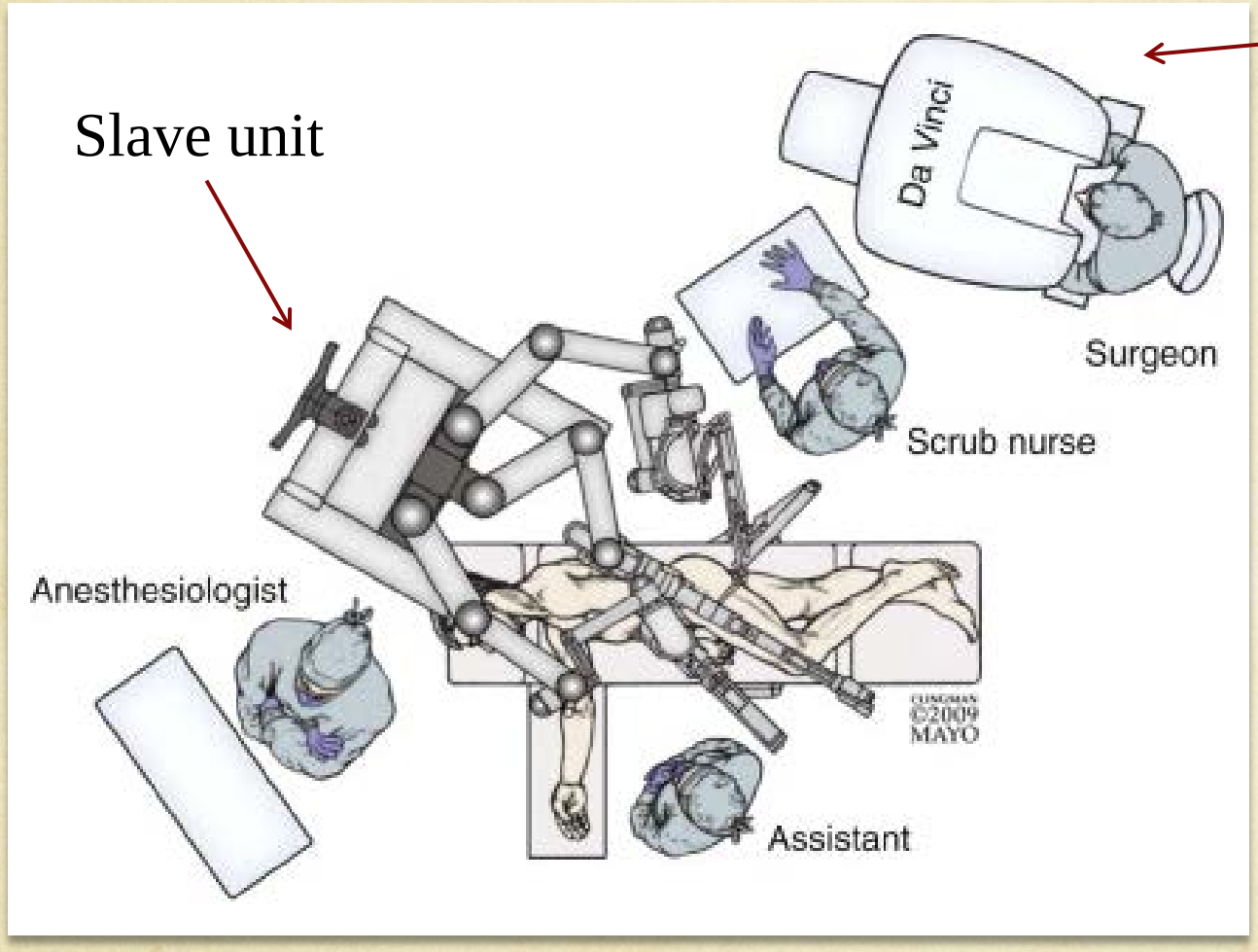
# Case 2: An Inherited Syndrome

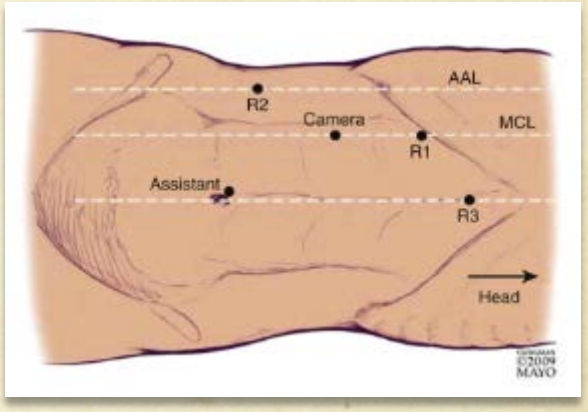
- She is unable to tolerate an MRI and undergoes a CT scan instead
- The radiologist finds a 6 x 2 cm mass c/o pheochromocytoma
- A 24-hour urinary fractionated metanephrines is ordered confirming the diagnosis
  - Urine metanephrine 794 ug/d (30-350)
  - Urine normetanephrine 752 ug/d (50-650)

# Case 2: An Inherited Syndrome

- The patient was scheduled for surgery
- SBP 120's at admission
  - α-blockade started 10 days pre-op (phenoxybenzamine)
  - β-blockade started after a week of α-blockade (propranolol)
- A transperitoneal right robotic adrenectomy was planned

# ROBOT-ASSISTED LAPAROSCOPIC RIGHT ADRENALECTOMY

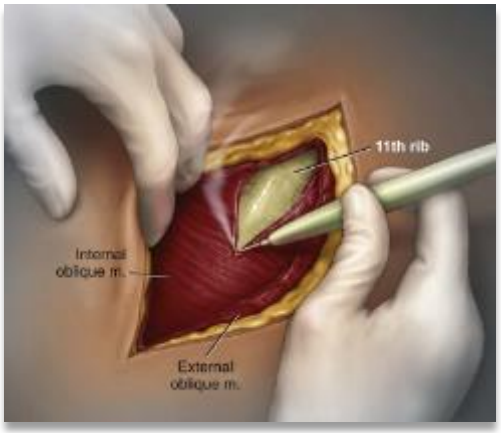


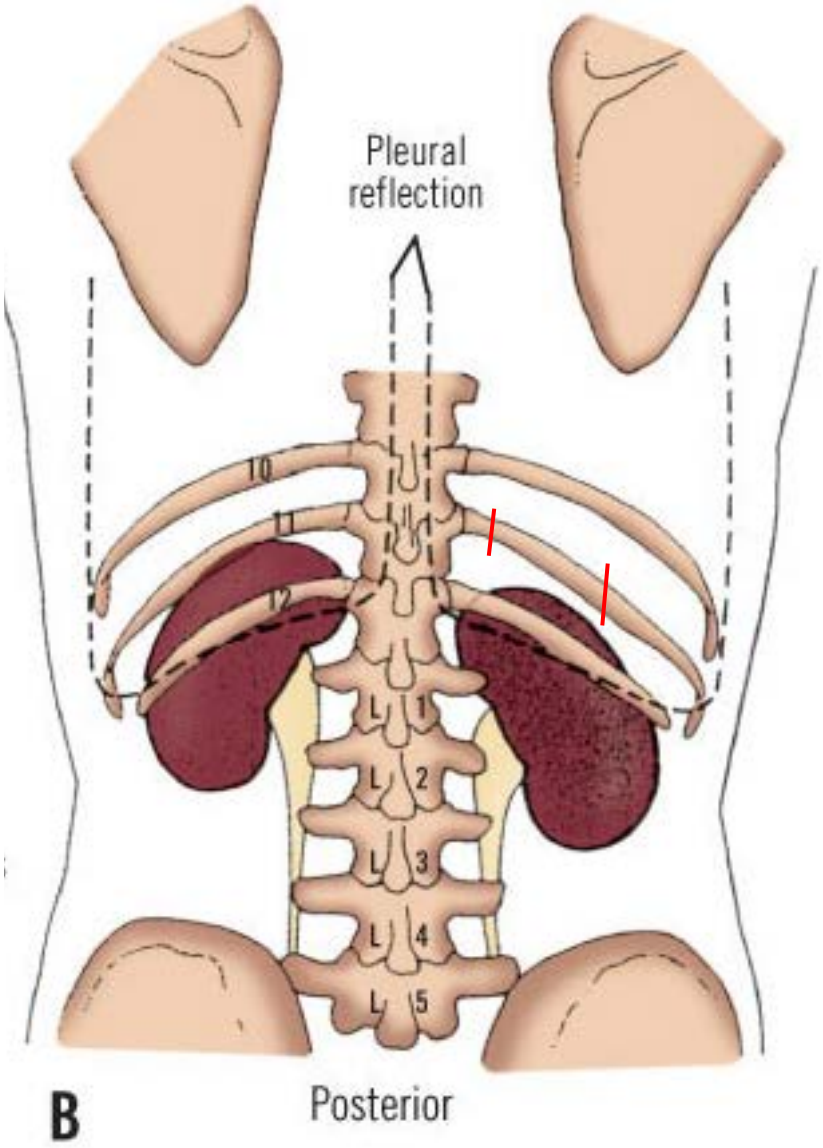

Campbell-Walsh Urology. 10th ed.

# Operative Course

- Attempted right robotic-assisted laparoscopic adrenalectomy aborted
  - Dense abdominal adhesions and poor access to retroperitoneum due to unusual liver anatomy
- Stopped the operation, sewed up the port sites, scrubbed in again
- Converted to right flank open adrenalectomy




Surgical incision over 11th rib for flank adrenalectomy




Campbell-Walsh Urology. 10th ed.

# Case 2: Surgical Specimen


Adrenal gland with two masses:

5.5 x 2.8 x 1.5 cm

1.5 x 1.3 x 1.0

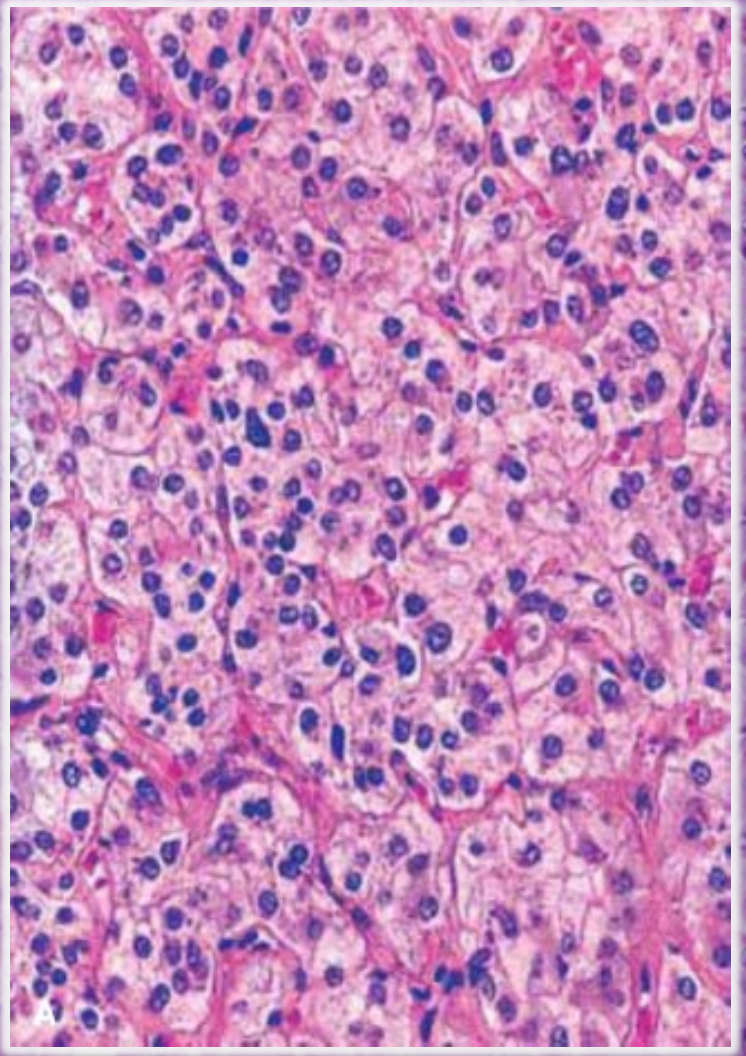
F

G

M

R

Zellballen




“Normal” sized nerve
Plexiform neurofibroma

# Neurofibromatosis type 1

- Neurofibromatosis type 1 (NF 1): first described pheochromocytoma associated syndrome
- Autosomal dominant  (1/3000) individuals in all populations
- The expression is **highly variable** but penetration is nearly 100%
  - Multiple neurofibromas
  - Café au lait spots
  - Axillary freckling of the skin
  - Lisch nodules of the iris
  - Optic nerve gliomas
  - Skeletal dysplasias

# Diagnostic Work Up

- **Biochemical testing**: **cornerstone of the diagnosis!!**
  - Should minimally include measurements of **plasma free** and/or **urinary fractionated metanephrines**
- Imaging:
  - CT and/or MRI
  - Consider functional imaging
- Genetic testing
  - **Endocrine Society Guidelines (2014)** recommend considering genetic testing for all patients
  - Familial or syndromic presentation merits high priority on genetic testing

# Summary

- Pheochromocytoma is a tumor of the chromaffin cells of the adrenal medulla
- The classic presentation is tachycardia, headache, and sweating but the dominant sign is hypertension
- Most are curable if detected, deadly if not
- **The recommended biochemical testing is**:
  - **Plasma free metanephrines** and/or
  - **Urinary fractionated metanephrines**

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