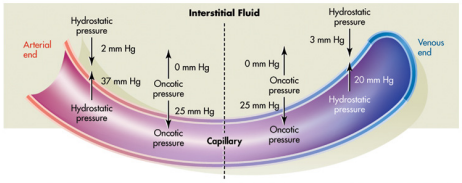
Inflammation and Repair

General Vocabulary words

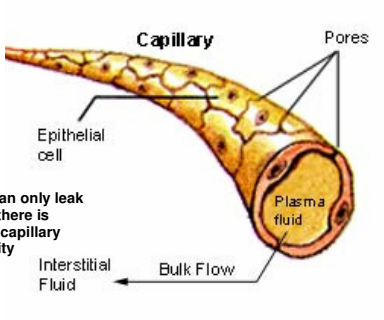
- Intracellular space
- Extracellular space
  - Vascular space
  - Interstitial space
- Read Lewis, 318 – 319
  - Hydrostatic Pressure
  - Oncotic Pressure
  - Fluid Shifts
- Edema



Arterial Capillary Pressures	
Capillary hydrostatic pressure	37 mm Hg
Interstitial fluid hydrostatic pressure	2 mm Hg
Net hydrostatic pressure	**35 mm Hg**
Capillary oncotic pressure	25 mm Hg
Interstitial fluid oncotic pressure	0 mm Hg
Net oncotic pressure	**25 mm Hg**
Net filtration pressure	**+10 mm Hg**

Venous Capillary Pressures	
Capillary hydrostatic pressure	20 mm Hg
Interstitial fluid hydrostatic pressure	3 mm Hg
Net hydrostatic pressure	**17 mm Hg**
Capillary oncotic pressure	25 mm Hg
Interstitial fluid oncotic pressure	0 mm Hg
Net oncotic pressure	**25 mm Hg**
Net filtration pressure	**–8 mm Hg**

Capillary Permeability



Proteins can only leak out when there is increased capillary permeability

Lymphatics

- Lymphatic membrane increases in permeability
  - Allows for greater removal of interstitial fluid
  - Allows proteins and other substances into the lymph drainage
    - Possible conduit for spreading infectious or toxic agents

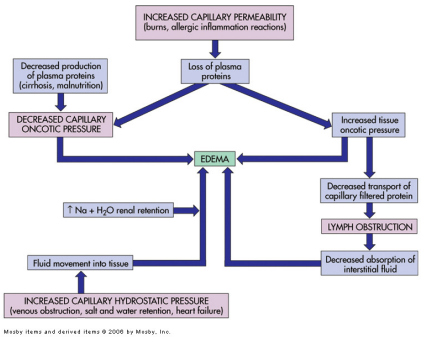
Factors Promoting Edema

- Increased Hydrostatic pressure
  - Hypertension
  - Fluid Overload (Renal, heart, or liver failure)
  - Increased Venous pressure (PVD, postural blockage)
- Decreased Oncotic Pressure
  - Inhibited Protein production (liver disease, protein malnutrition)
  - Capillary permeability (local inflammation)
- Lymph obstruction

Factors Inhibiting Edema

- Hydrostatic Pressure
  - Compression
  - Drugs reducing fluid volume (diuretics)
  - Postural
- Oncotic Pressure
  - Colloids (natural or artificial albumin)
  - Reduce inflammation

Factors Affecting Edema



Inflammation

- Response of surrounding tissue to injury
- Allows substances in blood to enter the tissue (due to increased capillary permeability)
  - Antibodies, Complement, Clotting factors
- Purpose
  - Neutralize and eliminate offending agents
  - Destroy necrosed tissue
  - Prepare tissue for reapir

Features of Acute Inflammation

- Redness (Erythema)
- Heat
- Pain
- Swelling (Edema)
- Altered Function

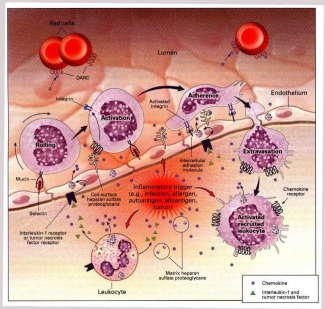
Fluid Mechanism of Inflammation

- Dilation of local arterioles
  - Increased local blood flow and pressure
- Increase in vascular permeability
  - Leakage of protein
- Viscosity of local blood increases
  - Blood flow slows down
  - Allows white blood cells to enter the site of injury

Cellular Aspects of Inflammation

- Margination and emigration (exit lane)
  - Allows leukocytes to exit the blood vessels and enter the inflamed tissue
  - Synonyms: Extravasation, diapedesis
- Chemokines (chemoattractants)
  - Chemicals that attract leukocytes to the site of inflammation
  - Process is called chemotaxis, gradient driven
- Cytokines
  - Chemicals that alter a cell's function

Chemotaxis and Emigration



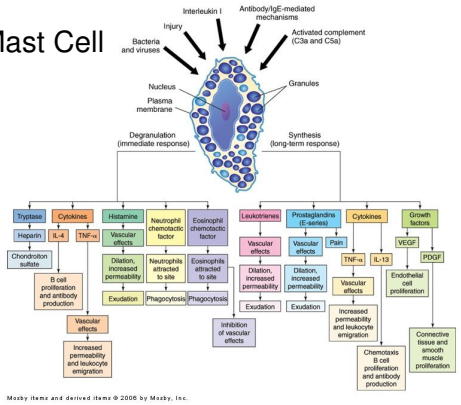
Inflammation vs Immunity

- Inflammation is nonspecific, nonadaptive
- Immunity is specific (to select antigens), adaptive
- Inflammation allows immunity to happen
- Immunity controls inflammation

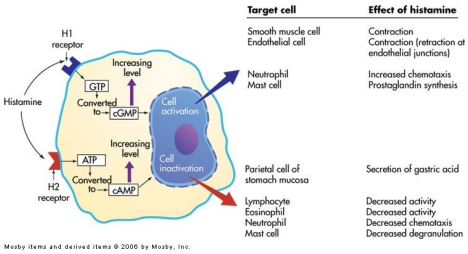
Mediation of Inflammation

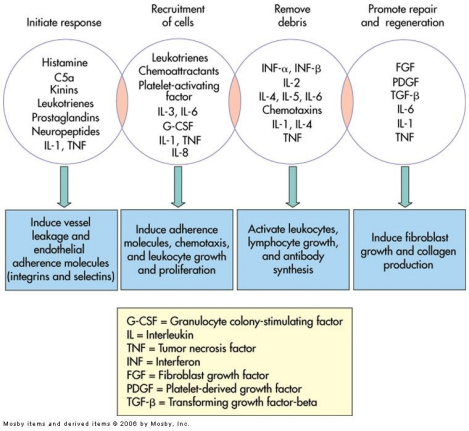
- **Vasoactive amines** – Histamine
- **Plasma enzyme products** – Clotting factors, complement, factor XII (Hageman)
- **Arachidonic acid metabolites** – prostaglandins, thromboxanes, leukotrienes
- **Miscellaneous cell products** – TNF, NO, selectins, integrins, ICAM, VCAM, interleukins

Mast Cell



Histamine Activity





Mediation Vocabulary

- Cytokine – substance that affects the way other cells function
- Zymogen – inactive storage form of an enzyme or other active substance. Examples:
  - Plasminogen → plasmin
  - Fibrinogen → fibrin
  - Pepsinogen → pepsin

Leukocytes

- Common ancestor – bone marrow pluripotent hematopoeitic stem cell
  - Common Lymphoid Progenitor
    - B cells, T cells, Natural Killer Cells
  - Common Myeloid Progenitor
    - Erythrocytes, Macrophages, Granulocytes, Dendritic Cells
- Progessive differentiation

Leul

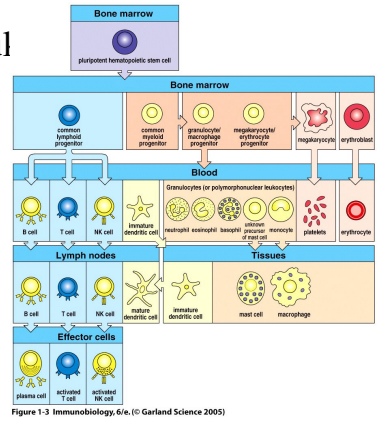


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

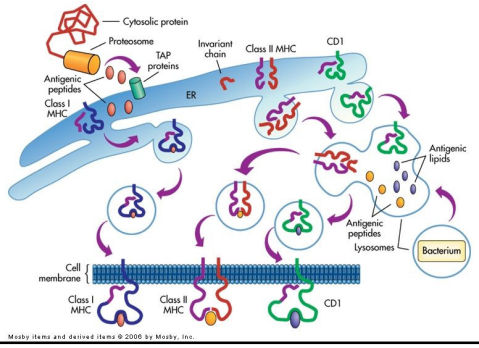
Monocytes-Macrophages

- Small quantities in the blood
- Spend most of their life cycle in Tissues
  - Tissue Macrophages may have other names
    - Liver – Kuppfer Cells
    - Nervous system – Microglial cells
    - Skin – Langerhans
    - Connective Tissue – Histiocytes
- Relatively long lived – weeks to months

Macrophage Functions

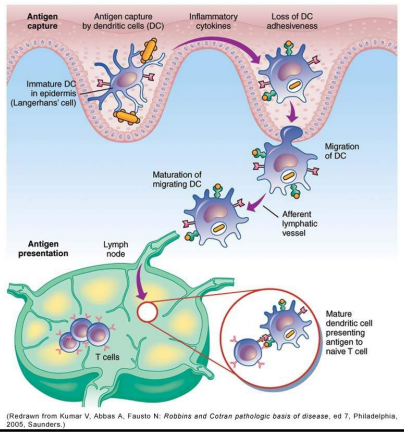
- Effector cell
- Phagocytic
- Antigen Presenting
- Common Pathogen Feature Receptors
  - Glucan, mannose, ligands, LPS
- Releases cytokines and chemokines
- Granuloma – multinucleated giant cell

Antigen Processing and Presentation



Dendritic Cells

- **<u>Not</u> to be confused with dendrites!!!**
- Relatively new discovery, 1973
- Phagocytic and Macropinocytic
  - Digest whatever is digested
  - Recognize digested pathogen features including bacterial DNA, heat shock proteins, and viral RNA
- Antigen Presenting



Dendritic Cells' Dual Role

- High levels of MHC – present antigens to T cells
- At end of life cycle or when activated, migrate to lymph nodes
  - Activate T cells against pathogenic antigens
  - Induce *Tolerance* to self antigens

Mast Cells

- Unknown blood precursor
- Granulated cells
  - Known to release at least 16 chemokines and cytokines
  - Best known for Histamine
- Major function is to activate inflammation
  - Membrane Permeability
  - Leukocyte chemotaxis

Granulocytes

- Named for cytoplasmic granules
  - Neutrophils
  - Basophils
  - Eosinophils

Neutrophils

- Most numerous
- Shortly lived – 6 hour half life in blood
- Phagocytic
- Primarily attack bacterial invaders
- Bone marrow holds 100 times circulating number of Neutrophils
  - Segmented Cells (segs) – fully mature
  - Banded Cells (bands) – slightly immature
- Neutropenia

Other Granulocytes

- Exocytic
- Mostly distributed throughout tissues
- Eosinophils
  - Parasites
  - IgE Allergic reactions
- Basophils
  - Fungus

Lymphocytes

- Immune cells that control and direct inflammation
- Present in small numbers in acute exudates
- Large numbers in chronic inflammation
- Destroy invaders
- Prepare for tissue reparation

Lymphocytes

- B lymphocyte → Plasma Cell → antibodies
- T lymphocytes
  - CD8 cells: Cytotoxic (Killer) T Cells – kill viral infected cells
  - CD4 cells: Helper T Cells (Types I and II) – direct B lymphocytes and macrophages
- (CD8 and CD4 are cell membrane proteins)

Lymphocyte Life Cycle

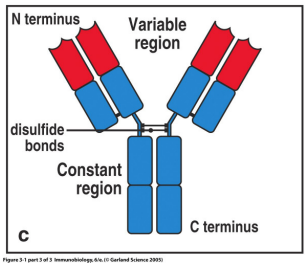
- Inactive (naïve) lymphocytes circulate through blood and lymph
  - T cells are activated by dendritic cells (and occasionally macrophages)
  - B cells are activated by T cells
- Once activated, lymphocytes must
  - Proliferate (replicate, multiply, reproduce)
  - Differentiate (mature)
- Once threat is neutralized
  - Most undergo apoptosis
  - A few remain as Memory Cells

B lymphocytes

- Mature in Bone Marrow (Bone, B, B cell. Get it?)
- Naturally produce IgM antibody and display it on their cell membranes (M for Membrane, get it?)
- Proliferation and Maturation are directed by CD4 T helper cells
- Purpose of maturation is to improve the quality (affinity) of antibody produced

Antibodies

- Immunoglobulin
- Variable region
  - Somatic hyper-mutation
- C region
  - Mediates inflammation
- Disulfide bonds can be cleaved



Immunoglobulin Polymers

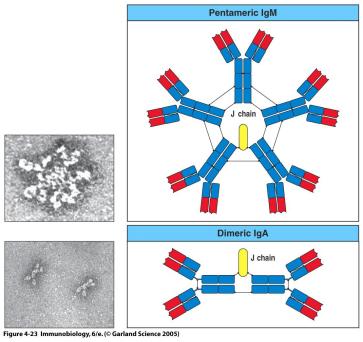


Figure 4-23 Immunobiology, 6/e. (© Garland Science 2005)

Antibody Function

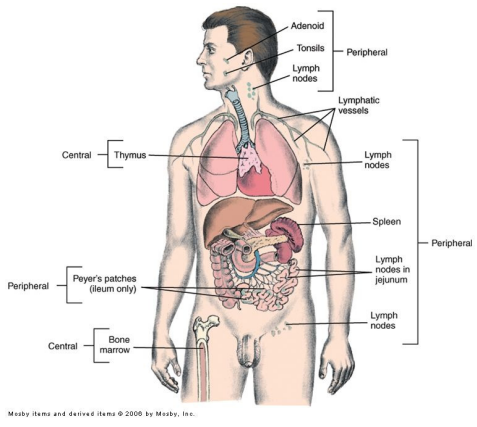
- Neutralization
- Opsonization – "painting"
- Activation of inflammation
- Activation of complement
- Antibody subtypes
  - IgM – first produced, low affinity
  - IgD – no known function
  - IgA – crosses barriers → placenta, milk, eyes
  - IgG – opsonin → helps macrophages kill
  - IgE – eosinophils → parasites and allergies

T Lymphocytes

- During childhood, T cells migrate to Thymus
  - TCR mutation and tolerance testing
  - Differentiation marked by CD8 and CD4 protein
  - CD8 binds to MHC I and marks Cytotoxic cells
  - CD4 binds to MHC II and marks Helper cells
    - Further differentiate into Helper I and II cells

Activated T Cell Function

- Cytotoxic cells
  - Virally infected cells present viral antigen via MHC I which binds to CD 8
  - The cytotoxic cell degranulates into the infected cell, killing it
- Helper cells
  - Direct B cell maturation and Macrophages
  - TH1 are better at directing Macrophages
  - TH2 are better at directing B cells



Complement Cascade

- Consists of 9 zymogens
  - C1 – C9
- Three activation pathways
- All end with C3 convertase
- Cleaves C3 into C3a and C3b
- C5 cleaves into C5a and C5b
- C3b and C5b activate membrane attack complex (MAC)
- C3a and C5a act as cytokines and chemokines

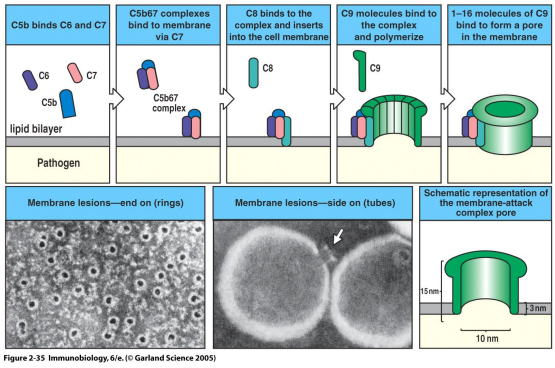
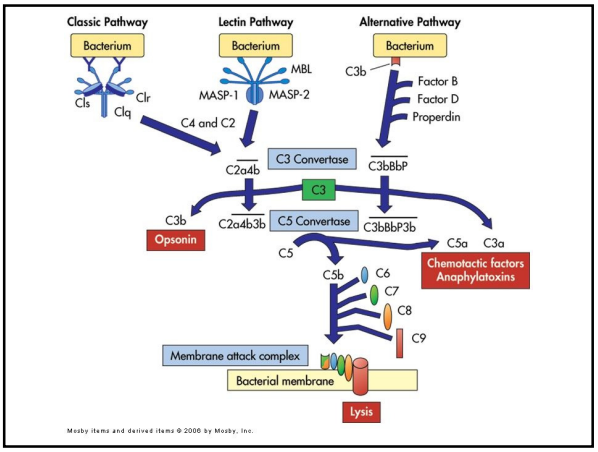


Figure 2-35 Immunobiology, 6/e. (© Garland Science 2005)



Complement activation pathways

- Classical - C1q binds
  - Directly to pathogen
  - CRP
  - Antibody-Antigen complex
- Mannose Binding Lectin
- Alternative (spontaneous)

Complement Functions

- Kill Pathogens through MAC – (puncture them and let the guts spill out)
- Opsonize pathogens
- Mediate inflammation through C3a and C5a

Basic Immunophysiology

- Three intertwining processes
  - Inflammation
  - Adaptive response
    - Cell mediated
    - Humoral

Non-specific response

- Pathogen recognition
  - Usually begins by recognizing common pathogenic features
  - Initiates inflammatory response
    - Brings effector cells to the site
    - Walls off infection
    - Prepares tissue for healing

Inflammatory Response

- Local effects of chemokines and cytokines: especially TNF-α
  - Vasodilation
  - Expression of adhesion molecules
  - Increase in vascular permeability
    - Leakage of plasma proteins
    - Clotting factors and complement
  - Blood clot walls off area from blood supply
    - Allows dendritic cell time to travel to lymph nodes

Inflammatory Response

- Systemic effects – TNF-α, IL1-β, IL-6
  - Fever
    - Inhibits pathogen growth
    - Enhances immune response
    - Protects body from TN-α
  - Acute Phase Response
    - Acute Phase Proteins released by liver
      - CRP
      - MBL
      - Lung surfactants
  - Leukocytosis
  - ↑ESR

Septic Shock – TNF-α run amok

- TNF-α
  - Vasodilation
  - Increases vascular permeability
  - Induces clotting
- TNF-α escapes into blood
  - Low blood pressure
    - Vasodilation
    - Decreased plasma volume from vascular permeability
  - Disseminated clotting

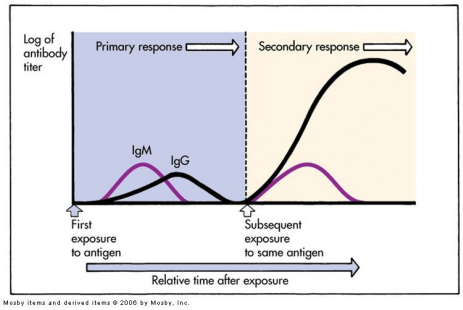
Adaptive Immunity

- Cell Mediated – T Cells
  - CD8 – Always become cytotoxic T cells
  - CD4 – Must choose to become T_H1 or T_H2
    - T_H1 regulate macrophages
      - Activate macrophages
      - Kill infected macrophages
      - Regulate B cells
    - T_H2 regulate B cells
- Humoral Immunity – Antibodies
  - B cells – become Plasma cells and produce antibodies

Memory

- Can take a month for full maturation of Plasma cells
- Memory cells are fully matured and developed effector cells
  - Quick response to infections
  - Suppress naïve immune cells
  - Do not require co-stimulation

Plasma Cells and Memory



Immunization

- Active – activates body's immune system against invaders
  - Goal is formation of Memory cells
- Passive – injection of antibodies to offer limited support against an invader

Patterns of Inflammation

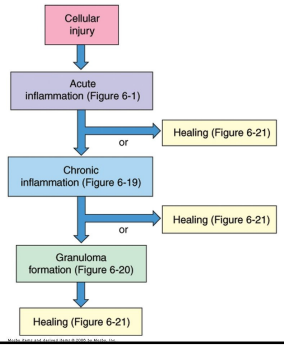
- Time factor
  - Acute
  - Chronic
- Types of Exudate
  - Serous (transudates)
  - Catarrhal (mucus)
  - Fibrinous (adhesions)
  - Purulent (furuncle, cellulitis)
  - Hemorrhagic (hematoma)

Inflammation vs Immunity

Fate of Inflammatory Reaction

- Resolution – Little damage
- Repair – Moderate to Severe damage
  - Regeneration – replacement of parenchyma
  - Scar formation – replacement of connective tissue
    - Organization – proliferation of nearby connective tissue into the damaged area
    - Granulation tissue
    - Collagen formation
    - Loss of vascularity

Inflammatory Phases

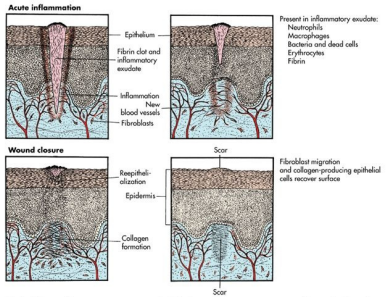


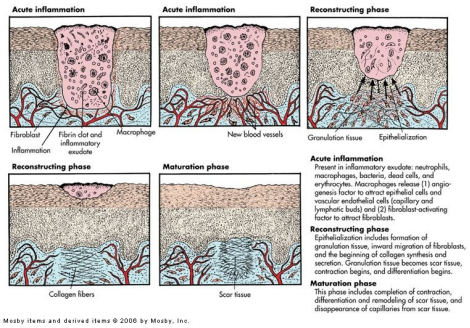
Wound Healing – Primary Intention

- Incision – Wound formation
- Fibrin clot – prevents bleeding, acts as glue to hold skin together
- Inflammatory response builds
  - Blood clot dissolved
  - Granulation tissue forms where clot was
  - Epithelium regenerates

Wound Healing
Secondary Intention

- Skin edges cannot be held together
- Similar to primary intention
  - Takes longer
  - Involves more granulation tissue and regeneration
  - May form underneath a scab
  - May show pinpoint bleeding





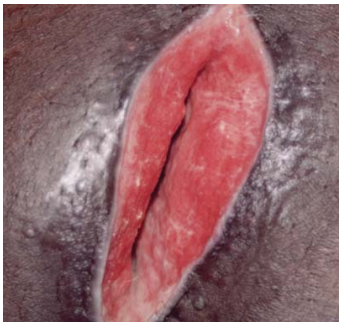
Factors affecting Inflammation

- Blood Supply
  - Elderly, Feet
- Bone marrow function
- Protein synthesis – plasma and repair
  - Liver Function
  - Nutrition
- Medication

Factors Affecting Wound Healing

- All from slide above
- Necrotic or foreign tissue in wound
- Wound infection
- Excessive movement
- Dehiscence – breaking open of a surgical wound

Dehiscence



Hypersensitivity Reactions

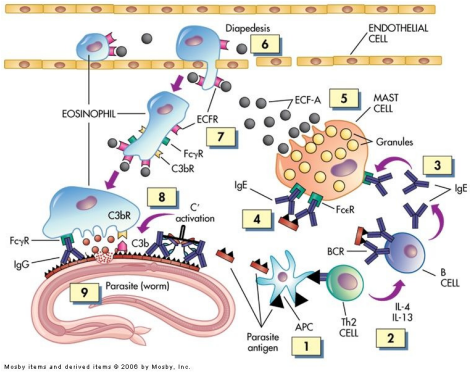
- Damage done to the body as a result of immune reactions
- Sometimes called allergies
- Four types of reactions
  I. Anaphylactic
  II. Cytotoxic
  III. Immune Complex
  IV. Cell-mediated

Anaphylactic

- Previously called immediate
- Requires previous sensitization to antigen
  - IgE is produced
  - IgE embeds in basophils and mast cells
- Upon subsequent exposure
  - Massive amounts of histamine released
  - Vasodilation and increased vascular perm
- Systemic
  - Laryngeal edema, Bronchospasm, seizures, shock

Common Anaphylactic

- Insect stings
- Penicillin
- Pollen
- Animal dander
- Foods
- Allergic rhinitis
- Anigoedema and urticaria
- Atopic Dermatitis
- Asthma



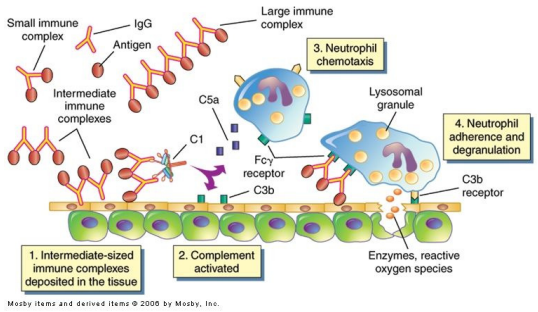
Cytotoxic

- Antibodies bind to antigens on host cells
- Host cells destroyed by
  - Complement
  - Phagocytes (ADCC)
- Common Disorders
  - ABO blood rejection
  - Myasthenia gravis

Immune Complex

- Antibody binds with antigen – Immune complex
- Immune complex diffuses out of blood into tissue
- Complement cascade activates in the tissue causing inflammation/immune response
- Damage is collateral
- Disorders: serum sickness, SLE, Stevens-Johnson syndrome

Immune-Complex



Cell-Mediated

- T_H1 cells stimulate Macrophage activity
- Macrophages activity causes tissue damage
  - If antigen is removed, reaction stops
  - If antigen persists, reaction continues and granulomas may form
- Common
  - Allergic dermatitis: poison ivy, detergents, etc.
  - Tissue transplant rejection
  - Tuberculosis

Inflammation Tests

- Erythrocyte Sedimentation Rates
- C-reactive protein: CRP
  - hs-CRP
- Anti-nuclear antibodies (ANA)
- WBC (with or without differential)
- Skin tests
- Ig levels

Anti-inflammatory and Anti-immune Drugs

- Anti-inflammatories
  - Inhibit prostaglandin – NSAIDS
  - Inhibit Leukotrienes – asthma drugs
  - Inihibt thromboxane – antiplatelet drugs
  - Antihistamines
- Anti-immune
  - Antiproliferative (Calcineurin inhibitors)
  - Cytotoxic
- Corticosteroids: both, depending on the dose

Calcineurin Inhibitors

- Calcineurin is needed to produce IL-2
- Without IL-2, T-cells cannot proliferate, so cannot mount an immune response
- Used for transplant graft rejection
- Drugs Cyclosporine: nephrotoxicity, infection
  - Kidney, liver, heart transplant
  - Psoriasis, rheumatoid arthritis
- Tacrolimus (FK506): same

Cytotoxic Drugs

- Kill proliferating B and T cells
- Are non-specific: kill all rapidly dividing cells (red blood cells, skin, epithelial cells)
- Azathioprine: Adjunct transplant
- Cyclophosphamide: cancer, SLE, MS
- Methotrexate: cancer, psoriasis, arthritis
- Mycophenolate Mofetil: selective, transplant

Glucocorticoids used for non-Endocrine purposes

- Pharmacologic Actions
  - Anti-inflammatory and Immune effects
    - Inhibit prostaglandin, leukotriene, and histamine synthesis
    - Suppress infiltration of phagocytes
    - Suppress proliferation of lymphocytes
  - Effects on Metabolism and Electrolytes
    - Glucose levels rise
    - Protein synthesis suppressed
    - Fat deposits mobilized
    - Fewer electrolyte effects, but can inhibit calcium absorption

Therapeutic Uses

- Rheumatoid Arthritis
- SLE
- Inflammatory Bowel Disease (IBD)
- Miscellaneous Inflammatory D/Os
- Allergic conditions (not acute anaphylaxis)
- Asthma
- Dermatologic disorders
- Neoplams
- Transplant rejection
- Preterm infant

Immunosuppressive effect

- Cause lysis of activated B and T cells
- Sequester T cells
- Reduce IL-2 production
- Reduce responsiveness to IL-1
- Immunosuppressive doses are large, e.g.
  - Methylprednisolone
    - Anti-immune doses: 500 – 1500mg (IV)
    - Anti-inflammatory doses: 5 – 60mg (IV)

Glucorticoids Adverse Effects

- Adrenal insufficiency
- Osteoporosis: long term therapy
- Infection
- Glucose intolerance
- Myopathy
- F&E disturbance
- Growth retardation
- Psychological disturbances

Glucorticoids Adverse Effects

- Cataracts and Glaucoma
- Peptic Ulcer Disease
- Iatrogenic Cushing's Disease
- Ischemic Necrosis – especially caution with ETOH

Agents

	Anti-inflammat
• Short Acting	
– Cortisone, Hydrocortisone	1
• Intermediate Acting	
– Prednisone	4
– Prednisolone	4
– Methylprednisolone	5
– Triamcinolone	5
• Long acting	
– Betamethasone	20-30
– Dexamethasone	20-30