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INNATE AND ADAPTIVE IMMUNITY

PHYSIOLOGIC FUNCTION- DEFENSE AGAINST INFECTIOUS MICROBES

INNATE
NATIVE IMMUNITY
EARLY REACTION
INFLAMMATION

ADAPTIVE
ACQUIRED IMMUNITY DEVELOPS SLOWLY BUT POTENT
HUMORAL- ANITBODY PROTEINS FROM B LYMPHOCYTES
CELL MEDIATED- T LYMPHOCYTES

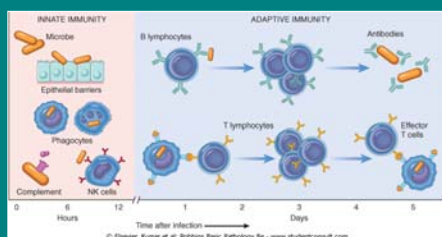


Figure 5-1 The principal mechanisms of innate immunity and adaptive immunity. NK cells, natural killer cells.

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HUMORAL IMMUNITY

- MEDIATED BY ANTIBODIES
- EXTRACELLULAR MICROBES
- SECRETED BY PLASMA CELLS
- NEUTRALIZES MICROBES
- PROMOTES PHAGOCYTOSIS AND DESTRUCTION
- PASSIVE IMMUNITY TO NEONATES



CELL MEDIATED IMMUNITY

- T LYMPHOCYTES
- PROTECTS AGAINST CELL ASSOCIATED MICROBES
- CD4+ HELPER CELLS
ACTIVATES B CELLS AND MACROPHAGES
FUNCTION MEDIATED BY CYTOKINES
REGULATES IMMUNE RESPONSES
- CD8+ CYTOTOXIC T LYMPHOCYTES
KILLS CELLS WITH FOREIGN ANTIGEN IN CYTOPLASM

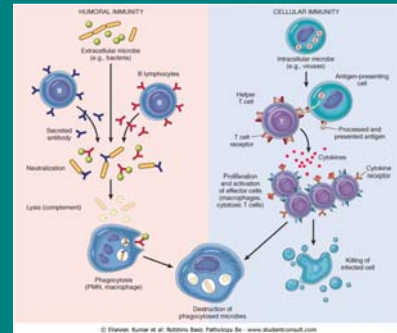


Figure 5-2 Humoral and cell-mediated immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, T lymphocytes either activate macrophages to destroy phagocytosed microbes or kill infected cells, such as polymorphonuclear leukocytes.

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ANTIGEN PRESENTING CELLS

- SPECIALIZED TO CAPTURE MICROBIAL ANTIGENS
- DISPLAYS TO LYMPHOCYTES
- DENDRITIC CELLS \Rightarrow
DISPLAY ANTIGENS TO NAÏVE T CELLS
NON PHAGOCYtic
HIGH LEVELS MHC II AND T CELL CO-STIMULATORY MOLECULES
- MHC I EXPRESSED ALL NUCLEATED CELLS- CD8+
- MHC II RESTRICTED DENDRITIC CELLS, MACROPHAGES, B CELLS- PRESENTS TO CD4+ T CELLS

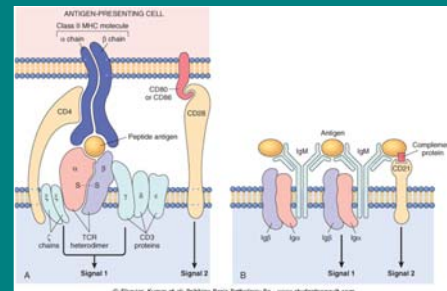
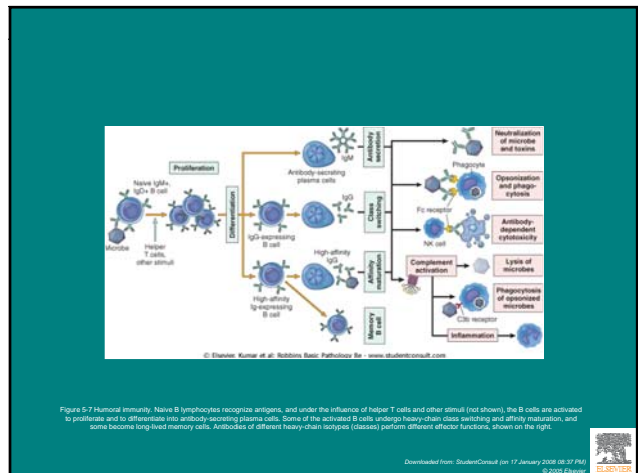
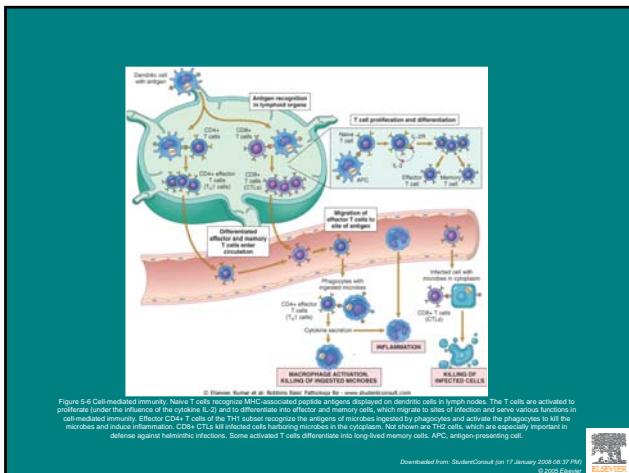
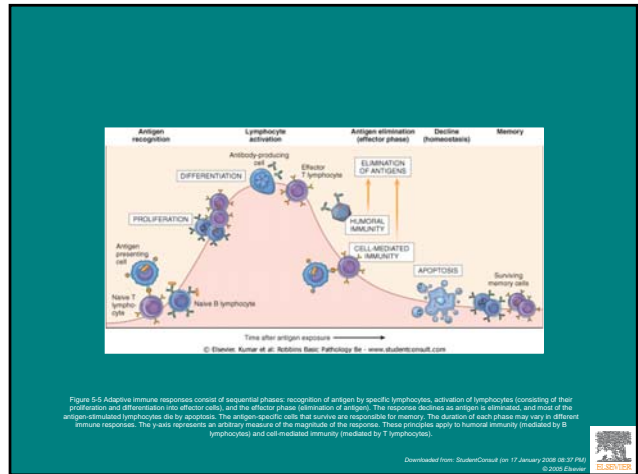
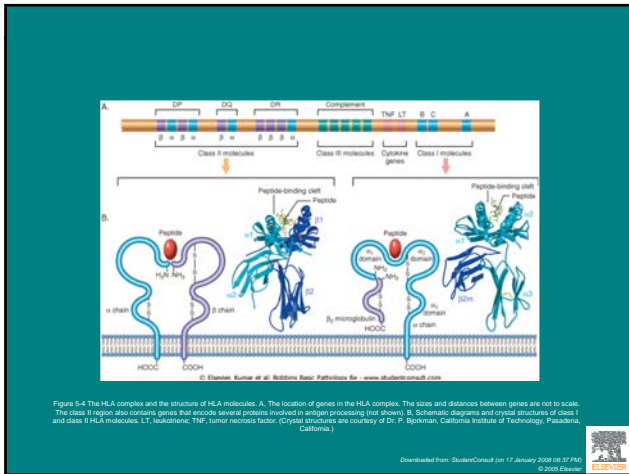


Figure 5-3 Lymphocyte antigen receptors. A, The T-cell receptor (TCR) complex and other molecules involved in T-cell activation. The TCR alpha and TCR beta chains recognize antigens in the form of peptide-MHC complexes expressed on antigen-presenting cells, and the linked CD3 complex initiates activating signals. CD4 and CD8 are also involved in T-cell activation. (Note that some T cells express CD8 and not CD4; these molecules serve analogous roles.) B, The B cell receptor complex is composed of membrane IgM (mu and delta chains) and the associated signaling proteins (lambda and gamma). CD21 is a receptor for a complement component that promotes B cell activation.

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CYTOKINES

- INNATE IMMUNITY
TNF, IL-1, CHEMOKINES, IL-12, IFN-GAMMA
- EFFECTOR FUNCTIONS IN ADAPTIVE IMMUNITY
IL-2, IL-4 PROLIFERATION AND DIFFERENTIATION OF LYMPHOCYTES
IFN-GAMMA ACTIVATES MACROPHAGES
IL-5 EOSINOPHILS
- STIMULATE HEMATOPOIESIS
COLONY STIMULATING FACTORS
- CD4+ SECRETE IL-2 AND EXPRESS IL-2R

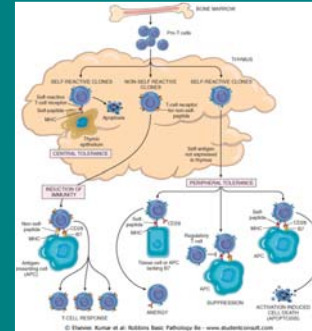


Figure 5-18 The principal mechanisms of central and peripheral self-tolerance in CD4+ T cells.

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DISEASES OF IMMUNE SYSTEM

- *Hypersensitivity reactions*, which give rise to immunologic injury in a variety of diseases, discussed throughout this book
- *Autoimmune diseases*, which are caused by immune reactions against self
- *Immunologic deficiency syndromes*, which result from genetically determined or acquired defects in some components of the normal immune system
- *Amyloidosis*, a poorly understood disorder having immunologic association.



HYPERSENSITIVITY DISEASES

- PATHOLOGIC IMMUNE RESPONSES
 - AUTOIMMUNITY
 - REACTIONS TO MICROBES
 - REACTIONS TO ENVIRONMENTAL ANTIGENS
- TYPE I- IMMEDIATE
 - ALLERGIES
 - STRONG TH2 AND IgE RESPONSES
- TYPE II- ANTIBODY MEDIATED
 - ANTIBODIES DIRECTED TARGET AG ON CELLS/TISSUE
- TYPE III- IMMUNE COMPLEX DISEASES
 - AG-AB COMPLEXES FORMED AND DEPOSITED
- TYPE IV- T CELL MEDIATED
 - DELAYED TYPE- CD4+ DIFFERENTIATE TO TH1 EFFECTORS
 - T CELL CYTOTOXICITY- CD8+ CTLs



TYPE I IMMEDIATE

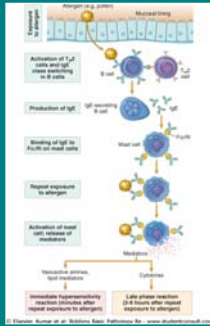


Figure 5-8 Sequence of events in immediate (type I) hypersensitivity. Immediate hypersensitivity reactions are initiated by the introduction of an allergen, which stimulates TH2 responses and IgE production. IgE binds to FcεR1 receptors (FcεR1α/βγδ) on mast cells, and subsequent exposure to the allergen activates the mast cells to secrete the mediators that are responsible for the pathologic manifestations of immediate hypersensitivity.

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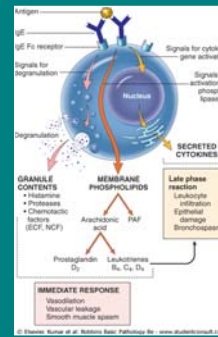


Figure 5-9 Mast cell mediators. Upon activation, mast cells release various classes of mediators that are responsible for the immediate and late-phase reactions. ECF, eosinophil chemotactic factor; NCF, neutrophil chemotactic factor (neither of these has been biochemically defined); PAF, platelet activating factor.

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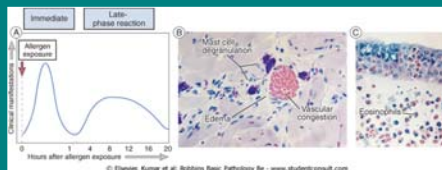


Figure 5-10 Immediate hypersensitivity. A, Kinetics of the immediate and late-phase reactions. The immediate vascular and smooth muscle reaction to allergen develops within minutes after challenge (allergen exposure in a previously sensitized individual), and the late-phase reaction develops 2 to 24 hours later. B, C, Morphology. The immediate reaction (B) is characterized by vasodilation, congestion, and edema, and the late-phase reaction (C) is characterized by an inflammatory infiltrate rich in eosinophils, neutrophils, and T cells. (Micrographs courtesy of Dr. Daniel Friend, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)

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TYPE II- ANTIBODY MEDIATED

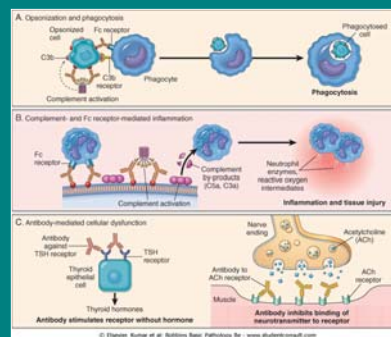


Figure 5-11 Effector mechanisms of antibody-mediated injury. A, Opsonization of cells by antibodies and complement components, and ingestion of opsonized cells by phagocytes. B, Inflammation induced by antibody binding to Fc receptors of leukocytes and by complement breakdown products. C, Antineurotoxic antibodies disturb the normal function of receptors. In these examples, antibodies against the thyroid-stimulating hormone (TSH) receptor activate thyroid cells in Graves disease, and acetylcholine (ACh) receptor antibodies impair neuromuscular transmission in myasthenia gravis.

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Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rb blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (glycyl-bilirubin integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor-mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells		

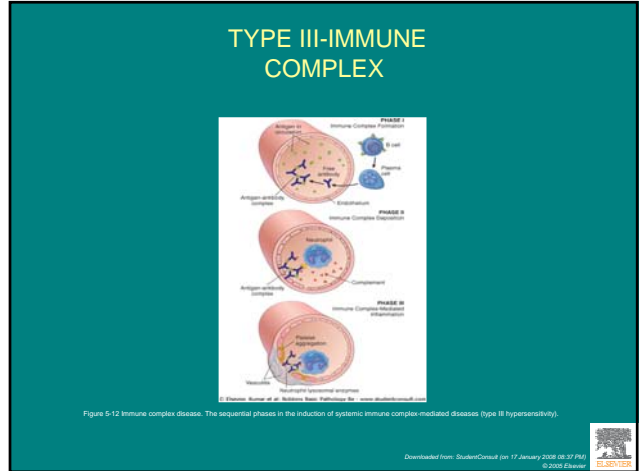


Table 6-5 -- Examples of Immune Complex-Mediated Diseases

Disease	Antigen Involved	Clinicopathologic Manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen (in some cases)	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Acute glomerulonephritis	Bacterial antigens (<i>Streptococcus</i>); parasite antigens (malaria, schistosomes); tumor antigens	Nephritis
Reactive arthritis	Bacterial antigens (<i>Yersinia</i>)	Acute arthritis
Arthus reaction	Various foreign proteins	Cutaneous vasculitis
Serum sickness	Various proteins, e.g., foreign serum (anti-thymocyte globulin)	Arthritis, vasculitis, nephritis

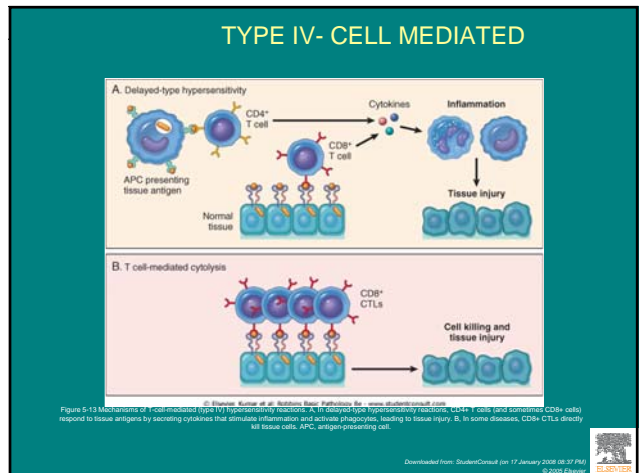


Table 6-6 -- Examples of T Cell-Mediated (Type IV) Hypersensitivity

Disease	Specificity of Pathogenic T Cells	Clinicopathologic Manifestations
Type 1 diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	Insulinitis (chronic inflammation in islets), destruction of β cells; diabetes
Multiple sclerosis	Protein antigens in central nervous system myelin (myelin basic protein, proteolipid protein)	Demyelination in CNS with perivascular inflammation; paralysis, ocular lesions
Rheumatoid arthritis	Unknown antigen in joint synovium (type II collagen?); role of antibodies?	Chronic arthritis with inflammation, destruction of articular cartilage and bone
Peripheral neuropathy; Guillain-Barré syndrome?	Protein antigens of peripheral nerve myelin	Neuritis, paralysis

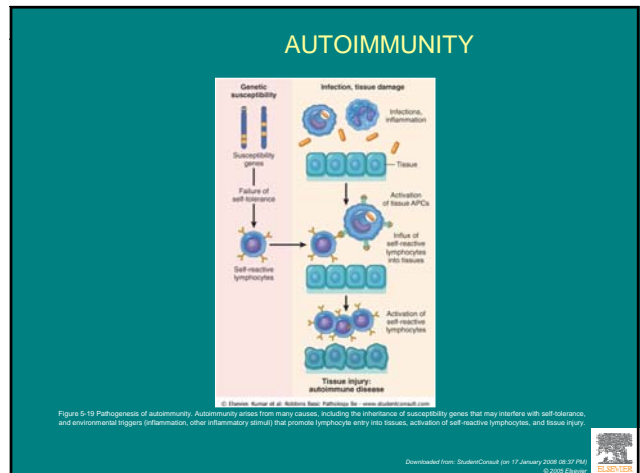
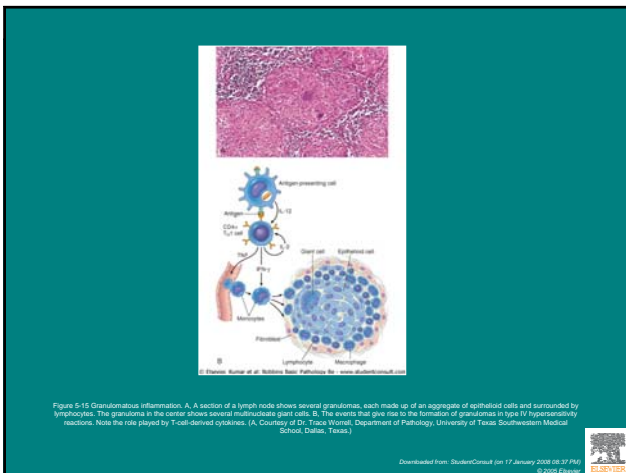
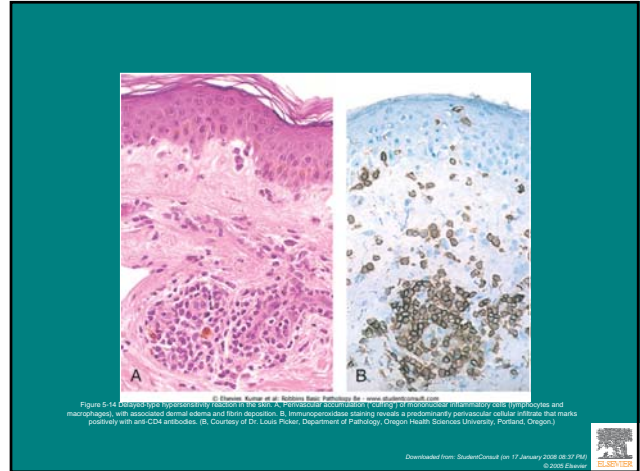
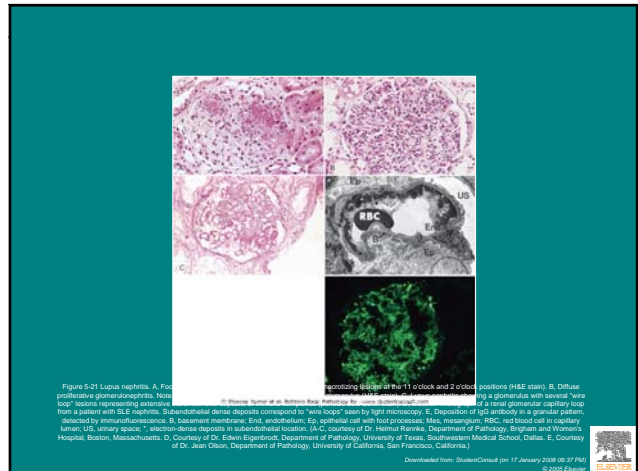
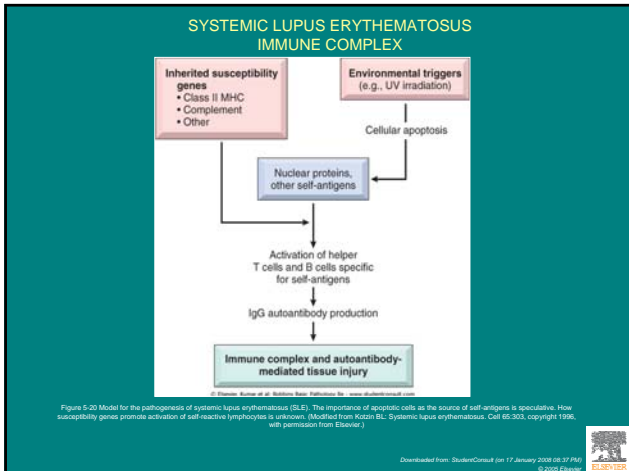


Table 6-7 -- Autoimmune Diseases

Organ-Specific	Systemic
Hashimoto thyroiditis	Systemic lupus erythematosus
Autoimmune hemolytic anemia	Rheumatoid arthritis
Autoimmune atrophic gastritis of pernicious anemia	Sjögren syndrome
Multiple sclerosis	Reiter syndrome
Autoimmune orchitis	Inflammatory myopathies *
Goodpasture syndrome	Systemic sclerosis (scleroderma) *
Autoimmune thrombocytopenia	Polyarteritis nodosa *
Insulin-dependent diabetes mellitus	
Myasthenia gravis	
Graves disease	
Primary biliary cirrhosis *	
Autoimmune (chronic active) hepatitis *	
Ulcerative colitis *	

Table 6-1 -- Association of HLA with Disease

Disease	HLA Allele	Relative Risk
Ankylosing spondylitis	B27	90
Postgonococcal arthritis	B27	14
Acute anterior uveitis	B27	14
Rheumatoid arthritis	DR4	4
Chronic active hepatitis	DR3	13
Primary Sjögren syndrome	DR3	9
Type-1 diabetes	DR3	5
	DR4	6
	DR3/DR4	20



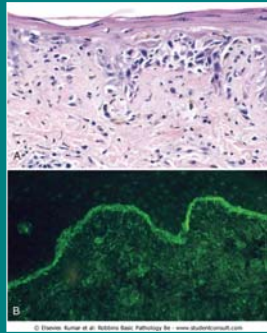


Figure 5-22 SLE involving the skin. A, An H&E-stained section shows liquefactive degeneration of the basal layer of the epidermis and edema at the dermoepidermal junction. B, An immunofluorescence micrograph stained for IgG reveals deposits of Ig along the dermoepidermal junction. (A, Courtesy of Dr. Jag Bhanan, Boston University School of Medicine, Boston, Massachusetts. B, Courtesy of Dr. Richard Sontheimer, Department of Dermatology, University of Texas Southwestern Medical School, Dallas, Texas.)

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RHEUMATOID ARTHRITIS CELL MEDIATED



Figure 5-23 Rheumatoid arthritis. A, A joint lesion. B, Low magnification reveals marked synovial hyperplasia with formation of villi. C, At higher magnification, dense lymphoid aggregates are seen in the synovium. (A, Modified with permission from Feldman M. Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol 2:364, 2002.)

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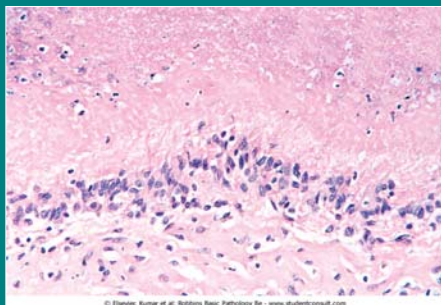


Figure 5-24 Rheumatoid nodule. Subcutaneous nodule with an area of necrosis (top) surrounded by a palisade of macrophages and scattered chronic inflammatory cells.

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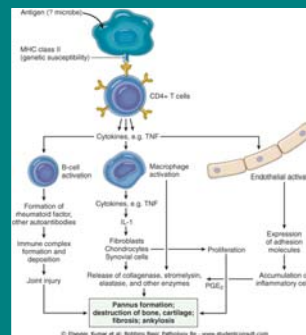


Figure 5-25 Model for the pathogenesis of rheumatoid arthritis. CD4+ T cells reacting against an unknown antigenic antigen are believed to stimulate autoantibody production and to activate macrophages and other cells in the joint synovium. PGE₂, prostaglandin E₂.

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SJOGREN SYNDROME

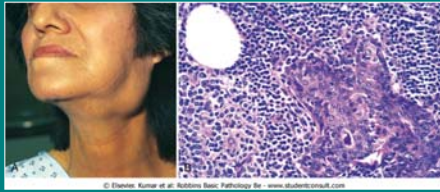


Figure 5-26 Sjogren syndrome. A, Enlargement of the salivary gland. B, The histologic view shows intense lymphocytic and plasma cell infiltration with atrophic epithelial hyperplasia. (A, Courtesy of Dr. Richard Sontheimer, Department of Dermatology, University of Texas Southwestern Medical School, Dallas, Texas. B, Courtesy of Dr. Dennis Bunnis, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

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SYSTEMIC SCLEROSIS

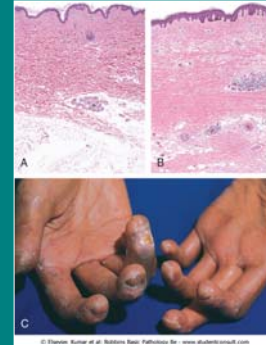


Figure 5-27 Systemic sclerosis. A, Normal skin. B, Extensive deposition of dense collagen in the dermis. C, The extensive subcutaneous fibrosis has virtually immobilized the fingers, creating a clawlike flexion deformity. Loss of blood supply has led to cutaneous ulcerations. (Courtesy of Dr. Richard Sontheimer, Department of Dermatology, University of Texas Southwestern Medical School, Dallas, Texas.)

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Nature of Antigen	Antibody System	Disease, % Positive					
		SLE	Drug-Induc ed LE	Systemic Sclerosis— Diffuse	Limited Scleroderma— CREST	Sjogren Syndrome	Inflammatory Myopathies
Many nuclear antigens (DNA, RNA, proteins)	Generic ANA (indirect IF)	>95	>95	70-90	70-90	50-80	40-60
Native DNA	Anti-double-stranded DNA	40-60	<5	<5	<5	<5	<5
Histones	Anti-histone	50-70	>95	<5	<5	<5	<5
Core proteins of small nuclear ribonucleoprotein particles (Smith antigen)	Anti-Sm	20-30	<5	<5	<5	<5	<5
Ribonucleoprotein (U1RNP)	Nuclear RNP	30-40	<5	15	10	<5	<5
RNP	SS-A(Ro)	30-50	<5	<5	<5	70-95	10
RNP	SS-B(La)	10-15	<5	<5	<5	60-90	<5
DNA topoisomerase I	Scl-70	<5	<5	28-70	10-18	<5	<5
Centromeric proteins	Anti-centromere	<5	<5	22-36	90	<5	<5
Histidyl-tRNA synthetase	Jo-1	<5	<5	<5	<5	<5	25

SLE, systemic lupus erythematosus; ANA, antinuclear antibodies; RNP, ribonucleoprotein.

IMMUNE DEFICIENCY DISEASES

- PRIMARY
 - X LINKED AGAMMAGLOBULINEMIA- MUTATION IN B CELL KINASE, EARLY ONSET
 - COMMON VARIABLE IMMUNODEFICIENCY- HETEROGENEOUS HYPOGAMMAGLOBULINEMIA, IMPAIRED ANTIBODY RESPONSE, SUSCEPTIBLE TO INFECTIONS
 - 2ND TO 3RD DECADE
 - ASSOCIATED WITH AUTOIMMUNE DISEASES
 - ISOLATED IgA DEFICIENCY- MOST COMMON
 - BLOCK IN DIFFERENTIATION B CELL TO PLASMA CELL
 - ASYMPTOMATIC OR DIARRHEA/SINOPULMONARY INFECTIONS
 - ASSOCIATED WITH AUTOIMMUNE DISEASES
 - HYPER IgM SYNDROME- MUTATION IN CD40L, - ISOTYPE SWITCH
 - SCID- DIVERSE UNDERLYING DEFECTS- ALLO BONE MARROW TRANS
 - X-LINKED
 - AUTO REC WITH ADENOSINE DEAMINASE MUTATION (ADA)
 - ALLOGENEIC BONE MARROW TRANSPLANT
- SECONDARY
 - MORE COMMON- THERAPY INDUCED BONE MARROW AND LYMPHOCYTE SUPPRESSION, CANCER, MALNUTRITION, INFECTION (HIV), RENAL DISEASE, SARCOIDOSIS