

# DISEASES OF THE IMMUNE SYSTEM

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# Outline

- Normal immune system
- Diseases of the immune system
- Hypersensitivity reactions
- Autoimmune diseases
- Immunodeficiency states
- Transplant medicine
- Amyloidosis

Normal immune system

# Normal immune system

- Inert and adaptive
- Adaptive
  - Humoral
  - Cellular immunity
- Lymphoid organs
  - Primary organs- BM and Thymus
  - Secondary lymphoid organs- Lymph nodes, Spleen, MALT

# DISEASES OF THE IMMUNE SYSTEM

# Diseases of the immune system

- Hypersensitivity reactions
- Autoimmune diseases
- Immunodeficiency states
- Graft vs host disease
- Amyloidosis

# HYPERSENSITIVITY REACTIONS

# Hypersensitivity reactions

- Type 1- Immediate type hypersensitivity
- Type 2- Antibody mediated hypersensitivity
- Type 3- Immune complex associated hypersensitivity reactions
- Type 4- Delayed type- hypersensitivity reactions

# Hypersensitivity reactions

Type	Immune Mechanisms	Histopathologic Lesions	Prototypical Disorders
Immediate (type I) hypersensitivity	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; later recruitment of inflammatory cells	Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation	Anaphylaxis; allergies; bronchial asthma (atopic forms)
Antibody-mediated (type II) hypersensitivity	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury	Autoimmune hemolytic anemia; Goodpasture syndrome
Immune complex-mediated (type III) hypersensitivity	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Inflammation, necrotizing vasculitis (fibrinoid necrosis)	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction
Cell-mediated (type IV) hypersensitivity	Activated T lymphocytes → (1) release of cytokines, inflammation and macrophage activation; (2) T cell-mediated cytotoxicity	Perivascular cellular infiltrates; edema; granuloma formation; cell destruction	Contact dermatitis; multiple sclerosis; type 1 diabetes; tuberculosis

Ig, Immunoglobulin.

# Type 1 hypersensitivity

- Immediate excessive immune reaction to an antigen that an individual was previously exposed to the antigen has.
- Typical conditions are allergic reactions
- Involve first exposure to antigen
  - IgE produced by plasma cells at first exposure is attached to mast cells
  - CD4+ TH2 cells produce IL-4 that activates B cells resulting in class-switching of B-cells to produce IgE
- Cross-linking of IgE on the surface of mast cells at second exposure results in degranulation of mast cells

# Type 1 hypersensitivity

- Early phase reaction- produced by mast cells degranulation products
- Late phase reaction- produced by inflammatory/ immunologic cells that come to the site of reaction.

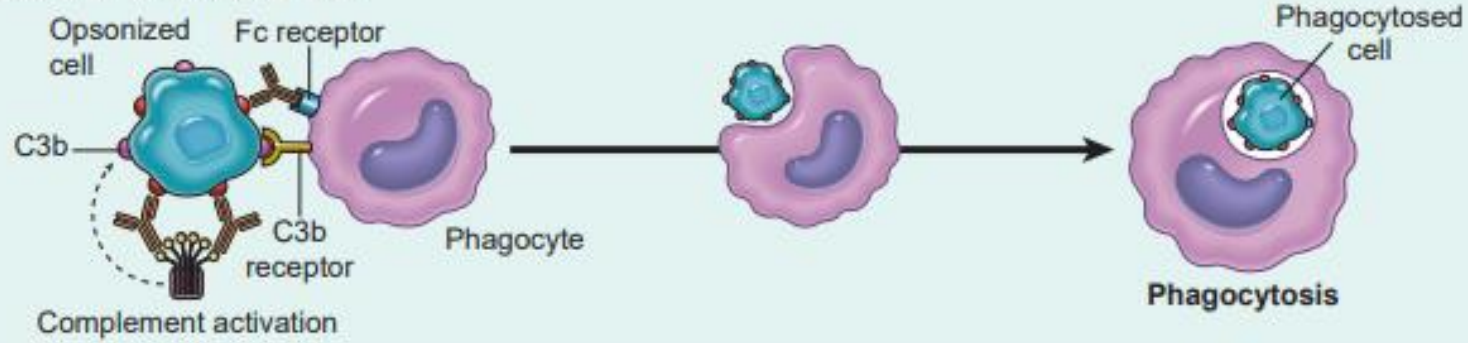
# Examples Hypersensitivity type 1

- Asthma
- Hives
- Allergic rhinitis

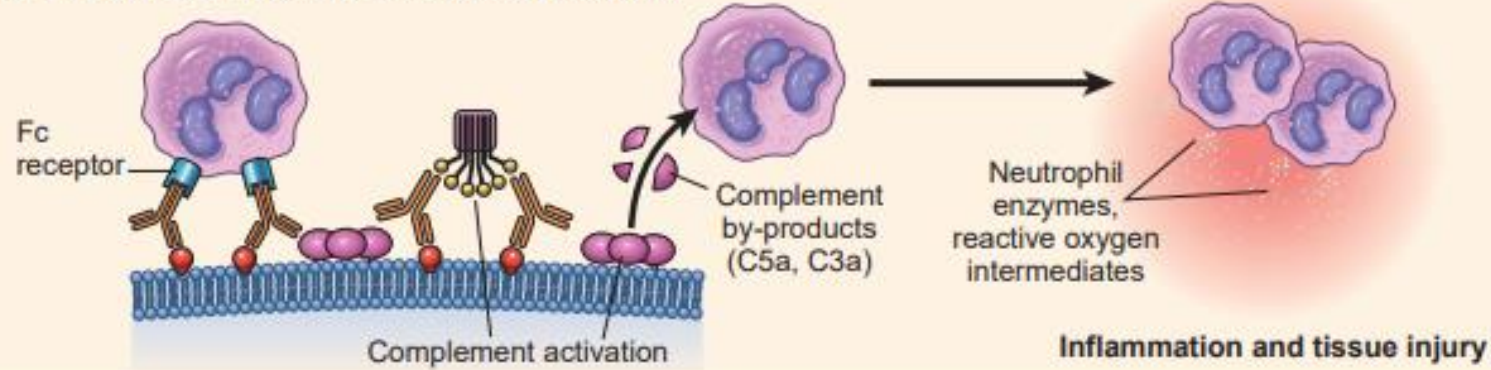
# Type 2 hypersensitivity

- Antibody driven
- Three main mechanisms
  - Antibody-driven cellular dysfunction
    - Antibodies activates hormone receptors- Graves disease
    - Antibodies block receptors for neurotransmitter- Myasthenia gravis
  - Opsonization and phagocytosis-  
Antibodies activate complement to target cells for destruction by phagocytes-
    - Autoimmune hemolytic anemia
  - Complement and Fc- receptor-mediated inflammation-
    - Goodpasture syndrome

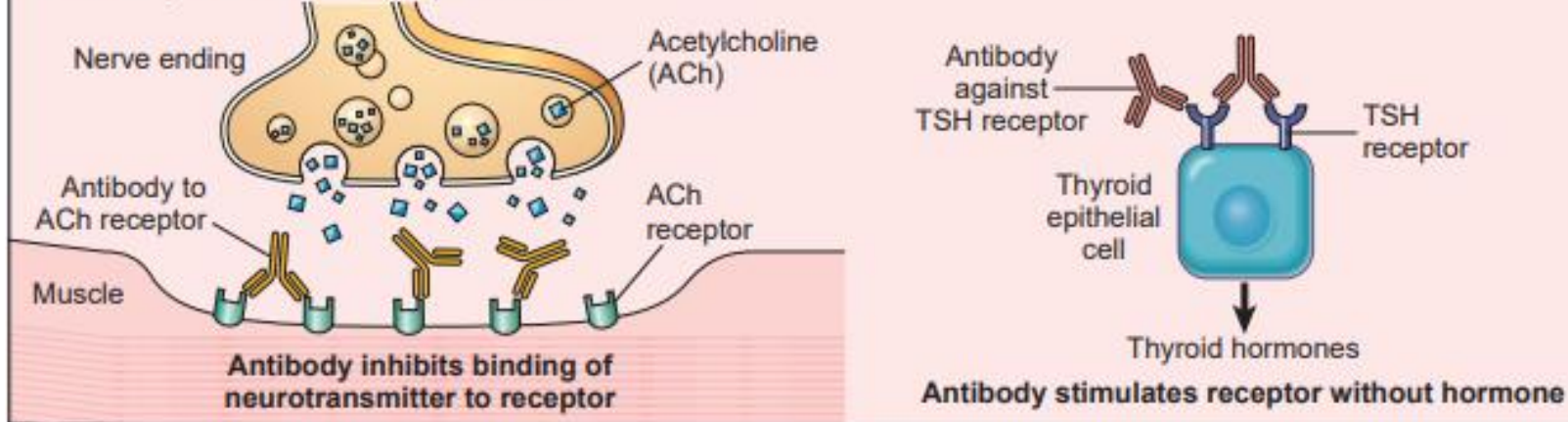
**A. Opsonization and phagocytosis**



**B. Complement- and Fc receptor-mediated inflammation**



**C. Antibody-mediated cellular dysfunction**



# Type 3 hypersensitivity reactions

- Immune complex deposition
- Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition

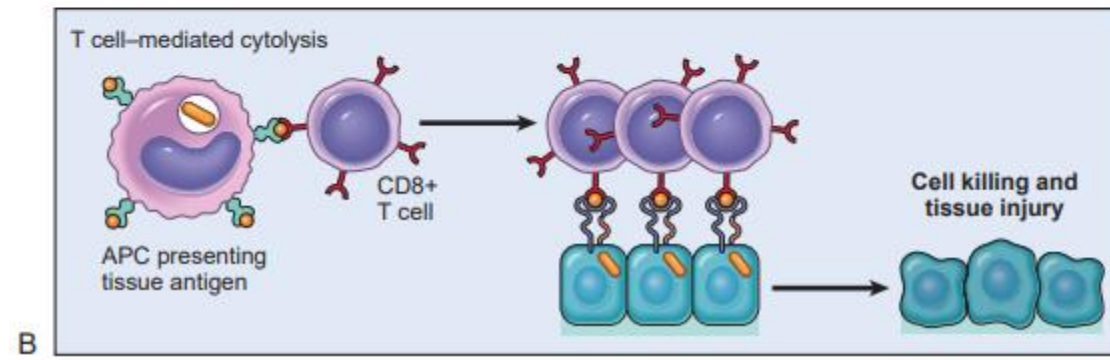
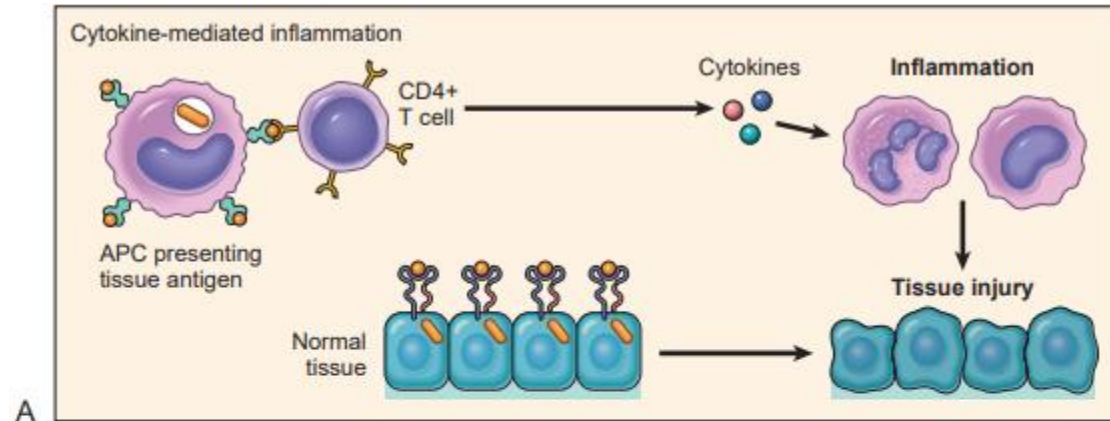
# Type 3 hypersensitivity reactions

Disease	Antigen Involved	Clinicopathologic Manifestations
Systemic lupus erythematosus	Nuclear antigens (circulating or "planted" in kidney)	Nephritis, skin lesions, arthritis, others
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Polyarteritis nodosa	Hepatitis B virus antigens in some cases	Systemic vasculitis
Reactive arthritis	Bacterial antigens (e.g., <i>Yersinia</i> )	Acute arthritis
Serum sickness	Various proteins, e.g., foreign serum protein (horse antithymocyte globulin)	Arthritis, vasculitis, nephritis
Arthus reaction (experimental)	Various foreign proteins	Cutaneous vasculitis

# Type 4 hypersensitivity reactions

- Driven by

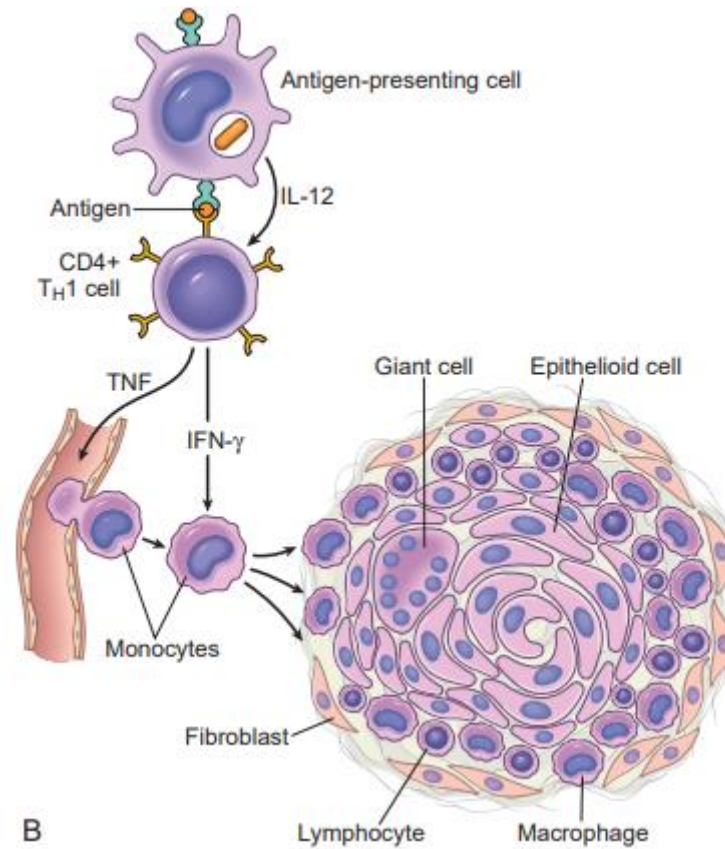
# Mechanisms in delayed type hypersensitivity reactions



# Type 4 hypersensitivity reactions

Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury	Clinicopathologic Manifestations
Rheumatoid arthritis	Collagen? Citruillinated self proteins?	Inflammation mediated by $T_H17$ (and $T_H1$ ?) cytokines; role of antibodies and immune complexes?	Chronic arthritis with inflammation, destruction of articular cartilage
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by $T_H1$ and $T_H17$ cytokines, myelin destruction by activated macrophages	Demyelination in CNS with perivascular inflammation; paralysis,
Type 1 diabetes mellitus	Antigens of pancreatic islet $\beta$ cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation, destruction of islet cells by CTLs	Insulinitis (chronic inflammation in islets), destruction of $\beta$ cells; diabetes
Inflammatory bowel disease	Enteric bacteria; self antigens?	Inflammation mediated by $T_H1$ and $T_H17$ cytokines	Chronic intestinal inflammation, obstruction
Psoriasis	Unknown	Inflammation mediated mainly by $T_H17$ cytokines	Destructive plaques in the skin
Contact sensitivity	Various environmental chemicals (e.g., urushiol from poison ivy or poison oak)	Inflammation mediated by $T_H1$ (and $T_H17$ ?) cytokines	Epidermal necrosis, dermal inflammation, causing skin rash and blisters

# Example of granuloma formation



# AUTOIMMUNE DISEASES

# Autoimmune disease

- Requirements to define as autoimmune disease
  - the presence of an immune reaction specific for some self antigen or self tissue
  - evidence that such a reaction is not secondary to tissue damage but is of primary pathogenic significance;
  - the absence of another well-defined cause of the disease

Organ-Specific	Systemic
<b>Diseases Mediated by Antibodies</b>	
Autoimmune hemolytic anemia	Systemic lupus erythematosus
Autoimmune thrombocytopenia	
Autoimmune atrophic gastritis of pernicious anemia	
Myasthenia gravis	
Graves disease	
Goodpasture syndrome	
<b>Diseases Mediated by T Cells*</b>	
Type 1 diabetes mellitus	Rheumatoid arthritis
Multiple sclerosis	Systemic sclerosis (scleroderma) <sup>†</sup> Sjögren syndrome <sup>†</sup>
<b>Diseases Postulated to Be Autoimmune</b>	
Inflammatory bowel diseases (Crohn disease, ulcerative colitis) <sup>‡</sup>	
Primary biliary cirrhosis <sup>†</sup>	Polyarteritis nodosa <sup>†</sup>
Autoimmune (chronic active) hepatitis	Inflammatory myopathies <sup>†</sup>

# Immunologic Tolerance and Autoimmunity

Tolerance (unresponsiveness) to self antigens is a fundamental property of the immune system,

Breakdown of tolerance is the basis of autoimmune diseases.

Central tolerance: immature lymphocytes that recognize self antigens in the central (generative) lymphoid organs are killed by apoptosis; in the B-cell lineage, some of the self-reactive lymphocytes switch to new antigen receptors that are not self-reactive.

Peripheral tolerance: mature lymphocytes that recognize self antigens in peripheral tissues become functionally inactive (anergic), or are suppressed by regulatory T lymphocytes, or die by apoptosis.

The factors that lead to a failure of self-tolerance and the development of autoimmunity include (1) inheritance of susceptibility genes that may disrupt different tolerance pathways, and (2) infections and tissue injury that may expose self antigens and activate APCs and lymphocytes in the tissues.

# Systemic Lupus Erythematosus (SLE)

# Antinuclear antibodies

- antibodies to DNA,
- antibodies to histones,
- antibodies to nonhistone proteins bound to RNA, and
- antibodies to nucleolar antigens

# SLE Diagnostic criteria

- A person is said to have SLE if any four or more of the 11 criteria are present, serially or simultaneously, during any period of observation

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	Persistent proteinuria >0.5 g/dL or >3 if quantitation not performed or Cellular casts—may be red blood cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance), or Psychosis—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
9. Hematologic disorder	Hemolytic anemia—with reticulocytosis, or Leukopenia— $<4.0 \times 10^9$ cells/L (4000 cells/mm <sup>3</sup> ) total on two or more occasions, or Lymphopenia— $<1.5 \times 10^9$ cells/L (1500 cells/mm <sup>3</sup> ) on two or more occasions, or Thrombocytopenia— $<100 \times 10^9$ cells/L ( $100 \times 10^3$ cells/mm <sup>3</sup> ) in the absence of offending drugs
10. Immunologic disorder	Anti-DNA antibody to native DNA in abnormal titer, or Anti-Sm—presence of antibody to Sm nuclear antigen, or Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test for lupus anticoagulant using a standard test, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by negative <i>Treponema pallidum</i> immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

# Clinical manifestations

- a butterfly rash over the face,
- fever,
- pain but no deformity in one or more peripheral joints (feet, ankles, knees, hips, fingers, wrists, elbows, shoulders),
- pleuritic chest pain, and
- photosensitivity

# Pathology/ morphology

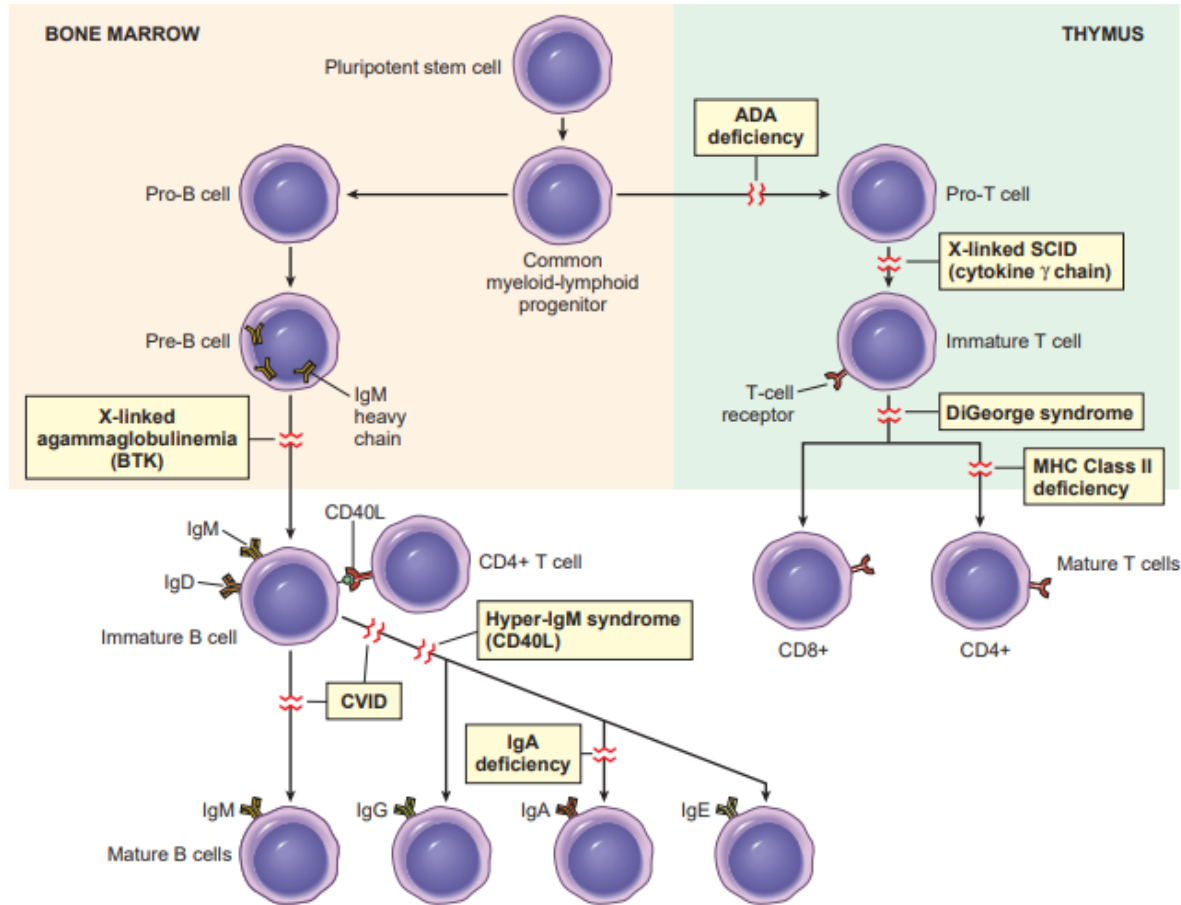
- Heart- Libman sacks endocarditis (more common prior to the widespread use of steroids)
- Lupus nephritis
- Cutaneous manifestations
- Joints

# IMMUNODEFICIENCY STATES

# Immunodeficiency

- Primary immunodeficiency
  - Inert immunity- defects in leukocyte function, defects in complement system
  - Adaptive immunity-
    - Di-George syndrome (Thymic hypoplasia)
    - SCID
    - X-linked hypogammaglobulinemia
    - Hyper-IgM syndrome
    - Specific antibody deficiencies
- Secondary immunodeficiency

# Primary immunodeficiencies



- SCID=Severe combined immunodeficiency- deficiency in both humoral and cellular immunity
  - X-linked or
  - Autosomal recessive
- X-linked agammaglobulinemia aka Bruton agammaglobulinemia
- CVID: common variable immunodeficiency
- ADA=Adenosine deaminase
- DiGeorge syndrome- failure of dev. Of 3<sup>rd</sup> and 4<sup>th</sup> pharyngeal pouches
- Hyper-IgM- Patients make IgM but deficient in ability to produce IgG, IgA, IgE

# Secondary immunodeficiencies

- Infections including HIV
- Immunosuppressive therapy
- Malnutrition
- Radiotherapy
- Chemotherapy

# HIV

- Prone to infections
- Opportunistic infections
- AIDS-defining illnesses

# HIV-associated lymphomas

- Unrestrained proliferation of EBV/ Kaposi sarcoma viruses in infected cells
- Lymph node Germinal center hyperplasia in early infection with HIV

# HIV and HPV

- HIV infected more likely to have persistent HPV
- HPV infected more likely to have HIV

## Infections

### Protozoal and Helminthic Infections

Cryptosporidiosis or isosporidiosis (enteritis)  
Pneumocystosis (pneumonia or disseminated infection)  
Toxoplasmosis (pneumonia or CNS infection)

### Fungal Infections

Candidiasis (esophageal, tracheal, or pulmonary)  
Cryptococcosis (CNS infection)  
Coccidioidomycosis (disseminated)  
Histoplasmosis (disseminated)

### Bacterial Infections

Mycobacteriosis ("atypical," e.g., *Mycobacterium avium-intracellulare*, disseminated or extrapulmonary; *Mycobacterium tuberculosis*, pulmonary or extrapulmonary)  
Nocardiosis (pneumonia, meningitis, disseminated)  
*Salmonella* infections, disseminated

### Viral Infections

Cytomegalovirus (pulmonary, intestinal, retinitis, or CNS infections)  
Herpes simplex virus (localized or disseminated infection)  
Varicella-zoster virus (localized or disseminated infection)  
Progressive multifocal leukoencephalopathy

## Neoplasms

Kaposi sarcoma  
Primary lymphoma of brain  
Invasive cancer of uterine cervix

CNS, Central nervous system.

# Graft rejection

- Rejection is a process in which T lymphocytes and antibodies produced against graft antigens react against and destroy tissue grafts

# Recognition and Rejection of Transplants (Allografts)

- The rejection response against solid organ transplants is initiated mainly by host T cells that recognize the foreign HLA antigens of the graft, either directly (on APCs in the graft) or indirectly (after uptake and presentation by host APCs).

# Types and mechanisms of rejection of solid organ grafts:

- **Hyperacute rejection.** Preformed antidonor antibodies bind to graft endothelium immediately after transplantation, leading to thrombosis, ischemic damage, and rapid graft failure.
- **Acute cellular rejection.** T cells destroy graft parenchyma (and vessels) by cytotoxicity and inflammatory reactions.
- **Acute humoral rejection.** Antibodies damage graft vasculature.
- **Chronic rejection.** Dominated by arteriosclerosis, this type is caused by T-cell activation and antibodies. The T-cells may secrete cytokines that induce proliferation of vascular smooth muscle cells, and the antibodies cause endothelial injury. The vascular lesions and T-cell reactions cause parenchymal fibrosis

# Amyloidosis

- Disorder characterized by the extracellular deposits of misfolded proteins that aggregate to form insoluble fibrils.
- The deposition of these proteins may result from:
  - excessive production of proteins that are prone to misfolding and aggregation;
  - mutations that produce proteins that cannot fold properly and tend to aggregate;
  - defective or incomplete proteolytic degradation of extracellular proteins

# Amyloidosis

- Amyloid deposits cause tissue injury and impair normal function by causing pressure on cells and tissues.
- They do not evoke an inflammatory response.

# Amyloidosis

- Systemic or
- localised

# Amyloidosis

Clinicopathologic Category	Associated Diseases	Major Fibril Protein	Chemically Related Precursor Protein
<b>Systemic (Generalized) Amyloidosis</b>			
Immunocyte dyscrasias with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal plasma cell proliferations	AL	Immunoglobulin light chains, chiefly $\lambda$ type
Reactive systemic amyloidosis (secondary amyloidosis)	Chronic inflammatory conditions	AA	SAA
Hemodialysis-associated amyloidosis	Chronic renal failure	A $\beta_2$ m	$\beta_2$ -microglobulin
<b>Hereditary Amyloidosis</b>			
Familial Mediterranean fever		AA	SAA
Familial amyloidotic neuropathies (several types)		ATTR	Transthyretin
Systemic senile amyloidosis		ATTR	Transthyretin
<b>Localized Amyloidosis</b>			
Senile cerebral	Alzheimer disease	A $\beta$	APP
Endocrine	Type 2 diabetes		
Medullary carcinoma of thyroid		A Cal	Calcitonin
Islets of Langerhans		AIAPP	Islet amyloid peptide
Isolated atrial amyloidosis		AANF	Atrial natriuretic factor