Immune Diseases

Lecture 23 - Chapter 16

- Allergies
- Autoimmunity
- Immunodeficiency

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Allergies

- **Allergens** (antigens, immunogens) can cause an exaggerated immune response, also called: "**Hypersensitivity**"
  - Type I (IgE-dependent hypersensitivity)
  - Type II (fixed non-self antigen-based hypersensitivity)
  - Type III (soluble non-self antigen-based hypersensitivity)
  - Type IV (cell-mediated 'delayed-type' hypersensitivity)

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Type I - Etiology

- 10% - 30% of population suffer from **allergies** - this is considered medium prevalence
- Involves production of the allergic antibody (IgE)
  - mediated via increased reactivity of mast cells (bind Fc end if IgE)
- Other risk determinants for allergies are:
  - Hereditary pedigree,
  - Age,
  - Infection
  - Geographic location

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Type I - Allergens

- Type I allergens are **protein** antigens or **haptens**
- Main portals of Entry for Type I allergens:
  - Respiratory tract
    - **Inhalants** (pollen, mold spores)
  - Gastrointestinal tract
    - **Ingestants** (food, drugs, water)
  - Skin
    - **Injectants** (bites, stabs)
    - **Contactants** (drugs, chemicals)
- => See Table 16.2

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Common allergens for the respiratory tract, GI tract, and skin.

TABLE 16.2 Common Allergens, Classified by Portal of Entry

Inhalants	Ingestants	Injectants	Contactants
Pollen	Food (milk, peanuts, wheat, shellfish, soybeans, nuts, eggs, fruits)	Hymenopteran venom (bee, wasp)	Drugs
Dust		Drugs	Cosmetics
Mold spores		Vaccines	Heavy metals
Dander		Serum	Detergents
Animal hair		Enzymes	Formalin
Insect parts		Hormones	Rubber
Formalin	Food additives		Glue
Drugs	Drugs (aspirin, penicillin)		Solvents
Enzymes			Dyes

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Table 16.2 Common allergens, classified by portal of entry

Type I - Mechanisms

First exposure

- **Sensitizing dose** - elicits normal IR, in which **memory** B cells are produced
- In addition to other Igs (IgM and IgG), a **small amount of IgE** antibodies is produced
- No allergy symptoms !!!!

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Type I Mechanisms

Second exposure

- Allergens bind to **memory B** cells (IgM receptor)
- B cells derived from memory B cells produce large amounts (high titer) of IgE antibodies
- IgE:allergen complex binds to mast cell and basophil receptors
  - > Degranulation and release chemical mediators

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Mast cells and basophils

- Contain receptors that bind IgE-Fc
- Ubiquitous location with regard to portals of entry (connective tissue for most organs)
- Secrete chemical mediators derived from cytoplasmic granules by degranulation

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Type I - chemical mediators

- Degranulation will release these **mediators** that are **responsible for allergic symptoms**
  - Histamine
  - Serotonin
  - Leukotriene
  - Platelet-activating factor (PAF)
  - Prostaglandins
  - Bradykinin

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Histamine

- **Fast-acting** allergic mediator
- **Constricts bronchial and intestinal smooth muscle layers**
- **Relaxes vascular smooth muscle**, dilates arterioles and venules
- Wheal and flare reactions in the skin
- Pruritis (itching)
- Headache
- Anaphylaxis
- Stimulator of glands and eosinophils

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Serotonin

- Complements histamine
- Increases vascular permeability, capillary dilation, smooth muscle contraction, intestinal peristalsis, respiratory rate
- Diminishes central nervous system activity by leading to a serotonin/dopamine imbalance

(serotonin plays an important role in the regulation of mood, sleep, vomiting, sexuality and appetite. Low levels of Serotonin have been associated with several disorders, notably depression, migraine, bipolar disorder and anxiety).

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Leukotriene

- Causes prolonged bronchio-spasms
- Increases vascular permeability
- Activates mucous secretions
- Stimulates polymorphonuclear leukocyte (granulocyte) activity

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Platelet-activating factor

- Lipid-like chemical nature
- Produced by basophils, neutrophils, monocytes and macrophages
- Response is similar to histamine

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Prostaglandins

- Cause vasodilation
  => Increase in vascular permeability
- Increase sensitivity to pain
- Bronchio-constriction

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Bradykinin

- Prolonged smooth muscle contractions of the bronchioles
- Dilatation of peripheral arterioles
- Increase capillary permeability
- Increase mucous secretion

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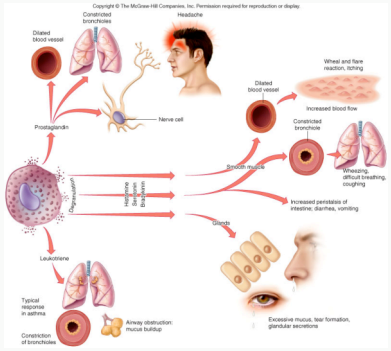

Fig. 16.4 The spectrum of reactions to inflammatory cytokines

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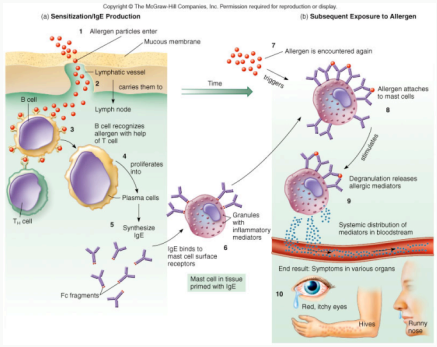

Fig. 16.3 A schematic view of cellular reactions during the **Type I** hypersensitive (allergic) response.

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Allergic Syndromes

- Atopic (non-systemic) diseases
- Anaphylaxis
- Treatment

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Atopic diseases

- Atopy – **chronic local allergy**
  - Hay fever (allergic rhinitis)
  - Asthma
  - Dermatitis

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Hay fever

- Reaction to pollen or molds
- Targets respiratory membranes
- Symptoms
  - Nasal congestion
  - Sneezing
  - Coughing
  - Mucous secretions
  - Itchy, red and teary eyes
  - Mild bronchio-constriction

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Asthma

- Severe bronchio-constriction
- Symptoms
  - Shortness of breath to suffocation
  - Wheezing
  - Cough
  - Inflamed respiratory tract

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Atopic dermatitis (eczema)

- Intense itchy inflammatory condition of the skin
- Can begin in infancy and progress to adulthood
- Symptoms
  - Dry, scaly, thickened skin
  - Face, scalp, neck, inner surface of limbs and trunk

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Fig. 16.5 Atopic dermitiitis in an infant.

Anaphylaxis

- Cutaneous
  - Wheal and flare inflammatory reaction to the local injection of an allergen
- Systemic
  - Rapid immune response that can disrupt respiratory and circulatory systems
  - Can result in death

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Treatment of atopic symptoms

- Diagnosis
  - Skin testing
- Drug
  - Anti-allergy medications
- Desensitizing (neutralization)
  - IgG antibodies that block IgE function

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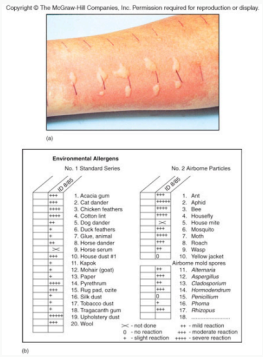

Fig. 16.6 A method for conducting an allergy skin test.

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Type II

- Interaction of antibodies with **antigen on foreign cells**, and complement, which then leads to foreign cell lysis
  - ABO blood group antigens (IgM-type Ab)
  - Rh factor antigen (IgG-type Ab)

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ABO blood groups

- Landsteiner blood types - genetically determined
- RBC markers (glyco/lipo-proteins)
- Alleles – A, B, O

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ABO blood groups

	Group A	Group B	Group AB	Group O
Red blood cell type	A	B	AB	O
Antibodies present	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens present	A antigen	B antigen	A and B antigens	None

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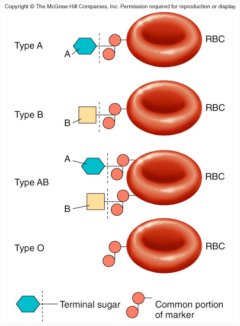

Fig. 16.9 Specific genes that encode for enzymes that add a unique sugar to the RBC receptor are the basis for the A and B antigens.

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Blood types

Each individual will have antibodies against another antigenic type (environmental sensitization).

- Type A will have anti-B antibodies
- Type B will have anti-A antibodies
- Type O will have anti-B and anti-A antibodies
  - Universal (cell) donor (RBC have no “A” & “B” antigens)
- Type AB has no anti-B or anti-A antibodies
  - Universal (cell) recipient (RBC have “A” & “B” antigens)

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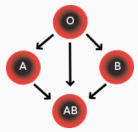
ABO blood groups

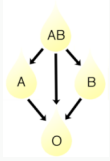
Universal RBC Donor



Universal RBC Recipient

Blood donation:
(cells lack or have
A, B or A&B antigens)

Universal Serum Donor



Universal Serum Recipient

Serum donation:
Serum contains none,
B, A or A&B IgM antibodies

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Country	O+	A+	B+	AB+	O−	A−	B−	AB−
Hong Kong	40%	26%	27%	7%	0.3% <0.3%	0.3% <0.3%	0.3%<0.3%	0.3%<0.3%
Korea	35.2%	28.1%	26.1%	11.3%	0.1%	0.1%	0.1%	0.05%
Estonia	30%	31%	20%	6%	4.5%	4.5%	3%	1%
Finland	27%	38%	15%	7%	4%	6%	2%	1%
Poland	31%	32%	15%	7%	6%	6%	2%	1%
Turkey	29.8%	37.8%	14.2%	7.2%	3.9%	4.7%	1.6%	0.8
Denmark	**35%**	**37%**	**8%**	**4%**	**6%**	**7%**	**2%**	**1%**
Norway	**34%**	**42.5%**	**6.8%**	**3.4%**	**6%**	**7.5%**	**1.2%**	**0.6%**
Sweden	**32%**	**37%**	**10%**	**5%**	**6%**	**7%**	**2%**	**1%**
France	**36%**	**37%**	**9%**	**3%**	**6%**	**7%**	**1%**	**1%**
Belgium	**38.1%**	**34%**	**8.5%**	**4.1%**	**7%**	**6%**	**1.5%**	**0.8%**
Netherlands	**39.5%**	**35%**	**6.7%**	**2.5%**	**7.5%**	**7%**	**1.3%**	**0.5%**
Germany	**35%**	**37%**	**9%**	**4%**	**6%**	**6%**	**2%**	**1%**
Austria	**30%**	**33%**	**12%**	**6%**	**7%**	**8%**	**3%**	**1%**
UK	**37%**	**35%**	**8%**	**3%**	**7%**	**7%**	**2%**	**1%**
USA	**37.4%**	**35.7%**	**8.5%**	**3.4%**	**6.6%**	**6.3%**	**1.5%**	**0.6%**
Canada	**39%**	**36%**	**7.6%**	**2.5%**	**7%**	**6%**	**1.4%**	**0.5%**
New Zealand	**38%**	**32%**	**9%**	**3%**	**9%**	**6%**	**2%**	**1%**
Australia	**40%**	**31%**	**8%**	**2%**	**9%**	**7%**	**2%**	**1%**
Ireland	47%	26%	9%	2%	8%	5%	2%	1%

Incompatible blood will result in agglutination, complement activation, and cell lysis.

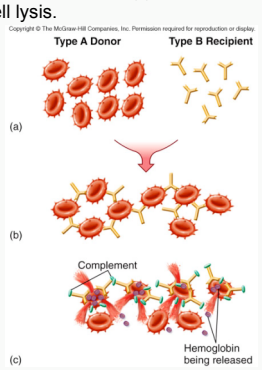

Fig. 16.11 Microscopic view of a transfusion.

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Rh factor

- Another RBC antigen
  - At least one dominant allele = Rh^+
  - Two recessive alleles = Rh^-
- => IgG-type Rh(D) antibody is “culprit”
- Hemolytic disease

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Hemolysis

- Rh^- mother and Rh^+ fetus
- First birth
  - Little anti-Rh antibody produced (B-cells)
  - But B Memory cells
- Second birth (= second exposure)
  - strong immune response
  - Hemolysis

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Type III

- Mechanism
- Immune complex reactions
- Diseases

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Type III Mechanisms

- Similar to Type II, except antibodies react with **free-antigens**, no fixed antigens
- Ab-Ag complexes deposit in tissue causing **immune complex** reactions

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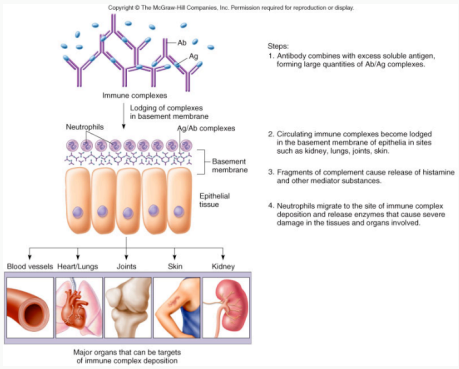

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Fig. 16.13 Pathogenesis of immune complex disease.

Type III diseases: Arthus reaction

- Injected antigen (eg. Vaccine, drug)
- Localized dermal injury due to inflamed blood vessels
- Acute response to a second similar antigen injection
- Severe cases result in necrosis and loss of tissue

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Type III diseases: Serum sickness

- Injection of serum, hormones, drugs
- Systemic injury
- Ag-Ab complexes circulate in the blood and eventually settle into membranes (kidney, heart, skin)
- Chronic – enlarged lymph nodes, rashes, painful joints, swelling, fever, and renal dysfunction

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Type IV

- **Cell-mediated** delayed-type hypersensitivity
  (Primarily a T cell response)
  - Infectious allergy
  - Contact dermatitis
  - Tissue rejection

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An example of an infectious allergy would be an individual that is sensitized by a tuberculosis infection.

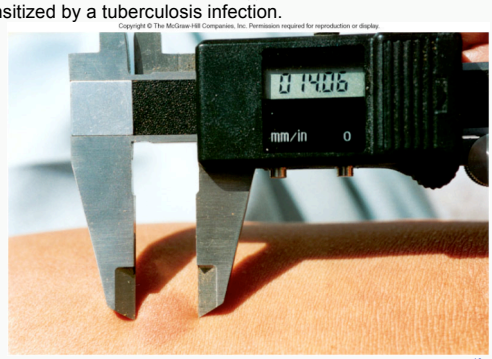

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Fig. 16.14 Positive tuberculin test.

Contact dermatitis can result from poison oak.

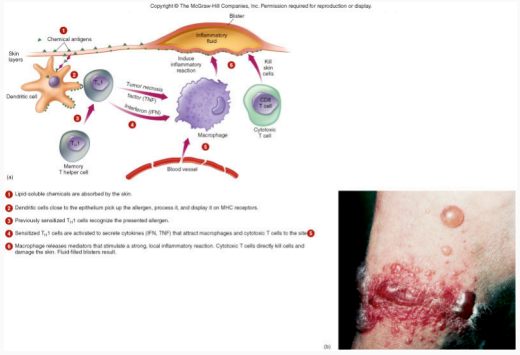

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Fig. 16.15 Contact dermatitis

Tissue rejection

- T cell-mediated recognition of foreign MHC receptors
  - Cytotoxic T cells
  - Host rejection of graft
  - Graft rejection of host

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Two possible reactions that can occur due to transplantation.

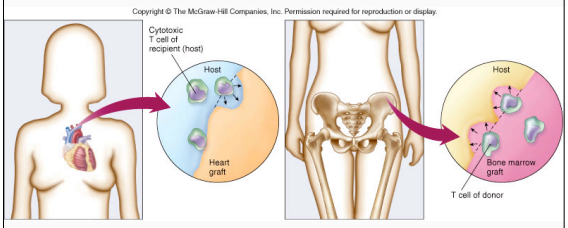

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Fig. 16.16 Potential reactions in transplantation.

Autoimmunity

- Antibodies, T cells or both, mount an **immune response against self antigens**
  - Systemic or organ-specific
  - Type II (fixed Ag) or III (soluble Ag) reactions

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An example some major autoimmune diseases.

TABLE 16.4 Selected Autoimmune Diseases

Disease	Target	Type of Hypersensitivity	Characteristics
Systemic lupus erythematosus (SLE)	Systemic	III	Inflammation of many organs; antibodies against red and white blood cells, platelets, clotting factors, nucleus DNA
Rheumatoid arthritis and ankylosing spondylitis	Systemic	III and IV	Vasculitis; frequent target is joint lining; antibodies against other antibodies (rheumatoid factor)
Scleroderma	Systemic	II	Excess collagen deposition in organs; antibodies formed against many intracellular organelles
Hashimoto's thyroiditis	Thyroid	II	Destruction of the thyroid follicles
Graves disease	Thyroid	II	Antibodies against thyroid-stimulating hormone receptors
Pernicious anemia	Stomach lining	II	Antibodies against receptors prevent transport of vitamin B_{12}
Myasthenia gravis	Muscle	II	Antibodies against the acetylcholine receptors on the nerve-muscle junction alter function
Type I diabetes	Pancreas	II	Antibodies stimulate destruction of insulin-secreting cells
Multiple sclerosis	Myelin	II and IV	T cells and antibodies sensitized to myelin sheath destroy neurons
Goodpasture syndrome (glomerulonephritis)	Kidney	II	Antibodies to basement membrane of the glomerulus damage kidneys
Rheumatic fever	Heart	II	Antibodies to group A *Streptococcus* cross-react with heart tissue

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Table 16.4 Selected autoimmune diseases.

Origins of autoimmunity

- Sequestered antigens
- Clonal selection against self
- Immune deficiency
- Inappropriate expression of MHC II
- Molecular mimicry
- Viral infections

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Diseases

- Systemic autoimmunities
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
- Endocrine
  - Graves disease
  - Hashimoto thyroiditis
  - Diabetes mellitus
- Neuromuscular
  - Myasthenia gravis
  - Multiple sclerosis

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An example of systemic lupus and rheumatoid arthritis.

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Fig. 16.17 Common autoimmune diseases.

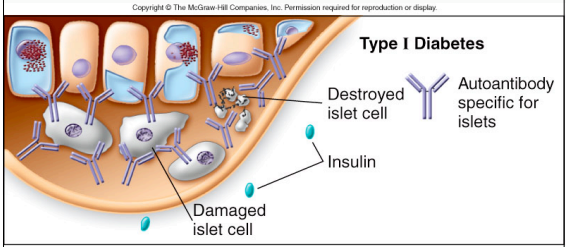

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Fig. 16.18 The autoimmune component in Type I diabetes mellitus.

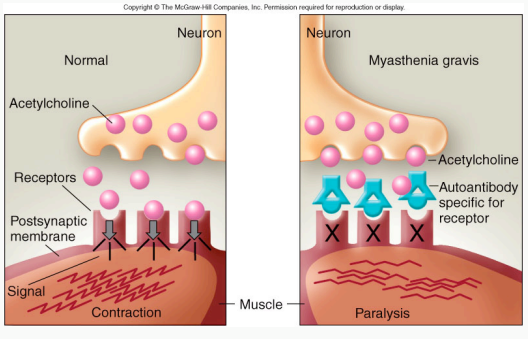

Fig. 16.19 Mechanism for involvement of auto-antibodies in myasthenia gravis (antibodies block the attachment of acetylcholine.).

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Immunodeficiency

- A person can be born with or develop a weakened immune system
  - Primary
  - Secondary

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Primary

- Antibody production and phagocytosis
- Inherited abnormality
  - Deficiencies in B-cell or T-cell and development and expression
  - Combined B- and T-cell deficiency

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Deficiencies in B and T cell development can reduce the level of protection by the immune system.

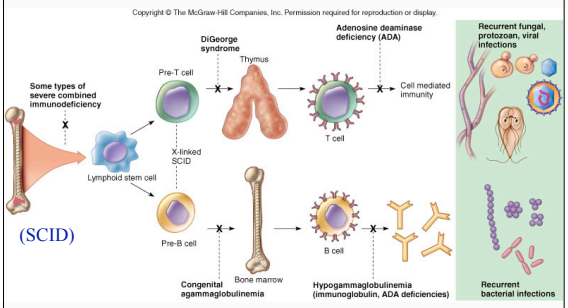

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Fig. 16.20 The stages of development and the function

Secondary

- Caused by
  - Infection
  - Chemotherapy
  - Radiation

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Summary of the primary and secondary immunodeficiency diseases.

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TABLE 16.5 General Categories of Immunodeficiency Diseases with Selected Examples

Primary Immune Deficiencies (Genetic)	Secondary Immune Deficiencies (Acquired)
B-Cell Defects (Low Levels of B Cells and Antibodies) Agammaglobulinemia (X-linked, non-sex-linked) Hypogammaglobulinemia Selective immunoglobulin deficiencies	**From Natural Causes** Infection: AIDS, leprosy, tuberculosis, measles Other disease: cancer, diabetes Nutrition deficiencies Stress Pregnancy Aging
T-Cell Defects (Lack of All Classes of T Cells) Thymic aplasia (DiGeorge syndrome) Chronic mucocutaneous candidiasis	**From Immunosuppressive Agents** Irradiation Severe burns Steroids (cortisones) Drugs to treat graft rejection and cancer Removal of spleen
Combined B-Cell and T-Cell Defects (Usually Caused by Lack or Abnormality of Lymphoid Stem Cell) Severe combined immunodeficiency disease (SCID) X-SCIDI due to an interleukin defect Adenosine deaminase (ADA) deficiency Wiskott-Aldrich syndrome Ataxia-telangiectasia	
Phagocyte Defects Chédiak-Higashi syndrome Chronic granulomatous disease of children (see In The News, chapter 14) Lack of surface adhesion molecules	
Complement Defects Lacking one of C components Hereditary angioedema Associated with rheumatoid diseases	

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Table 16.5 General categories of immunodeficiency diseases