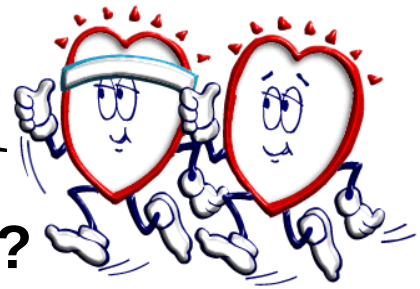
BI 358 Lecture 10

Next Tues Dr. Jacobson, next Thurs Dr. Padgett! Hip! Hip! Hooray!!



I. ***Announcements*** **Guest lectures all next week!**
Quiz after lecture in Discussion on Tuesday. Q?

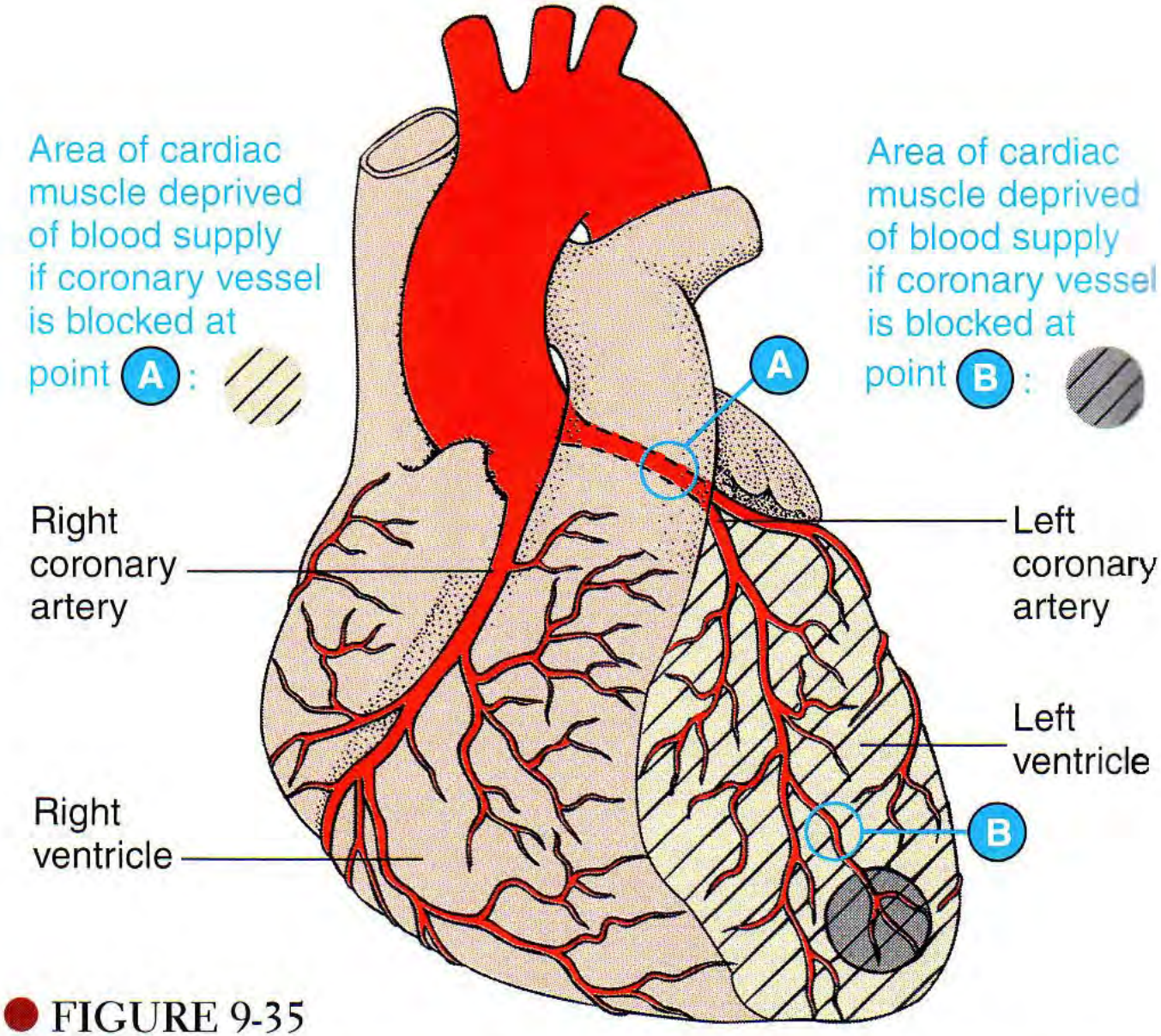
II. ***CVD-Atherosclerosis Connections*****: Lecture 9 slides ≥ # 34**

III. ***Endocrinology Overview*** **G&H ch 74+75, LS, Norris, Fox...**

- **A. Endocrine vignette: Cushing's Syndrome LS**
- **B. What's an endocrine? Hormone criteria & classifications?**
- **C. Mechanisms of hormonal action fig 74-6, 74-2, 74-7,...**
- **D. Endocrinology focuses on the relationship between the Hypothalamus - Controller → Pituitary - Subcontroller**
- **E. Endocrine organ & hormonal overview fig 74-1, tab 74-1**
- **F. Hypothalamus-Post & Ant Pituitary fig 75-9, 75-4, 75-2**
- **G. Anterior pituitary hormone functions tab 75-1, Fox + LS**
- **H. Negative feedback loops G&H p 885 + LS**
- **I. Growth Hormone (GH/STH) fig 75-5, 75-6, tab 75-3**
  Body builder's dream or fountain of youth? Neither!

IV. ***Peripheral Endocrine Organs*** **G&H ch 76, 77, 78**

- **A. Pancreas: insulin vs. glucagon, diabetes, G&H ch 78 + Fox**
- **B. Thyroid: T3 & T4 G&H fig 76-2 thru fig 76-9 + DC**
- **C. Adrenal cortices G&H fig 77-1 & 77-2 + DC**



● FIGURE 9-35

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

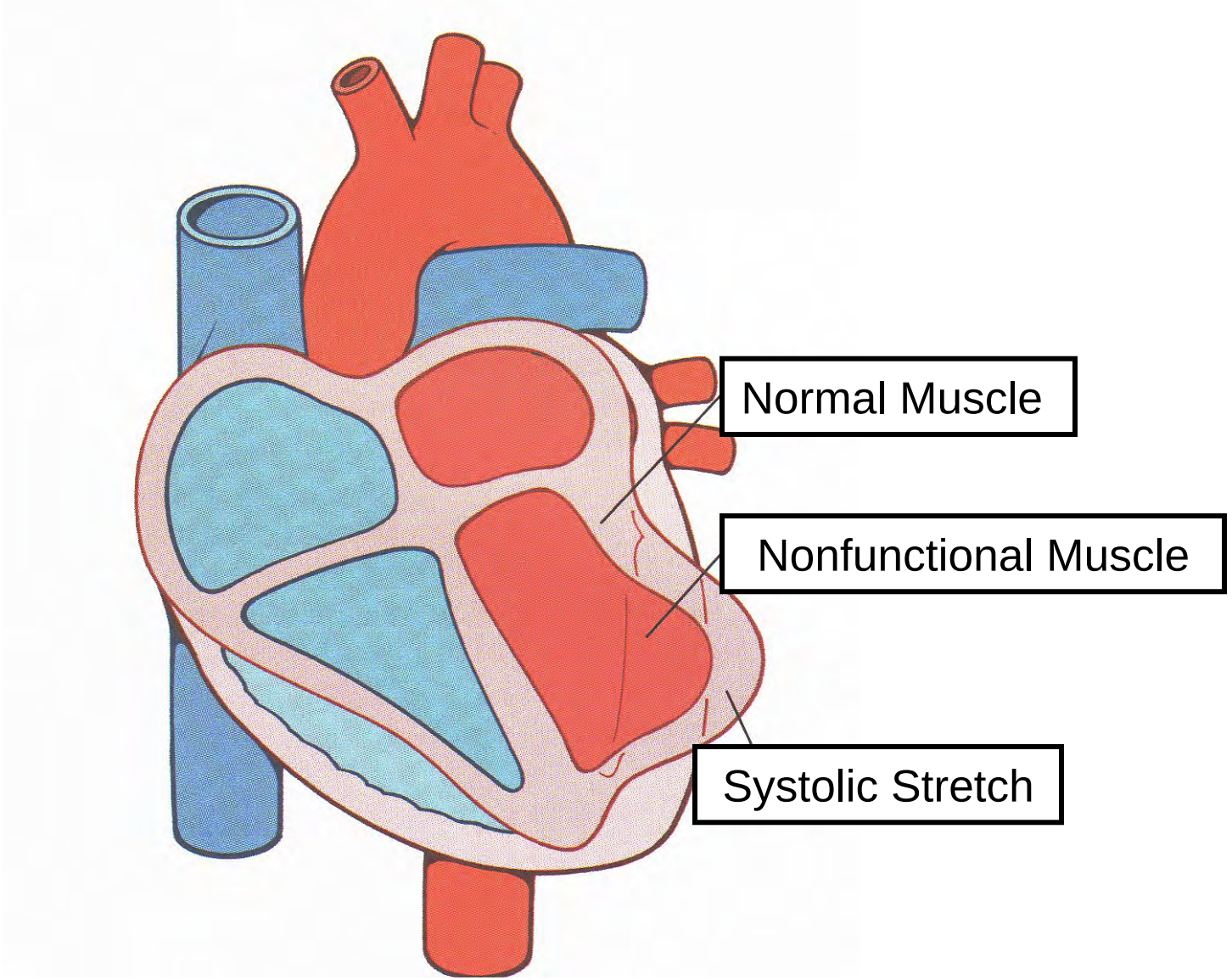
L Sherwood 2004 p 336

What is the Ultimate Cause of Death?

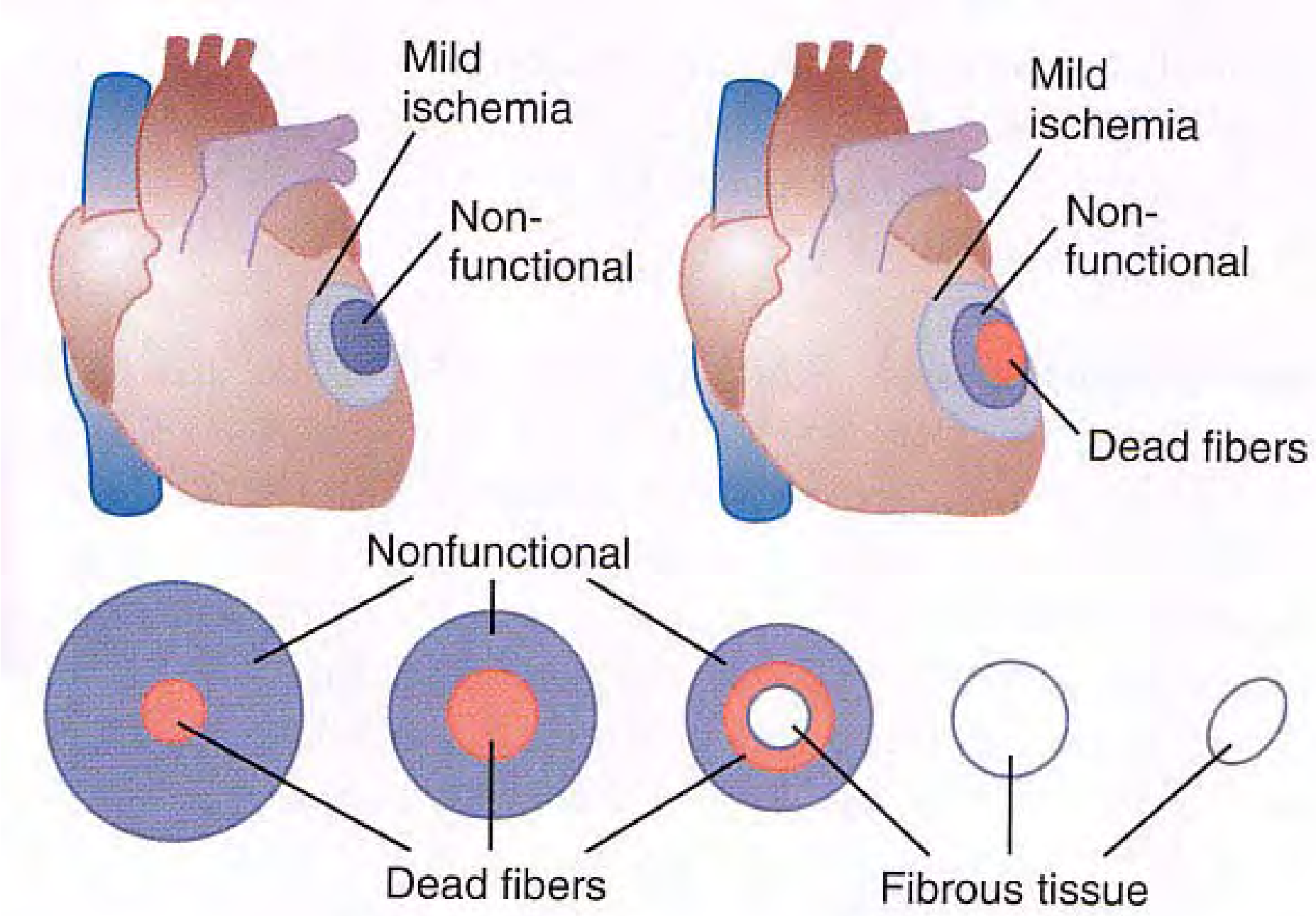
1. ↓ $\dot{Q}$, CO or Cardiac Output
2. Pulmonary damming w/edema
3. Cardiac fibrillation
4. Thromboembolism
5. Cardiac rupture

G&H 2011 p 250

Systolic Stretch Due to Necrotic Tissue



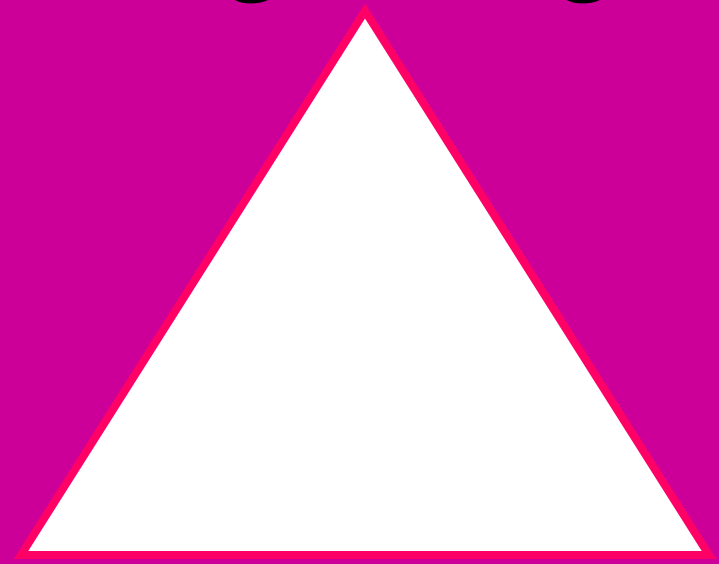
G&H 2011 fig 21-7


Mild ischemia
Non-functional
Mild ischemia
Non-functional
Dead fibers
Nonfunctional
Dead fibers
Fibrous tissue

G&H fig 21-8

Treatment Triad

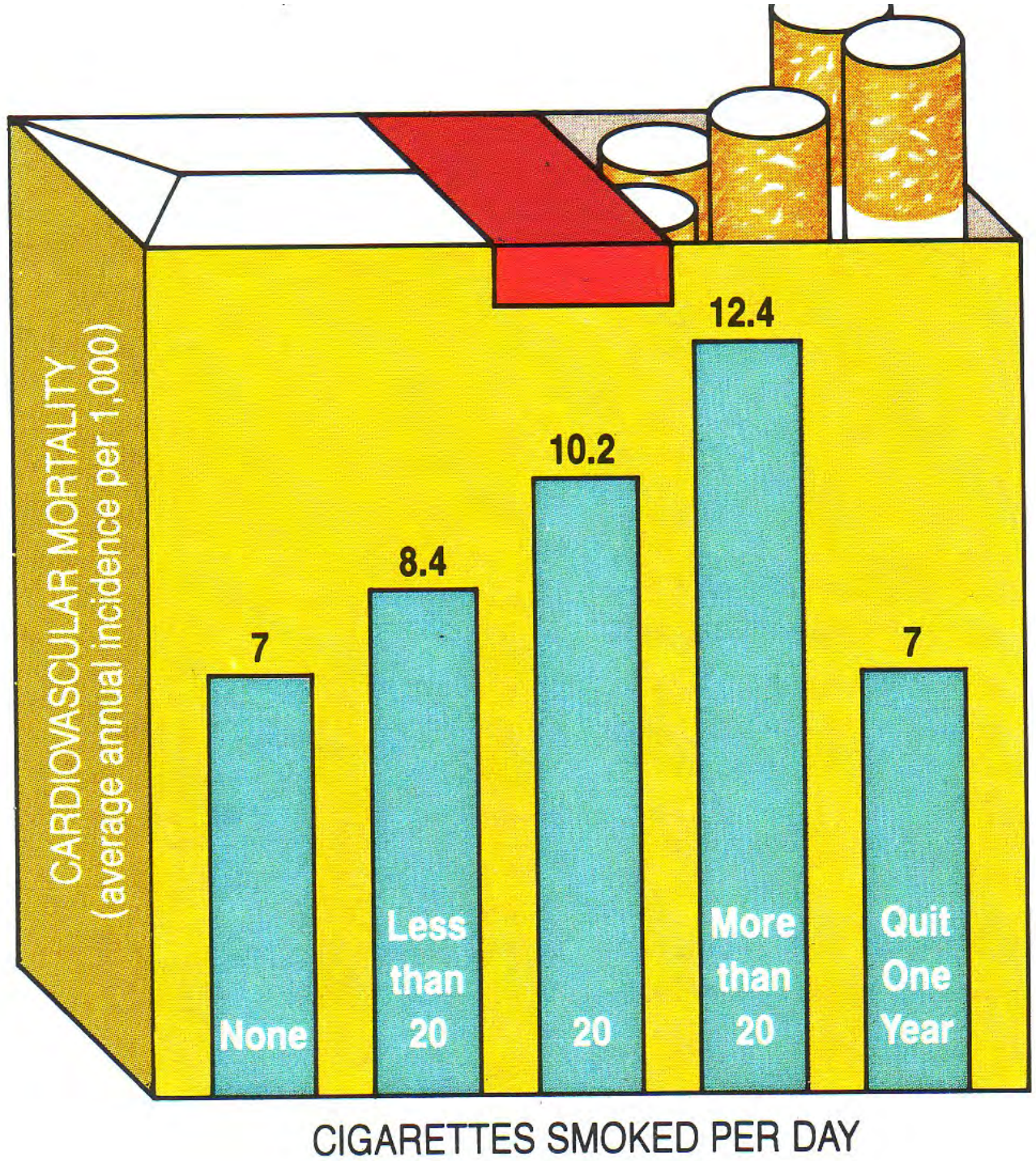
NB: Last blasted resort!!



Drugs/Surgery

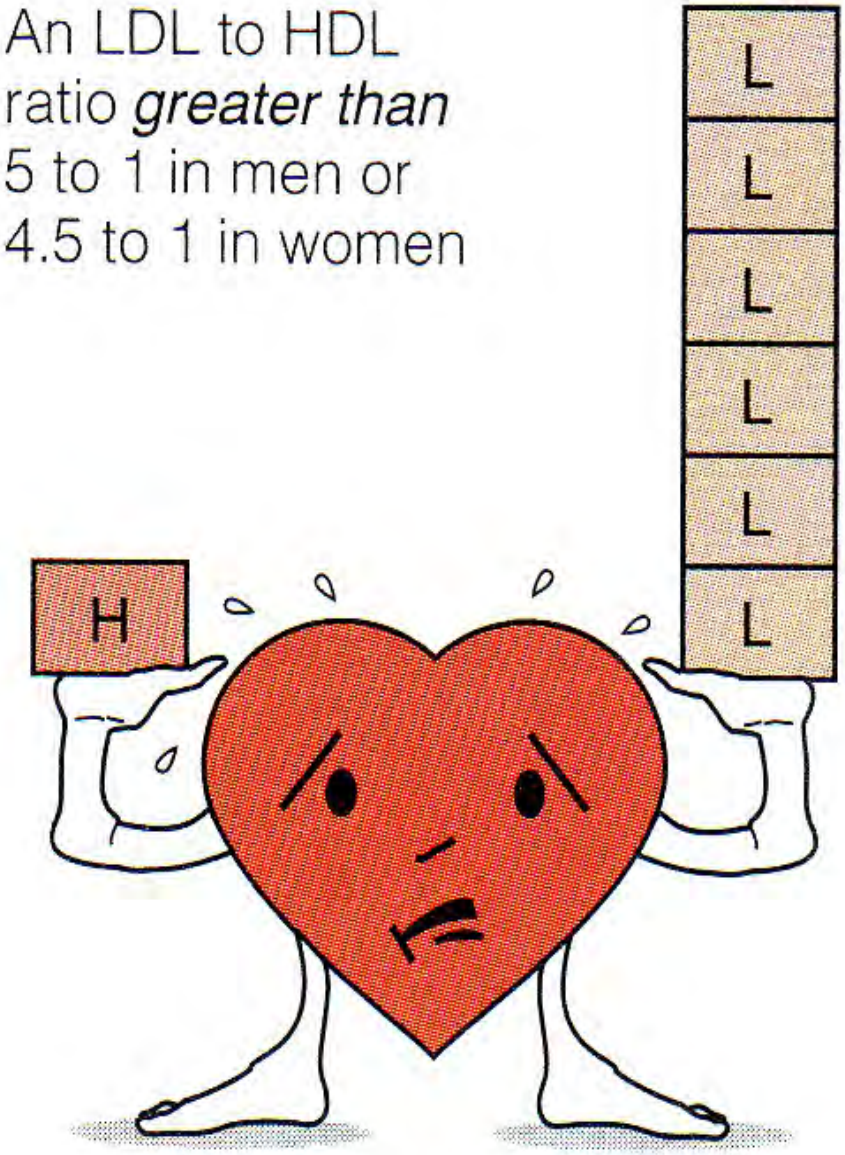
Dietary Modification

Exercise


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

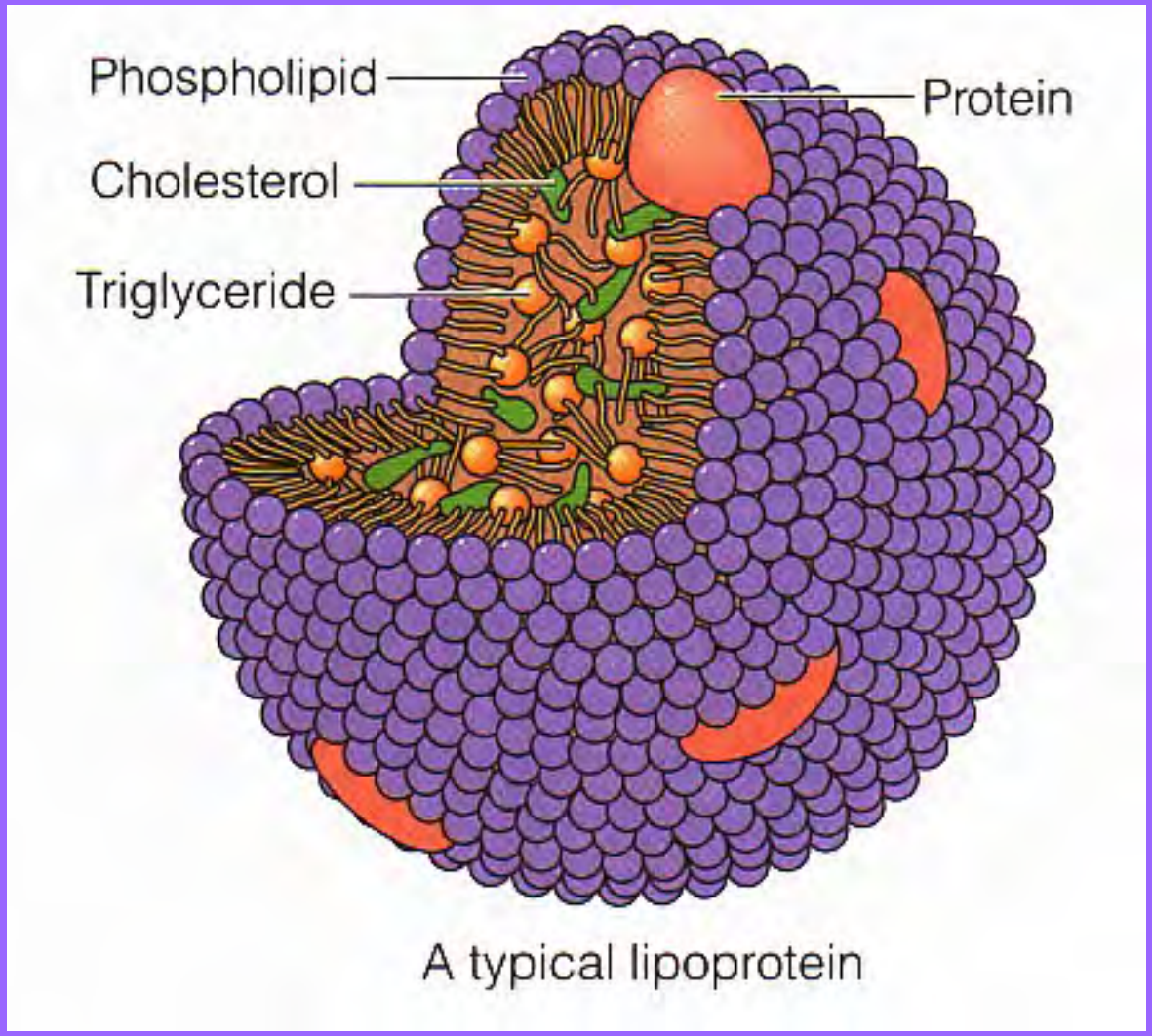

KA-BOOM!
300/200
Hg

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



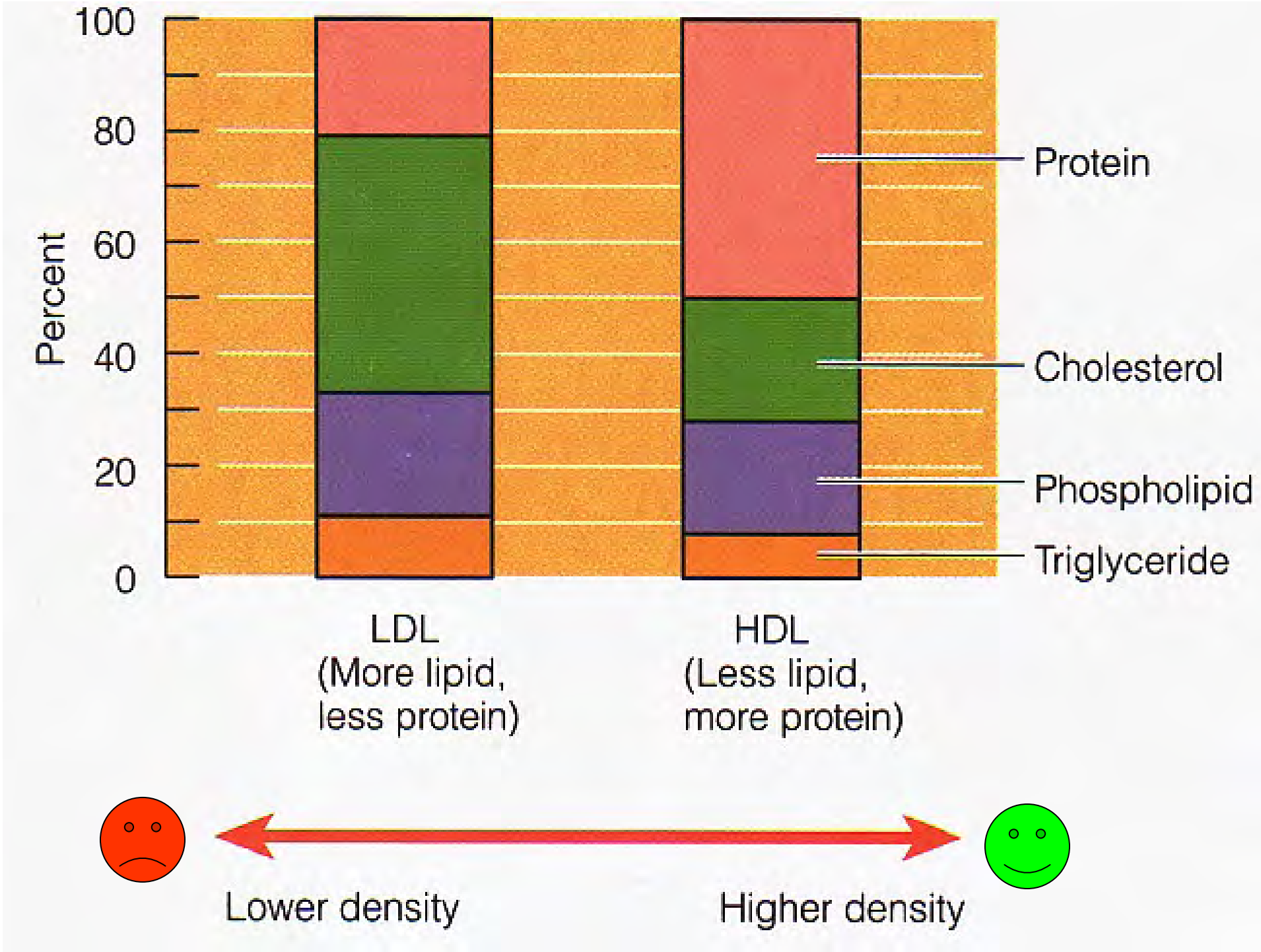
Increased risk of heart disease

Sizer & Whitney



A typical lipoprotein

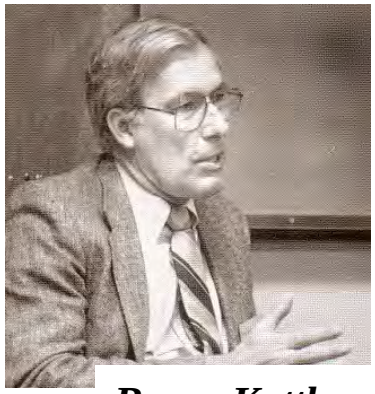
F Sizer & E Whitney 2003 p 147 +


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

? *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…

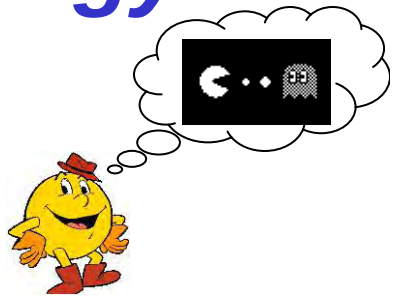
Bruce Kottke's Bathtub Analogy



Bruce Kottke

5 forms of cholesterol:

Chylomicrons, VLDL, LDL, IDL, HDL

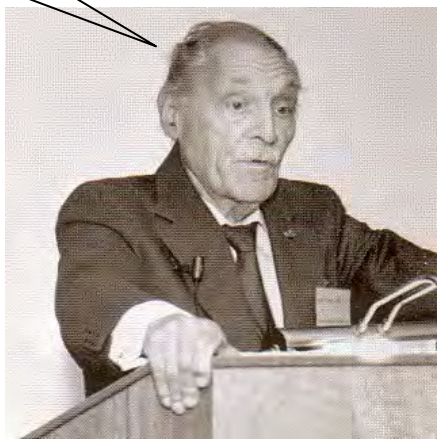


β

Atherogenic | **Anti-Atherogenic**

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

Biological Artifact!?



β-VLDL

+ **= Faucet**

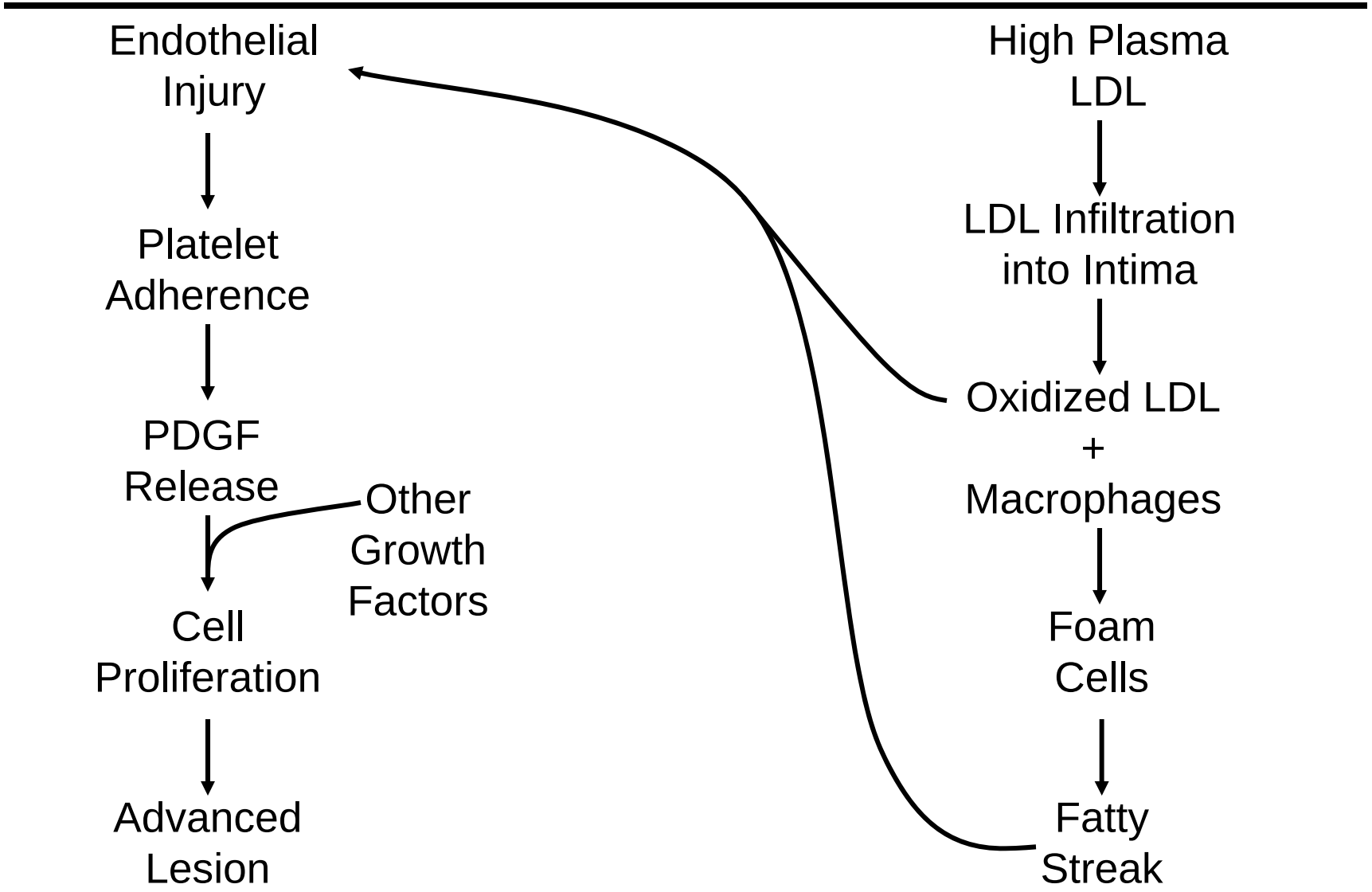
LDL

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

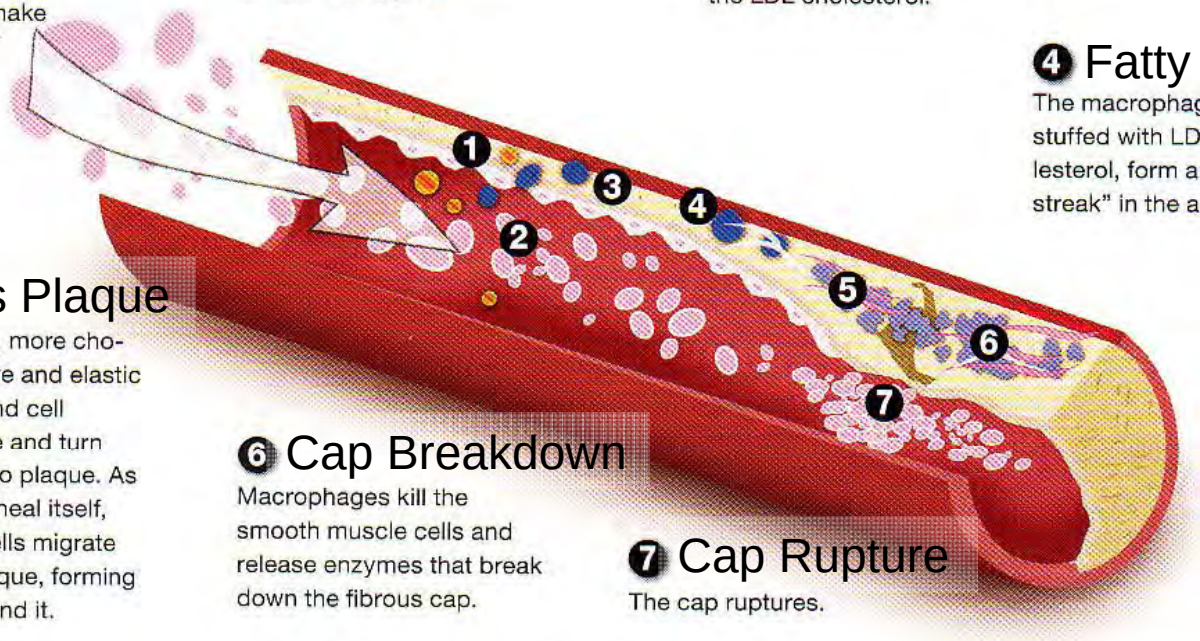
In response to the injury, the immune system sends in a team of inflammatory cells, including white blood cells called monocytes.

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

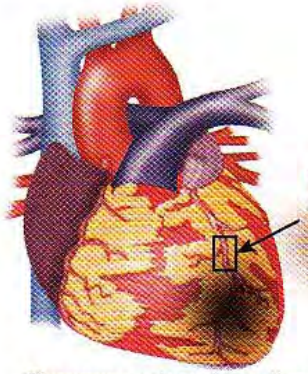
Macrophages kill the smooth muscle cells and release enzymes that break down the fibrous cap.

❼ Cap Rupture

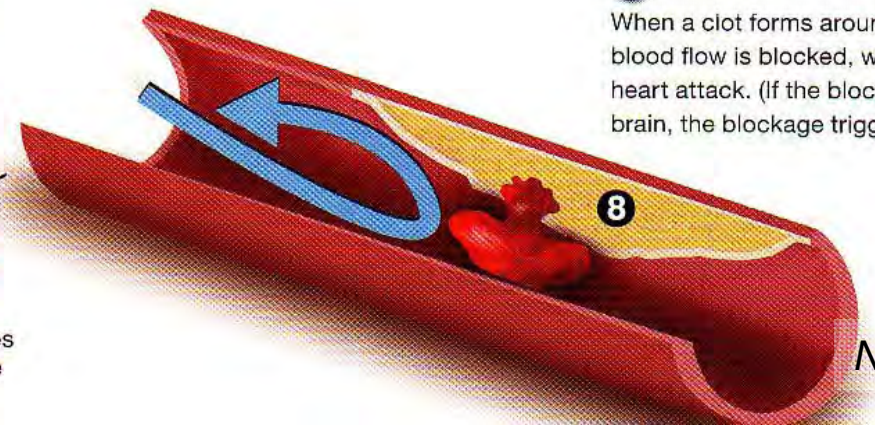
The cap ruptures.

❽ Clot Formation

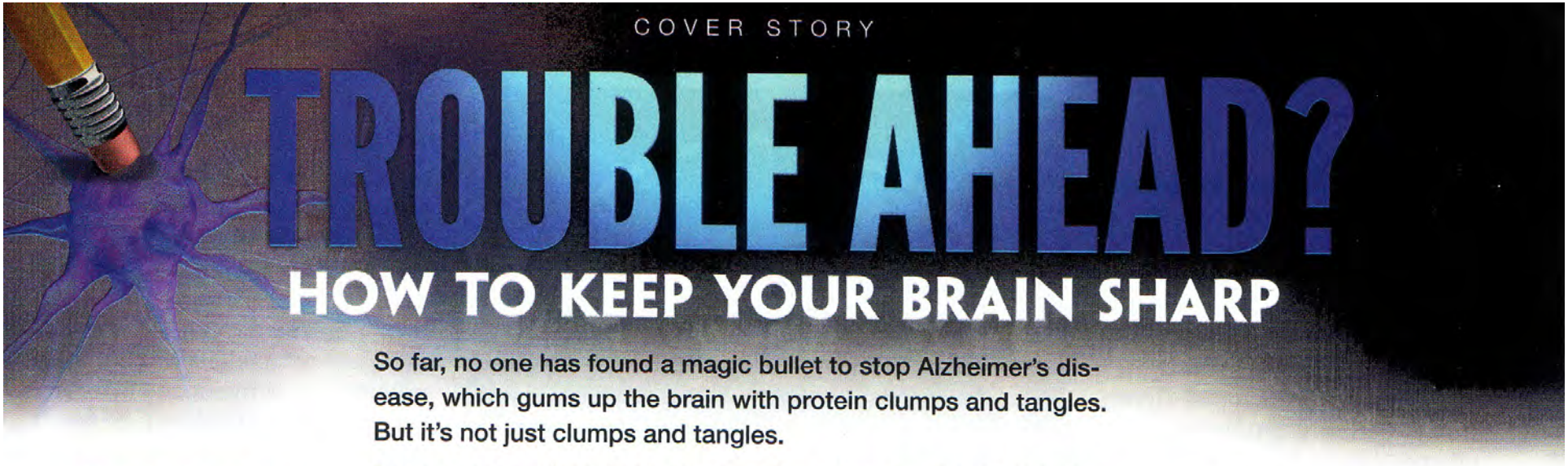
When a clot forms around the rupture, blood flow is blocked, which triggers a heart attack. (If the blocked artery feeds the brain, the blockage triggers a stroke.)



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



NAHL Jan/Feb 2009, p 5



COVER STORY

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.

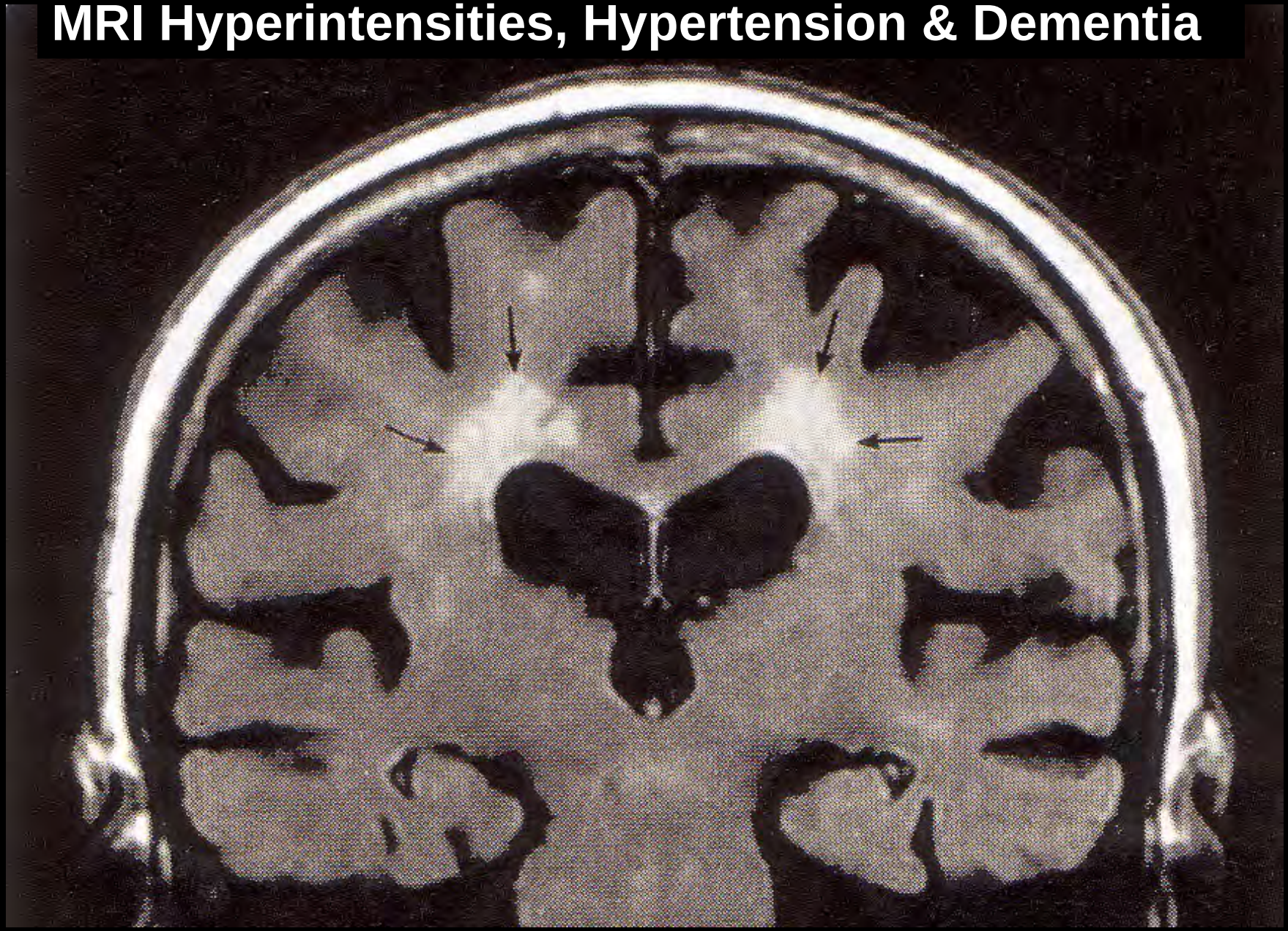
The causes of Alzheimer's pathology are more murky. But new evidence suggests that insulin may play a role.

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

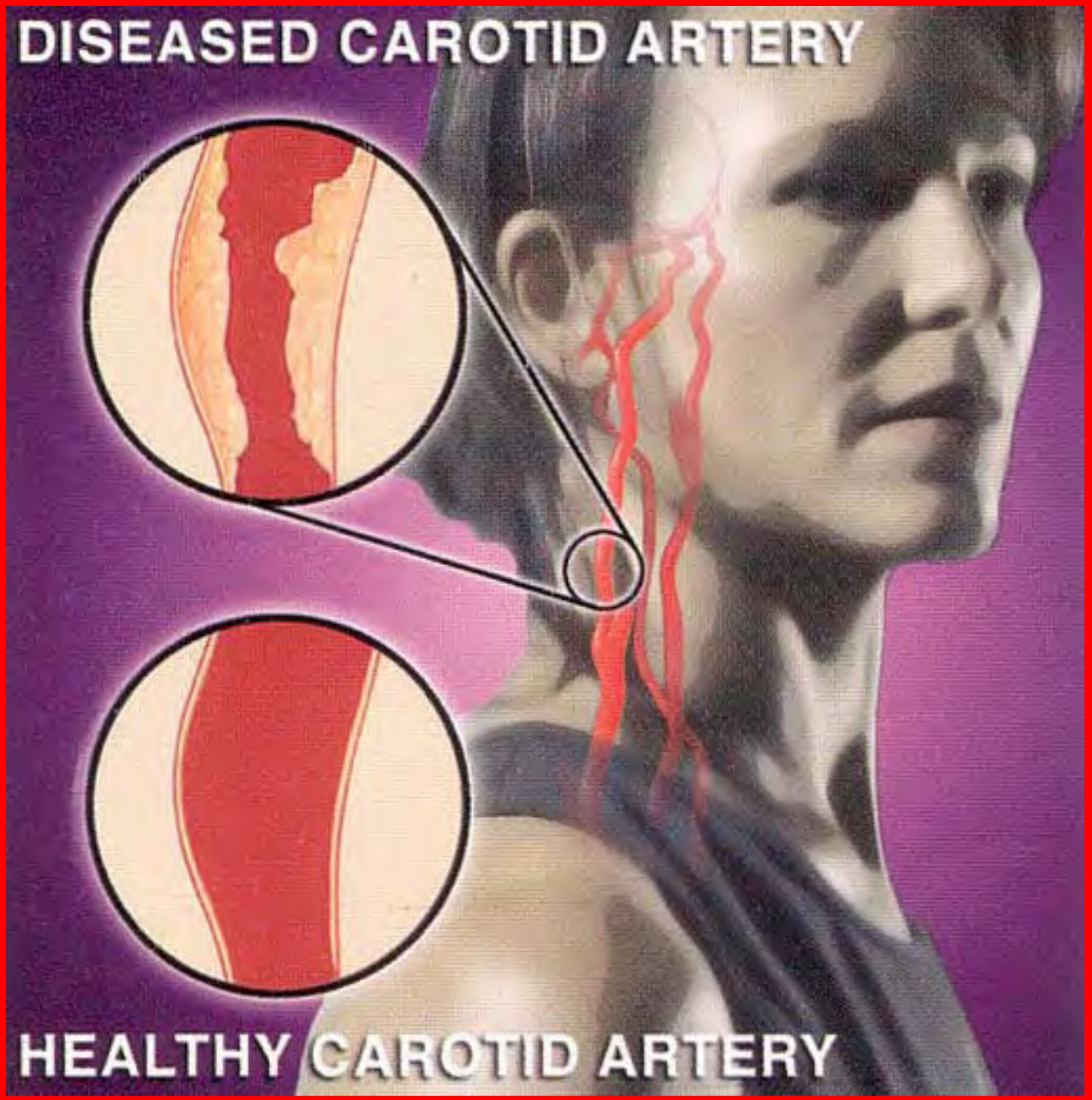
1. Watch your blood pressure

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

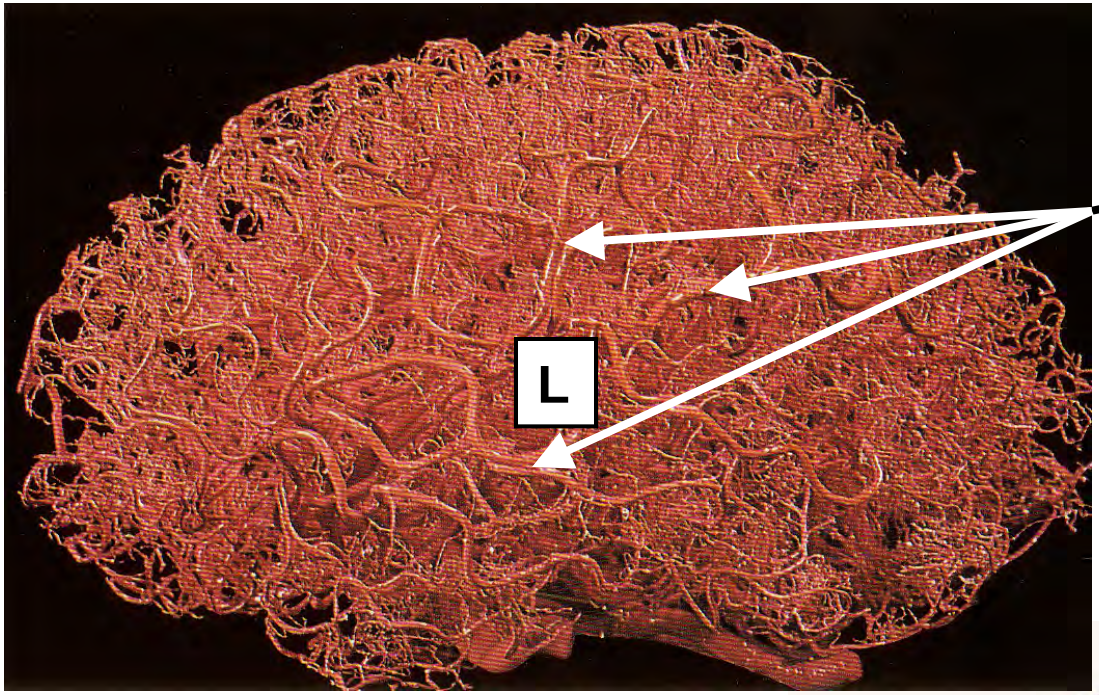
MRI Hyperintensities, Hypertension & Dementia



NAHL CSPI, Jan-Feb 2014

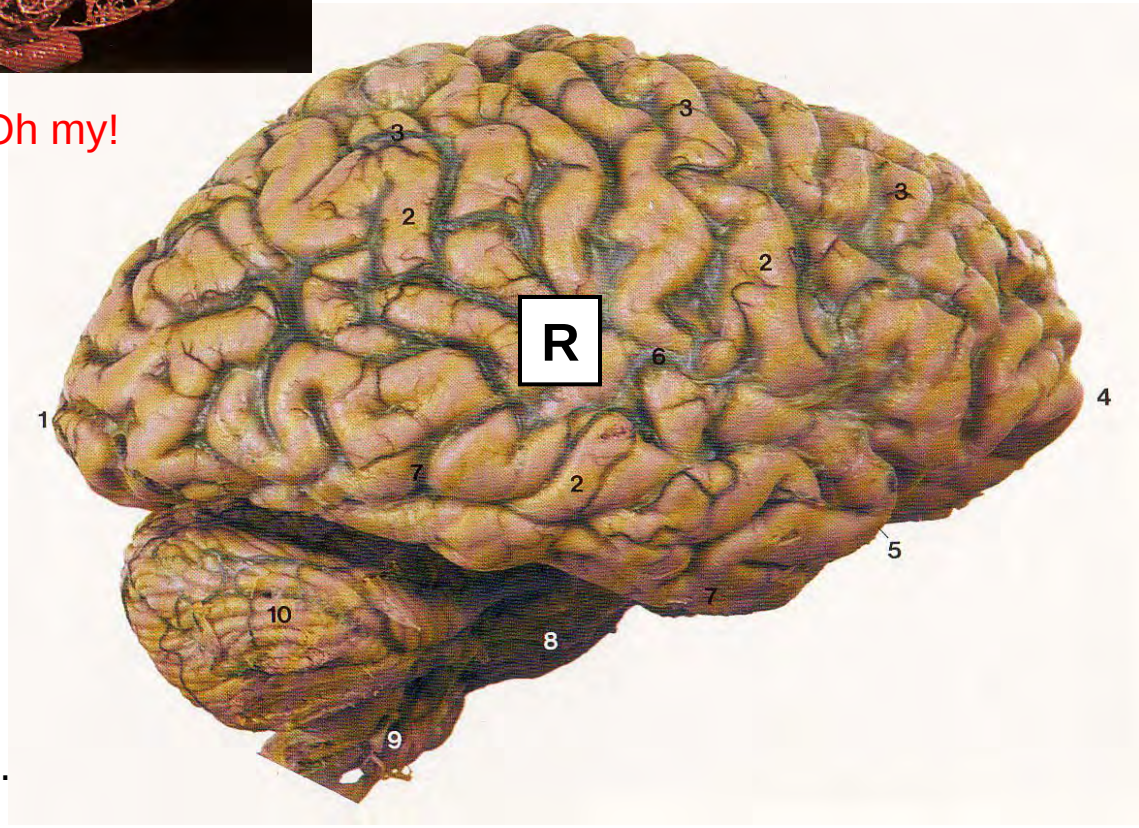


SOURCE: Lifeline Screening, 2007

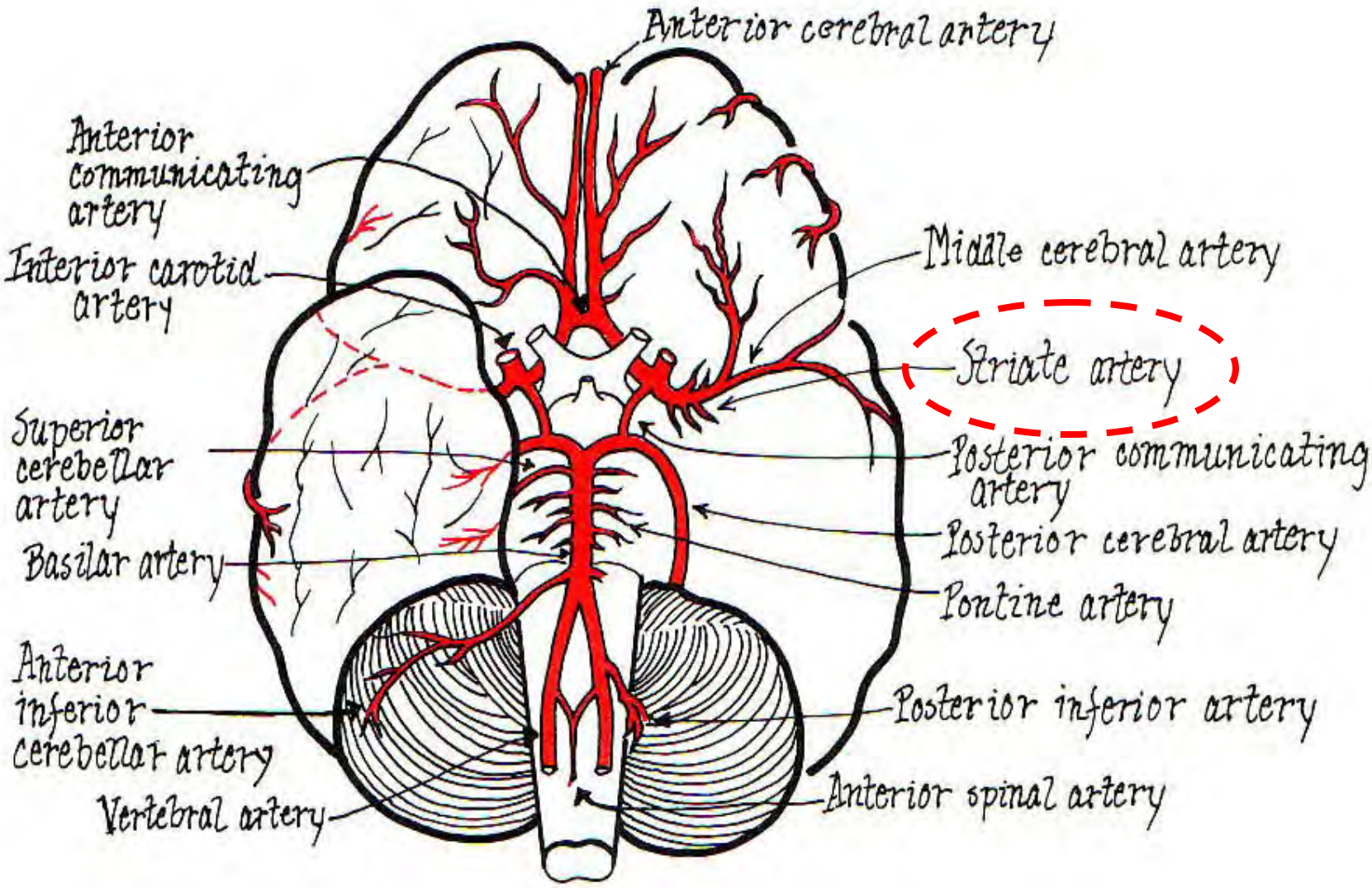


Middle Cerebral Artery Branches

…Cerebral vasculature! Oh my!

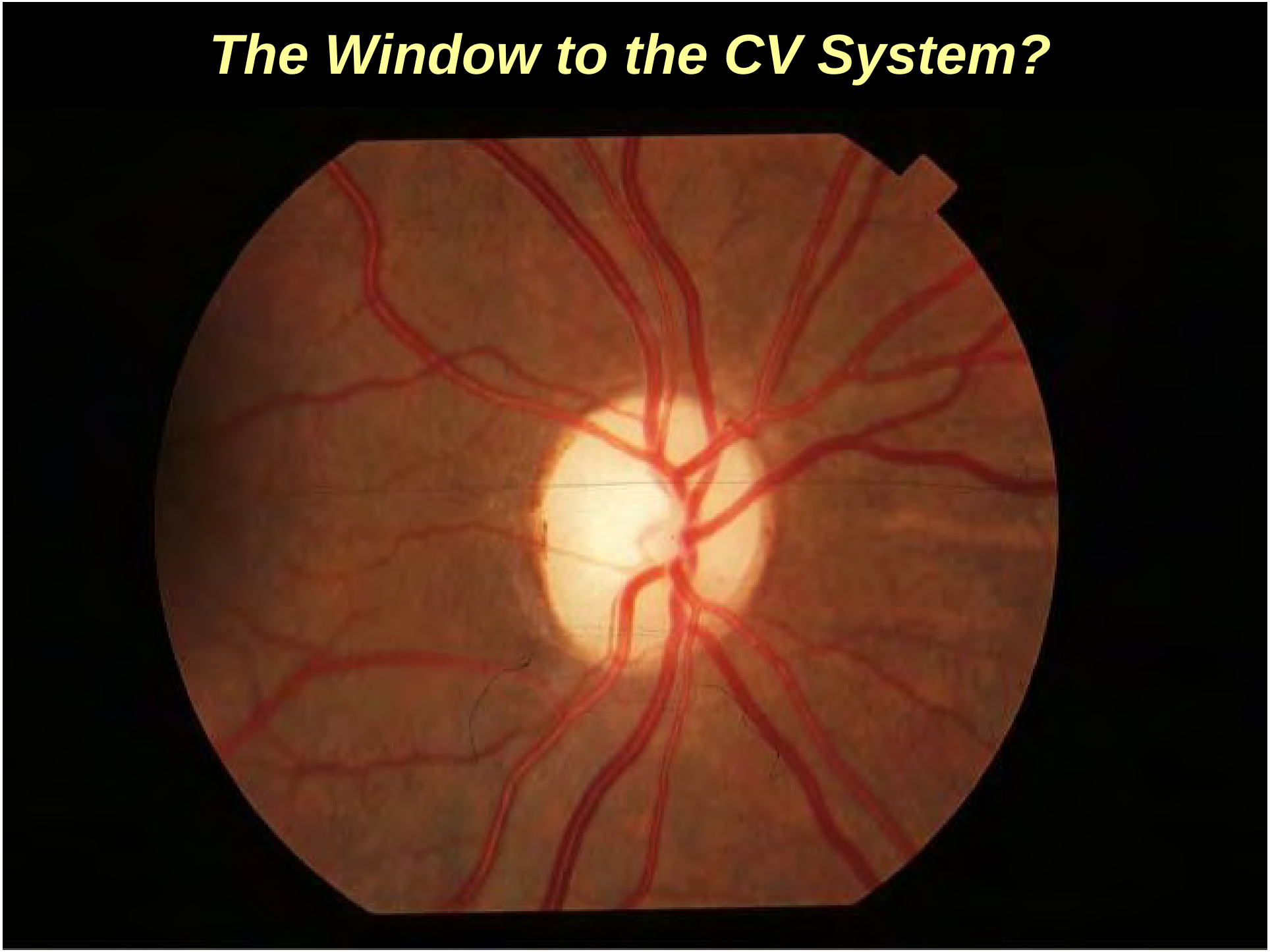


SOURCE: McMinn & Hutchins, 1977.

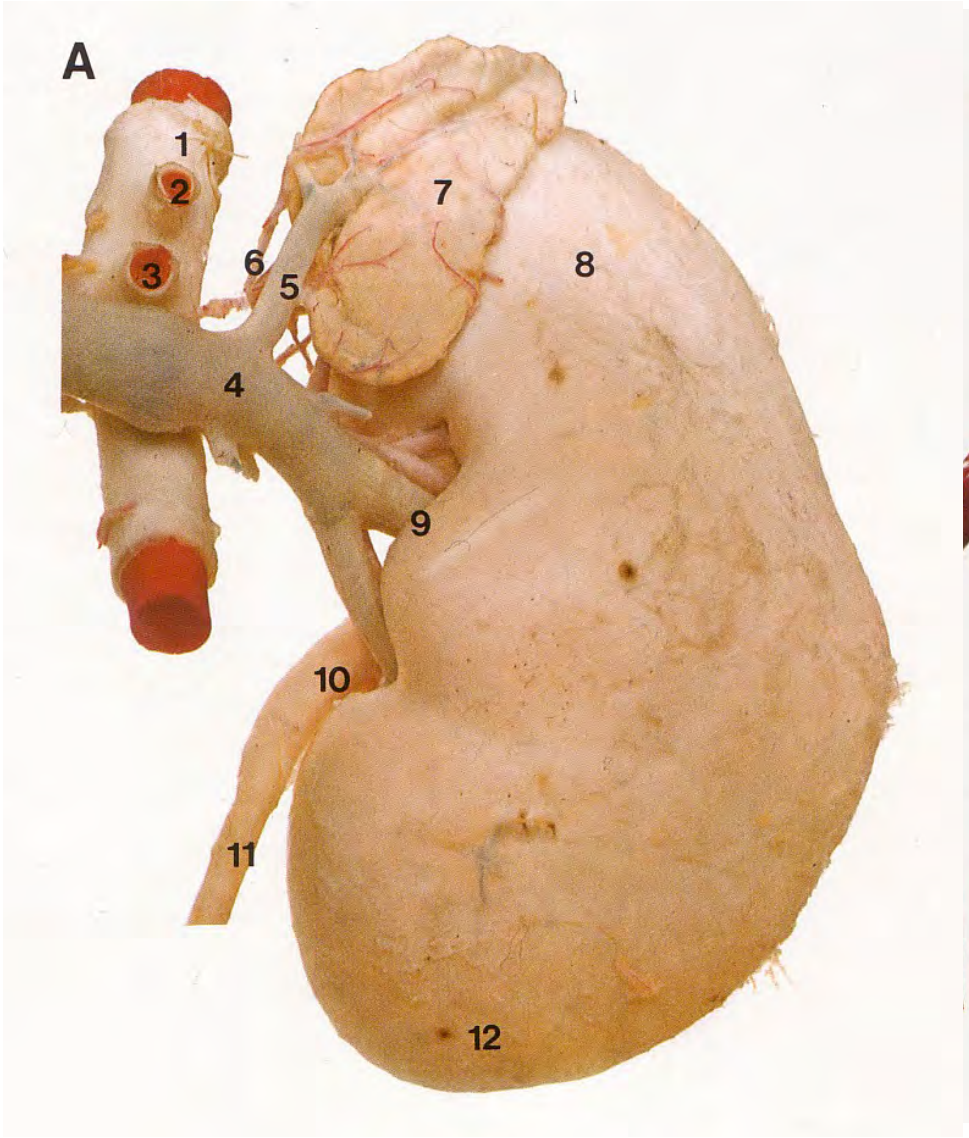


SOURCE: Liebman, 1979.

The Window to the CV System?



Renal Vasculature



SOURCE: McMinn & Hutchins, 1977.

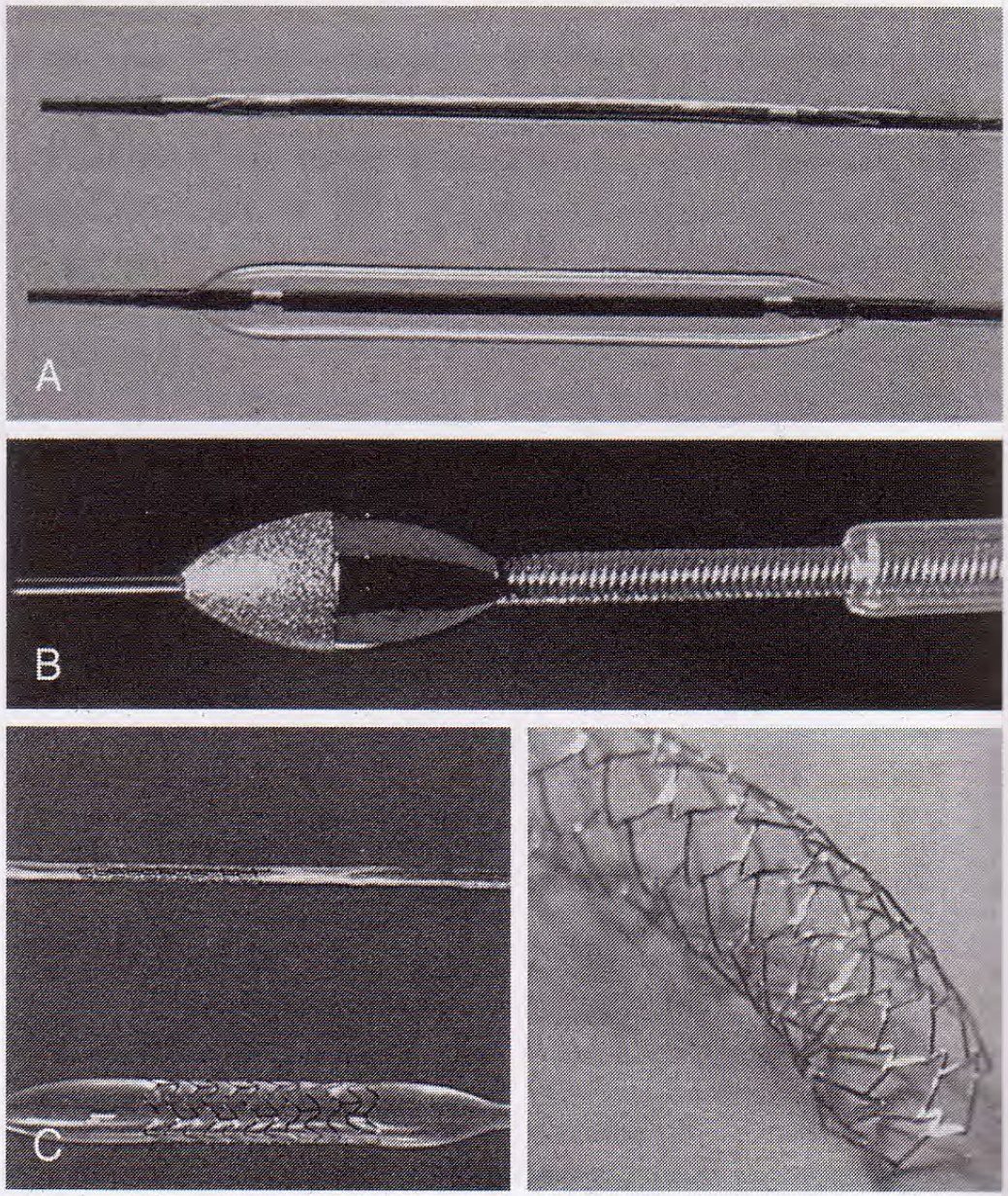
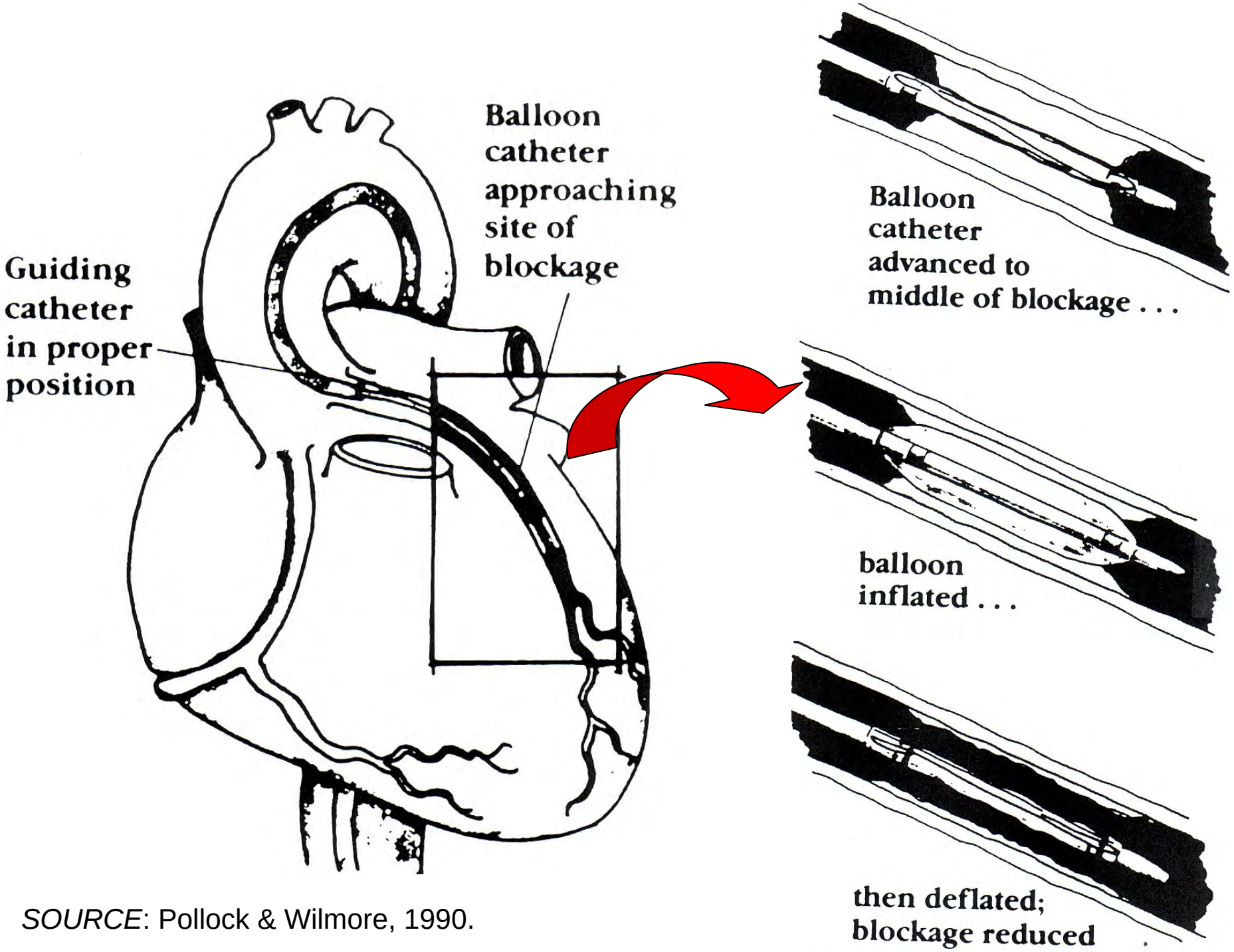
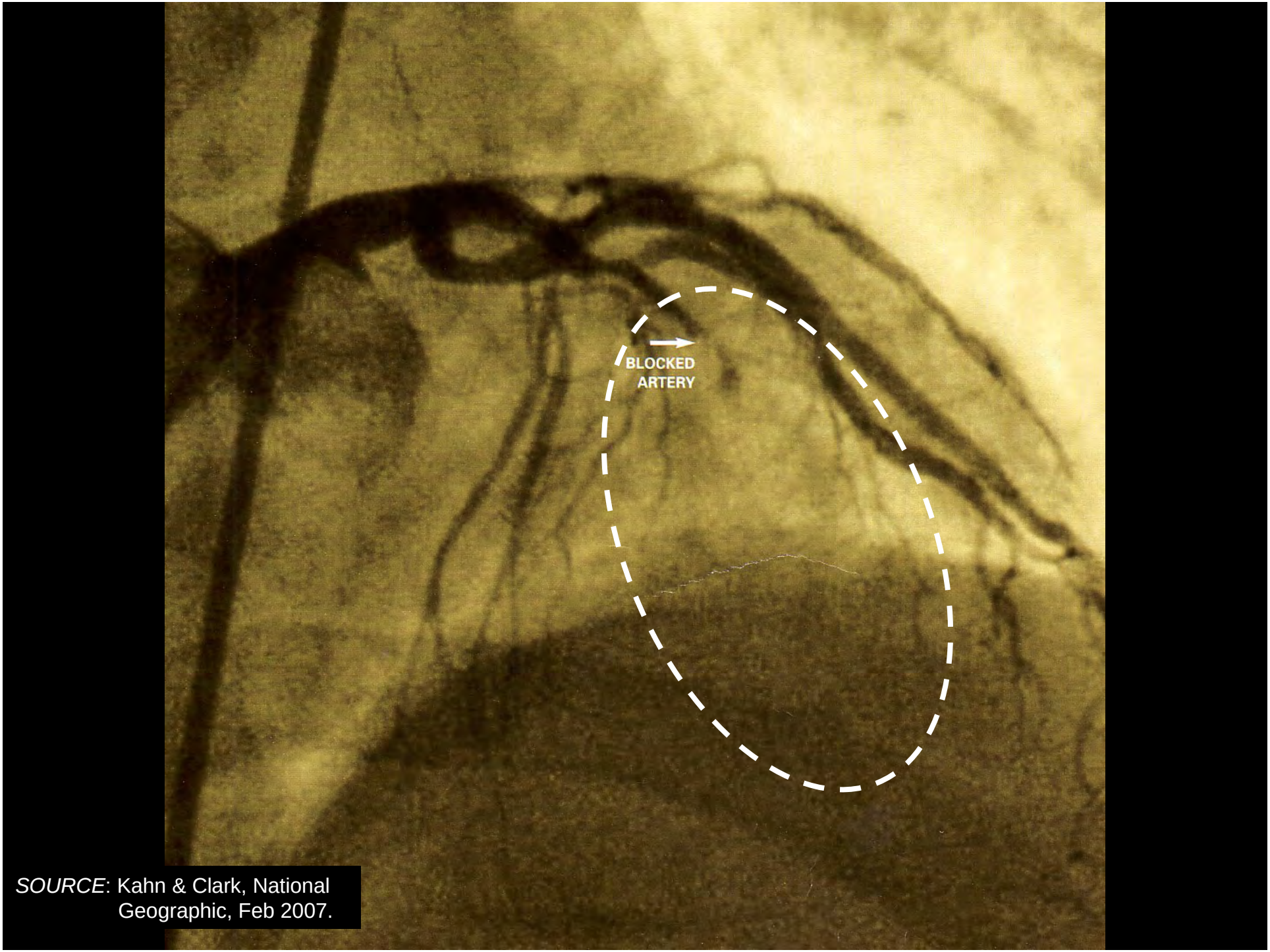


FIGURE 37–1 Devices for percutaneous transluminal coronary interventions. **A,** Coronary balloon. **B,** Rotational atherectomy burr (Rotablator). **C,** Coronary stent.

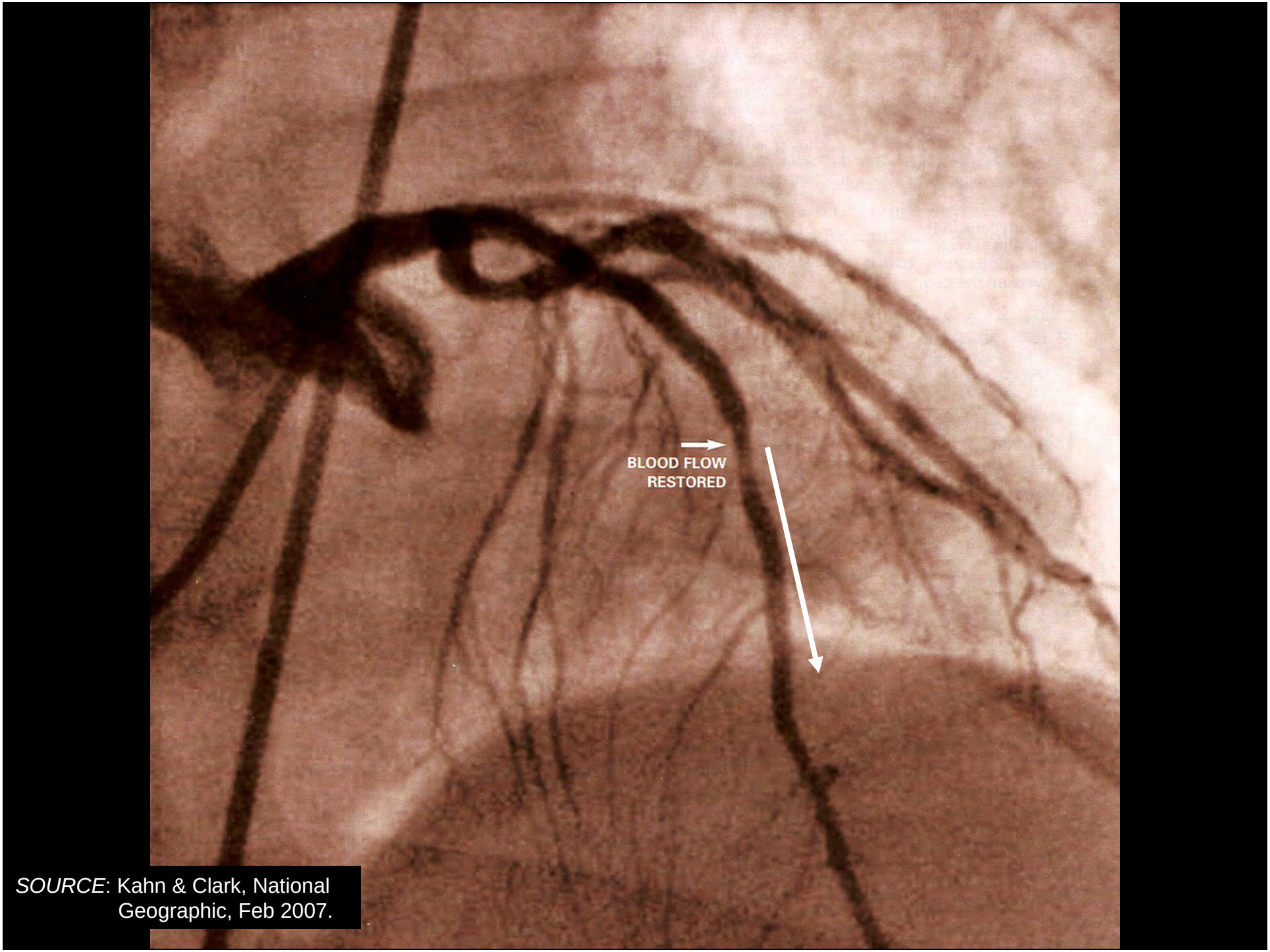
SOURCE: Willerson & Cohn, 2000.



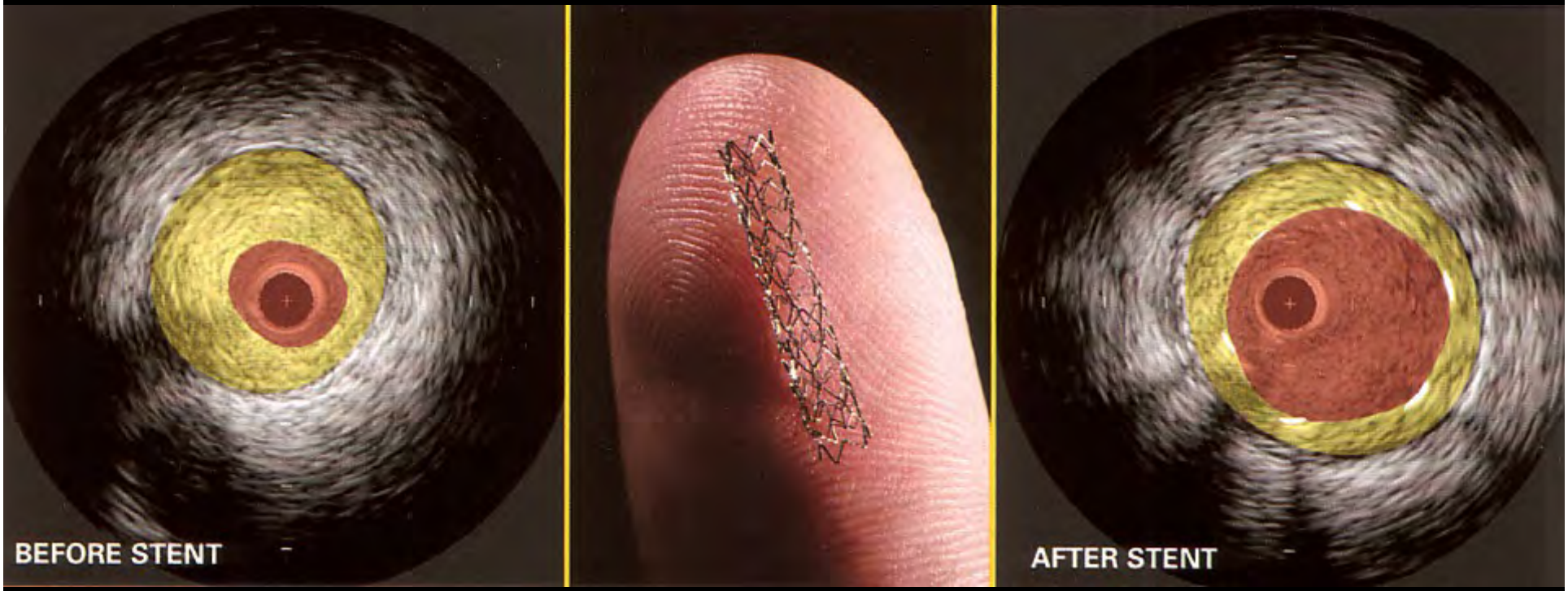
SOURCE: Pollock & Wilmore, 1990.



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

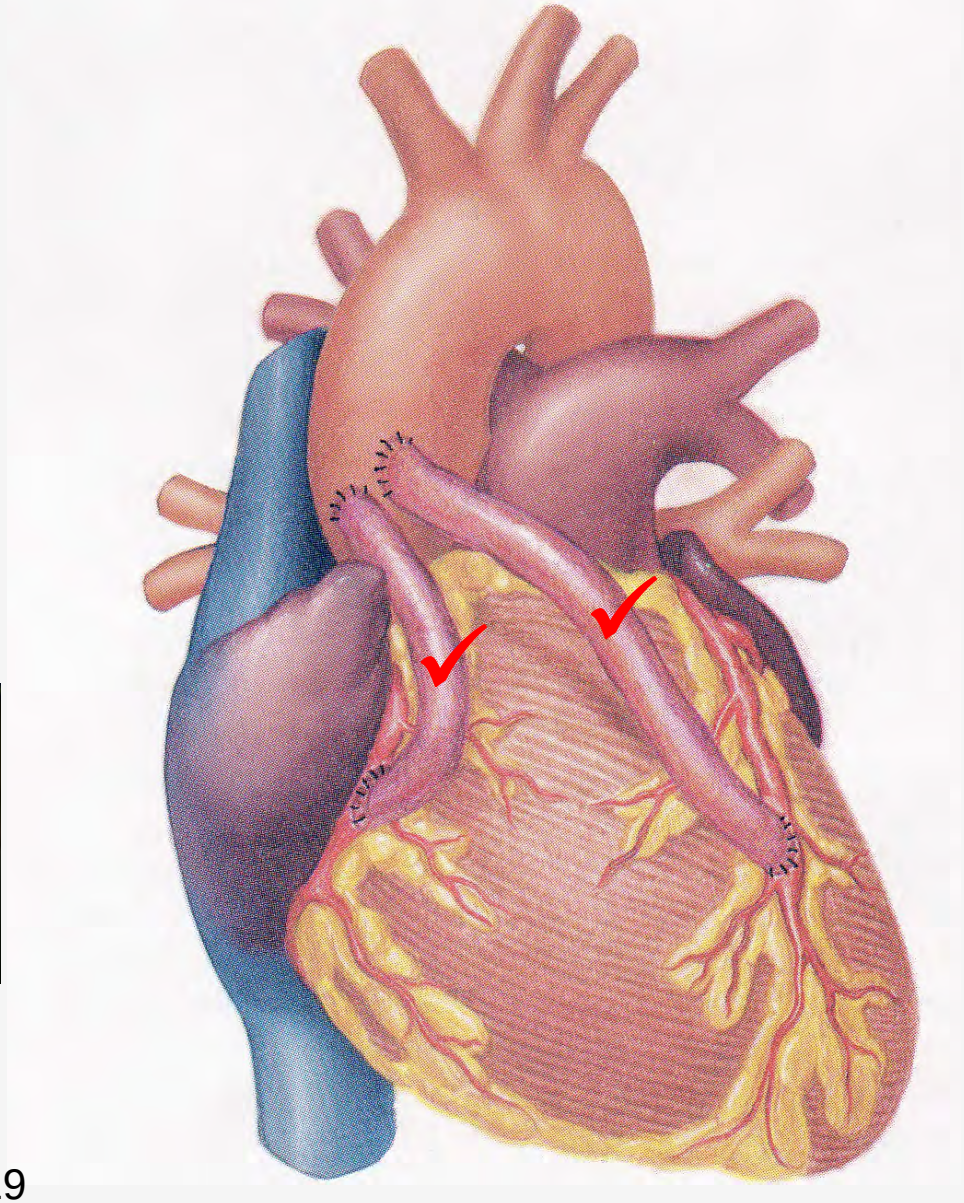


SOURCE: Kahn & Clark, National Geographic, Feb 2007.



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

CABG = Coronary Artery Bypass Graft



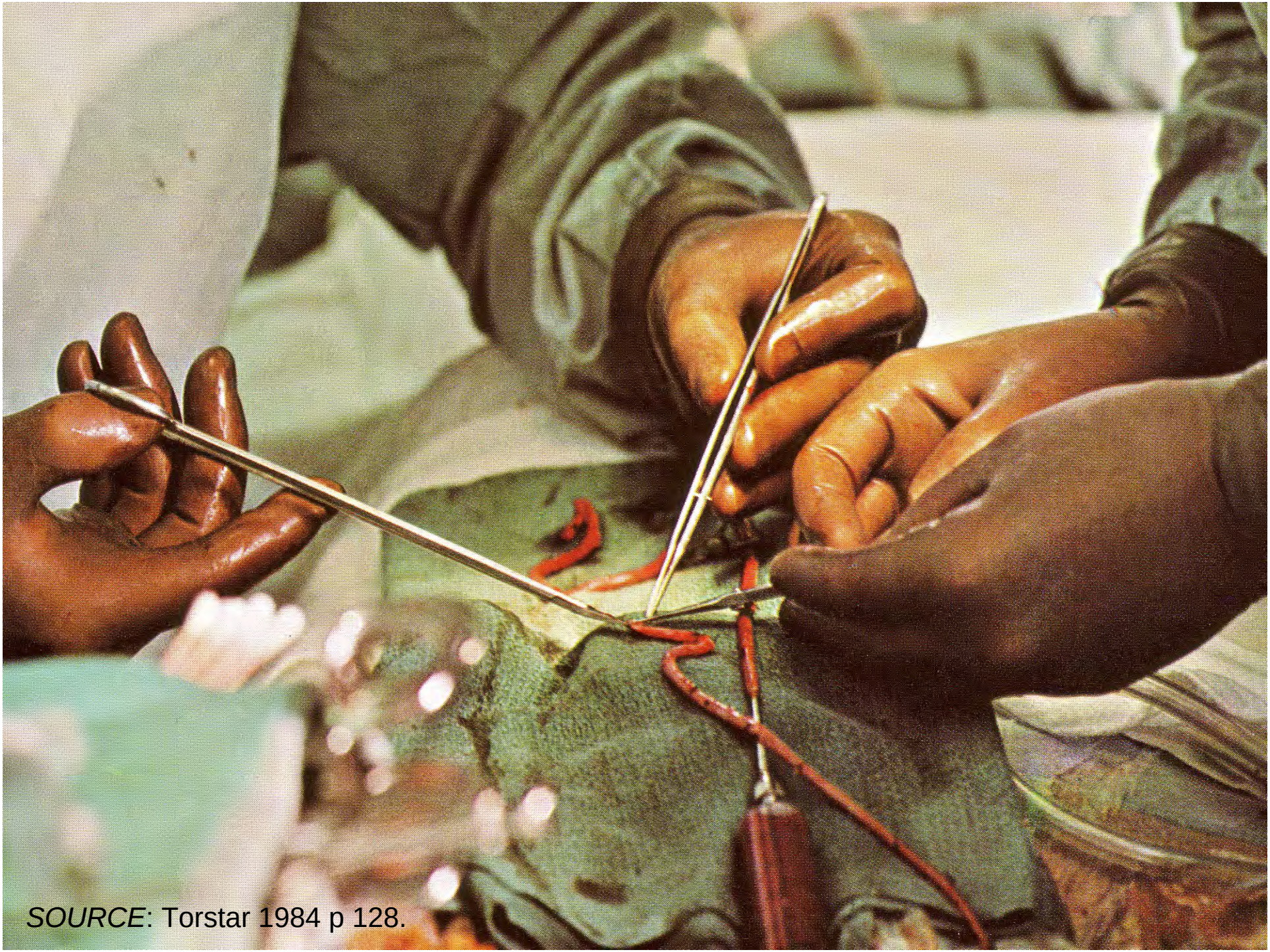
Double?

Triple?

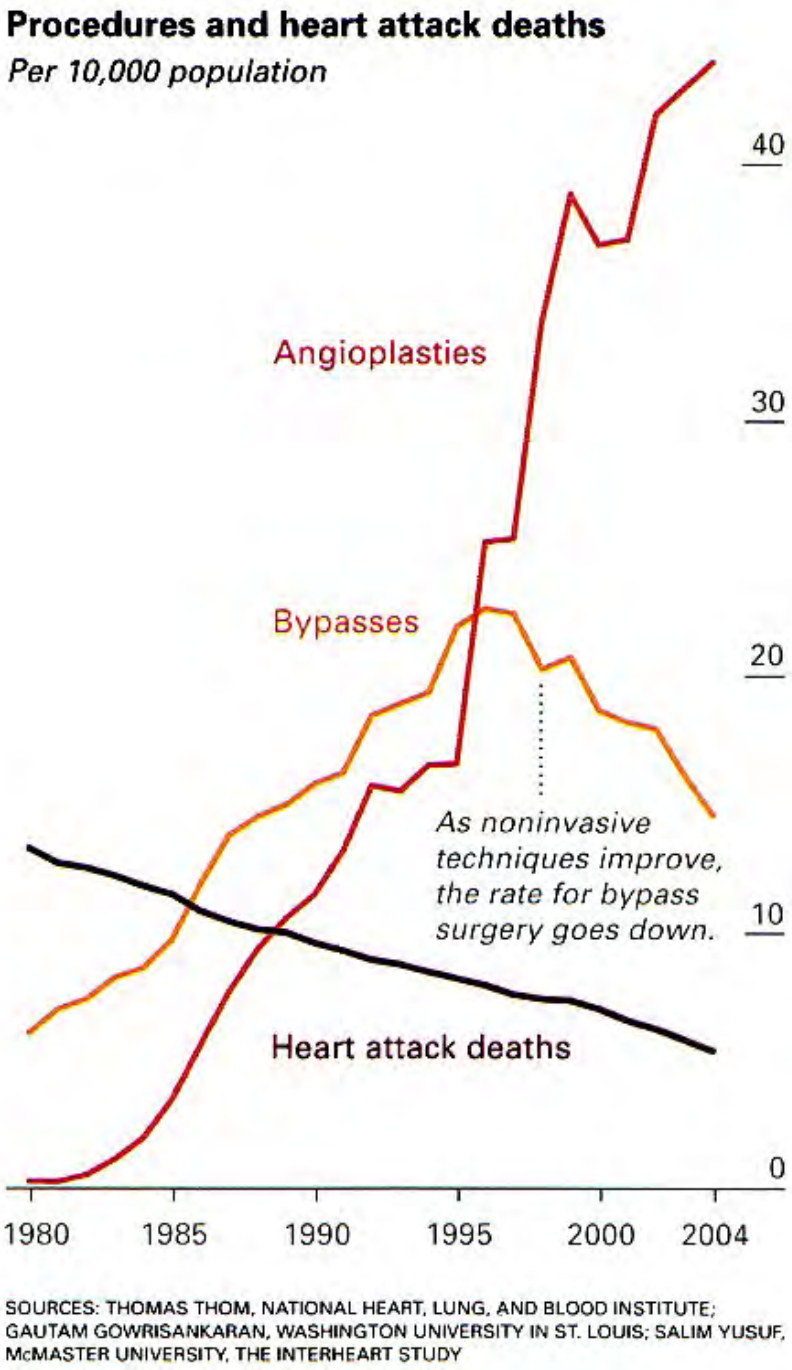
Quadruple?

Quintuple?

SI Fox 2013 fig 14.19



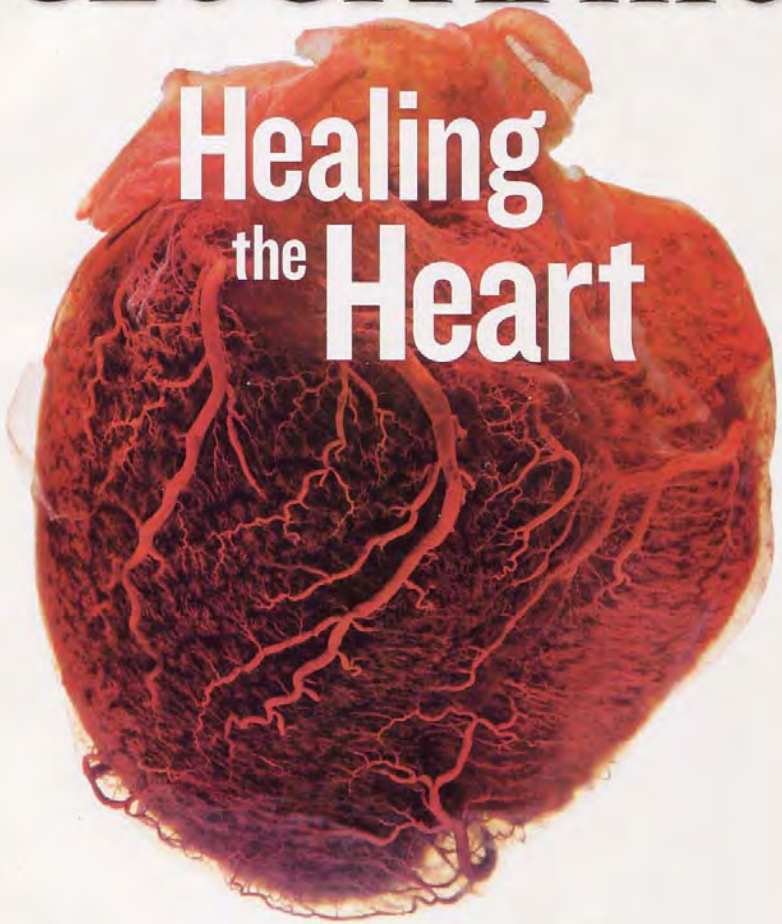
SOURCE: Torstar 1984 p 128.



National Geographic, 2007

NATIONALGEOGRAPHIC.COM/MAGAZINE FEBRUARY 2007

NATIONAL GEOGRAPHIC



Healing the Heart

Beauty on the Border 66 Curse of Nigerian Oil 88
Hawaii's Unearthly Worms 118 Forests of the Tide 132

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

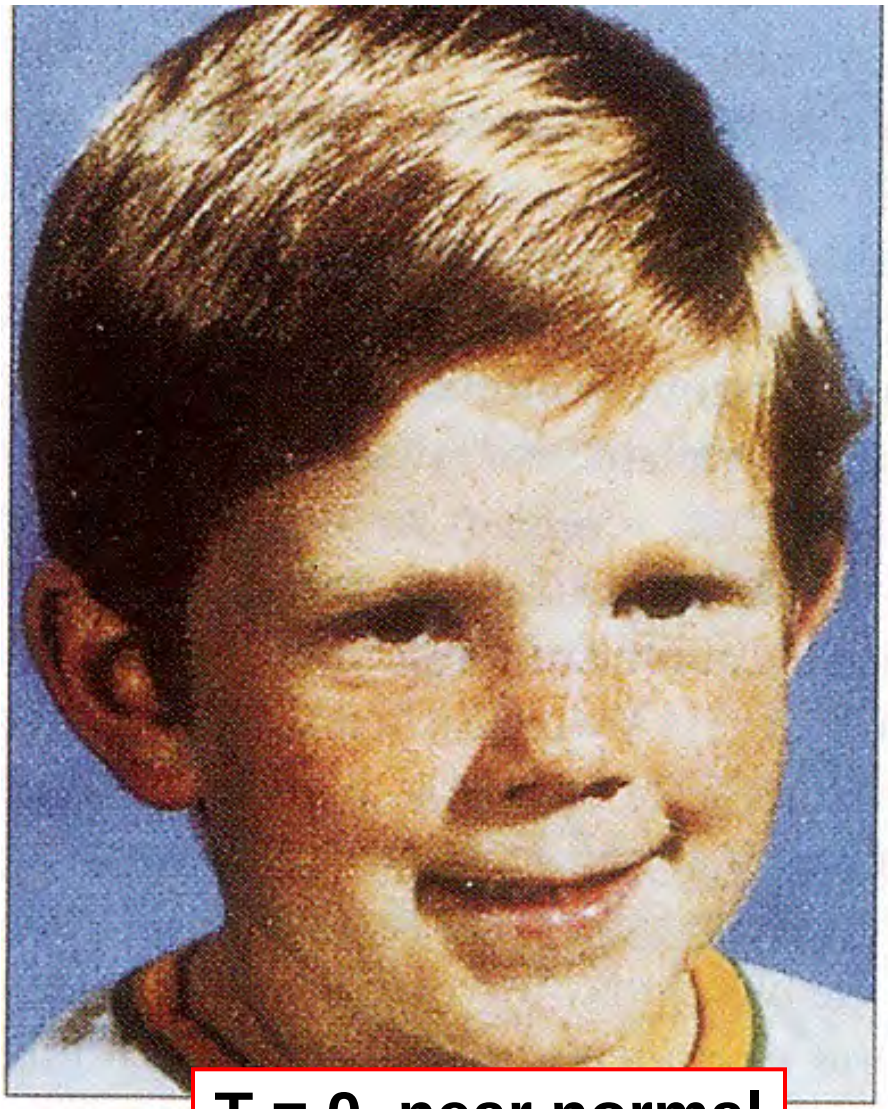

http://ngm.nationalgeographic.com/2007/02/hearts/hearts-text.html
Photograph by Robert Clark

Discussion

Comments

Q?

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



T = 0, near normal

T = 4 months later

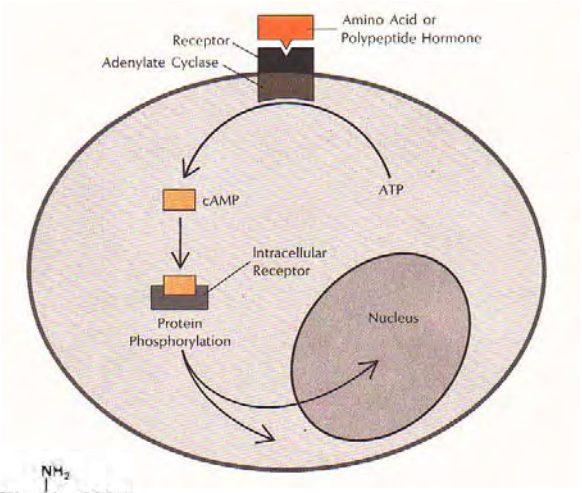
Endocrine/Hormone?

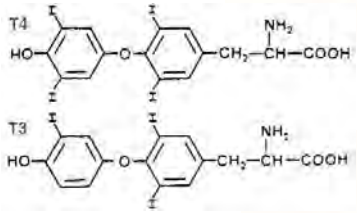
1. ***Made by gland?***
2. ***Secreted into blood?***
3. ***Acts on target?***

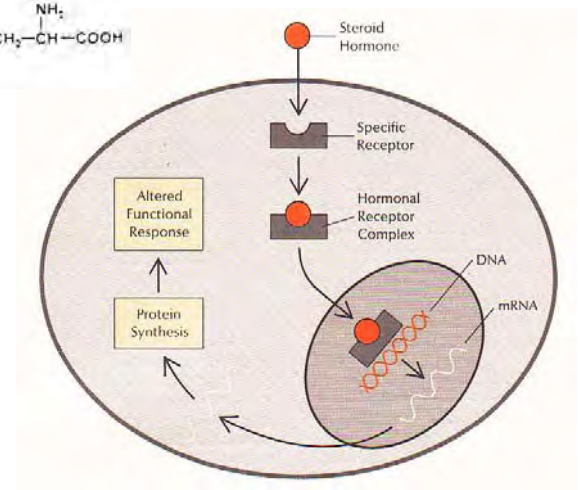
Hormone/Endocrine Classifications

Exogenous

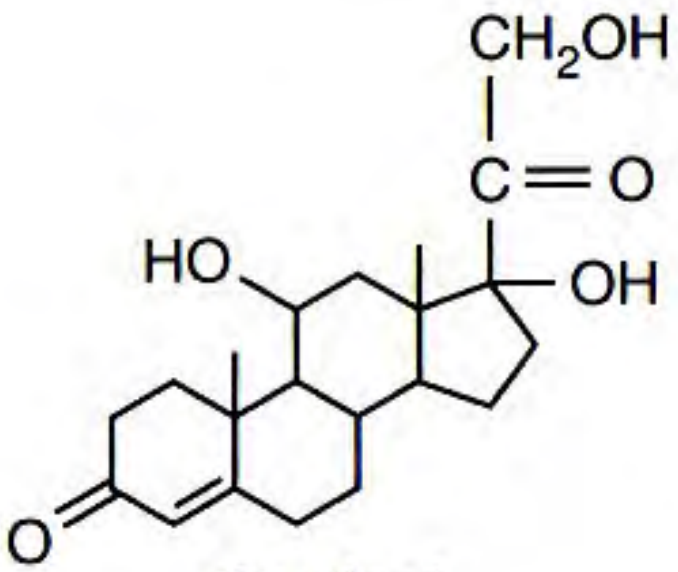
Endogenous



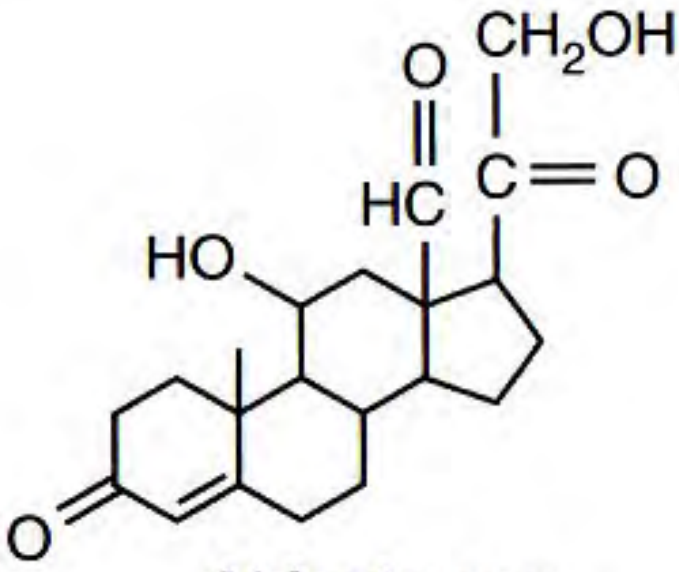




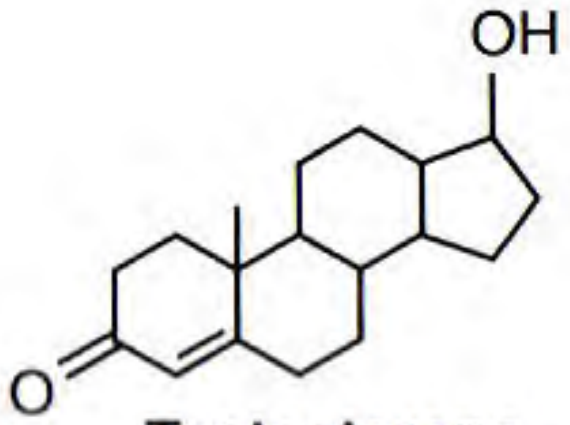
Steroid Hormone Structure: Cholesterol Backbone



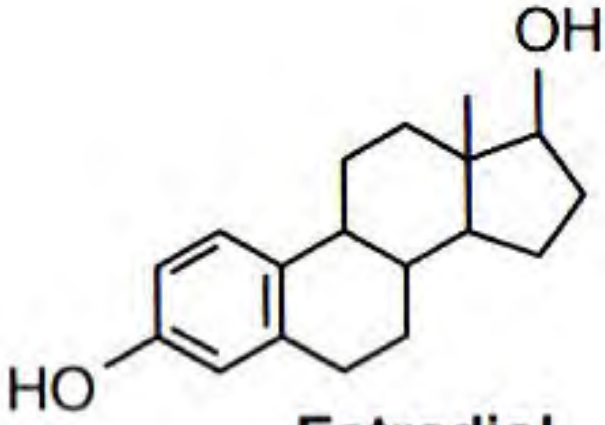
Cortisol



Aldosterone



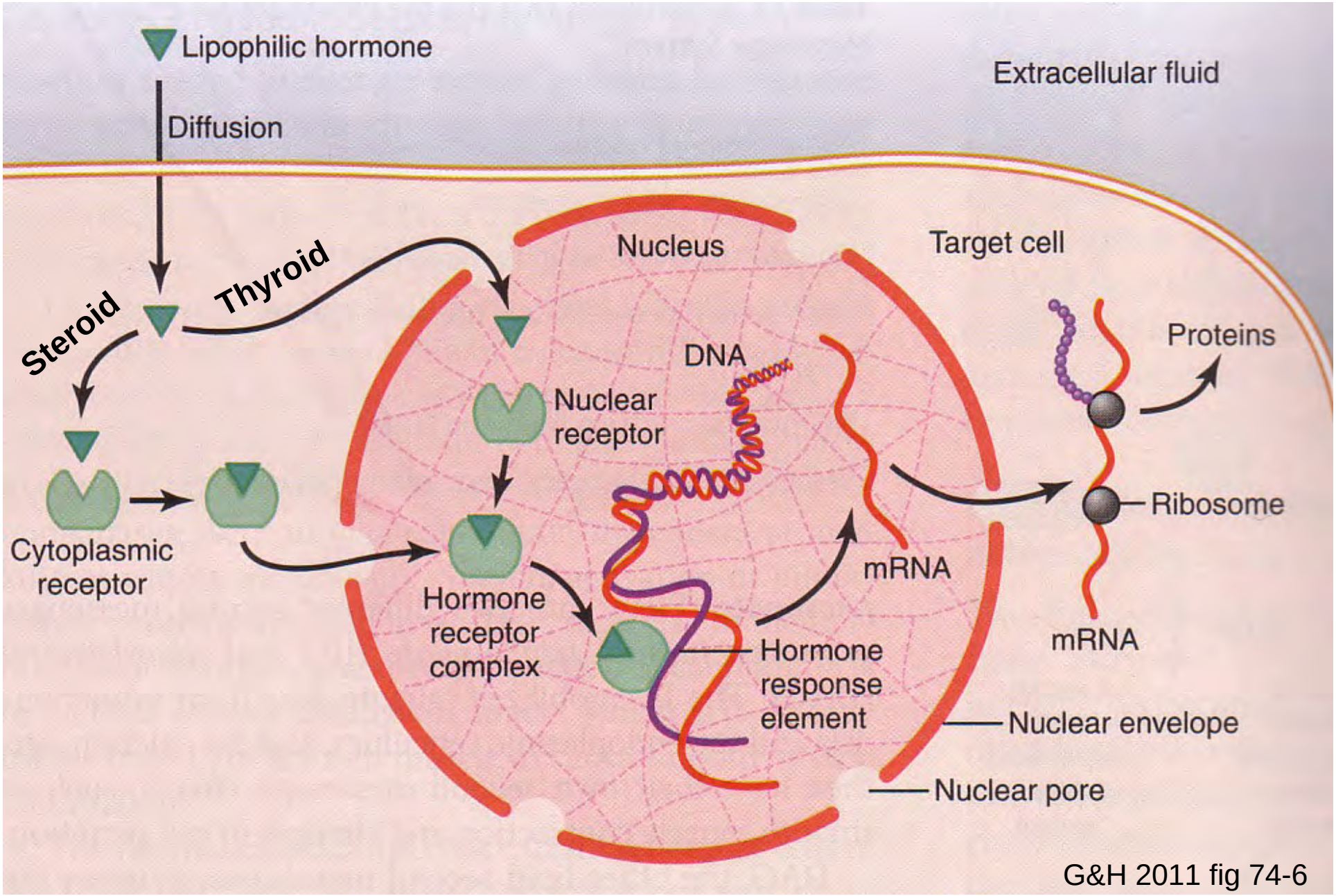
Testosterone



Estradiol

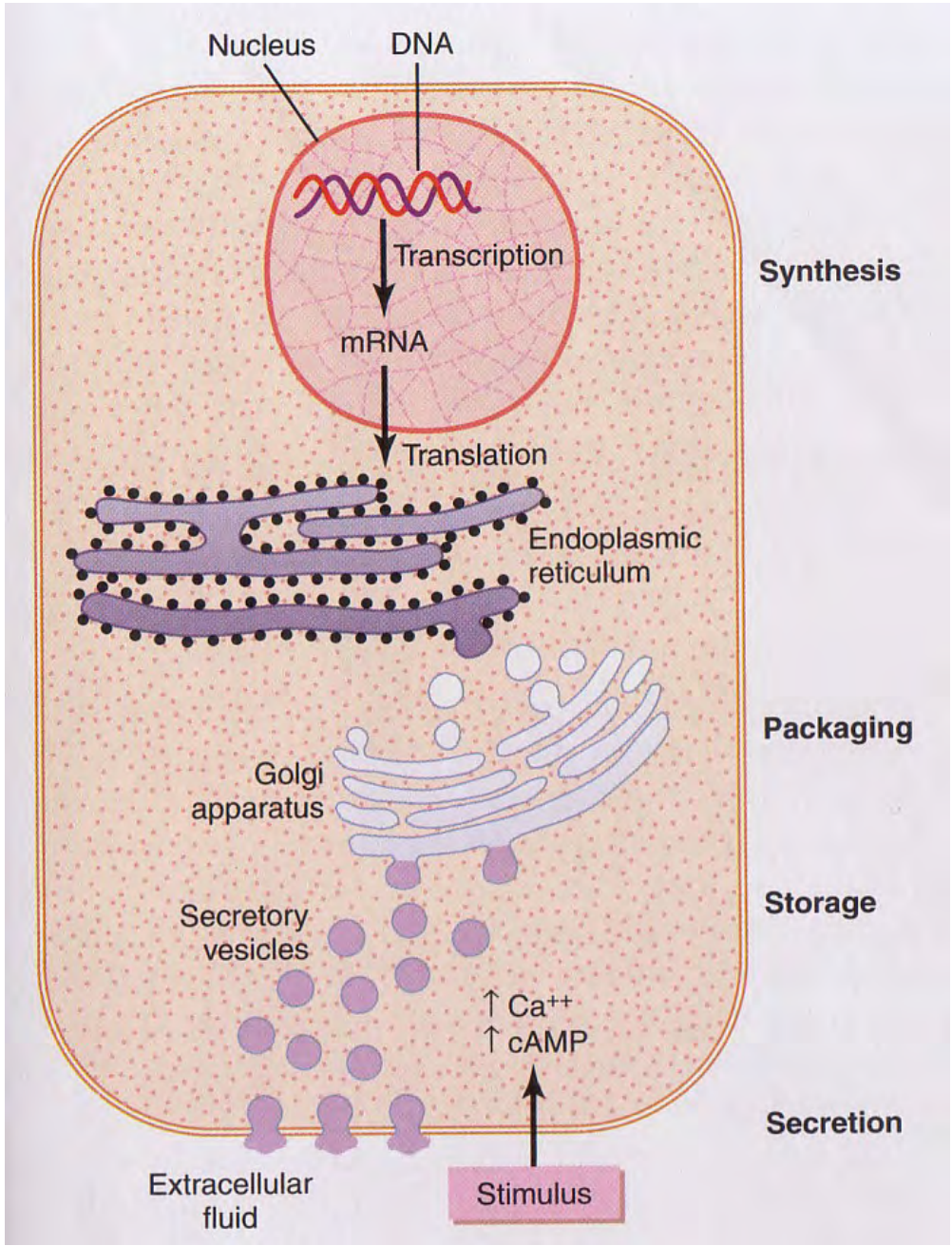
G&H 2011 fig 74-3; cf: fig 77-2

Lipophilic (Steroid+Thyroid) Hormone Mechanisms



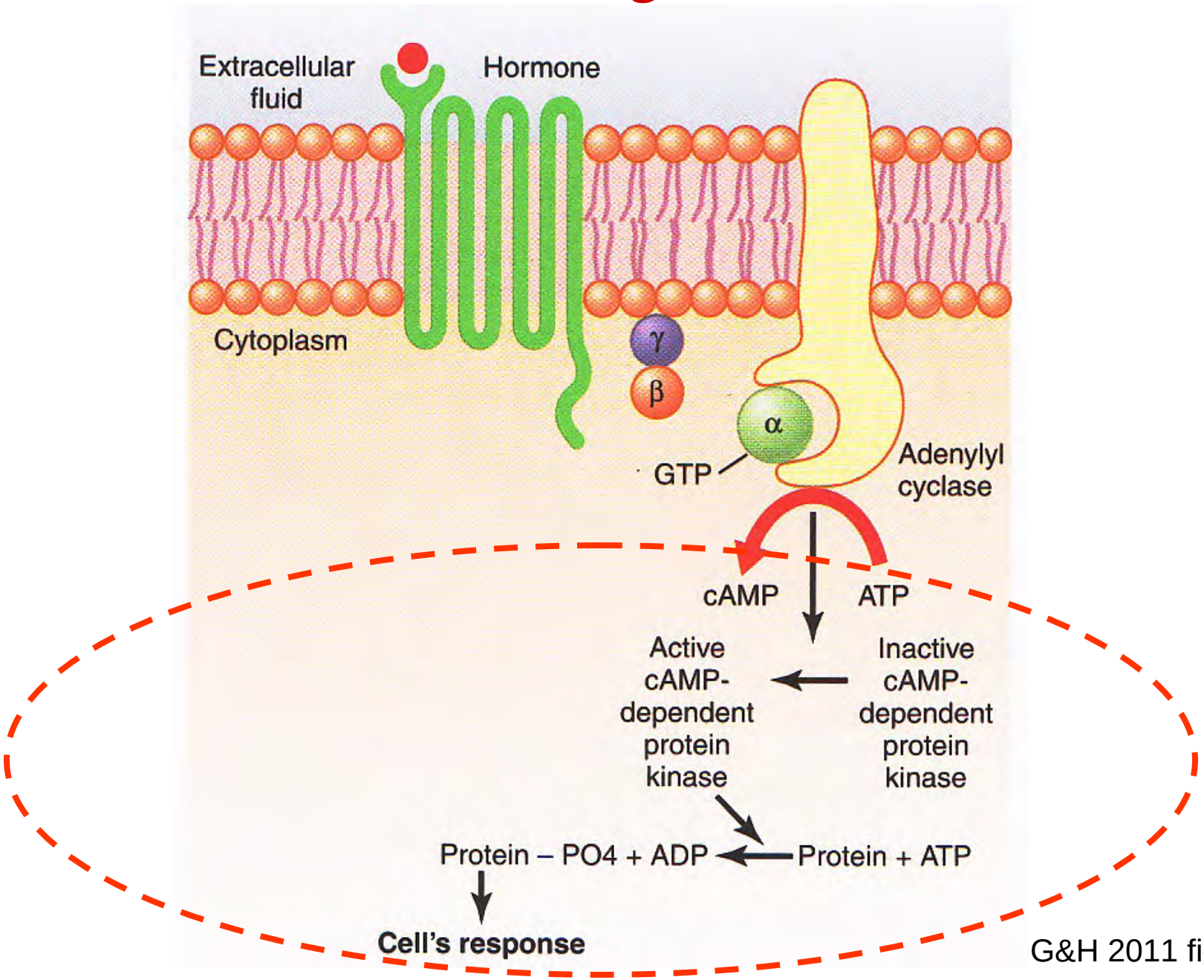
G&H 2011 fig 74-6

Peptide Hormone Synthesis & Secretion



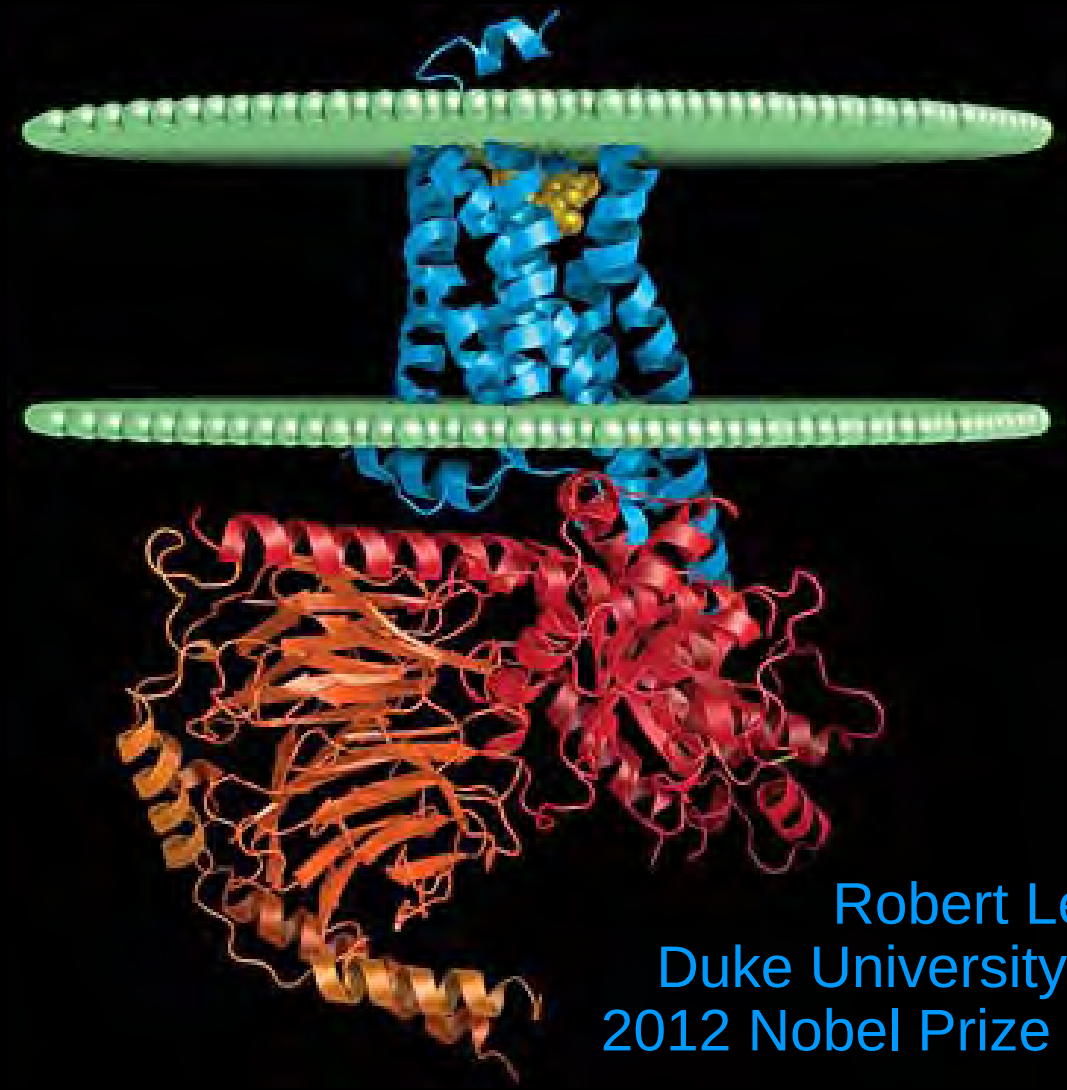
G&H 2011 fig 74-2

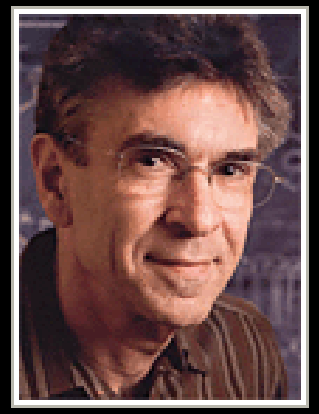
cAMP 2nd Messenger Mechanism



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

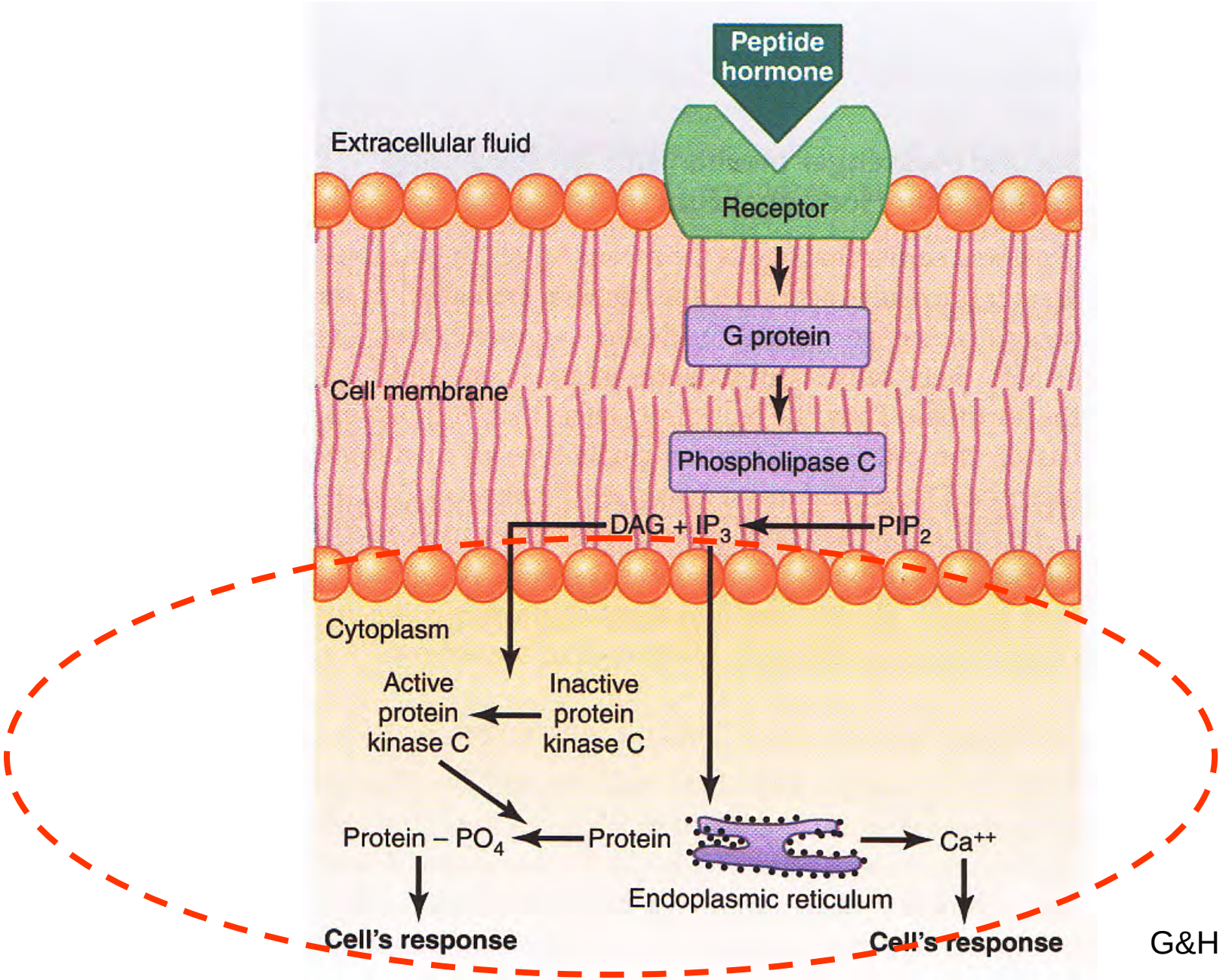
http://www.hhmi.org/bulletin/winter2013/features/index.html
Image by Wayne Decatur

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 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)

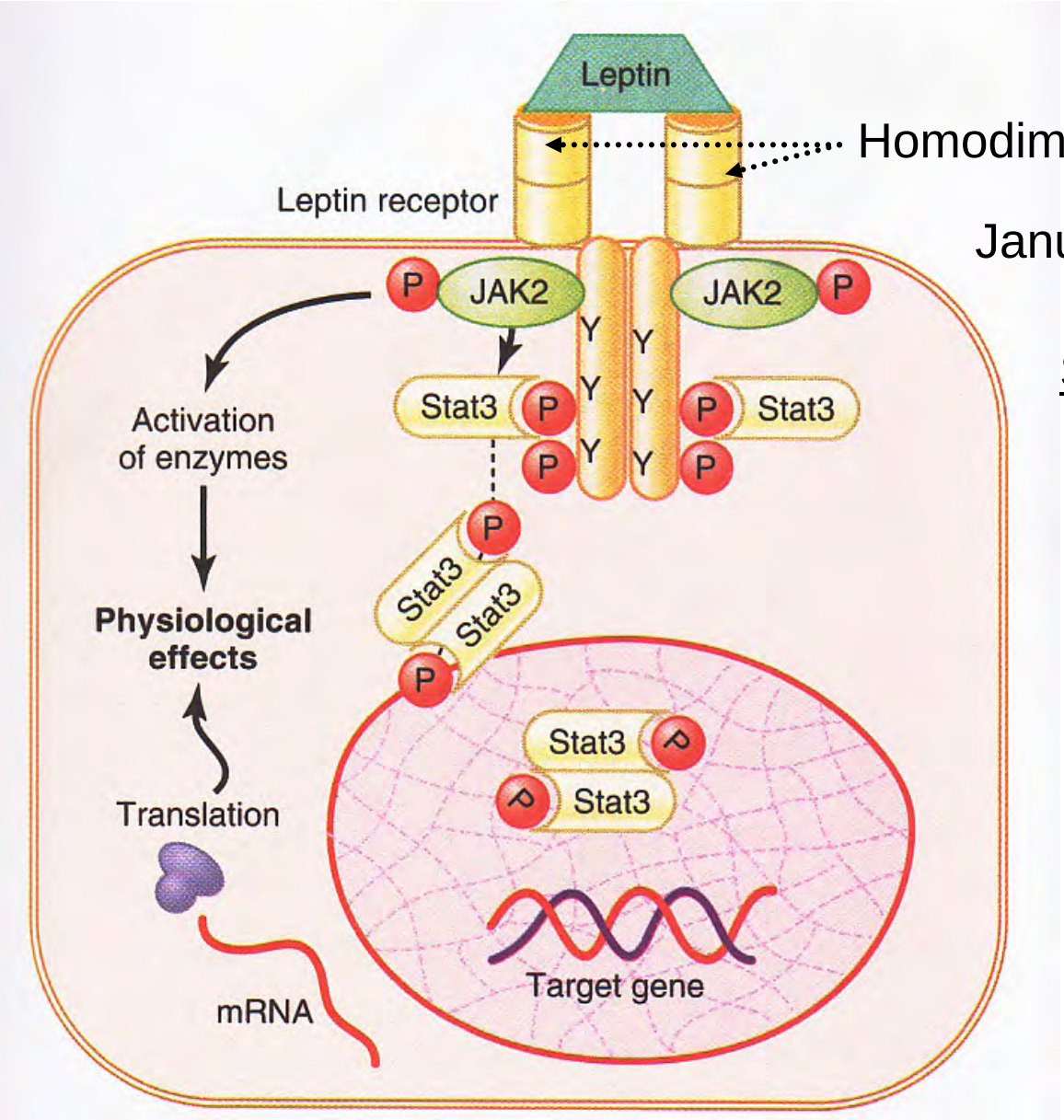
Growth-hormone-releasing hormone (GHRH)

Oxytoxin (OXY, hypothalamus production, posterior pituitary storage)

Thyrotropin releasing hormone TRH)

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

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 2011 fig 74-5

ANP = Atrial Natriuretic Polypeptide

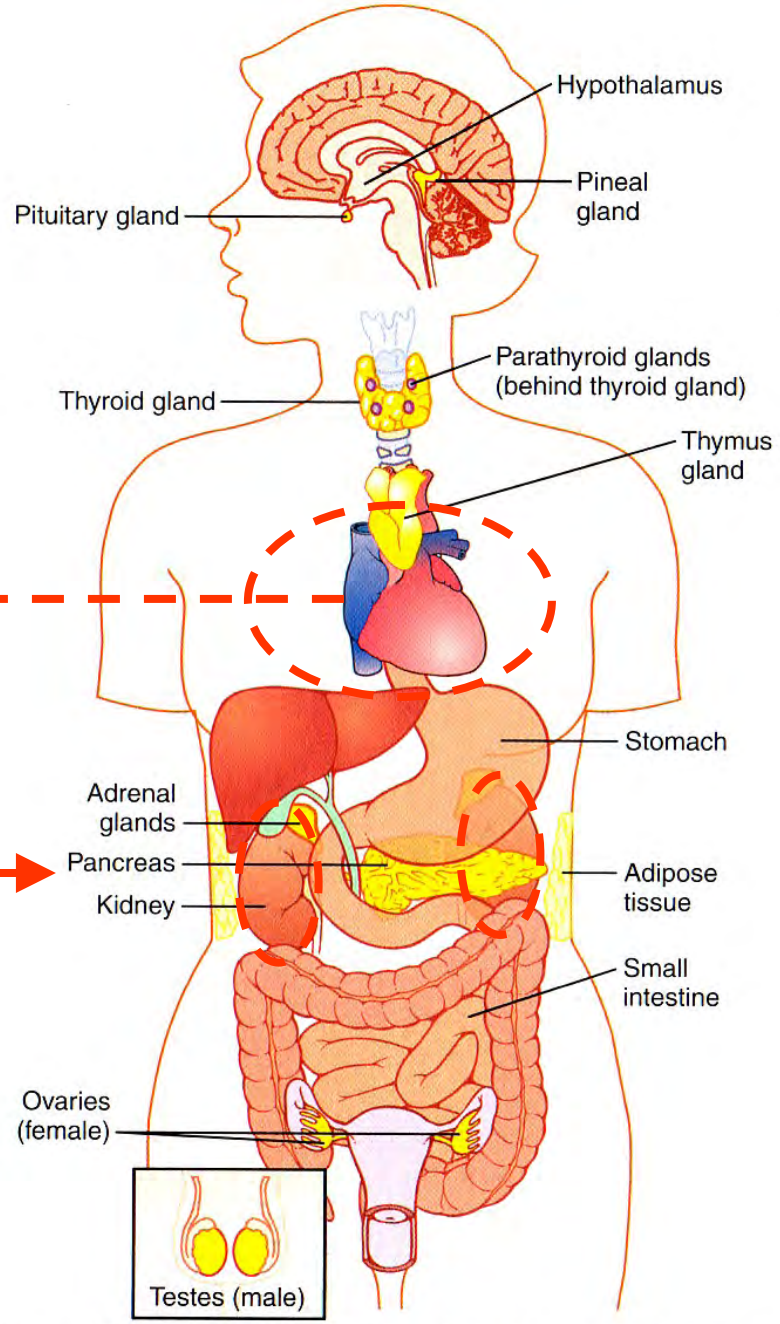
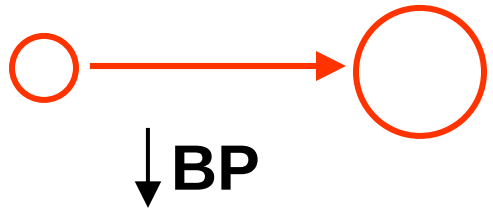


Figure 74-1 Anatomical loci of the principal endocrine glands and tissues of the body.

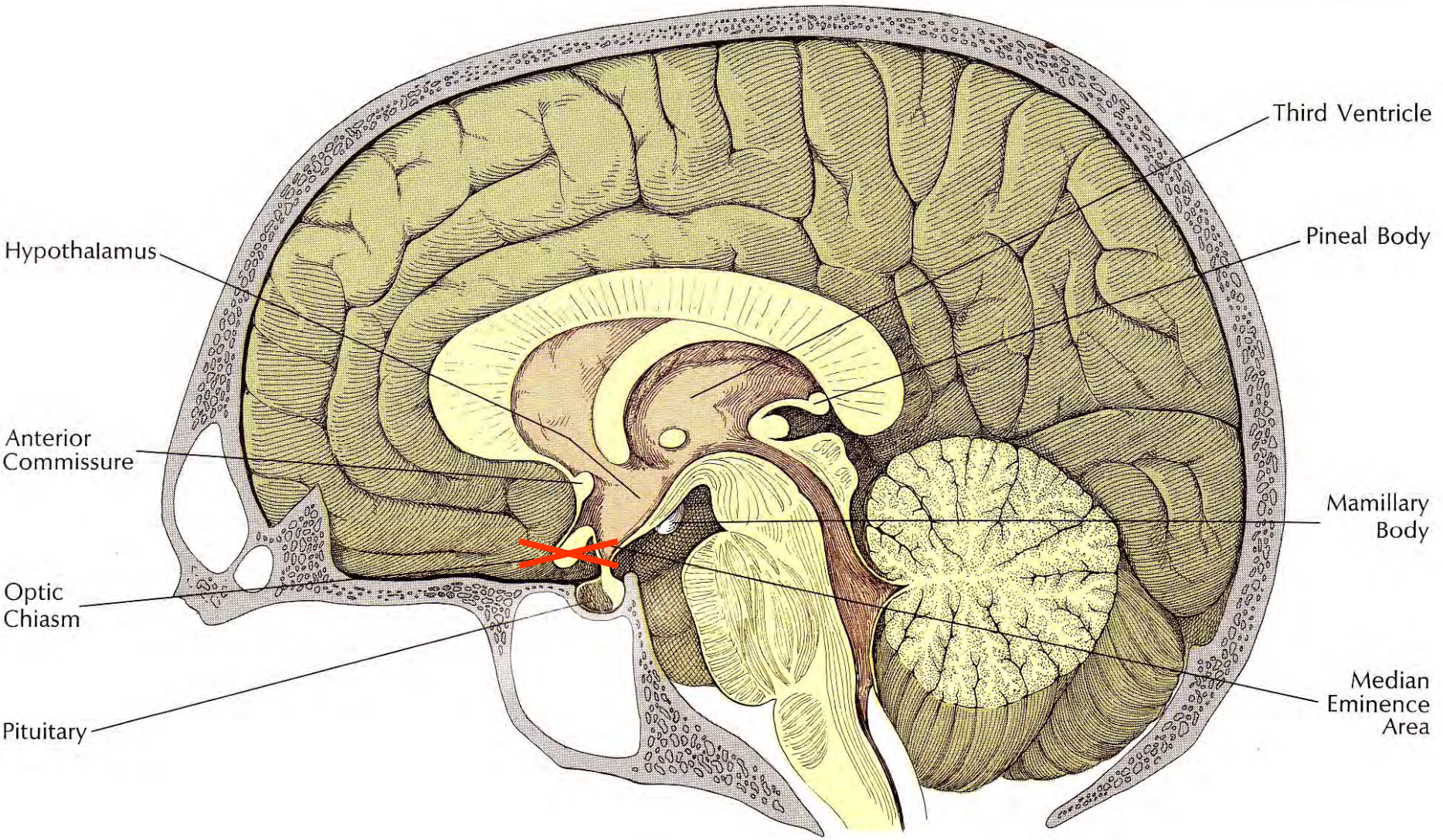
2 **Vasodilation**



↓**BP**

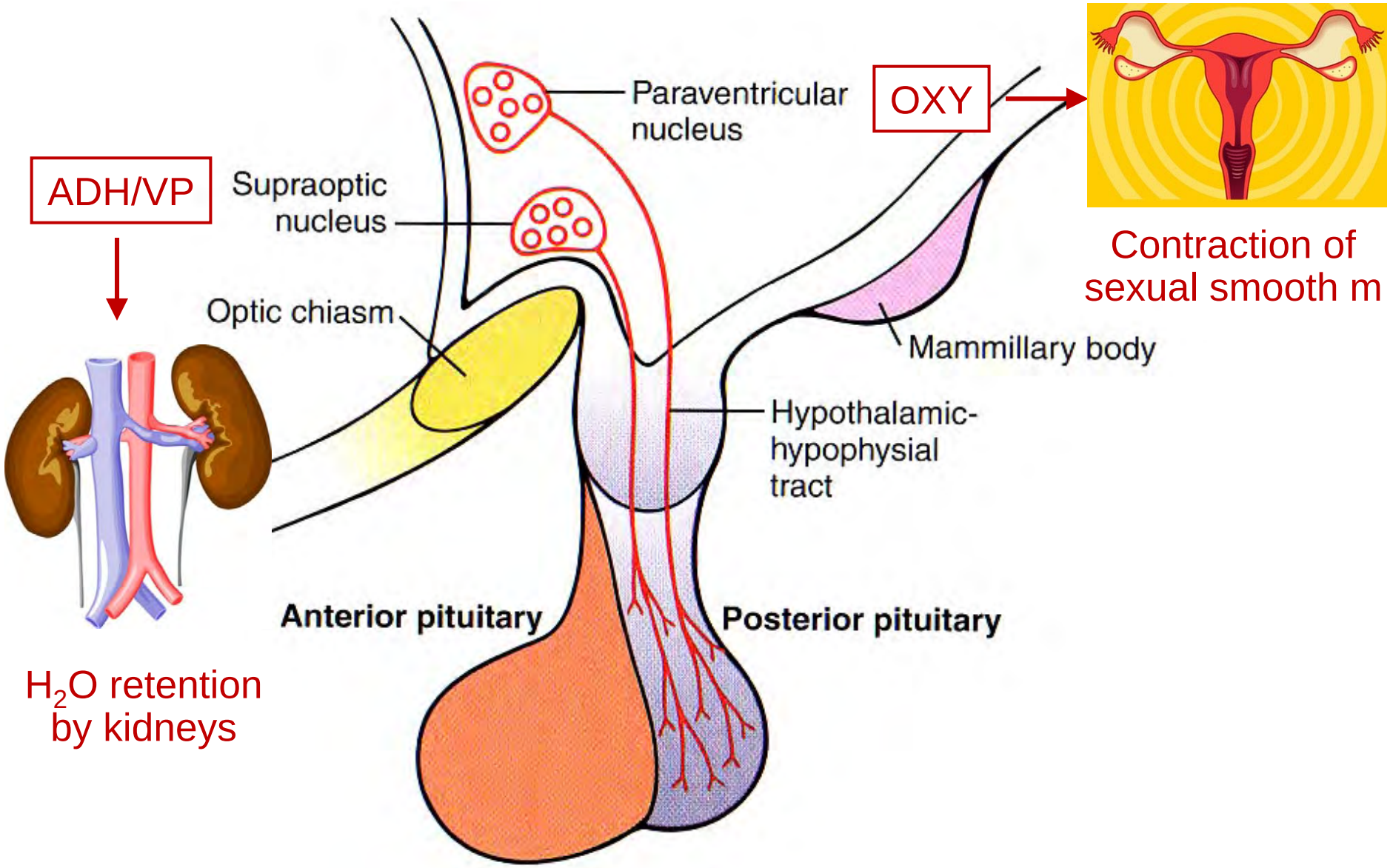
G&H 2011

Lateral View Showing Relationship of the Pituitary Gland to the Hypothalamus



Krieger & Hughes 1980

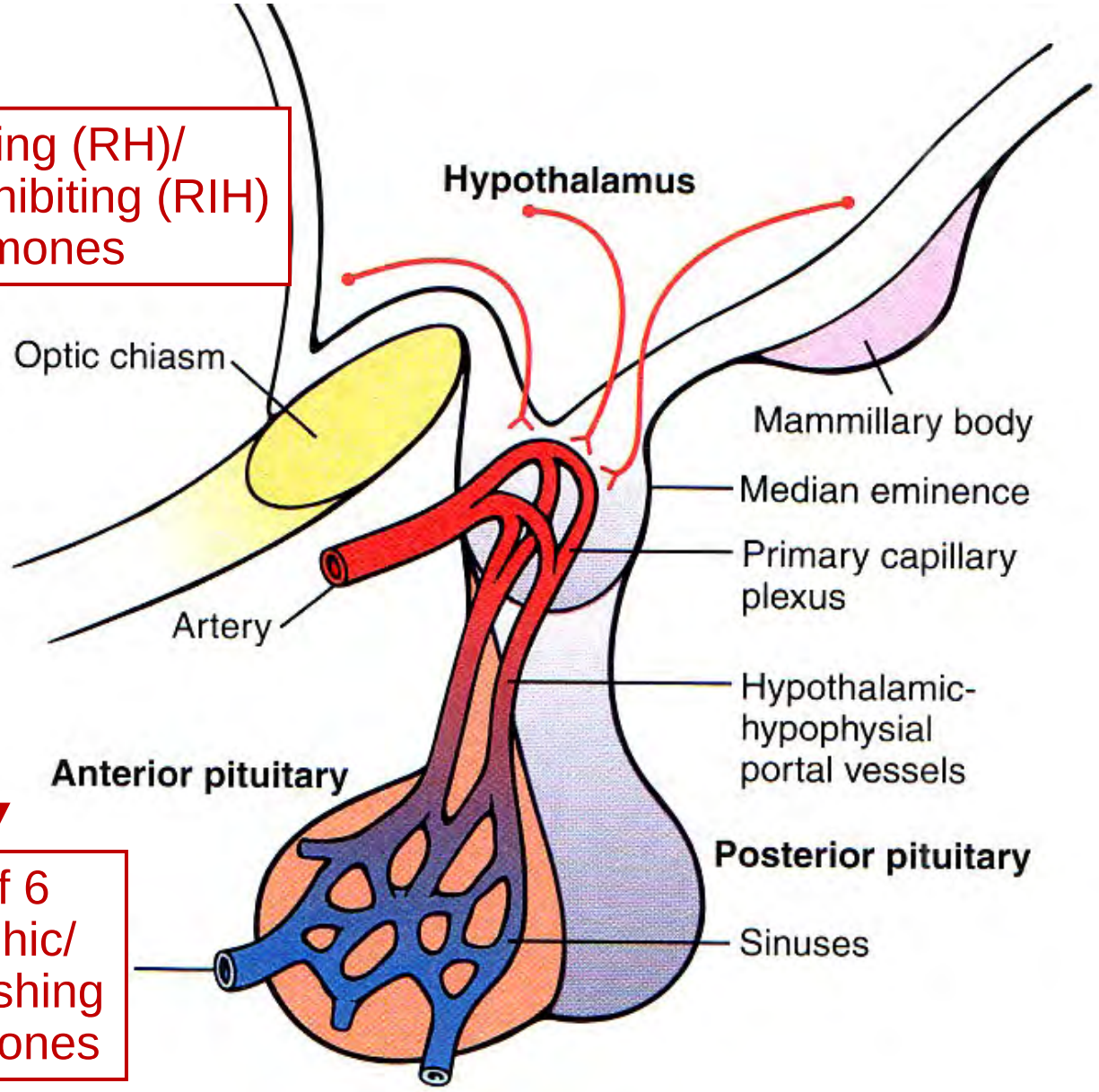
Hypothalamus – Posterior Pituitary Nervous Connection



G&H 2011 fig 75-9

Hypothalamus – Anterior Pituitary Vascular Connection

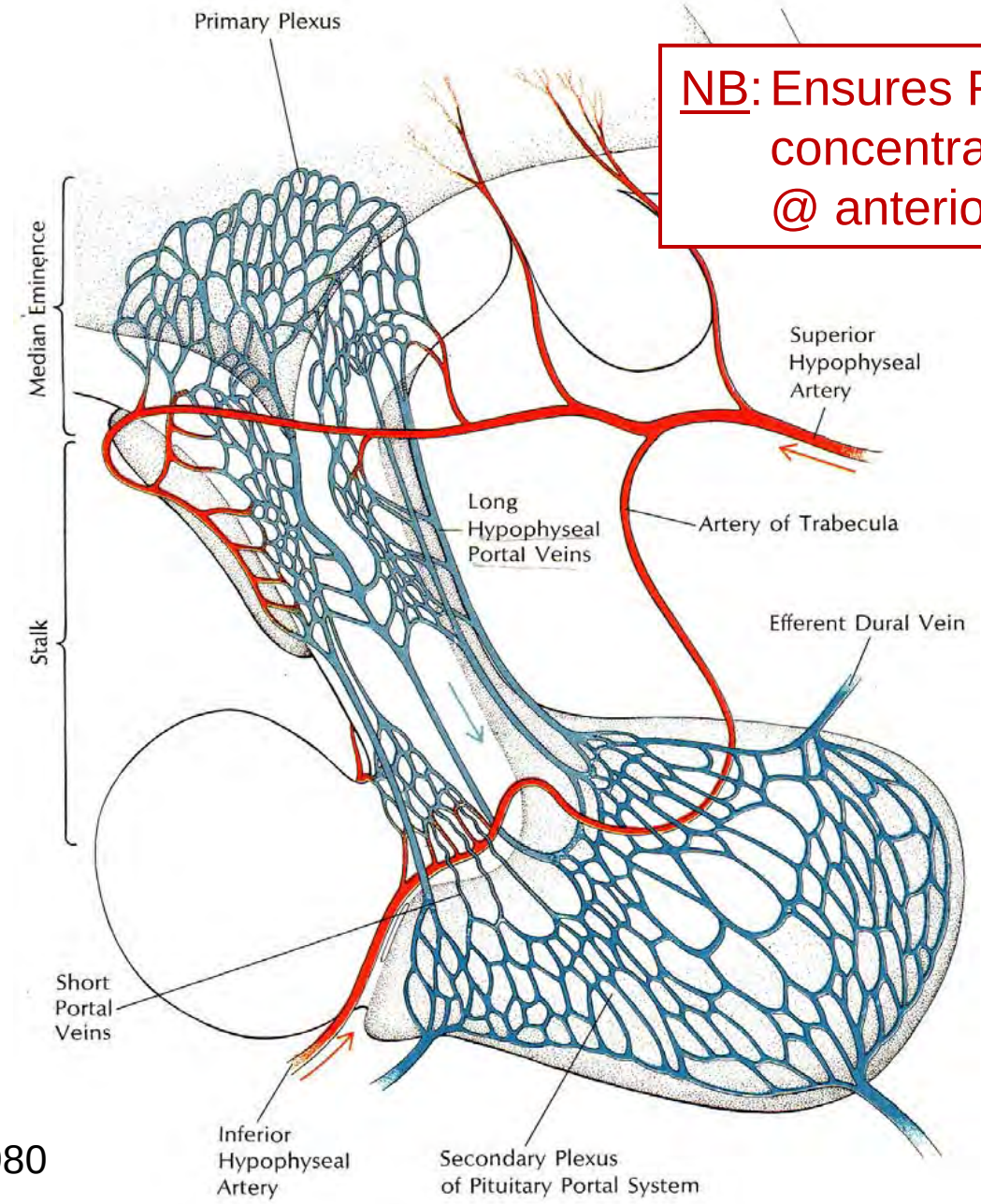
Releasing (RH)/ Release-Inhibiting (RIH) Hormones



1 of 6 Trophic/ Nourishing Hormones

G&H 2011 fig 75-4

Capillary-Venule-Capillary Circulation



NB: Ensures RH/RIH super-concentrated upon arrival @ anterior pituitary!

Krieger & Hughes 1980

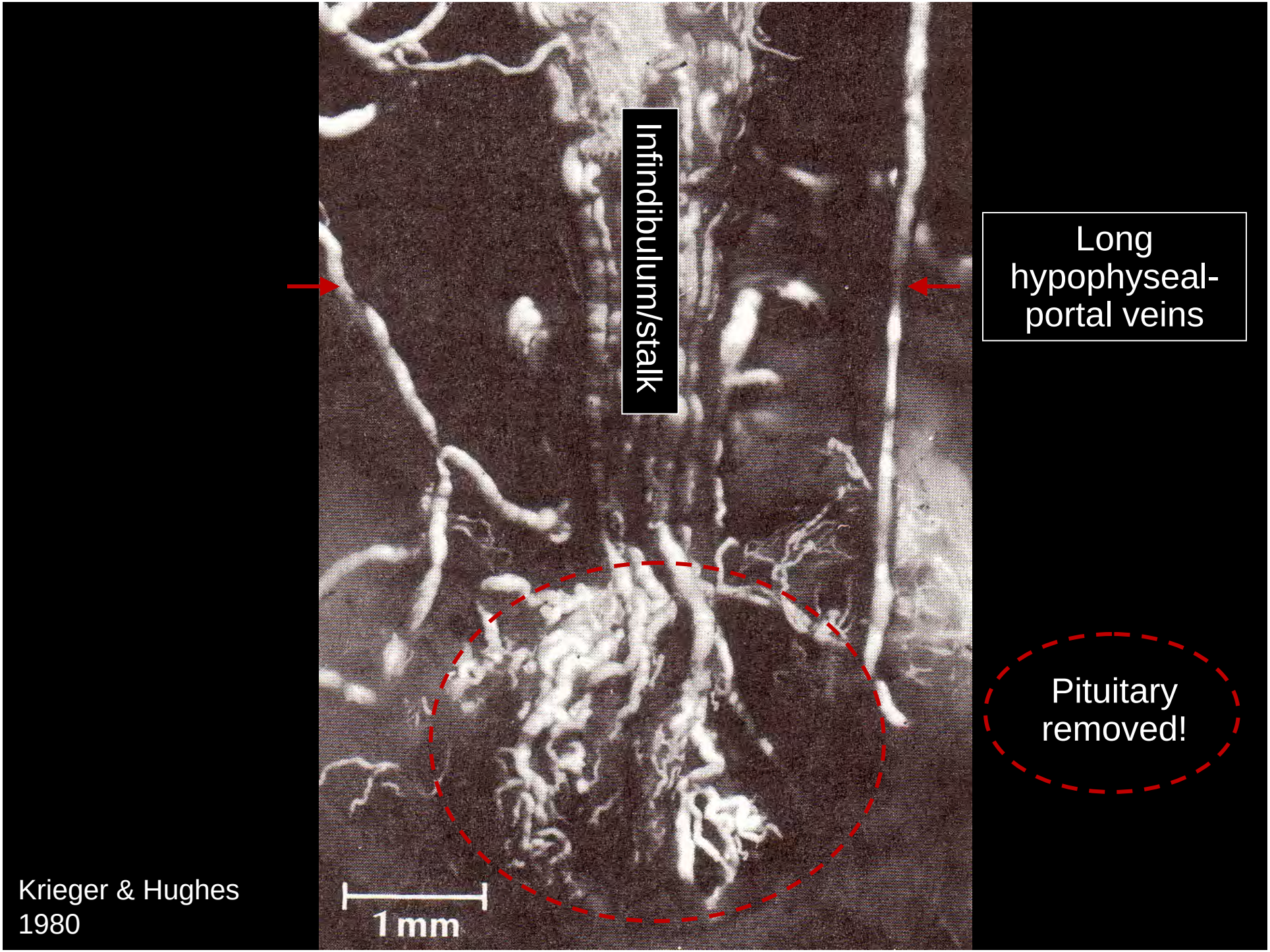
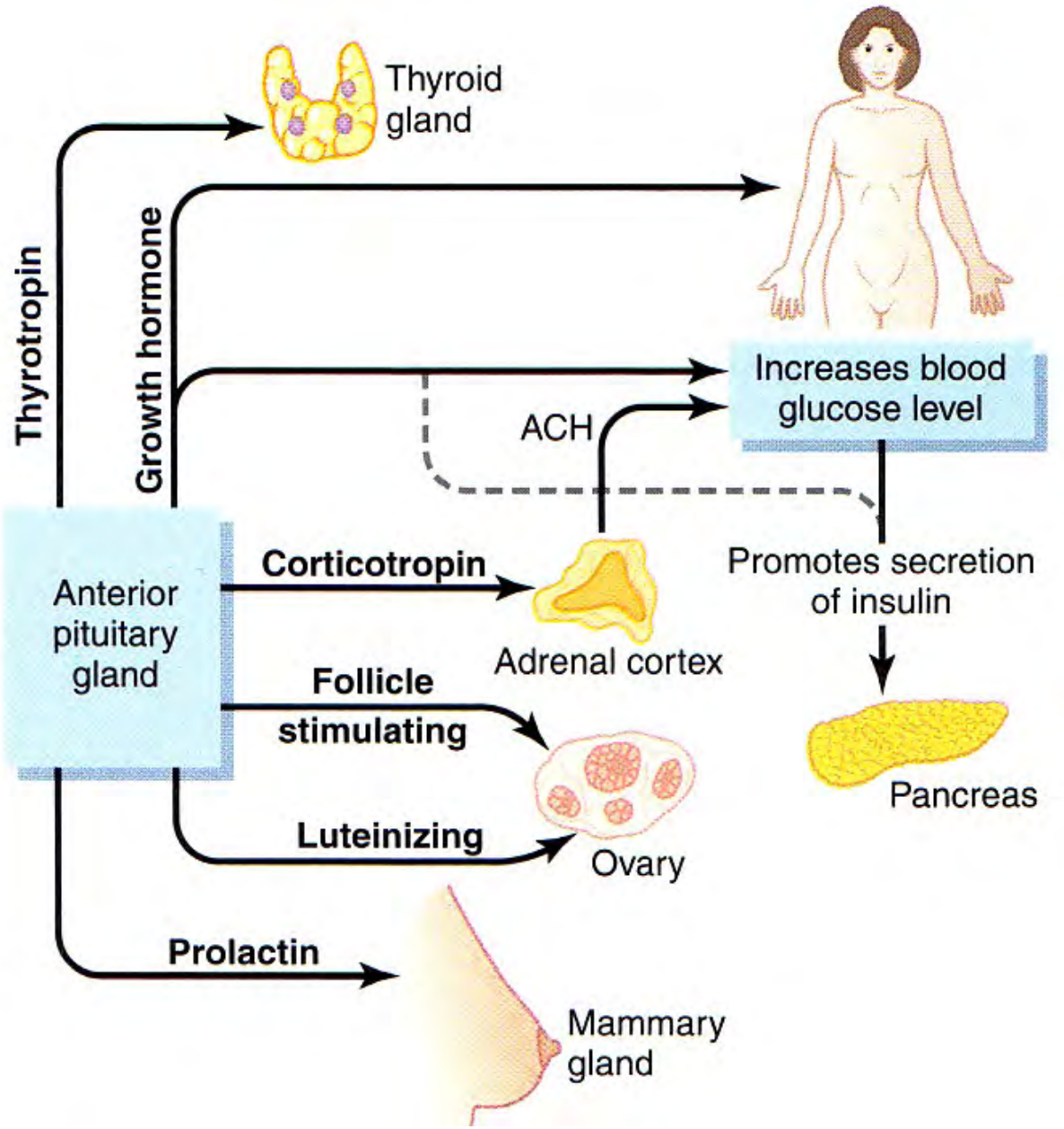

Infindibulum/stalk
Long hypophyseal-portal veins
Pituitary removed!
1 mm
Krieger & Hughes 1980

Table 74-1 Endocrine Glands, Hormones, and Their Functions and Structure

Gland/Tissue	Hormones	Major Functions	Chemical Structure
Hypothalamus (Chapter 75)	Thyrotropin-releasing hormone (TRH)	Stimulates secretion of thyroid-stimulating hormone (TSH) and prolactin	Peptide
	Corticotropin-releasing hormone (CRH)	Causes release of adrenocorticotropic hormone (ACTH)	Peptide
	Growth hormone–releasing hormone (GHRH)	Causes release of growth hormone	Peptide
	Growth hormone inhibitory hormone (GHIH) (somatostatin)	Inhibits release of growth hormone	Peptide
	Gonadotropin-releasing hormone (GnRH)	Causes release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	
	Dopamine or prolactin-inhibiting factor (PIF)	Inhibits release of prolactin	Amine
Anterior pituitary (Chapter 75)	Growth hormone	Stimulates protein synthesis and overall growth of most cells and tissues	Peptide
	TSH	Stimulates synthesis and secretion of thyroid hormones (thyroxine and triiodothyronine)	Peptide
	ACTH	Stimulates synthesis and secretion of adrenocortical hormones (cortisol, androgens, and aldosterone)	Peptide
	Prolactin	Promotes development of the female breasts and secretion of milk	Peptide
	FSH	Causes growth of follicles in the ovaries and sperm maturation in Sertoli cells of testes	Peptide
	LH	Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone synthesis in ovaries	Peptide

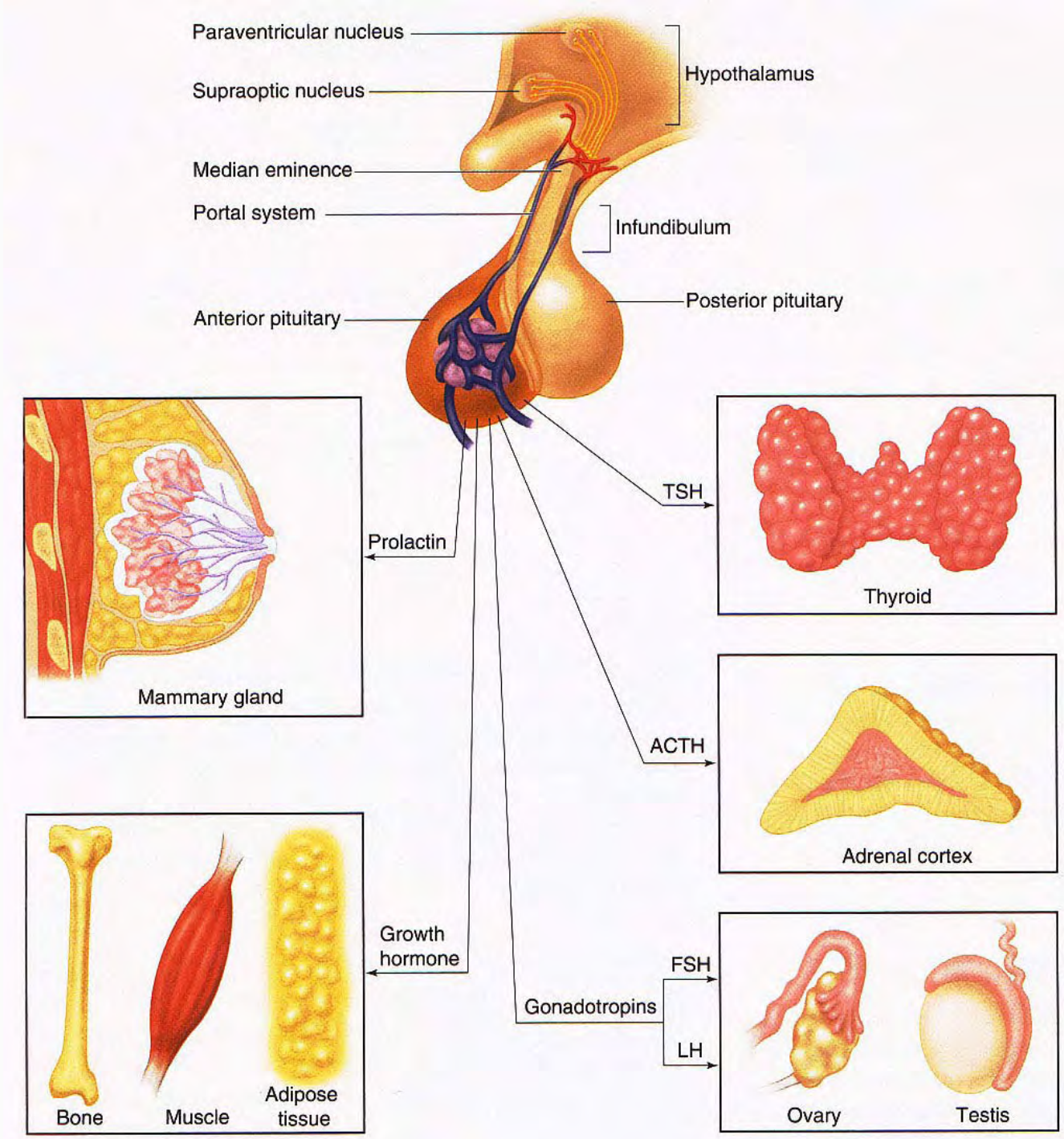
G&H 2011

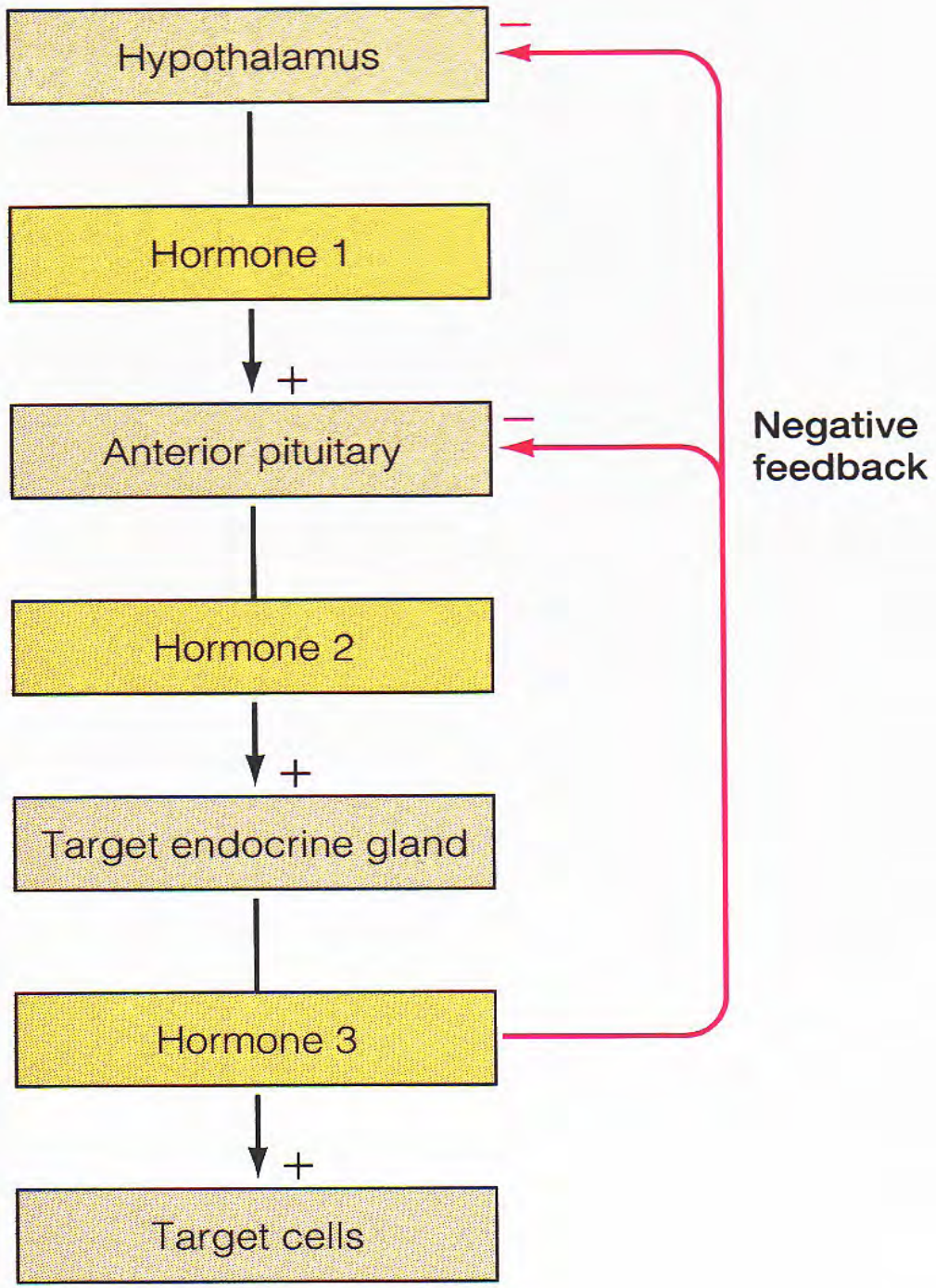
Anterior Pituitary Metabolic Functions



G&H 2011 fig 75-2

Fox 2008


Paraventricular nucleus
Supraoptic nucleus
Hypothalamus
Median eminence
Portal system
Infundibulum
Posterior pituitary
Anterior pituitary
Prolactin
TSH
Thyroid
Mammary gland
ACTH
Adrenal cortex
Growth hormone
Gonadotropins
FSH
LH
Bone
Muscle
Adipose tissue
Ovary
Testis


Hypothalamus
Hormone 1
+
Anterior pituitary
Hormone 2
+
Target endocrine gland
Hormone 3
+
Target cells
−
−
Negative feedback

LS 1991

GH, a Protein Hormone (191 AA)

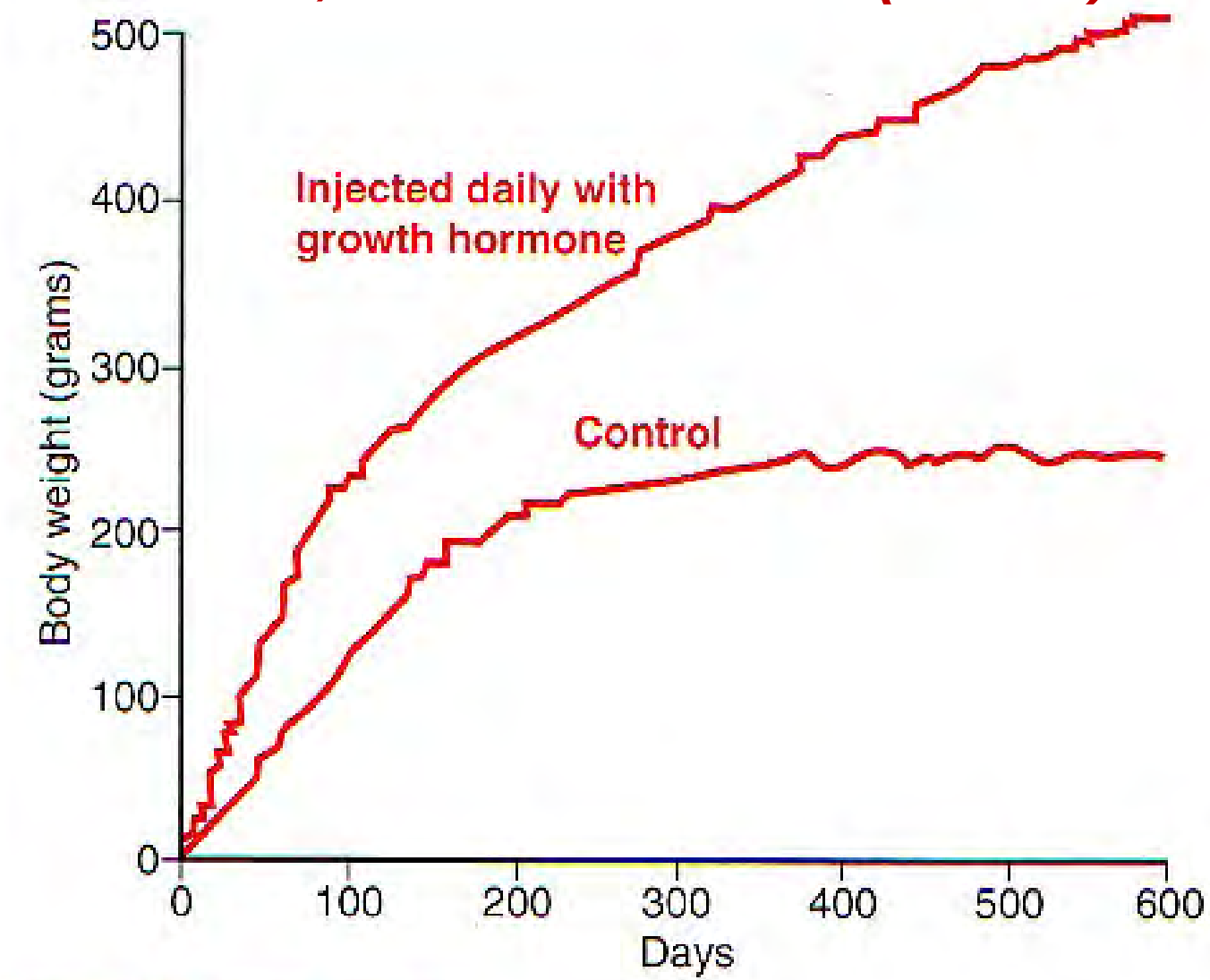


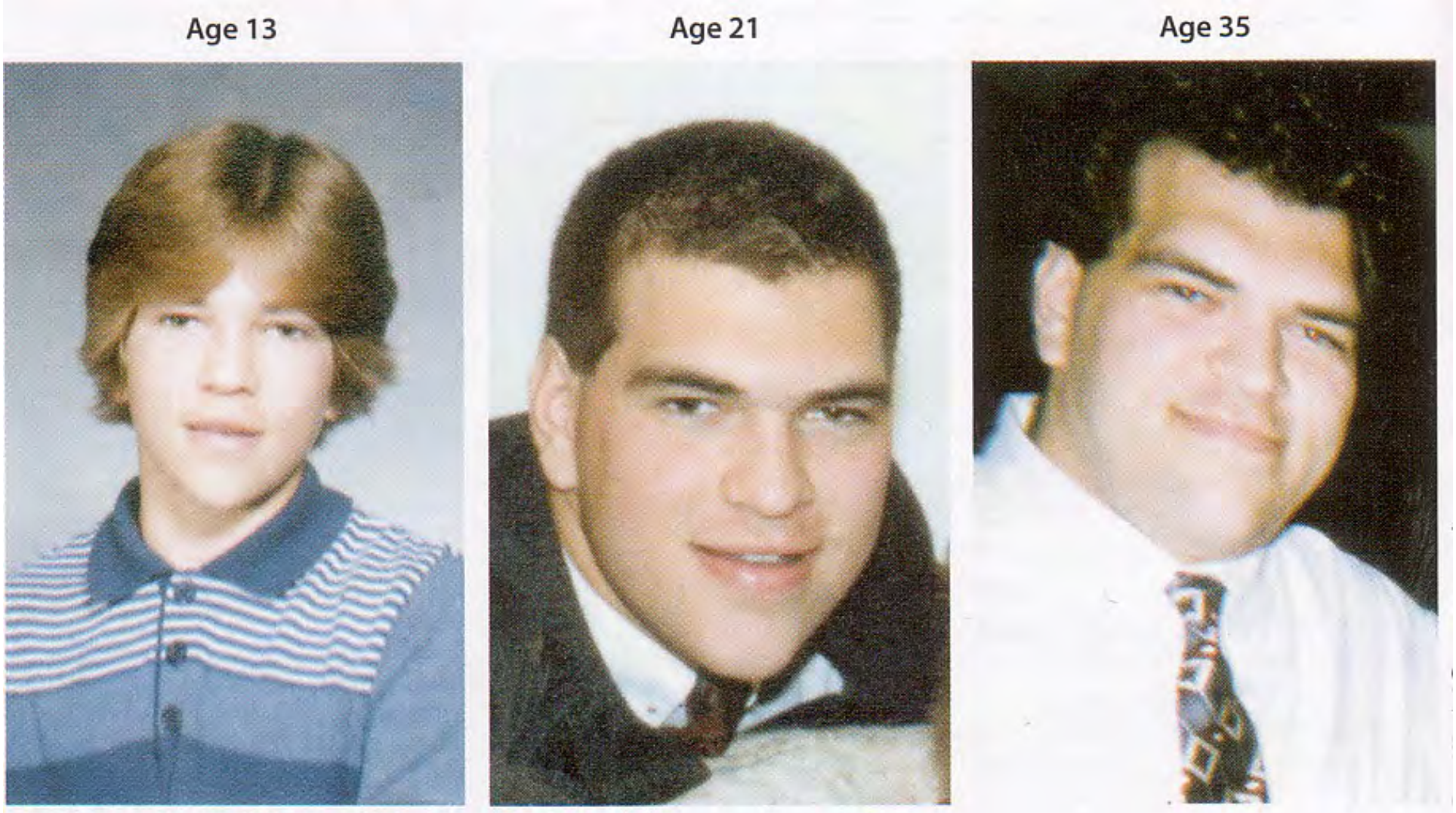
FIGURE 75–5

Comparison of weight gain of a rat injected daily with growth hormone with that of a normal littermate.

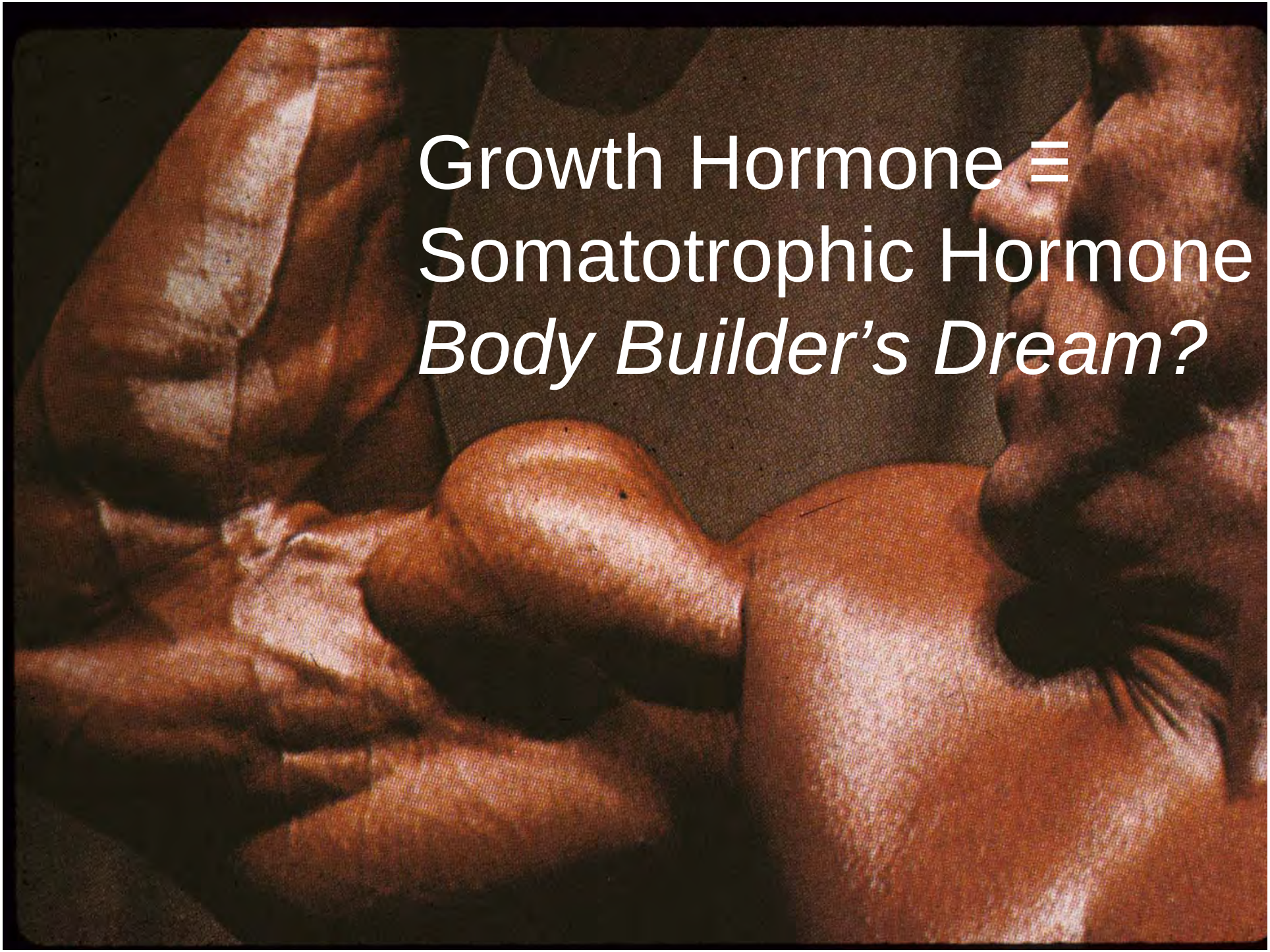
G&H 2006

LS2 2006

Progression & Development of Acromegaly



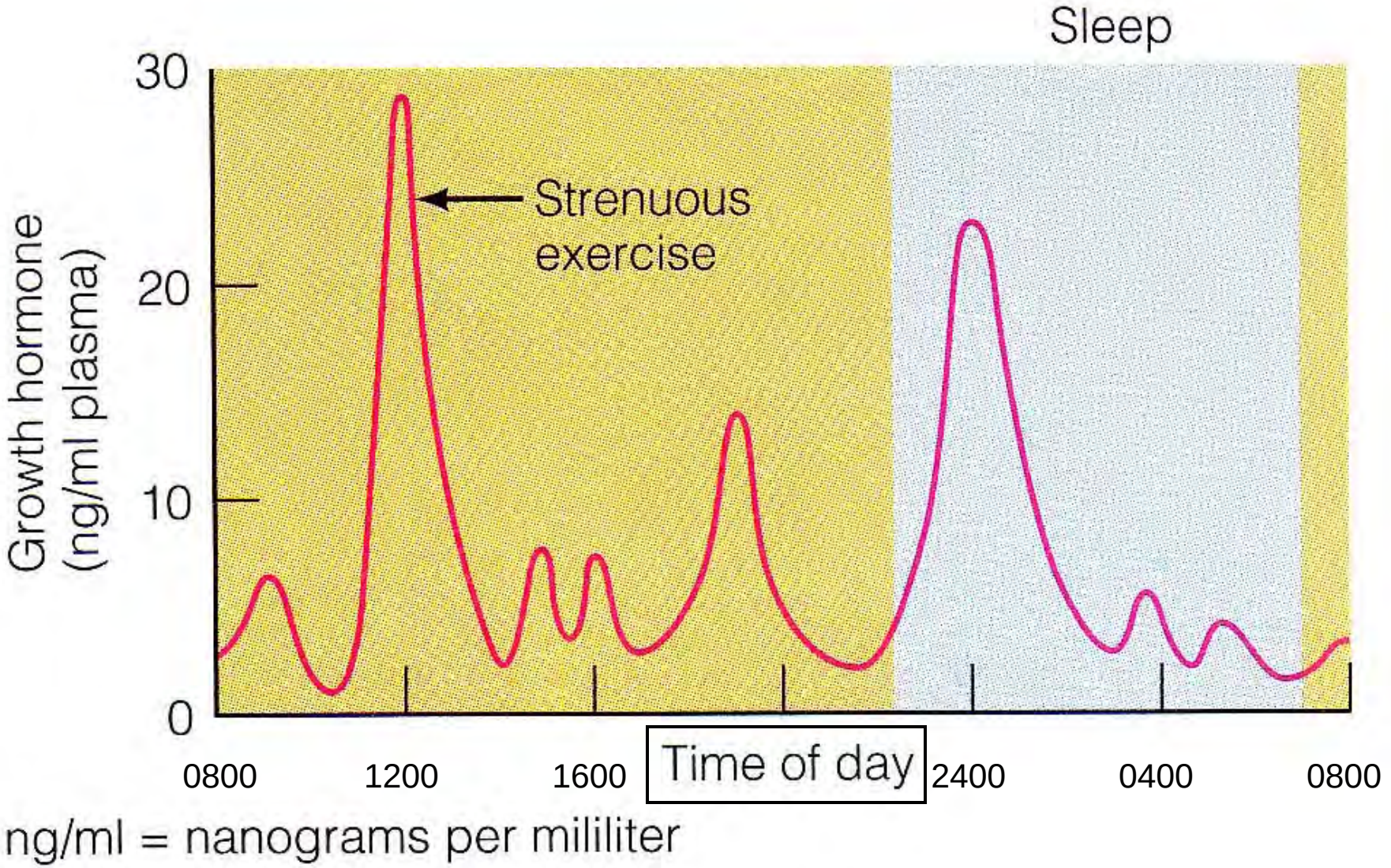
LS 2012 fig 17-11


Growth Hormone ≡
Somatotrophic Hormone
Body Builder's Dream?

GH/STH Effects: Insulin Resistance/Type II Diabetes?

- ↑ Amino acid uptake & protein synthesis
- ↑ Lipolysis & fatty acid mobilization
- ↓ Glucose uptake
  (skeletal muscle & adipocytes)
- ↑ Glucose production
  (liver glycogenolysis)
- ↑ Insulin secretion

Increase GH naturally with exercise & sleep!!



cf: G&H 2011 fig 75-6

Proinsulin with C-Connecting Peptide

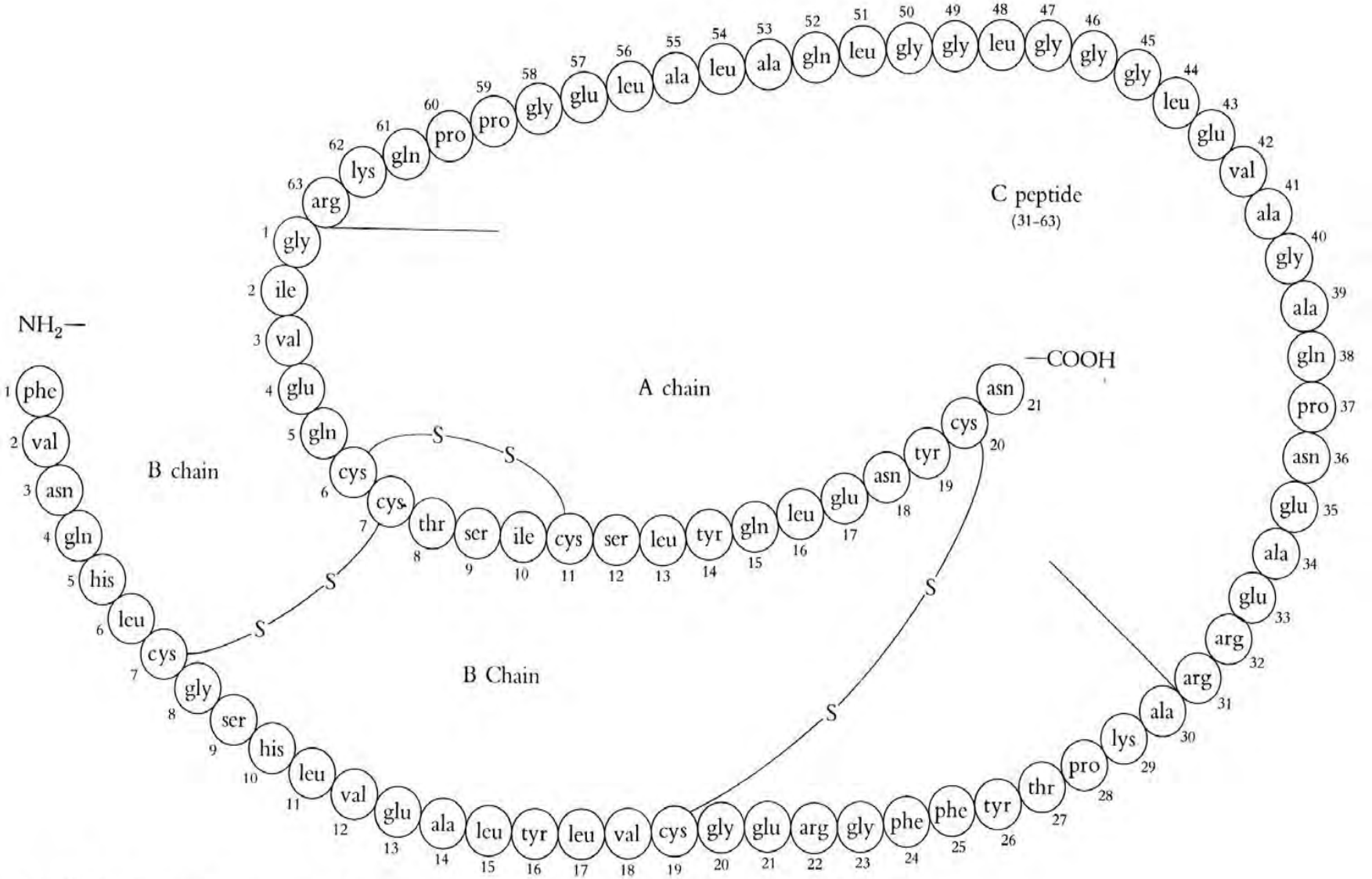
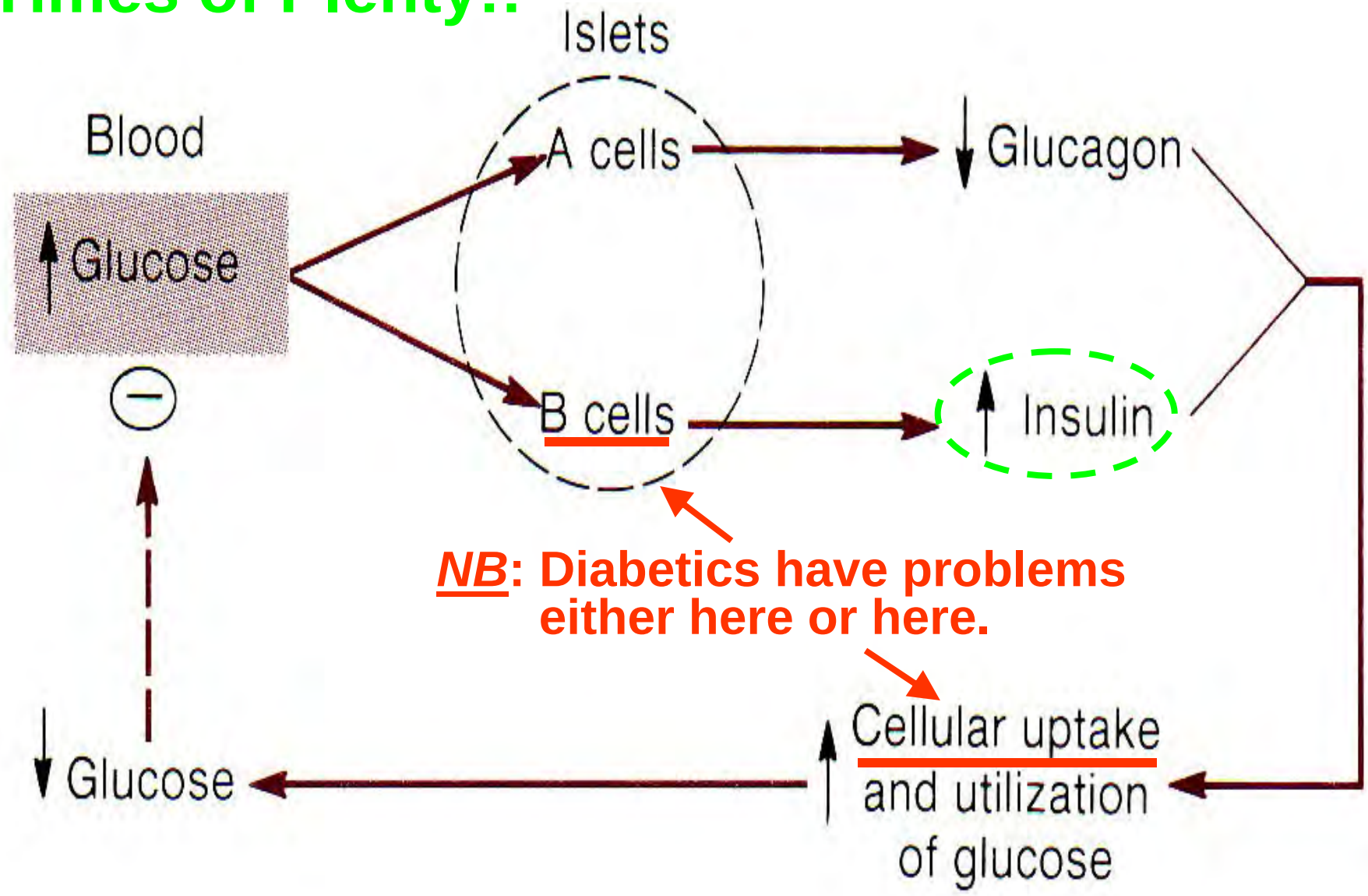


FIG. 10-4. Amino acid sequence of a mammalian proinsulin molecule. Note how the insulin molecule can be formed by cleaving this polypeptide chain at two locations to liberate the C peptide.

DO Norris 1980

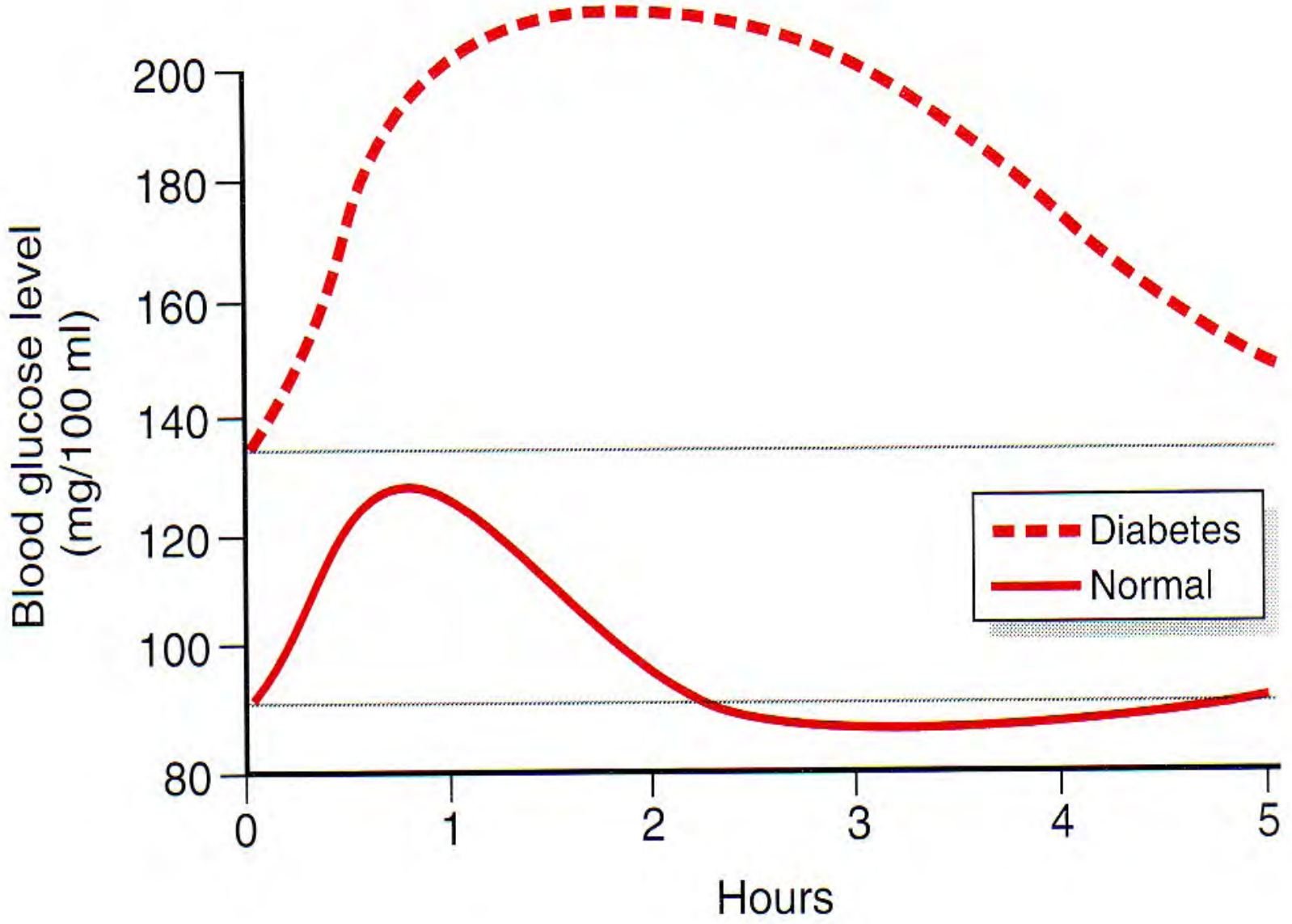
Times of Plenty!!



Fox 1987

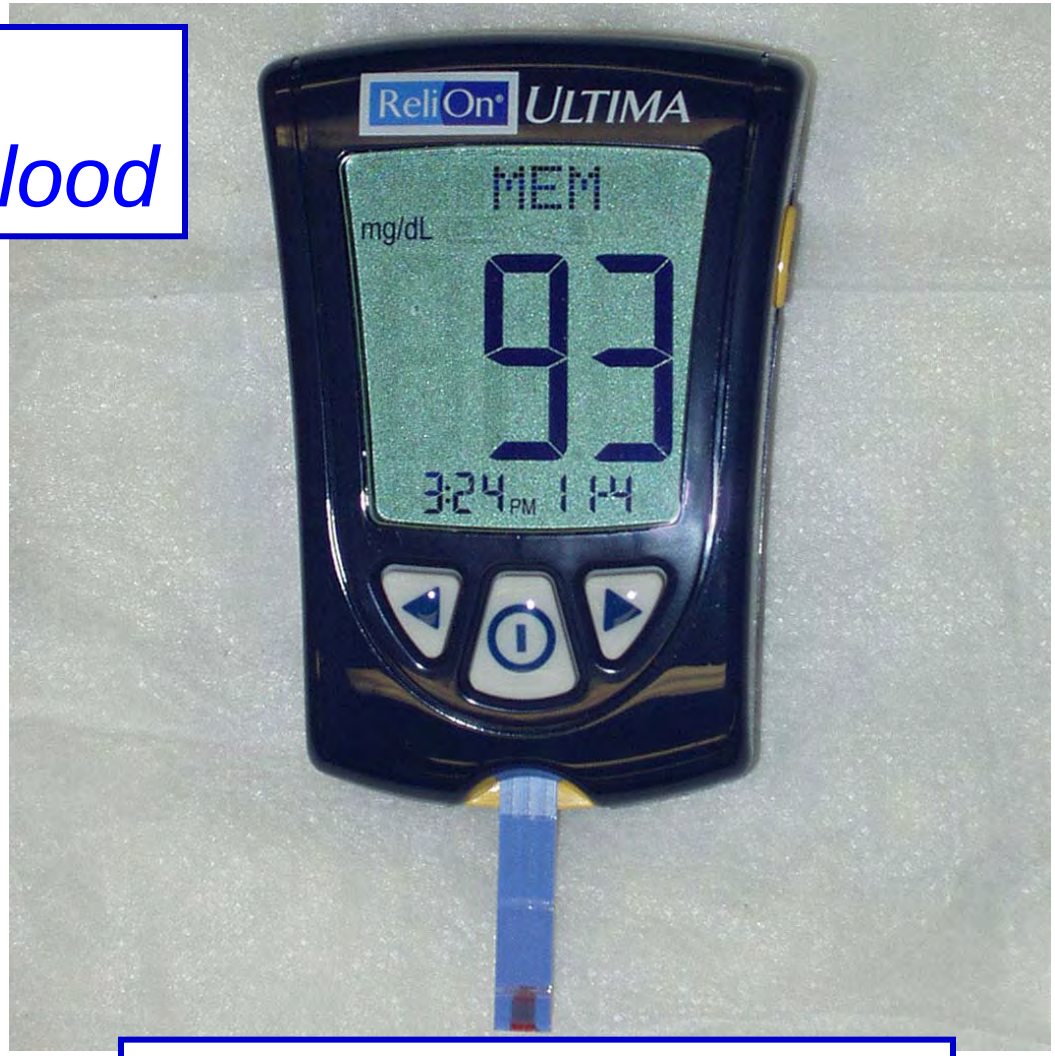
Store!

Diabetic & Normal Response to Glucose Load

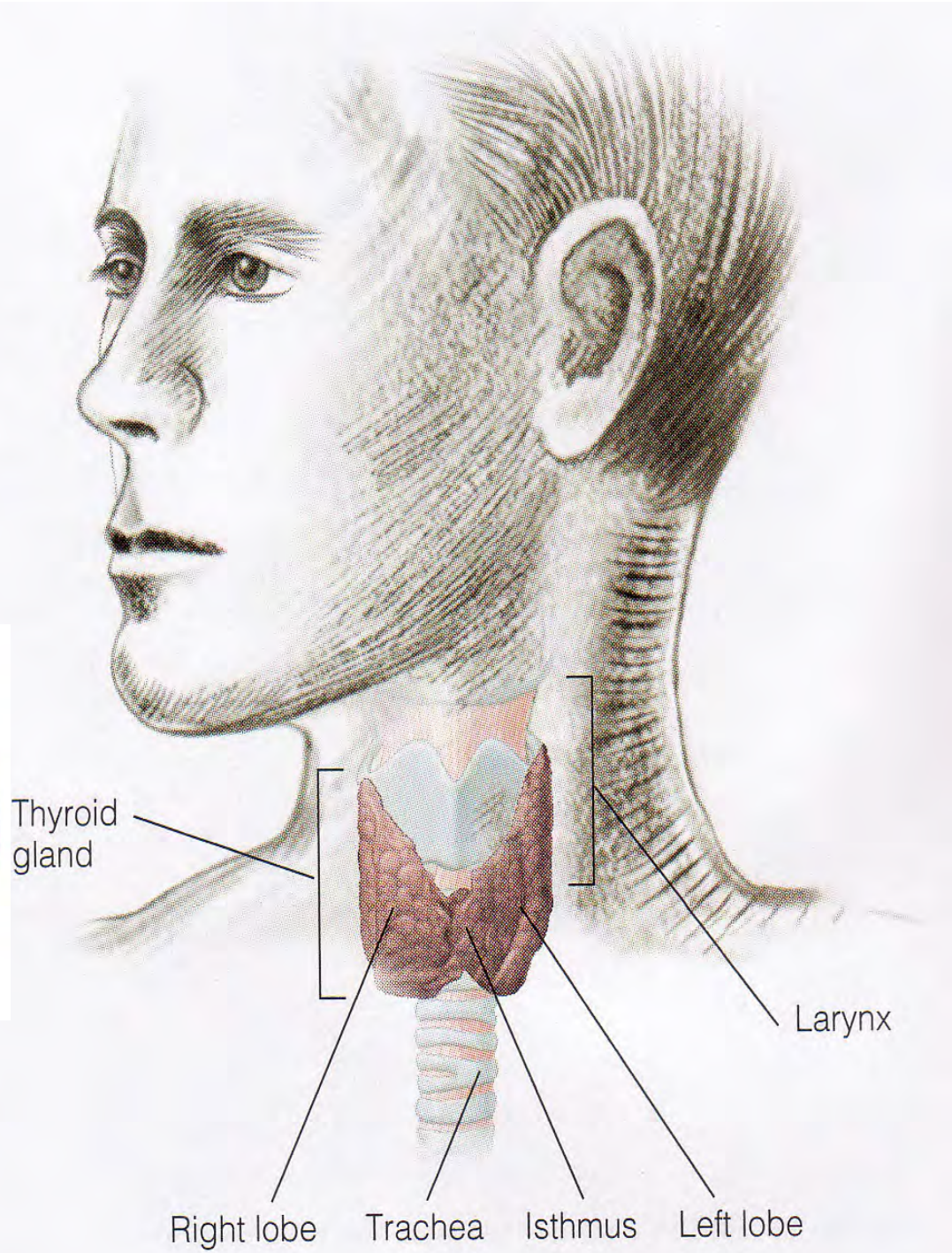


G&H 2000 cf: G&H 2011 fig 78-12

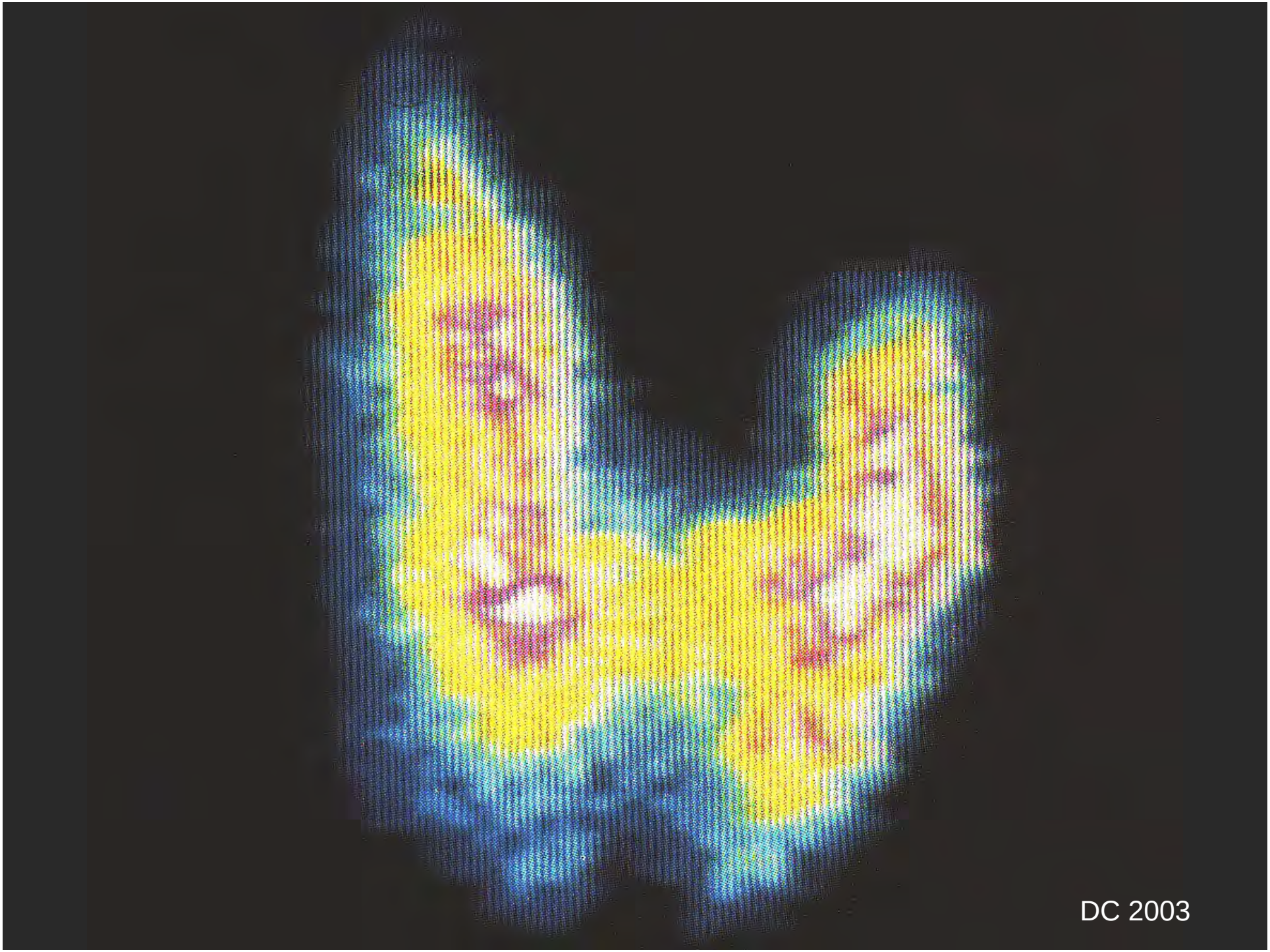
Glucose:
Sugar in Blood

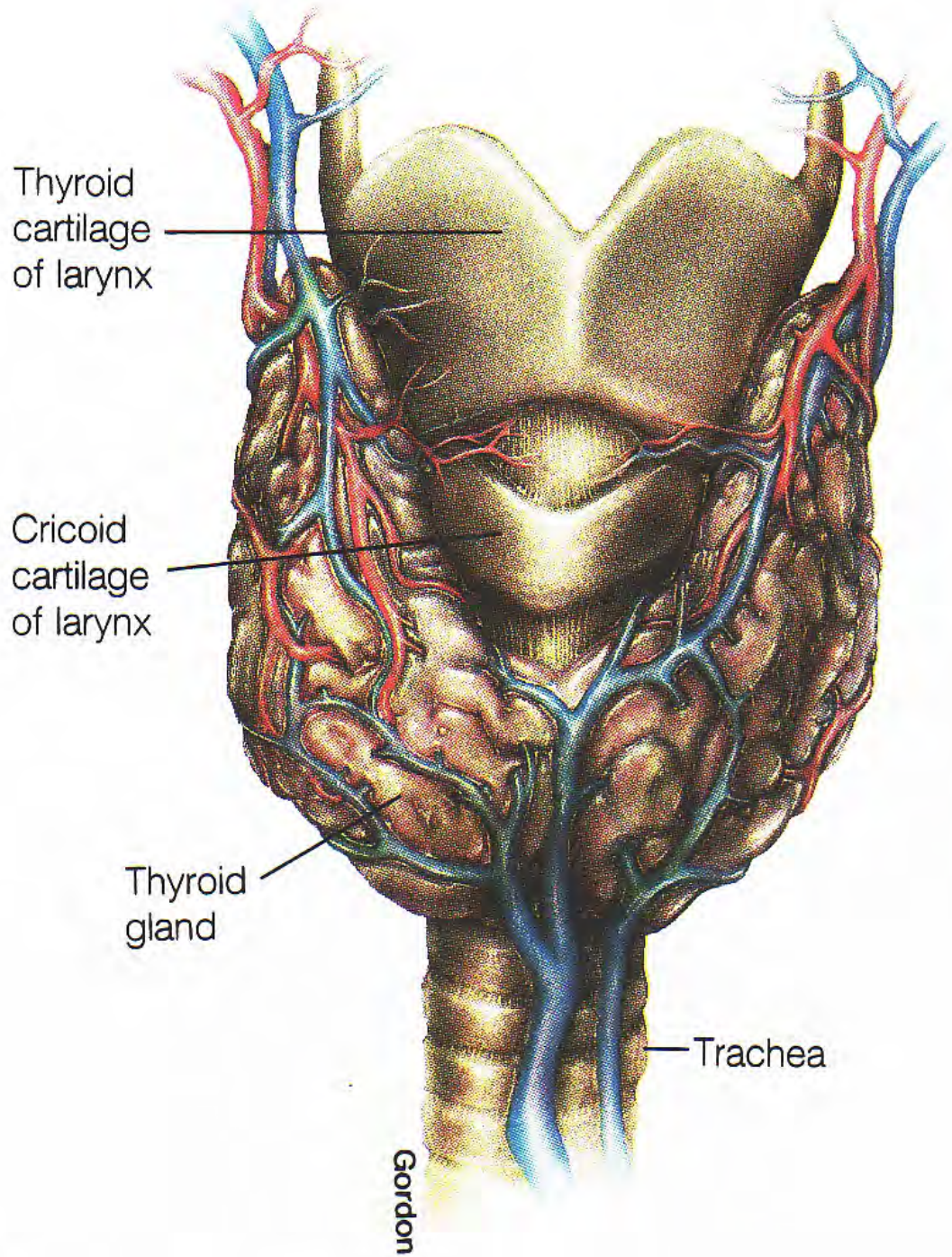


Normal: 70-99
Pre-Diabetes: 100-125
Diabetes: ≥ 126 mg/dL



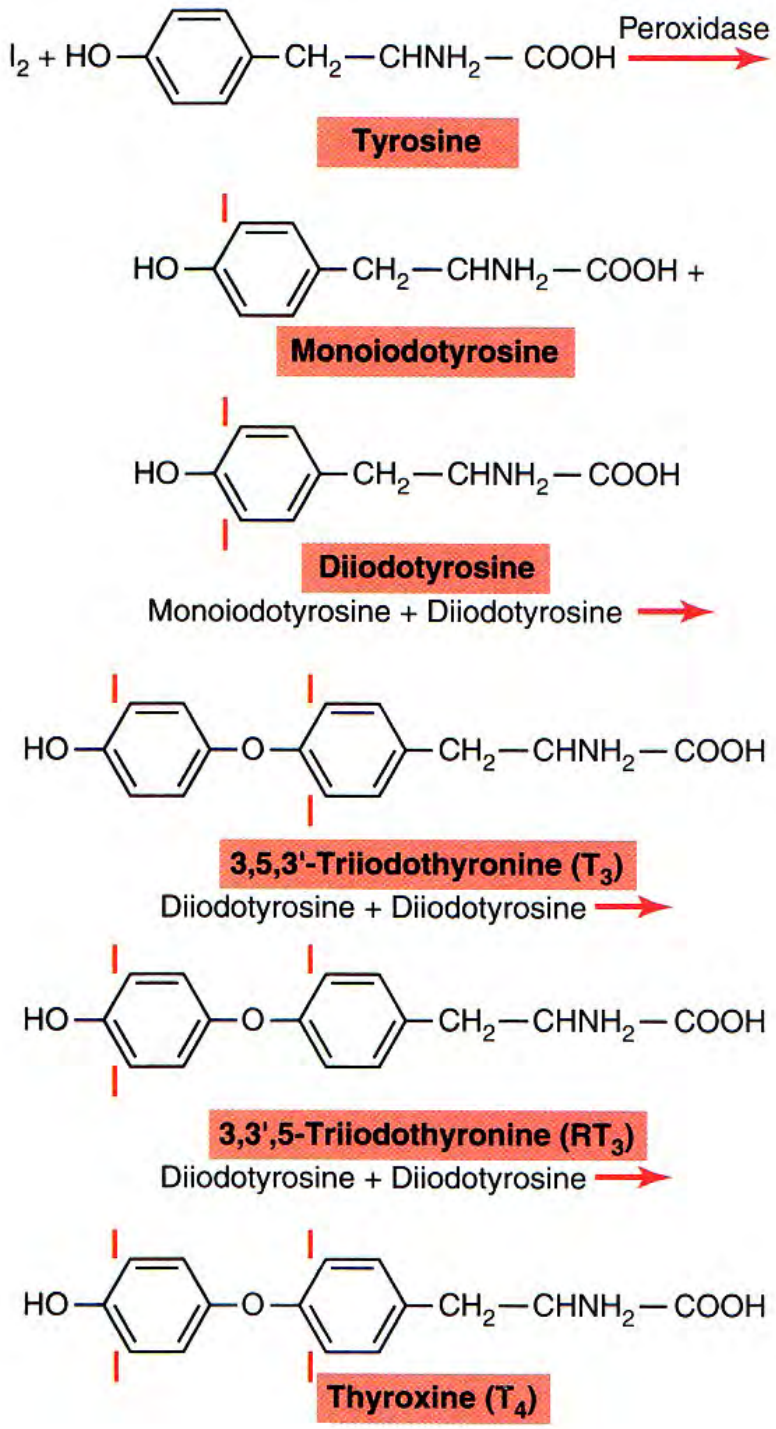
DC 2003


DC 2003

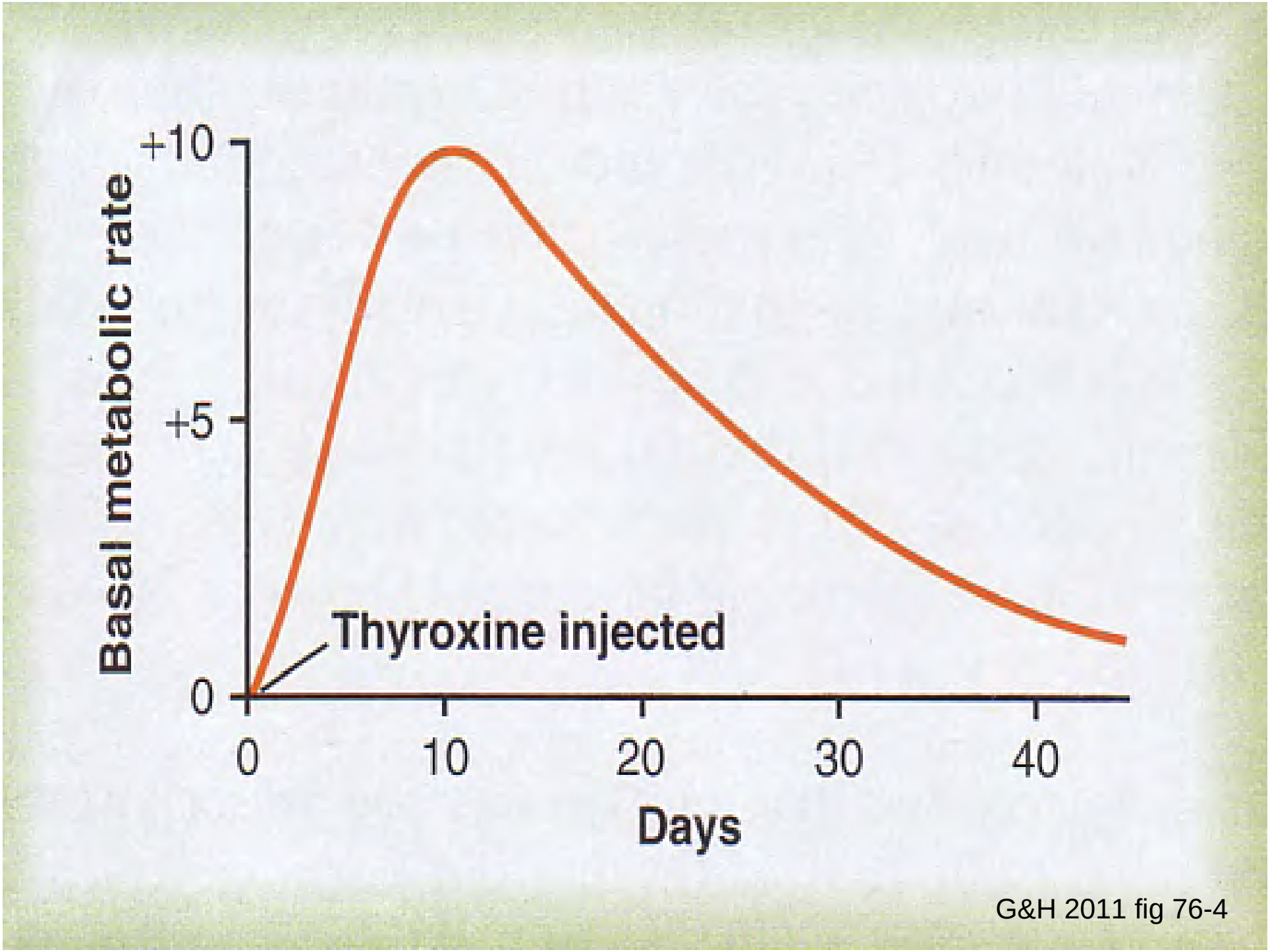

Thyroid cartilage of larynx
Cricoid cartilage of larynx
Thyroid gland
Trachea
Gordon

(a)

DC 2003



G&H 2011 fig 76-3



G&H 2011 fig 76-4

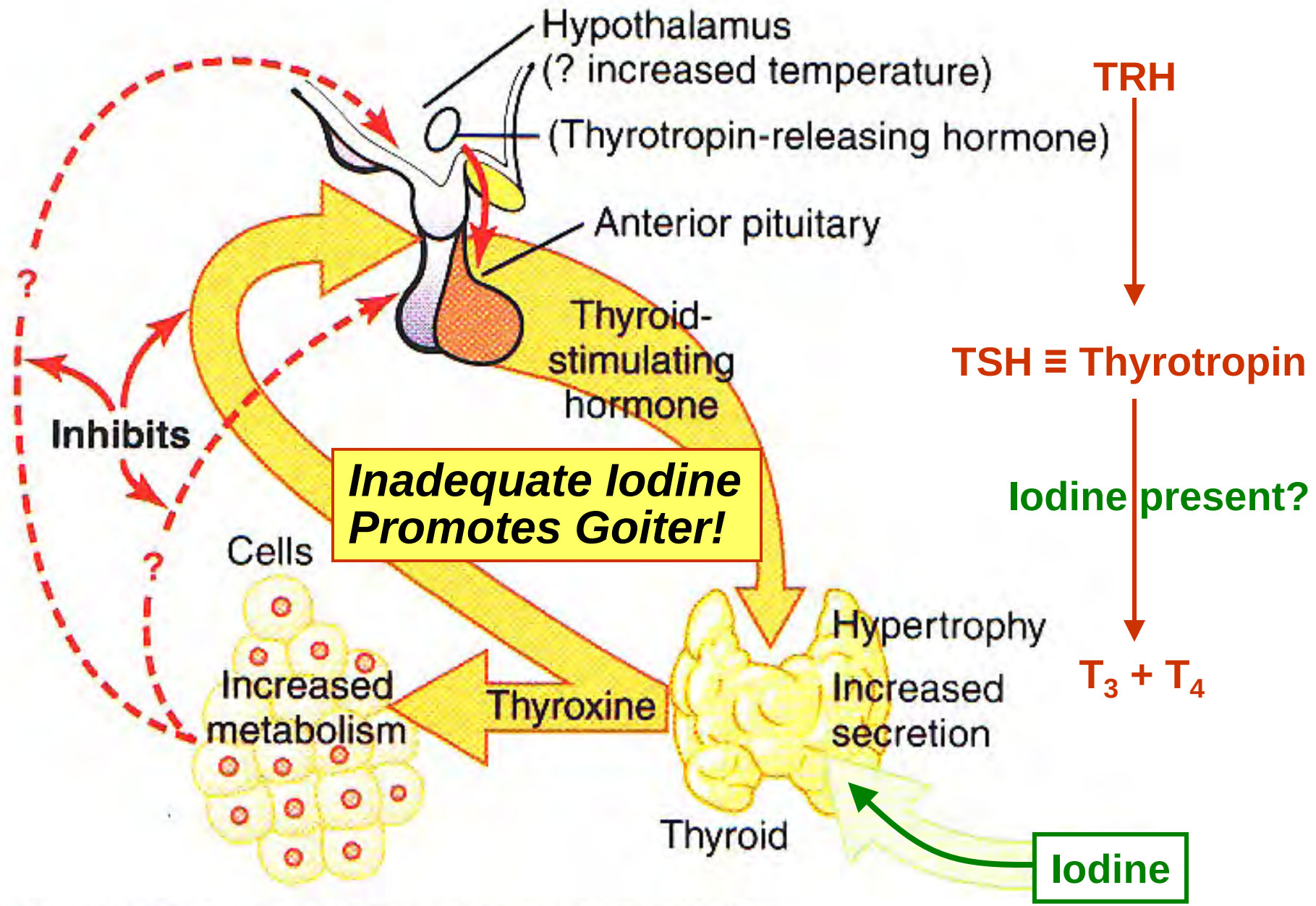


Figure 76-7 Regulation of thyroid secretion.

G&H 2011

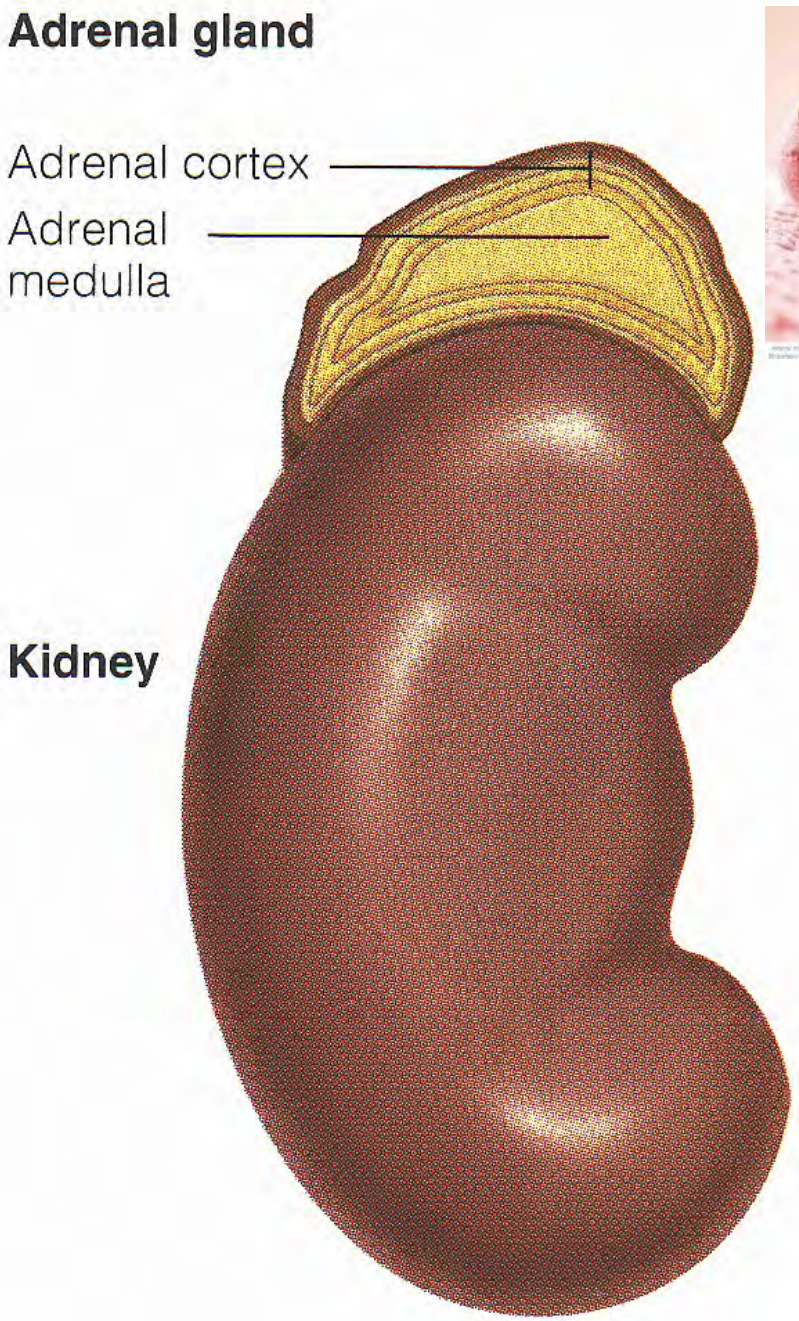
DC 2003


cf: G&H
2011
fig 76-8
DC
2003

Near absence of thyroid-hormone function + myedema

Figure 76–8. Patient with myxedema. (Courtesy of Dr. Herbert Langford.)

G&H 2006

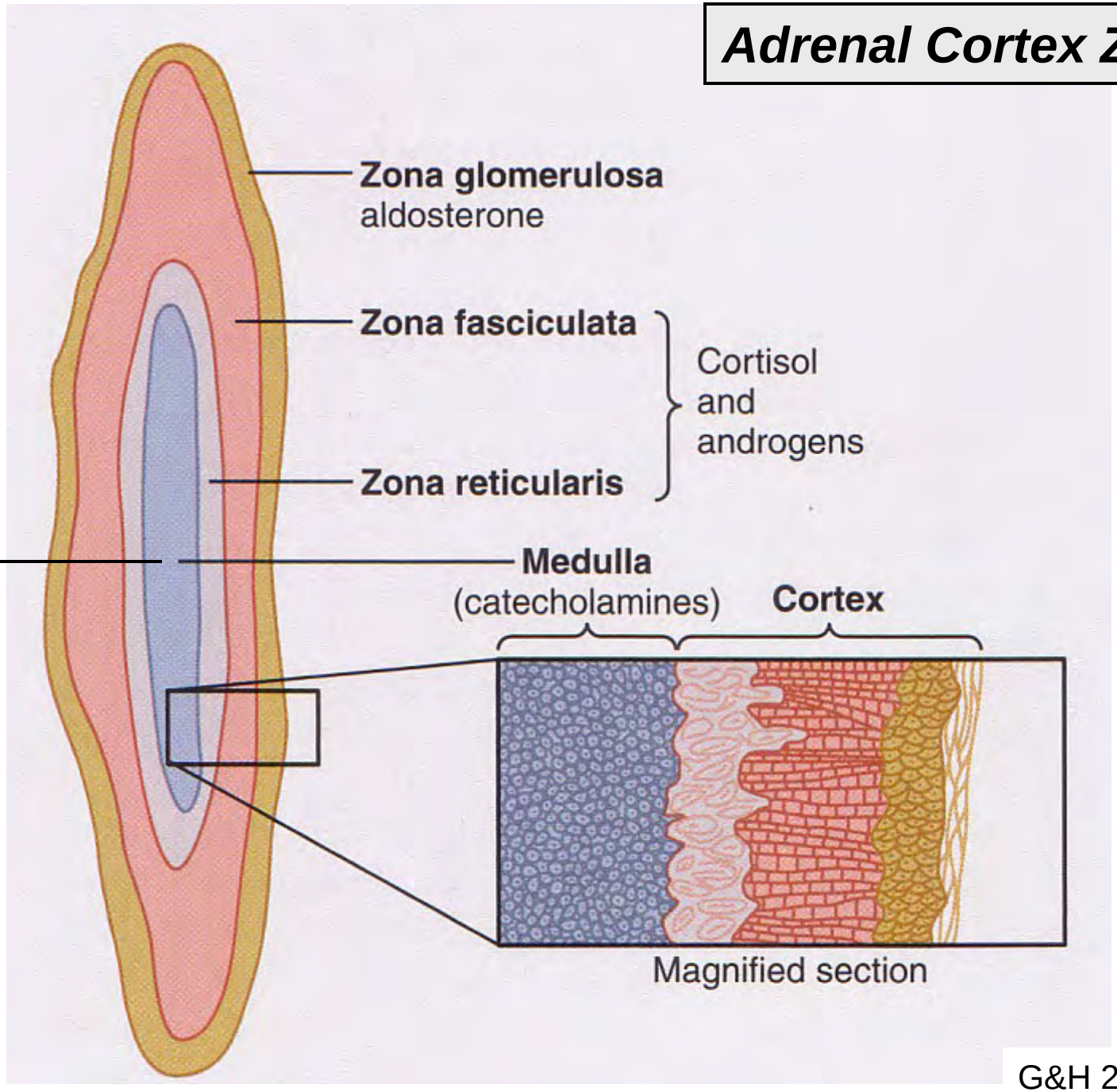


Scoop of ice cream on North pole!

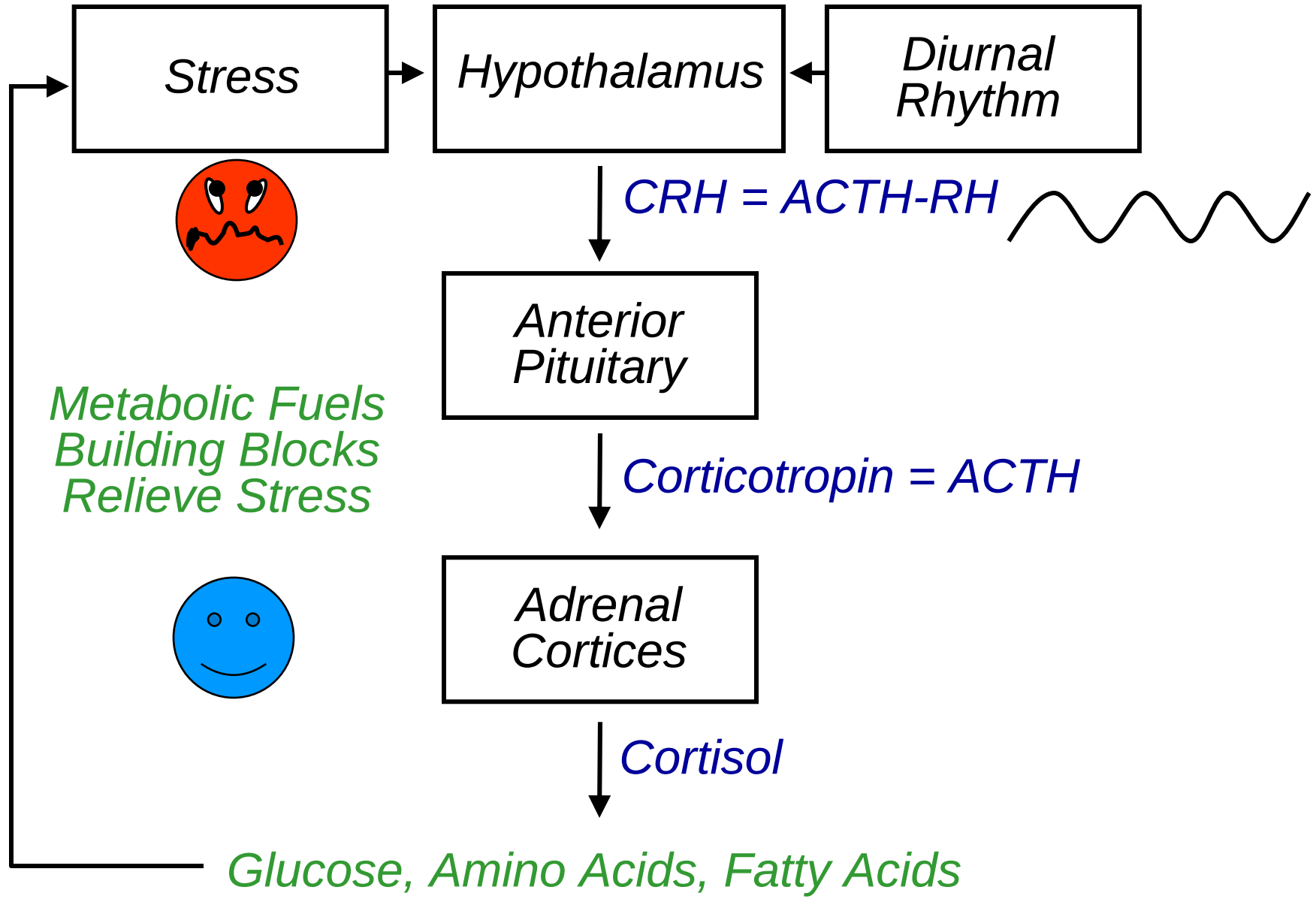
FIGURE 13-12
Adrenal Gland The adrenal glands sit atop the kidney and consist of an outer zone of cells, the adrenal cortex, which produces a variety of steroid hormones, and an inner zone, the adrenal medulla. The adrenal medulla produces adrenalin and noradrenalin.

DC 2003

Adrenal Cortex Zones



G&H 2011 fig 77-1



SOURCE: Modified after D Chiras 2003