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° 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??
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
Elephantiasis: Lymphatic Blockage Due to Mosquito-Borne Parasitic Worm

L Sherwood 2007
Human heart = 4 unique valves?
2 valve sets?

**Semilunar** = Half-moon shaped

1. Pulmonic/Pulmonary
2. Aortic

**AV** = Atrioventricular

3. Right AV = Tricuspid
4. Left AV = Mitral/Bicuspid
MITRAL VALVE

Cusp

Chordae tendineae

Papillary muscles

AORTIC VALVE

Cusp

G&H 2011 fig 9-7; G&H 2016 fig 9-8
Heart Valve Orientation & Scaffolding

- Pulmonary ring
- Aortic ring
- Mitral ring
- Tricuspid ring
- Muscle fiber
What the heck’s a *bruit*? (brwe, brôôt) [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!
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.
Coronary Arteries Pierce the Heart from Epi to Endo

Diagram showing Epicardial coronary arteries and Subendocardial arterial plexus within cardiac muscle.
Anastomoses May Provide Lifesaving Collateral Circulation!!

G&H 2011 & 2016 fig 21-6
Cardiac Cycle

Systole
Contract & Empty

Diastole
Relax & Fill
Coronary blood flow (ml/min)

- Systole: Contract & Empty
- Diastole: Relax & Fill

G&H 2011 & 2106 fig 21-4
(Automatically) Shock the Heart then it Contracts!
Intrinsic Regulation: Autorhythmic
(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).

Ectopic focus
Extrinsic Regulation: Nervous

NB: + Extrinsic Hormonal e.g. Adrenal Epi + NE
Electrical Events Precede Mechanical Events!
AMI
CVDs
CVA
HTN
TIA
PVD
??
Area of cardiac muscle deprived of blood supply if coronary vessel is blocked at point A:

Right coronary artery

Right ventricle

Area of cardiac muscle deprived of blood supply if coronary vessel is blocked at point B:

Left coronary artery

Left ventricle

---

**FIGURE 9-35**

Extent of myocardial damage as a function of the size of the occluded vessel
What is the Ultimate Cause of Death?

1. ↓ 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

- Normal Muscle
- Nonfunctional Muscle
- Systolic Stretch
Treatment Triad

Drugs/Surgery

Exercise

Dietary Modification

NB: Last blasted resort!!
300/200

KA-BOOM!

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
A typical lipoprotein

- Phospholipid
- Cholesterol
- Triglyceride
- Protein
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, cystathionine 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 paroxonase (PON1), lysosomal acid lipase (LAL), MEF2A protein affecting artery walls…
Bruce Kottke’s Bathtub Analogy

5 forms of cholesterol:
Chylomicrons, VLDL, LDL, IDL, HDL

Total Cholesterol Level

HDL = Drain

Bruce Kottke

“I don’t think the total cholesterol test by itself is worth a damn.” —Eliot Corday

Biological Artifact!?
Historical Hypotheses for Atherosclerosis Development

**Ross & Glomset**
- Endothelial Injury
  - Platelet Adherence
    - PDGF Release
      - Other Growth Factors
      - Cell Proliferation
      - Advanced Lesion

**Steinberg & Witztum**
- High Plasma LDL
  - LDL Infiltration into Intima
    - Oxidized LDL + Macrophages
      - Foam Cells
      - Fatty Streak

[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2032127/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2032127/)
[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC295745/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC295745/)
How Inflammation Attacks the Heart

1. **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.

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

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

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

5. **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.

6. **Cap Breakdown**
   Macrophages kill the smooth muscle cells and release enzymes that break down the fibrous cap.

7. **Cap Rupture**
   The cap ruptures.

8. **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).
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
SOURCE: Lifeline Screening, 2007
Middle Cerebral Artery Branches

...Cerebral vasculature! Oh my!

The Window to the CV System?
Renal Vasculature

Figure 37-1 Devices for percutaneous transluminal coronary interventions. A, Coronary balloon. B, Rotational atherectomy burr (Rotablator). C, Coronary stent.
CABG = Coronary Artery Bypass Graft

Double?
Triple?
Quadruple?
Quintuple?
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
Procedures and heart attack deaths
Per 10,000 population

As noninvasive techniques improve, the rate for bypass surgery goes down.

Sources: Thomas Thom, National Heart, Lung, and Blood Institute; Gautam Gowrisankaran, Washington University in St. Louis; Salim Yusuf, McMaster University, the InterHeart Study.
CardioWest artificial heart = $106,000!

3000 await transplants, but only 2100 donors are available…
Questions + Discussion
Cushing’s Syndrome = Hypersecretion of Cortisol: Hypothalamic (CRH), Pituitary (ACTH), or Adrenal (Cortisol)

\[ T = 0, \text{ near normal} \]

\[ T = 4 \text{ months later} \]
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

- **Lipophilic hormone**
- **Diffusion**
- **Steroid**
- **Thyroid**
- **Cytoplasmic receptor**
- **Nuclear receptor**
- **Hormone receptor complex**
- **DNA**
- **Hormone response element**
- **Nuclear envelope**
- **Nuclear pore**
- **Proteins**
- **Ribosome**
- **Target cell**
- **Extracellular fluid**

G&H 2016 fig 75-6
G&H 2011 fig 74-6
Peptide Hormone Synthesis & Secretion
cAMP 2nd Messenger Mechanism

Extracellular fluid

Hormone

Cytoplasm

GTP

α

β

γ

Adenylyl cyclase

cAMP

ATP

Active cAMP-dependent protein kinase

Inactive cAMP-dependent protein kinase

Protein – PO4 + ADP

Protein + ATP

Cell’s response

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).
<table>
<thead>
<tr>
<th>Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
</tr>
<tr>
<td>Angiotensin II (ANG II, epithelial cells)</td>
</tr>
<tr>
<td>Calcitonin</td>
</tr>
<tr>
<td>Catecholamines (β receptors)</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
</tr>
<tr>
<td>Glucagon</td>
</tr>
<tr>
<td>Human chorionic gonadotropin (hCG)</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
</tr>
<tr>
<td>Secretin</td>
</tr>
<tr>
<td>Somatostatin (SS, GH RIH)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Vasopressin (ADH, VP, V_2 receptor, epithelial cells)</td>
</tr>
</tbody>
</table>
Phospholipase C 2\textsuperscript{nd} 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

<table>
<thead>
<tr>
<th>Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II (ANG II, vascular smooth muscle)</td>
</tr>
<tr>
<td>Catecholamines (α receptors)</td>
</tr>
<tr>
<td>Gonatotropin-releasing hormone (GnRH)</td>
</tr>
<tr>
<td>Growth-hormone-releasing hormone (GHRH)</td>
</tr>
<tr>
<td>Oxytoxin (OXY, hypothalamus production, posterior pituitary storage)</td>
</tr>
<tr>
<td>Thyrotropin releasing hormone TRH)</td>
</tr>
<tr>
<td>Vasopressin (ADH, VP, V₁ receptor, vascular smooth muscle)</td>
</tr>
</tbody>
</table>
Leptin: Enzyme-Linked Hormone Receptor

- Homodimer receptor
- Janus-kinase 2 enzyme
- Signal transducer & activator of transcription proteins (STAT)

- Transcription of target genes
- Protein synthesis

Leptin receptor

Activation of enzymes

Physiological effects

Translation

mRNA

Target gene


G&H 2016 fig 75-5
G&H 2011 fig 74-5
\( \text{ANP} = \text{Atrial Natriuretic Polypeptide} \)

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

Vasodilation

\( \downarrow \text{BP} \)