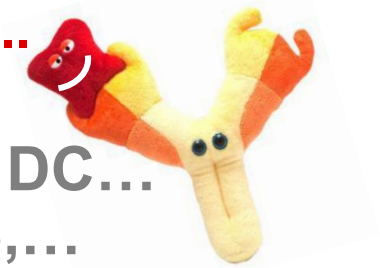
BI 358 Lecture 9

Hooray! > Guest lectures!...



I. Announcements **Dr. Jacobson R, Dr. Padgett U!**

II. Lymphatic System **Alternative circulation Torstar, DC…**

III. Cardiovascular Physiology **Torstar, G&H, Katz, LS,…**

- **A. ♥ structure & function G&H fig 9-7, LS**
- **B. Blood flow through ♥ & periphery G&H fig 9-1, LS…**
- **C. Coronary circulation & the cardiac cycle, composite events G&H fig 21-3, Katz, G&H fig 21-5, 21-6, 21-4; ch 9 fig 9-7**
- **D. Autorhythmic cells & ♥'s electrical highway G&H fig 10-1**

IV. CVDs **Definitions, US Disease Statistics: CDC 2012 + AHA**

V. Atherosclerosis + Mechanisms **Torstar Books, G&H, +…**

- **A. Linking proposed historical mechanisms**
  Endothelial Injury Hypothesis (Ross & Glomset)
  Lipid Infiltration Hypothesis (Steinberg & Witzum) + new!
- **B. Cholesterol metabolism: Dr. Kottke's bathtub analogy**
- **C. 1^0 modifiable risks: cigarette smoking, hypertension, hypercholesterolemia/hyperlipidemia, lack of exercise**
- **D. Treatment triad, *PTCA*, *CABG*, prevention, practical tips!**

VI. Endocrinology Overview **G&H ch 75 + 76, LS, Norris, Fox...**

- **A. Endocrine vignette: Cushing's Syndrome LS**
- **B. What's an endocrine? Hormone criteria & classifications?**
- **C. Mechanisms of hormonal action G&H fig 75-6, 75-2, 75-7,...**

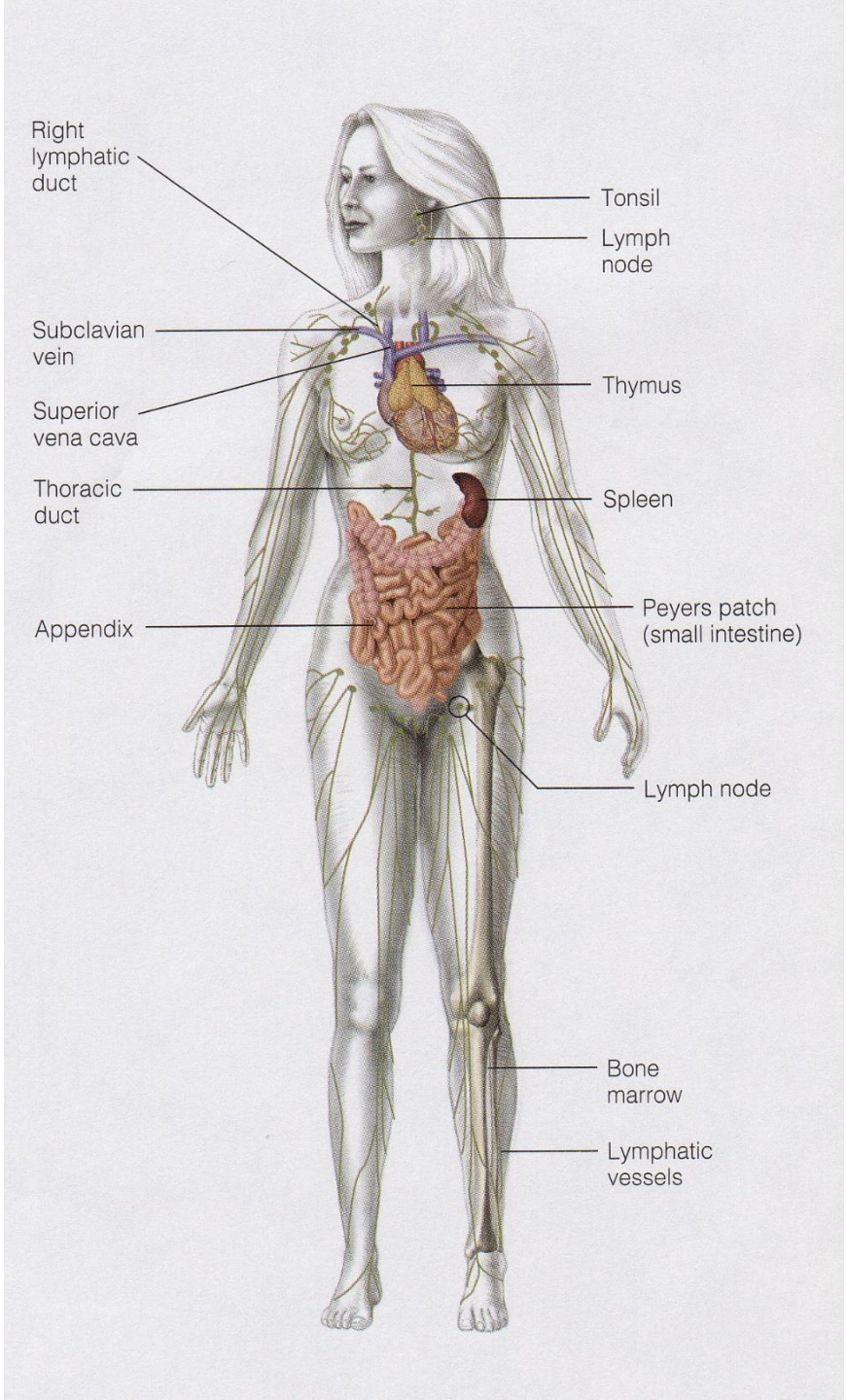

Dr. Kraig's lecture is this Thursday!
Yes, Sherlock! Avian & human immune systems evolved from a common reptilian ancestor!!
Whoopee! For the birds??

Richard C. Padgett
Medical Director

Sacred Heart Medical Center
PeaceHealth

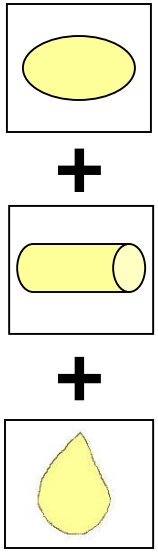
Oregon Heart & Vascular INSTITUTE

https://www.peacehealth.org/ohvi?from=/sacred-heart-ri



Lymphatic System

1. **Lymph Nodes**
2. **Vessels**
3. **Lymph**



No pump!

D Chiras 2003

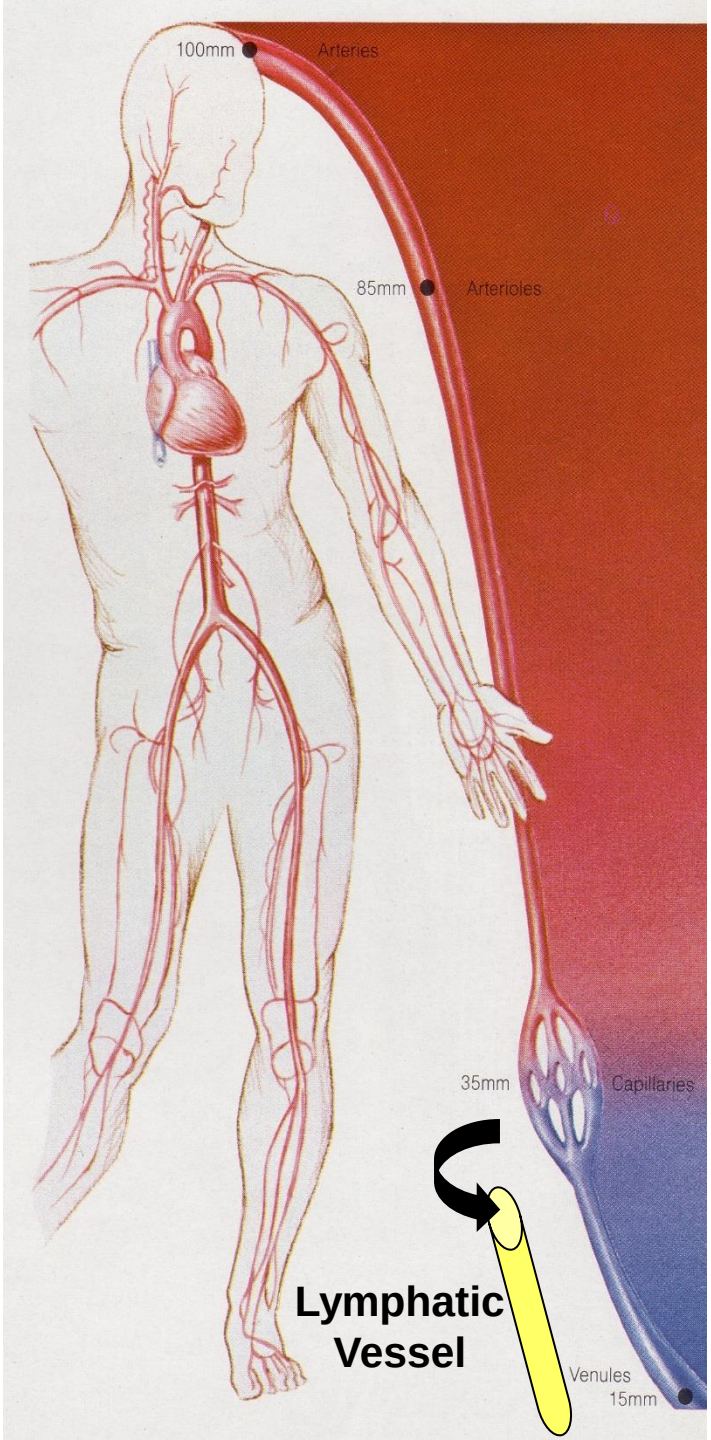
Lymphatic System

Alternative System of Circulation

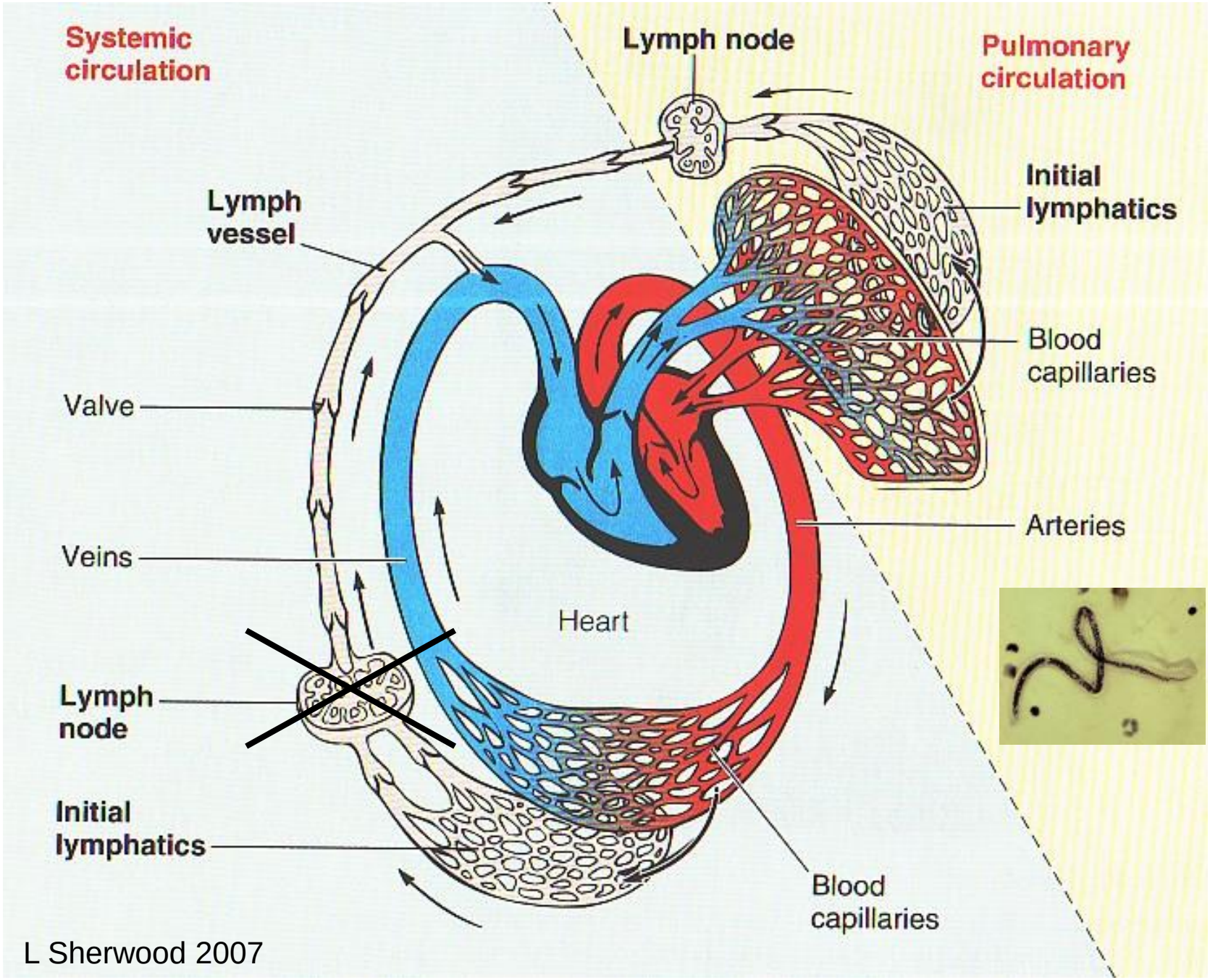
or

Drainage System

Lymph Vessels* || *Veins

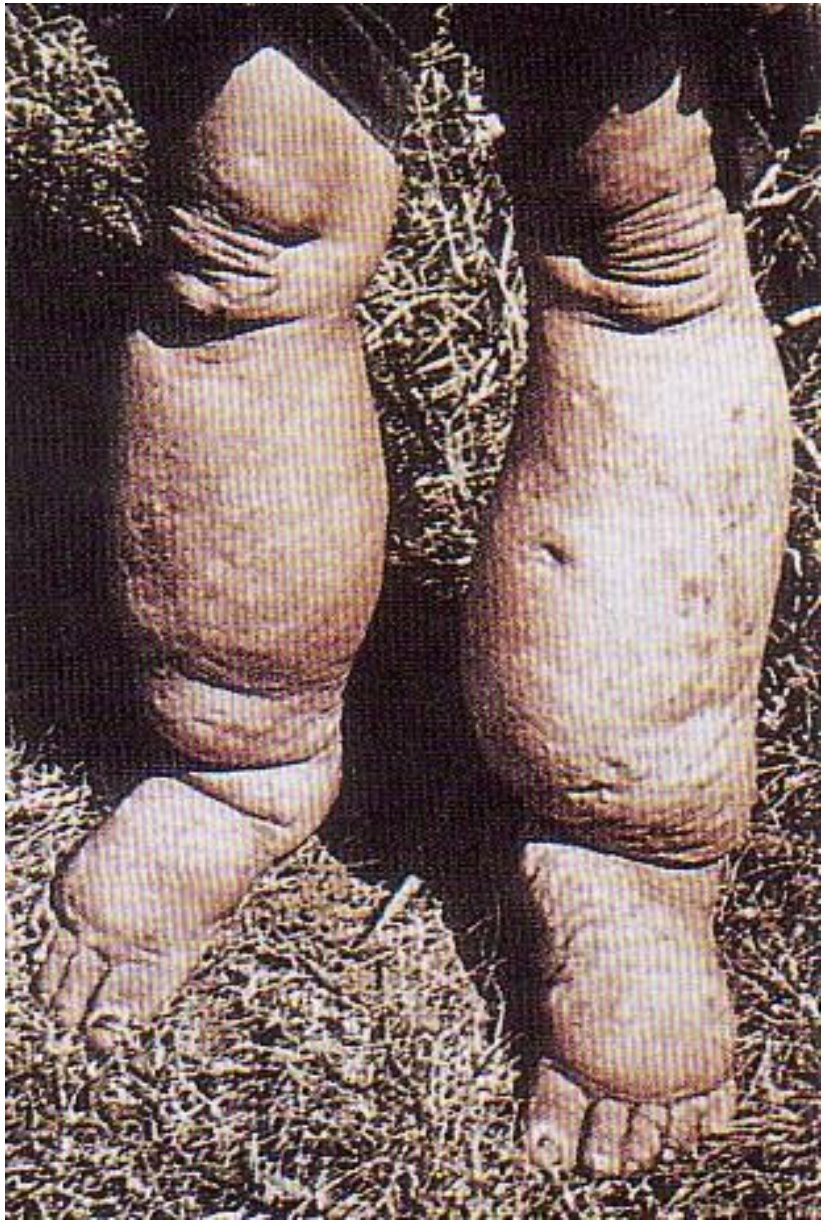


Torstar Books 1984

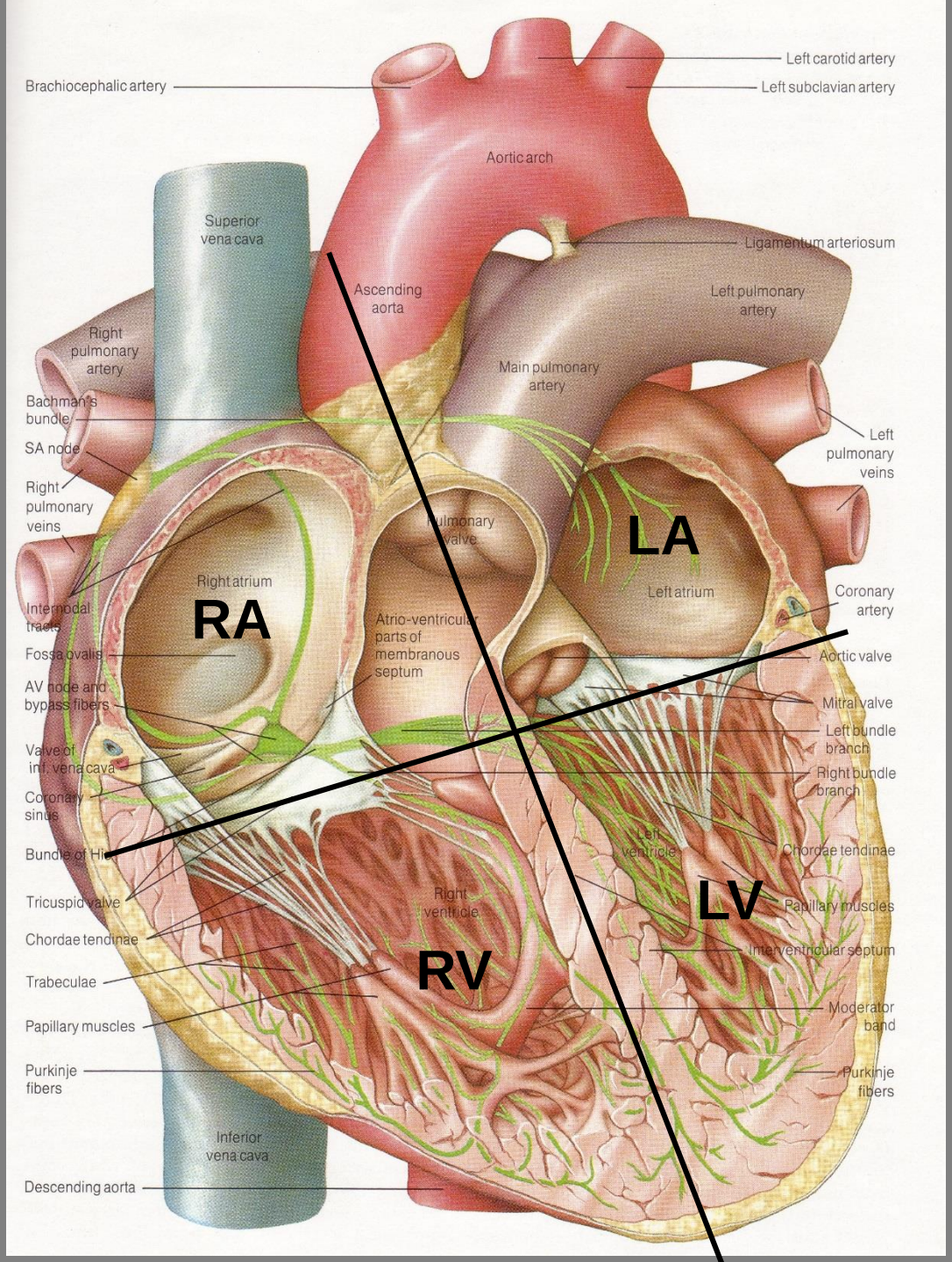


L Sherwood 2007

Elephantiasis: Lymphatic Blockage Due to Mosquito-Borne Parasitic Worm



L Sherwood 2007



Torstar 1984 p 53

Human ♥ = 4 unique valves?
2 valve sets?

Semilunar = *Half-moon shaped*

More rigid

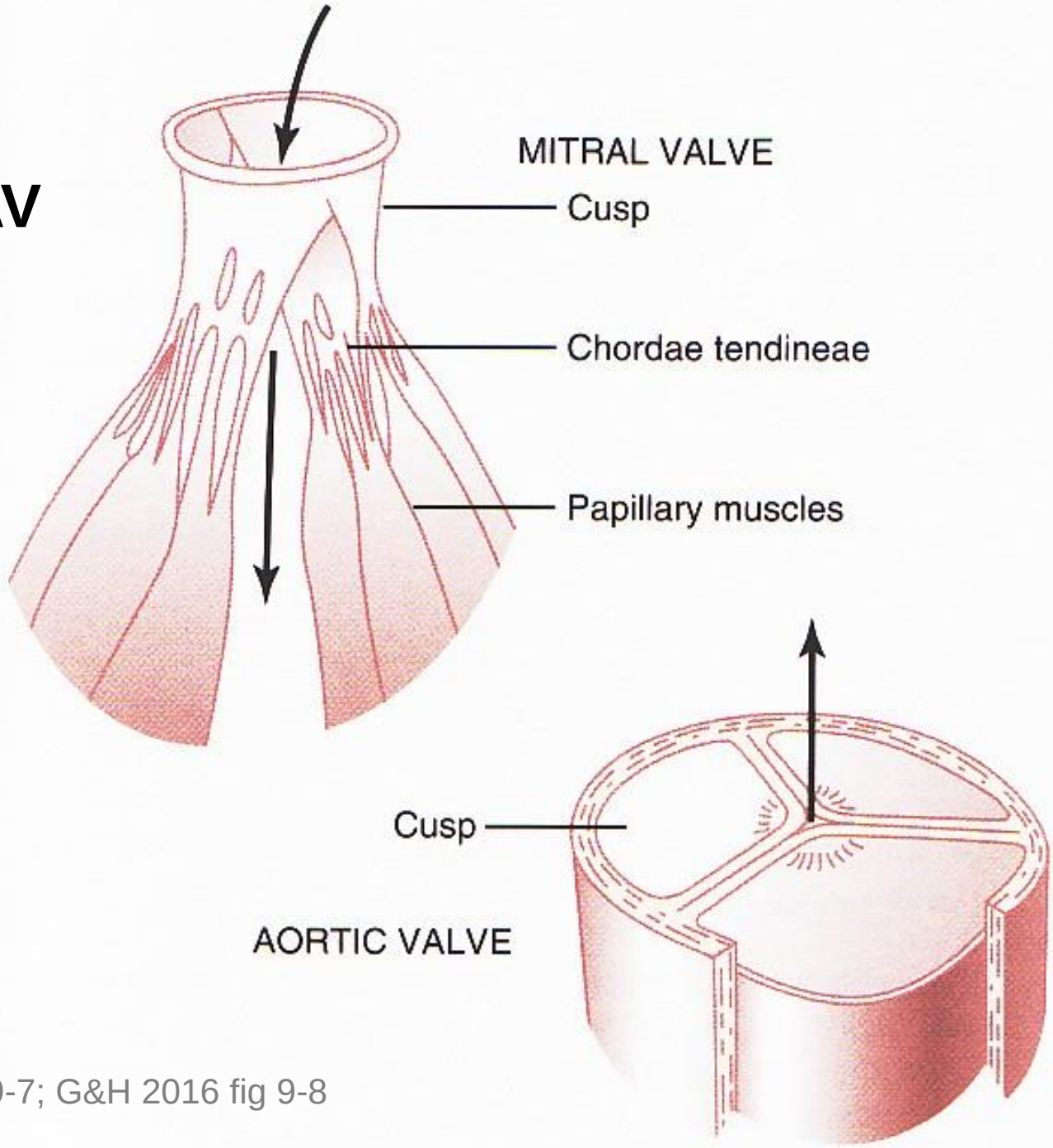
1. Pulmonic/Pulmonary
2. Aortic

AV = *Atrioventricular*

More flimsy

3. (R) AV = Tricuspid
4. (L) AV = Mitral/Bicuspid

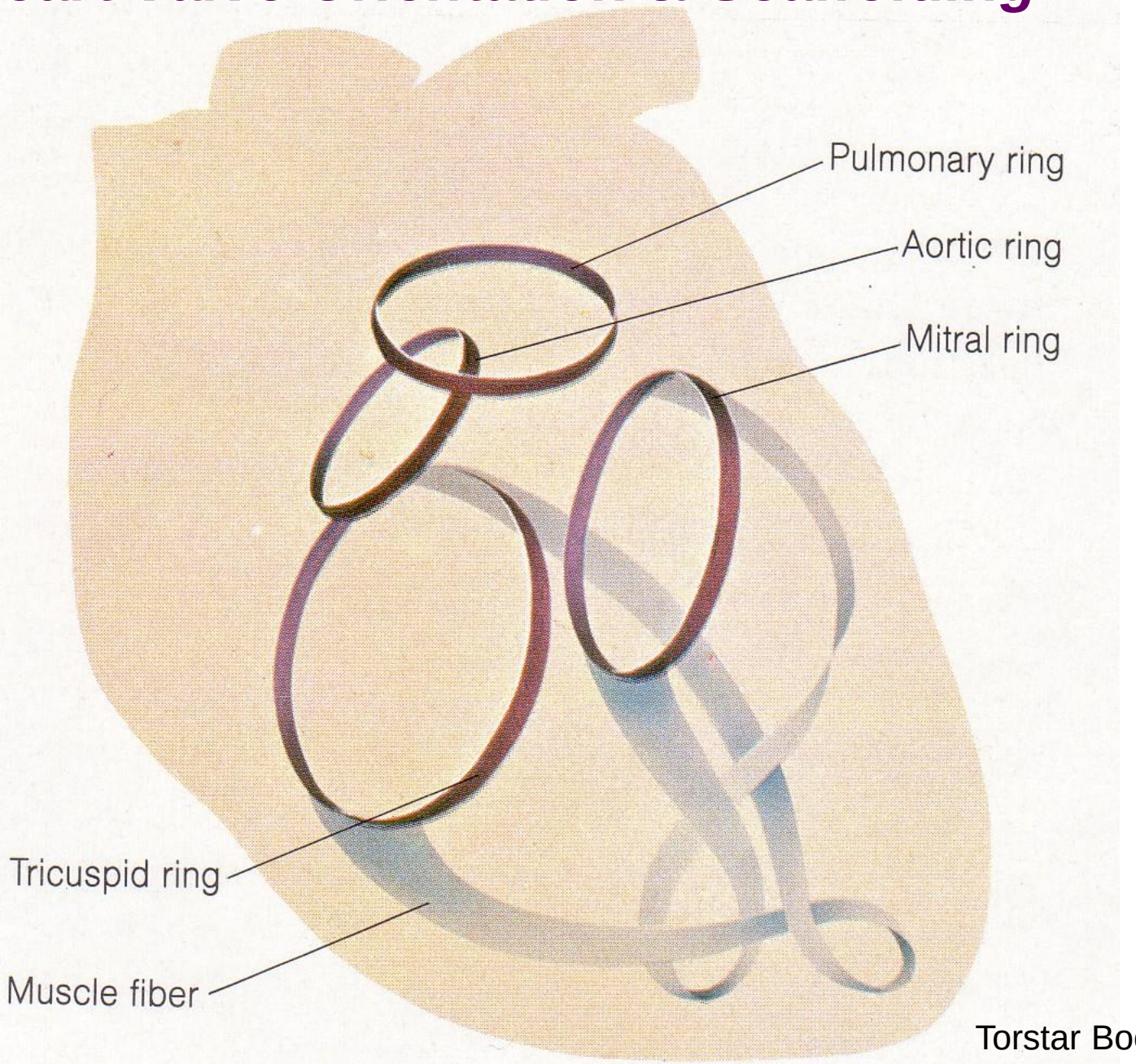
Ⓛ AV



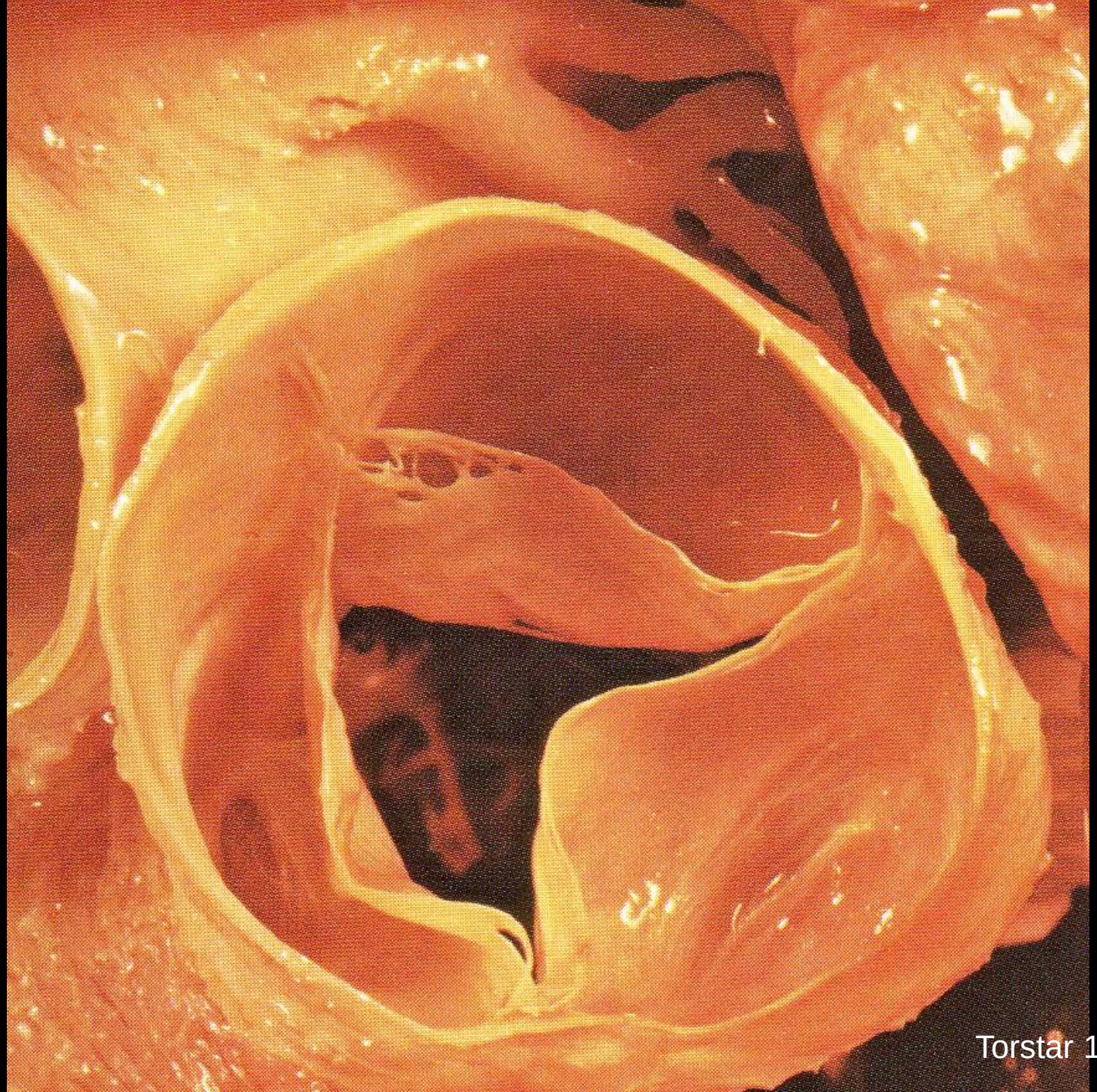
SL

G&H 2011 fig 9-7; G&H 2016 fig 9-8

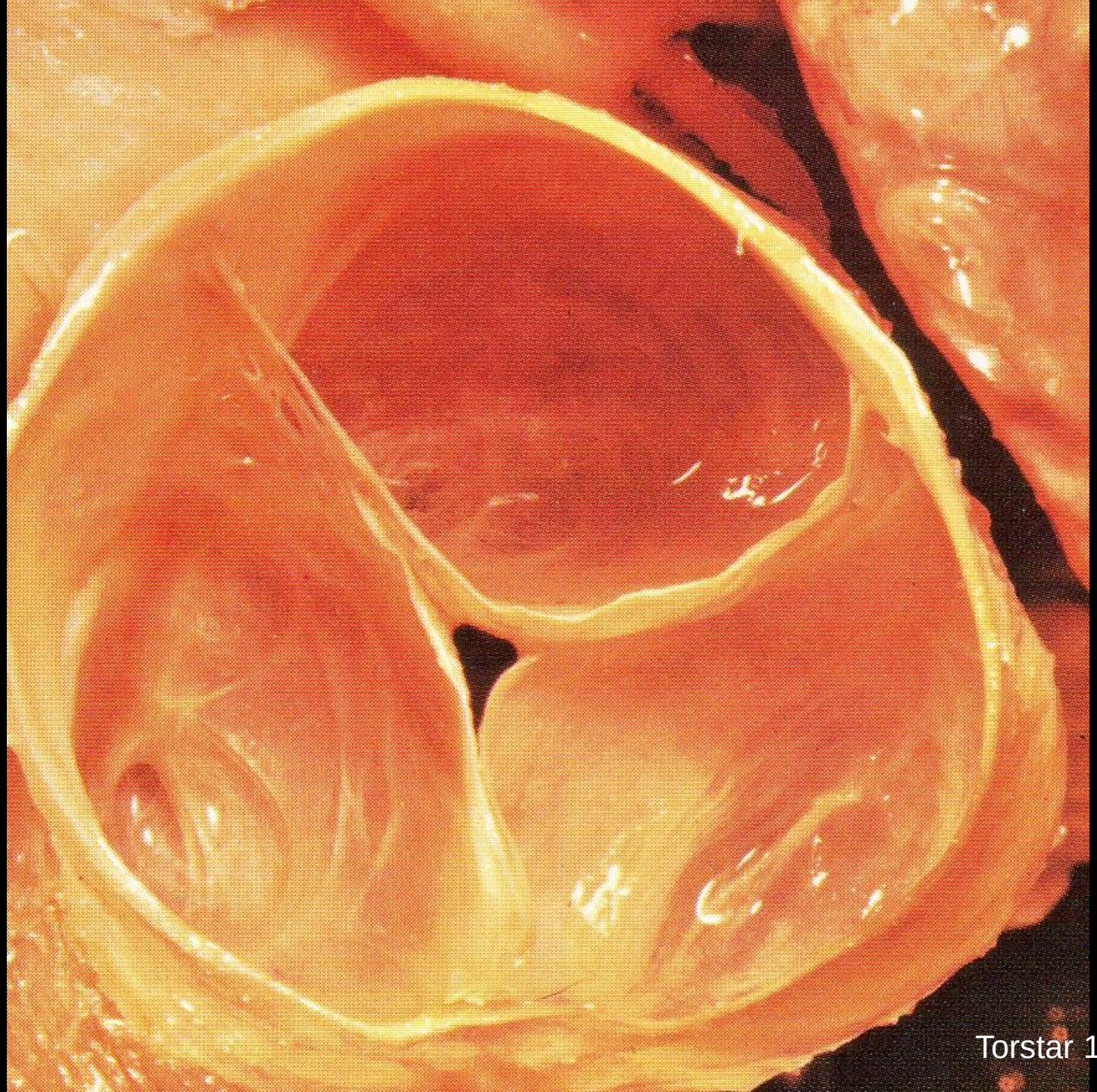
Heart Valve Orientation & Scaffolding



Torstar Books 1984



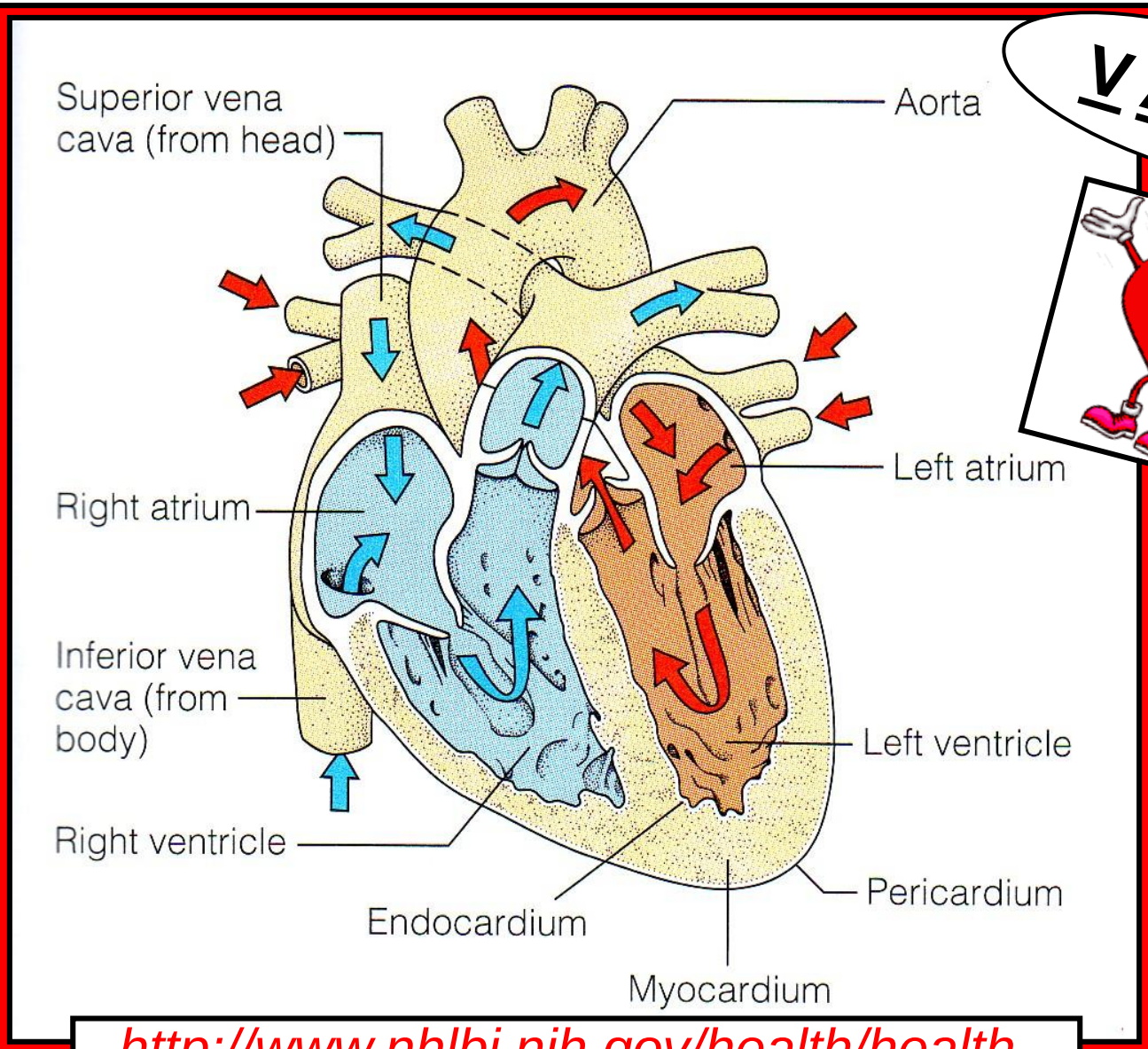
Torstar 1984 p 40

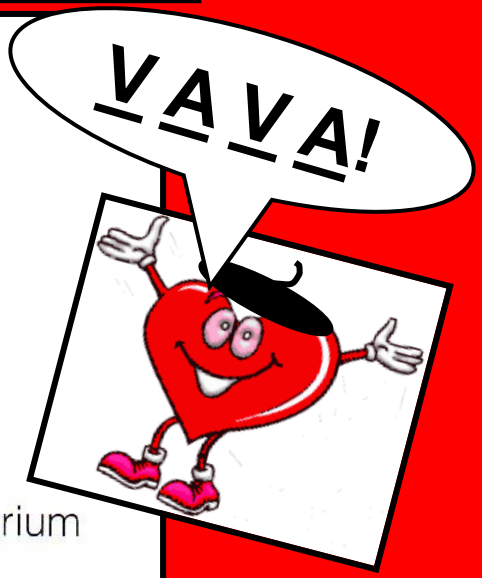


Torstar 1984 p 40

Torstar 1984 p 41

Veins → Atria → Ventricles → Arteries





http://www.nhlbi.nih.gov/health/health-topics/topics/hhw/contraction.html

LS2007

What the heck's a *bruit?*
(brwe, brōōt) [Fr.] sound ≥ 25 subclassifications!

Aneurysmal b. **a blowing sound over an aneurysm.**

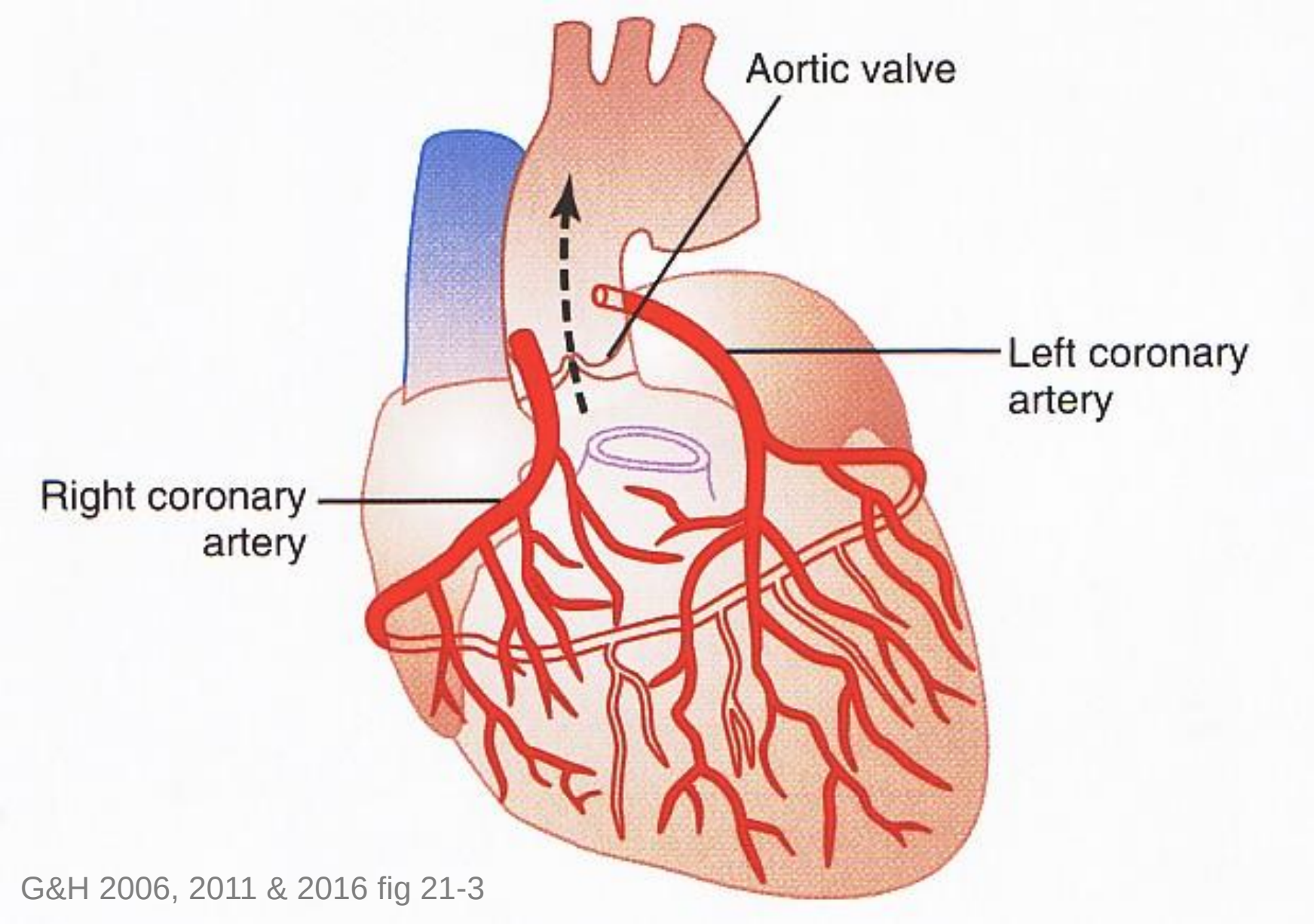
b. de canon **[Fr. sound of cannon] abnormally loud 1st heart sound heard in complete heart block.**

b. de craquement **[Fr. sound of crackling] a crackling pericardial or pleural bruit.**

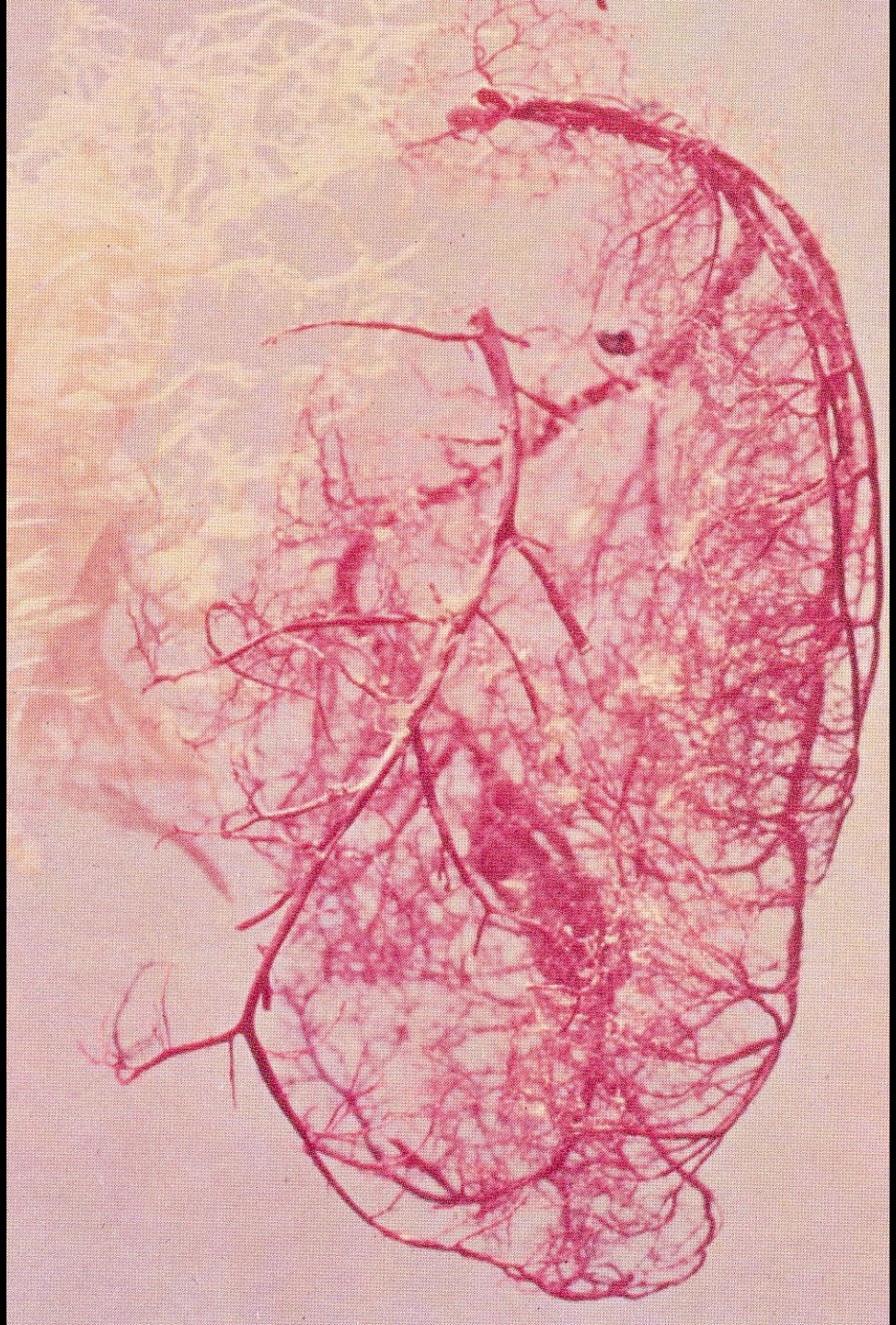
False b. **artifact caused by pressure of the stethoscope or derived from circulation of the ear.**

b. de lime **[Fr. sound of a file] cardiac sound resembling filing.**

Coronary Circulation ≡ Crowns the Heart!



G&H 2006, 2011 & 2016 fig 21-3



Torstar 1984 p 47

Heart Dominance May Influence Survival

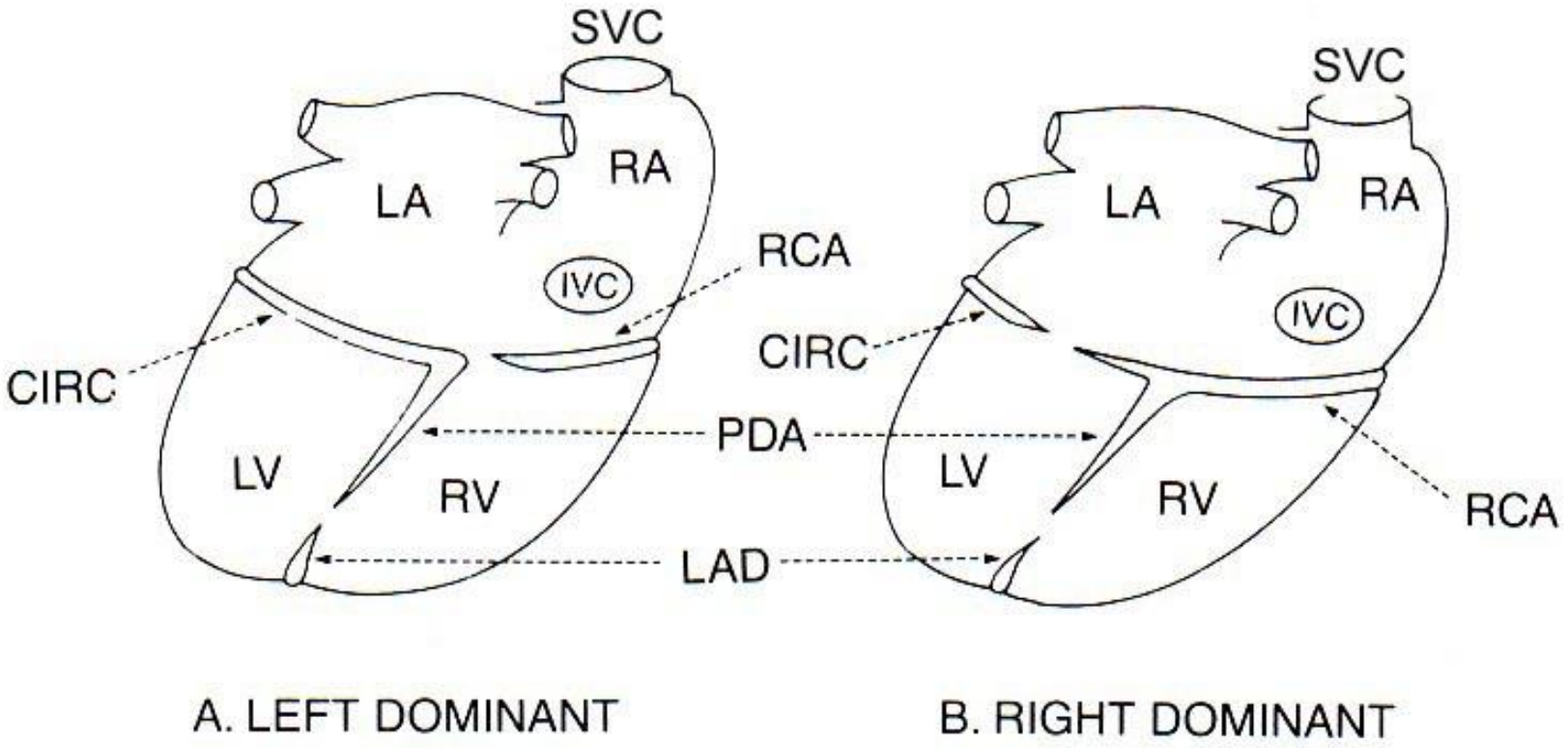
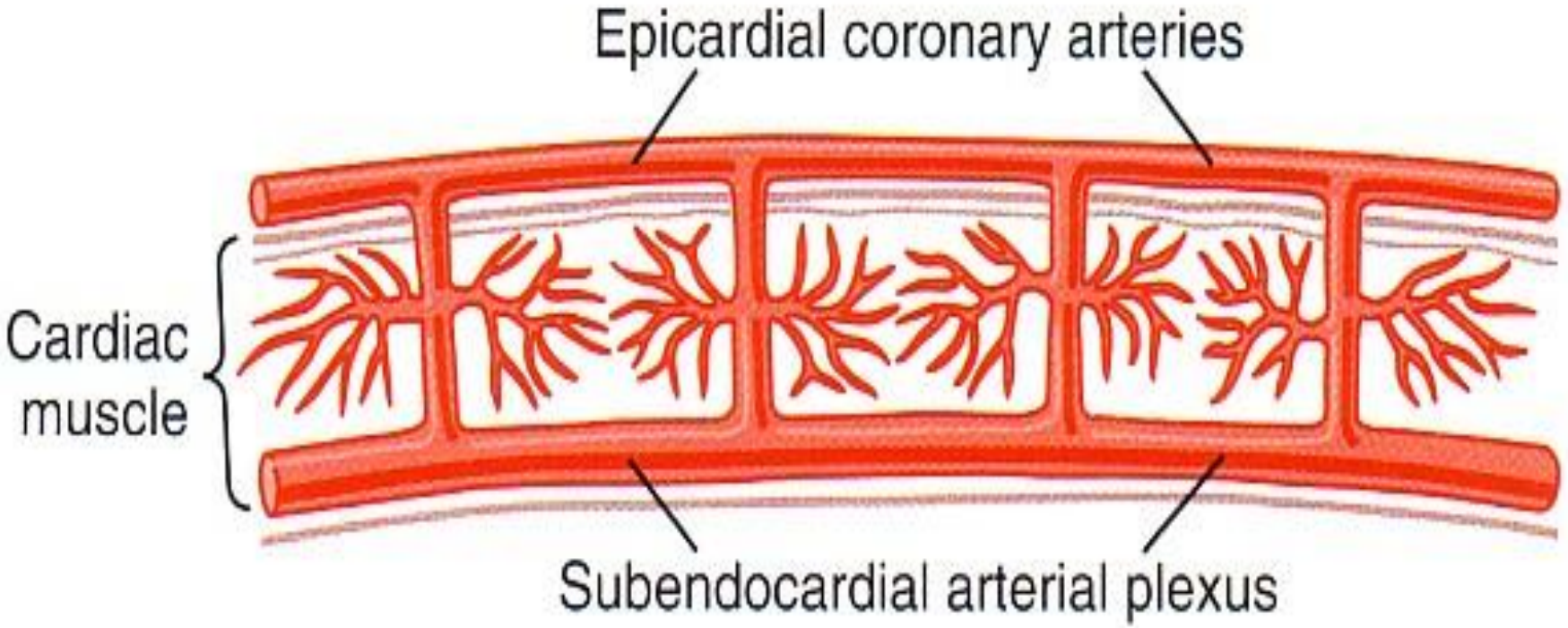


FIG. 1.9. Diagrammatic views of the posterior surfaces of the human heart showing left (A) and right dominant (B) patterns of coronary artery supply. In the left dominant pattern, the posterior descending artery (PDA) is supplied by the circumflex branch of the left coronary artery (CIRC). In the right dominant pattern, the posterior descending artery is supplied by the right coronary artery (RCA). Other abbreviations: LAD, left anterior descending coronary artery; LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle; SVC, superior vena cava; IVC, inferior vena cava.

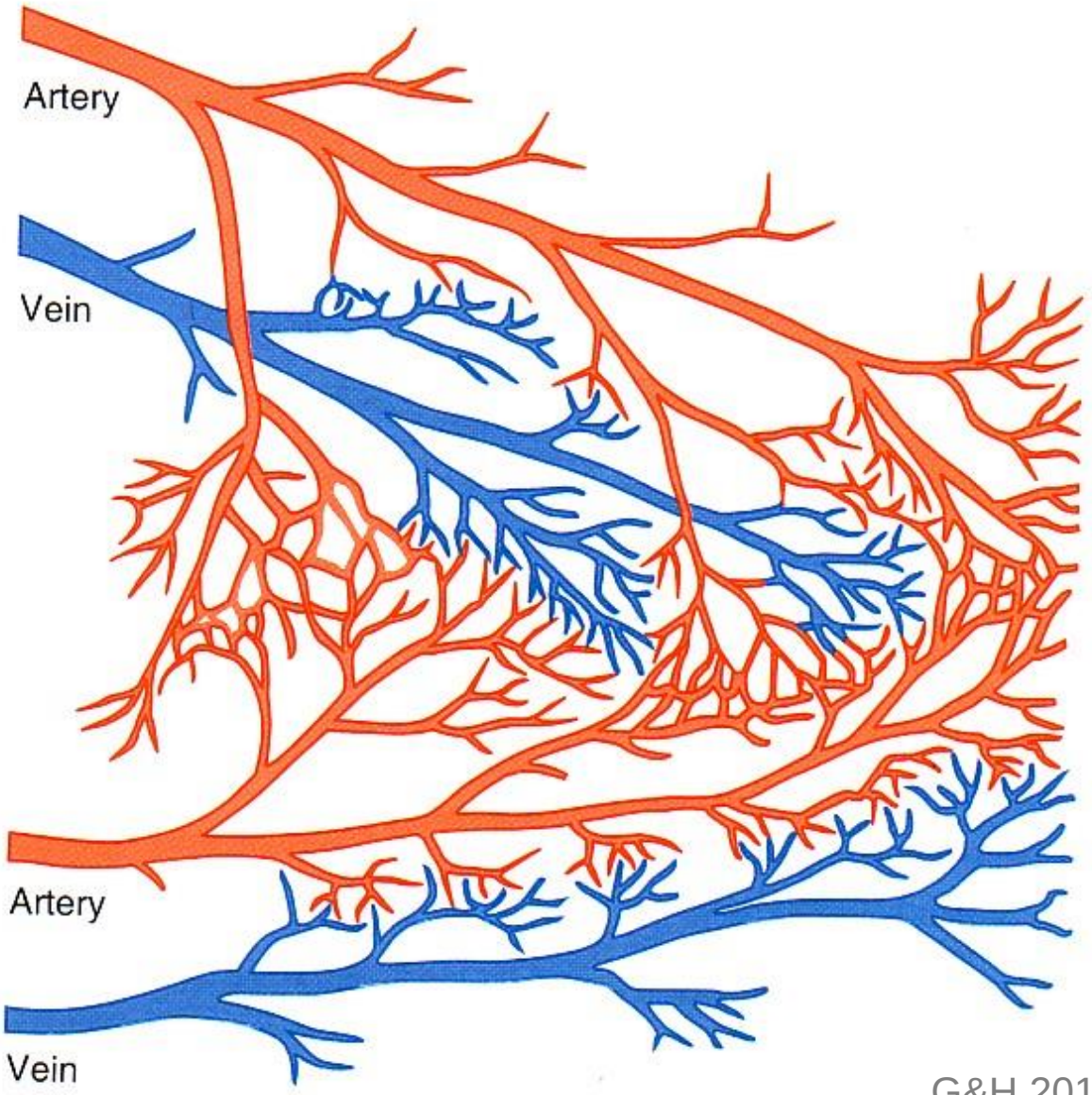
AM Katz 1992 p 12

Coronary Arteries Pierce the Heart from Epi to Endo



G&H 2011 & 2016 fig 21-5

Anastomoses May Provide Lifesaving Collateral Circulation!!



G&H 2011 & 2016 fig 21-6

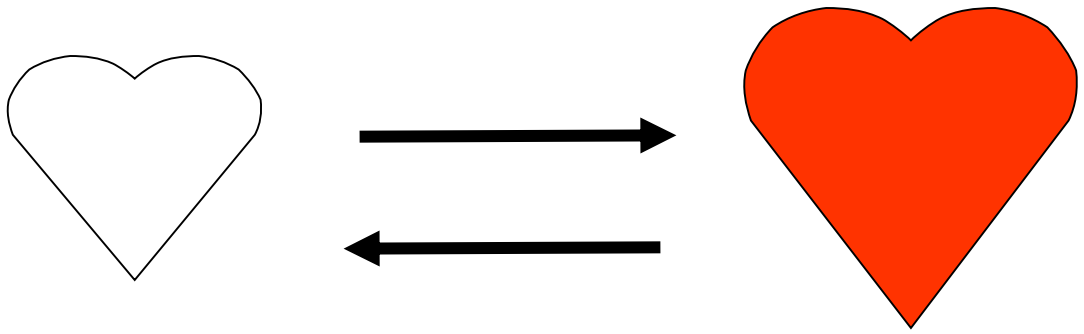
Cardiac Cycle

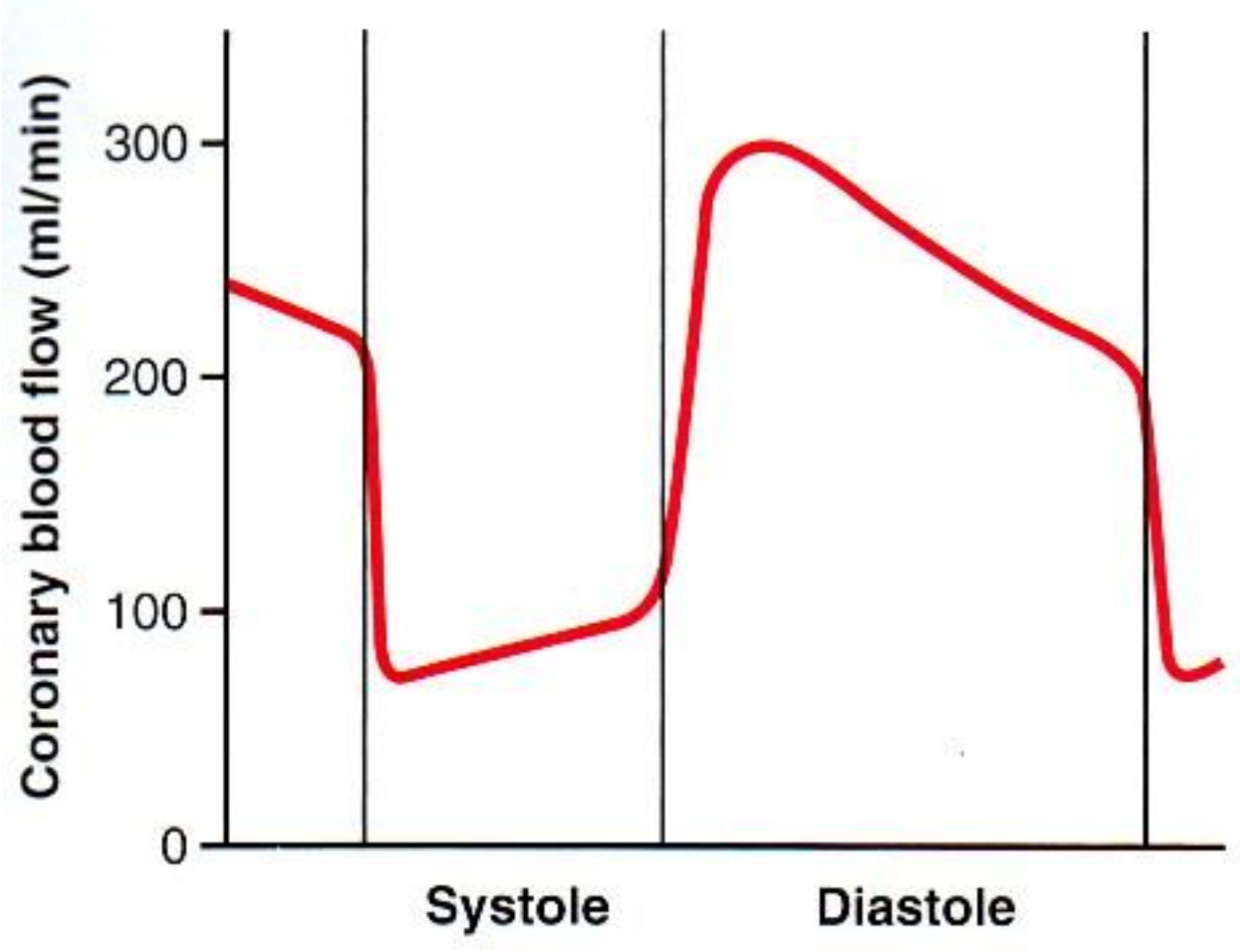
Systole

Contract
& Empty

Diastole

Relax
& Fill



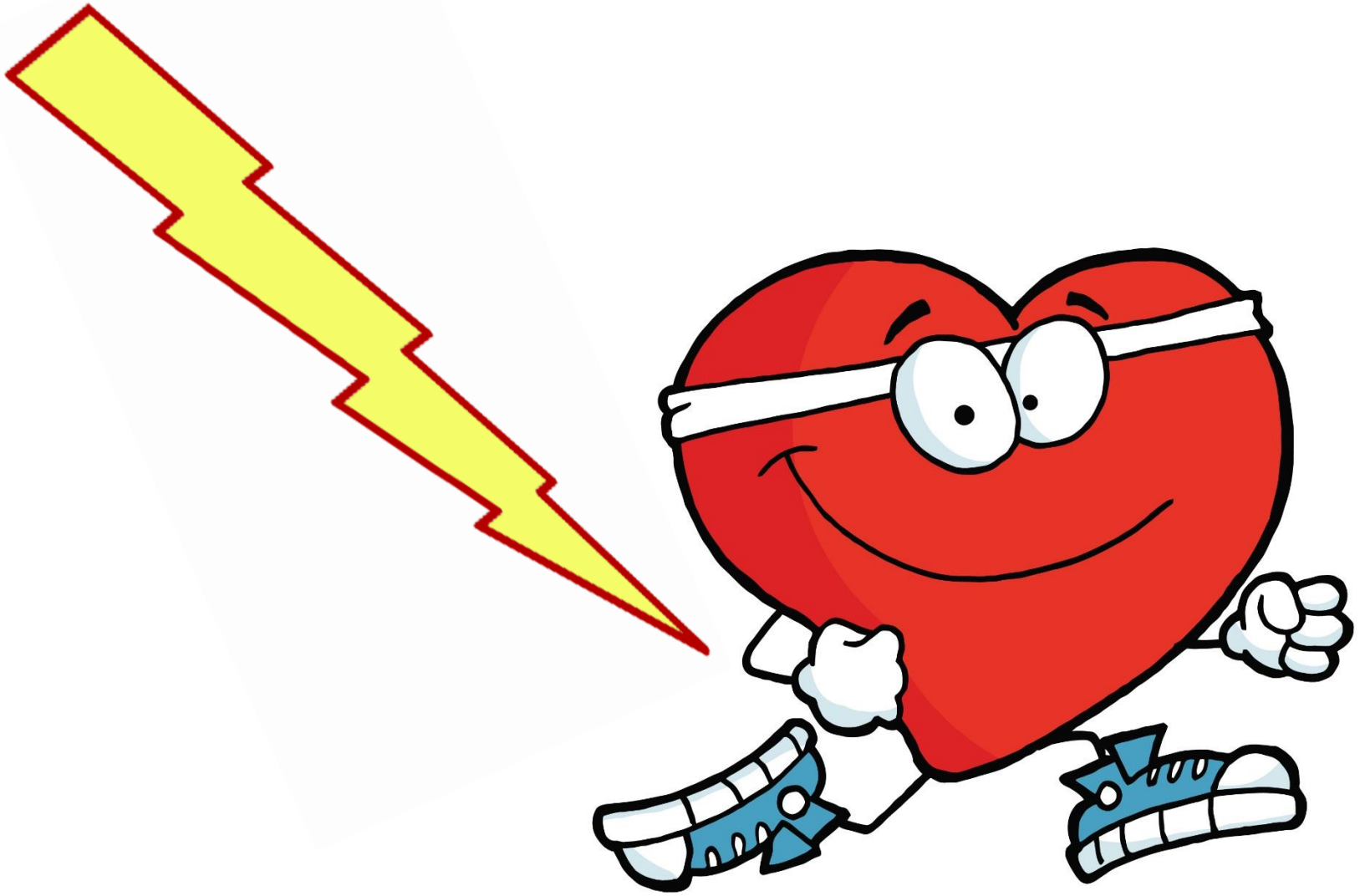


Contract & Empty

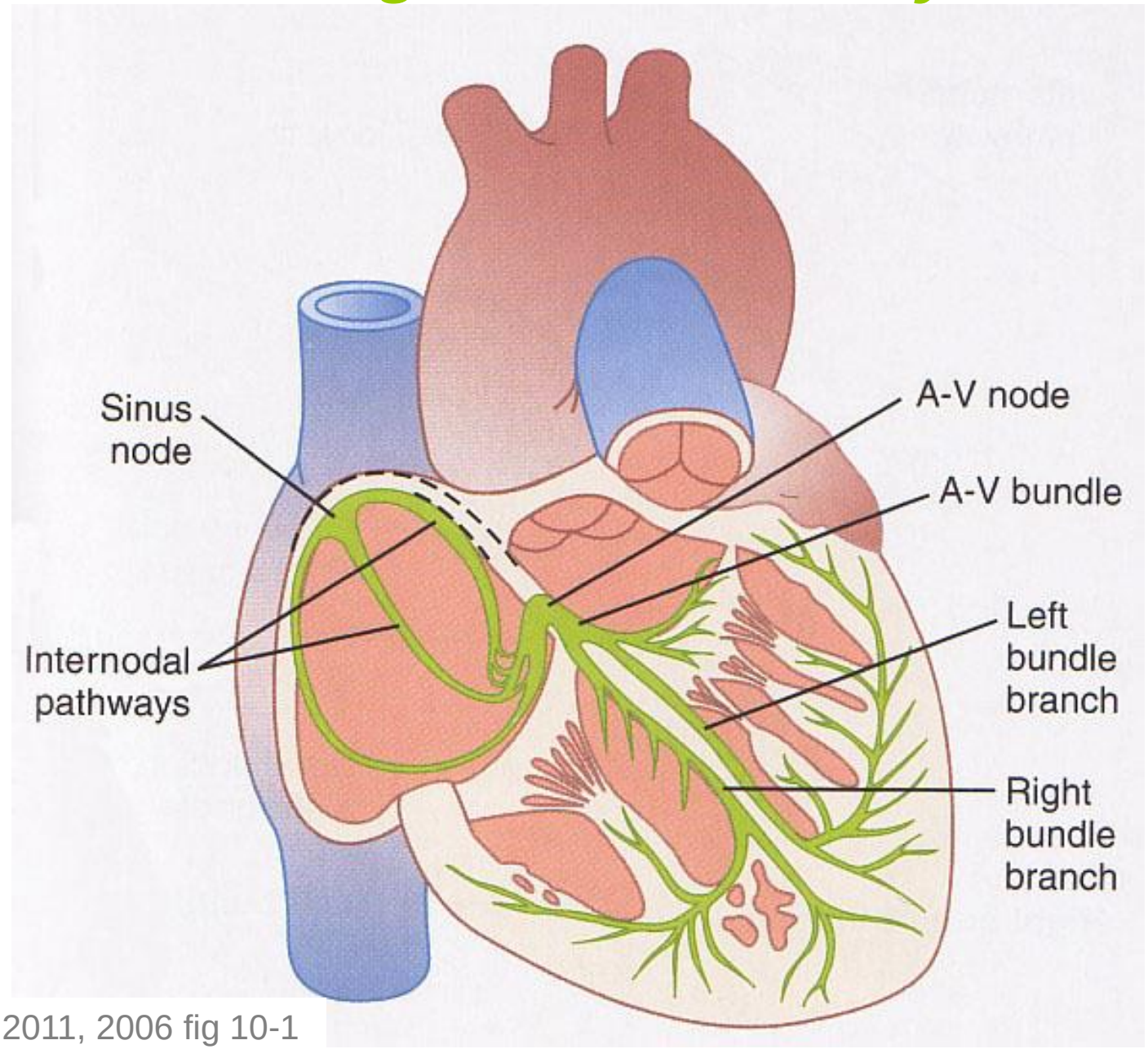
Relax & Fill

G&H 2011 & 2106 fig 21-4

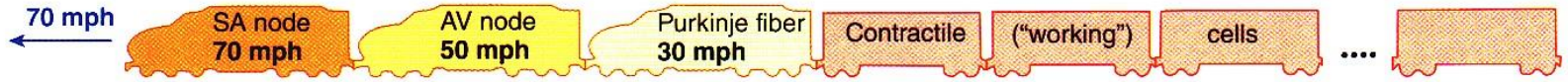
(Automatically) Shock the Heart then it Contracts!



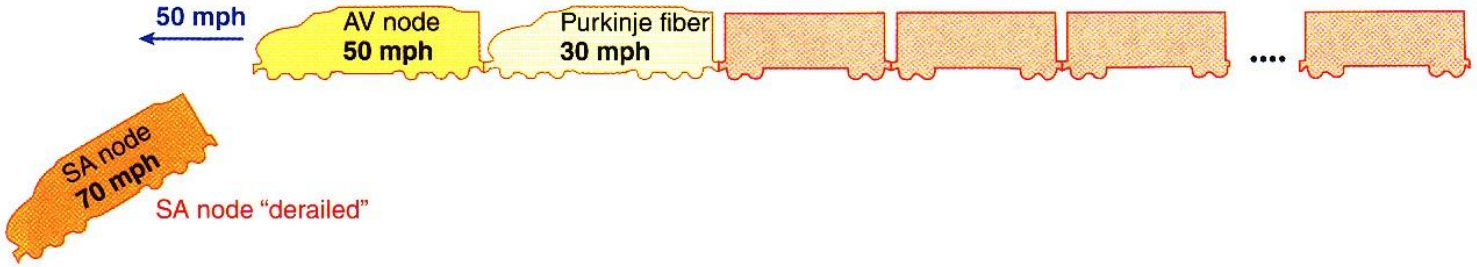
Intrinsic Regulation: Autorhythmic



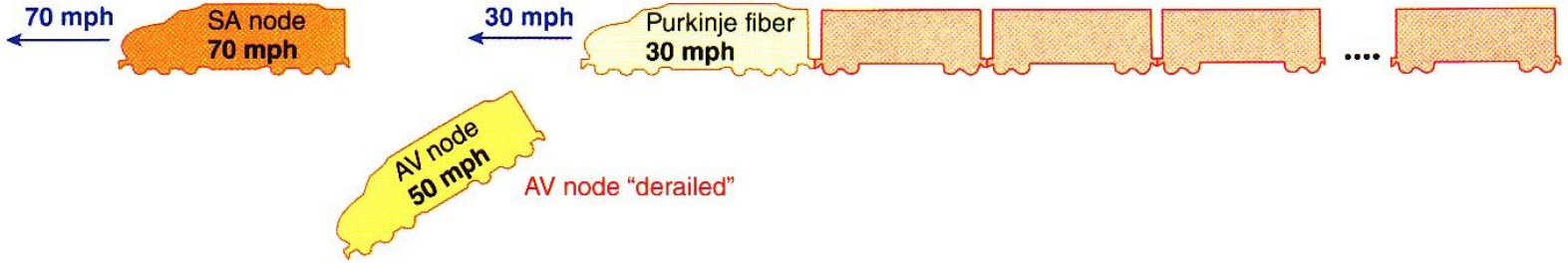
G&H 2016, 2011, 2006 fig 10-1



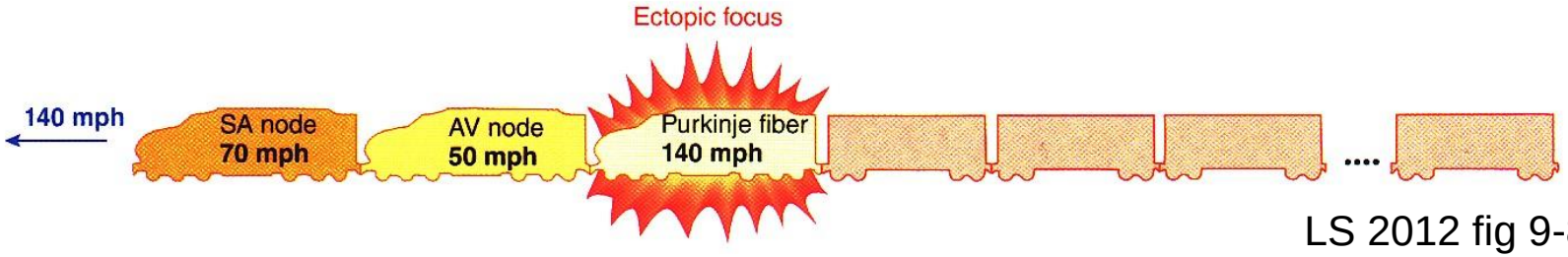
(a) Normal pacemaker activity: Whole train will go **70 mph** (heart rate set by SA node, the fastest autorhythmic tissue).



(b) Takeover of pacemaker activity by AV node when the SA node is nonfunctional: Train will go **50 mph** (the next fastest autorhythmic tissue, the AV node, will set the heart rate).

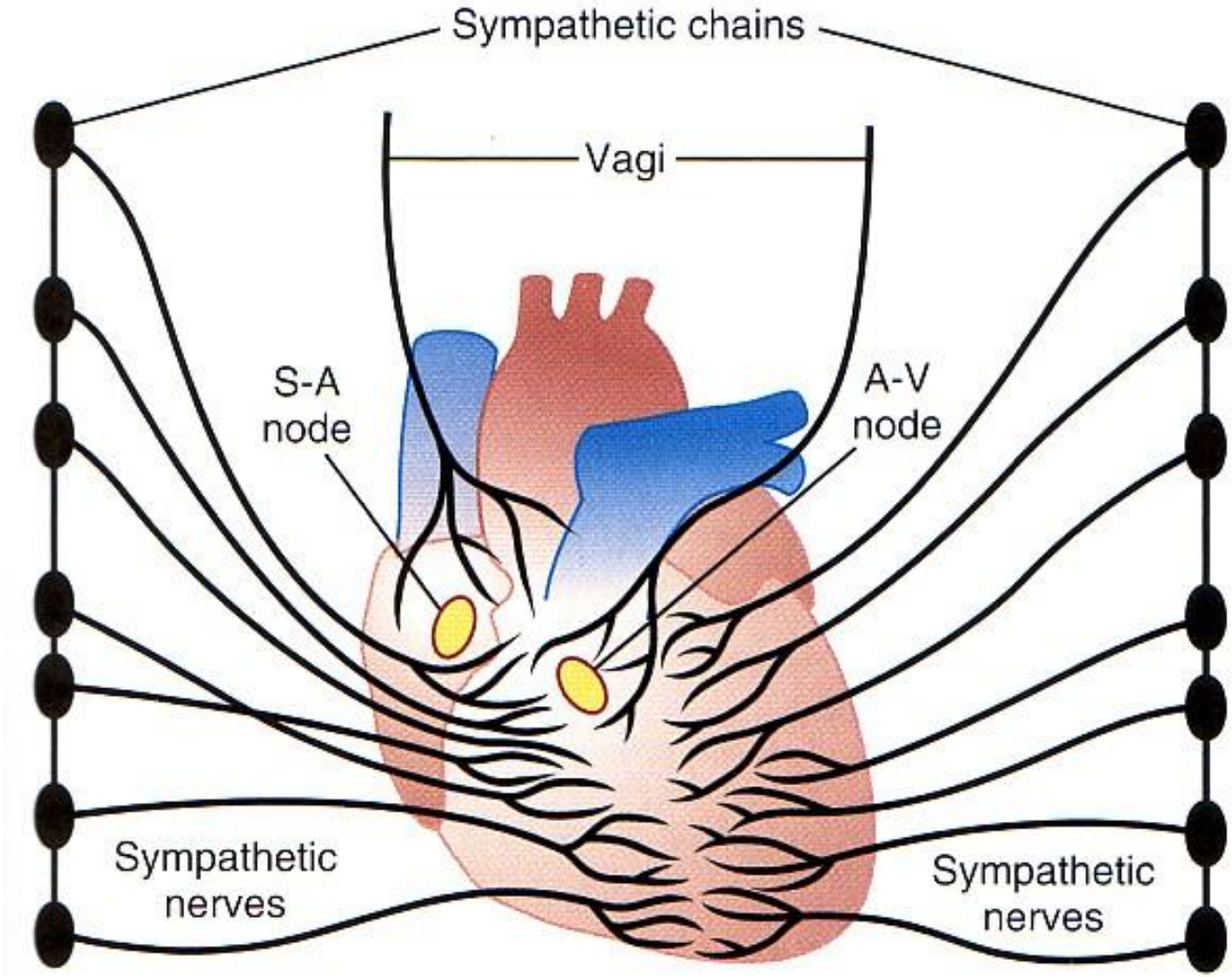


(c) Takeover of ventricular rate by the slower ventricular autorhythmic tissue in complete heart block: First part of train will go **70 mph**; last part will go **30 mph** (atria will be driven by SA node; ventricles will assume own, much slower rhythm).



LS 2012 fig 9-8 p 237

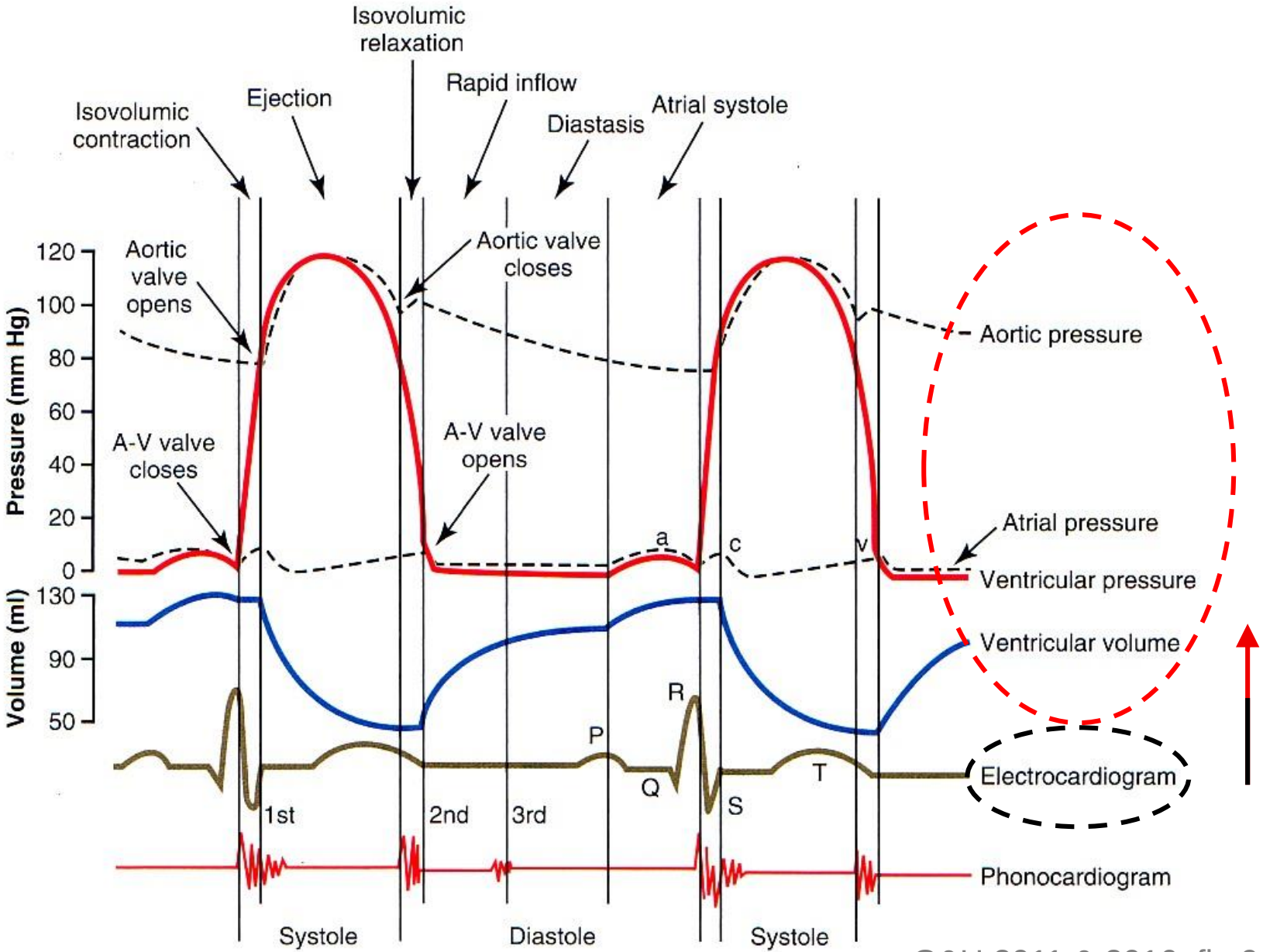
Extrinsic Regulation: Nervous



NB: + Extrinsic Hormonal
e.g. Adrenal Epi + NE

G&H 2011 fig 9-12
G&H 2016 fig 9-13

Electrical Events Precede Mechanical Events!



G&H 2011 & 2016 fig 9-6

CVDs

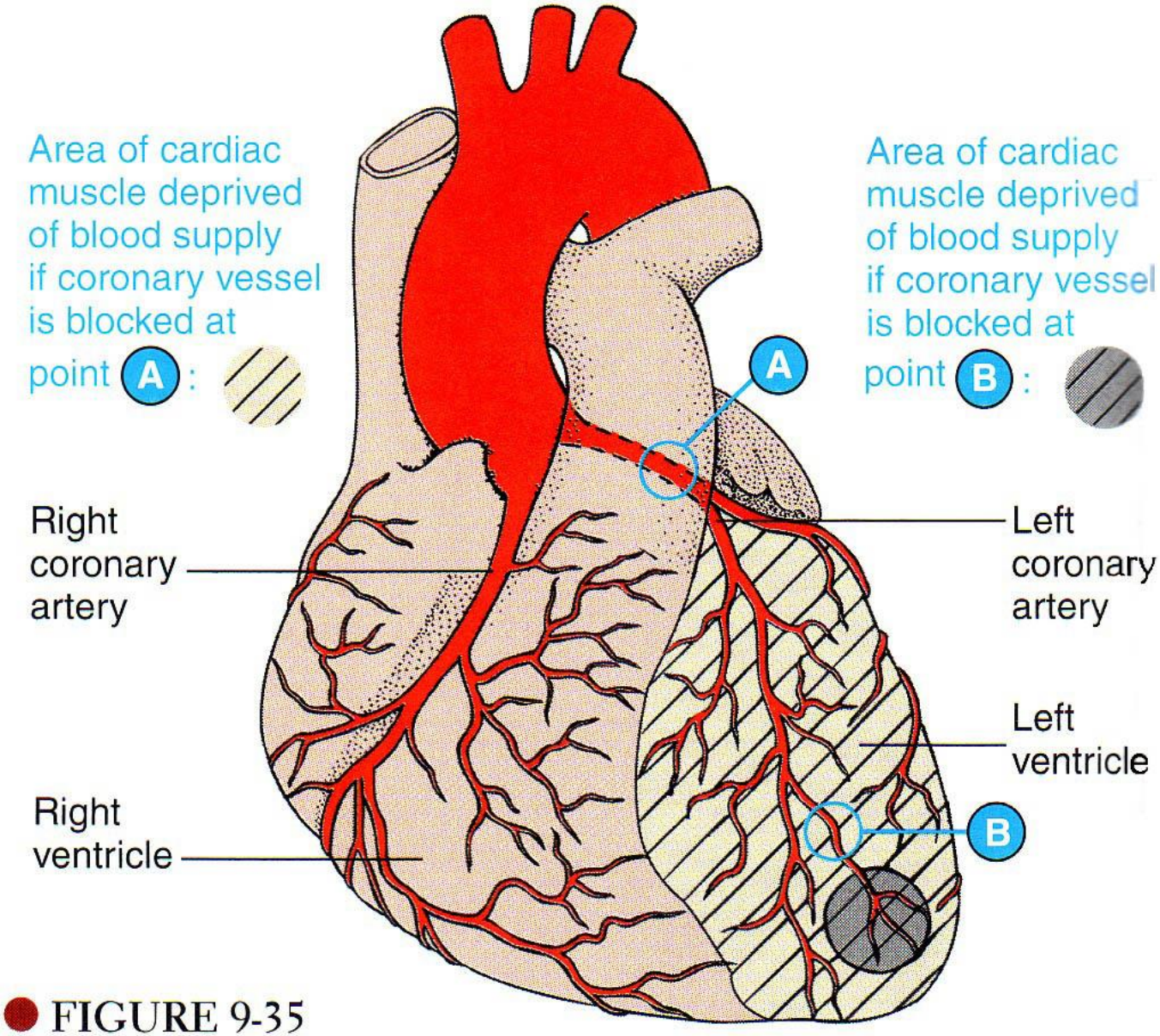
AMI

CVA

TIA

HTN

PVD



● FIGURE 9-35

Extent of myocardial damage as a function of the size of the occluded vessel

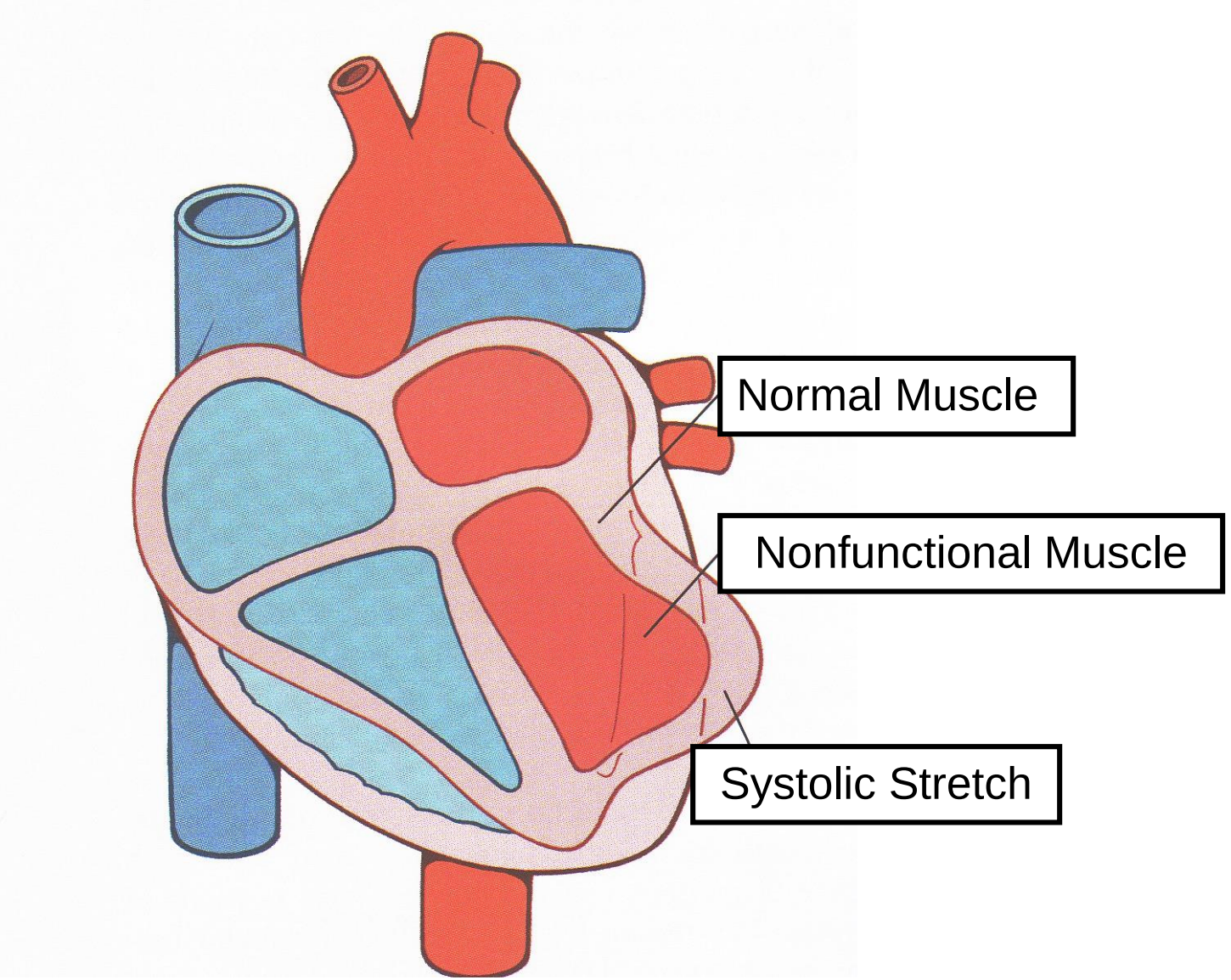
L Sherwood 2004 p 336

What is the Ultimate Cause of Death?

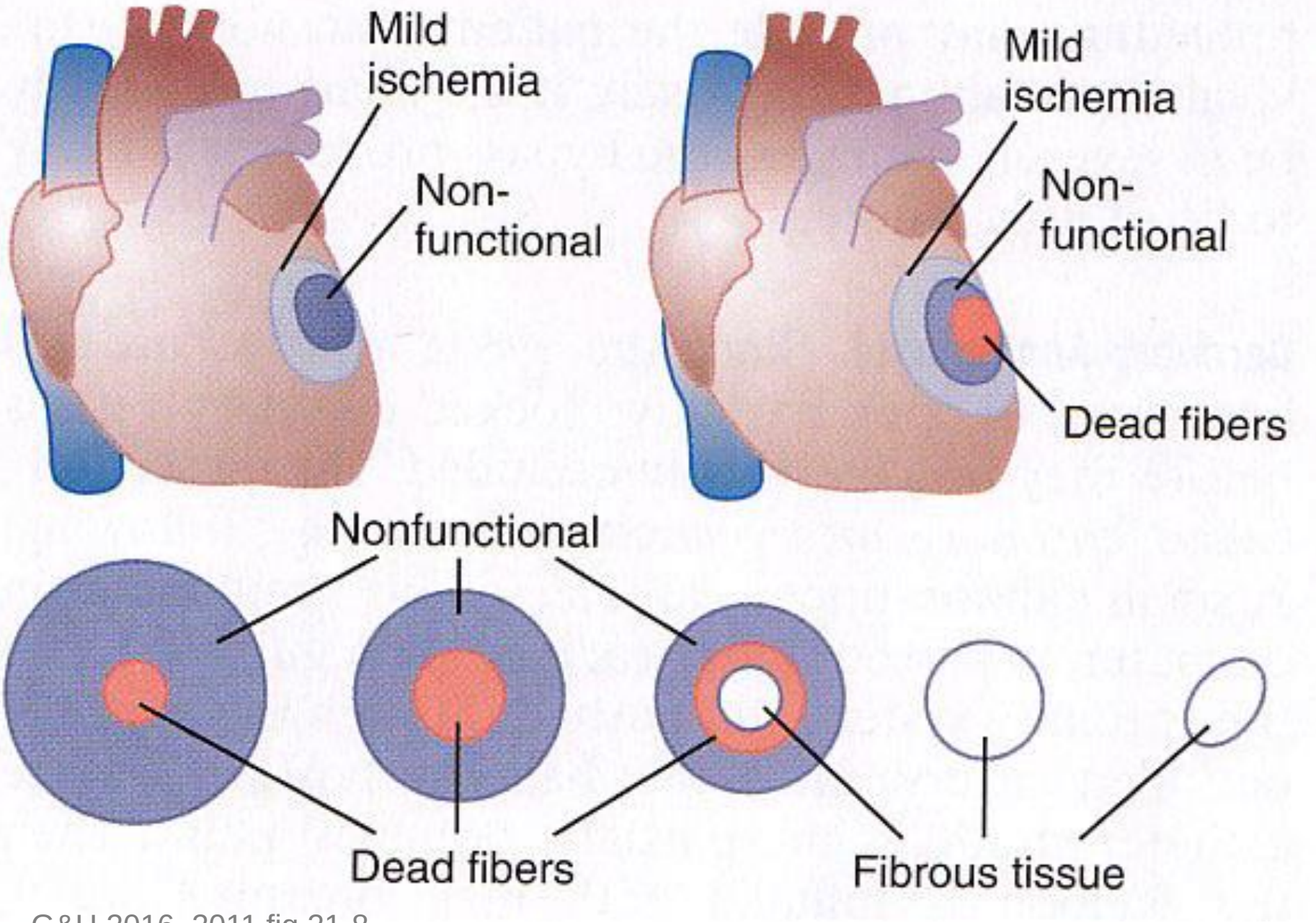
1. ↓ $\dot{Q}$, **CO** or Cardiac Output
2. **Pulmonary damming** w/edema
3. **Cardiac fibrillation**
4. **Cardiac rupture** (occasionally)
5. Thromboembolism
   (2011 ed. but not 2016)

G&H 2016 p 266
G&H 2011 p 250

Systolic Stretch Due to Necrotic Tissue



G&H 2016, 2011 fig 21-7

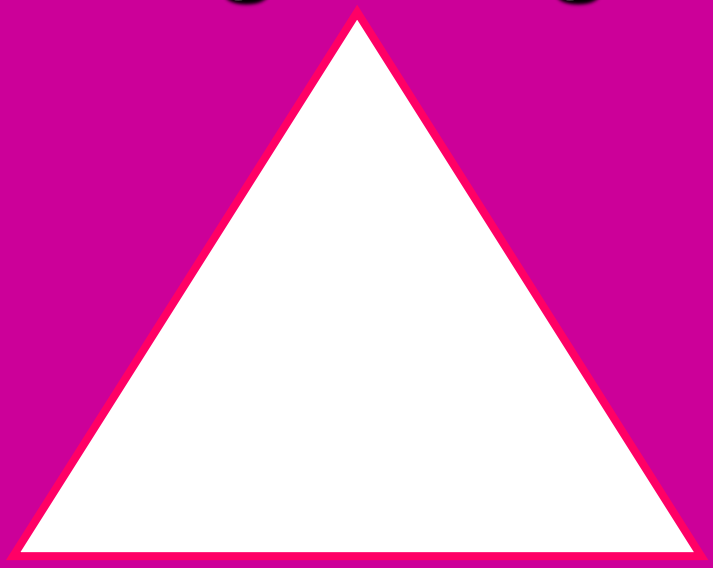


G&H 2016, 2011 fig 21-8

Treatment Triad

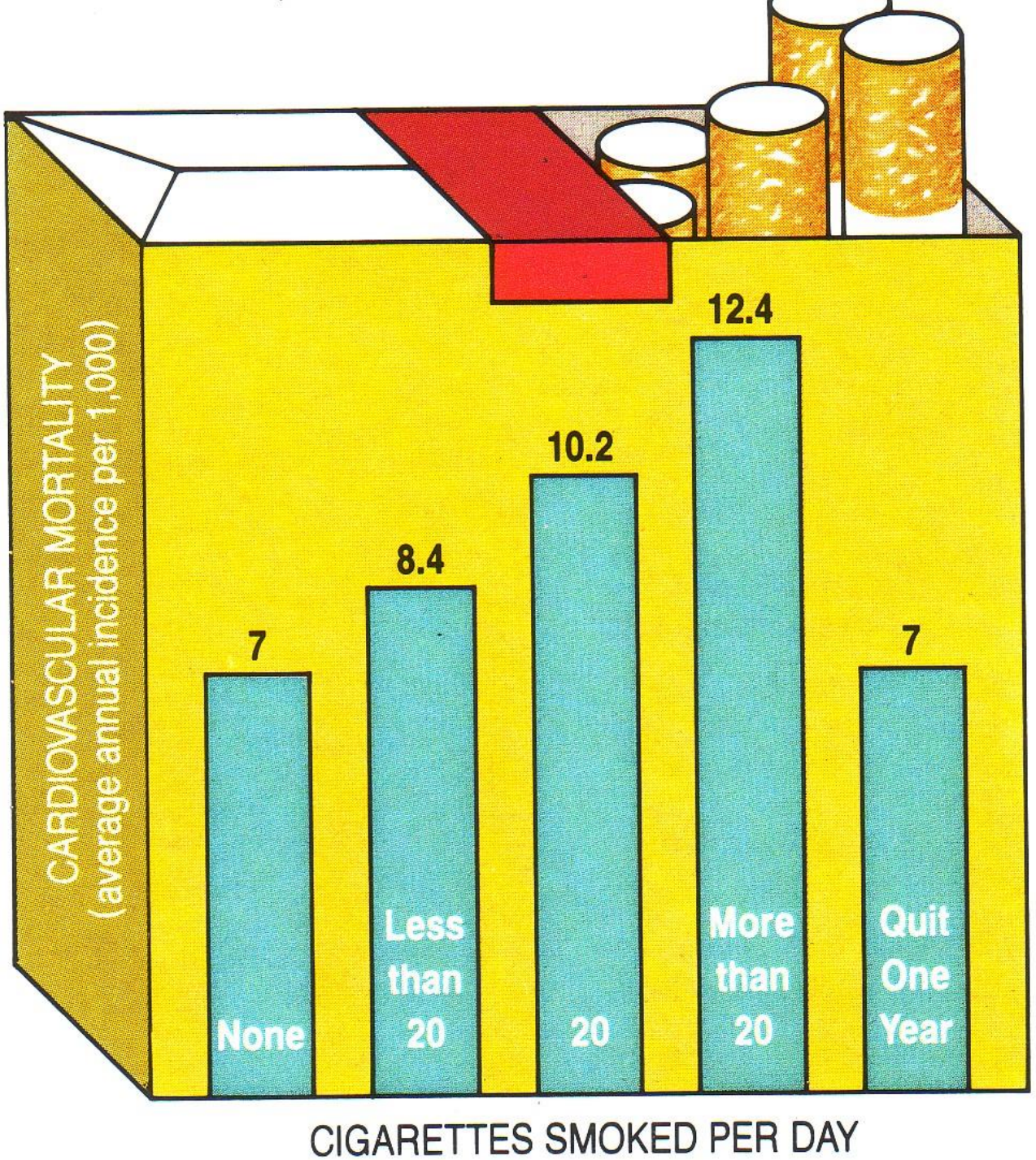
NB: Last blasted resort!!

Drugs/Surgery



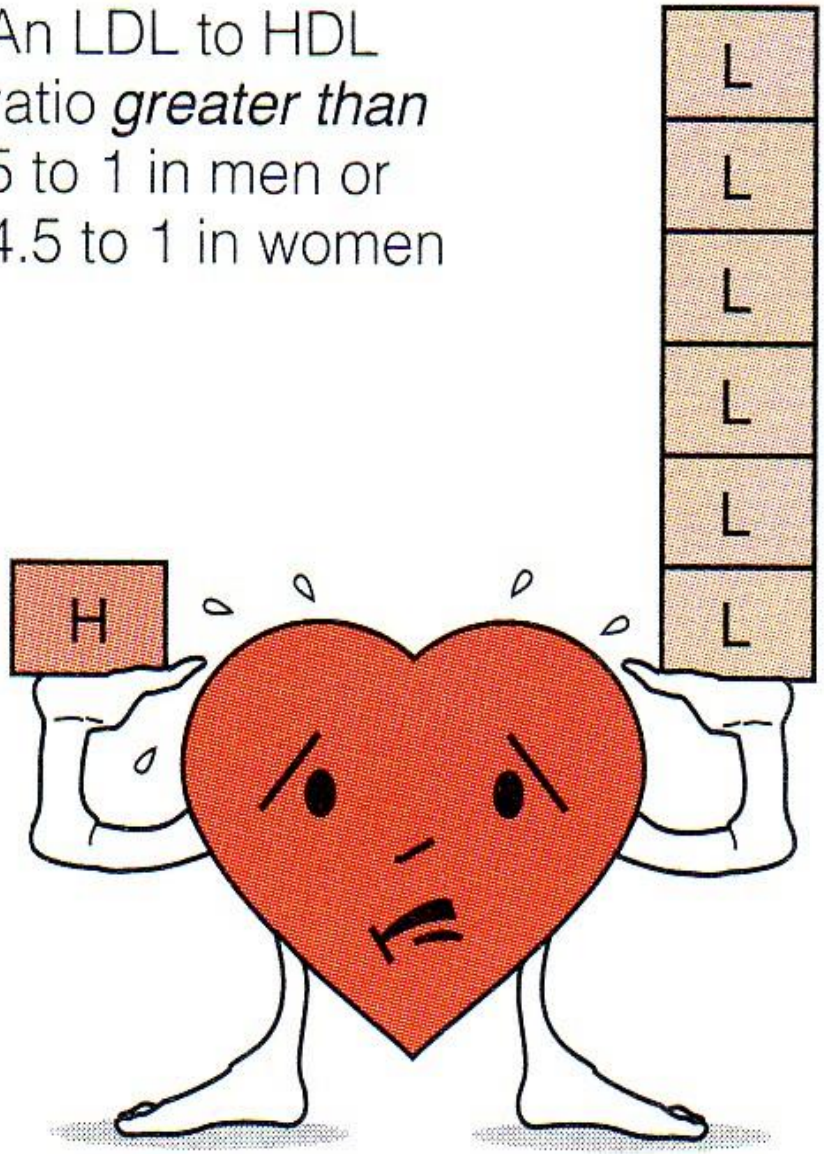
Exercise

Dietary Modification


CARDIOVASCULAR MORTALITY
(average annual incidence per 1,000)
7
8.4
10.2
12.4
7
None
Less than 20
20
More than 20
Quit One Year
CIGARETTES SMOKED PER DAY

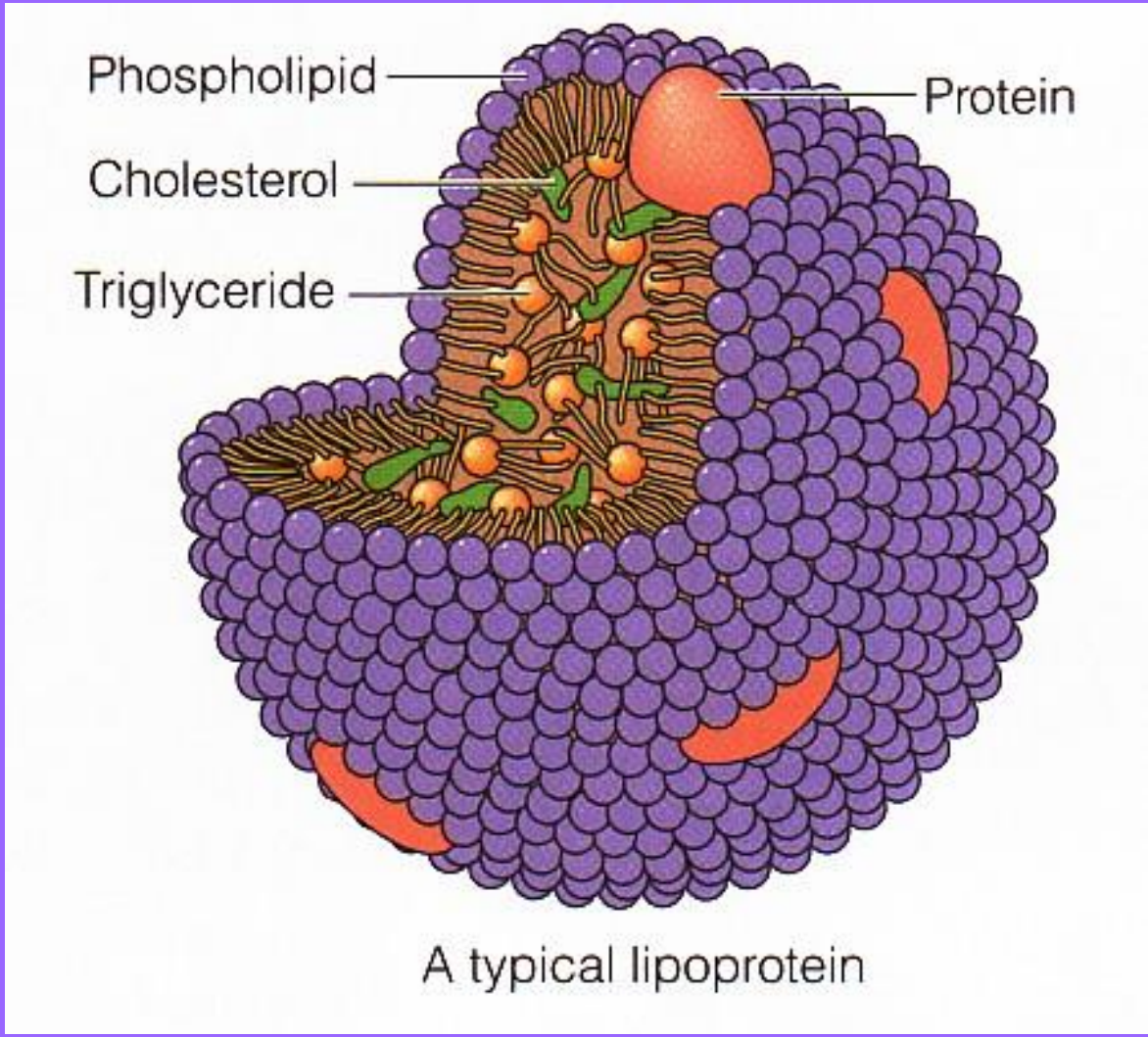

KA-BOOM!
300/200
Hg

An LDL to HDL ratio *greater than* 5 to 1 in men or 4.5 to 1 in women



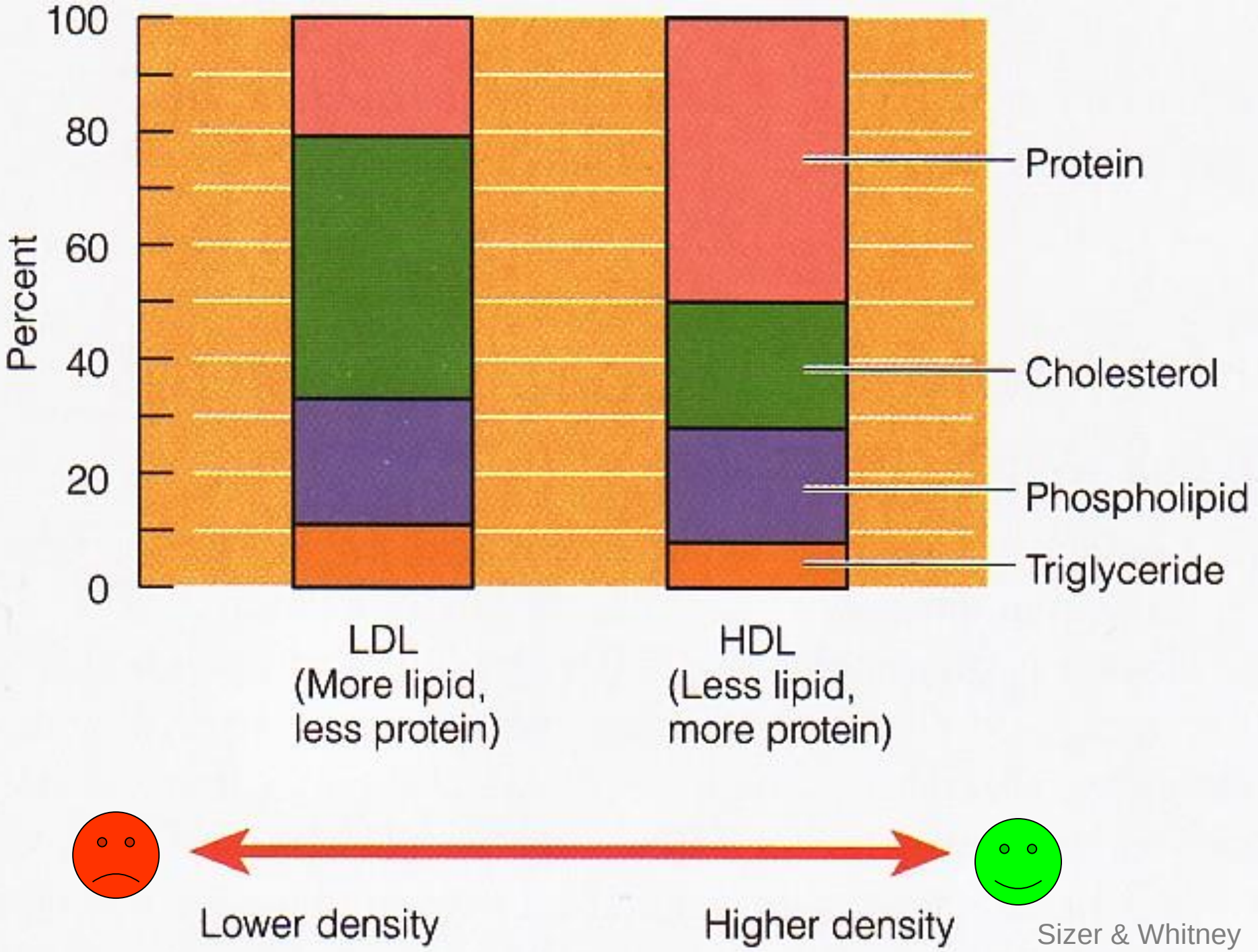
Increased risk of heart disease

Sizer & Whitney



A typical lipoprotein

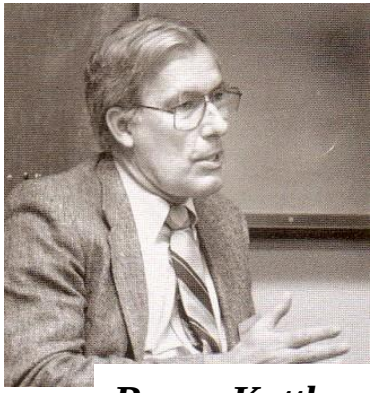
F Sizer & E Whitney (S&W) 2003 p 147 +


100
80
60
40
20
0
Percent
Protein
Cholesterol
Phospholipid
Triglyceride
LDL
(More lipid,
less protein)
HDL
(Less lipid,
more protein)
Lower density
Higher density
Sizer & Whitney

? *Selected Atherosclerotic Genetic Determinants – Ultra-short List!* ?

Genes for HDL, LDL+ receptors, Apolipoproteins Apo B-100, Apo-E, Apo-M, lipoprotein a/Lp_a, homocysteine metabolism enzymes N5,N10-methylene-tetrahydrofolate reductase, cystathione beta-synthase, Type I antithrombin, mitochondrial haplogroup A, Protein tyrosine phosphate PTPN22 C/T single nucleotide polymorphism (SNP) @ + 1858, HMG COA reductase, SNPs in TNF-alpha, IL-1beta & TGF-beta1, IL-6, IL-10, CD14, TLR-4 receptors, Human Leukocyte Antigens HLA-DRB1*01, HLA-B*07 + haplotype LTA+253a-LTA+633g-C4A3-C4B1, HDL-associated paraoxonase (PON1), lysosomal acid lipase (LAL), MEF2A protein affecting artery walls…

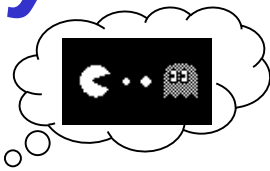
Bruce Kottke's Bathtub Analogy

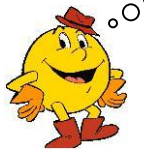


Bruce Kottke

5 forms of cholesterol:

Chylomicrons, VLDL, LDL, IDL, HDL





β

Atherogenic

Anti-Atherogenic

Biological Artifact!?

"I don't think the total cholesterol test by itself is worth a damn."
—Eliot Corday

β-VLDL

\+

= Faucet

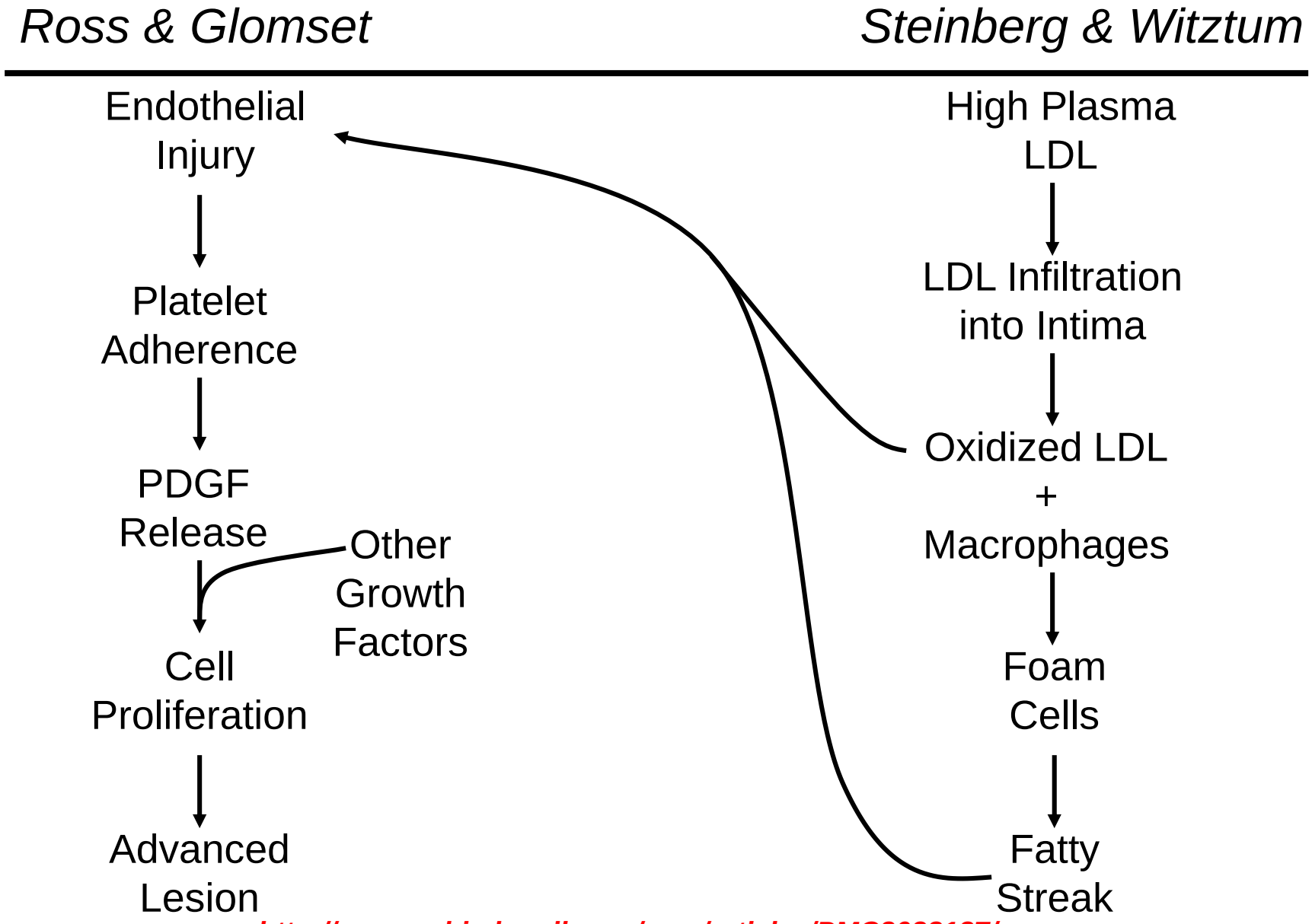
LDL

Total Cholesterol Level

HDL = Drain

Bathtub

Historical Hypotheses for Atherosclerosis Development



http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2032127/
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC295745/

How Inflammation Attacks the Heart

❶ LDL Oxidized

Oxidized LDL cholesterol creates the "injury" by burrowing into the artery wall. Cigarette smoking, high blood pressure, and high blood sugar make the injury worse.

❷ Monocytes Migrate

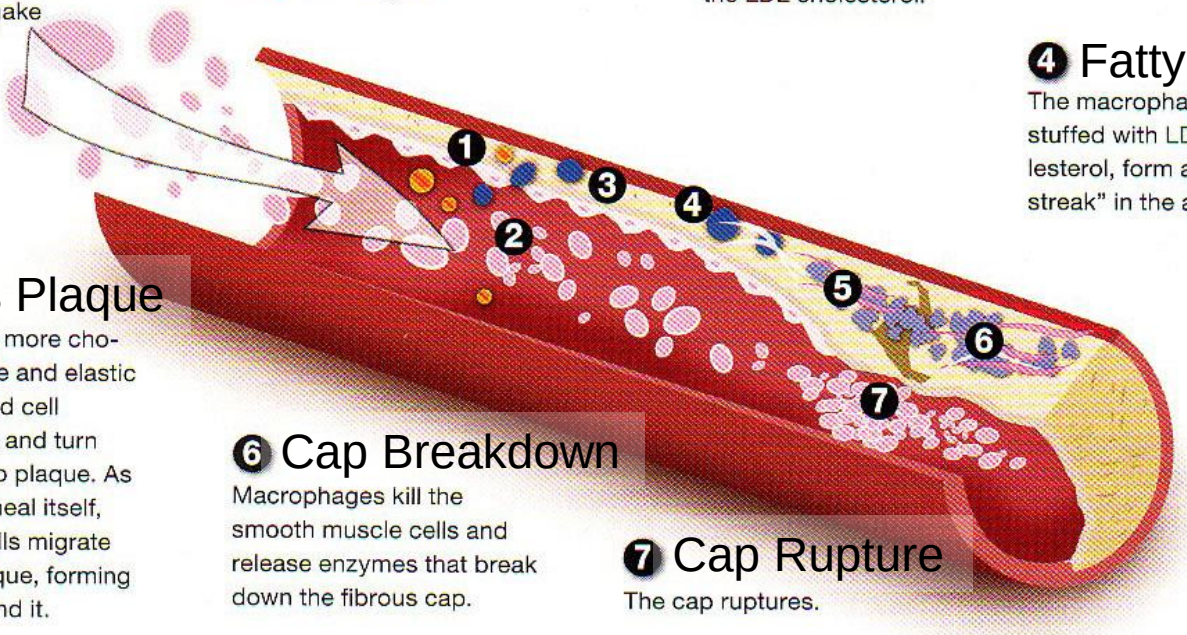
In response to the injury, the immune system sends in a team of inflammatory cells, including white blood cells called monocytes.

❸ Monocytes → Macrophages

Monocytes migrate into the artery wall, where they turn into macrophages. The macrophages' job: gobble up the LDL cholesterol.

❹ Fatty Streak

The macrophages, now stuffed with LDL cholesterol, form a "fatty streak" in the artery wall.



❺ Fibrous Plaque

Over the decades, more cholesterol, connective and elastic tissue, calcium, and cell debris accumulate and turn the fatty streak into plaque. As the artery tries to heal itself, smooth muscle cells migrate in to cover the plaque, forming a fibrous cap around it.

❻ Cap Breakdown

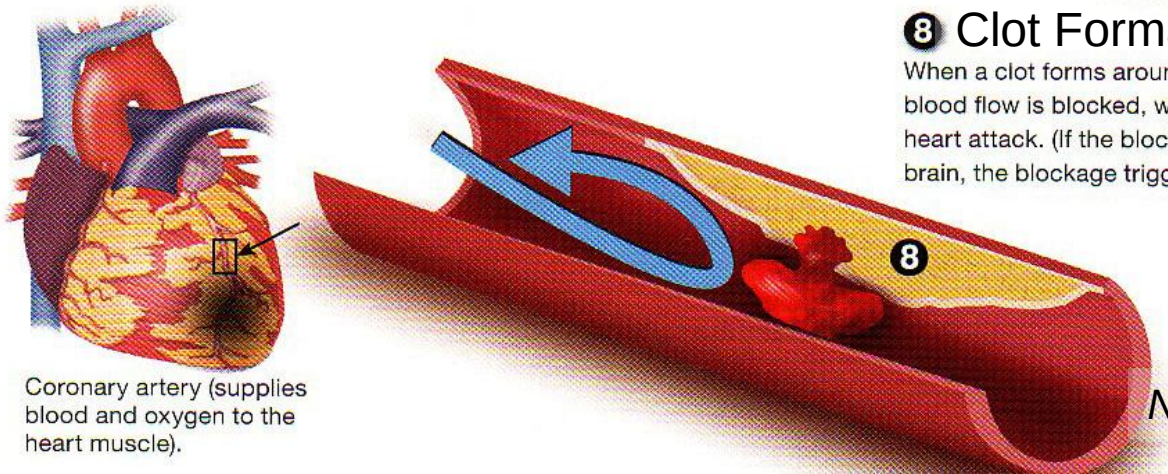
Macrophages kill the smooth muscle cells and release enzymes that break down the fibrous cap.

❼ Cap Rupture

The cap ruptures.

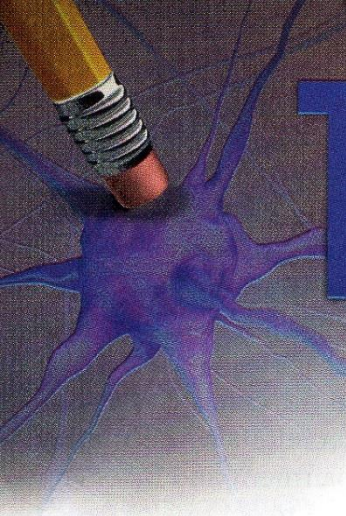
❽ Clot Formation

When a clot forms around the rupture, blood flow is blocked, which triggers a heart attack. (If the blocked artery feeds the brain, the blockage triggers a stroke.)



Coronary artery (supplies blood and oxygen to the heart muscle).

NAHL Jan/Feb 2009, p 5



TROUBLE AHEAD?

HOW TO KEEP YOUR BRAIN SHARP

So far, no one has found a magic bullet to stop Alzheimer's disease, which gums up the brain with protein clumps and tangles. But it's not just clumps and tangles.

Damage to the brain's blood vessels—often due to high blood pressure, smoking, or diabetes—can also play a role, not just in dementia but in milder memory loss as well.

Here's how to keep a clear head for as long as possible.

Brain Basics

Plaques and tangles. Those are the classic hallmarks of Alzheimer's disease.

The plaques are clumps of a protein fragment called beta-amyloid. The tangles are clusters of misshapen "tau" proteins that show up later in the disease.

But plaques and tangles alone don't explain what happens to many aging brains.

"Thirty percent of people over the age of 70 have elevated beta-amyloid and are cognitively normal," says David Knopman, professor of neurology at the Mayo Clinic in Minnesota.

Scientists aren't sure why.

"The most prevalent idea is that amyloid deposits are only the initiating step

often assume that it's just Alzheimer's," notes Reed. "But it's uncommon to find people with dementia who just have a single pathology. Very often, it's mixed pathology."

The most common other problem: damaged blood vessels in the brain.[1,2]

"The arteries become stiffened, narrowed, and sort of tortuous," says Reed. "It's much harder for the blood flow to occur normally."

That can lead to a stroke that's obvious, or to one that's never noticed. "Around

"In fact, some of the symptoms we think of as normal brain aging may be due to injury to the brain's blood vessels," he notes.

Researchers know the major threats. "The big risks for vascular brain injury are smoking, high blood pressure, and diabetes," says Reed.

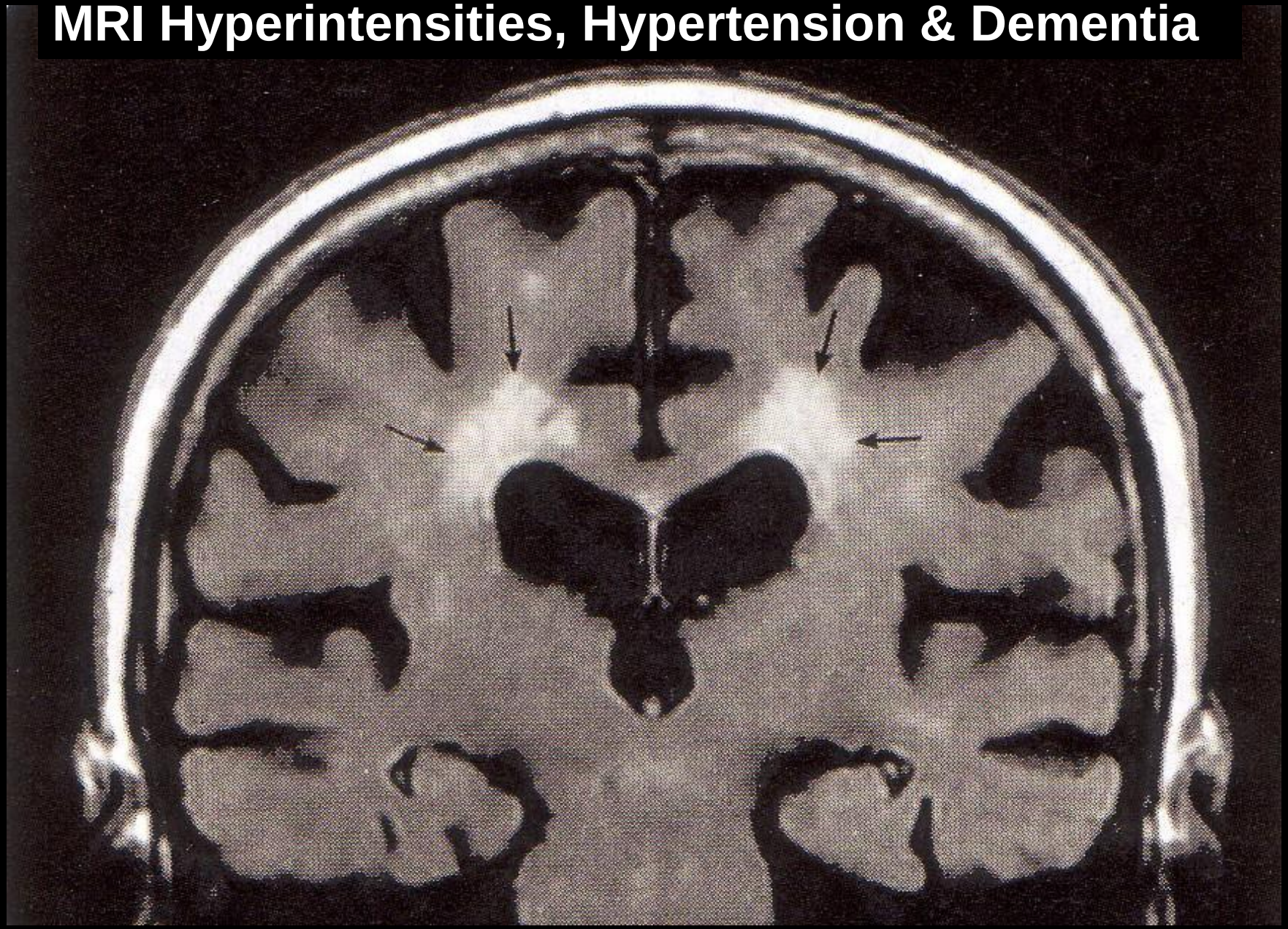
The causes of Alzheimer's pathology are more murky. But new evidence suggests that insulin may play a role.

Here's how to keep your brain in good working order.

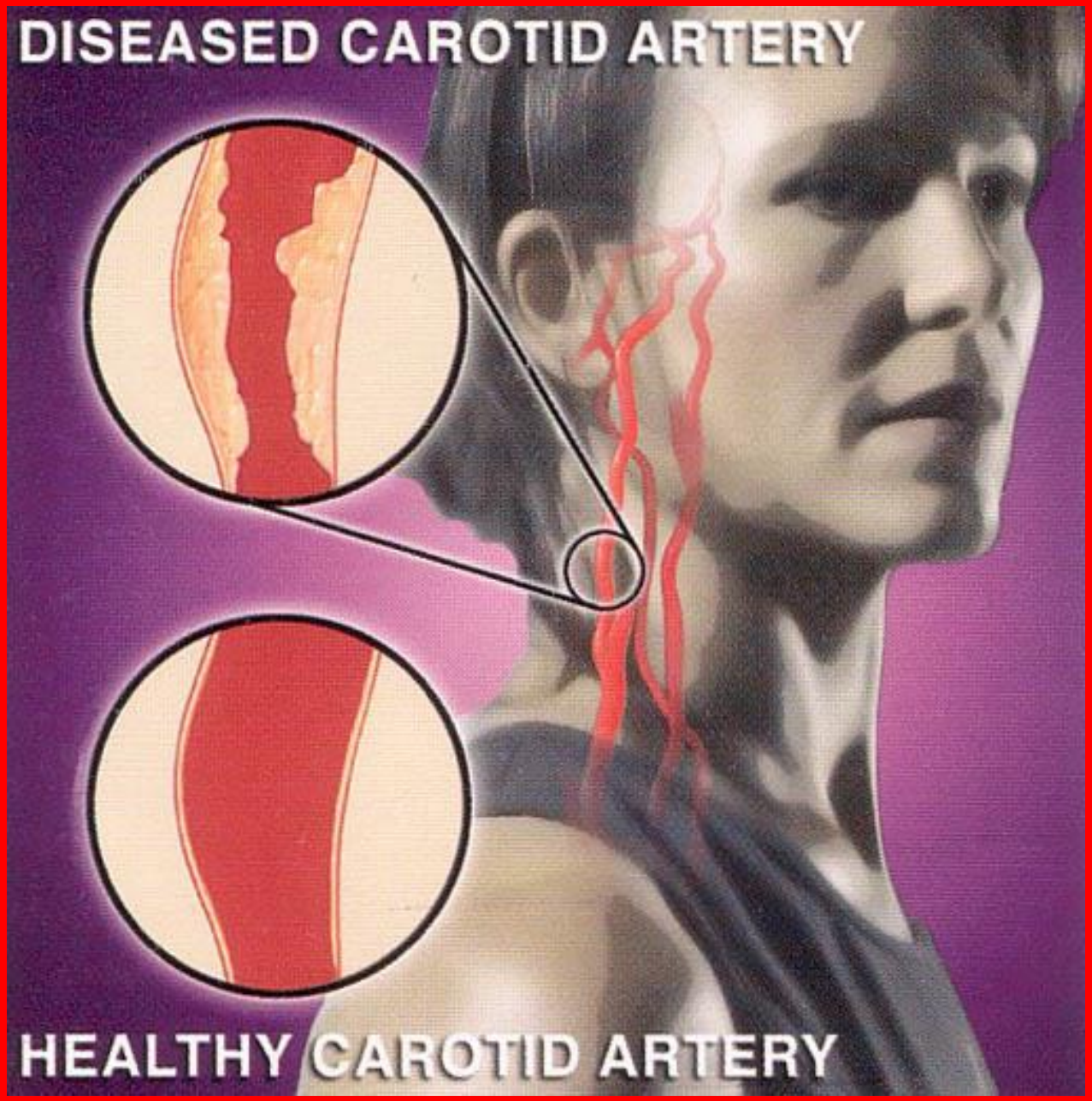
1. Watch your blood pressure

"There's a wealth of evidence that high blood pressure is a risk factor for late-life cognitive impairment," says Knopman.

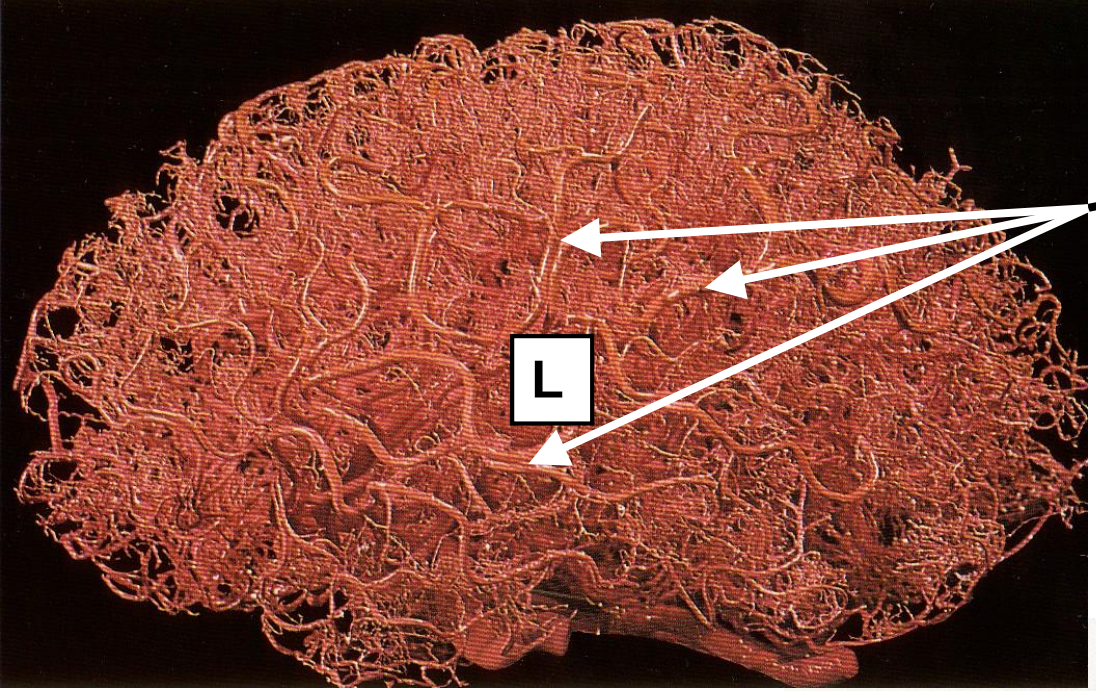
MRI Hyperintensities, Hypertension & Dementia



NAHL CSPI, Jan-Feb 2014

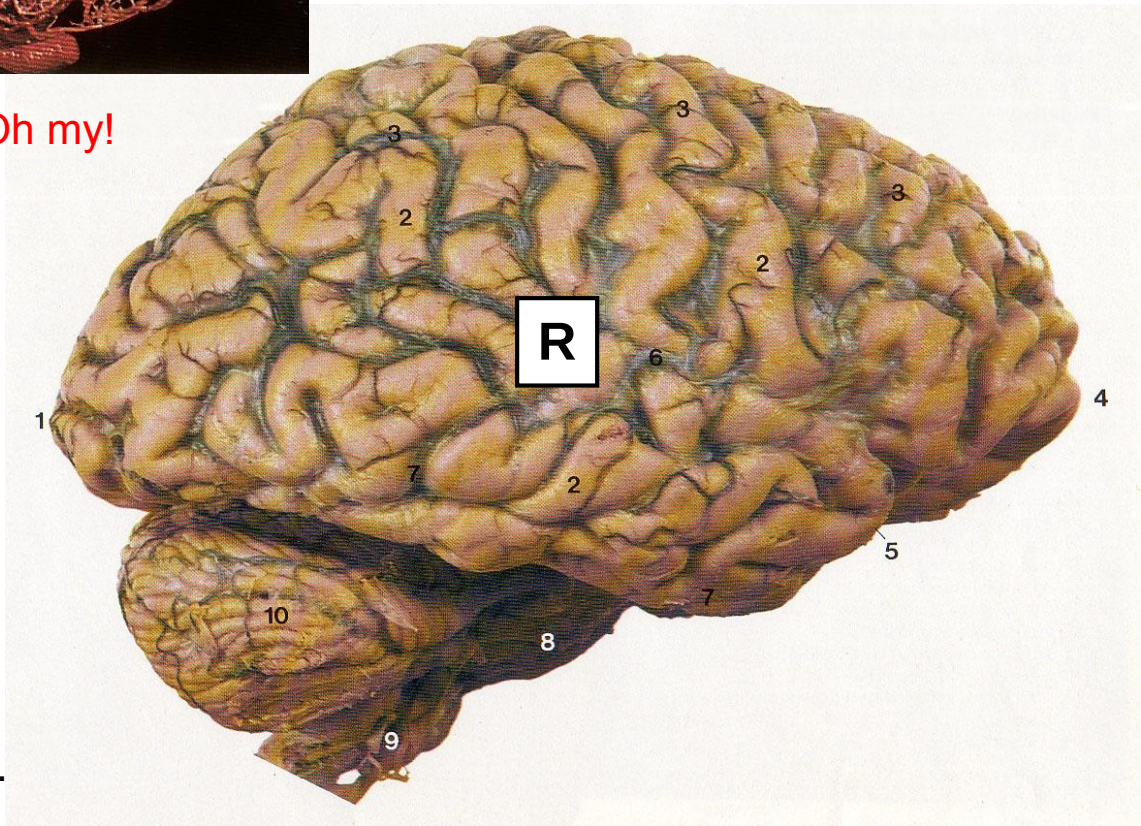


SOURCE: Lifeline Screening, 2007

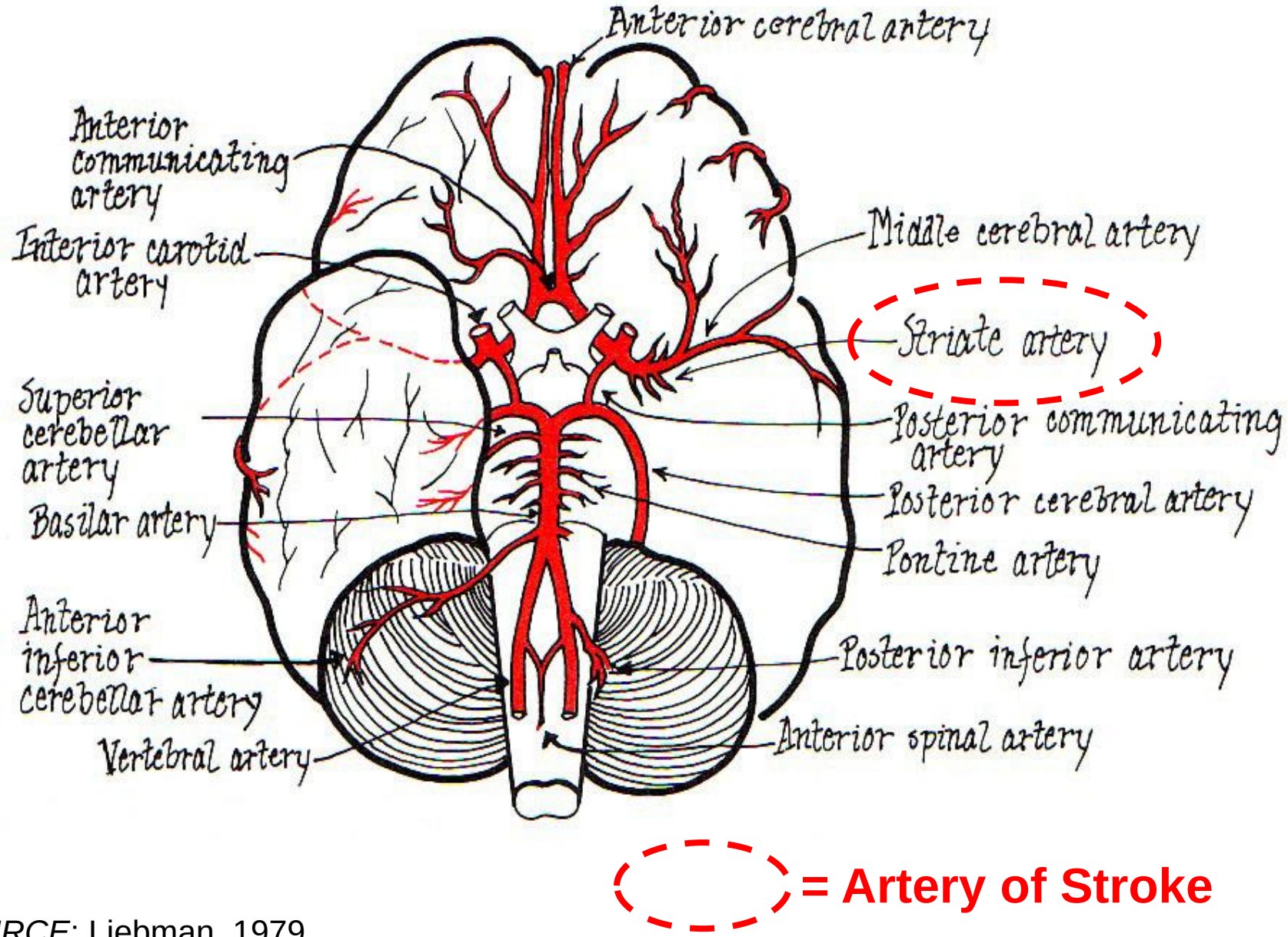


Middle Cerebral Artery Branches

…Cerebral vasculature! Oh my!

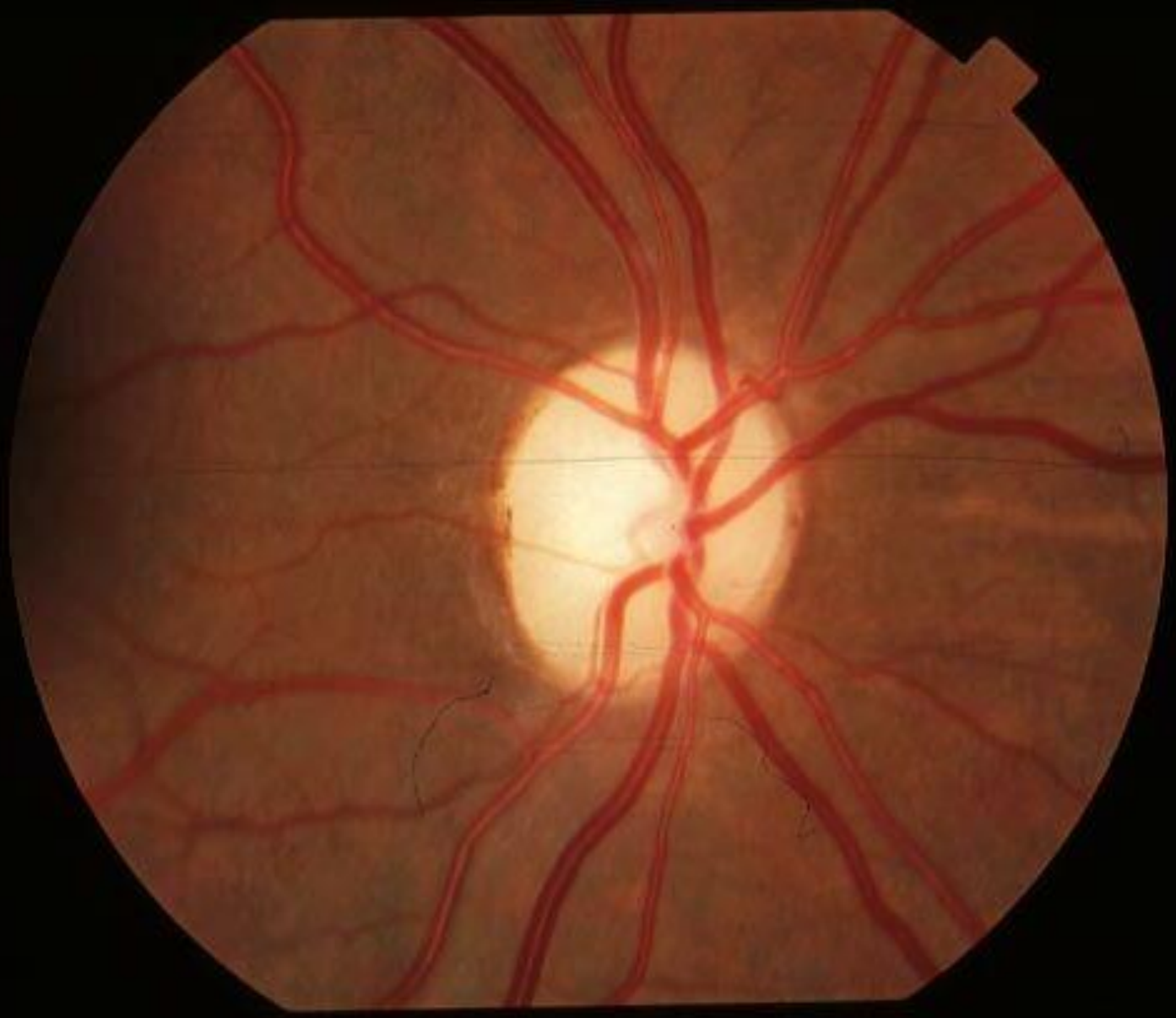


SOURCE: McMinn & Hutchins, 1977.

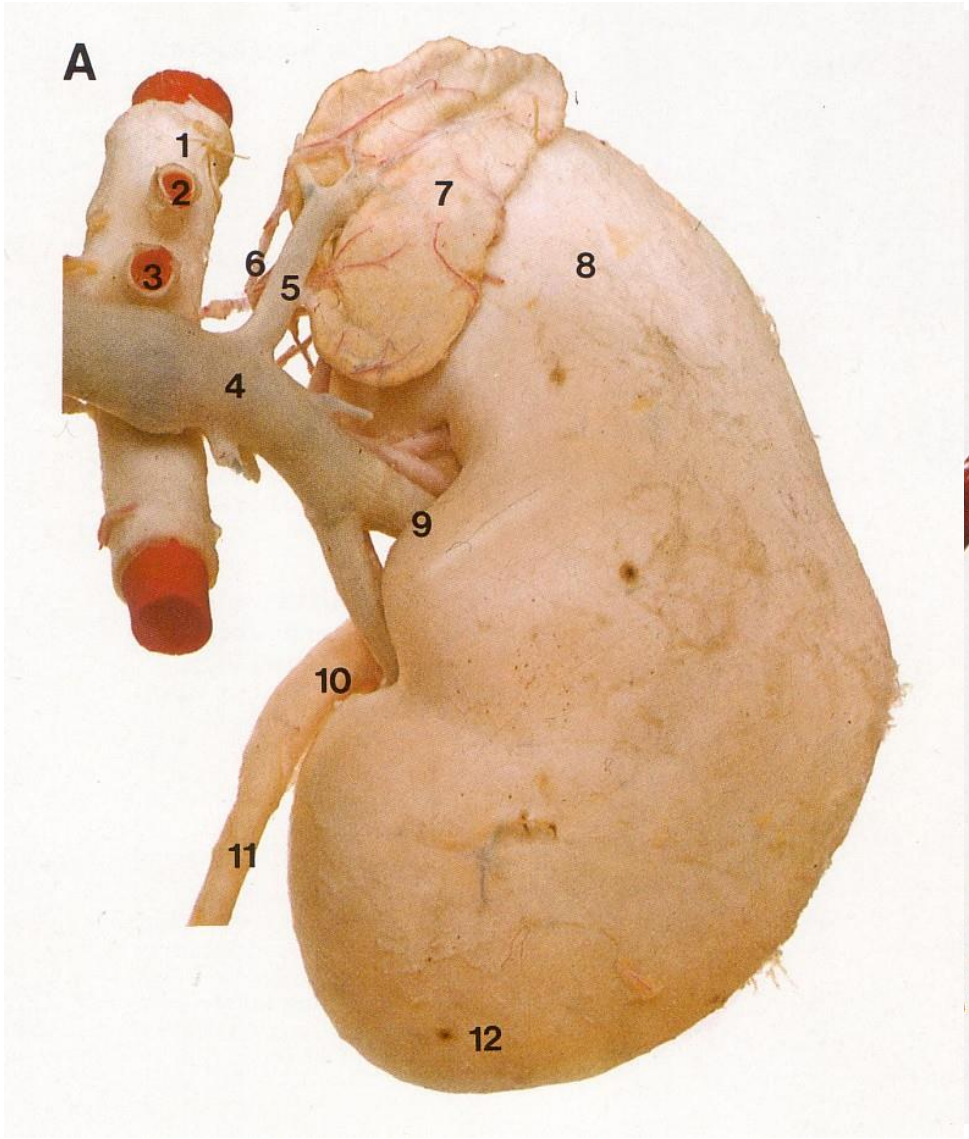


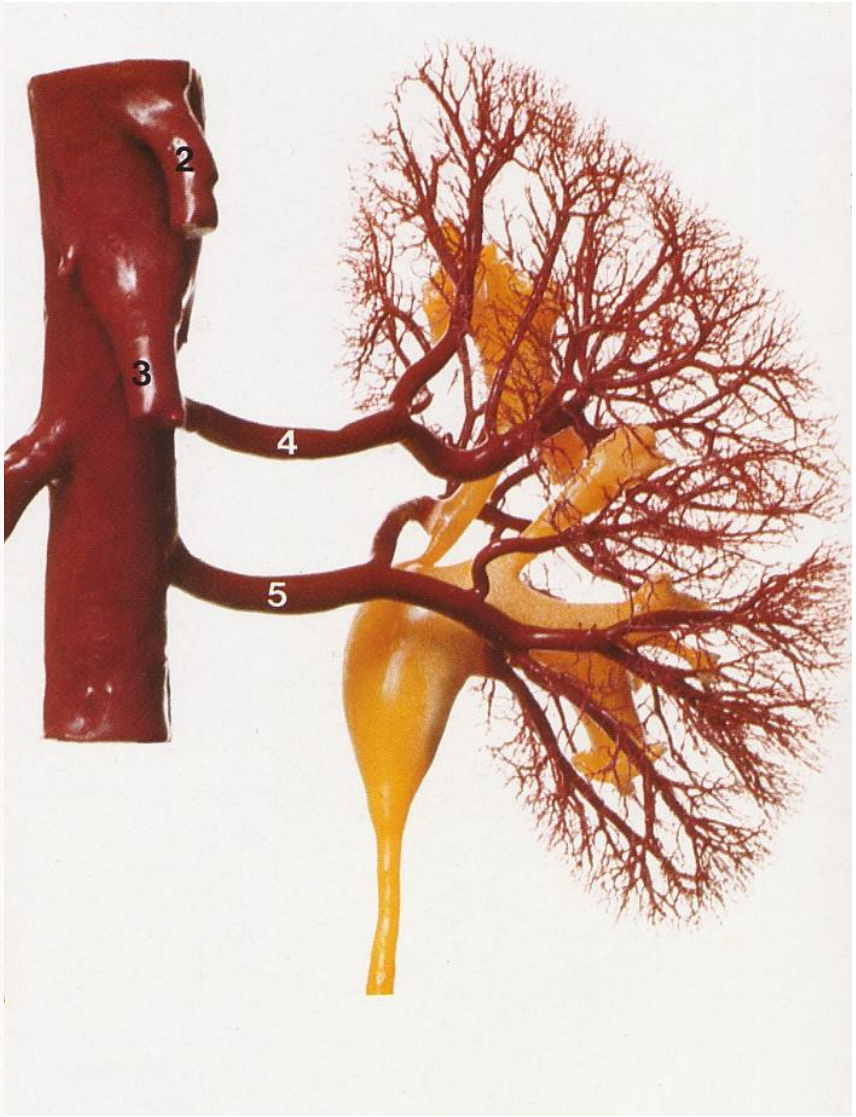
SOURCE: Liebman, 1979.

The Window to the CV System?



Renal Vasculature





SOURCE: McMinn & Hutchins, 1977.

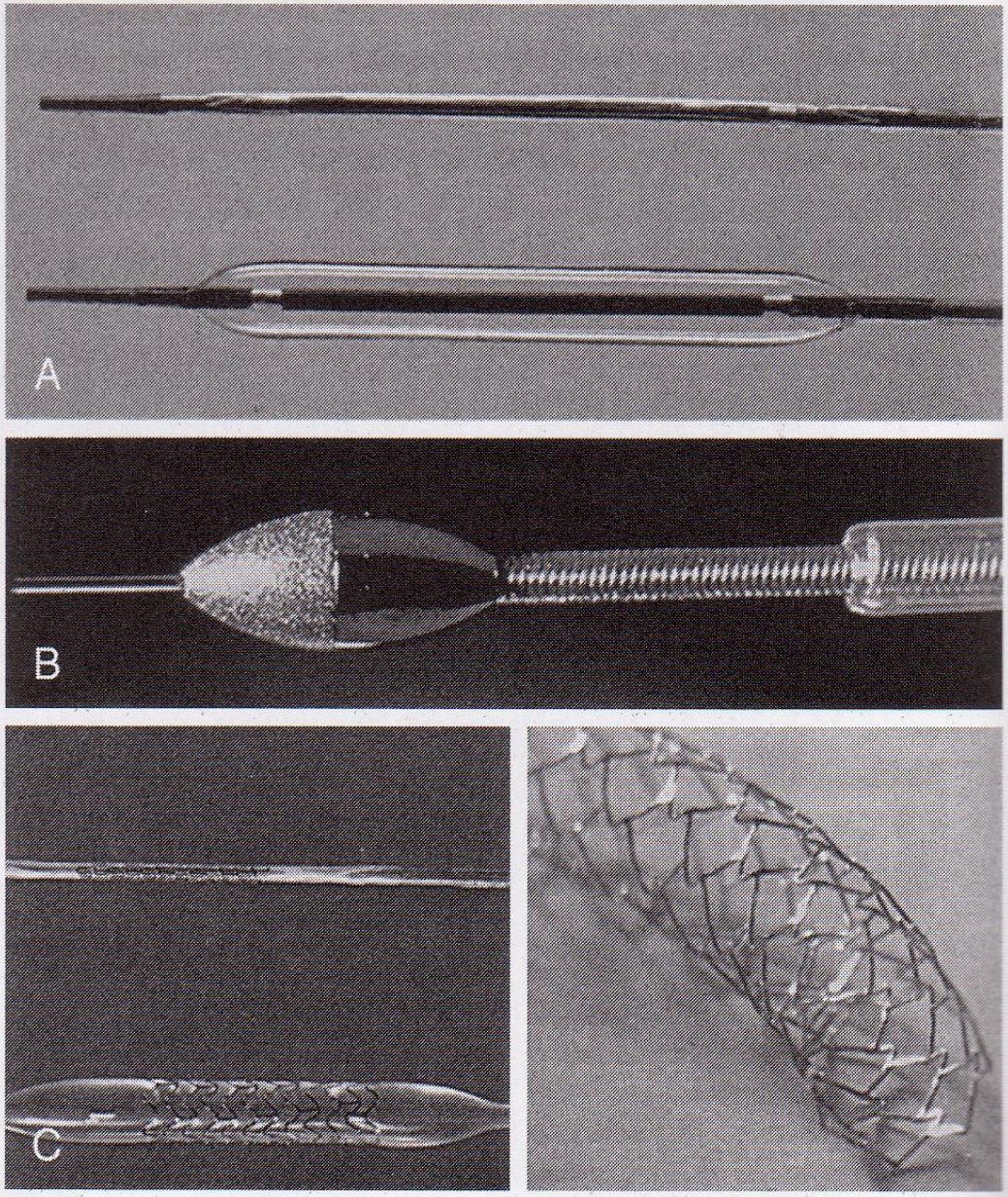
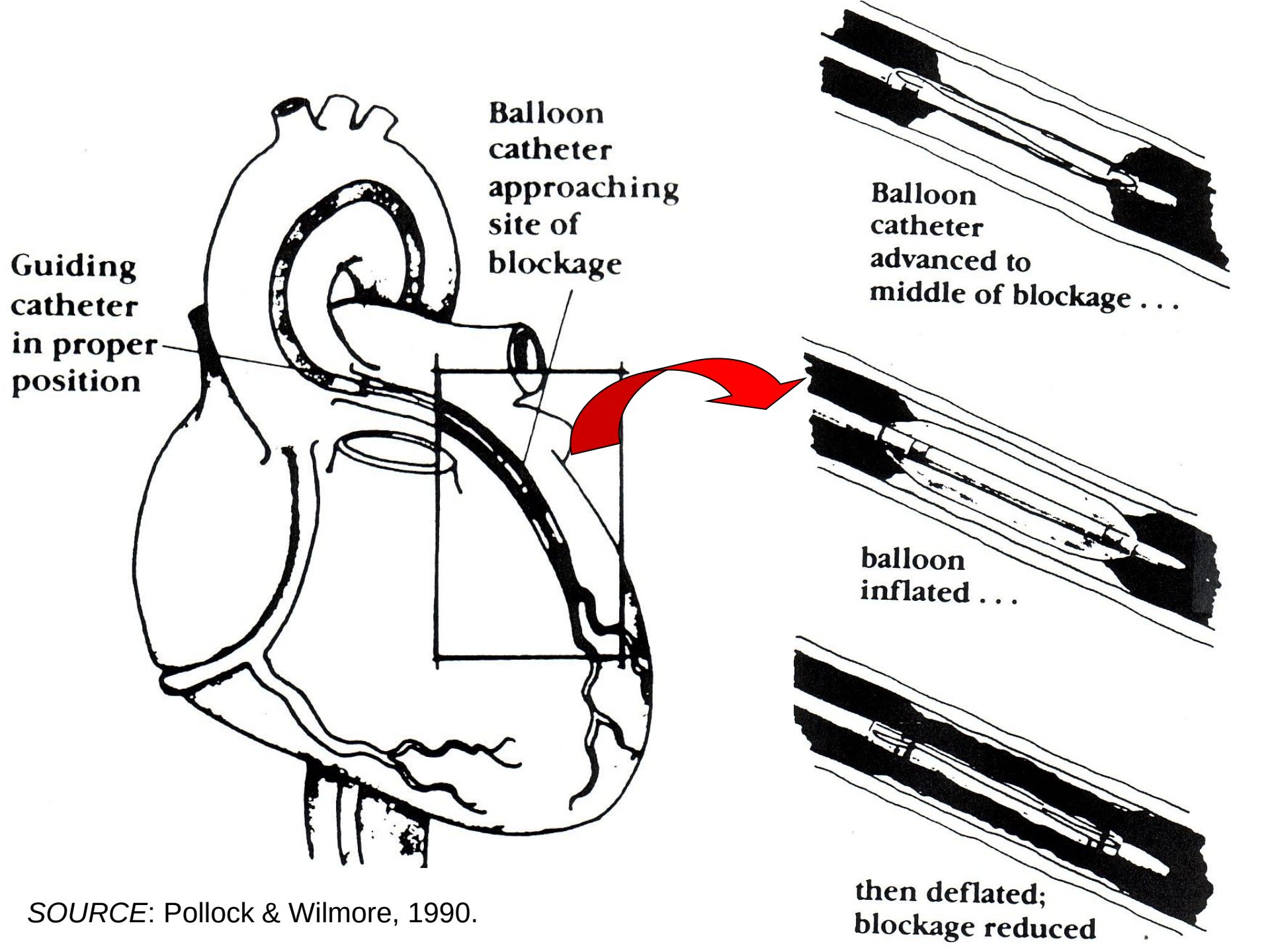
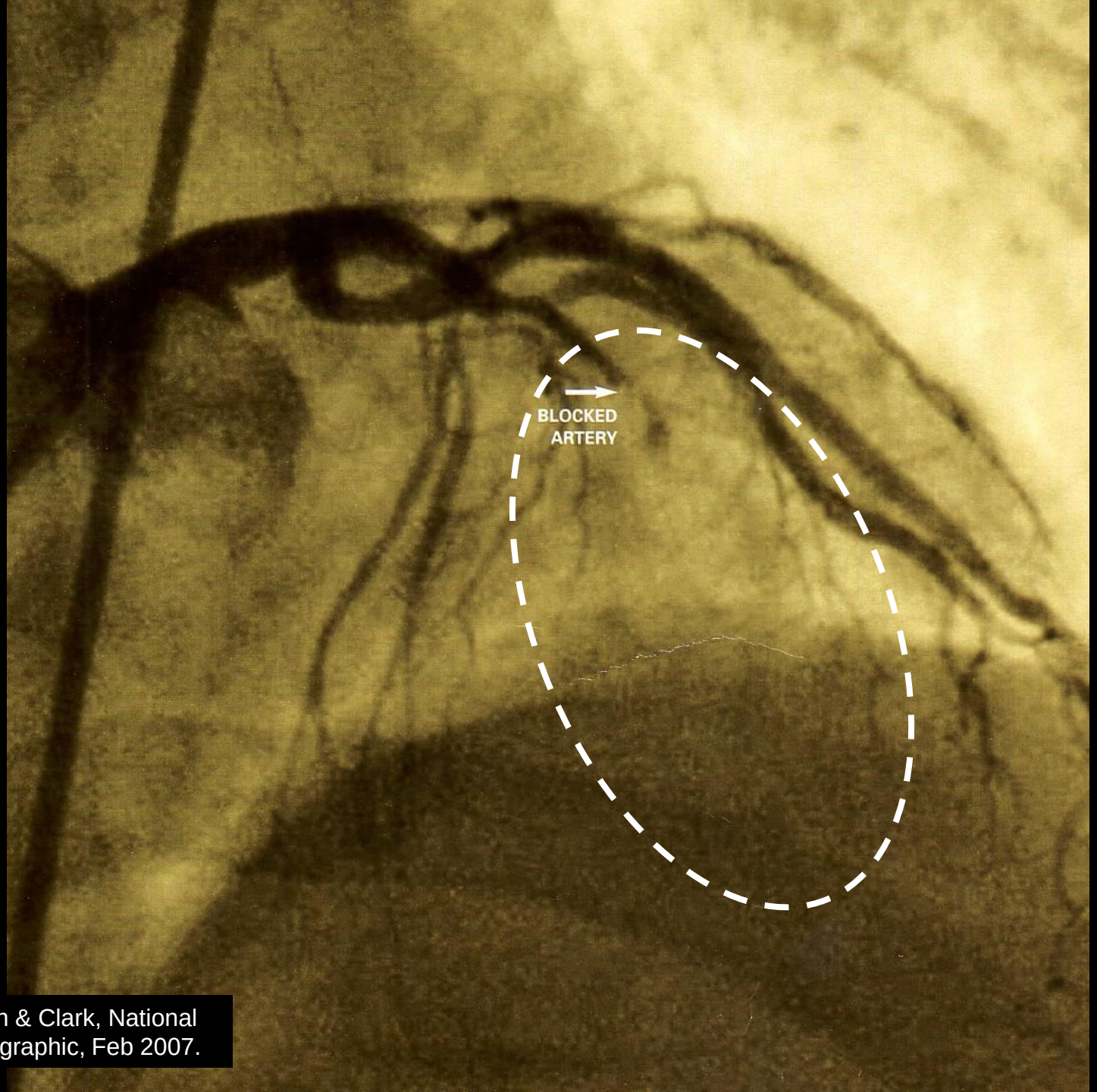


FIGURE 37–1 Devices for percutaneous transluminal coronary interventions. **A,** Coronary balloon. **B,** Rotational atherectomy burr (Rotablator). **C,** Coronary stent.

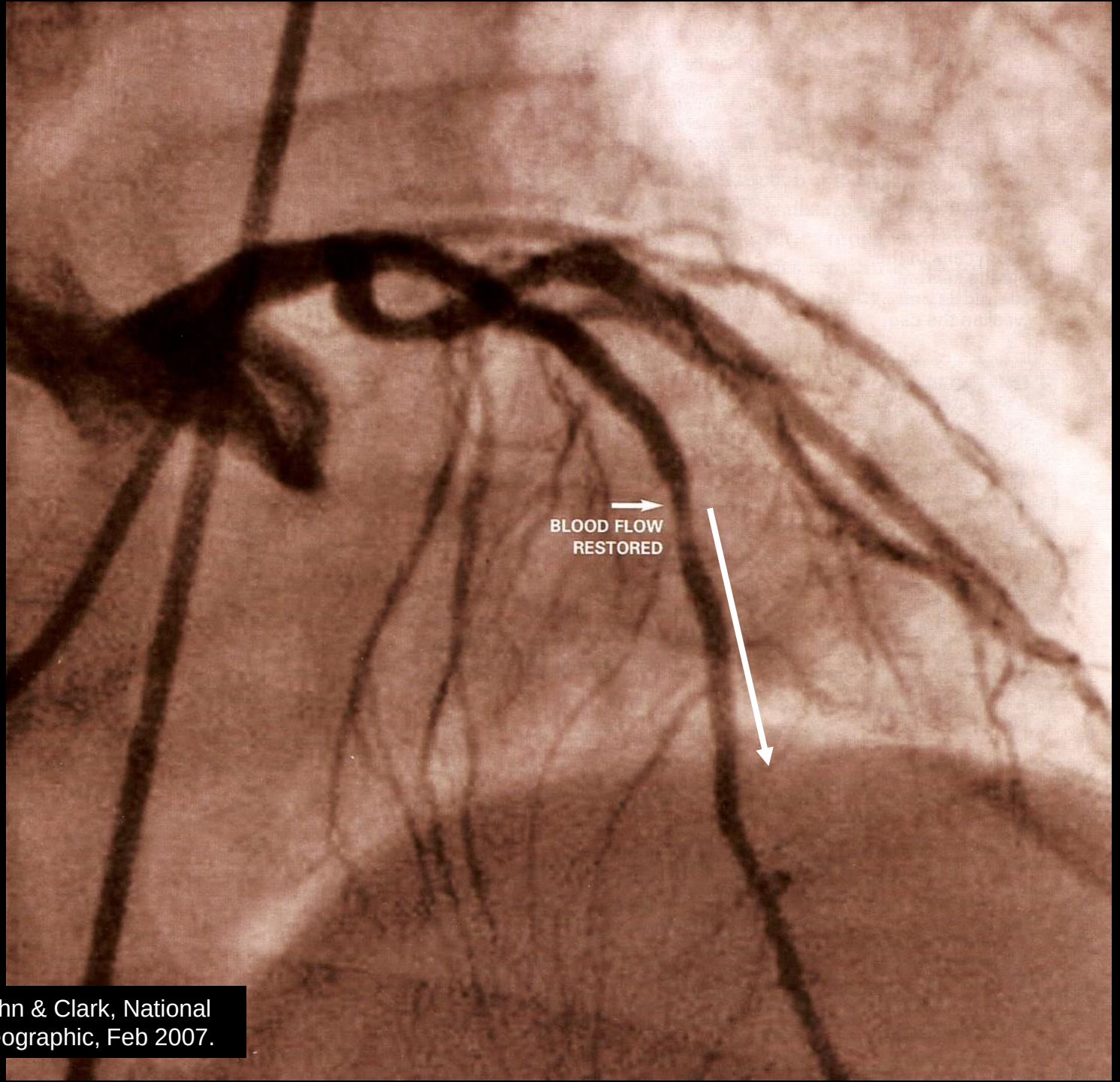
SOURCE: Willerson & Cohn, 2000.



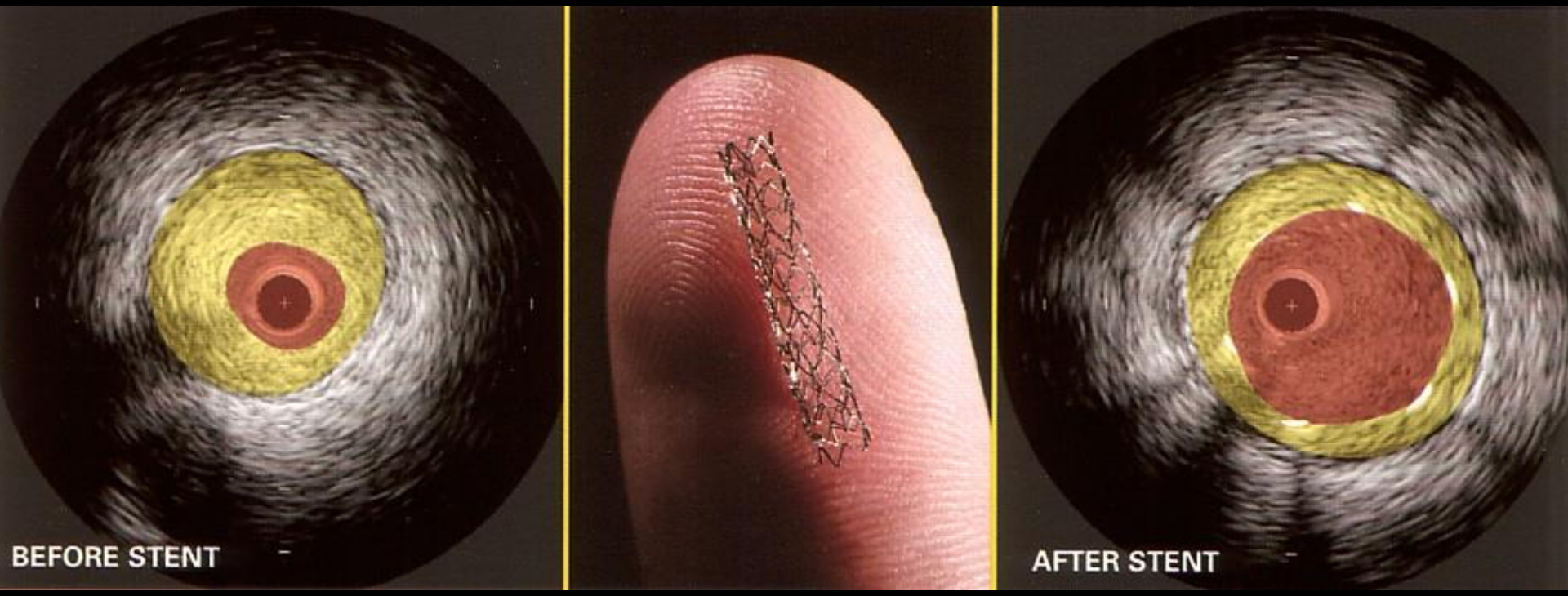
SOURCE: Pollock & Wilmore, 1990.



SOURCE: Kahn & Clark, National Geographic, Feb 2007.

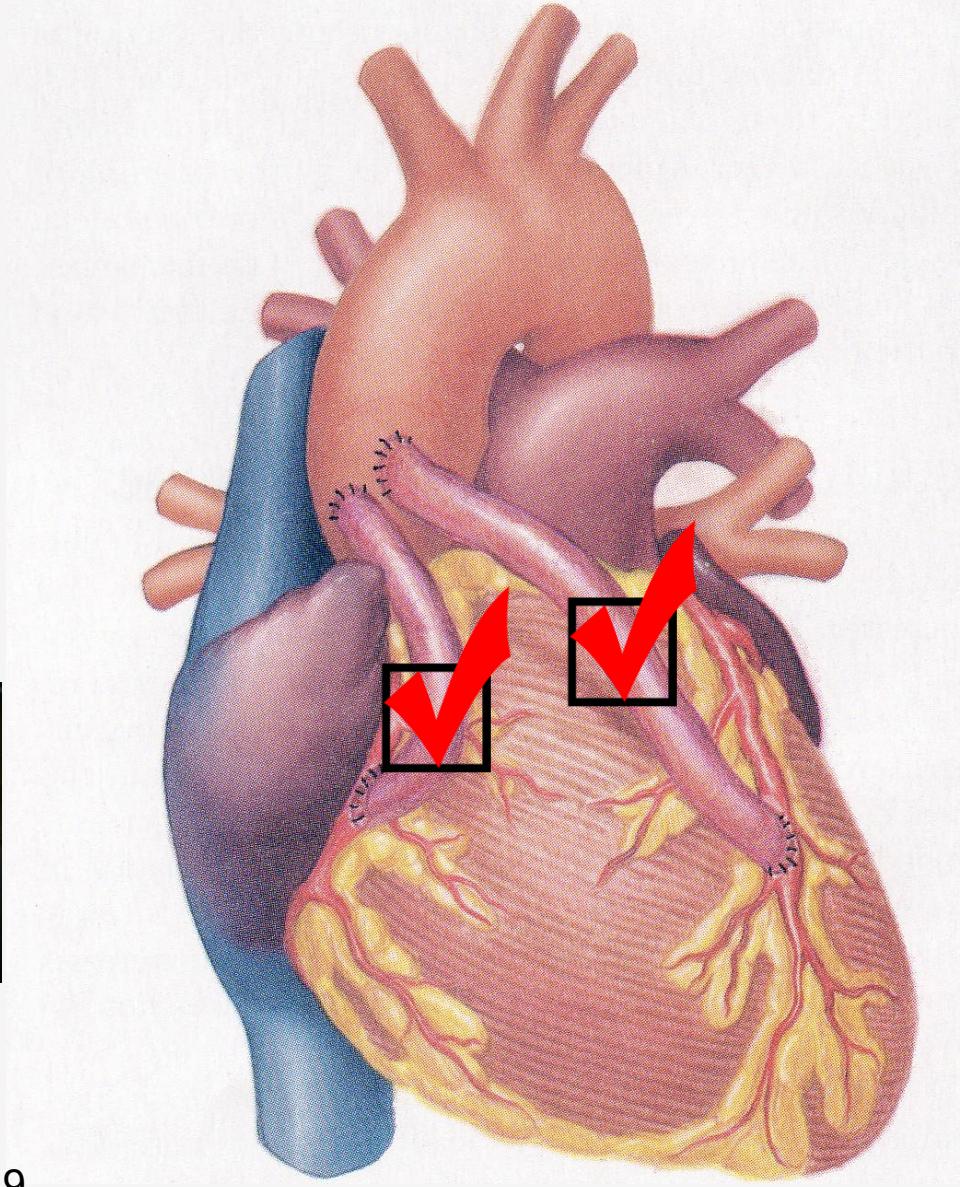


SOURCE: Kahn & Clark, National Geographic, Feb 2007.



SOURCE: Kahn & Clark, National Geographic, Feb 2007.

CABG = Coronary Artery Bypass Graft



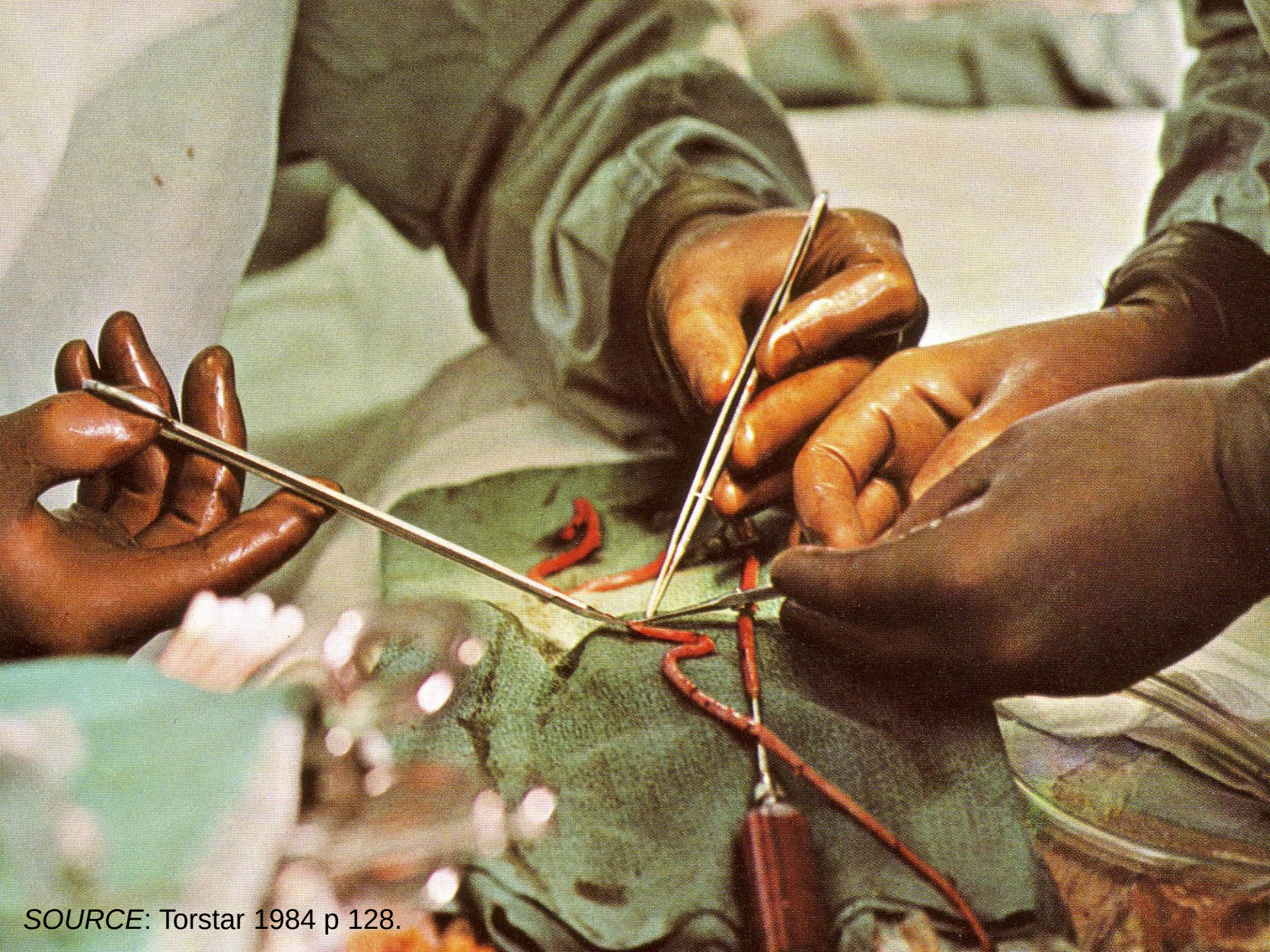
Double?

Triple?

Quadruple?

Quintuple?

SI Fox 2013 fig 14.19



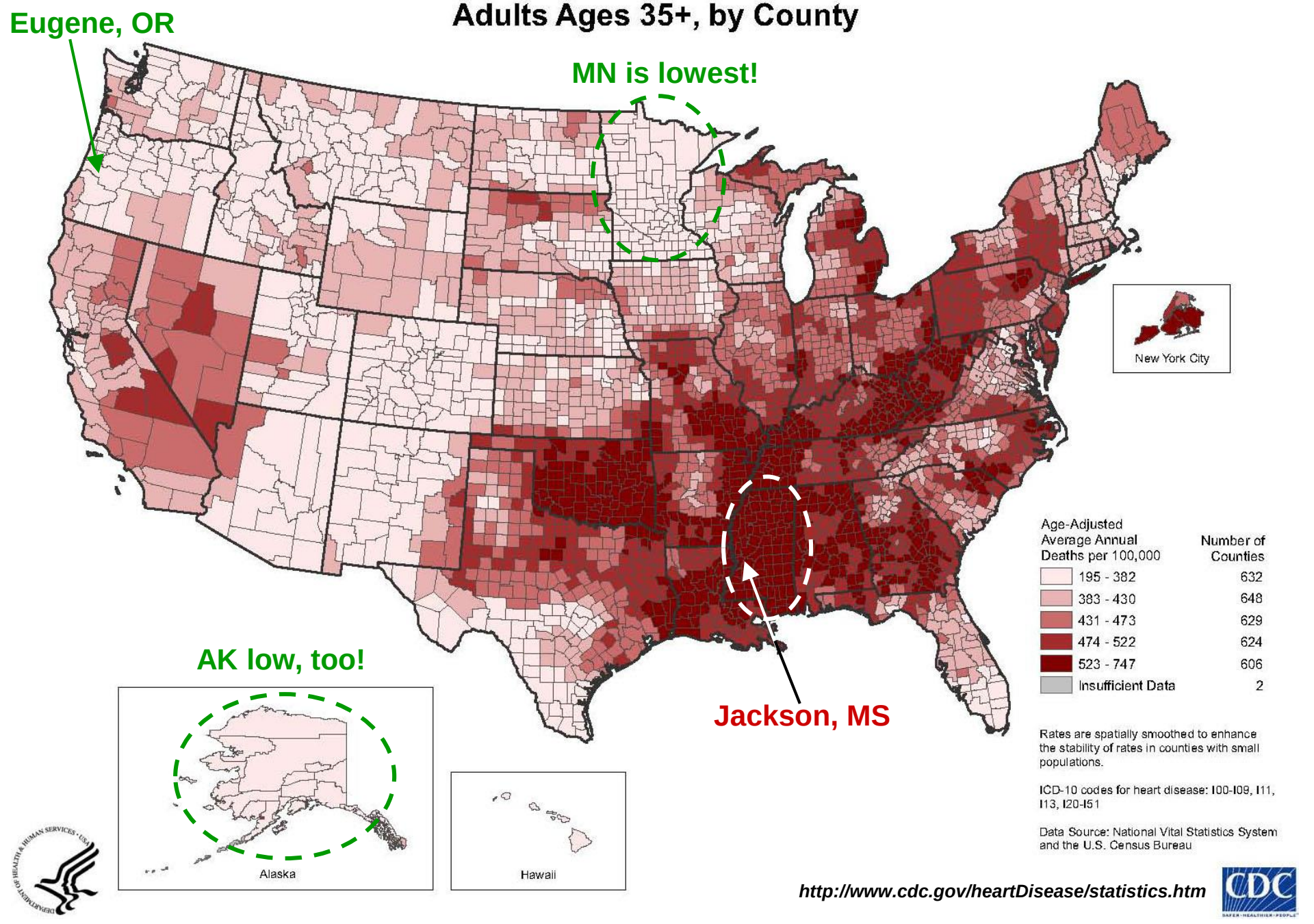
SOURCE: Torstar 1984 p 128.

Did you know?

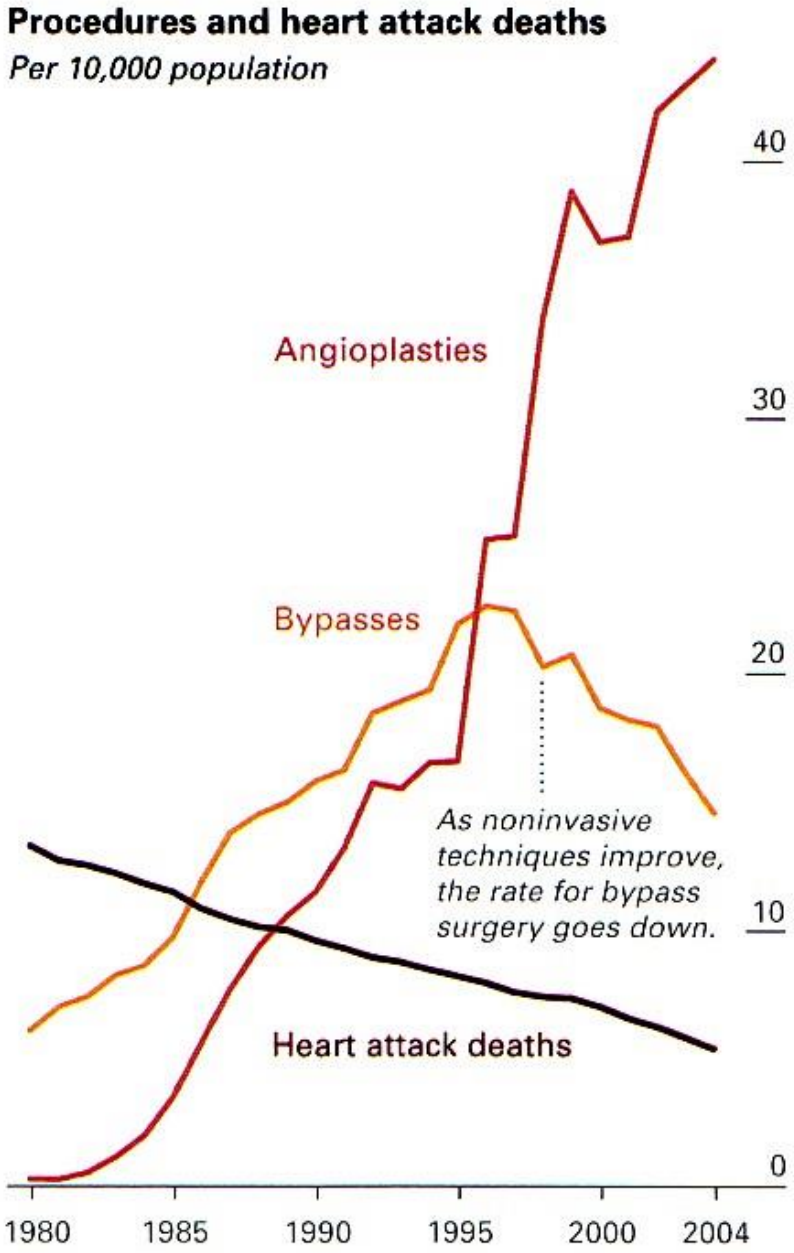
- **Every year ~785,000 Americans have a first heart attack. Another 470,000 who've had ≥ 1 have another attack.**
- **In 2008, > 616,000 people died of heart disease. Heart disease caused almost 25% of deaths in the US.**
- **In 2010, coronary heart disease US costs ~$108.9 billion including health care, medications & lost productivity.**

SOURCE: Heart Disease Facts, Centers for Disease Control, 2012

Heart Disease Death Rates, 2000-2006
Adults Ages 35+, by County



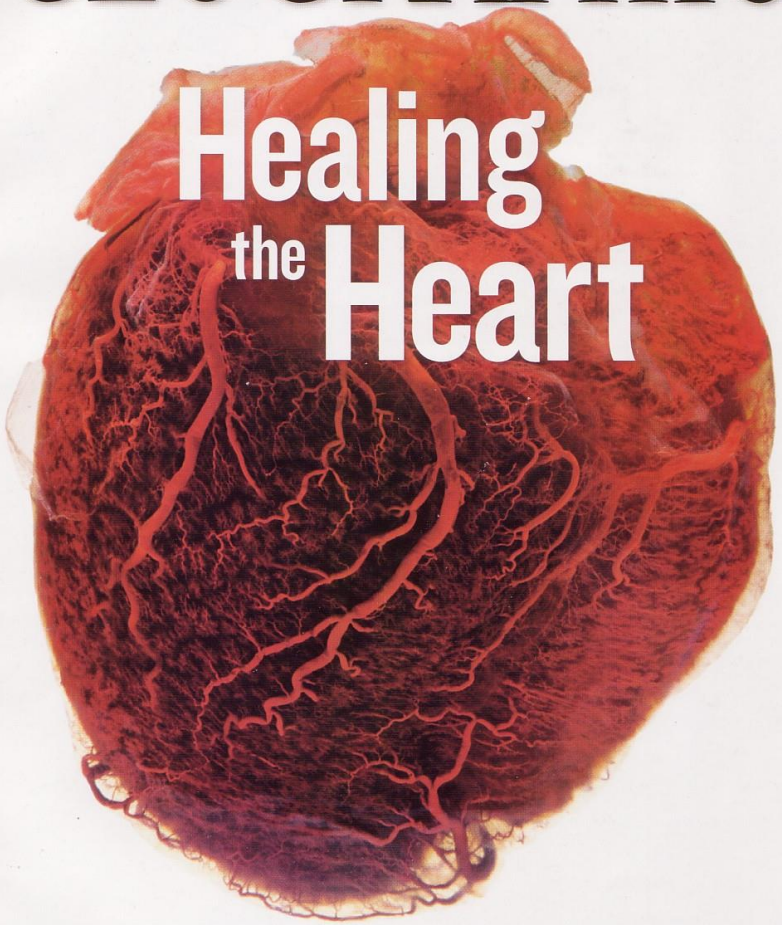
http://www.cdc.gov/heartDisease/statistics.htm



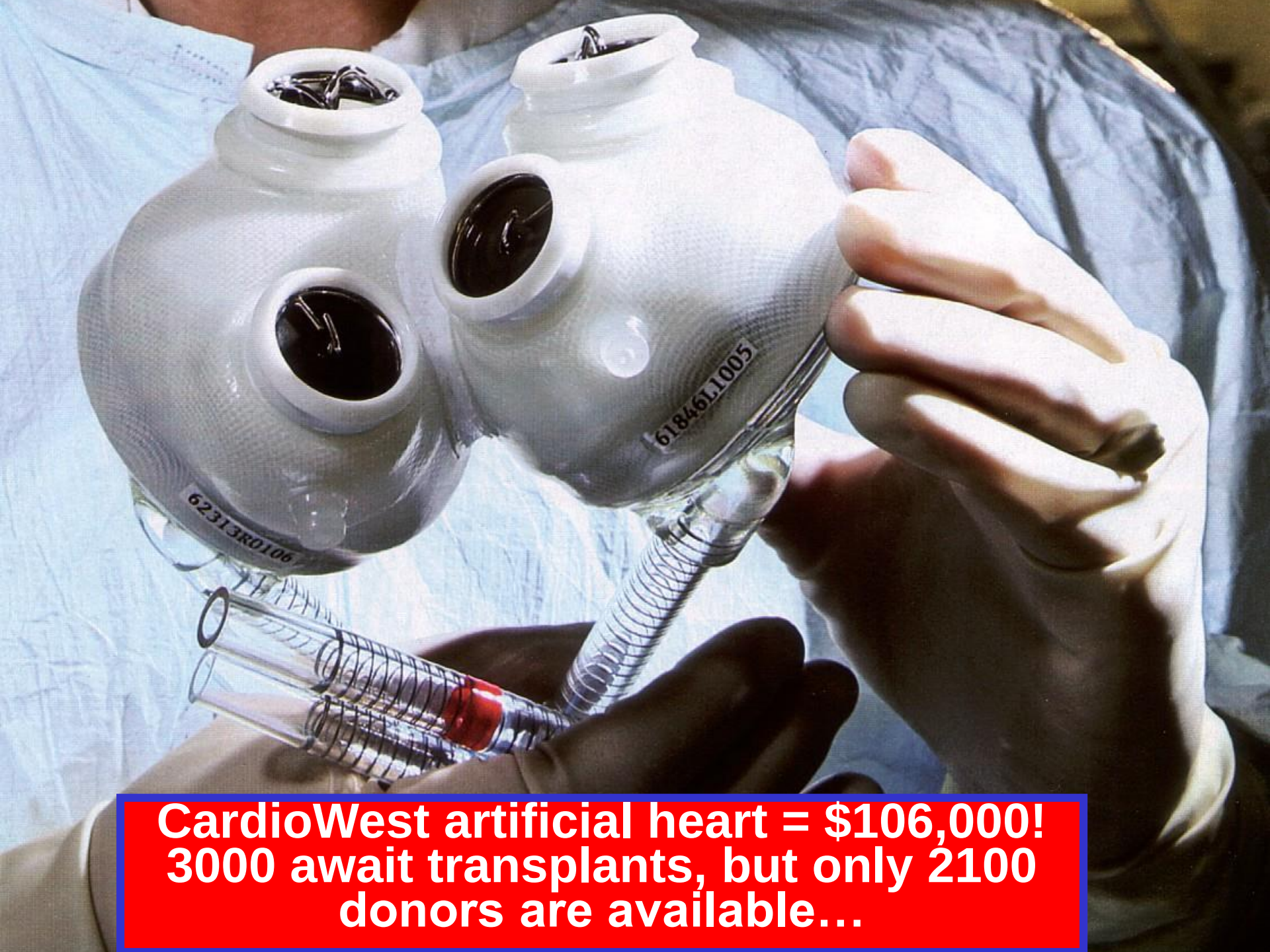
National Geographic, 2007

NATIONALGEOGRAPHIC.COM/MAGAZINE FEBRUARY 2007

NATIONAL GEOGRAPHIC



Healing the Heart



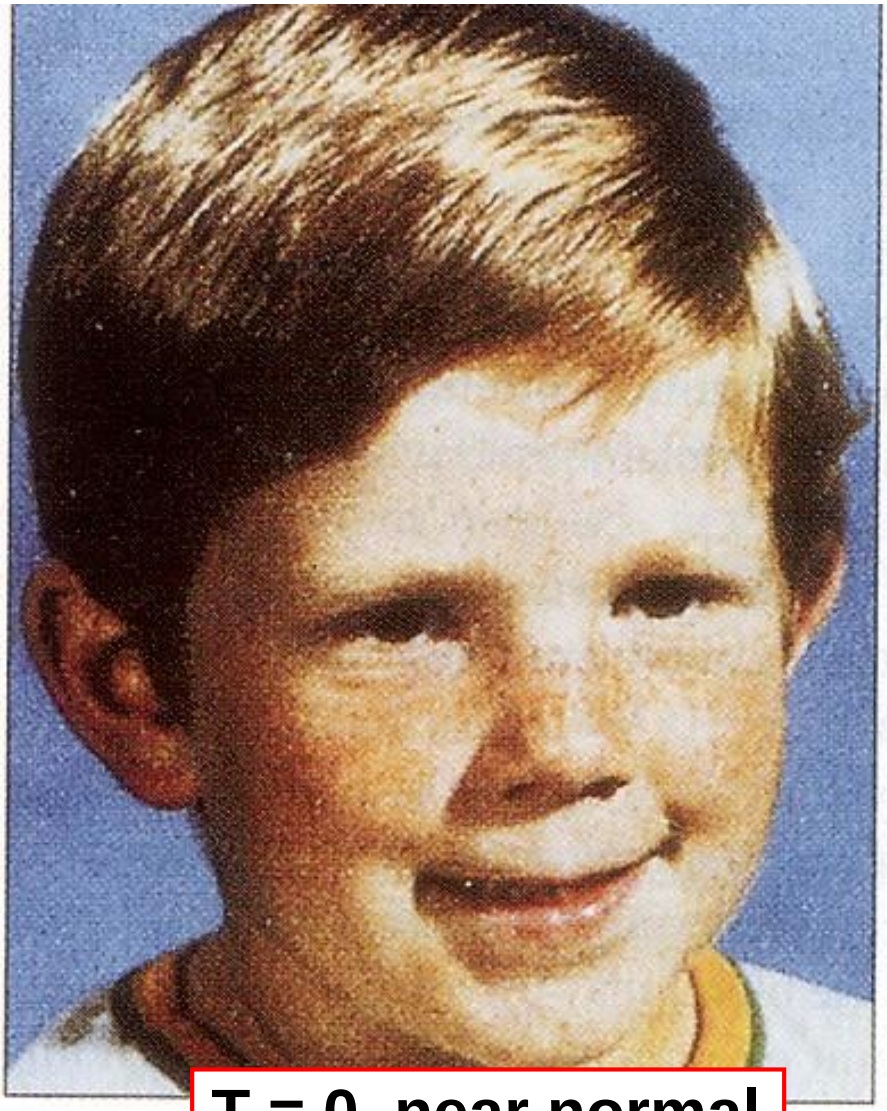
CardioWest artificial heart = $106,000!
3000 await transplants, but only 2100 donors are available…

http://ngm.nationalgeographic.com/2007/02/hearts/hearts-text.html

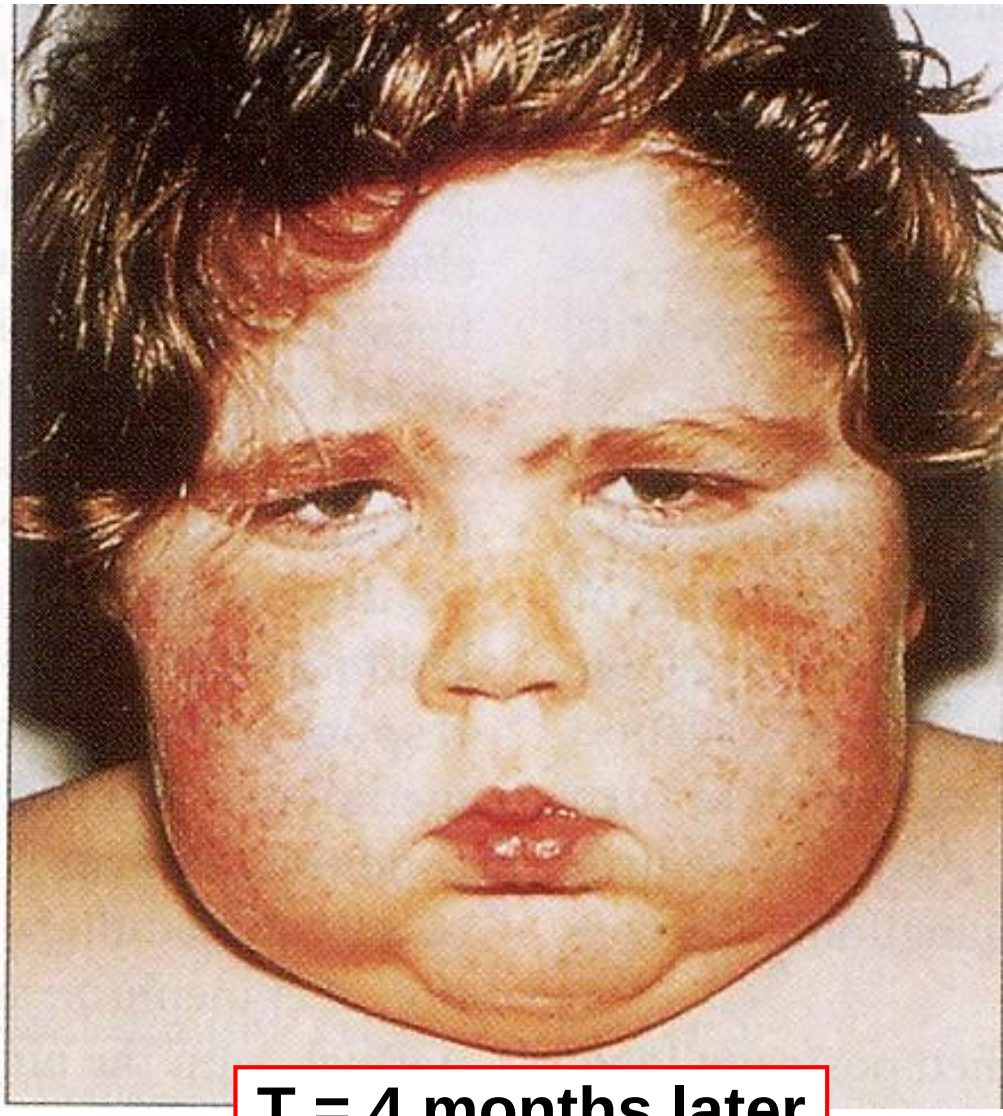
Photograph by Robert Clark

Questions + Discussion

Cushing's Syndrome = Hypersecretion of Cortisol: Hypothalamic (CRH), Pituitary (ACTH), or Adrenal (Cortisol)



T = 0, near normal



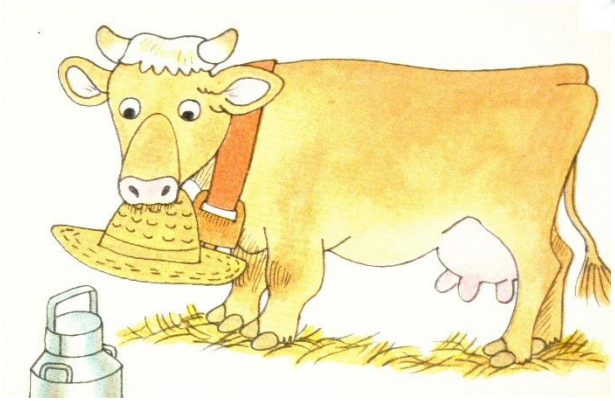
T = 4 months later

Endocrine/Hormone?

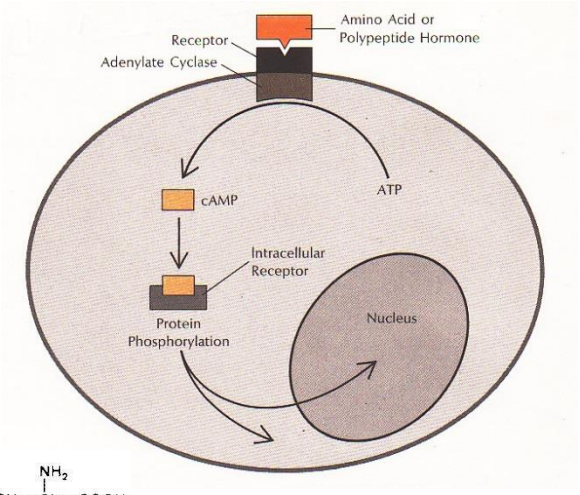
1. ***Made by gland?***
2. ***Secreted into blood?***
3. ***Acts on target?***

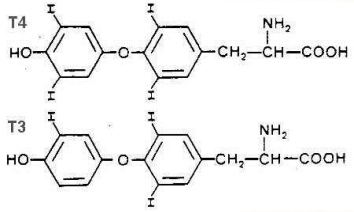
Hormone/Endocrine Classifications

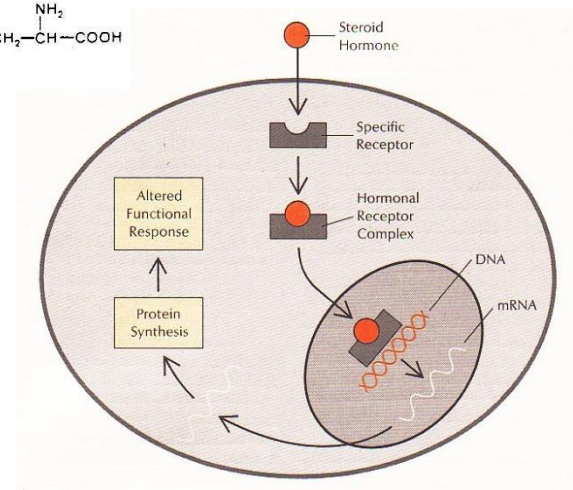
Exogenous



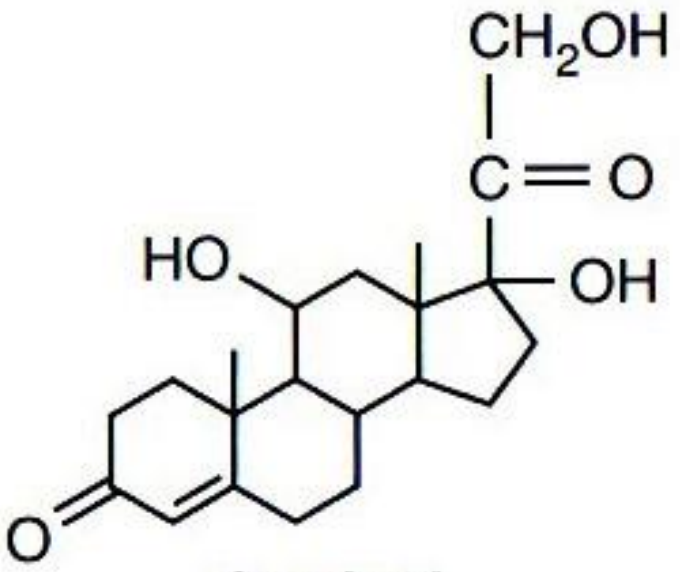
Endogenous



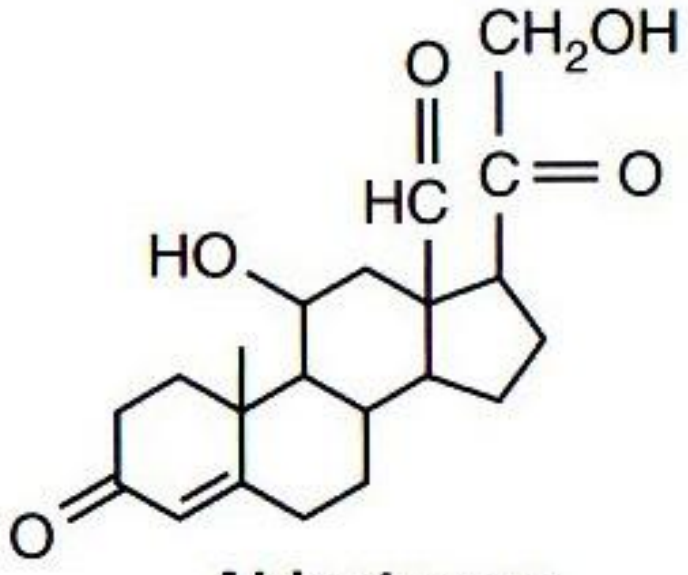




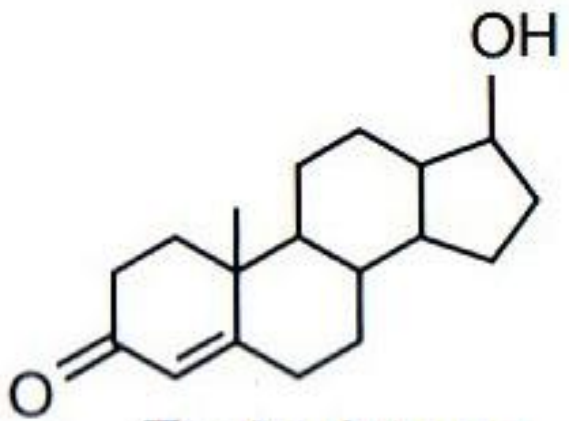
Steroid Hormone Structure: Cholesterol Backbone



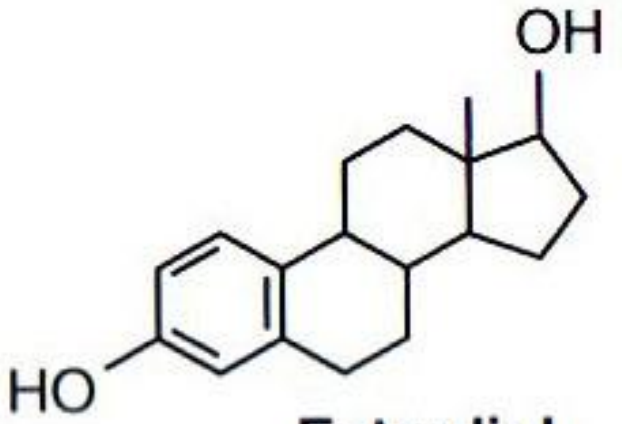
Cortisol



Aldosterone



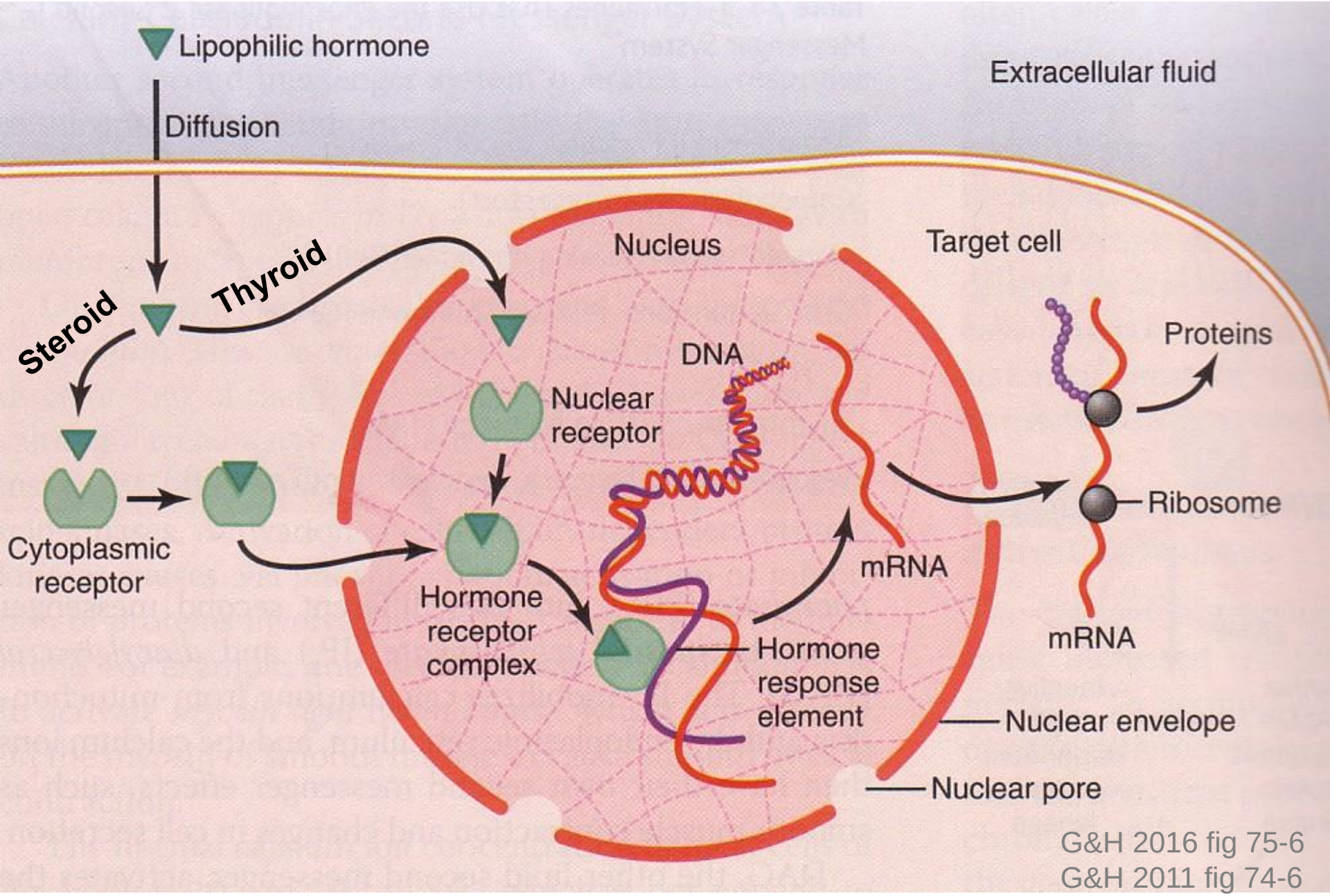
Testosterone



Estradiol

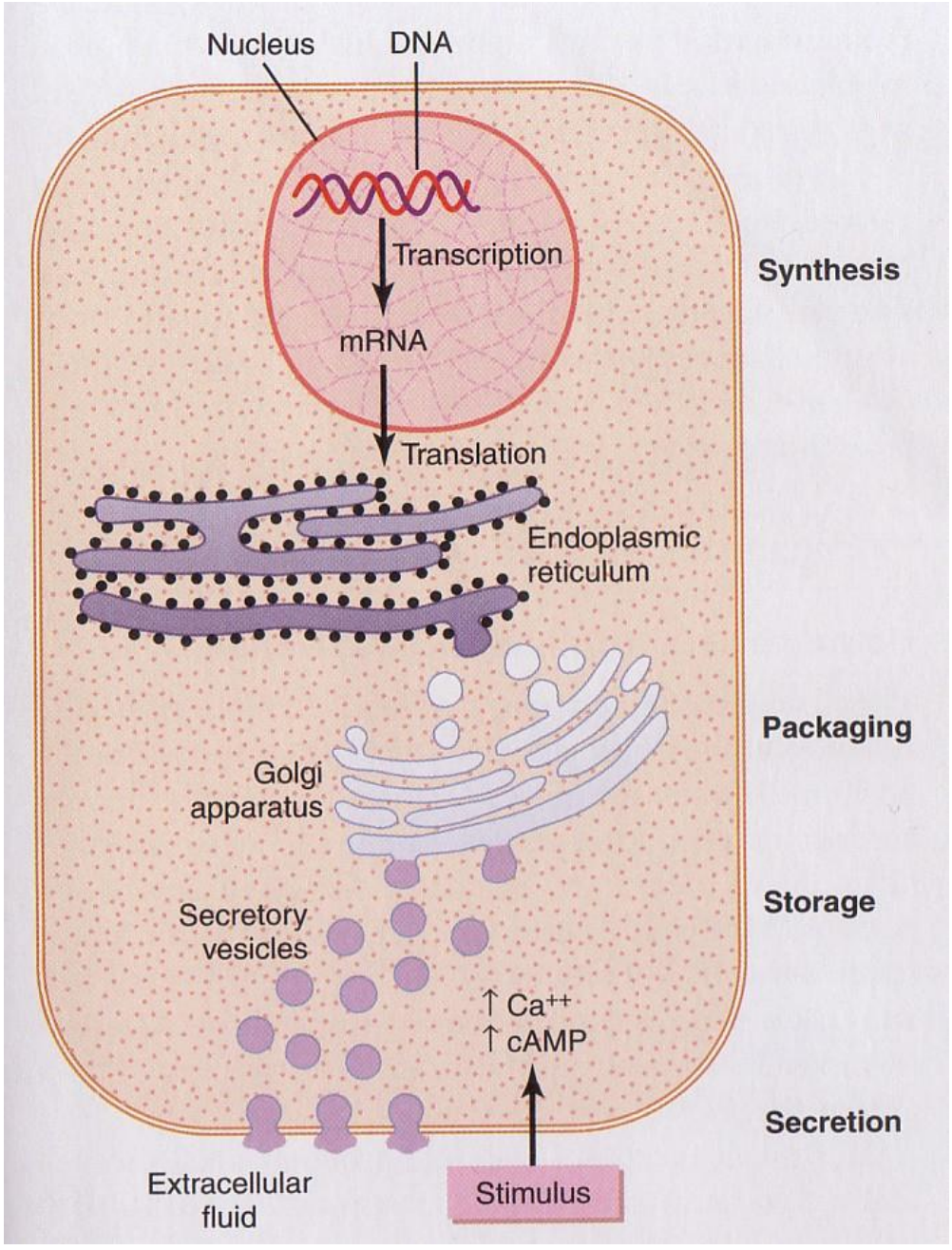
G&H 2016 fig 75-3, G&H 2011 fig 74-3

Lipophilic (Steroid+Thyroid) Hormone Mechanisms



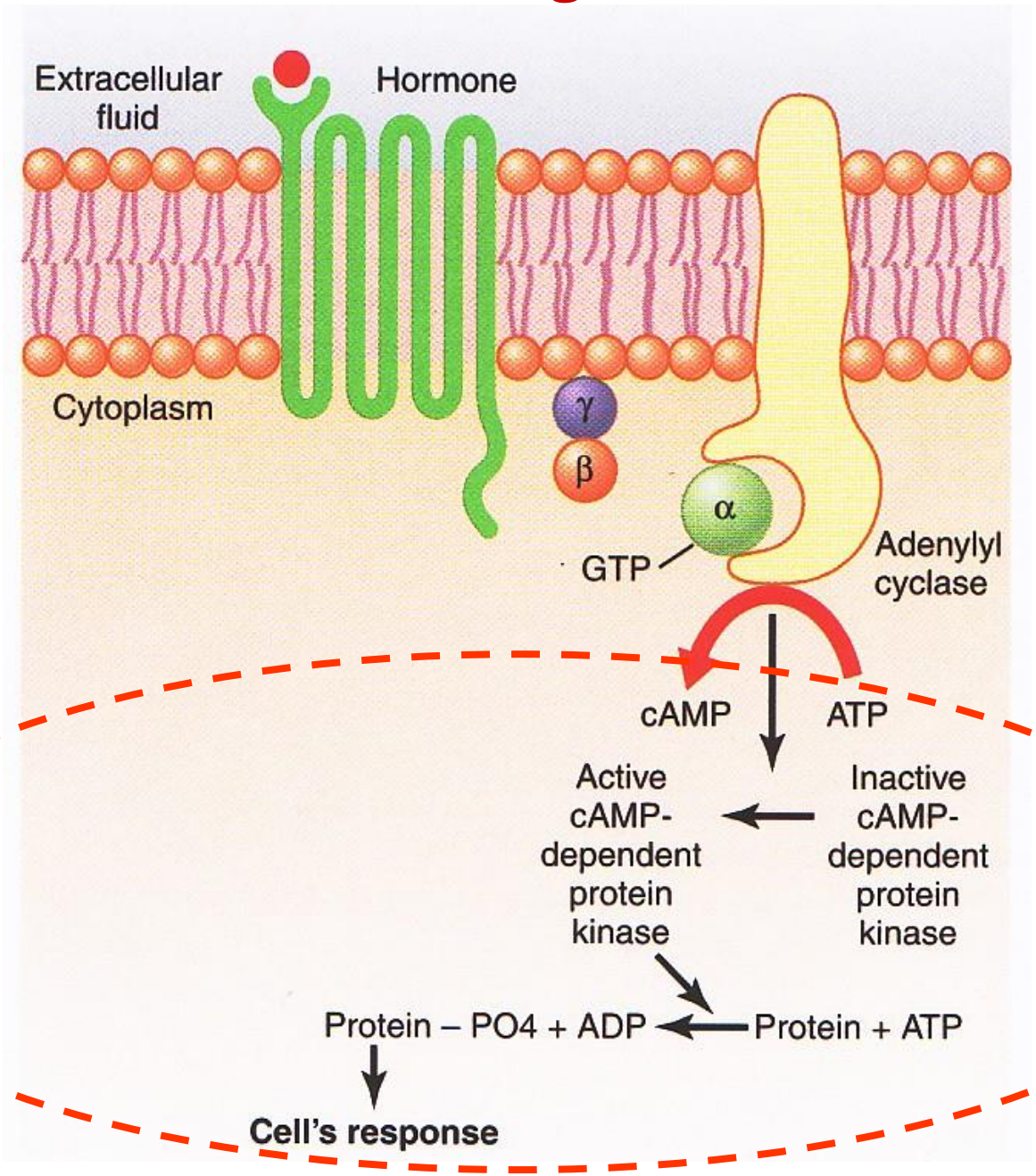
G&H 2016 fig 75-6
G&H 2011 fig 74-6

Peptide Hormone Synthesis & Secretion



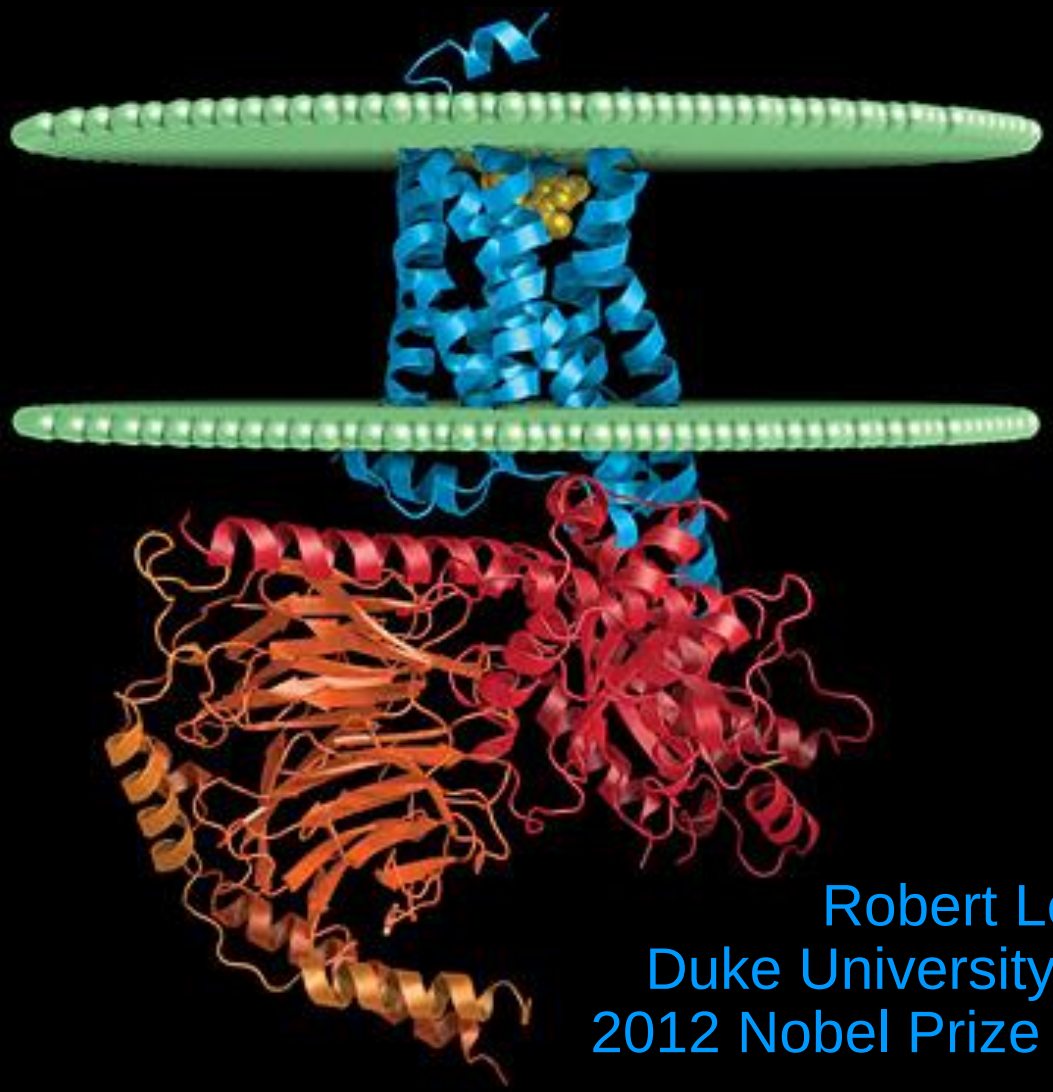
G&H 2016 fig 75-2
G&H 2011 fig 74-2

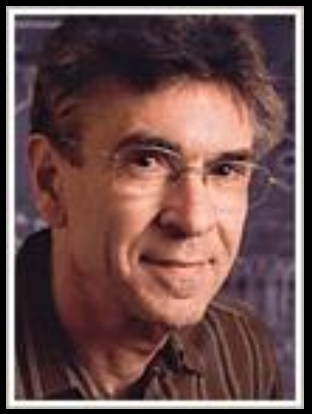
cAMP 2nd Messenger Mechanism



G&H 2016 fig 75-7
G&H 2011 fig 74-7

G-Protein Coupled Receptor (blue) sits within lipid bilayer (green) to respond to hormone (yellow)





Robert Lefkowitz, MD
Duke University Cardiologist
2012 Nobel Prize in Chemistry

http://www.hhmi.org/bulletin/winter2013/features/index.html

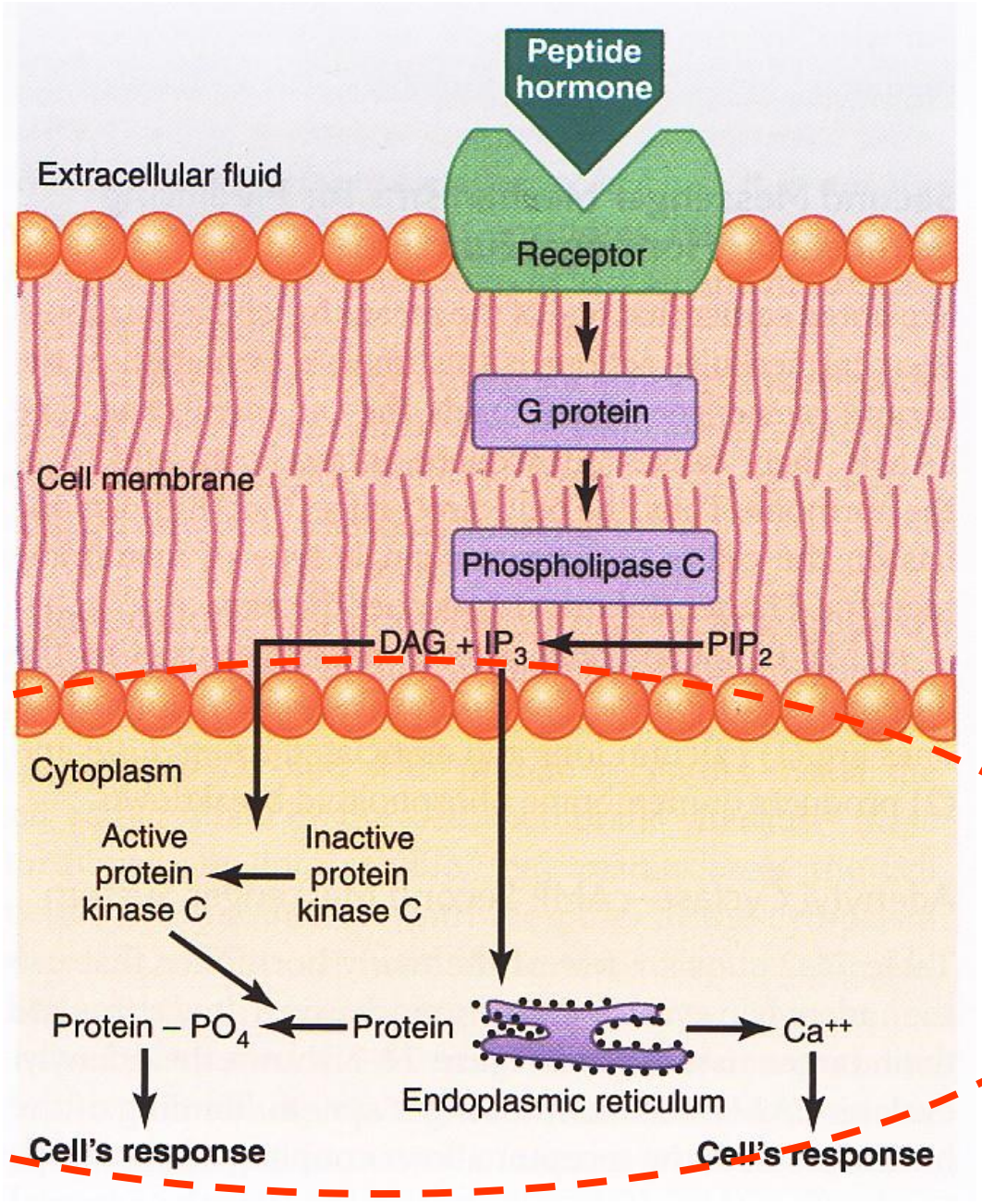
Image by Wayne Decatur

Table 74-2 Hormones That Use the Adenylyl Cyclase – Cyclic AMP Second Messenger System

Adrenocorticotropic hormone (ACTH)
Angiotensin II (ANG II, epithelial cells)
Calcitonin
Catecholamines (β receptors)
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Glucagon
Human chorionic gonadotropin (hCG)
Luteinizing hormone (LH)
Parathyroid hormone (PTH)
Secretin
Somatostatin (SS, GH RIH)
Thyroid-stimulating hormone (TSH)
Vasopressin (ADH, VP, V_2 receptor, epithelial cells)

G&H 2011

Phospholipase C 2nd Messenger Mechanism



G&H 2016 fig 75-8
G&H 2011 fig 74-8

Table 74-3 Hormones That Use the Phospholipase C Second Messenger System

Angiotensin II (ANG II, vascular smooth muscle)

Catecholamines (α receptors)

Gonatotropin-releasing hormone (GnRH)

Growth-hormone-releasing hormone (GHRH)

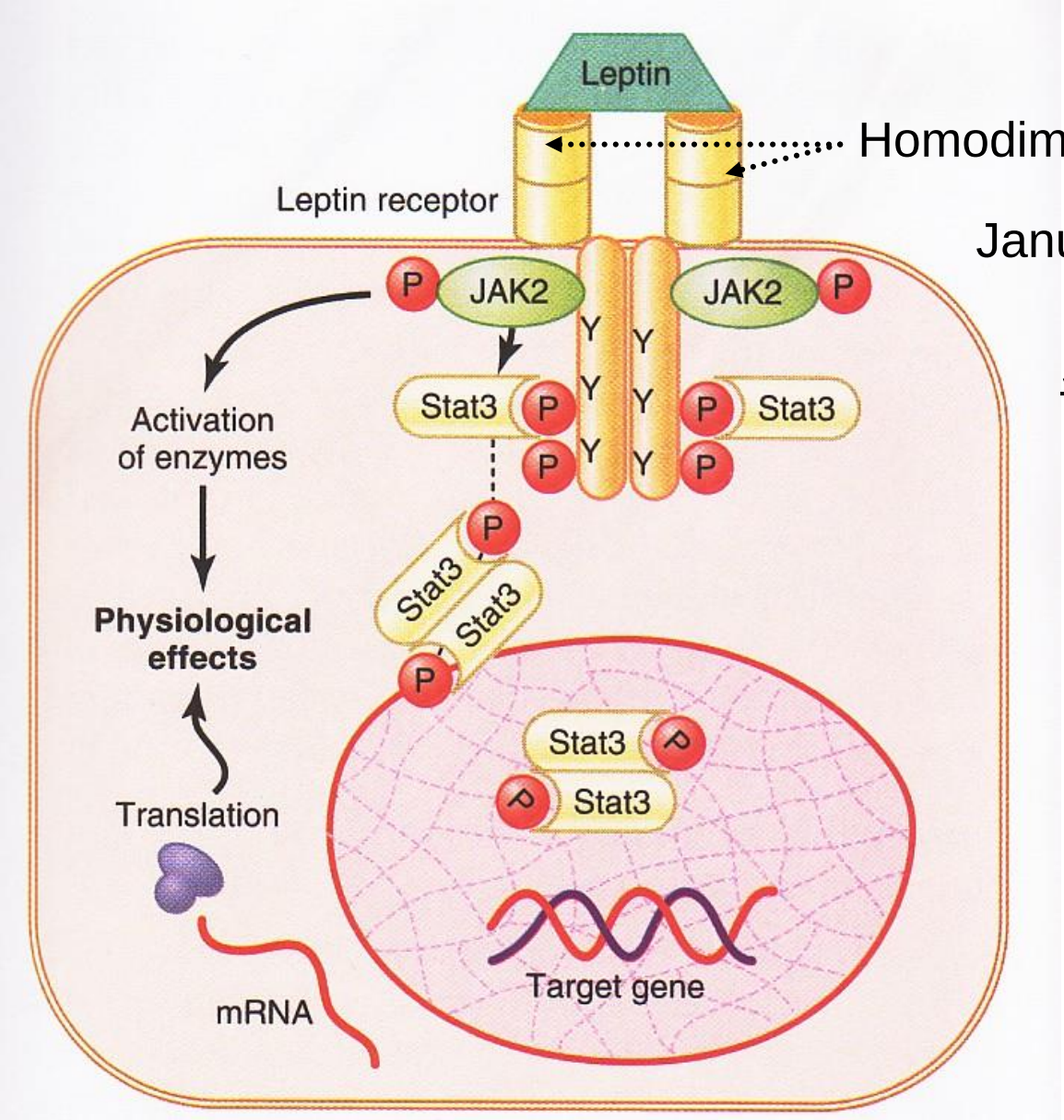
Oxytoxin (OXY, hypothalamus production, posterior pituitary storage)

Thyrotropin releasing hormone TRH)

Vasopressin (ADH, VP, V_1 receptor, vascular smooth muscle

G&H 2011 tab 74-3
G&H 2016 tab 75-4

Leptin: Enzyme-Linked Hormone Receptor



Homodimer receptor

Janus-kinase 2 enzyme

↓

Signal transducer & activator of transcription proteins (STAT)

↓

transcription of target genes

↓

Protein synthesis

http://www.ncbi.nlm.nih.gov/pubmed/22249808

G&H 2016 fig 75-5
G&H 2011 fig 74-5

ANP =
_A_trial
_N_atriuretic
_P_olypeptide

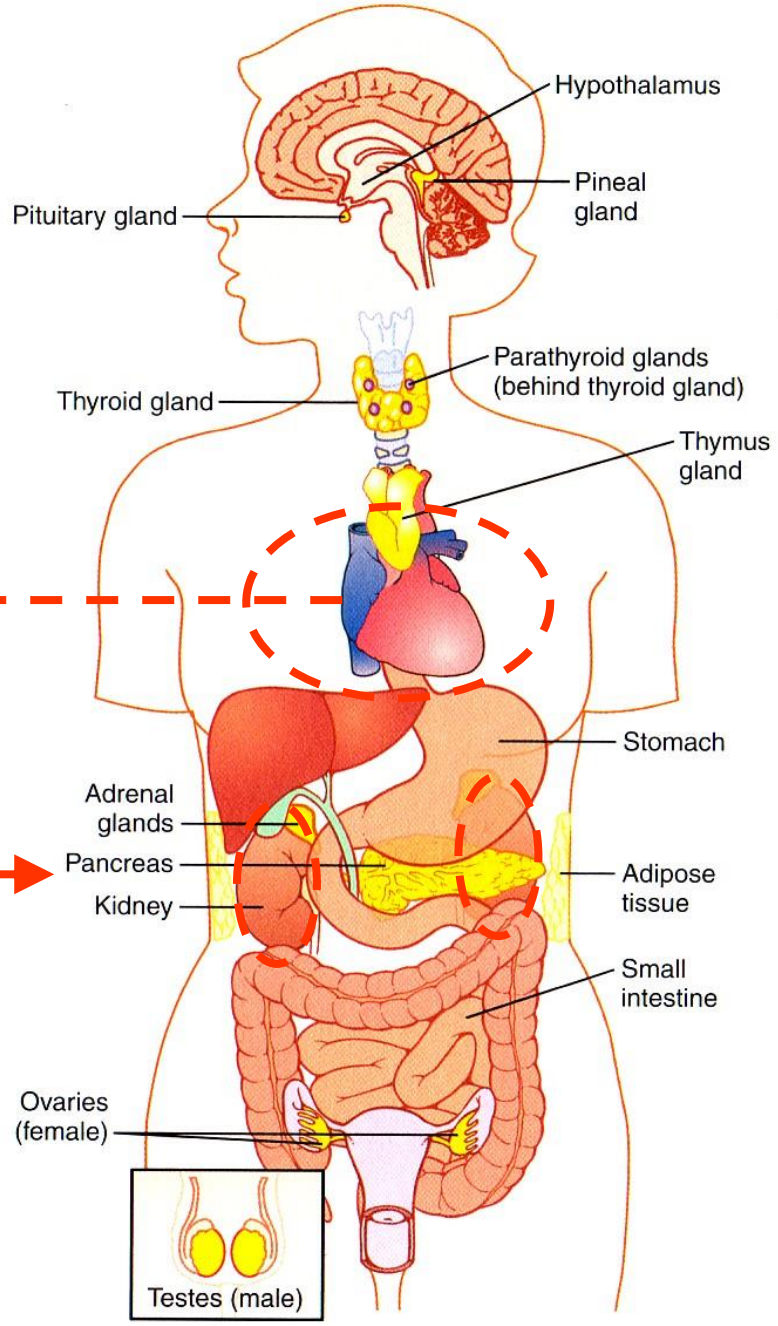
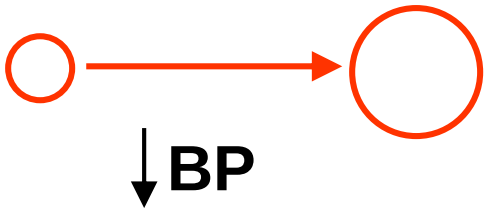


Figure 74-1 Anatomical loci of the principal endocrine glands and tissues of the body.

2 **Vasodilation**



G&H 2011 fig 74-1
G&H 2016 fig 75-1