# PATHOLOGY OF THE IMMUNE SYSTEM

| | INNATE IMMUNITY | ADAPTIVE IMMUNITY |
|---|---|---|
| **Lag phase** | Absent<br>Response is IMMEDIATE | Present<br>Response is within DAYS |
| **Specificity/diversity** | Limited<br>Non-specific: same response to variety of agents | Highly specific |
| **Memory** | Absent<br>Subsequent exposures generate same response | Present<br>Subsequent exposures results in amplified response |

## INNATE IMMUNITY

- Barrier function: skin; mucosa of GI, genitourinary, & respiratory tracts; mechanical & chemical aspects
- Cells & mediators: neutrophils, macrophages, dendritic cells, NK cells, plasma proteins & complement
- Molecular components: lysozyme, low pH (skin, GIT, vagina), normal flora, antimicrobials, complement, surfactant, coagulation system

| | MECHANICAL FACTORS | |
|---|---|---|
| **SYSTEM OR ORGAN** | **CELL TYPE** | **MECHANISM** |
| **Skin** | Squamous epithelium | Physical barrier; Desquamation |
| **Mucous membranes** | Non-ciliated epithelium (GI tract) | Peristalsis |
| | Ciliated epithelium (respiratory tract) | Mucociliary elevator |
| | Epithelium (nasopharynx) | Flushing action of tears, saliva, mucus, & urine |

| | CHEMICAL FACTORS | |
|---|---|---|
| **SYSTEM OR ORGAN** | **COMPONENT** | **MECHANISM** |
| **Skin** | Sweat | Anti-microbial fatty acids |
| **Mucous membranes** | HCl (parietal cells); tears & saliva | Low pH; lysozyme & phospholipase A |
| | Defensins (respiratory & GI) | Anti-microbial |
| | Surfactants (lung) | Opsonin |

### NEUTROPHILS & MACROPHAGES

- Phagocytize
- G protein receptors recognize **NfMet**
- **Mannose** receptors

### DENDRITIC CELLS

- APCs found in epithelia, lymphoid organs, & most tissues; they capture & display peptides for recognition by T lymphocytes

### NK CELLS

- Protect against viruses & intracellular bacteria
- *Innate & adaptive*

### PATTERN RECOGNITION RECEPTORS (PRRs)

- Recognize highly conserved microbial components
- 4 Major Classes of Innate Immune Receptors:
  - **Toll-like receptors (TLRs)** – plasma membrane & endosomal
  - **NOD-like receptors** – cytosolic, mediates via caspase-1/IL-1 pathway
  - **C-type lectin receptors** – **FUNGAL**
  - **RIG-like receptors** – cytosolic, recognize **VIRAL** nucleic acid

# ADAPTIVE IMMUNITY

- **CELL MEDIATED**: protects primarily against INTRACELLULAR pathogens; i.e. virally infected cells, tumor cells, fungi, parasites, & intracellular bacteria (mycobacteria)
  - Production of (1) T-helper cells that help either cells like B cells or macrophages or (2) cytotoxic T cells that kill infected cells or tumor cells
- **HUMORAL**: protects against EXTRACELLULAR pathogens
  - Production of antibodies can: (1) bind to/neutralize antigen, (2) opsonize bug, or (3) activate complement

## LYMPHOCYTES

- Progenitor cells in the bone marrow
- B cells mature in the marrow
- T cells mature in the thymus
- Migrate to secondary (peripheral) lymphoid organs

## IMMUNOGLOBULINS – 5 CLASSES

- Neutralize toxins, opsonize microorganisms
- Fc recognized by FcR on phagocytes
- IgG & IgM activate complement system

| IgG | IgM | IgA | IgD | IgE |
|---|---|---|---|---|
| Monomer<br>Major serum component<br>4 subclasses<br>**Placental transfer**<br>Fixes complement<br>Binds Fc receptors | Pentamer<br>Made first<br>B cell surface<br>Agglutinates<br>Fixes complement<br>Binds Fc receptors | Dimer,<br>2nd largest in serum<br>Secretions<br>Binds Fc receptors | Monomer with a tail<br>B cell surface | Monomer<br>Binds basophils/mast cells<br>Important in **allergic reactions & parasitic infections** |

## DENDRITIC CELLS

- Most important in activating/initiating a T cell response

## MACROPHAGES

- Present angtigens to T cells
- Phagocytize opsonized pathogens

## NK CELLS

- Kill virally infected cells, tumor cells, & cells coated with IgG

## CYTOKINE FUNCTIONS

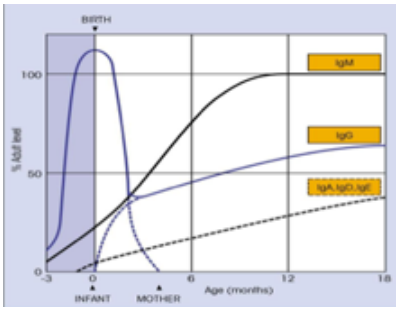
- Autocrine, paracrine, endocrine
- Pleiotropic
- IL-1 secreted by macrophages activate $T_H$ cells
- IL-2 secreted by $T_H$ cells activates $T_H$ & $T_C$ cells
- IL-4 & IL-5 activate B cells
- IFN secreted by $T_H$ cells activate macrophages

## MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) & HUMAN LEUKOCYTE ANTIGENS (HLA)

- Cell surface proteins
- HLA antigens – alloantigens
- Genes located on chromosome 6
- Required for T cell recognition of antigens
  - Class I present on all nucleated cells & platelets present endogenously synthesized antigens to $CD8^+$ T cells – HLA-A, HLA-B, HLA-C – *important for self vs non-self*
  - Class II present only on APCs present phagocytized antigens to $CD4^+$ T cells – HLA-DR, HLA-DP, HLA-DQ – *important for graft matching (DR)*
- Major determinant of graft success, highly polymorphic
- Many disease associations

**CELL-MEDIATED RESPONSE**

- $T_H$ cells are activated by antigens
  - Release IL-2, express CD40 ligand
  - Differentiate into $T_H1$, $T_H2$, & $T_H17$
- $T_C$ cells are activated
  - Differentiate into an effector cytotoxic cell




**HUMORAL RESPONSE**

- B cells are activated & differentiated into plasma cells
  - T cell dependent & independent
- Plasma cells secrete antibody specific for the original activating antigen
- IgM produced FIRST
- Isotype switching (IgM switches to IgG, A, or E) is mediated by IFNγ & IL-4
- PRIMARY ENCOUNTER
  - An antigen is encountered
  - A small clone is formed (7-10 days lag time)
  - IgM appears first then followed by a class switch to IgG or IgA
- SECONDARY ENCOUNTER
  - Rapid rise in serum Igs (3-5 days)
  - Due to persistence of memory B cells

**DIVERSITY**

- Multiple gene segments
- Rearranging into different sequences
- Light & heavy chain assembly
- Mutations (for Ig's, not TCRs)

**MEMORY**

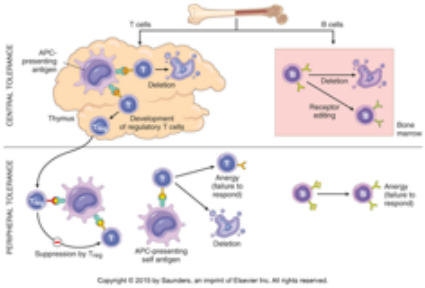
- Memory T & B cells are produced following primary exposure to antigens
- Allows for rapid vigorous response for years
  - Many memory cells produced
  - Live for many years, or reproduce
  - Require smaller amounts of antigen & co-stimulation
  - Produce greater amounts of product

**SPECIFCITY**

- Lymphocytes specific for a large number of antigens exist before exposure to antigen & when an antigen enters, it selectively activates the antigen-specific cells → clonal selection

**TOLERANCE**

- Specific unresponsiveness
- Central tolerance: clonal deletion
- Peripheral tolerance: clonal anergy




**IMMUNITY: MANNER OF ACQUISTION**

- Passive: receipt of preformed Ig; rapid acting, short term; antitoxins, IgG via placental transfer, IgA via lactation
- Active: manufactured after exposure; slow onset, long-term
- Combined: heterologous anti-rabies serum; rabies vaccine series

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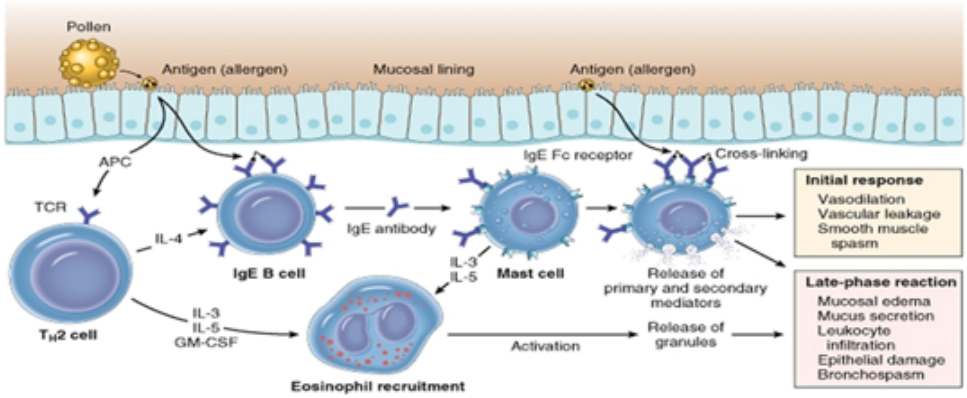
# HYPERSENSITIVITY REACTIONS

| | TYPE I | TYPE II | TYPE III | TYPE IV |
|---|---|---|---|---|
| MNEUMONIC-ISH | A<br>Allergic, Anaphylactic | C<br>Cell-surface*<br>Cytotoxic | I<br>Immune Complex | D<br>Delayed |
| **TIME FRAME** | **IMMEDIATE** | Intermediate | Intermediate | **DELAYED** |
| **IMMNUNE REACTANT** | IgE | IgG, IgM | IgG | Antibody-independent |
| **IMMUNOLOGIC MECHANISM** | IL-4, IL-5, IL-13<br>Mast cells+basophils<br>(^EARLY)<br>Eosinophils+$T_H2$ cells<br>(^LATE) | Antibody-mediated<br>(Tissue specific autoantibodies)<br>IgM or IgG = complement | IC-mediated<br>IgG = complement<br>Phagocytosis | Cell-mediated<br>Ag-specific T cells<br>$T_H1$ + macrophages |
| **ANTIGEN** | SOLUBLE ANTIGENS | Antigens on surface of specific cells or tissues | Soluble antigens (usually *circulating*)<br>Fungal antigen | Haptens, PPD, intracellular pathogens |
| **COMMON CAUSES** | Inhaled material: pollen, dust mite feces<br>Ingested materials: peanuts, shellfish | Transfusion<br>Rh incompatibility<br>Autoantibodies to self<br>Drug reactions | Abnormal deposition of ICs in tissues & blood vessels | Delayed (proteins: insect venom, mycobacterial proteins)<br>**Haptens**, metal ions<br>Gliadin (gluten)<br>Graft rejection |
| **CLINICAL DISEASE** | *Allergic* asthma<br><br>*Allergic* rhinitis (Hay Fever)<br><br>Acute urticaria (hives)<br><br>Atopic eczema<br><br>Systemic anaphylaxis<br><br>Food allergies | CYTOTOXIC DISEASE:<br>Erythroblastosis fetalis (HDNB)/Autoimmune Hemolytic Anemia<br>Transfusion Rxns<br>Penicillin reaction<br>Rheumatic Fever<br>Autoimmune Thrombocytopenic Purapura<br>Goodpasture Syndrome<br>Lambert Eaton<br>Pemphigus Vulgaris<br>NON-CYTOTOXIC:<br>Myasthenia Gravis<br>Grave's Disease<br>Type II DM<br>Pernicious anemia | Serum Sickness<br><br>Arthus Reaction<br>Farmer's Lung<br>(^fungal antigen)<br><br>Systemic Lupus Erythematosus<br><br>Post-Streptococcal Glomerulonephritis<br><br>Sjogren's Syndrome<br><br>Scleroderma | CHRONIC INFECTION<br>Mycobacterium tuberculosis<br>Schistosomiasis<br><br>CONTACT DERMATITIS<br>Poison ivy, nickel, rxns to cosmetics<br><br>AUTOIMMUNE:<br>Celiac Disease<br>Multiple Sclerosis<br>Type I DM<br>Hashimoto's<br>Inflammatory Bowel Disease (Crohn's, Ulcerative Colitis) |
| **DIAGNOSTIC TEST** | Wheal & Flare (skin)<br>RAST (blood) | Direct Coomb's or blood smear (HDNB)<br><br>Direct Immunofluorescent staining (Goodpasture) | HSR III Skin Test (Arthus Reaction -- Wheal & Flare) | Tuberculin Skin Test<br><br>Patch Test for non-microbial antigens<br><br>Abs to tissue transglutaminase – Celiac Disease |
| **TREATMENT** | Allergen avoidance<br>Antihistamines, leukotriene inhibition, corticosteroid inhibition of NFκB, desensitization, prevent IgE mediated degranulation (anti-IgE antibodies) | Rhogam for HDNB (^**PREVENTION**)<br><br>Acetylcholinesterase inhibitor for MG | Symptom control – Steroids(?) | |
| **ADDITIONAL** | Immune response elicited is usually directed againsts *parasites (helminthes)* | | | Immune response (DTH) is usually directed against intracellular bacterial & fungal infections |

## TYPE I HSR: IMMEDIATE, IgE





- Ag exposure induces IgE formation which binds by Fc to mast cells
- Re-exposure results in crosslinking & release of mediates within minutes
- **Immediate/initial response** occurs in minutes, secondary to vasoactive amines & lipid mediators
  - Vasodilation, smooth muscle spasms, & secretions
- **Late phase response** occurs within hours & may last days, secondary to cytokine pathways
  - Cellular infiltration & tissue damage
  - Does not require continued antigen exposure!

### TYPE I HSR: MEDIATORS

- Mediators play role in *vasodilation, increased vascular permeability, & smooth muscle contraction*
- **HISTAMINE**: preformed, released from mast cell granules
- **SRS-A (leukotrienes)**, PROSTAGLANDINS, & THROMBOXANES: derived from arachidonic acid via lipoxygenase & cyclooxygenase pathways
- SEROTONIN: preformed, released from mast cell granules
- Platelet activating factor

### TYPE I HSR: CONSEQUENCES

- Urticaria (hives), eczema, rhinitis (runny nose), conjunctivitis, asthma, systemic anaphylaxis, some drug hypersensitivities

### ATOPY

- Type I reactions may have a familial disposition & are associated with elevated serum IgE levels
- "Hay fever," asthma, eczema

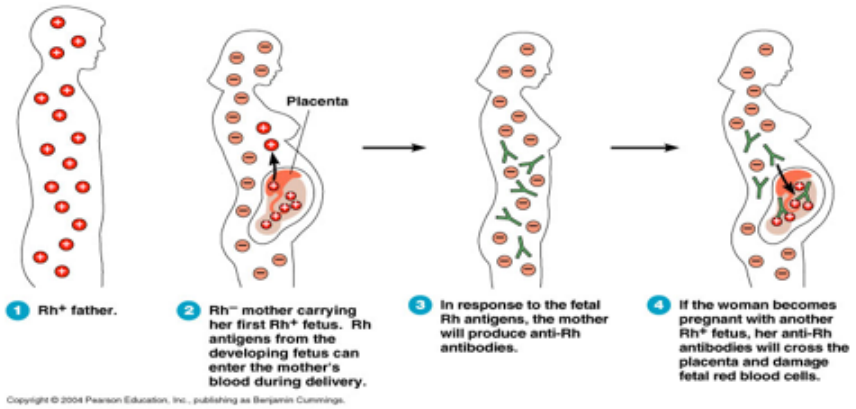
### ANAPHYLAXIS

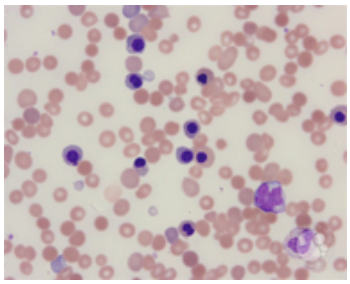
- Most dangerous of the type I reactions
- Vascular shock edema, dyspnea, death
- Requires very small doses of antigen
- Sequence of events usually predictable
  - MINUTES: itching, hives, erythema
  - Dyspnea & respiratory distress
  - Laryngeal edema/hoarseness
  - Vomiting, diarrhea, & airway obstruction
  - Shock, death

## TYPE II HSR: ANTIBODY MEDIATED; CELL SURFACE

- *Hemolytic anemia, Rh hemolytic disease, ABO transfusion reactions, rheumatic fever, PCN allergy*
- Antigens on cell membranes recognized by Fab of IgG or IgM
- Complement is activated causing cell lysis
- Bound IgG Fc can be recognized by NK cells in antibody-dependent cellular toxicity
- Ag-Ab reaction is at the cell membrane
- DRUG INDUCED
  - PCN attaches to RBC membrane proteins
  - Hydralazine-drug induced lupus
- INFECTION INDUCED
  - Mycoplasma induces Ab, which cross-reactions with RBCs
  - Group A strep antibody cross-reacts with cardiac tissue → rheumatic fever

### ***Rh DISEASE



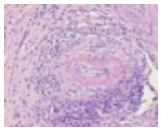
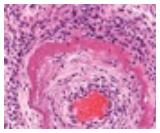
- RhD negative mother, RhD positive fetus – Rh incompatibility
- Maternal IgG anti-Rh antibodies cross placenta to fetus → hemolysis of fetal RBCs → anemia
- **PREVENTION*** OF HDNB WITH **RHOGAM** (IgG anti-RhD)
  - 1st pregnancy – mother is treated with the anti-Rh IgG Rhogam at 28 weeks, 36 weeks, & at birth
    - Prevents maternal B cell activation & memory cell formation by blocking Rh antigen from activating maternal B cells.
    - *If you prevent the fetal RBCs from stimulating maternal B cell activation, you avoid HDNB*
- If proper precautions or prevention are not taken, EACH subsequent pregnancy with another Rh+ fetus will result in HDNB because maternal anti-Rh Ab (from memory B cells) will cross the placenta & destroy fetal RBCs
- If proper precautions are not taken, **2nd pregnancy** will result in **hydrops fetalis**
  - ***Pathophysiology***: *With severe hemolysis, may result in hypoxic injury to heart and liver. The combination of reduced plasma oncotic pressure (due to decreased synthesis of plasma proteins) and increased hydrostatic pressure in the circulation (secondary to cardiac failure) results in generalized edema and anasarca, culminating in hydrops fetalis.*

## TYPE III HSR – IMMUNE COMPLEX MEDIATED

- Ag-ab complex deposit in tissues & vessels & cause inflammatory response
- Complement is activated causing secondary tissue damage
- DRUG INDUCED – Quinidine attaches to platelets

### VASCULITIS

- Ag-ab complexes, neutrophils, debris & proteins form **Fibrinoid necrosis** in the vessel wall

### ARTHUS REACTION

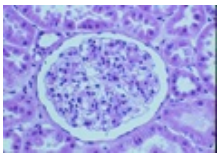
- Occurs after repeated exposures
- Hypersensitivity pneumonitis – localized reaction

### SERUM SICKNESS

- Fever, urticarial, arthralgia, lymphadenopathy, splenomegaly, eosinophilia 1-2 weeks after systemic exposure to Ag

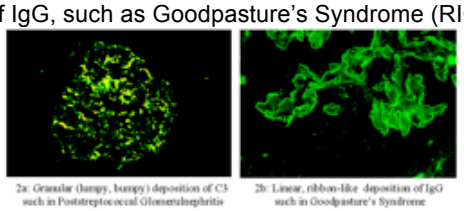
### ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS

- Weeks after infection (often skin) with nephritogenic serotypes of *S. pyogenes*
- Lumpy deposits of C3 & Ag-Ab complexes seen along glomerular basement membrane

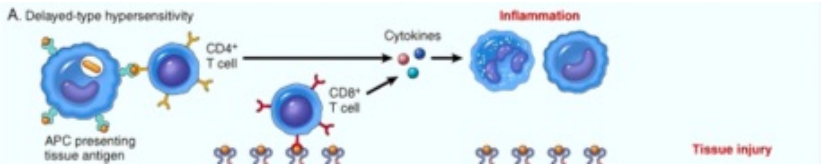


### HSR TYPE III vs HSR TYPE II

- Granular (lumpy, bumpy) depositon of C3, such as Poststreptococcal Glomerulonephritis (LEFT)
- Linear, ribbon-like deposition of IgG, such as Goodpasture's Syndrome (RIGHT)




## TYPE IV HSR – CELL MEDIATED, DELAYED




- Involved $T_H$ (particularly $T_H1$ & $T_H17$ memory cells) & $T_C$ cells
- Delayed-type hypersensitivity
- Sensitized T cells
- Contact hypersensitivity
- Tuberculin-type hypersensitivity

### CONTACT

- Extremely common (simple chemicals like nickel, plant substances like poison ivy, topical drugs, etc.)
- Substances are usually haptens
- Erythema, itching, vesicles, eczema

### TB SKIN TEST

- Used as an aid in diagnosis of exposure
- Positive test indicates at least prior infection
- Test conversion suggests recent infection

### GRANULOMAS

- When antigens are persistent macrophages become "epithelioid"

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**TYPE OF GRAFTS**

- Autograft, syngeneic (isograft), allograft, xenograft

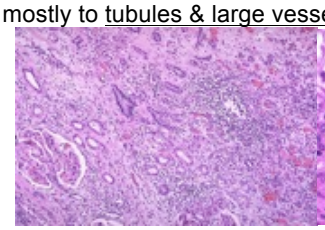
**GRAFT REJECTION**

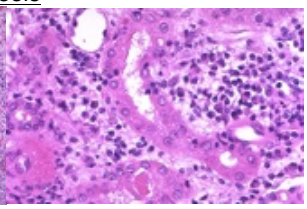
- ACUTE ALLOGRAFT REJECTION – a function of a **T cell-mediated** immunity
- HYPERACUTE REJECTION – occurs secondary to preformed antibody; usually within minutes; often ABO issue
- CHRONIC REJECTION – most likely due to mild acute rejection & drug toxicity

**ACUTE ALLOGRAFT REJECTION –** T CELL MEDIATED

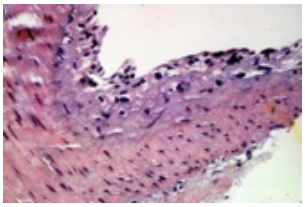
- *Takes a few months*
- Recipient T cells recognize foreign antigens from the donated tissue
- MHC alloantigens activate host $T_H$ & $T_C$
- Kidney's are the most grafted organ
- Damage mostly to tubules & large vessels

Bunch of lymphocytes & fibrosis in between the tubules.





***TUBULOINTERSTITIAL PATTERN**



**VASCULAR PATTERN**

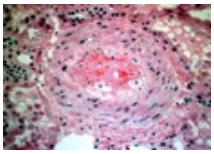
Vessel from host tissue: Underneath the endothelium you see lymphocytes.

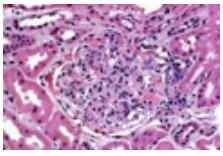
**ANTIBODY-MEDIATED**

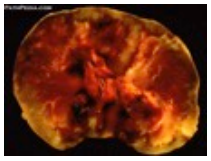
- HYPERACUTE REJECTION: involves preformed Ab
  - ABO incompatibility
  - Multiparous women (women with multiple pregnancies), multiple transfusions – exposure multiple different HLA antigens
- ACUTE ANTIBODY MEDIATED REJECTION: Ab formed after transplantation
- CHRONIC ANTIBODY MEDITATED REJECTION: occurs without preceding acute rejection

**HYPERACUTE REJECTION**

- Short time period – *immediate*
- Can be intraoperative (in the OR)
- Rare due to current cross-matching protocols
- ***Left image***: occluded vessel with antibody mediated inflammation

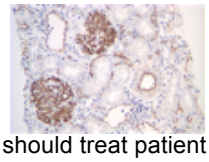






**ACUTE ANTIBODY-MEDIATED REJECTION**

- Longer time to onset
- Damage mostly in glomeruli & small vessels
- Complement activation, C4d: *stains brown*
  - Treatment related decision – if they see the brown stain, they know they should treat patient with plasmaphoresis to filter out immunoglobulin. If it does not stain brown, they give patient immunosuppressants (to suppress T cell).



**GRAFT vs HOST DISEASE**

- Usually an issue of **bone marrow transplants** (liver, non-irradiated transfusions)
- Some T cells present in the donor marrow proliferate & attack tissues in the irradiated immunocompromised host
- Symptoms: rash, jaundice, hepatosplenomegaly, diarrhea, infection, death
- Reduced by **pre-treatment** with antithymocyte globulin

# AUTOIMMUNE DISEASE

- Occurs when tolerance is lost & immune reactions to self antigens develop
  - *Self-reactive lymphocytes are regularly generated but undergo apoptosis (negative selection) in the thymus or bone marrow or become anergic due to recognition of antigen in peripheral lymphoid tissues*
- Can be antibody mediated or cell mediated or both; organ-specific or systemic
- Genetic predisposition – association with HLA
- Multifactoral-Environment exposure to cross reacting antigen
- *Characterized by immune-mediated damage of tissues*

****THREE TYPES OF AUTOIMMUNE DISORDERS**

1. CYTOTOXIC (TYPE II HSR) – involve antibody reactions to cell surface molecules, without cytotoxic destruction of cells; i.e. Grave's Disease & Myasthenia Gravis
2. IMMUNE COMPLEX (TYPE III HSR) – i.e Systemic Lupus Erythematosus & RA (RA involves formation of IgM against IgG, complexes form & deposit in joints)
3. CELL-MEDIATED (TYPE IV HSR) – i.e. insulin dependent diabetes mellitus

| DISEASE | TARGET OF IMMUNE RESPONSE |
|---|---|
| Systemic lupus erythematosus | dsDNA, histones, nucleolus, (ANA) |
| Rheumatoid arthritis | IgG in joints |
| Rheumatic fever | Heart and joint tissue |
| Hemolytic anemia | RBC membrane |
| Idiopathic thrombocytopenic purpura | Platelet membrane |
| Goodpasture syndrome | Basement membrane of lung and kidney |
| Pernicious anemia | Intrinsic factor and parietal cells |
| Hashimoto thyroiditis | Thyroglobulin |
| Insulin-dependent diabetes | Islet cells |
| Guillain barre syndrome | Myelin proteins |
| Wegener granulomatosis | Cytoplasmic enzymes of neutrohils |

**GRAVE'S DISEASE – CYTOTOXIC, TYPE II HSR**

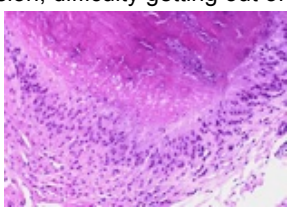
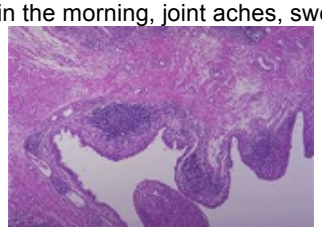
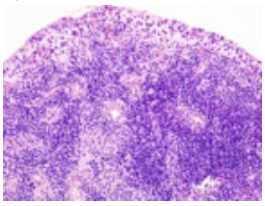
- A common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid gland & other symptoms, such as exophthalmos, heat intolerance, weight loss, dizziness, anxiety, edematous rash to BLE
- Autoimmune B cells make antibodies to TSH receptor that also stimulates thyroid hormone production
- Thyroid hormones shut down TSH production, but have no effect on autoantibody production, which continues to cause excessive thyroid hormone production

**MYASTHENIA GRAVIS – CYTOTOXIC, TYPE II HSR**

- Blurry vision, dry eyes, difficulty putting her dishes away over the past several weeks; symptoms worsen as the day goes on
- Autoantibodies to acetylcholine receptors cause AChR to be internalized & degraded, so there is no $Na^+$ influx or muscle contraction taking place

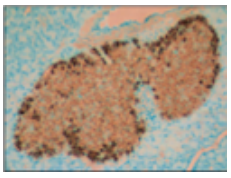
**RHEUMATOID ARTHRITIS – IMMUNE COMPLEX, TYPE III HSR**

- Depression, difficulty getting out of bed in the morning, joint aches, swelling

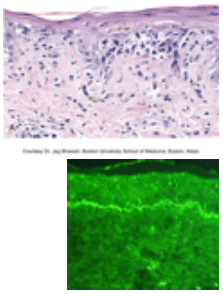
**INSULIN-DEPENDENT DIABETES MELLITUS – CELL MEDIATED, TYPE IV HSR**

- Enuresis
- In IDDM, an effector T cell recognizes peptides from a β cell-specific protein & kills the β cell
- Glucagon & somatostatin are still produced, but insulin cannot be made!



**SYSTEMIC LUPUS ERYTHEMATOSUS – IMMUNE COMPLEX, TYPE III HSR**

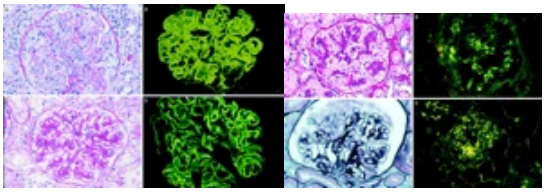
- Autoimmune disease due to deposition of Ag-Ab complexes within the vasculature of multiple organs
- Immune complexes deposit on vasculature * in basement membranes, forming "lupus bands"
- Malar "butterfly" rash, fever, weight loss, arthritis
- Antinuclear antibodies (ANA)
  - Test uses neutrophils & immunofluorescence
- Different patterns: homogeneous, rim/peripheral, speckled, nucleolar, centromeric
- Other autoantibodies to phospholipids-glycoprotein complexes
  - Clotting abnormalities
  - False positive syphilis serology (anti-cardiolipin test)
- 50% have some renal involvement – *diffuse proliferative glomerulonephritis is the most common injury, though other patterns of injury also occur*
- Vasculitis, pleuritis, pericarditis
- Effusions
- Endocarditis, valvular dysfunction (**Libman Sacks**), coronary artery disease



LUPUS NEPHRITIS

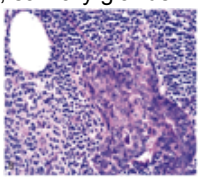
- CLASS I: minimal, immune complex in mesangium
- CLASS II: mesangial proliferative
- CLASS III: focal (involves less than 50% of glomeruli)
- CLASS IV: diffuse, most common & most severe
- CLASS V: membranous, nephrotic syndrome
- CLASS VI: advanced, end-stage

MEMBRANOUS vs MESANGIAL



**SJOGREN SYNDROME**

- 10X more common in females
- Can occur alone or with other autoimmune disorders, *especially rheumatoid arthritis*
- **Salivary & lacrimal gland** involvement: immune attack on exocrine glands, tear duct, salivary glands
- SS-A (Ro) & SS-B (La) autoantibodies
- Intense infiltration of lymphocytes & plasma cells
- Formation of germinal centers – tertiary lymphoid tissue
- Dry eyes, red eyes, dry mouth
- SCHIRMER TEST



**OTHERS**

- Systemic Sclerosis (Scleroderma): *AI damage with activation of fibroblasts & deposition of collagen (fibrosis)*
  - $CD4^+$ T cells release cytokines, which stimulate fibroblasts & collagen production
  - Anti-Scl-70, Anti-centromere
- Dermatomyositis: affects skeletal muscle AND skin; anti-Jo-1
- Polymyositis: affects skeletal muscle but NOT skin; anti-Srp1
- Vasculitides
- **IgG4 related disease**
  - Plasma cell infiltrates, which produce IgG4, fibrosis, & obliterative phlebitis
  - Any organ system
  - Reidel's thyroiditis, idiopathic retroperitoneal fibrosis, autoimmune pancreatitis, inflammatory pseudotumors

- **MOLECULAR MIMICRY** – environmental trigger mimics a self antigen; M protein of *S. pyogenes* & myosin
- ALTERATION OF NORMAL PROTEINS (DRUG BINDS & MAKES IMMUNOGENIC) – procainamide induced SLE **haptens!
- RELEASE OF SEQUESTERED ANTIGENS – testis, CNS, lens & uveal tract – immunologically privileged
- EPITOPE SPREADING – possibly the result of viral infections

**ANTIBODIES TO RECEPTORS**

- GRAVE'S DISEASE: autoAb stimulates TSH receptors → hyperthyroidism
- DIABETES (INSULIN RESISTANT): autoAb blocks the insulin receptors → HYPERGLYCEMIA
- MYASTHENIA GRAVIS: autoAb down modulates AChR → paralysis, muscle weakness
- LAMBERT-EATON MYASTHENIA: autoAb against calcium channel receptors; associated with small cell carcinoma of the lung

# IMMUNODEFICIENCY

- Can occur in any segment of the immune system: B cells, T cells, complement, phagocytes
- Can be congenital or acquired
- Recurrent & opportunistic infections are common
- Pattern of infection can indicate where deficiency lies
  - **Pyogenic bacteria → B CELL DEFICIENCY**
  - **Fungal, viral, intracellular pathogens → T CELL DEFICIENCY**

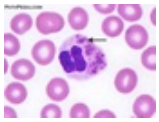
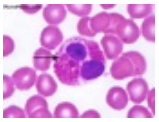
**IMMUNODEFICIENCIES OF THE INNATE SYSTEM**

*Leukocyte Adhesion Deficiency, Chediak Higashi, Chronic Granulomatous Disease, Myeloperoxidase Deficiency, Complement Deficiency, Complement Regulatory Protein Deficiency*

**CHRONIC GRANULOMATOUS DISEASE**

- Phagocyte deficiency
- Can be X-linked or autosomal recessive
- Lack of NADPH oxidase in neutrophils → no oxidative killing burst
- *Susceptible to bacteria and fungal infections*, granulomatous inflammation
- **Nitroblue tetrazolium (NBT) dye reduction test**: patient's with disease with have negative-NBT

**CHEDIAK HIGASHI SYNDROME**

- Phagocyte deficiency
- Autosomal recessive defect in LYST gene → defective lysosomes
- Aberrant lysosome functioning, abnormal fusion, inadequate killing by phagocytes
- Albinism, neurologic deficits & platelet malfunction

**COMPLEMENT DEFICIENCY**

- Deficiency of C1, C3, C5-8 have increased susceptibility to bacterial infections (*Neisseria)*

**HEREDITARY ANGIOEDEMA**

- Autosomal dominant
- C1 inhibitor deficiency → C1 continues to activate C4 → C4a → etc.
- Affects mucosa, skin, airway, & GI tract
- Can lead to life threatening asphyxia
- Massive edema
- Trigger: stress & trauma

**PAROXYSMAL NOCTURAL HEMOGLOBINURIA** – *"Probably won't write a question on it"*

- X-linked mutation in PIG-A gene
- DAF deficiency leads to complement-mediated hemolysis
- Hemolytic anemia, pancytopenia, & thrombosis
- *Lysis of RBCs at NIGHT due to MAC attack by complement – urine will be red in the morning*

**IMMUNODEFICIENCIES OF THE ADAPTIVE SYSTEM**

*Ataxia Telangiectasia, Wiscott-Aldrich Syndrome, defects in maturation, defects in activation/function*

**X-LINKED HYPOGAMMAGLOBULINEMIA (BRUTON'S) –** B CELL DEFICIENCY

- X-linked → young boys
- Mutation in BTK gene → failure of B cell maturation/differentiation
  - *Complete lack of immunoglobulin due to disordered B cell maturation (naïve B cells cannot mature to plasma cells)*
- Recurrent bacterial infections (OM, upper airway infections, pneumonia at 6 months)
  - *Maternal antibodies during first 6 months are protective*
- Virtually absent B cells from circulation, autoimmune disease susceptibility
- *Live vaccines must be avoided*

**SELECTIVE IMMUNOGLOBULIN DEFICIENCY**

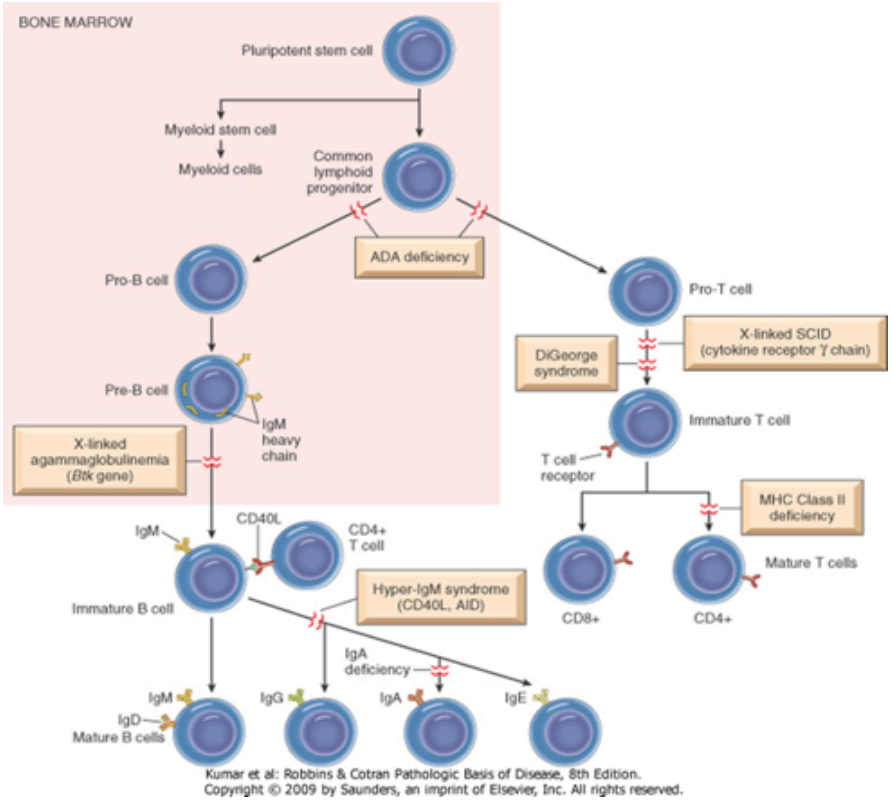
- IgA most common
- Increased risk for mucosal infections – recurrent sinus & lung infections
- Anti-IgA is found in some cases
  - Following blood diffusion

**DiGEORGE SYNDROME –** T CELL DEFICIENCY

- Developmental failure of **the 3rd-4th pharyngeal pouches** due to 22q11 deletion syndrome
- Profound T cell deficiency leads to severe viral, fungal, & protozoal infections
- T cell deficiency (lack of thymus), *hypocalcaemia* (lack of parathyroid glands), & abnormalities of the heart, great vessels, & face
- ***Abnormalities associated with DiGeorge****: abnormally increased distance between the eyes, low set eats with notched ear fold, underdeveloped jaw, small mouth*

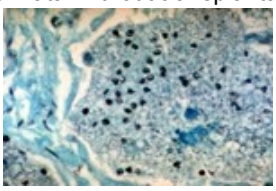
**HYPER-IgM SYNDROME** – T CELL DEFICIENCY

- Defect in CD40L (on helper T cells) leads to inability to class switch
  - *Second signal cannot be delivered to helper T cells during B cell activation*
  - *Consequently, cytokines necessary for immunoglobulin class switching are not produced*
- Low IgA, IgG, IgE result in **recurrent pyogenic infections** *(due to poor opsonization), especially at mucosal sites*

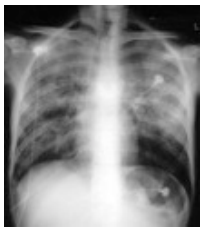


## SEVERE COMBINED IMMUNODEFICIENCY (SCID)

- Multiple genetic etiologies with similar clinical consequences
- *Defective cell-mediated & humoral immunity* – combined B & T cell deficiencies
- Susceptibility to *Candida* (thrush), *pneumocytis jirovecii*, pseudomonas, viruses, & other bacteria
- Often fatal without transplantation



Cup-shaped organism:
*pneumocytis jirovecii*
(also seen in HIV)



Diffuse bilateral infiltrate

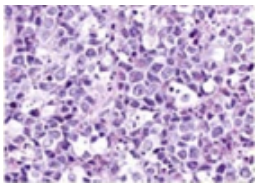
- **X-LINKED SCID** is the most common; defect in IL-2
- Autosomal recessive defects in ZAP70, RAG genes
- **ADA DEFICIENCY** is autosomal recessive
  - *ADA is necessary to deaminate adenosine & deoxyadenosine for excretion as waste products; buildup of these is toxic to lymphocytes*
- **BARE LYMPHOCYTE SYNDROME**: defective MHC proteins

## COMMON VARIABLE IMMUNODEFICIENCY

- Frequent, sporadic or inherited
- Multiple pathways to immunoglobulin deficiency
- Pyogenic infections, autoimmune disease, parasitic infections

## ATAXIA TELANGIECTASIA

- *Systemic syndrome*
- Autosomal recessive
- Progressive cerebellar ataxia (lack of muscle control)
- Lymphopenia & IgA deficiency
- Ocular & mucosal telangiectasias
- Telangiectasia: abnormal dilation of capillary vessels



## WISKOTT ALDRICH SYNDROME

- *Systemic syndrome*
- X-linked
- Defect in **WASP gene** at Xp11,23
- Cell signaling & cytoskeletal abnormalities in hematopoietic cells
- Defective humoral & cell mediated immunity
- Treated with stem cell transplant
- **CLASSIC TRIAD**: thrombocytopenia (low platelets), severe eczema by 1 year of age (elevated IgE), recurrent pyogenic infections, bloody diarrhea
- **Other clinical features**: petechiae due to thrombocytopenia, pneumonia & other infections, more susceptible to neoplasia, i.e. B-cell lymphoma ***(histo slide image of B cell lymphoma)***

## DUNCAN'S SYNDROME – X-LINKED LYMPHOPROLIFERATIVE SYNDROME

- Defect in SAP protein that results in exquisite susceptibility to EPSTEIN BARR VIRUS
- High risk for lymphoproliferative disorders

**ACQUIRED IMMUNODEFICIENCIES**

- Malnutrition, age
- **HIV/AIDS** – present with opportunistic infections, neurological changes, & higher incidence of tumors due to failure of immune surveillance
- Drug-induced neutropenia, leukemia
- **Neoplasia**

**HIV**

- Retrovirus transmitted via sexual contact, parenteral product contamination & maternal-fetal/neonatal/infant
- Infects **CD4$^+$** T cells via **gp120**
- Also infects macrophages, dendritic (APC), & microglial cells via **vpr**

**HIV – STAGES OF INFECTION: ACUTE PHASE**

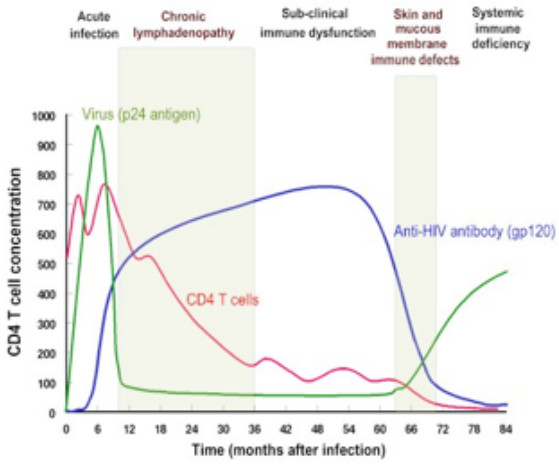
- Virus infects memory CD4$^+$ T cells at *mucosal sites*: viral replication & cell death
- Dendritic cells (APCs) carry virus to lymph nodes: further viral replication & viremia
- Immune response detectable (**seroconversion**) at **3-6 weeks** post-exposure & probable cause of ***acute retroviral syndrome***
    - Sore throat, myalgia, fever, weight loss, flu-like

**HIV – STAGES OF INFECTION: CHRONIC PHASE**

- *Clinical latency*, viral replication continues in lymph nodes & spleen
- Destruction of CD4$^+$ cells continue
- Range of *asymptomatic* to *minor opportunistic* infections (*Candida*, Herpes virus)

**HIV – STAGES OF INFECTION: AIDS**

- Constitutional symptoms return
- Severe opportunistic infections, neurological symptoms, secondary neoplasia




**AIDS**

- *Pneumocystic jirovecii, Candida, Cytomegalovirus, Mycobacteria, Cryptococcus, Toxoplasma, Cryptosporidium, Histoplasma,* **Herpes virus, HPV**, JC virus
- **Kaposi sarcoma**, HPV related squamous cell carcinoma, lymphomas, EBV related lymphomas
- HAART (Highly Active Anti-Retroviral Therapy)