I. **Announcements** Quiz 2 on Digestion & Nutrition! Q? Also, nutrition reports (.doc/.docx + .pdfs) by e-mail to Kelsey or Hannah by 5 pm today! Outlines? Lab review.

II. **Connections + Body Resistance to Infection II** G&H ch 33,34,35 + L Sherwood 2012, Stuart Fox, Daniel Chiras, Basiro Davey

A. **Med Physiology News** Louis Picker @ OHSU on track to cure HIV! Laughter is Medicine, Handwashing SEBB News + CDC

B. Connections: WBC differential, demonstration?

C. Immune response, pathogens, evolution Davey pp 5-12

D. Recap *cf*: Innate vs. adaptive immunity G&H pp 465-70, LS+... Innate immunity *eg* inflammation, interferon, complement

E. Antibody (Ab=Ig) structure, subclasses, mechanisms G&H fig 35-4 + LS + Davey fig 2.4 p19, fig 4.2 p42, tab 4.1 p49

F. Mom’s milk overview *Scientific American*

G. Immune Regulation + Allergy: G&H fig 35-7, 35-8,...35-3 + *National Geographic, The Wars Within*, Lennart Nilsson


http://pinterest.com/susanknauff/immunology/
Dr. Louis Picker of OHSU on track to cure HIV!


https://www.youtube.com/watch?v=ITwG6O9G81g
Laughter = Medicine!

- Laughter’s most profound effects occur on the immune system.
- Laughter $\uparrow \gamma$-interferon, $\uparrow$ B-cells, $\uparrow$ T-cells and $\downarrow$ stress hormones
- The average child laughs 100s of x/day
- The average adult laughs 12 x/day
- We need to find these lost laughs—and use them to our advantage!

Ah Ha!

SEBB Newsletter 1997
Hand-washing

The right way to wash your hands:

Thoroughly wash with soap and warm running water — rubbing your hands together for at least 10 seconds.

Hand-washing is the single most effective thing you can do to reduce the spread of colds and other infectious disease.

It’s not necessary to use anti-bacterial soaps when washing up. Regular soap and water do the job just fine.

Also, using germicidal soaps too often may produce antibiotic-resistant bacteria.

Source: Hospital Infections Program, U.S. Centers for Disease Control and Prevention

http://www.squidsoap.com/
Immunology Websites for Fun Learning!

http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter24/animation_the_immune_response.html

http://www.guardian.co.uk/science/video/2010/nov/01/immune-system-viruses-cells

http://www.nobelprize.org/educational/medicine/immunity/game/index.html
Immune Response

1. Detect invader or ID toxic product.
2. Communicate to network.
3. Recruit coordinated, multi-pronged attack.
4. Amplify & if yes to success, then –
5. Suppress

Davey 1990 p 6
Pathogen?

Microbes that cause disease!

- Bacteria
- Viruses
- Protozoa
- Fungi
+ Multicellular Parasites, e.g., ticks & lice

Davey 1990 p 5
Pathogens & Parasites Cause:

1. 70-80% of deaths in less developed countries

2. Tens of millions of deaths due to infectious diseases

3. > 20 million childhood deaths per year in Asia, Africa & Latin America due to diarrheal infections alone

4. Yet < 2% deaths in modern, industrialized countries!

World Health Organization 2016 Statistics

Davey 1990 p 5
Why such striking differences across the world?

1. Poor sanitation
2. Contaminated water supply
3. Contaminated food supply
4. Malnutrition
5. Existing infections
6. Patchy, inadequately-funded vaccinations
7. AIDS superimposed on top of 1-6!

Davey 1990 p 5
FIGURE 2.1 Summary of the main physical, chemical and mechanical barriers to infection entering the human body.
Good phagocytes!

Davey 1990 p 13
Figure 33-2 Movement of neutrophils by *diapedesis* through capillary pores and by *chemotaxis* toward an area of tissue damage.
Widespread Location of Lymphoid Tissues!
**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!
Macrophage

Neutrophil

Hypothalamus

EP, endogenous pyrogen

NSAIDs e.g. Aspirin

Lactoferrin binds Fe$^{2+}$ ↓ Replication

NO, nitric oxide toxic to microbes

Prostaglandins

↑ Set point

Hypothalamus

Lactoferrin

NETs! Neutrophil Extracellular Traps

NETs!

1. ↑ Phagocytosis
2. ↑ Enzymatic rxns, Q10?
3. ↓ Bacterial replication by ↑ Fe$^{2+}$ requirement

Prostaglandins

↑ Set point

Hypothalamus

Lactoferrin binds Fe$^{2+}$ ↓ Replication

NO, nitric oxide toxic to microbes

Prostaglandins

↑ Set point

Hypothalamus

NETs!

Neutrophil Extracellular Traps

NETs!

Histamine

↑ Vasodilation

↑ Capillary permeability

Antihistamines

Mast Cells

Kinins activated

Pain receptors ↑ Chemotaxis

Kinins activated

Pain receptors ↑ Chemotaxis

Mast Cells

Histamine

↑ Vasodilation

↑ Capillary permeability

Anti-histamines
**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**

**ASTHMA**

- Asthma drawing by Rachel Novak
1. Break in skin → Bacteria enter & reproduce
2. Mast cells release histamine
3. Vessel wall becomes sticky → Neutrophils & monocytes attach → diapedesis → chemotaxis
4. Chemotaxins attract more Neutrophils & monocytes
5. Monocytes swell → 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.
Viruses coming!

Don’t breathe on me, Paul!

Interferon Mechanisms

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

Virus cannot replicate
Activated Complement

The Big MAC to Osmotic explosion!

Plasma membrane of pathogen

Membrane attack complex

Proteins of membrane attack complex

C5b–6, C7, C8, C9

L Sherwood 2012
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!!

Davey 1990 p 30
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.
Clonal Selection

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.

B cell specific to antigen

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

Plasma cells

Rough ER

Antibodies

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

Memory B cells

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?

Immunoglobulin G

Source: Visual Science
1. **Agglutination**

2. **Complement**
   - Inactive C1 complement molecule (binds with)
   - Invading bacterium coated with antibodies specific to it
   - Activated by binding with antigen-attached antibody
   - Formation of C5–C9, the membrane attack complex
     - (leads to)
     - Formation of holes in foreign cell
   - Membrane attack complex
   - Lysis (rupture) of cell

3. **Opsonization**
   - Invading bacterium coated with antibodies specific to it
   - Phagocyte

4. **Killer Cells**
   - Invading bacterium coated with antibodies specific to it
   - Lysis induced by killer cell
   - Natural killer (NK) cell

L Sherwood 2012
IgE skyrockets in allergies, parasitism, vasculitis, Hodgkin's disease!

### 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>IgG, IgA, IgM, IgD, IgE</td>
<td>γ, α, μ, δ, ε</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Number of constant domains in each heavy chain</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>3, 3, 4, 3, 4</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Relative molecular mass ($M_r$) of monomer</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>150,000, 160,000, 180,000, 185,000, 200,000</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Normally found as polymer?</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>no, dimer, pentamer, no, no</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Valency: number of antigen binding sites in normal form (i.e. monomer or polymer)</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>2, 4, 10, 2, 2</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Percentage of total immunoglobulin in serum</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>70–80, 13–20, 6–10, 0–1, 0.002</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Serum half-life (days)</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>23, 5.8, 5.1, 2.8, 2.3</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Ability to trigger complement cascade*</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>++, −, +++, −, −</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Can cross placenta from mother to foetus*</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>+, −, −, −, −</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Binds to Staphylococcal cell walls*</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>+, −, −, −, −</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Binds to macrophage Fc receptors*</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>+, −, (+)?, −, −</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Binds to neutrophil Fc receptors*</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>+, +, (+)?, −, −</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Binds to mast cell and basophil Fc receptors</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>−, −, −, −, +++, −</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
<tr>
<td>Binds to platelets</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>+, −, −, −, −</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
<td>IgG, IgA, IgM, IgD, IgE</td>
</tr>
</tbody>
</table>

* For IgG this refers only to some subclasses.
IgA = Secretory $A_b$

Dimer!!

Antigen/$A_g$

Valence? 4
### 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><em>B</em> 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, ingesting bacteria in baby’s digestive system.</td>
</tr>
<tr>
<td><em>T</em> 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>Description</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&lt;sub&gt;12&lt;/sub&gt; binding protein</td>
<td>Reduces amount of vitamin B&lt;sub&gt;12&lt;/sub&gt;, 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>Hormones and growth factors</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>Lactoferrin</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>Lysozyme</td>
<td>Kills bacteria by disrupting their cell walls.</td>
</tr>
<tr>
<td>Mucins</td>
<td>Adhere to bacteria and viruses, thus keeping such microorganisms from attaching to mucosal surfaces.</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>Bind to microorganisms and bar them from attaching to mucosal surfaces.</td>
</tr>
</tbody>
</table>
IgM = Macroglobulin Pentamer!!!!!

Valence? 10
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 cell secretes 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 BCDF, 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.