BI 358 Lecture 8

I. **Announcements**  Kraig Jacobson MD, Allergy & Asthma Research Associates, Oak Street Medical, Feb 9th Tuesday! Update on outlines and paper drafts. WBC lab photo! Q?

II. **Immunology II**

A. Immune response, pathogens, evolution Davey pp 5-12
B. Recap *cf:* Innate vs. adaptive immunity G&H pp 433-7, LS +... Innate immunity eg inflammation, interferon, complement
C. Antibody (Ab=Ig) structure, subclasses, mechanisms  
   G&H fig 34-4 + LS + Davey fig 2.4 p19, fig 4.2 p42, tab 4.1 p49
D. Mom’s milk *Scientific American*
E. Immune Regulation + Allergy: G&H fig 34-7, 34-3 + ...

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

A. Cardiovascular system? Figure-8 loop D Chiras (DC), LS
B. Fetal development & circulation Torstar..., G&H fig 83-4
C. Layers: peri-, epi-, myo- & endocardium Torstar Books
D. ♥  structure & function G&H fig 9-7, LS1...
E. Blood flow through ♥ & periphery G&H fig 9-1, LS, DC
F. 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 9-6

Dr. Kraig is... I g GGGGREAT!!
Lymphocyte

Lymphocyte

Lymphocyte

Neutrophil Twins!!

Lymphocyte

Lymphocyte

Lymphocyte

Josef Khalifeh
WBC Differential
Lab 012715
Lymphoid Tissues

- BALT
- GALT

- Adenoid
- Tonsil
- Thymus
- Lymph node
- Spleen
- Lymphatic vessel
- Peyer's patches in small intestine (gut-associated lymphoid tissue)
- Appendix
- Bone marrow

L Sherwood 2012
Widespread Location of Lymphoid Tissues!

- Thymus
- Lymph nodes, tonsils, and adenoids
- Lymph nodes in axilla
- Spleen
- Diffuse lymphoid tissue in lungs, bronchi, gut, and urinogenital tract
- Gut-associated lymph nodes
- Lymph nodes in groin

Davey 1990 p 36
Immunity

Innate/Inborn/Nonspecific

1. **Immediate**, upon exposure to threatening agent

2. $1^0$ effectors phagocytic specialists: neutrophils & macrophages

3. "Eyes" are Toll-like receptors (TLRs) which recognize & bind with generic invader markers

4. Inflammation, interferon, natural killer cells, complement (plasma proteins)

Adaptive/Acquired/Specific

1. **Delayed**, selective targeting based on prior exposure

2. $1^0$ effectors lymphocytes: T- & B-lymphocytes

3. "Eyes" are T- and B-cell receptors which bind with specific antigens

4. Cell-mediated & Humoral (Ab mediated) immunity

Really, a false separation, as incredible overlap & synergism!
Lactoferrin binds Fe$^{2+}$ ↓ Replication

Prostaglandins ↑ Set point

Hypothalamus

EP, endogenous pyrogen

X NSAIDs e.g. Aspirin

Should we use?

Neutrophils are important in the immune response. They can phagocytose invading organisms, activate kinins to enhance chemotaxis, extracellular traps (NETs) to immobilize microbes, and release histamine to increase vasodilation and capillary permeability. Lactoferrin, which binds Fe$^{2+}$, can suppress bacterial replication. Nitric oxide (NO) is toxic to microbes. Prostaglandins can increase the set point in the hypothalamus. Anti-histamines are used to block histamine effects.

Mast cells release histamine upon activation, which can cause vasodilation and increased capillary permeability.
Allergic Reactions, Mast Cells & Basophils?

Allergen = ●
IgE = Y

up to ½ million per cell!

Mucous Membranes/Blood

Bradykinin
Eosinophil & Neutrophil
Chemotactic Substances
Heparin
Histamine
Platelet Activating Factors
Protease
Serotonin
Toxic Leukotrienes/SRSA

ASHTMA

Rachel Rozens

Emily McInerney

Amy McInerney

Joe McInerney

Rachel McInerney
Inflammation Steps

1. Break in skin \(\rightarrow\) Bacteria enter & reproduce
2. Mast cells release histamine
3. Vessel wall becomes sticky \(\rightarrow\) Neutrophils & monocytes attach \(\rightarrow\) diapedesis \(\rightarrow\) chemotaxis
4. Chemotaxins attract more Neutrophils & monocytes
5. Monocytes swell \(\rightarrow\) Macrophages

Redness, Heat, Swelling, Pain!
Glucocorticoids throw blanket over entire inflammatory process!

1. Certainly warranted to quiet down immune system during extreme flare ups of arthritis, asthma, poison ivy, rash, but must consider:

2. Destroy lymphocytes in lymphoid tissues.

3. ↓ Antibody/Immunoglobulin (Ig) production.

4. Make susceptible to bacterial infections.
**Interferon Mechanisms**

Viruses coming!

Don’t breathe on me, Paul!

1. Virus enters a cell
2. Virus replicates in invaded cell
3. Cell releases interferon
4. Interferon binds with receptors on uninvaded cells
5. Uninvaded cells produce inactive enzymes capable of breaking down viral messenger RNA and of inhibiting protein synthesis
6. Virus enters cell that has been acted upon by interferon
7. Virus-blocking enzymes are activated
8. Virus is unable to multiply in newly invaded cells

Subsequent cells invaded by a virus

Viral entry activates virus-blocking enzymes

Host cell

Virus cannot replicate
Activated Complement

The Big MAC to Osmotic explosion!
WBC Adverse Effects

Leukocytes

Anti-cancer drugs
Benzene
Nuclear blast
Radiation

↓ Professional phagocytes esp:
Neutrophils
Macrophages

↓ Body defense vs. μ organisms!

Savior Lymphoid tissues or bone marrow transplant?

cf: Leukemia ≡ uncontrolled WBC proliferation, yet inadequate defense → other cell lines displaced → overwhelming infections & bleeding...
Commander-in-Chief of the Immune System!!

HIV tips the balance!!
Cell-cell adhesion proteins → T-cell receptor
Foreign protein → MHC protein

T cell

Antigen-presenting cell

G&H fig 34-7 2011
The vital union that activates a helper T cell takes place only when the T cell recognizes both a “self” marker (rectangle) and a “nonself” antigen (triangle) on a macrophage.
Population of unactivated B cells, each a member of a different B-cell clone that makes a specific receptor, which is displayed on the membrane surface as a BCR.

Binding of antigen and interaction with helper T cell stimulates the matching B cells to divide and expand the clone of selected cells.

Most of the new B cells differentiate into plasma cells, which secrete antibodies.

A few of the new B cells differentiate into memory B cells, which respond to a later encounter with the same antigen.

L Sherwood 2012; cf: G&H fig 34-2
Typical IgG Antibody Structure

How do antibodies work?

Antigens

Antigen

Identical, specific antigen-binding sites

Antibody

KEY

V = variable region
C = constant region

L Sherwood 2012; cf. G&H, fig 34-4
Immunoglobulin G

Source: Visual Science
1. **Agglutination**

   ![Agglutination Diagram]

   - Antigen
   - Antibody
   - Invading bacterium

2. **Complement**

   ![Complement Diagram]

   - Inactive C1 complement molecule
   - Antibody
   - Invading bacterium coated with antibodies specific to it
   - Activated by binding with antigen-attached antibody
   - Formation of C5–C9, the membrane attack complex
   - Membrane attack complex
   - Lysis (rupture) of cell

3. **Opsonization**

   ![Opsonization Diagram]

   - Invading bacterium coated with antibodies specific to it
   - Phagocyte

4. **Killer Cells**

   ![Killer Cells Diagram]

   - Invading bacterium coated with antibodies specific to it
   - Lysis induced by killer cell
   - Natural killer (NK) cell

L Sherwood 2012
TABLE 4.1 Characteristics and functions of the human immunoglobulin classes

<table>
<thead>
<tr>
<th>immunoglobulin class</th>
<th>G</th>
<th>A</th>
<th>M</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>heavy-chain type</td>
<td>γ</td>
<td>α</td>
<td>μ</td>
<td>δ</td>
<td>ε</td>
</tr>
<tr>
<td>number of constant domains in each heavy chain</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>relative molecular mass ($M_r$) of monomer</td>
<td>150,000</td>
<td>160,000</td>
<td>180,000</td>
<td>185,000</td>
<td>200,000</td>
</tr>
<tr>
<td>normally found as polymer?</td>
<td>no</td>
<td>dimer</td>
<td>pentamer</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>valency: number of antigen binding sites in normal form (i.e. monomer or polymer)</td>
<td>2</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>percentage of total immunoglobulin in serum</td>
<td>(70-80)</td>
<td>13-20</td>
<td>6-10</td>
<td>0-1</td>
<td>0.002</td>
</tr>
<tr>
<td>serum half-life (days)</td>
<td>23</td>
<td>5.8</td>
<td>5.1</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>ability to trigger complement cascade*</td>
<td>++</td>
<td>–</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>can cross placenta from mother to foetus*</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>binds to Staphylococcal cell walls*</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>binds to macrophage Fc receptors*</td>
<td>+</td>
<td>–</td>
<td>(+)?</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>binds to neutrophil Fc receptors*</td>
<td>+</td>
<td>+</td>
<td>(+)?</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>binds to mast cell and basophil Fc receptors</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>binds to platelets</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* For IgG this refers only to some subclasses.

IgE skyrockets in allergies, parasitism, vasculitis, Hodgkin's disease!
G A M E D!
IgA = Secretory $A_b$

Antigen/A$_g$

Valence? 4

Dimer!!

Davey 1990 p 50
# Immune Benefits of Breast Milk at a Glance

<table>
<thead>
<tr>
<th>Component</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White Blood Cells</strong></td>
<td></td>
</tr>
<tr>
<td>B lymphocytes</td>
<td>Give rise to antibodies targeted against specific microbes.</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Kill microbes outright in the baby’s gut, produce lysozyme and activate other components of the immune system.</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>May act as phagocytes, injecting bacteria in baby’s digestive system.</td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>Kill infected cells directly or send out chemical messages to mobilize other defenses. They proliferate in the presence of organisms that cause serious illness in infants. They also manufacture compounds that can strengthen a child’s own immune response.</td>
</tr>
<tr>
<td>Molecules</td>
<td>Function</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Antibodies of secretory IgA class</td>
<td>Bind to microbes in baby's digestive tract and thereby prevent them from passing through walls of the gut into body's tissues.</td>
</tr>
<tr>
<td>B$_{12}$ binding protein</td>
<td>Reduces amount of vitamin B$_{12}$, which bacteria need in order to grow.</td>
</tr>
<tr>
<td>Bifidus factor</td>
<td>Promotes growth of <em>Lactobacillus bifidus</em>, a harmless bacterium, in baby's gut. Growth of such nonpathogenic bacteria helps to crowd out dangerous varieties.</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Disrupt membranes surrounding certain viruses and destroy them.</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>Increases antimicrobial activity of macrophages; helps to repair tissues that have been damaged by immune reactions in baby's gut.</td>
</tr>
<tr>
<td>Gamma-interferon</td>
<td>Enhances antimicrobial activity of immune cells.</td>
</tr>
<tr>
<td><strong>Hormones and growth factors</strong></td>
<td>Stimulate baby's digestive tract to mature more quickly. Once the initially “leaky” membranes lining the gut mature, infants become less vulnerable to microorganisms.</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Lactoferrin</strong></td>
<td>Binds to iron, a mineral many bacteria need to survive. By reducing the available amount of iron, lactoferrin thwarts growth of pathogenic bacteria.</td>
</tr>
<tr>
<td><strong>Lysozyme</strong></td>
<td>Kills bacteria by disrupting their cell walls.</td>
</tr>
<tr>
<td><strong>Mucins</strong></td>
<td>Adhere to bacteria and viruses, thus keeping such microorganisms from attaching to mucosal surfaces.</td>
</tr>
<tr>
<td><strong>Oligosaccharides</strong></td>
<td>Bind to microorganisms and bar them from attaching to mucosal surfaces.</td>
</tr>
</tbody>
</table>

http://www.scientificamerican.com/article.cfm?id=got-smarts-mothers-milk-m
IgM = Macroglobulin
Pentamer!!!!!

Valence? 10

Antigen/A_g

Davey 1990 p 51
Dendritic Cells: Specialized Antigen-Presenting Cells (APCs) Sentinels in Almost Every Tissue!
Protein messages trigger responses

The pivotal discovery of lymphokines, the proteins by which immune cells communicate with each other, ushered in a new era of medical research. Scientists now produce some of them in sufficient quantities for promising therapies against a host of immunologic diseases.

1. Engulfing an invading organism and coupling with a helper T cell, a macrophage secretes the lymphokine interleukin-1 (IL-1), which activates the helper T cell. IL-1 also stimulates the brain to raise the body's temperature, causing fever, which enhances the activity of immune cells.

2. The activated helper T cell produces interleukin-2 (IL-2), which stimulates other helper and killer T cells to grow and divide. The helper T's secrete a lymphokine called B-cell growth factor (BCGF), which causes B cells to multiply.

3. As the number of B cells increases, helper T cells produce another lymphokine, B-cell differentiation factor (BCDF), which instructs some of the B cells to stop replicating and start producing antibodies.

4. Helper T cells also produce a lymphokine called gamma interferon (IF), which has multiple effects. Like IL-2, it helps activate killer T cells, enabling them to attack the invading organism. Like BCGF, it increases the ability of B cells to produce antibodies. It also affects macrophages, keeping them at the site of the infection and helping them digest the cells they have engulfed.

5. Gathering momentum with each exchange of signals between macrophages and T cells, a lymphokine cascade amplifies the immune response until the enemy is overwhelmed by sheer strength of numbers.
Figure 34-3 Time course of the antibody response in the circulating blood to a primary injection of antigen and to a secondary injection several weeks later.
Wear **Red** next Friday (Feb 5\(^{th}\)!)
Help raise awareness about Women & ♥️ disease

http://www.goredforwomen.org/
https://www.goredforwomen.org/about-heart-disease/facts_about_heart_disease_in_women-sub-category/statistics-at-a-glance/
7 Resolutions to Improve Health

• Quit smoking
• Avoid 2\textsuperscript{nd} –hand smoke
• Know your numbers
• Process out processed foods
• Get moving
• Get your friends & family on board
• Spread awareness

Cardiovascular (CV) = Heart + Vessels + Blood!
**NB:** Figure-8 loop

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arteries</td>
<td>Pulmonary veins</td>
</tr>
<tr>
<td>Vena cavae</td>
<td>Aorta and branches</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>Left ventricle</td>
</tr>
<tr>
<td><strong>Systemic circuit</strong></td>
<td><strong>Systemic circulation</strong></td>
</tr>
<tr>
<td><strong>Pulmonary circuit</strong></td>
<td><strong>Pulmonary circulation</strong></td>
</tr>
</tbody>
</table>

Capillary beds of lungs where gas exchange occurs

Capillary beds of all body tissues where gas exchange occurs

Oxygen-poor, CO₂-rich blood

Oxygen-rich, CO₂-poor blood

D Chiras 2013 fig 4-1b
Dual Pump Action & Parallel Circulation
Fetal Circulation
≡ Aqua Animal
Bypass Lungs
$R \rightarrow L$ ❤ Shunt

G&H 2011 fig 83-4
Aorta
Superior vena cava
Right atrium
Right ventricle
Inferior vena cava
Pericardial cavity
Fibrous pericardium
Parietal pericardium

Torstar 1984 p 34
Human \( \heartsuit = 4\)-chambered box? 2 separate pumps?

Upper = Atria

Lower = Ventricles

Pulmonary

Systemic

RA

LA

RV

LV

R \( \heartsuit \)

L \( \heartsuit \)

Primer Pumps

Power Pumps
Human ❤️ = 4 unique valves?  
2 valve sets?

**Semilunar** = *Half-moon shaped*

1. Pulmonic/Pulmonary
2. Aortic

**AV** = *Atrioventricular*

3. ❔ AV = Tricuspid
4. ❣ AV = Mitral/Bicuspid
G&H 2006 fig 9-6;  
cf: G&H 2011 fig 9-7
What the heck’s a *bruit*? 
(brwe, bro̞ot) [Fr.] sound > 25 subclassifications!

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

**b. de canon** [Fr. sound of cannon] abnormally loud 1\(^{st}\) 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
Anastomoses May Provide Lifesaving Collateral Circulation!!
Cardiac Cycle

- **Systole**
  - Contract & Empty

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

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

G&H 2011 fig 21-4
Electrical Events Precede Mechanical Events!