Overview of Lecture: Immune Systems.
Read: Text ch 43

Bullet Points:
- Selfish Clones
- Innate immunity
- Cells
- Inflammation
- Fever & Toxic Shock
- Chemicals; RNAi
- Acquired immunity
- Antibodies
- 'Thymic Education'
- Cell-mediated (T) immunity
- Humoral (B) Immunity
- Diseases
- Stress

Think Happy Thoughts for better ‘humoral immunity’!
Evolution by Natural Selection is a **Selfish Process**

Things that survive & reproduce relatively more of **self** become relatively more common over time. An important way to increase survival & reproduction is to **form cooperative coalitions**.

In evolutionary theory, the main mechanisms that underpin cooperation (discourage cheating) are **mutualism**, **reciprocity** and **kin selection**.

By helping kin, a ‘unit’ helps reproduce copies of shared genes.

All the **cells within a body** that descend from a fertilized egg are a **clone**.

\[
\therefore \text{kinship} = 1; \text{ (except mutations; cancers)}
\]

this makes for a **very cooperative coalition - a body**.

Most cells in a body don’t reproduce across generations; they increase copies of shared genes in their ‘close kin’ - the gametes.

It is the job of the **immune system** to stabilize this cooperative coalition by making sure everyone is on the same team - the ‘**self team.**’

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**Self/non-self Discrimination in Basal Metazoa** ...

Integrative and Comparative Biology, Sep 2005 by Cadavid, Luis F

... the basal metazoan phyla Porifera and Cnidaria have the ability to distinguish between their own tissues and those of unrelated members of the same species.

... maintains the genetic integrity of the colony.

{and might be necessary for the evolution of multicellularity}
Cells of the Immune System (Fig 42.16)

Lymphoid stem cells develop into lymphocytes: B cells and T cells.

Myeloid stem cells develop into erythrocytes (red blood cells) platelets (clotting Fig 42.18) leucocytes (white blood cells)

**Lymphoid**
- B cells
- T cells
- Lymphocytes

**Myeloid**
- Erythrocytes (red blood cells)
- Platelets (clotting)
- Leucocytes (white blood cells)
  - Neutrophils & Monocytes → macrophages
  - Basophils & Mast cells - release histamins, prostaglandins, cytokines, pyrogens, etc.
  - Eosinophils & Natural Killer cells - ‘bombs’
  - Neutrophils & Monocytes → macrophages
  - Dendritic (antigen presenting) cells (pg 943)

**INNATE IMMUNITY**
- Rapid responses to a broad range of microbes
- Recognition of traits specific to particular pathogens, using a vast array of receptors to ‘PAMPs’
- Slower response

**INNATE IMMUNITY**
- Recognition of traits shared by broad ranges of pathogens, using a small set of receptors
- Rapid response

**ACQUIRED IMMUNITY Adaptive**
- Recognition of traits specific to particular pathogens, using a vast array of receptors
- Slower response

**BARRIER DEFENSES**
- Skin
- Mucous membranes
- Secretions

**INTERNAL DEFENSES**
- Phagocytic cells
- Antimicrobial proteins
- Inflammatory response
- Natural killer cells

**HUMORAL RESPONSE**
- Antibodies defend against infection in body fluids.

**CELL-MEDIATED RESPONSE**
- Cytotoxic lymphocytes defend against infection in body cells.

**Pathogens (microorganisms and viruses)**

**Mucus** contains **lysozyme**, which digests peptidoglycan is also rich in phagocytes & IgA antibodies.
All organisms have ‘innate’ mechanisms to discriminate self from non-self.

**Bacterial endonucleases**, aka phage growth ‘**restriction enzymes**’
cleave specific DNA sequences found in viruses but not in bacterial self; We use them for genetic fingerprinting (restriction length polymorphisms).

All plants & animals have **lectins**, many-handed glycoproteins that bind sugars on cell surfaces of ‘others.’ Called ‘opsonization’ in vert’s; *{Fig 43.21}*

**Defensins** *{small proteins}, antibodies & complement* *{Fig 43.21}*
are vertebrate analogs to lectins.

Lectin ‘**phytohemagglutinins**’ selectively clump RBCs into A, B & O groups. Some lectins in our food (esp beans) are poisonous if not destroyed by cooking:
http://www.biotype.net/diets/Lectin.pdf

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**The lectin-complement pathway – its role in innate immunity and evolution**
Fujita et al 2004 Immunological Reviews 198: 185-

*{In jawed vertebrates}* Immunity to infection is mediated by two general systems: **acquired** (or adaptive) and **innate** (or natural).

**The innate immune system** is an evolutionarily ancient form.

... specific receptors *{ex Toll-like receptors pg 933}* recognize conserved Pathogen-Associated Molecular Patterns (PAMPs) shared by many microorganisms *{ex: bacterial peptidoglycan, flagellin – Fig 43.6}*

**Acquired immunity** arose early in vertebrate evolution. Genes encoding several pivotal molecules including immunoglobulin (Ig), major histocompatibility complex (MHC) I & II, ...

have been identified only **in sharks and higher vertebrates**.
When injured, **mast cells** \( \{ \text{specialized basophils in connective tissue \& mucosa} \} \) release **histamine**, triggering dilation of nearby capillaries.  
\{**antihistamines fill receptor cell ‘locks’ w/o turning the key - preempt histamine keys;**\}

Activated macrophages discharge additional signals, such as **prostaglandins**, that further **promote blood flow to the injured site**: causes the swelling, redness and heat typical of inflammation.  
... help deliver antimicrobial proteins and clotting elements to the injured area.  
\{**prostaglandins potentiate pain; a target of painkillers – more on that later**\}

Small proteins called **chemokines** \( \{ \text{or cytokines} \} \) are secreted by many cell types: **attract** phagocytic **neutrophils \& monocyte–macrophages** and signal them to increase production of microbe–killing compounds.
Leukocytes also release molecules called **pyrogens**, which set the body's thermostat at a higher temperature – **fever**. Phagocytized bits of bacterial pyrogens (cell wall etc) increase the production of **interleukin-1** in phagocytes. **IL-1** (‘leukocyte pyrogen’) increases the local production of **prostaglandins** in the anterior hypothalamus: **increase the temperature set-point**. Fever can be reduced by **aspirin** which **inhibits** the synthesis of prostaglandins. {more on this in nervous system}

Certain bacterial infections can induce an **overwhelming systemic inflammatory response** known as **septic shock**.

Characterized by high fever and low blood pressure, septic shock is the most common cause of death in U.S. critical care units. {especially bad after quorum sensing & ‘surprise attack’}
RNAi scoops medical Nobel \{in 2006\}
Gene silencers get something to shout about.

Andrew Fire and Craig Mello, who revealed the process of RNA interference (RNAi) in 1998 have received a Nobel prize ...

RNAi serves as a natural defence against viruses, which attempt to co-opt a host's protein-production mechanism by inserting their own \{double-stranded RNA\} genes into the host DNA.

Double-stranded RNA is recognized by a protein called Dicer ... cutting it into strips and destroying it, silencing its parent gene.

The process also protects a cell from rampant expression of host gene fragments that replicate and insinuate themselves all over the genome.

Mechanisms of gene silencing by double-stranded RNA 343
GUNTER MEISTER AND THOMAS TUSCHL | Full text | PDF

RNA silencing mechanisms were first recognized as antiviral mechanisms that protect organisms from RNA viruses, or prevent the random integration of \{self\} transposable elements. The role of silencing in the regulation of \{self\} gene expression became apparent when it was realized that specific genes encode short forms of fold-back dsRNA ... function as siRNAs that guide the cleavage of sequence-complementary mRNAs.

\{some siRNA genes ‘silence’ mRNA from other gene loci\}
Bacteria detected by Dendritic Cells (DC) ... are internalized into the phagosome where bacterial antigens are processed for presentation on MHC class II.

Bacterial antigens (red) and PAMPs (Pathogen-Associated Molecular Patterns, blue) in the same phagosome indicates to the DC their common origin.

... recognition of bacterial PAMPs promotes the selection of bacterial antigens for optimal presentation on MHC class II.

TLR \{Toll-Like Receptor\} signaling also leads to the induction of costimulatory molecules and cytokines necessary for activation and differentiation of T lymphocytes. - adaptive
Nobel announcement ... Immunology takes prize for medicine

Before the immune system can attack an invading pathogen, it must identify the intruder. Breakthroughs in understanding this process have garnered three scientists {the 2011} Nobel Prize in Physiology or Medicine.

Ralph Steinman discovered a type of immune cell, known as a dendritic cell, that is vital to the 'adaptive' immune system, {also called 'acquired' immunity} which works out exactly which pathogen has invaded the body in order to trigger a targeted response.

Steinman showed that these dendritic cells are much more important than macrophages in activating T cells.

Jules Hoffmann and Bruce Beutler earned their share of the prize for discovering a key to a more immediate line of defence, the 'innate' immune system, ...

Hoffmann was investigating why fruitflies, which lack an adaptive immune system, don't succumb to fungal infection ... they reported that the Toll gene was important.

Beutler ... looking for an immune-system gene in mice that produces a protein to recognize lipopolysaccharide (LPS) a molecule produced by bacteria ...

The team eventually found its LPS-sensing gene, and it looked remarkably like Hoffmann’s Toll. ... paved the way for the discovery of other Toll-like receptors that sense molecules made by pathogens but not their hosts, and form a critical part of the innate immune system.
Our bodies are covered by epithelial layers inside and out … How then can the immune system, inside the wall of epithelial cells, sense potentially pathogenic antigens without making holes in this protective barrier? Kubo et al. (2009 J. Exp. Med. 206, 2937) show that during inflammation, epidermal Langerhans cells acquire external antigens by extending cellular protrusions, known as dendrites, through the tight seals between keratinocytes in the skin. To maintain the seal despite breaching the tight junctions, the Langerhans cells form secondary junctions … This ability to screen incoming antigens provides an important first defense against attack.

NATURE | NEWS 26 July 2012 Virginia Gewin
The skin’s secret surveillance system
Microorganisms that reside on the skin found to influence host immunity.
... the skin’s surface creates a multitude of diverse habitats, each with its own community of microbes. ... these benign residents are not just innocent bystanders - according to a paper published today in Science, Naik, S. et al. Science http://dx.doi.org/10.1126/science.1225152 (2012)
... skin-specific bacteria also influence the response from the host's immune system to help fight off infection. – commensals tuned the function of local T cells.
Acquired \{Adaptive\} immunity: Foreign invaders inevitably come into contact with **B cell** or **T cell** lymphocytes.

Each **B cell** or **T cell** (lymphocyte) has on its surface many antigen receptor proteins (attached antibodies) that can bind a particular piece (epitope) of a foreign antigen. The antigen (epitope) receptors on a given lymphocyte are all the same, but there are millions of different clonal lineages of lymphocytes in the body, each lineage targeting a different antigen (epitope).

**Figure (a)** A B cell receptor consists of two identical heavy chains and two identical light chains linked by disulfide bridges. Called IgD ~attached IgG.

**Figure (b)** A T cell receptor consists of one α chain and one β chain linked by a disulfide bridge.
Vertebrate chromosomes have only hundreds of receptor-encoding genes, but ~10^8 different kinds of B cells making ~10^8 different antibodies.

**Antibody Genes**

Scientists long wondered how all the genetic information needed to make millions of different antibodies could fit in a limited number of genes.

The answer is that antibody genes are pieced together from widely scattered bits of DNA, in a process combining somatic DNA rearrangement

{via Recombination-Activating Genes RAG; the RAG genes came from a transposon? http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823946/}

and the possible combinations are nearly endless. (see Fig 43.13)

As this gene forms, it assembles segments that will determine the variable-V, joining-J, and constant-C segments of this antibody molecule …

{∞ variety of mutant antibodies recognize ∞ molecules, including ‘self’}
Antibodies are large protein molecules known as immunoglobulins.

**IgM** combines in star-shaped clusters. It tends to remain in the bloodstream, where it is very effective in killing bacteria.

**IgG**, the major immunoglobulin in the blood, is also able to enter tissue spaces; it works efficiently to coat microorganisms, **{interfere with function & flag for destruction}**

**IgA** - a doublet - concentrates in body fluids such as tears, saliva, milk, mucous; ... in a position to guard the entrances to the body.

**IgE** is normally present in only trace amounts, but it is responsible for the symptoms of allergy **{it triggers mast cells in mucous membranes to release histamines}**.

**IgD** is inserted into the membrane of B cells, where it regulates the cell's activation.
The Organs of the Immune System

All the cells of the immune system are initially derived from the bone marrow… stem cells differentiate into … B cells ... and immature thymocytes

Immature thymocytes ... migrate into the thymus.

\{∞ random thymocyte antibody genotypes created by mutation and splicing processes. (fig 43.13)

Immature T cells are screened against self-antigens.

Self-tolerance results from clonal deletion in thymus of any immature T cells that react strongly to self \}

**Nature** 420, 468 - 469 (05 December 2002);

**Immunology: Education and promiscuity.** WILLIAM R. HEATH AND HAMISH S. SCOTT

To fight off microbial infections, our bodies call into action a type of immune cell known as the T cell. Sometimes, however, these cells mistake part of our body (self) for a microbe (non-self), ... lead to autoimmune diseases such as multiple sclerosis and juvenile diabetes.

To prevent this, T cells must undergo a strict education in the thymus, where they are tested for reactivity to as many self-proteins as possible; if reactive, they are eliminated.

Writing in *Science*, Anderson and colleagues report that organ-specific self-proteins (such as insulin, from the pancreas) can be 'promiscuously' expressed in the thymus ... allows developing T cells to become familiar with many of the body's molecules, including those normally not expressed in the thymus ...
at the “heart” of the immune system
The receptors on **B cells** recognize intact antigens.

The receptors on **T cells** recognize small (9 AA) fragments of antigens ‘presented’ at the surface by **major histocompatibility complex (MHC)** molecules, which pick up chopped-up protein fragments in cytoplasm and display them on surface for inspection: **antigen presentation**.

If a **cytotoxic T cell** detects ‘foreign’ bits in **somatic cell MHC I**: kills the cell!

“**helper T cell**”

“**APC macrophage MHC II**: ‘sounds alarm!’

Recall – **MHC(II)-dependent**

mate preferences in humans.

Wedekind et al.1995.

**T-Cells**

are divided into two major subsets.

1. After an antigen-presenting cell engulfs and degrades a bacterium, it displays bacterial antigen fragments (peptides) complexed with a class II MHC molecule on the cell surface. A specific helper T cell binds to the displayed complex via its TCR with the aid of CD4. This interaction promotes secretion of cytokines by the antigen-presenting cell.

2. Proliferation of the helper T cell, stimulated by cytokines from both the antigen-presenting cell and the helper T cell itself, gives rise to a clone of activated helper T cells (not shown), all with receptors for the same MHC-antigen fragment complex.

3. Following proliferation, helper T cells secrete other cytokines, which help activate B cells and cytotoxic T cells.

**Humoral immunity** (secretion of antibodies by plasma cells)

**Cell-mediated immunity** (attack on infected cells)

**Humoral (antibody-mediated) immune response**

**Cell-mediated immune response**

1. **Antigen-presenting cell**

2. **Bacterium**

3. **Class II MHC molecule**

4. **TCR (T cell receptor)**

5. **CD4**

6. **Antigen fragment**

7. **B cell**

8. **Helper T cell**

9. **Cytotoxic T cell**

10. **Cytokines**

11. **Clone of plasma cells**

12. **Secreted antibody molecules**

13. **Clone of memory B cells**

14. **Endoplasmic reticulum of plasma cell**

15. **Perforin**

16. **Granzymes**

17. **Target cell**

18. **Antigen fragment**

19. **Dying target cell**

20. **Released cytotoxic T cell**

21. **Cytotoxic T cell**

22. **Class I MHC molecule**

23. **CD8**

24. **TCR**
HIV is a complex animal virus.

- HIV can only enter cells that possess a cell-surface marker \{a `lock'\} recognized by a glycoprotein on the HIV particle surface. \{a `key'\}
- HIV infects & kills CD4+ \{helper T\} cells, \{so does hepatits C\} \{disrupting both cellular & humoral immunity to everything\} eventually causing the patients to die of an infection.

Medscape Medical News
CD4 T Cells From "Elite Controllers" Resist Infection by HIV
Daniel M. Keller, PhD
October 22, 2010
Elite controllers, the very small proportion of HIV-infected individuals who, without treatment, have undetectable viral levels, have CD4 T cells that resist infection with the virus.
Immunity: Short- and Long-Term Cell Memory
Whenever T cells and B cells are activated, some become **memory cells**.
The next time that an individual encounters that same antigen, the immune system is primed to destroy it quickly.
Long-term immunity can be stimulated not only by infection but also by **vaccines** made from inactivated infectious agents or, more commonly, from minute portions of the microbe.

{ ‘Memory’ is useless if pathogen evolves new surface antigens: antigen shifting – ex influenza, malaria}

Short-term immunity can be transferred passively via antibody-containing serum; similarly, **infants are protected by antibodies they receive from their mothers** (IgG antibodies cross the placenta, IgA antibodies are passed in breast milk).

Note the use of passive immunity w/ IgG at 1st birth of Rh+ baby by Rh- mom: pre-empts development of active Rh+ memory & strong attack on 2nd Rh+ child.
The surge in food allergies, asthma & autoimmune disease in Europe and North America is thought to be related to the plunge in infectious disease in early childhood. **The "hygiene hypothesis,"** as it’s known, postulates that exposure to pathogens trains the immune system to regulate itself. 

**Mechanisms of Disease: the hygiene hypothesis revisited**

When naive CD4+ T-helper cells are activated by antigen-presenting cells they differentiate into TH-1 or TH-2 cells... Activation of TH-1 cells leads to production of cytokines such as interferon-γ, tumor-necrosis factor and interleukin-2, while activated TH-2 cells are mainly capable of secreting il-4, il-5, and il-13. In addition, under certain as yet unclear conditions, antigen-presenting cells can induce regulatory T cells, which can suppress both TH-1 and TH-2 responses ... {see s. Kivity et al. 2009}
Early exposure to germs has lasting benefits.
Findings help to explain how microbes programme a developing immune system.
Exposure to germs in childhood is thought to alter the immune system and protect children from developing allergies and asthma, but the pathways by which this occurs have been unclear.
Now, researchers have identified a mechanism in mice ...

In a study published online today in Science, researchers show that in mice, exposure to microbes in early life can reduce the body’s inventory of invariant natural killer T (iNKT) cells, which help to fight infection but can also turn on the body, causing a range of disorders such as asthma or inflammatory bowel disease.
The study supports the 'hygiene hypothesis', which contends that such autoimmune diseases are more common in the developed world where the prevalence of antibiotics and antibacterials reduce children’s exposure to microbes. {and fail to “tame” immune system}

http://well.blogs.nytimes.com/2013/05/06/why-dirty-pacifiers-may-be-your-childs-friend/
MAY 6, 2013 … In a study published Monday in the journal Pediatrics, scientists report that infants whose parents sucked on their pacifiers to clean them developed fewer allergies than children whose parents typically rinsed or boiled them.
People w/ systemic lupus erythematosus have developed an immune response to their own DNA, and the presence of anti-DNA antibodies in their serum is one way to diagnose lupus …

Rheumatoid Arthritis:
Some people produce the rheumatoid factor which is an IgM autoantibody {against own IgG}. This auto IgM binds to the Fc part of IgG, forming immune complexes, which lodge in the joints and cause inflammation of the joint.
{see Vinuesa & Goodnow 2002. Nature 416,595-598}
When normal cells turn into cancer cells, some of the antigens on their surface change. These altered antigens flag immune defenders, including cytotoxic T cells, natural killer cells, & macrophages.
... patrolling cells of the immune system provide continuing bodywide surveillance, spying out and eliminating cells that undergo malignant transformation.
Tumors develop when the surveillance system fails
   {or when the immune system is suppressed, ex by stress}

Spectrum of cancer risk among US solid organ transplant recipients.
Solid organ transplant recipients have elevated cancer risk due to immunosuppression and oncogenic viral infections.

Social stress in laboratory rats - Behavior, immune function, and tumor metastasis.
Stefanski V. PHYSIOLOGY & BEHAVIOR 73 (3): 385-391 JUN 2001
... in subdominant males after 2 days of continuous social confrontation elevated plasma concentrations of adrenal hormones ...
   {adrenal-cortical cortisol is an immune suppressant}
   lower numbers of blood CD4 and CD8 T cells as well as reduced activity levels of natural killer (NK) cells ...
A 10-fold lower tumor clearance in subdominant males ...

Excess mortality among the bereaved was evident ...
The Immune System and the Nervous System
... links between the immune system and the nervous system exist at several levels.

**How stress influences the immune response.**

**Affective style and in vivo immune response:**
Neurobehavioral mechanisms.
Rosenkranz et al. 2003 PNAS 100:11148-11152.
Participants were vaccinated for influenza & antibody titers after the vaccine were assayed to provide an in vivo measure of immune function.
Higher right-prefrontal electroencephalographic activation (assoc w/ depression), and greater magnitude of the startle reflex (assoc w/ anxiety) reliably predicted poorer immune response. (lower antibody titer)

**Enhancement of antibody responses to influenza vaccination ... following a ... stress management intervention**
... The immune response to influenza vaccination appears amenable to improvement through stress management

*Think Happy Thoughts for better ‘humoral immunity’!*