Robbins Pathology Summary Tables
General Pathology

Compiled by T'Challa

Table 1–1 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic; means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage

DNA, deoxyribonucleic acid.

Table 1–2 Diseases Caused by Misfolding of Proteins

Disease	Affected Protein	Pathogenesis
Cystic fibrosis	Cystic fibrosis transmembrane conductance regulator (CFTR)	Loss of CFTR leads to defects in chloride transport
Familial hypercholesterolemia	LDL receptor	Loss of LDL receptor leading to hypercholesterolemia
Tay-Sachs disease	Hexosaminidase β subunit	Lack of the lysosomal enzyme leads to storage of GM_2 gangliosides in neurons
Alpha-1-antitrypsin deficiency	α-1 antitrypsin	Storage of nonfunctional protein in hepatocytes causes apoptosis; absence of enzymatic activity in lungs causes destruction of elastic tissue giving rise to emphysema
Creutzfeld-Jacob disease	Prions	Abnormal folding of PrP^{sc} causes neuronal cell death
Alzheimer disease	A_β peptide	Abnormal folding of A_β peptides causes aggregation within neurons and apoptosis

Shown are selected illustrative examples of diseases in which protein misfolding is thought to be the major mechanism of functional derangement or cell or tissue injury.

Table 2–2 Endothelial and Leukocyte Adhesion Molecules

Endothelial Molecule	Leukocyte Molecule	Major Role(s)
Selectins and Selectin Ligands		
P-selectin	Sialyl–Lewis X–modified proteins	Rolling
E-selectin	Sialyl–Lewis X–modified proteins	Rolling and adhesion
GlyCam-1, CD34	L-selectin*	Rolling (neutrophils, monocytes)
Integrins and Integrin Ligands		
ICAM-1 (immunoglobulin family)	CD11/CD18 integrins (LFA-1, Mac-1)	Firm adhesion, arrest, transmigration
VCAM-1 (immunoglobulin family)	VLA-4 integrin	Adhesion
Others		
CD31	CD31 (homotypic interaction)	Transmigration of leukocytes through endothelium

*L-selectin is also involved in the binding of circulating lymphocytes to the high endothelial venules in lymph nodes and mucosal lymphoid tissues, and subsequent homing of lymphocytes to these tissues.

ICAM-1, intercellular adhesion molecule-1; LFA-1, leukocyte function–associated antigen-1; Mac-1, macrophage-1 antigen; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late antigen-4.

Table 2–3 Clinical Examples of Leukocyte-Induced Injury

Disorder*	Cells and Molecules Involved in Injury
Acute	
Acute respiratory distress syndrome	Neutrophils
Acute transplant rejection	Lymphocytes; antibodies and complement
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, monocytes
Septic shock	Cytokines
Chronic	
Rheumatoid arthritis	Lymphocytes, macrophages; antibodies?
Asthma	Eosinophils; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes?
Chronic transplant rejection	Lymphocytes, macrophages; cytokines
Pulmonary fibrosis	Macrophages; fibroblasts

*Listed are selected examples of diseases in which the host response plays a significant role in tissue injury. Some, such as asthma, can manifest with acute inflammation or a chronic illness with repeated bouts of acute exacerbation. These diseases and their pathogenesis are discussed in much more detail in relevant chapters.
IgE, immunoglobulin E.

Table 2–4 Defects in Leukocyte Functions

Disease	Defect
Acquired	
Bone marrow suppression: tumors (including leukemias), radiation, and chemotherapy	Production of leukocytes
Diabetes, malignancy, sepsis, chronic dialysis	Adhesion and chemotaxis
Anemia, sepsis, diabetes, malnutrition	Phagocytosis and microbicidal activity
Genetic	
Leukocyte adhesion deficiency 1	Defective leukocyte adhesion because of mutations in β chain of CD11/CD18 integrins
Leukocyte adhesion deficiency 2	Defective leukocyte adhesion because of mutations in fucosyl transferase required for synthesis of sialylated oligosaccharide (receptor for selectins)
Chronic granulomatous disease	Decreased oxidative burst
X-linked	Phagocyte oxidase (membrane component)
Autosomal recessive	Phagocyte oxidase (cytoplasmic components)
Myeloperoxidase deficiency	Decreased microbial killing because of defective MPO–H_2O_2 system
Chédiak-Higashi syndrome	Decreased leukocyte functions because of mutations affecting protein involved in lysosomal membrane traffic

H_2O_2, hydrogen peroxide; MPO, myeloperoxidase.
Modified from Gallin JI: Disorders of phagocytic cells. In Gallin JI, et al (eds): Inflammation: Basic Principles and Clinical Correlates, 2nd ed. New York, Raven Press, 1992, pp 860, 861.

diabetes (causing abnormal leukocyte functions). These are described elsewhere in the book.

The genetic disorders, although individually rare, illustrate the importance of particular molecular pathways in the complex inflammatory response. Some of the better understood inherited diseases are the following:

Table 2–5 Actions of the Principal Mediators of Inflammation

Mediator	Source(s)	Actions
Cell-Derived		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasoconstriction
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nitric oxide	Endothelium, macrophages	Vascular smooth muscle relaxation; killing of microbes
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	*Local*: endothelial activation (expression of adhesion molecules). *Systemic*: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Plasma Protein–Derived		
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (MAC), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruitment

IL-1, IL-6, interleukin-1 and -6; MAC, membrane attack complex; TNF, tumor necrosis factor.

Table 2–6 Principal Inflammatory Actions of Arachidonic Acid Metabolites (Eicosanoids)

Action	Eicosanoid
Vasodilation	Prostaglandins PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4, HETE

HETE, hydroxyeicosatetraenoic acid.

Table 2–7 Role of Mediators in Different Reactions of Inflammation

Inflammatory Component	Mediators
Vasodilation	Prostaglandins Nitric oxide Histamine
Increased vascular permeability	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Bradykinin Leukotrienes C_4, D_4, E_4 PAF Substance P
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4 Bacterial products (e.g., *N*-formyl methyl peptides)
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species Nitric oxide

IL-1, interleukin-1; PAF, platelet-activating factor; TNF, tumor necrosis factor.

Table 2–8 Examples of Diseases with Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease	Immune reaction against intestinal bacteria, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

Table 2–9 Growth Factors Involved in Regeneration and Repair

Growth Factor	Sources	Functions
Epidermal growth factor (EGF)	Activated macrophages, salivary glands, keratinocytes, and many other cells	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration; stimulates formation of granulation tissue
Transforming growth factor-α (TGF-α)	Activated macrophages, keratinocytes, many other cell types	Stimulates proliferation of hepatocytes and many other epithelial cells
Hepatocyte growth factor (HGF) (scatter factor)	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility
Vascular endothelial growth factor (VEGF)	Mesenchymal cells	Stimulates proliferation of endothelial cells; increases vascular permeability
Platelet-derived growth factor (PDGF)	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis
Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis
Transforming growth factor-β (TGF-β)	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation
Keratinocyte growth factor (KGF) (i.e., FGF-7)	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

ECM, extracellular membrane.

Table 2–10 Principal Signaling Pathways Used by Cell Surface Receptors

Receptor Class	Ligands	Signaling Mechanism(s)
Receptors with intrinsic tyrosine kinase activity	EGF, VEGF, FGF, HGF	Ligand binding to one chain of the receptor activates tyrosine kinase on the other chain, resulting in activation of multiple downstream signaling pathways (RAS-MAP kinase, PI-3 kinase, PLC-γ) and activation of various transcription factors.
G protein–coupled seven-transmembrane receptors (GPCRs)	Multiple inflammatory mediators, hormones, all chemokines	Ligand binding induces switch from GDP-bound inactive form of associated G protein to GTP-bound active form; activates cAMP; Ca^{2+} influx leading to increased cell motility; multiple other effects.
Receptors without intrinsic enzymatic activity	Many cytokines including interferons, growth hormone, CSFs, EPO	Ligand binding recruits kinases (e.g., Janus kinases [JAKs]) that phosphorylate and activate transcription factors (e.g., signal transducers and activators of transcription [STATs]).

cAMP, cyclic adenosine monophosphate; CSFs, colony-stimulating factors; EGF, epidermal growth factor; EPO, epopoietin; FGF, fibroblast growth factor; GDP, guanosine diphosphate; GTP, guanosine triphosphate; HGF, hepatocyte growth factor; PI3, phosphatidylinositol-3; PLC-γ, phospholipase Cγ; MAP, microtubule-associated protein; VEGF, vascular endothelial growth factor.

Table 3–1 Pathophysiologic Causes of Edema

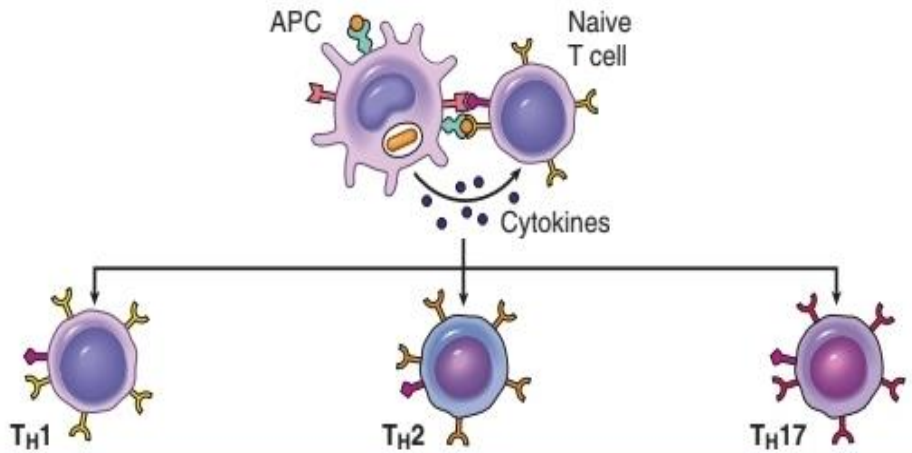
Increased Hydrostatic Pressure
Impaired Venous Return
Congestive heart failure
Constrictive pericarditis
Ascites (liver cirrhosis)
Venous obstruction or compression
Thrombosis
External pressure (e.g., mass)
Lower extremity inactivity with prolonged dependency
Arteriolar Dilation
Heat
Neurohumoral dysregulation
Reduced Plasma Osmotic Pressure (Hypoproteinemia)
Protein-losing glomerulopathies (nephrotic syndrome)
Liver cirrhosis (ascites)
Malnutrition
Protein-losing gastroenteropathy
Lymphatic Obstruction
Inflammatory
Neoplastic
Postsurgical
Postirradiation
Sodium Retention
Excessive salt intake with renal insufficiency
Increased tubular reabsorption of sodium
Renal hypoperfusion
Increased renin-angiotensin-aldosterone secretion
Inflammation
Acute inflammation
Chronic inflammation

Table 3–2 Hypercoagulable States

Primary (Genetic)
Common (>1% of the Population)
Factor V mutation (G1691A mutation; factor V Leiden) Prothrombin mutation (G20210A variant) 5,10-Methylene tetrahydrofolate reductase (homozygous C677T mutation) Increased levels of factor VIII, IX, or XI or fibrinogen
Rare
Antithrombin III deficiency Protein C deficiency Protein S deficiency
Very Rare
Fibrinolysis defects Homozygous homocystinuria (deficiency of cystathione β-synthetase)
Secondary (Acquired)
High Risk for Thrombosis
Prolonged bed rest or immobilization Myocardial infarction Atrial fibrillation Tissue injury (surgery, fracture, burn) Cancer Prosthetic cardiac valves Disseminated intravascular coagulation Heparin-induced thrombocytopenia Antiphospholipid antibody syndrome
Lower Risk for Thrombosis
Cardiomyopathy Nephrotic syndrome Hyperestrogenic states (pregnancy and postpartum) Oral contraceptive use Sickle cell anemia Smoking

Table 3–3 Three Major Types of Shock

Type of Shock	Clinical Examples	Principal Pathogenic Mechanisms
Cardiogenic	Myocardial infarction Ventricular rupture Arrhythmia Cardiac tamponade Pulmonary embolism	Failure of myocardial pump resulting from intrinsic myocardial damage, extrinsic pressure, or obstruction to outflow
Hypovolemic	Hemorrhage Fluid loss (e.g., vomiting, diarrhea, burns, trauma)	Inadequate blood or plasma volume
Septic	Overwhelming microbial infections Endotoxic shock Gram-positive septicemia Fungal sepsis Superantigens (e.g., toxic shock syndrome)	Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage; disseminated intravascular coagulation; activation of cytokine cascades



	T_H1	T_H2	T_H17
Cytokines produced	IFN-γ	IL-4, IL-5, IL-13	IL-17, IL-22, chemokines
Cytokines that induce this subset	IFN-γ, IL-12	IL-4	TGF-β, IL-6, IL-1, IL-23
Immunologic reactions triggered	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
Host defense against	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
Role in disease	Immune-mediated chronic inflammatory diseases (often autoimmune)	Allergies	Immune-mediated chronic inflammatory diseases (often autoimmune)

Figure 4–5 Subsets of CD4+ effector T cells. In response to stimuli (mainly cytokines) present at the time of antigen recognition, naive CD4+ helper T cells may differentiate into populations of effector cells that produce distinct sets of cytokines and perform different functions. The types of immune reactions elicited by each subset, and its role in host defense and immunological diseases, are summarized. Two other populations of CD4+ T cells, regulatory cells and follicular helper cells, are not shown.

Table 4–1 Mechanisms of 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

IgE, IgG, IgM, immunoglobulins E, G, M.

Table 4–2 Summary of the Action of Mast Cell Mediators in Immediate (Type I) Hypersensitivity

Action	Mediators
Vasodilation, increased vascular permeability	Histamine PAF Leukotrienes C_4, D_4, E_4 Neutral proteases that activate complement and kinins Prostaglandin D_2
Smooth muscle spasm	Leukotrienes C_4, D_4, E_4 Histamine Prostaglandins PAF
Cellular infiltration	Cytokines (e.g., chemokines, TNF) Leukotriene B_4 Eosinophil and neutrophil chemotactic factors (not defined biochemically)

PAF, platelet-activating factor; TNF, tumor necrosis factor.

Table 4–3 Examples of Antibody-Mediated Diseases (Type II Hypersensitivity)

Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Red cell membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (GpIIb/IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal desmoglein)	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 (NC1) 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
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, downmodulates 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	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal myelopoiesis, anemia

ANCA, antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

Table 4–5 T Cell–Mediated Diseases*

Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury	Clinicopathologic Manifestations
Rheumatoid arthritis	Collagen?; citrullinated 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 and bone
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, ocular lesions
Type I diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation, destruction of islet cells by CTLs	Insulitis (chronic inflammation in islets), destruction of β cells; diabetes
Hashimoto thyroiditis	Thyroglobulin, other thyroid proteins	Inflammation, CTL-mediated killing of thyroid epithelial cells	Hypothyroidism
Inflammatory bowel disease	Enteric bacteria; self antigens?	Inflammation mediated mainly by T_H17 cytokines	Chronic intestinal inflammation, ulceration, obstruction
Autoimmune myocarditis	Myosin heavy chain protein	CTL-mediated killing of myocardial cells; inflammation mediated by T_H1 cytokines	Cardiomyopathy
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 with skin rash and blisters

*Examples of human T cell–mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue injury are inferred on the basis of similarity to experimental animal models of the diseases.
CNS, central nervous system; CTL, cytotoxic T lymphocyte.

Table 4–6 Autoimmune Diseases

Organ-Specific	Systemic
Diseases Mediated by Antibodies	
Autoimmune hemolytic anemia	Systemic lupus erythematosus
Autoimmune thrombocytopenia	
Autoimmune atrophic gastritis of pernicious anemia	
Myasthenia gravis	
Graves disease	
Goodpasture syndrome	
Diseases Mediated by T Cells*	
Type I diabetes mellitus	Rheumatoid arthritis
Multiple sclerosis	Systemic sclerosis (scleroderma)
Hashimoto thyroiditis	Sjögren syndrome
Crohn disease	
Diseases Postulated to Be of Autoimmune Origin†	
Primary biliary cirrhosis	Polyarteritis nodosa
Autoimmune (chronic active) hepatitis	Inflammatory myopathies

*A role for T cells has been demonstrated in these disorders, but antibodies also may be involved in tissue injury.
†An autoimmune basis for these disorders is suspected, but the supporting evidence is not strong.

Table 4–7 Association of Human Leukocyte Antigen (HLA) Alleles with Autoimmune Diseases

Disease	HLA Allele	Odds Ratio*
Rheumatoid arthritis (anti-CCP Ab–positive)†	DRB1	4–12
Type 1 diabetes	DRB1*0301-DQA1*0501-DQB1*0201 haplotype	4
	DRB1*0401- DQA1*0301-DQB1*0302 haplotype	8
	DRB1*0301/0401 haplotype heterozygotes	35
Multiple sclerosis	DRB1*1501	3
Systemic lupus erythematosus	DRB1*0301	2
	DRB1*1501	1.3
Ankylosing spondylitis	B*27 (mainly B*2705 and B*2702)	100–200
Celiac disease	DQA1*0501-DQB1*0201 haplotype	7

*The *odds ratio* (also called *relative risk*) is the approximate value of the increased risk of the disease associated with the inheritance of particular HLA alleles. The data are from European-derived populations.

†Anti-CCP Ab, antibodies directed against cyclic citrullinated peptides. Data are from patients who tested positive for these antibodies in serum.

Table courtesy of Dr. Michelle Fernando, Imperial College London.

Table 4–8 Selected Non–Human Leukocyte Antigen (HLA) Genes Associated with Autoimmune Diseases

Putative Gene Involved*	Diseases	Postulated Function of Encoded Protein and Role of Mutation/Polymorphism in Disease
Genes Involved in Immune Regulation		
PTPN22	RA, T1D, IBD	Protein tyrosine phosphatase, may affect signaling in lymphocytes and may alter negative selection or activation of self-reactive T cells
IL23R	IBD, PS, AS	Receptor for the T_H17-inducing cytokine IL-23; may alter differentiation of CD4+ T cells into pathogenic T_H17 effector cells
CTLA4	T1D, RA	Inhibits T cell responses by terminating activation and promoting activity of regulatory T cells; may interfere with self-tolerance
IL2RA	MS, T1D	α chain of the receptor for IL-2, which is a growth and survival factor for activated and regulatory T cells; may affect development of effector cells and/or regulation of immune responses
Genes Involved in Immune Responses to Microbes		
NOD2	IBD	Cytoplasmic sensor of bacteria expressed in Paneth and other intestinal epithelial cells; may control resistance to gut commensal bacteria
ATG16	IBD	Involved in autophagy; possible role in defense against microbes and maintenance of epithelial barrier function
IRF5, IFIH1	SLE	Role in production of type I IFN, involved in the pathogenesis of SLE (see text)

*The probable linkage of these genes with various autoimmune diseases has been defined by genome-wide association studies (GWAS) and other methods for studying disease-associated polymorphisms.

AS, ankylosing spondylitis; IBD, inflammatory bowel disease; IFN, interferon; MS, multiple sclerosis; PS, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes.

Adapted from Zenewicz L, Abraham C, Flavell RA, Cho J: Unraveling the genetics of autoimmunity. Cell 140:791, 2010.

Table 4–9 1997 Revised Criteria for Classification of Systemic Lupus Erythematosus*

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 occurring as an unusual reaction to sunlight, reported in patient history or as 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—$<4.0 \times 10^9$/L ($4000/mm^3$) total on two or more occasions *or* Lymphopenia—$<1.5 \times 10^9$/L ($1500/mm^3$) on two or more occasions *or* Thrombocytopenia—$<100 \times 10^9$/L ($100 \times 10^3/mm^3$) 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 *Treponema pallidum* 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

*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person is said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any period of observation.

From Tan EM, Cohen AS, Fries JF, et al: The revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271, 1982; and Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725, 1997.

Table 4–10 Selected Autoantibodies Associated with Presumed Autoimmune Diseases

Autoantibody (Specificity)	Major Disease Association(s)	Likely Role(s) in Disease
Anti-dsDNA (double-stranded DNA)	SLE*	Formation of immune complexes
Anti-Sm (ribonuclear core protein, Sm antigen)	SLE*	Formation of immune complexes
Anti-RNP U1 (ribonuclear protein)	SLE, mixed connective tissue disease	Formation of immune complexes
Anti–SS-A (Ro), anti–SS-B (La) (ribonucleoproteins)	Sjögren syndrome, SLE	Role in Sjögren syndrome not known
Anti–Scl-70 (DNA topoisomerase I)	Systemic sclerosis*	Unknown
Anti-histones (histone proteins)	SLE	Formation of immune complexes
Anti-centromere (centromere proteins)	Limited scleroderma, systemic sclerosis*	Unknown
Antiphospholipid (phospholipid–protein complexes involved in blood coagulation)	Antiphospholipid syndrome, SLE	Thrombotic episodes
Anti-Jo1 (histidyl tRNA ligase)	Inflammatory myopathies*	Unknown
Anti-mitochondrial	Primary biliary cirrhosis*	Unknown
Anti-eTg (transglutaminase)	Dermatitis herpetiformis	Unknown
Anti–neutrophil cytoplasmic antibody (ANCA) (proteins in neutrophil cytoplasm)	Various vasculitides*	Formation of immune complexes? Neutrophil degranulation?
Anti–smooth muscle	Chronic autoimmune hepatitis	Unknown

Each antibody specificity is detected in 30% to 90% of patients with a particular disease. Asterisks indicate high correlation between the antibody specificity and the disease.

SLE, systemic lupus erythematosus.

Table 4–11 Major Abnormalities of Immune Function in AIDS

Lymphopenia
Predominantly caused by selective loss of the CD4+ helper T cell subset; reduced CD4+/CD8+ ratio
Decreased T Cell Function in vivo
Preferential loss of activated and memory T cells Decreased delayed-type hypersensitivity Susceptibility to opportunistic infections Susceptibility to neoplasms
Altered T Cell Function in vitro
Decreased proliferative response to mitogens, alloantigens, and soluble antigens Decreased cytotoxicity Decreased helper function for B cell antibody production Decreased interleukin-2 and interferon-γ production
Polyclonal B Cell Activation
Hypergammaglobulinemia and circulating immune complexes Inability to mount de novo antibody response to a new antigen Poor responses to normal signals for B cell activation in vitro
Altered Monocyte or Macrophage Functions
Decreased chemotaxis and phagocytosis Decreased HLA class II antigen expression Diminished capacity to present antigen to T cells Increased spontaneous secretion of interleukin-1, tumor necrosis factor, interleukin-6

HLA, human leukocyte antigen.

Table 4–12 AIDS-Defining Opportunistic Infections and Neoplasms Found in Patients with Human Immunodeficiency Virus (HIV) infection

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.

Table 4–13 Classification of Amyloidosis

Clinicopathologic Category	Associated Disease(s)	Major Fibril Protein	Chemically Related Precursor Protein
Systemic (Generalized) Amyloidosis			
Immunocyte dyscrasias with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal plasma cell proliferations	AL	Immunoglobulin light chains, chiefly λ type
Reactive systemic amyloidosis (secondary amyloidosis)	Chronic inflammatory conditions	AA	SAA
Hemodialysis-associated amyloidosis	Chronic renal failure	$A\beta_2m$	β_2-Microglobulin
Hereditary Amyloidosis			
Familial Mediterranean fever		AA	SAA
Familial amyloidotic neuropathies (several types)		ATTR	Transthyretin
Systemic senile amyloidosis		ATTR	Transthyretin
Localized Amyloidosis			
Senile cerebral	Alzheimer disease	Aβ	APP
Endocrine			
Medullary carcinoma of thyroid		A Cal	Calcitonin
Islets of Langerhans	Type 2 diabetes	AIAPP	Islet amyloid peptide
Isolated atrial amyloidosis		AANF	Atrial natriuretic factor

Table 5–1 Nomenclature of Tumors

Tissue of Origin	Benign	Malignant
Composed of One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
Endothelial and related tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Tumors of epithelial origin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Urothelial papilloma	Urothelial carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma
More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived from One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)	Malignant mixed tumor of salivary gland
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived from More Than One Germ Cell Layer—Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Table 5–2 Occupational Cancers

Agent/Group of Agents	Human Cancer Site and Type for Which Reasonable Evidence Is Available	Typical Use/Occurrence
Arsenic and arsenic compounds	Lung, skin, hemangiosarcoma	Byproduct of metal smelting Component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, mesothelioma; gastrointestinal tract (esophagus, stomach, large intestine)	Formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire-resistant textiles, friction materials (e.g., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Leukemia	Principal component of light oil Many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents Formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung	Missile fuel and space vehicles Hardener for lightweight compounds metal alloys, particularly in aerospace applications and nuclear reactors
Cadmium and cadmium compounds	Prostate	Uses include yellow pigments and phosphors Found in solders Used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung	Component of metal alloys, paints, pigments, and preservatives
Ethylene oxide	Leukemia	Ripening agent for fruits and nuts Used in rocket propellant and chemical synthesis, in fumigants for foodstuffs and textiles, and in sterilants for hospital equipment
Nickel compounds	Nose, lung	Nickel plating Component of ferrous alloys, ceramics, and batteries Byproduct of stainless steel arc welding
Radon and its decay products	Lung	From decay of minerals containing uranium Can be serious hazard in quarries and mines
Vinyl chloride	Angiosarcoma, liver	Refrigerant Monomer for vinyl polymers Adhesive for plastics Formerly used as inert aerosol propellant in pressurized containers

Modified from Stellman JM, Stellman SD: Cancer and workplace. CA Cancer J Clin 46:70–92, 1996, with permission from Lippincott Williams & Wilkins.

Table 5–3 Inherited Predisposition to Cancer

Autosomal Dominant Cancer Syndromes	
Gene(s)	**Inherited Predisposition**
RB	Retinoblastoma
TP53	Li-Fraumeni syndrome (various tumors)
p16INK4A	Melanoma
APC	Familial adenomatous polyposis/colon cancer
NF1, NF2	Neurofibromatosis 1 and 2
BRCA1, BRCA2	Breast and ovarian tumors
MEN1, RET	Multiple endocrine neoplasia 1 and 2
MSH2, MLH1, MSH6	Hereditary nonpolyposis colon cancer
PATCH	Nevoid basal cell carcinoma syndrome
Autosomal Recessive Syndromes of Defective DNA Repair	
Xeroderma pigmentosum Ataxia-telangiectasia Bloom syndrome Fanconi anemia	
Familial Cancers of Uncertain Inheritance	
Breast cancer (not linked to *BRCA1* or *BRCA2*) Ovarian cancer Pancreatic cancer	

Table 5–4 Major Chemical Carcinogens

Direct-Acting Carcinogens
Alkylating Agents
β-Propiolactone Dimethyl sulfate Diepoxybutane Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
Acylating Agents
1-Acetyl-imidazole Dimethylcarbamyl chloride
Procarcinogens That Require Metabolic Activation
Polycyclic and Heterocyclic Aromatic Hydrocarbons
Benz(*a*)anthracene Benzo(*a*)pyrene Dibenz(*a*,*h*)anthracene 3-Methylcholanthrene 7, 12-Dimethylbenz(*a*)anthracene
Aromatic Amines, Amides, Azo Dyes
2-Naphthylamine (β-naphthylamine) Benzidine 2-Acetylaminofluorene Dimethylaminoazobenzene (butter yellow)
Natural Plant and Microbial Products
Aflatoxin B_1 Griseofulvin Cycasin Safrole Betel nuts
Others
Nitrosamine and amides Vinyl chloride, nickel, chromium Insecticides, fungicides Polychlorinated biphenyls

Table 5–5 Paraneoplastic Syndromes

Clinical Syndrome	Major Forms of Neoplasia	Causal Mechanism(s)/Agent(s)
Endocrinopathies		
Cushing syndrome	Small cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	Small cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T cell leukemia/lymphoma Ovarian carcinoma	Parathyroid hormone–related protein, TGF-α, TNF, IL-1
Hypoglycemia	Fibrosarcoma Other mesenchymal sarcomas Hepatocellular carcinoma	Insulin or insulin-like substance
Carcinoid syndrome	Bronchial adenoma (carcinoid) Pancreatic carcinoma Gastric carcinoma	Serotonin, bradykinin
Polycythemia	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
Nerve and Muscle Syndrome		
Myasthenia	Bronchogenic carcinoma, thymoma	Immunologic
Disorders of the central and peripheral nervous systems	Breast carcinoma, teratoma	
Dermatologic Disorders		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunologic; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic and breast carcinoma	Immunologic
Osseous, Articular, and Soft Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Anemia	Thymoma	Immunologic
Others		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

ACTH, adrenocorticotropic hormone; IL-1, interleukin-1; TGF-α, transforming growth factor-α; TNF, tumor necrosis factor.