Foundations of Public Health Immunology

Hypersensitivity

Type I hypersensitivity reactions can be caused by a variety of allergens

Objectives

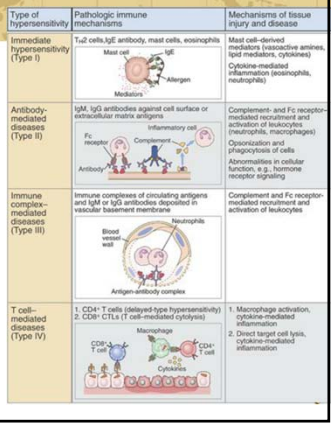
- Describe the hypersensitivity reaction to antigen exposure
- Identify and explain the similarities and differences in the mechanism of the four types of hypersensitivity reactions
- Identify selected disorders for each type of hypersensitivity reaction (selected disorders of autoimmunity)
- Identify and explain the mechanisms of sepsis

Hypersensitivity

- Normally beneficial immune responses that occur in **an exaggerated or inappropriate form**
  - Results in **inflammation, tissue damage** or other problems known as immunopathology
- Hypersensitivity reaction only occur on the **second or subsequent exposure to an allergen**
  - The host must first be sensitized to the allergen!!

Hypersensitivity

- **Four types** of hypersensitivity diseases
- Mechanism of immune injury is different in each type



Characteristics of Hypersensitivity

Comparison of Hypersensitivity Types				
Characteristics	Type I (anaphylactic)	Type II (cytotoxic)	Type III (immune complex)	Type IV (delayed type)
antibody	IgE	IgM, IgG	IgM, IgG	None
antigen	exogenous	cell surface	soluble	tissues & organs
response time	15-30 minutes	minutes-hours	3-8 hours	48-72 hours
appearance	wheal & flare	lysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	monocytes and lymphocytes
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	Erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, Poison ivy, granuloma

Table Source: http://pathmicro.med.sc.edu/ghaffar/hyper00.htm

Type I: Immediate Hypersensitivity

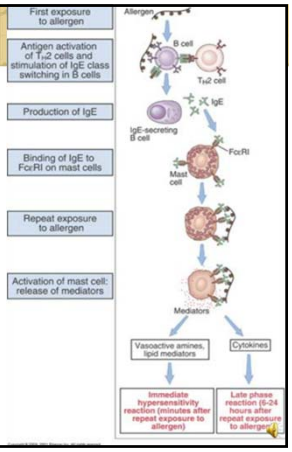
- Also know as:
  - Allergy
  - Atopy
  - Anaphylaxis
    - Most severe form of Type I reaction
- Examples of Type I reactions
  - Asthma
  - Hay fever
  - Some food and drug allergies

Clinical syndrome	Clinical and pathologic manifestations
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles
Bronchial asthma	Bronchial hyper-responsiveness caused by smooth muscle contraction; inflammation and tissue injury caused by late phase reaction
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) caused by vascular dilatation; airway obstruction due to laryngeal edema

Normal appearance | Severe allergic reaction (anaphylaxis)

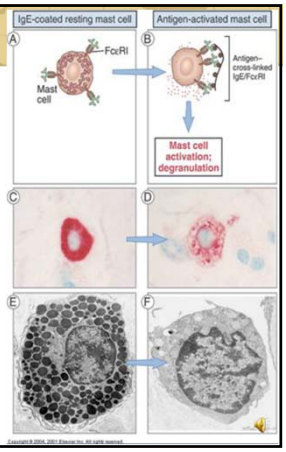
Type I Hypersensitivity Reaction

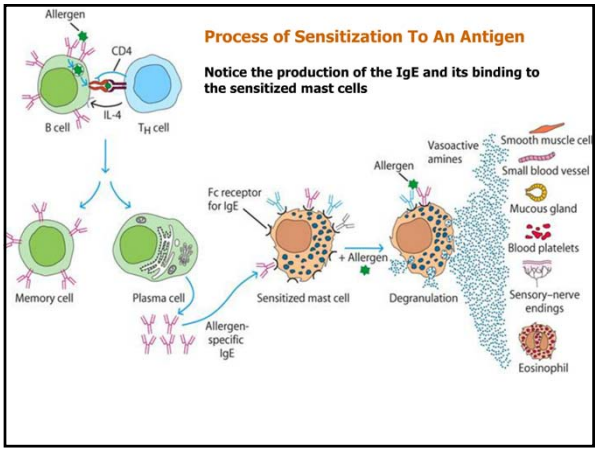
- IgE is produced in **1st** exposure to an antigen
- **IgE** proteins **bind to Fc receptors** on mast cells (on both the connective tissue and in the mucosa) and basophils
- **Repeat exposure** to the antigen then **cross-links** the IgE molecules



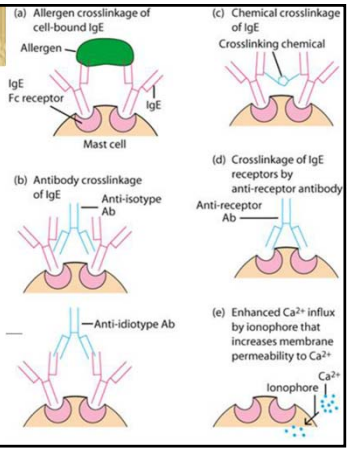
Type I Reaction cont'd

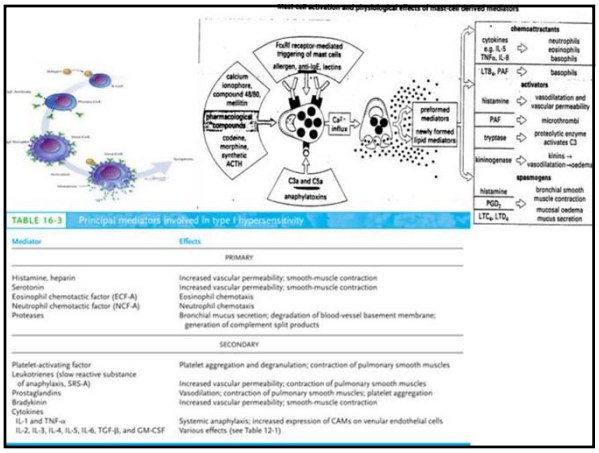
- **Cross-linking induces degranulation** of the involved mast cells and basophils- **on 2nd & later exposures**
- **Mediators are released** during degranulation
- **Trigger the symptoms** of Type I hypersensitivity
  - One mediator released during this reaction is **histamine**
  - Anaphylatoxins, C3a & C5a, also released in complement cascade triggered by released mediators.





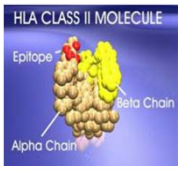
Process of the cross-linking of IgE with the antigen

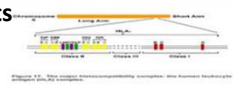




Type I: Immediate Hypersensitivity

- **Th2 cytokines promote Type I hypersensitivity**
- **Genetic predisposition** for allergen which appears to be Human Leukocyte Antigen (HLA)-linked
- **Environmental pollutants** can promote allergies
  - These pollutants can act as IgE adjuvants





Th2 Mediation of Type I Hypersensitivity

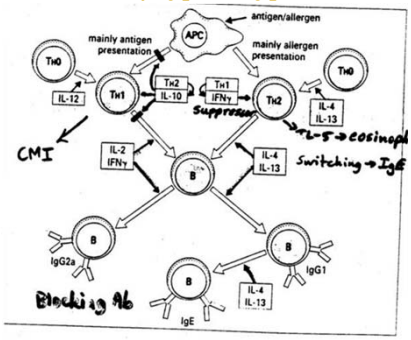


TABLE 16-1 Common allergens associated with type I hypersensitivity


Proteins
Foreign serum
Vaccines


Foods
Nuts
Seafood
Eggs
Peas, beans
Milk


Plant pollens
Rye grass
Ragweed
Timothy grass
Birch trees


Insect products
Bee venom
Wasp venom
Ant venom
Cockroach calyx
Dust mites


Drugs
Penicillin
Sulfonamides
Local anesthetics
Salicylates

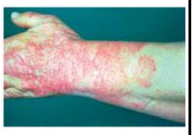
Mold spores
Animal hair and dander

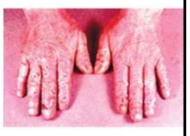
Type I: Immediate Hypersensitivity

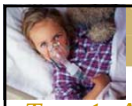
- Allergies can be diagnosed by the Skin Prick Test
  - "Wheal & Flare" is characteristic of an allergic reaction
  - Common allergens include pollen, foods, dander
- A variety of medication and treatments are used to control allergies
  - Hyposensitization (Desensitization) therapy
  - Person is exposed in increasing levels of the antigen until tolerance develops

Type I: Latex Allergy

- Occurs when the immune system reacts to proteins in natural rubber latex
- An estimated 1 – 6% of general population has been sensitized to latex
  - **5 – 10% of healthcare workers are sensitized!**
  - Should **substitute synthetic gloves** for latex
- Products that commonly cause reactions included gloves, balloons & condoms
- May also react to rubber bands, erasers, rubber parts of toys, pacifiers, etc.

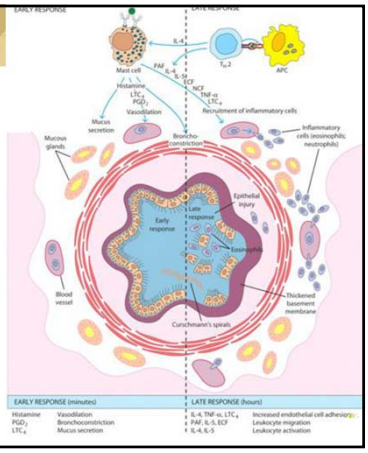






Type 1: Asthma

- Effects of an asthmatic reaction can occur **both immediately and over a prolonged time** period
- Results in both an **early & late response** during an asthmatic attack from inflammatory response



Ascaris (Roundworm)

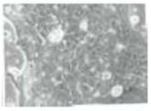
- Strong immune response to larval stage *Ascaris lumbridoides* infestation
  - Ascaris allergen is the most potent of all allergens or parasitic origin
- Bronchial asthma, urticaria (hives), angioedema (diffuse swelling and hives) frequently occur with the larval stage parasite
- However, the immune system is frequently tolerant of adult *Ascaris* intestinal infestation

Dracunuliasis

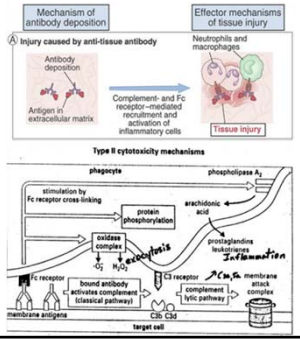
- Also known as **Guinea Worm** disease
- The female worm forms a painful blister on the skin (usually the feet) and when the foot is placed in water, the female worm releases numerous eggs
- The worm can be removed by winding it slowly around a stick over many days (see photo w/ match stick)
- If **worm ruptures** during removal, it will **release numerous antigens & produce a severe allergic reaction**.

Type 2: Cytotoxic Hypersensitivity

- With Type 2 reactions, the **reaction is against an antigen located on a cell surface**
  - The antigen being attacked is an integral part of the cell!!
- **IgM and IgG antibodies** bind to the cell surface or tissue antigens in conjunction **with complement activation**
- The **complement activation** results in:
  - Chemotaxis
  - Inflammation
  - Opsonization
  - Cellular activation

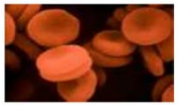


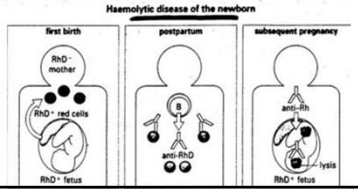
Type 2 Mediated Immunopathology



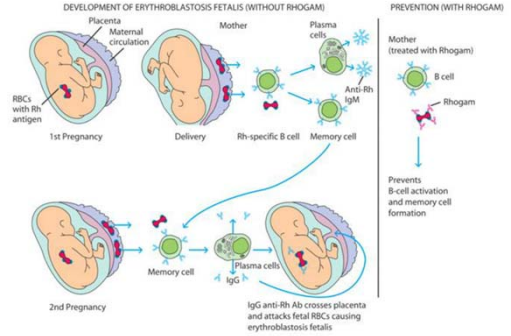
Type 2: Blood Immunopathologies

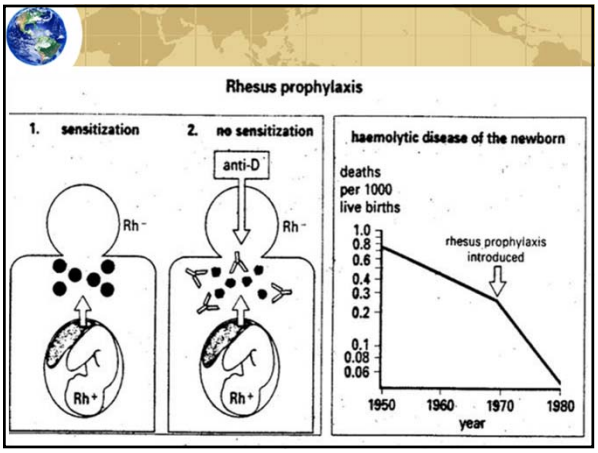
- Blood transfusion reactions
- Hemolytic Disease of the Newborn
  - RhD factor
  - Reaction involves IgG
  - Also called erythorblastosis fetalis



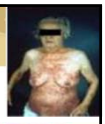


Erythroblastosis fetalis

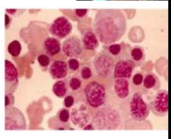




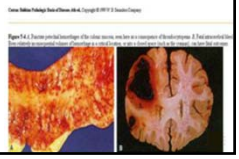
Type 2: Autoimmune Blood Reactions



Bleeding under the skin due to low platelets.



- Spontaneous reactions that destroy erythrocytes
  - Warm antibody hemolytic anemia involve **autoantibodies** that **attach to and destroy erythrocytes** at temperatures above normal body temperature
  - Cold antibody hemolytic anemia involve autoantibodies that attach to and destroy erythrocytes at temperatures below normal body temperature
- Thrombocytopenia (low platelet count)



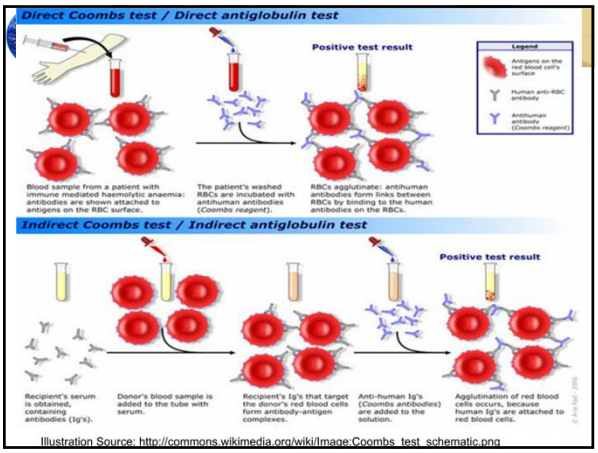
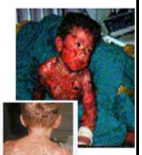
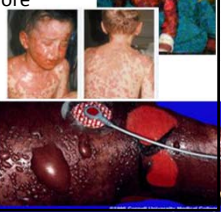


Illustration Source: http://commons.wikimedia.org/wiki/Image:Coombs_test_schematic.png

Type 2: Adverse Drug Reactions

- **Drug-induced reactions** involving drug-Ab immune complex and erythrocyte antigens
- Steven-Johnson Syndrome (SJS)
  - Affects people of all ages, but more child cases
  - If untreated, can result in death
- Toxic Epidermal Necrolysis Syndrome
  - Another form of SJS





Toxic Epidermal Necrosis

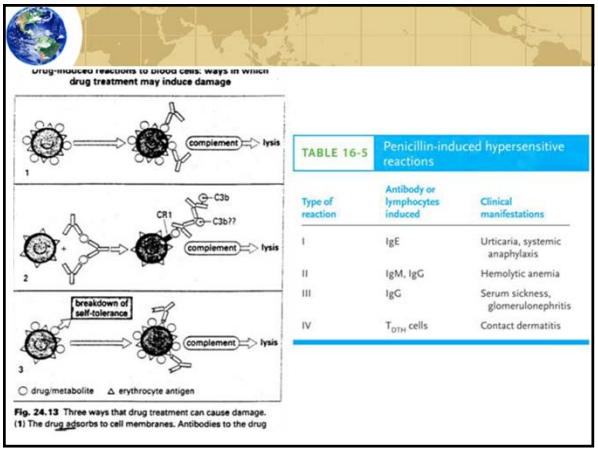


Fig. 24.13 Three ways that drug treatment can cause damage. (1) The drug adsorbs to cell membranes. Antibodies to the drug

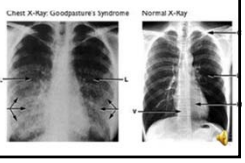
TABLE 16-5 Penicillin-induced hypersensitive reactions

Type of reaction	Antibody or lymphocytes induced	Clinical manifestations
I	IgE	Urticaria, systemic anaphylaxis
II	IgM, IgG	Hemolytic anemia
III	IgG	Serum sickness, glomerulonephritis
IV	T_{DTH} cells	Contact dermatitis

Type 2: Autoimmune Diseases

- Goodpasture's syndrome
- Involves **IgG and complement**
- **Lungs & kidneys** are effected
- Results in kidney basement membrane damage
- May be triggered by viral respiratory infections or inhaling hydrocarbon solvents
- Treat with immunosuppressive drugs and plasmapheresis (to remove harmful autoantibodies from the blood)

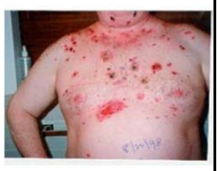
Goodpasture's syndrome may result in serious kidney damage; patients may need dialysis or a transplant.



Type 2: Autoimmune Diseases

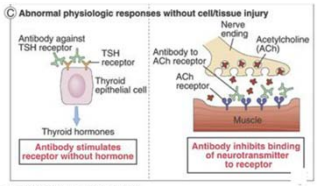
- Pemphigus vulgaris
  - Involves **antibodies against chromosome proteins, skin and mucous membranes**
  - Results in blistering
  - Exact cause is unknown
  - Disease is uncommon, occurs mostly in middle-aged (or older) patients

www.pemphigus.org



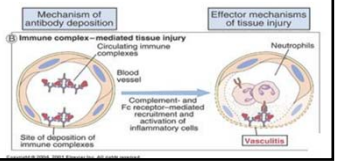
Type 2: Autoimmune Diseases

- Myasthenia Gravis
- Involves **IgG and complement against acetylcholine receptors** on muscle cell membranes
- Results in **muscle weakness and fatigue**
- Thymus abnormalities often present
  - Thymic tumors found in 10% of patients
  - Changes in germinal centers found in 70% of patients



Type 3: Immune Complex Hypersensitivity

- With type 3 hypersensitivity, damage occurs to tissues at sites of **immune complex deposition**
- Antigens involved in Type 3 reactions are **insoluble, small immune complexes** which have not been removed by phagocytes, the liver, or the spleen
- Involves the deposited antigen, antibodies (IgG), complement deposition & effector cells
  - The **antigen-antibody complexes induce complement activation** & result in inflammation mediated by neutrophils



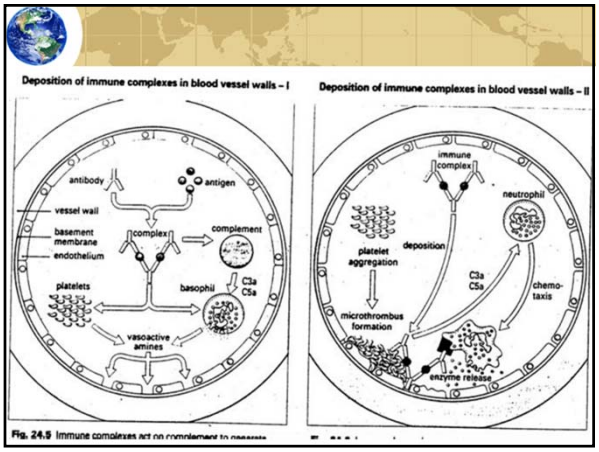
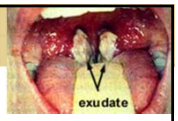


Fig. 24.9 Immune complexes act on complement to cause

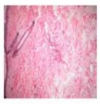
Factors Contributing to Deposition of Immune Complexes

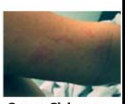
- Complement deficiencies
- Low affinity antibodies
- Antibody isotype
- Ineffective phagocytois
- Abnormal carbohydrate on antibody molecules
- Size of immune complex and the antibody isotype
- Increased vascular permeability (due to vasoactive amines)
- High blood pressure and turbulence (for example in the glomerular capillaries of the kidneys)
- Affinity of the antigen for specific tissues

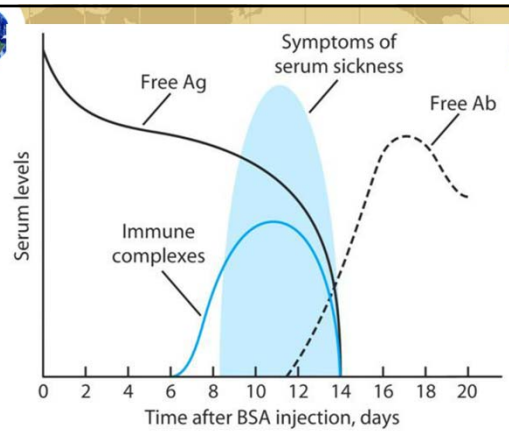
Type 3 Hypersensitivity



- Three General Groups:
  - **Persistent infection** involving microbial antigens and the kidneys
  - Autoimmune disease against **self antigen**
    - Damage can occur to the kidneys, joints, & arteries etc.
  - **Extrinsic** antigens
    - Inhaled antigen – (mold) lung
    - Serum Sickness
    - Arthus Reaction

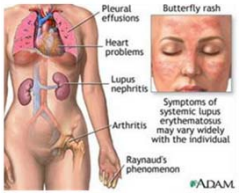

Arthus Reaction

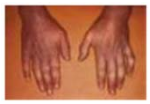

Serum Sickness

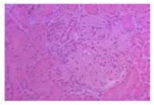


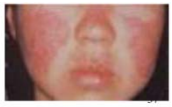
Type 3: Autoimmune Disease

- Systemic Lupus Erythematosus (SLE)
  - Formation of **immune complexes** cause inflammation & tissue injury
  - Affects many parts of the body (joints, skin, kidneys, heart, lungs, brain, blood vessels)
  - Characterized by periods of illness (flares) & times of health (remission)
  - More common in young women



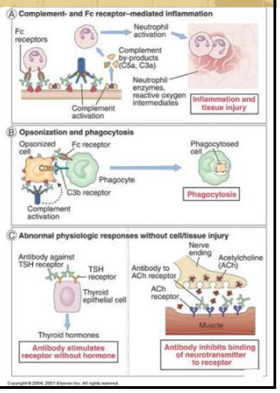

Vasculitis


Renal damage


Butterfly Rash

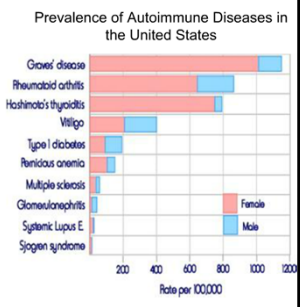
Types 1 - 3

- Antibody Mediated Hypersensitivity
  - Different effector mechanisms that cause pathology
- **Autoantibodies** are antibodies specific for self antigens
  - Damage cells & tissues
  - Present in excess in many autoimmune diseases (including SLE)



Autoimmune Diseases: Autoantibodies

- Not always a direct hypersensitivity link, but formation of autoantibodies can cause autoimmunity
- **Graves disease & Hashimoto's thyroiditis** are 2 disease where **autoantibodies target** a single organ – **the thyroid**
- **Rheumatoid arthritis** is a **systemic autoimmune disorder** – high levels of circulating autoantibodies target multiple organs but most commonly affect the joints

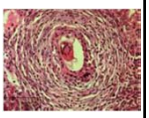


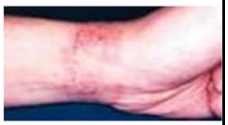
Autoantibody Tests

- Antinuclear antibody (ANA): may be found in autoimmune disorders [especially lupus, scleroderma, Sjorgren's syndrome, polymyositis, certain types of chronic active hepatitis]
- Anti-DNA antibody: may be present in lupus
  - Titers will decrease when treatment is successful
  - **Usually not found in other autoimmune diseases**
- Antiphospholipid antibody: may be found in lupus and certain other conditions
  - Associated with miscarriages and clots
- Rheumatoid factor: often found in blood and joint synovial fluid in rheumatoid arthritis patients

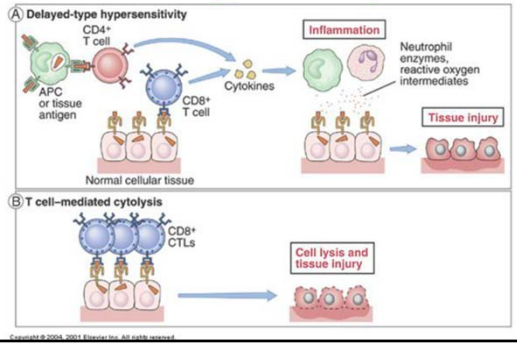
Type 4: Delayed Hypersensitivity

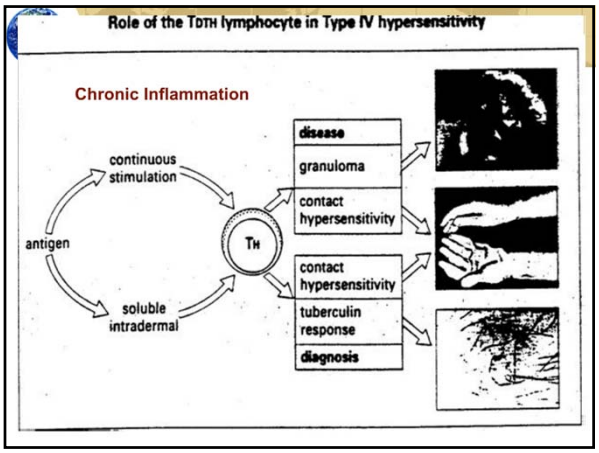
- Type 4 reactions are regulated by **cell-mediated** reactions
- Type 4 reactions usually **take longer than 12 hours to develop** due to mediation via T-cells
- Protective immunity does not always occur with Type 4 reactions
- Three varieties of Type IV Hypersensitivity:
  - Contact hypersensitivity
  - Tuberculin type hypersensitivity
  - Granulomatous hypersensitivity


Granuloma formation around a schistosome egg (center) destroys the liver tissue.


Wristwatches may stimulate contact hypersensitivity reactions.

T Cell Mediated Hypersensitivity





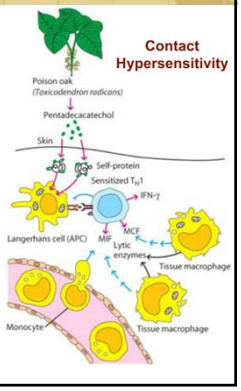
Contact Hypersensitivity

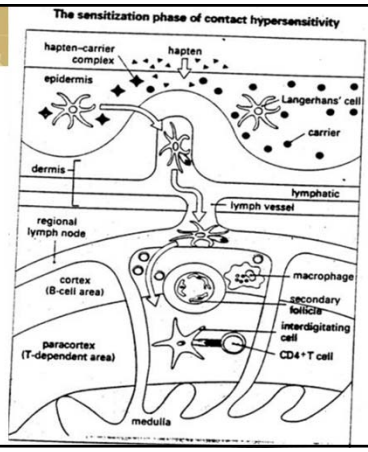
- With contact hypersensitivity, **haptens penetrate the epidermis and conjugate with protein** (which acts as a carrier for the hapten)
  - Examples of possible haptens include nickel, poison ivy, chromate, DNCB, etc.
  - CD4+ T-cells and macrophages are involved in contact hypersensitivity reaction
  - There is down regulation of the reaction by cytokines

Examples of contact hypersensitivity reactions to poison ivy.

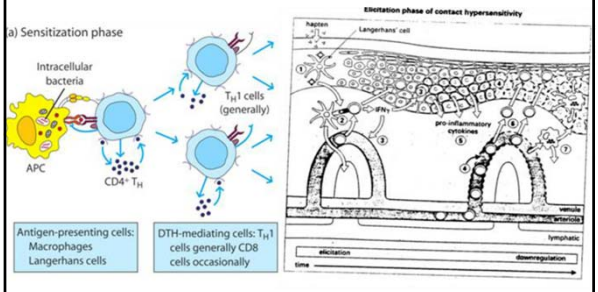
Contact Hypersensitivity

- The reaction involves both **sensitization and elicitation** phases
- Maximal reaction occurs at **48 to 72 hours**
- The reaction produces an eczematous reaction of the skin



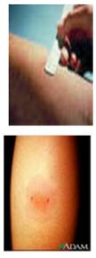


Type 4 Contact Hypersensitivity



Tuberculin Type Hypersensitivity

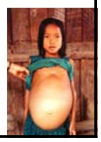
- Examples of tuberculin type hypersensitivity reactions include the tuberculin skin test and the intradermal tuberculin injection
- CD4+ T cells and macrophages are involved in tuberculin type hypersensitivity
- With previous exposure to the antigen, a localized induration occurs at the site of the injection
- A maximal reaction occurs at 48 to 72 hours
- The induration usually resolved within 5 to 7 days



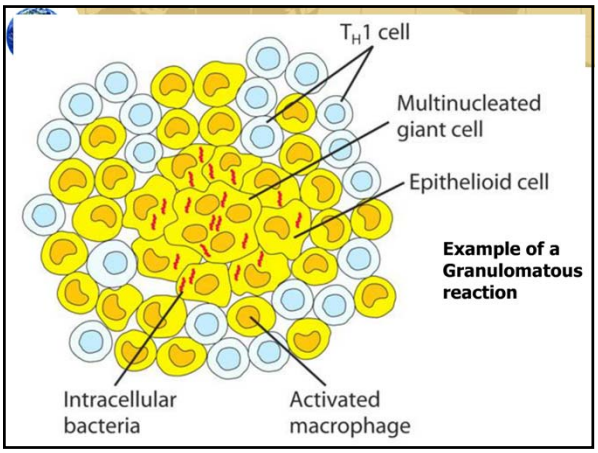
Example of + PPD test

Granulomatous Hypersensitivity

- **Persistent antigen** and can be considered "Pathologic CMI"
- Chronic inflammation can produce these reactions
- Reactions result from secretory epithelioid and giant cells, macrophages, and lymphocytes
- **Granulomatous hypersensitivity produces hardening or fibrosis of tissue**
- These reactions may take 21 to 28 days or longer to develop
- Diseases that may exhibit granulomatous hypersensitivity include Tuberculosis, Leprosy, Schistosomiasis, Sarcoidosis



Enlarged liver and spleen occurs in schistosomiasis due to granuloma formation, blocking abdominal circulation.



Example of a Granulomatous reaction

TABLE 16-6 Intracellular pathogens and contact antigens that induce delayed-type (type IV) hypersensitivity

Intracellular bacteria
- *Mycobacterium tuberculosis*
- *Mycobacterium leprae*
- *Listeria monocytogenes*
- *Brucella abortus*

Intracellular fungi
- *Pneumocystis carinii*
- *Candida albicans*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*

Intracellular parasites
- *Leishmania* sp.

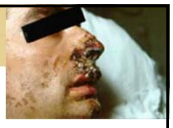
Intracellular viruses
- Herpes simplex virus
- Variola (smallpox)
- Measles virus

Contact antigens
- Picrylchloride
- Hair dyes
- Nickel salts
- Poison ivy
- Poison oak

Summary of Delayed Hypersensitivity Reactions

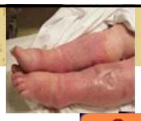
Type	Reaction Time	Clinical	Histology	Antigen
Contact	48-72 hrs	Eczema	Lymphocytes macrophages edema	Epidermal nickel poison ivy
Tuberculin	48-72 hrs	Local Induration	Lymphocytes macrophages monocytes	Intradermal tuberculin
Granuloma	21-28 days	Hardened skin & lung	Fibrosis Epithelioid Giant Cells Macrophage	Persistent Ag or Ag/Ab complexes

Innate Hypersensitivity: Systemic Inflammatory Response Syndrome (SIRS)

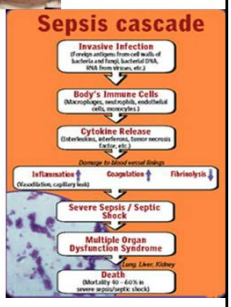


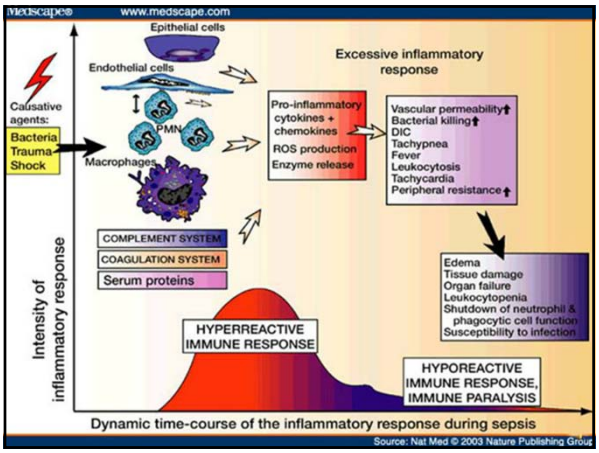
- Effects of a systemic activation of the innate immune response without regard to the cause
  - The body produces an exaggerated response to the stimulus
- Everyone is potentially at risk for SIRS
  - However, certain individuals are at greater risk including critically ill patients and immunocompromised patients
  - Factors contributing to increased mortality from sepsis
    - underlying disease
    - older age

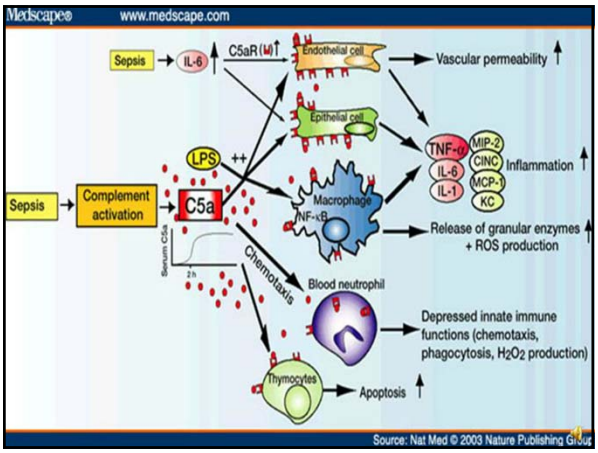
SIRS

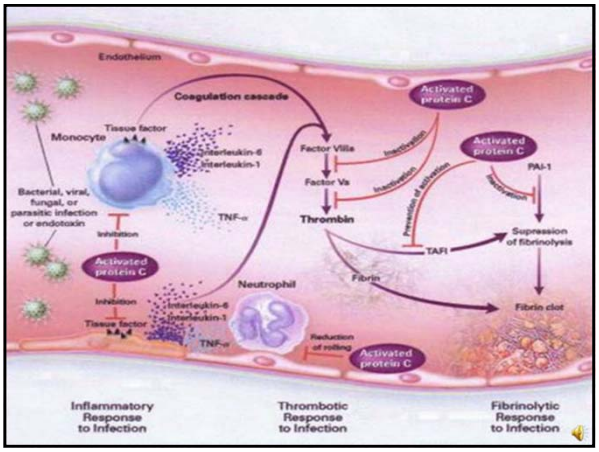


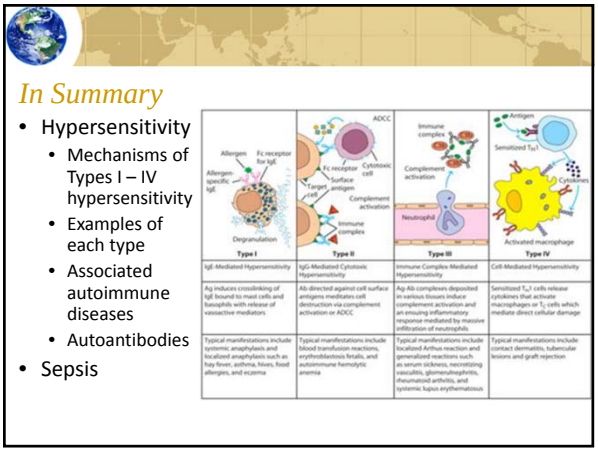
- SIRS represents a continuum of disease:
  - Bacteremia – bacteria in the bloodstream
  - **Sepsis** – SIRS due to an infection regardless of infecting organism (bacterial, viral, fungal)
  - Severe sepsis – Sepsis associated with at least one acute organ dysfunction, poor perfusion, or low blood pressure (hypotension)
  - Septic shock – Sepsis-induced hypotension persists despite adequate fluid replacement
  - MODS (Multiple organ dysfunction syndrome) – Presence of altered function in two or more organs in an acutely ill patient
  - Death

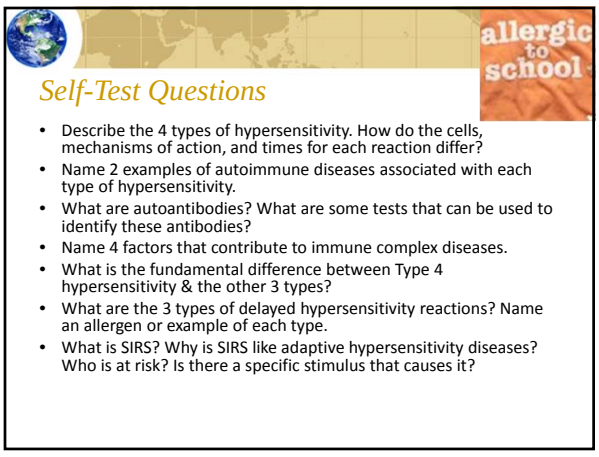



Medscape
www.medscape.com
Epithelial cells
Endothelial cells
Excessive inflammatory response
Causative agents:
Bacteria
Trauma
Shock
PMN
Macrophages
Pro-inflammatory cytokines + chemokines
ROS production
Enzyme release
Vascular permeability
Bacterial killing
DIC
Tachypnea
Fever
Leukocytosis
Tachycardia
Peripheral resistance
COMPLEMENT SYSTEM
COAGULATION SYSTEM
Serum proteins
Edema
Tissue damage
Organ failure
Leukocytopenia
Shutdown of neutrophil & phagocytic cell function
Susceptibility to infection
Intensity of inflammatory response
HYPERREACTIVE IMMUNE RESPONSE
HYPOREACTIVE IMMUNE RESPONSE, IMMUNE PARALYSIS
Dynamic time-course of the inflammatory response during sepsis
Source: Nat Med © 2003 Nature Publishing Group


Medscape
www.medscape.com
Sepsis
IL-6
C5aR
Endothelial cell
Vascular permeability
Epithelial cell
LPS
++
TNF-α
IL-6
IL-1
MIP-2
CINC
MCP-1
KC
Inflammation
Sepsis
Complement activation
C5a
Macrophage
NF-κB
Release of granular enzymes + ROS production
Serum C5a
2 h
Chemotaxis
Blood neutrophil
Depressed innate immune functions (chemotaxis, phagocytosis, H_2O_2 production)
Thymocytes
Apoptosis
Source: Nat Med © 2003 Nature Publishing Group


Endothelium
Coagulation cascade
Activated protein C
Monocyte
Tissue factor
Interleukin-6
Interleukin-1
Factor VIIIa
Inactivation
Activated protein C
Bacterial, viral, fungal, or parasitic infection or endotoxin
TNF-α
Factor Va
PAI-1
Thrombin
Inhibition of activation
Inactivation
Inhibition
TAFI
Supression of fibrinolysis
Activated protein C
Neutrophil
Fibrin
Fibrin clot
Inhibition
Interleukin-6
Interleukin-1
Tissue factor
TNF-α
Reduction of rolling
Activated protein C
Inflammatory Response to Infection
Thrombotic Response to Infection
Fibrinolytic Response to Infection


In Summary
Hypersensitivity
Mechanisms of Types I – IV hypersensitivity
Examples of each type
Associated autoimmune diseases
Autoantibodies
Sepsis
Type I
Type II
Type III
Type IV


allergic to school
Self-Test Questions
Describe the 4 types of hypersensitivity. How do the cells, mechanisms of action, and times for each reaction differ?
Name 2 examples of autoimmune diseases associated with each type of hypersensitivity.
What are autoantibodies? What are some tests that can be used to identify these antibodies?
Name 4 factors that contribute to immune complex diseases.
What is the fundamental difference between Type 4 hypersensitivity & the other 3 types?
What are the 3 types of delayed hypersensitivity reactions? Name an allergen or example of each type.
What is SIRS? Why is SIRS like adaptive hypersensitivity diseases? Who is at risk? Is there a specific stimulus that causes it?