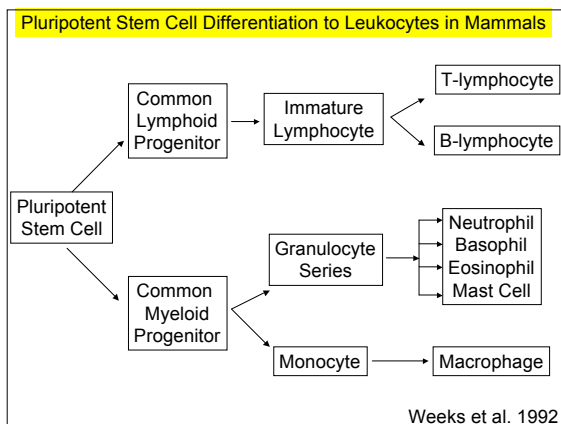
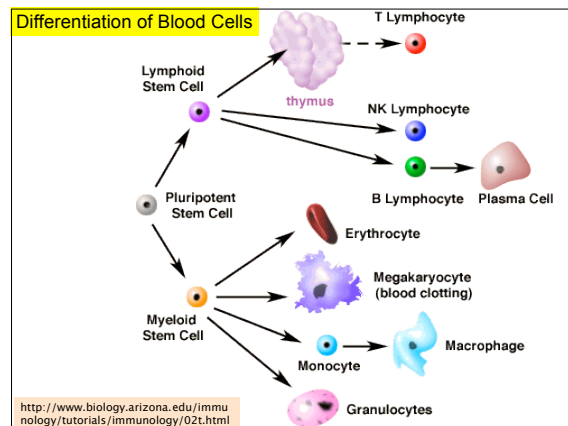
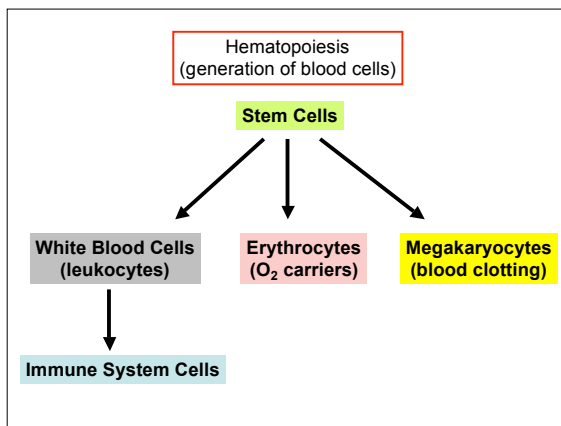
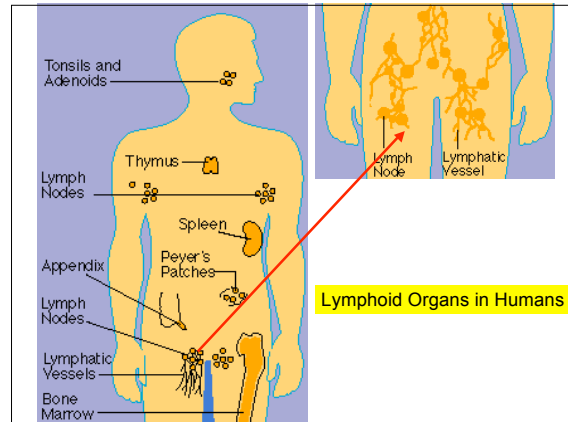


ES/RP 531  
Fundamentals of Environmental Toxicology

Lecture 14  
Immunotoxicity



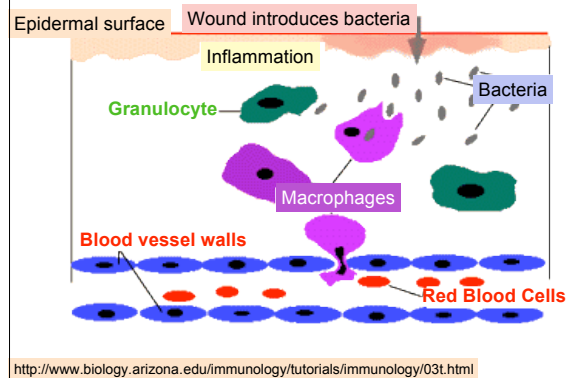
### Immunity

- **"Non-specific", Innate Immunity**
  - "First line of defense"
  - More accurately described as broadly specific
  - No memory
    - i.e., after infection, cells do not recognize specifically the pathogen or toxin
- **Specific, Adaptive (or Acquired) Immunity**
  - "Second line of defense"
  - Activated by and directed against specific antigens
    - Antigen: "a protein or other substance that elicits immune system activation"
    - Antigen: "anything that can be bound by an antibody"
  - Has memory: increases with strength after each encounter with pathogen or toxin

## Innate Immunity

- Physical Barriers
  - Skin, mucous membranes
- Physiological factors
  - pH, temperature, oxygen tension limit pathogen growth
- Protein secretions into external body fluids
  - Lysozyme enzyme (saliva, tears)
  - Complement, interferons, C-reactive proteins
- Phagocytic cells
  - Including macrophages & polymorphonuclear leukocytes
  - Recognize foreign cells by broadly specific receptors (usually for carbohydrate structures on cell)

## Nonspecific Innate Immunity: Phagocytosis of Foreign Cells



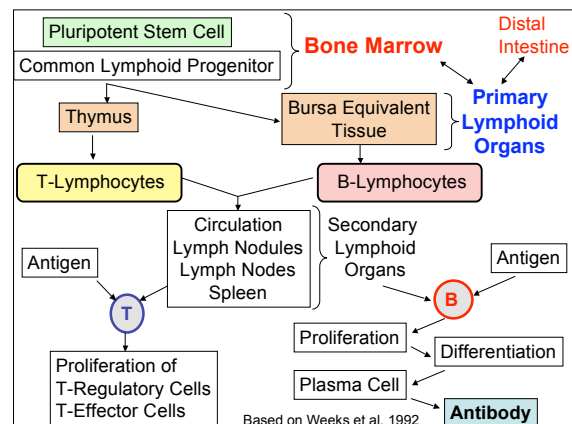
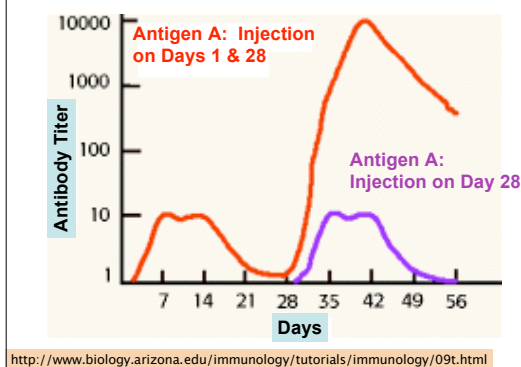
## Acute Inflammation

- Acute inflammatory response is a key characteristic of the innate immune system
  - Many infections, especially where small wounds are entry routes, are eliminated by the combination of complement and recruitment of phagocytes
- Functionality
  - Reduces spread of damaging agents to nearby tissues
  - Increases disposals of cell debris and pathogens
  - Facilitates repair processes
  - Caused by release of histamine and prostaglandins by certain leukocytes

## Adaptive Immunity

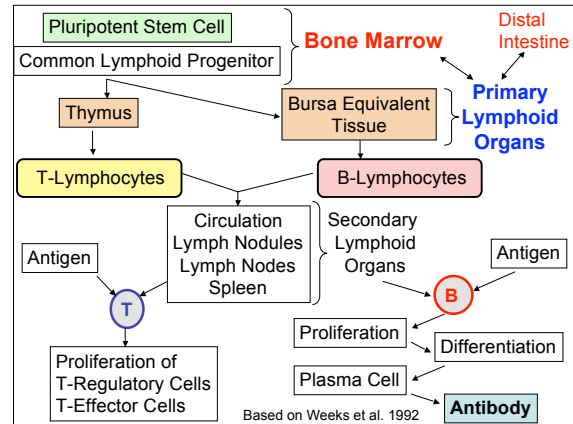
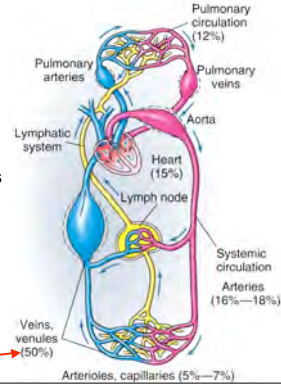
- Immune response activated by and directed against specific antigens
  - I.e., response mechanism is “adapted” to idiosyncrasies of the foreign cell or toxin
- Characterized by “memory”
  - Once challenged with an antigen, immunity will persist to this specific antigen
  - Causes a decrease in lag time and an increase in response level to repeated infections
- Two Types of Mechanisms (both involving differentiated lymphocyte cells)
  - Humoral Immunity (involves B cells)
  - Cellular Immunity (involves T cells)

**Memory in Adaptive Immunity:** Second exposure to antigen produces a faster and higher level of response

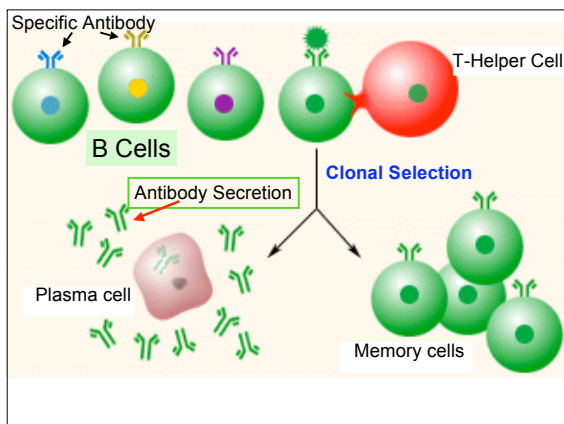
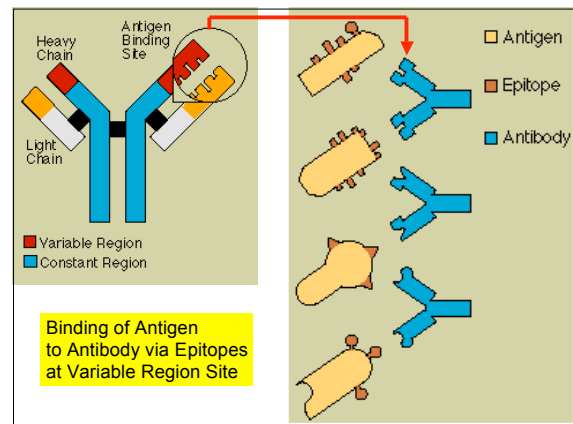
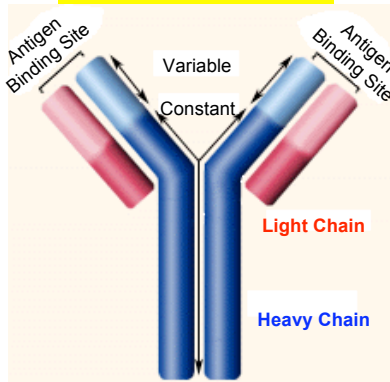


## Closed Circulatory System of Mammals

- Capillary walls are permeable, so under high pressure there is some leakage of fluid across the walls into the spaces between cells
- Lymphatic system recovers the fluid lost to tissues
- Lymph returns to the blood circulation through the portal venous system

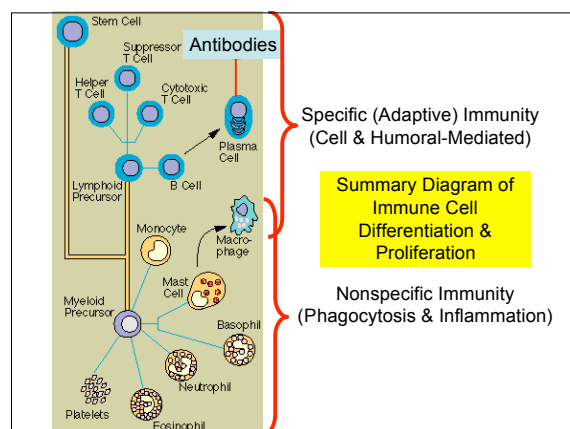
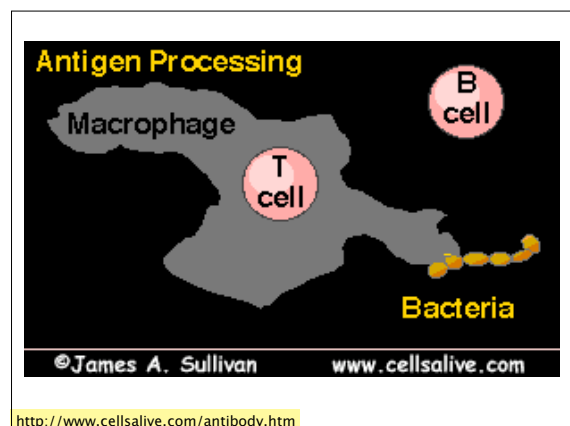
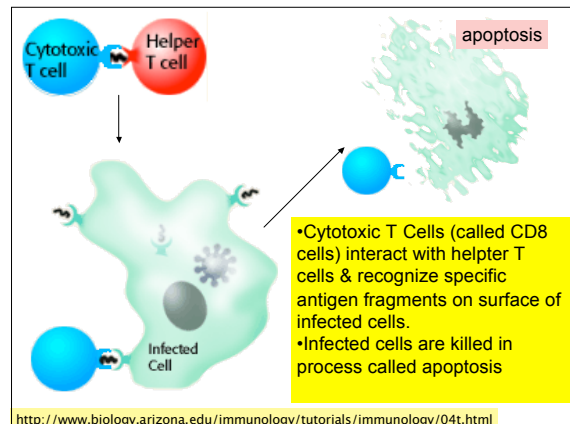


## Basic Structure of Antibody



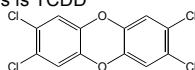
Scanning electron micrograph showing interaction between a macrophage (gray structure) and lymphocyte (red structure) during the attack on a *Streptococcus* bacterium



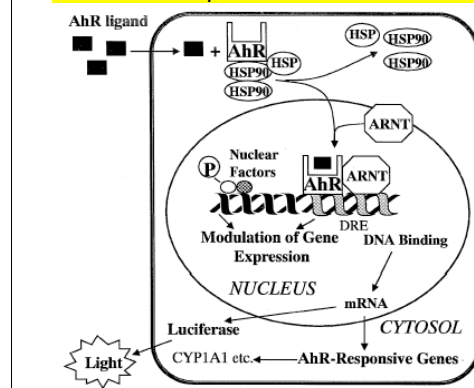


### Ah Receptor Mediated Immunotoxicity

- Certain polyhalogenated hydrocarbons, dibenzodioxins, and dibenzofurans cause immunotoxicity characterized by a "wasting" syndrome, atrophy of the thymus, & alterations in T-cell mediated immune functions
  - Especially includes certain PCB congeners and chlorinated dibenzodioxin & dibenzofuran congeners
- The detailed mechanism of how these compounds cause immunotoxicity is unknown but all of them react with a receptor called AhR that causes the transcription of arylhydrocarbon hydroxylase, a P-450 mediated microsomal enzyme (i.e., P-4501A1)
- The most potent of these immunotoxins is TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin)



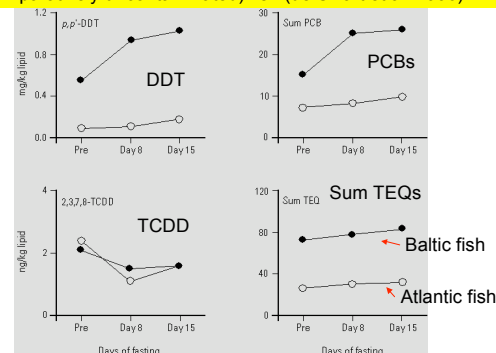
### Ah Receptor Mediated Toxicities



### Case Study: Marine Mammals Exposed to Polyhalogenated Aromatic Hydrocarbons

- Problem: Marine mammals seem to be exhibiting high incidence of disease
  - In some cases "beachings" seem to have no natural cause
- de Swart et al. (1996) fed contaminated herring to one group of seals and comparatively uncontaminated herring to another group of seals
  - The contaminants included PCBs, DDT, and dioxin (expressed as toxic equivalents based on TCDD, tetrachlorodibenzo-*p*-dioxin)
- Measured residues in fat and blood and immunological activity before & after fasting

Contaminant levels observed in seals after fasting for 15 days following consumption of Baltic (contaminated) fish and Atlantic (comparatively uncontaminated) fish (de Swart et al. 1996)



### Immunological Parameters--Contaminated Herring Group Relative to "Uncontaminated" Herring Group

de Swart et al. 1996, EHP Supplements

Immunological Parameter	Effect
NK (natural killer) cells	Down
T lymphocytes	Down
B lymphocytes	No Difference
Hematology: Lymphocyte Counts in Peripheral Blood	No Difference
Hematology: Neutrophil Counts in Peripheral Blood	Up

### Conclusions from Herring Feeding Study

- Immunological parameters representing specific immunity (lymphocytes) were down regulated in association with higher levels of polyhalogenated aromatic hydrocarbon compounds in fat and blood
- Neutrophils in blood (represented nonspecific immune response) were upregulated
- Natural populations exposed to similar levels of contaminants may experience effects on immune system

de Swart et al. 1996

### Conclusion from Herring Feeding Study--Fasting Effects

- Fasting was associated with a 2-fold increase in blood levels of polyhalogenated organochlorines, but no effect on blood levels of Ah receptor-binding compounds
- Fasting alone, regardless of diet caused a 35% drop in circulating lymphocytes and a slight increase in NK-cell activity
  - However other lymphoproliferative response remained the same in the contaminated herring group.
- Short-term fasting did not present an additional immunotoxic threat

### Do PCBs Cause Immunotoxicity in Fish?

- PCBs have been implicated as immunotoxins based on rat studies
- Powell et al. 2003 fed different levels of PCBs to fish
  - PCBs were formulated as Aroclor 1254
- Challenged fish with pathogen
- Some fish vaccinated, others not vaccinated

