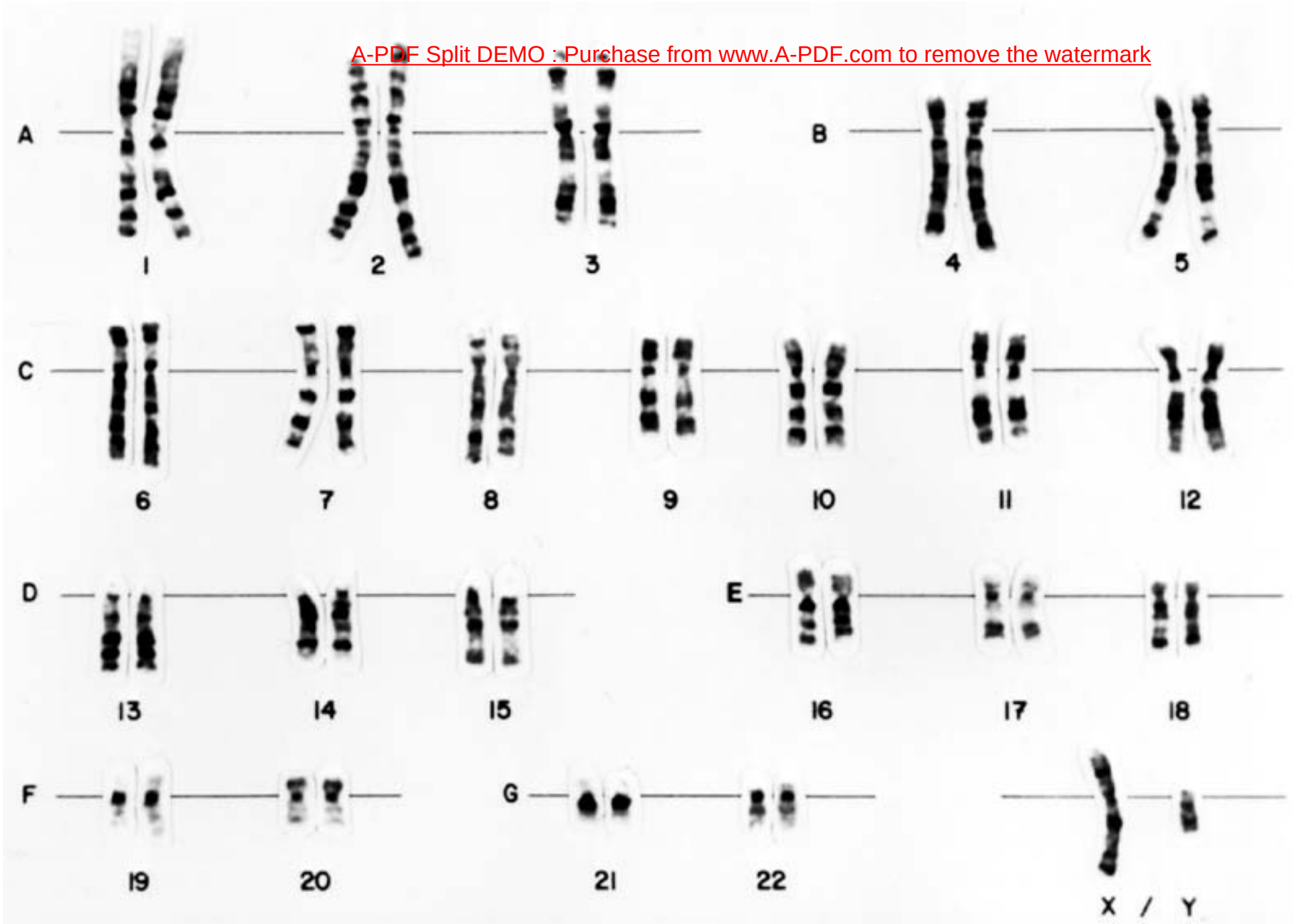


Figure 5-21 Details of banding pattern of the X chromosome (also called "idiogram"). Note the nomenclature of arms, regions, bands, and sub-bands. On the right side, the approximate locations of some genes that cause disease are indicated.

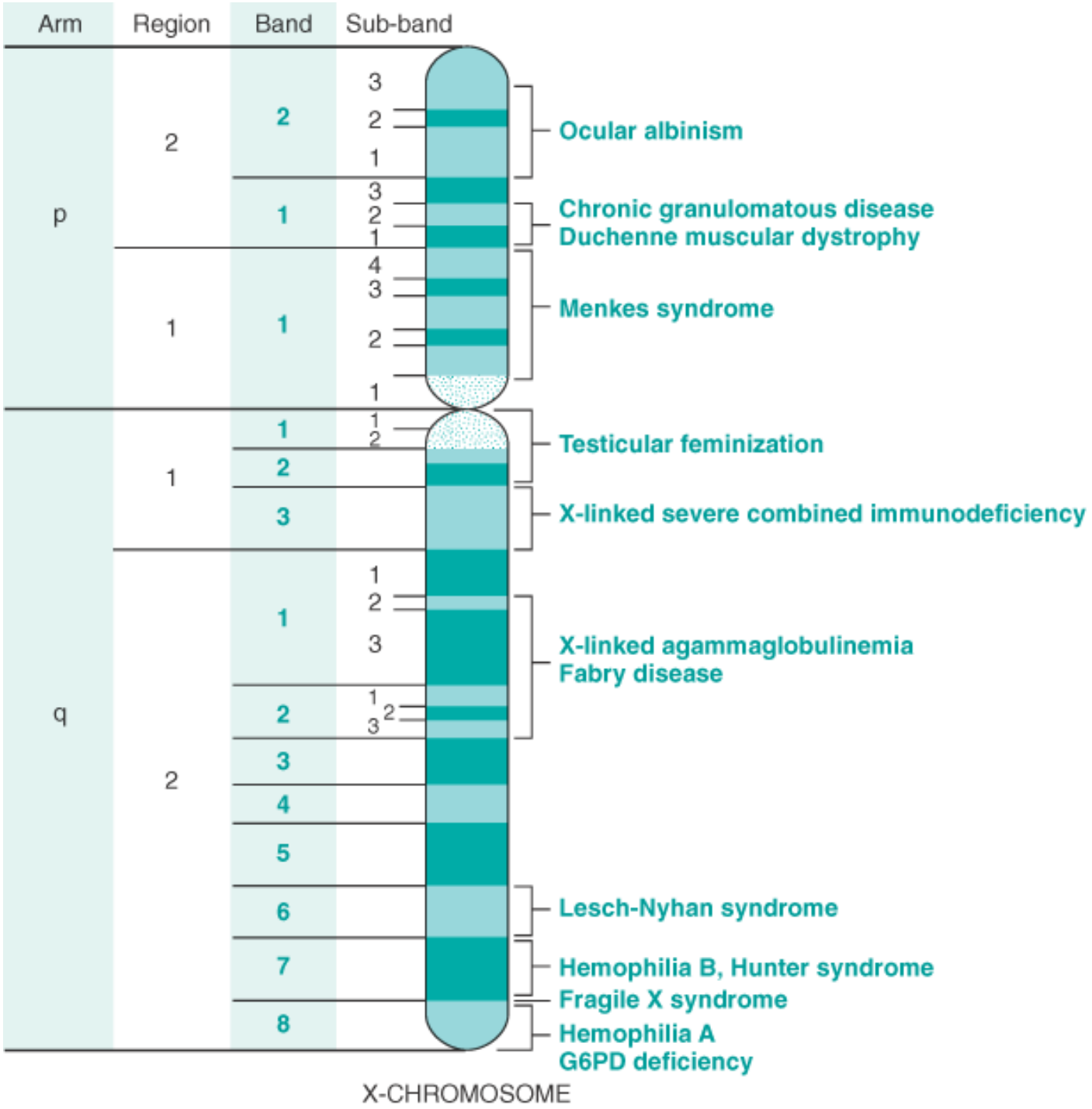


Figure 5-22 Fluorescence in situ hybridization (FISH). Interphase nuclei of a childhood hepatic cancer (hepatoblastoma) stained with a fluorescent DNA probe that hybridizes to chromosome 20. Under ultraviolet light, each nucleus reveals three bright yellow fluorescent dots, representing three copies of chromosome 20. Normal diploid cells *(not shown)* have two

fluorescent dots. *(Courtesy of Dr. Vijay Tonk, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX.)*

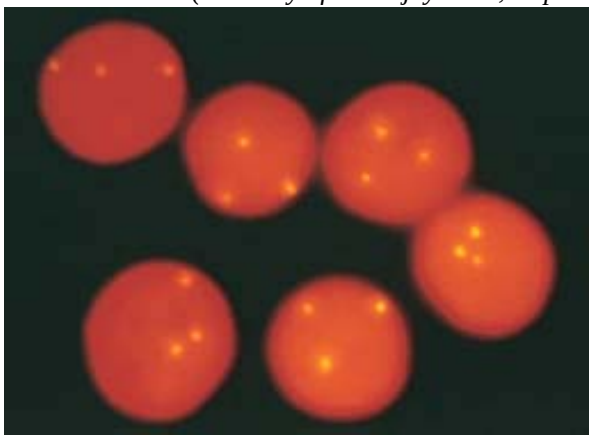


Figure 5-23 FISH. A metaphase spread in which two fluorescent probes, one for the terminal ends of chromosome 22 and the other for the D22S75 locus, which maps to chromosome 22, have been used. The terminal ends of the two chromosomes 22 have been labeled. One of the two chromosomes does not stain with the probe for the D22S75 locus, indicating a microdeletion in this region. This deletion gives rise to the 22q11.2 deletion syndrome. *(Courtesy of Dr. Nancy Schneider, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX.)*

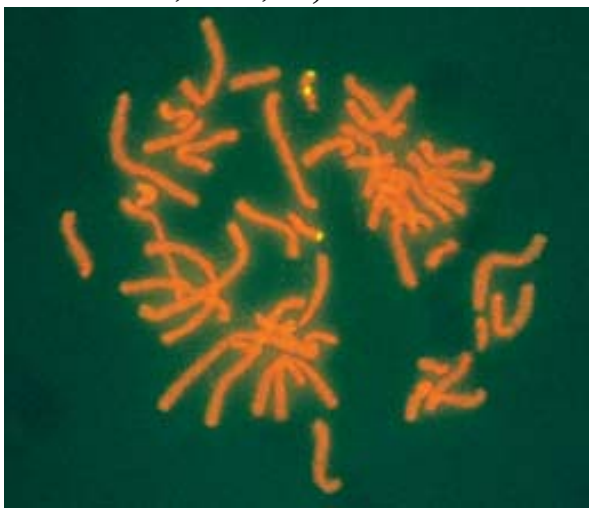


Figure 5-24 Chromosome painting with a library of chromosome 22-specific DNA probes. The presence of three fluorescent chromosomes indicates that the patient has trisomy 22. *(Courtesy of Dr. Charleen M. Moore, The University of Texas Health Science Center at San Antonio, TX.)*

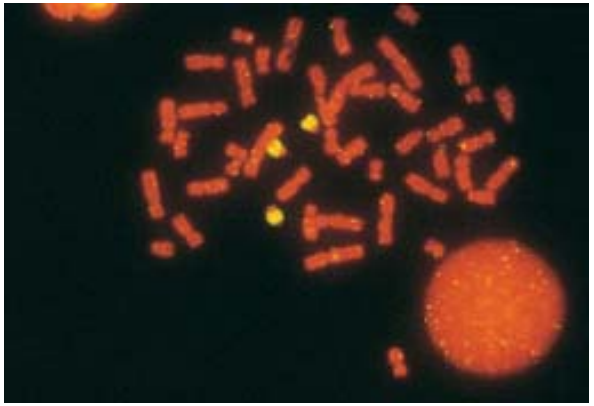


Figure 5-25 Spectral karyotype. *(Courtesy of Dr. Janet D. Rowley, University of Chicago Pritzker Medical School, Chicago, IL.)*

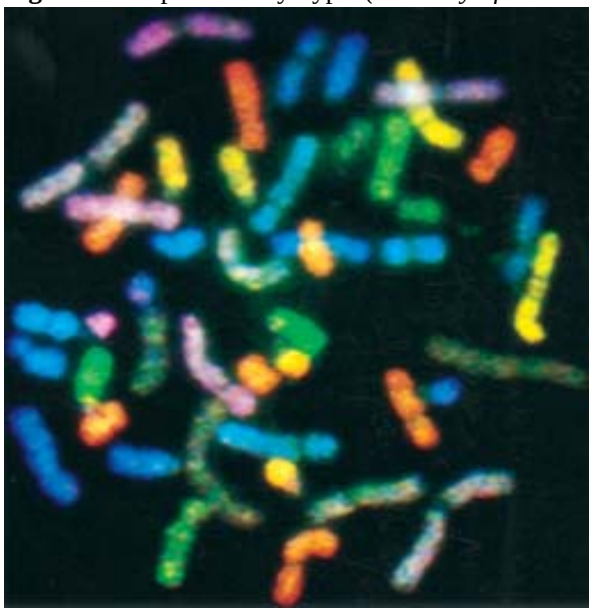


Figure 5-26 Types of chromosomal rearrangements.

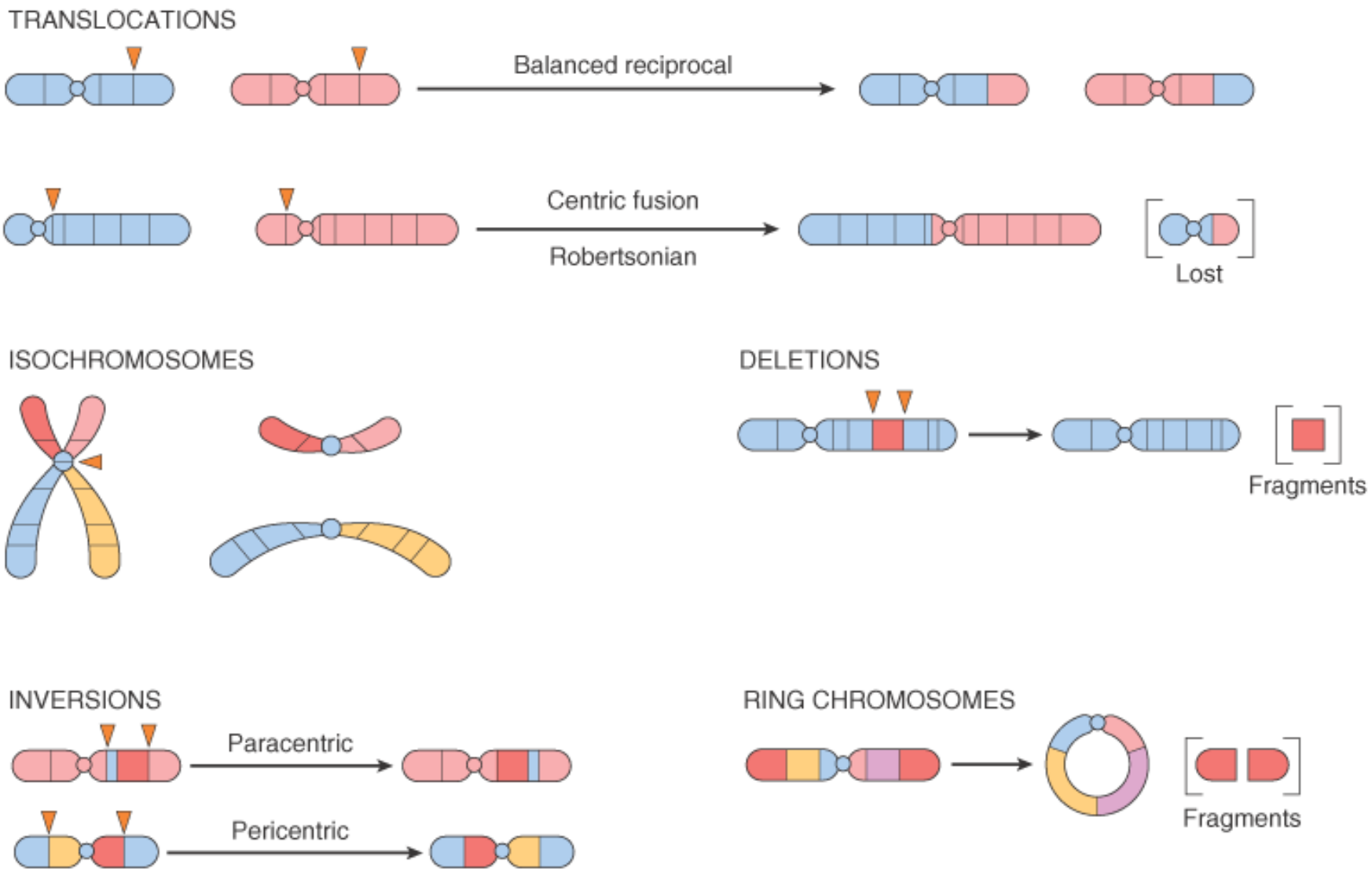


Figure 5-27 G banded karyotype of a male with trisomy 21. *(Courtesy of Dr. Nancy Schneider, University of Texas Southwestern Medical Center, Dallas, TX.)*

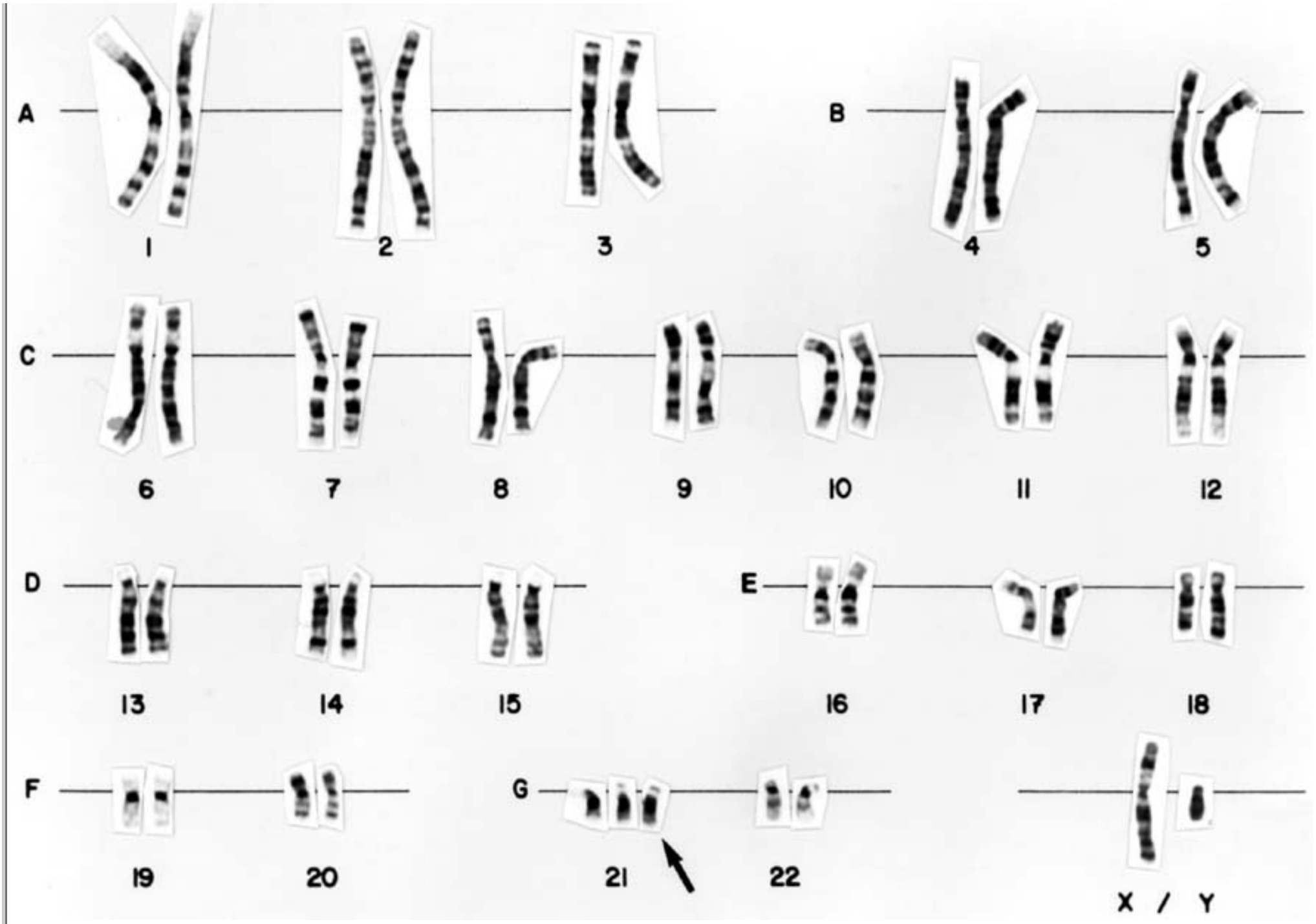
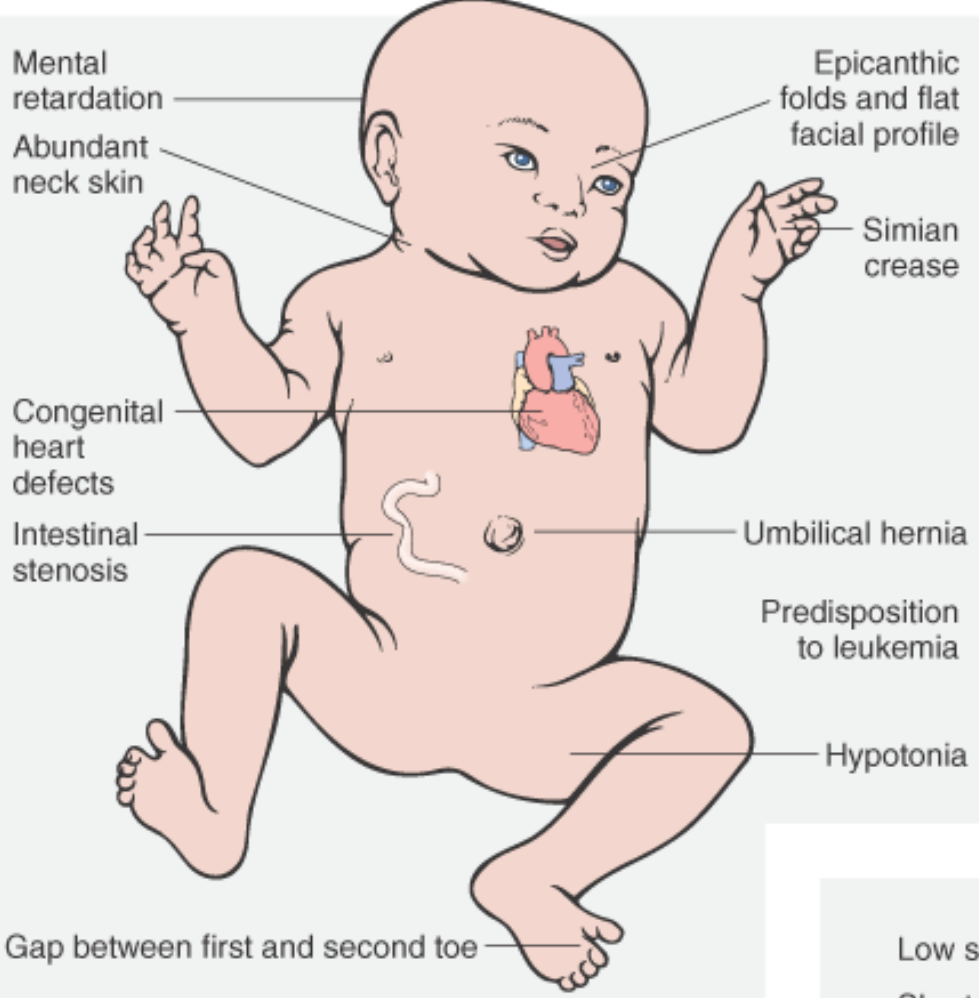


Figure 5-28 Clinical features and karyotypes of selected autosomal trisomies.

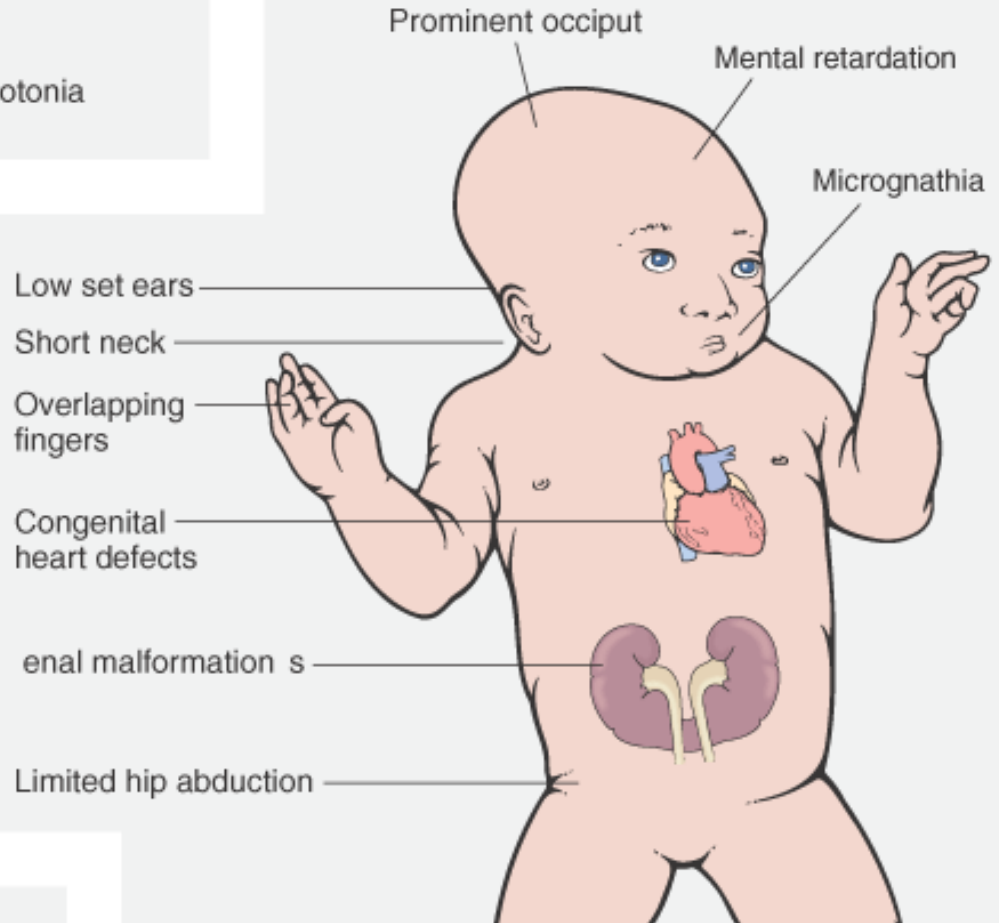


TRISOMY 21: DOWN SYNDROME

Incidence: 1 in 700 births

Karyotypes:

Trisomy 21 type:	47,XX, +21
Translocation type:	46,XX,der(14;21)(q10;q10),+21
Mosaic type:	46,XX/47,XX, +21



TRISOMY 18: EDWARDS SYNDROME

Incidence: 1 in 8000 births

Karyotypes:

Trisomy 18 type:	47,XX, +18
Mosaic type:	46,XX/47,XX, +18

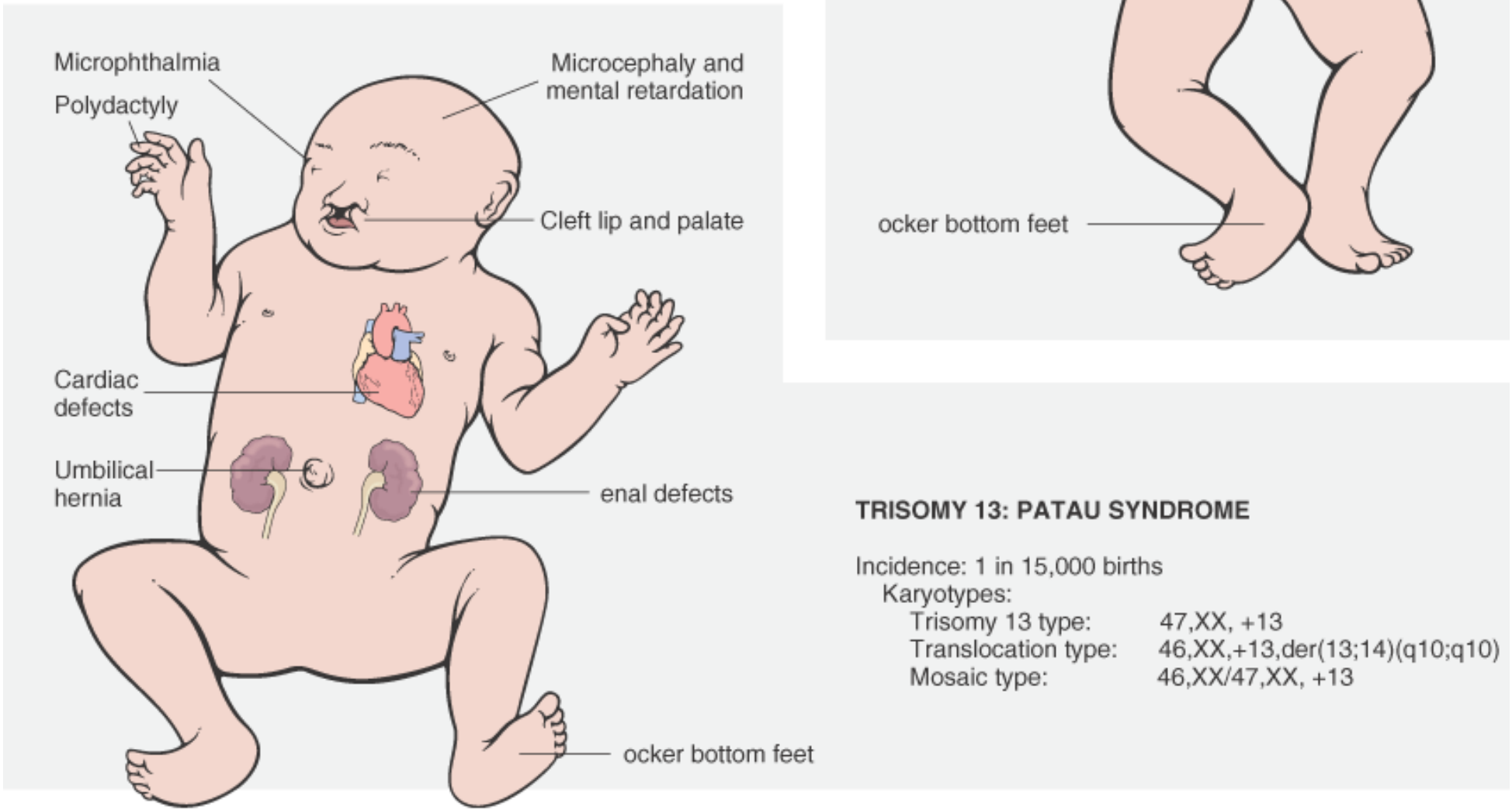


Figure 5-29 Clinical features and karyotypes of Turner syndrome.

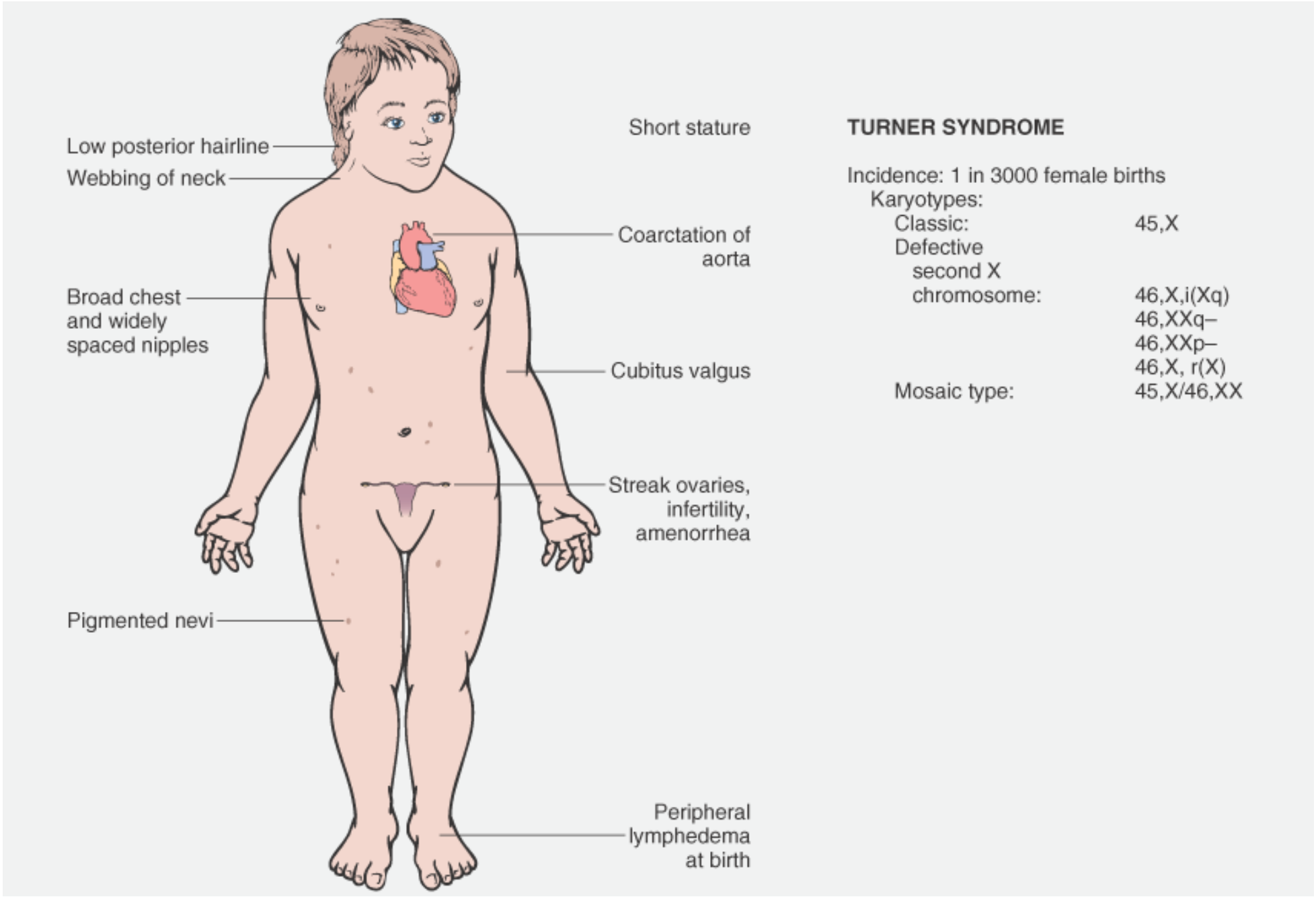


Figure 5-30 Turner syndrome critical regions and (candidate) genes. *SHOX*, short homeobox gene; *EIF1AX*, eukaryotic initiation factor 1A; *ZFX*, zinc finger X (transcription factor); *USP9X*, homologue of *Drosophila* gene involved in öogenesis; *DBX*, dead box polypeptide 3,X, a spermatogenesis gene; *UTX*, ubiquitously transcribed tetratricopeptide repeat gene, X chromosome; *SMCX*, homologue of the Y-encoded male antigen HY; *RPS4X* isoform of ribosomal protein S4 involved in lymphatic development. *(Courtesy of Dr. Andrew Zinn, University of Texas Southwestern Medical School, Dallas, TX.)*

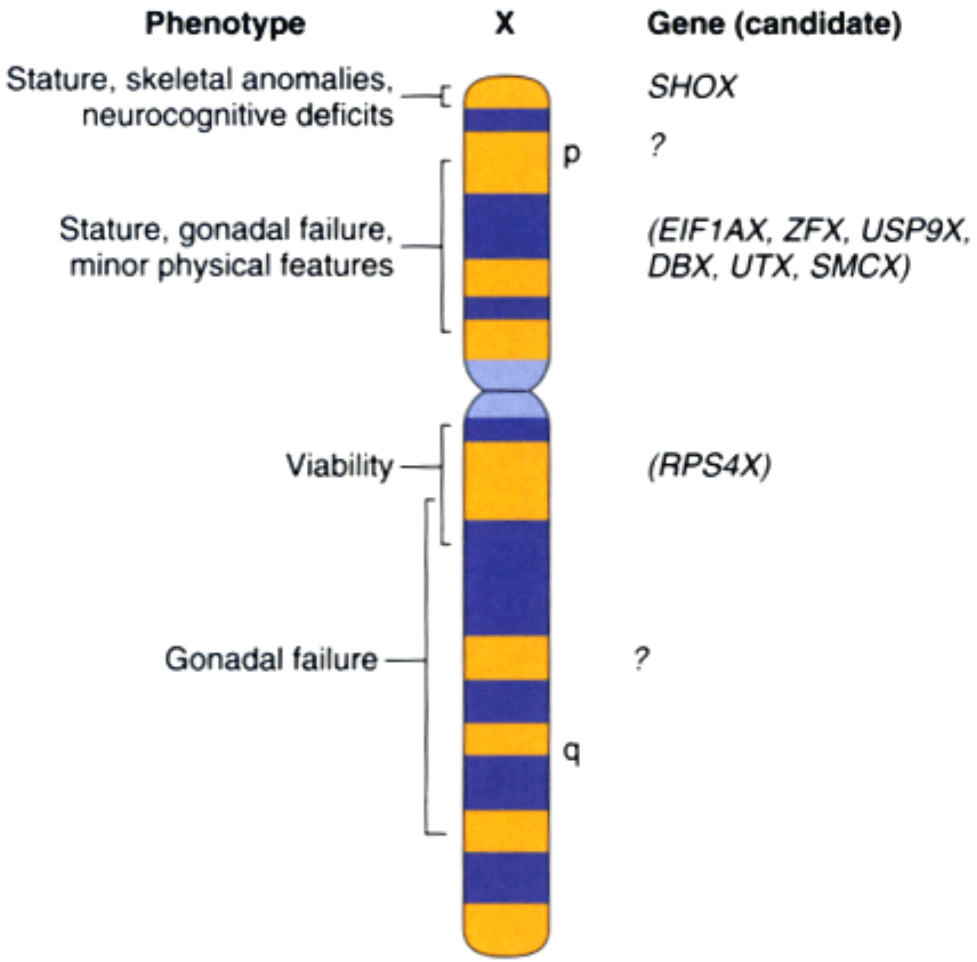


Figure 5-31 Fragile-X, seen as discontinuity of staining. *(Courtesy of Dr. Patricia Howard-Peebles, University of Texas Southwestern Medical Center, Dallas, TX.)*

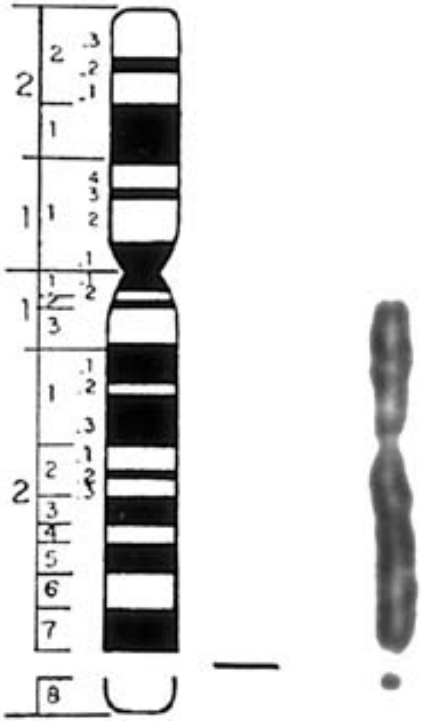


Figure 5-32 Fragile-X pedigree. Note that in the first generation all sons are normal and all females are carriers. During oogenesis in the carrier female, premutation expands to full mutation; hence in the next generation, all males who inherit the X with full mutation are affected. However, only 50% of females who inherit the full mutation are affected, and only mildly. *(Courtesy of Dr. Nancy Schneider, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX.)*

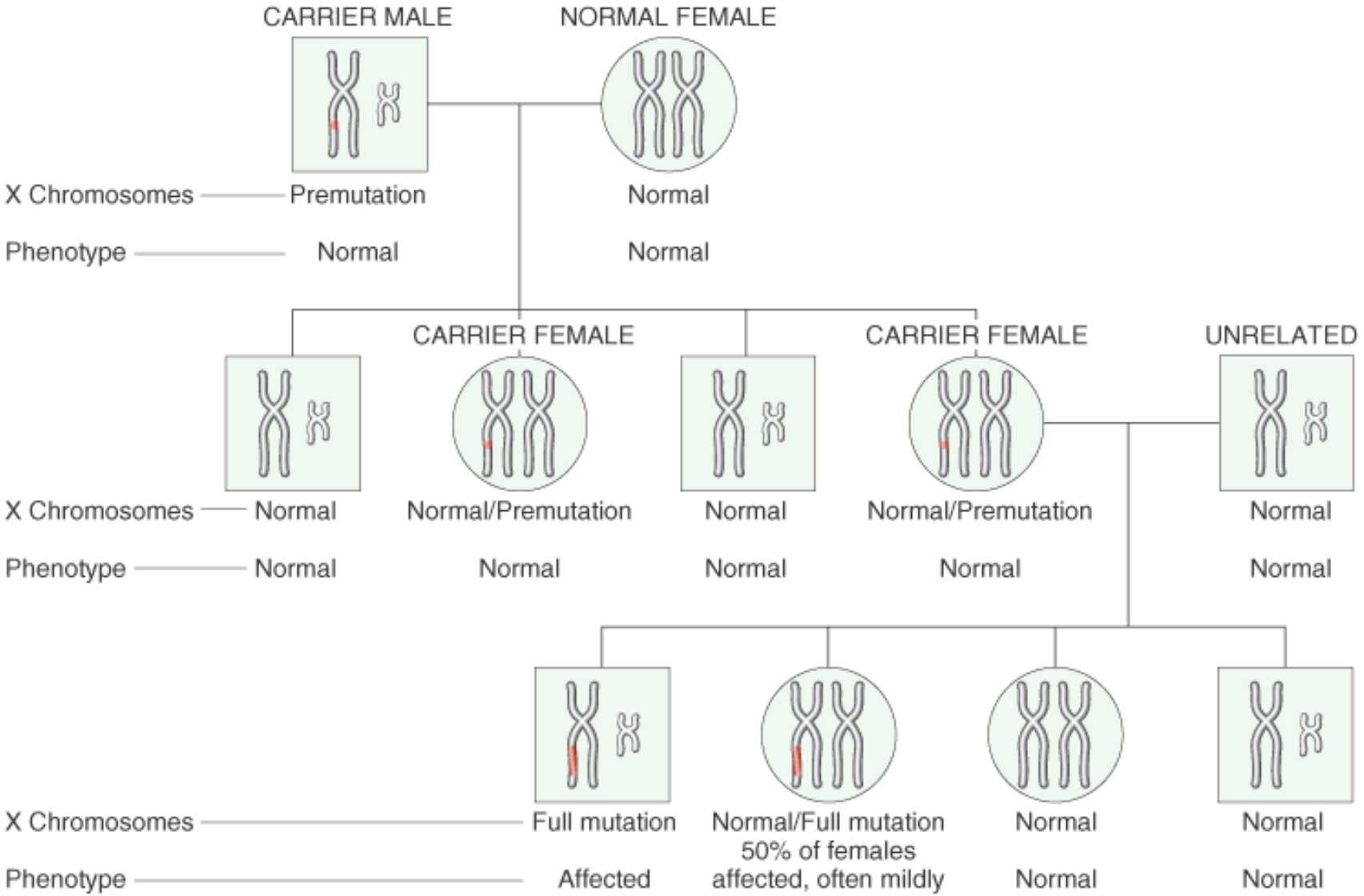


Figure 5-33 A model for the action of familial mental retardation protein (FMRP) in neurons. *(Adapted from Hin P, Warren ST: New insights into fragile-X syndrome: from molecules to neurobehavior. Trends Biochem Sci 28:152, 2003.)*

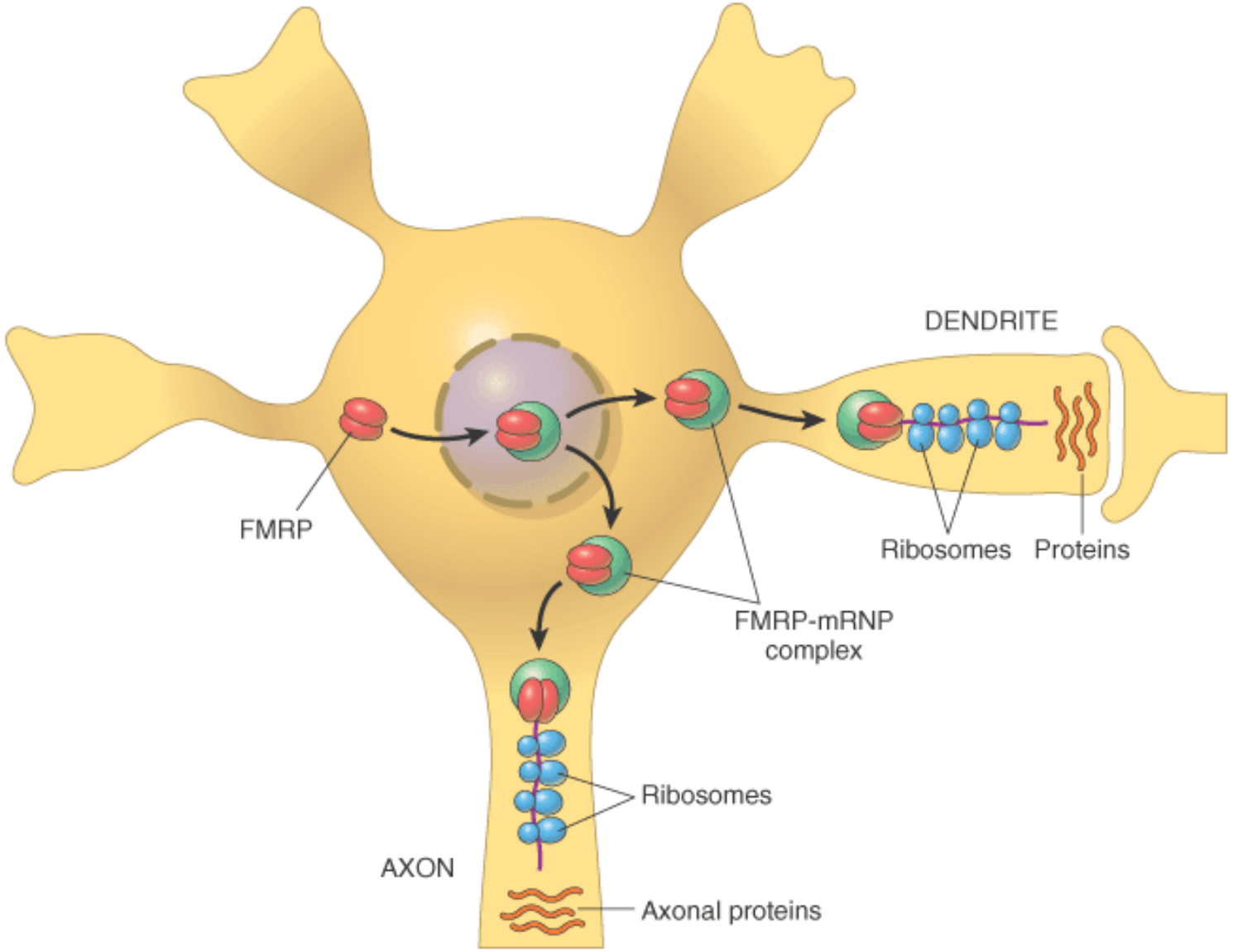


TABLE 5-9 -- Summary of Trinucleotide Repeat Disorders

Disease	Gene	Locus	Protein	Repeat	Normal	Disease
Expansions Affecting Noncoding Regions						
Fragile-X syndrome	*FMRI(FRAXA)*	Xq27.3	FMR-1 protein (FMRP)	CGG	6–53	60–200 (pre) >230 (full)
Friedreich ataxia	*X25*	9q13-21.1	Frataxin	GAA	7–34	34–80 (pre) >100 (full)

Myotonic dystrophy	*DMPK*	19q13	Myotonic dystrophy protein kinase (DMPK)	CTG	5–37	50-thousands
Expansions Affecting Coding Regions						
Spinobulbar muscular atrophy (Kennedy disease)	*AR*	Xq13-21	Androgen receptor (AR)	CAG	9–36	38–62
Huntington disease	*HD*	4p16.3	Huntingtin	CAG	6–35	36–121
Dentatorubral-pallidoluysian atrophy (Haw River syndrome)	*DRPLA*	12p13.31	Atrophin-1	CAG	6–35	49–88
Spinocerebellar ataxia type 1	*SCA1*	6p23	Ataxin-1	CAG	6–44	39–82
Spinocerebellar ataxia type 2	*SCA2*	12q24.1	Ataxin-2	CAG	15–31	36–63
Spinocerebellar ataxia type 3 (Machado-Joseph disease)	*SCA3 (MJD1)*	14q32.1	Ataxin-3	CAG	12–40	55–84
Spinocerebellar ataxia type 6	*SCA6*	19p13	α_{1A} -Voltage-dependent calcium channel subunit	CAG	4–18	21–33
Spinocerebellar ataxia type 7	*SCA7*	3p12-13	Ataxin-7	CAG	4–35	37–306

Figure 5-34 Sites of expansion and the affected sequence in selected diseases caused by nucleotide repeat mutations. UTR, untranslated region. *Although not strictly a trinucleotide repeat disease, progressive myoclonus epilepsy is caused, like others in this group, by a heritable DNA expansion. The expanded segment is in the promoter region of the gene.

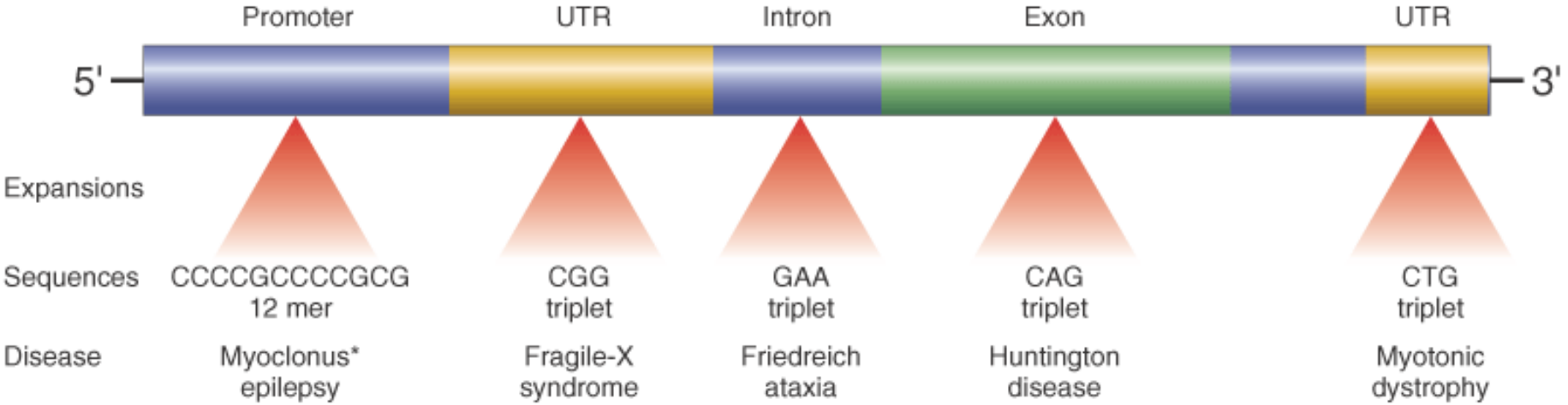


Figure 5-35 Pedigree of Leber hereditary optic neuropathy, a disorder caused by mutation in mitochondrial DNA. Note that all progeny of an affected male are normal, but all children, male and female, of the affected female manifest disease.

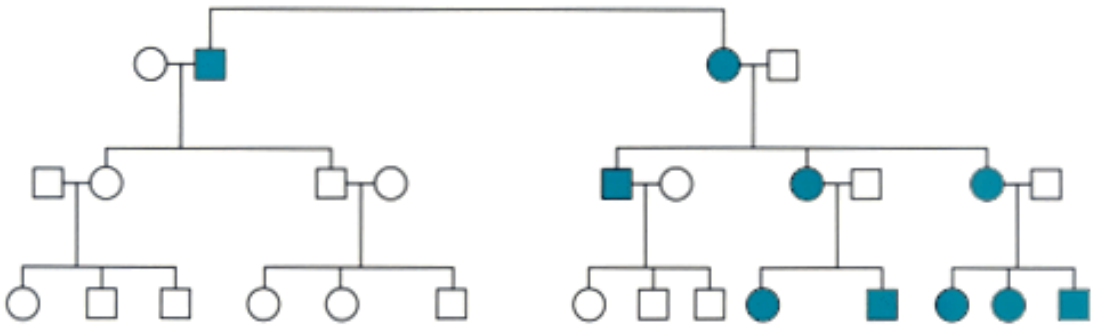
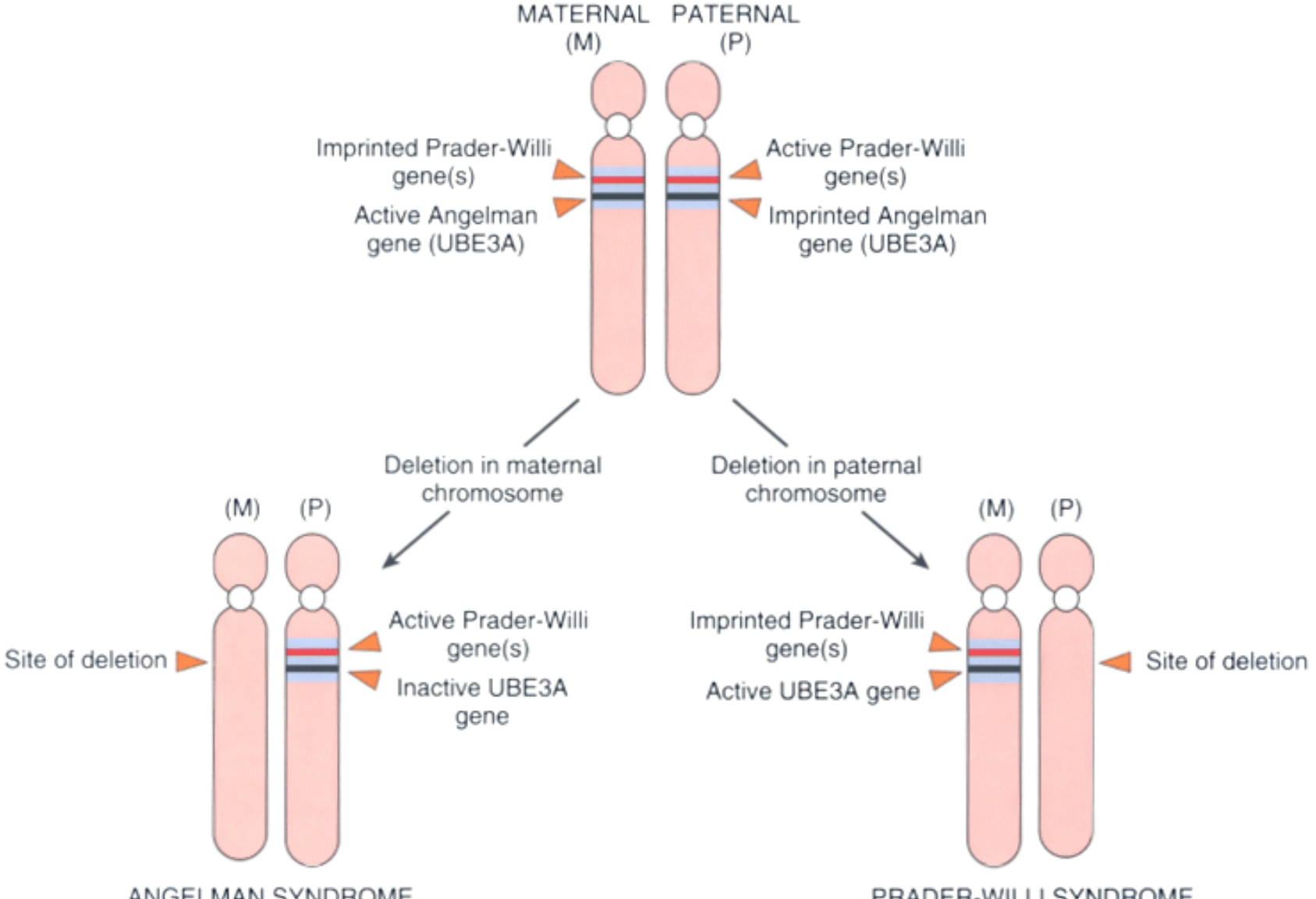


Figure 5-36 Diagrammatic representation of Prader-Willi and Angelman syndromes.



ANGELMAN SYNDROME

PRADER-WILLI SYNDROME

Figure 5-37 Direct gene diagnosis: detection of coagulation factor V mutation by polymerase chain reaction (PCR) analysis. A G→A substitution in an exon destroys one of the two Mnl1 restriction sites. The mutant allele therefore gives rise to two, rather than three, fragments by PCR analysis.

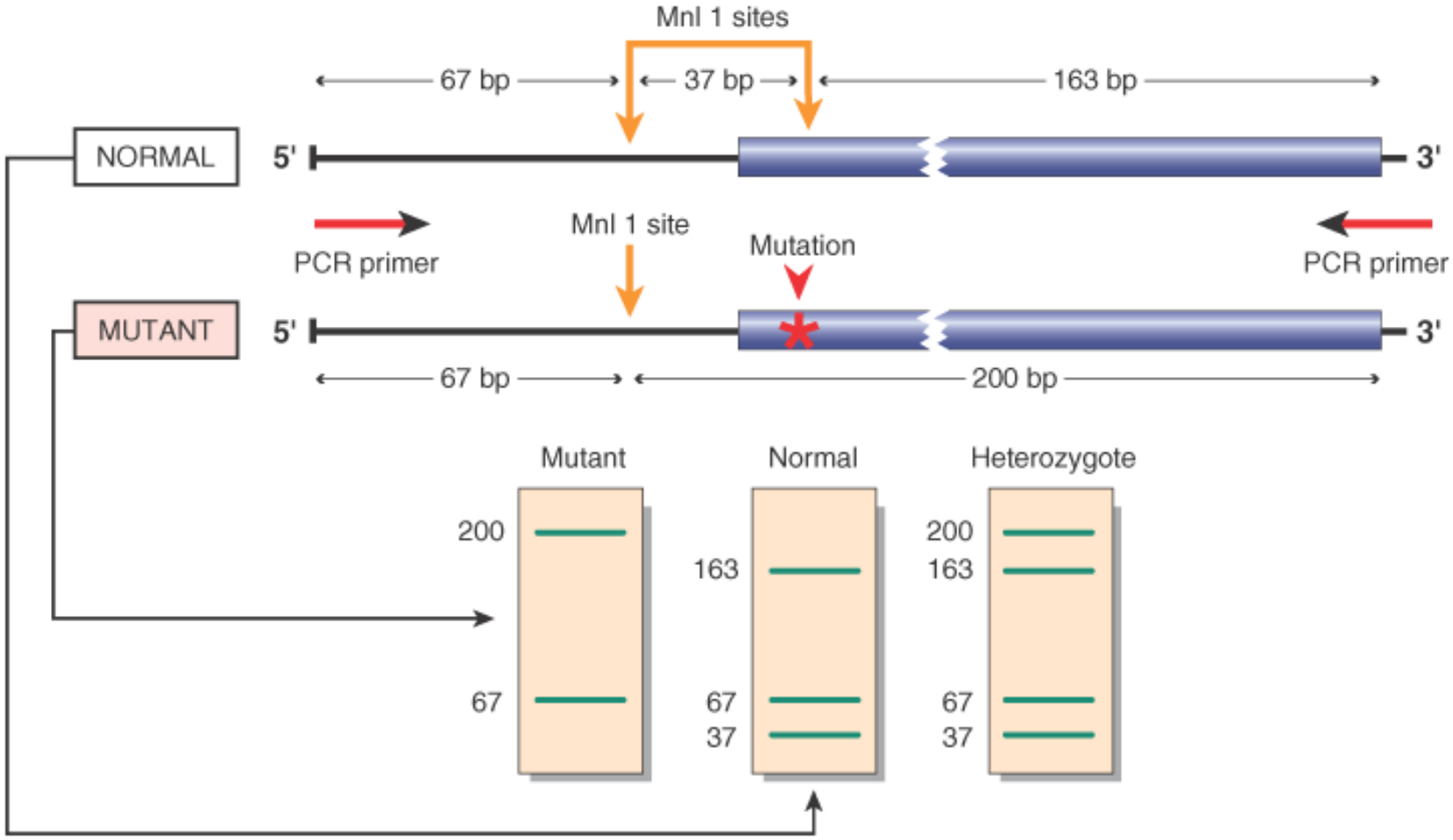
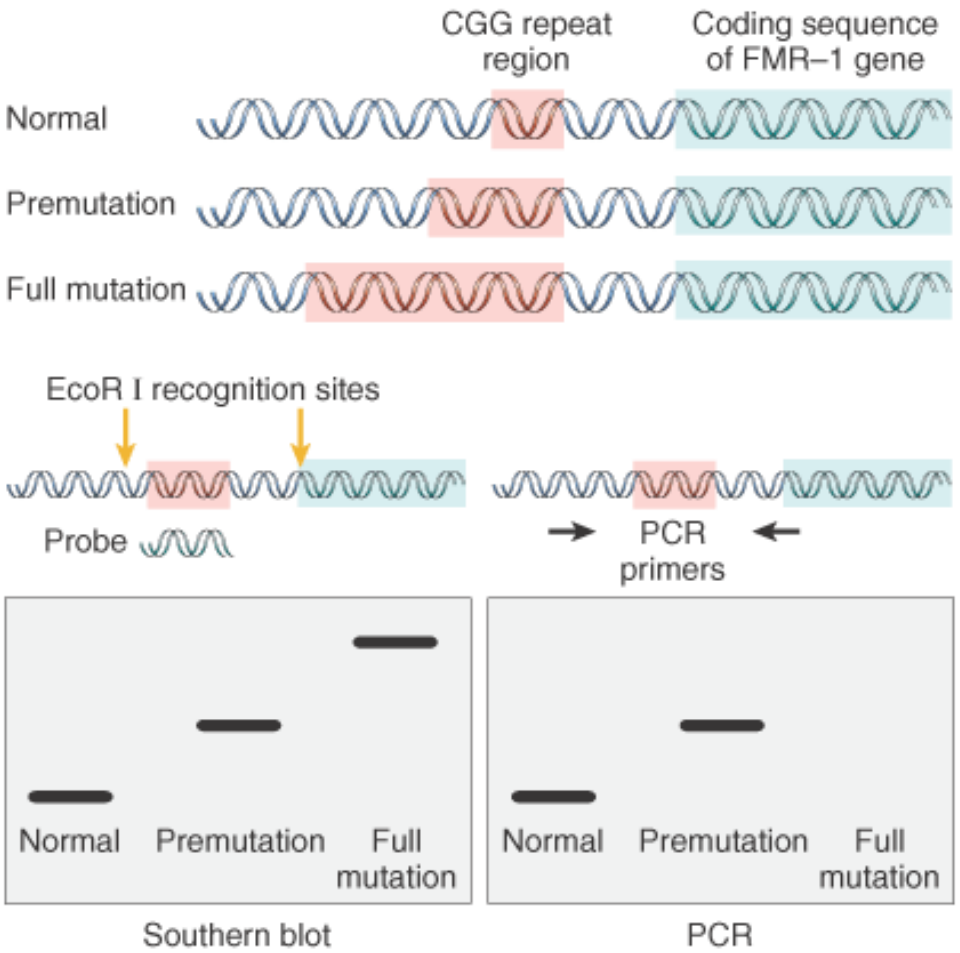


Figure 5-38 Diagnostic application of PCR and Southern blot analysis in fragile-X syndrome. With PCR, the differences in the size of CGG repeat between normal and premutation give rise to products of different sizes and mobility. With a full mutation, the region between the primers is too large to be amplified by conventional PCR. In Southern blot analysis the DNA is cut by enzymes that flank the CGG repeat region, and is then probed with a complementary DNA that binds to the affected part of the gene. A single small band is seen in normal males, a higher-molecular-weight band in males with premutation, and a very large (usually diffuse) band in those with the full mutation.



With this background, we can discuss how RFLPs can be used in gene tracking. Figure 5-39 illustrates the principle of RFLP analysis. In this example of an autosomal recessive disease, both of the parents are heterozygote carriers and the children are normal, are carriers, or are affected. In the illustrated example, the normal chromosome (A) has two restriction sites, 7.6 kb apart, whereas chromosome B, which carries the mutant gene, has a DNA sequence polymorphism resulting in the creation of an additional (third) restriction site for the same enzyme. Note that the additional restriction site has not resulted from the mutation but from a naturally occurring polymorphism. When DNA from such an individual is digested with the appropriate restriction enzyme and probed with a cloned DNA fragment that hybridizes with a stretch of sequences between

---

the restriction sites, the normal chromosome yields a 7.6 kb band, whereas the other chromosome (carrying the mutant gene) produces a smaller, 6.8 kb, band. Thus, on Southern blot analysis, two bands are noted. It is possible by this technique to distinguish family members who have inherited both normal chromosomes from those who are heterozygous or homozygous for the mutant gene. PCR followed by digestion with the appropriate restriction enzyme and gel electrophoresis can also be used to detect RFLPs if the target DNA is of the size that can be amplified by conventional PCR.

• *Length polymorphisms:* Human DNA contains short repetitive sequences of noncoding DNA. Because the number of repeats affecting such sequences varies greatly between different individuals, the resulting length polymorphisms are quite useful for linkage analysis. These polymorphisms are often subdivided on the basis of their length into microsatellite

repeats and minisatellite repeats. Microsatellites are usually less than 1 kb and are characterized by a repeat size of 2 to 6 base pairs. Minisatellite repeats, by comparison, are larger (1 to 3 kb), and the repeat motif is usually 15 to 70 base pairs. It is important to note that the number of repeats, both in microsatellites and minisatellites, is extremely variable within a given population, and hence these stretches of DNA can be used quite effectively to distinguish different chromosomes (Fig. 5-40*A*). Figure 5-40*B* illustrates how microsatellite polymorphisms can be used to track the inheritance of autosomal dominant polycystic kidney disease (PKD). In this case, allele C, which produces a larger PCR product than allele A or B, carries the disease-related gene. Hence all individuals who carry the C allele are affected. Microsatellites have assumed great importance in linkage studies and hence in the development of the human genome map. Currently, linkage to all human chromosomes can be identified by microsatellite polymorphisms.[86]

Figure 5-39 Schematic illustration of the principles underlying restriction fragment length polymorphism analysis in the diagnosis of genetic diseases.

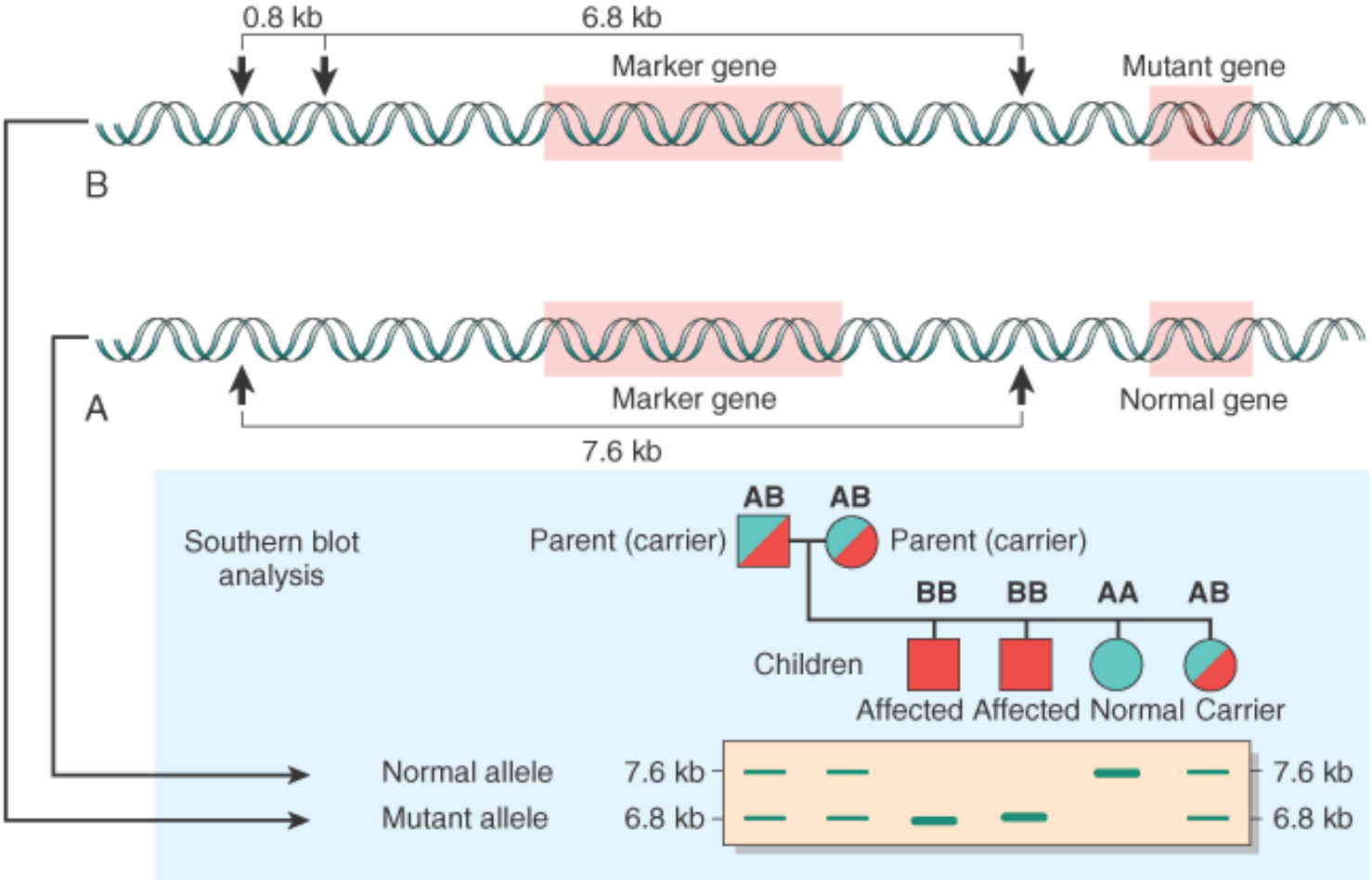
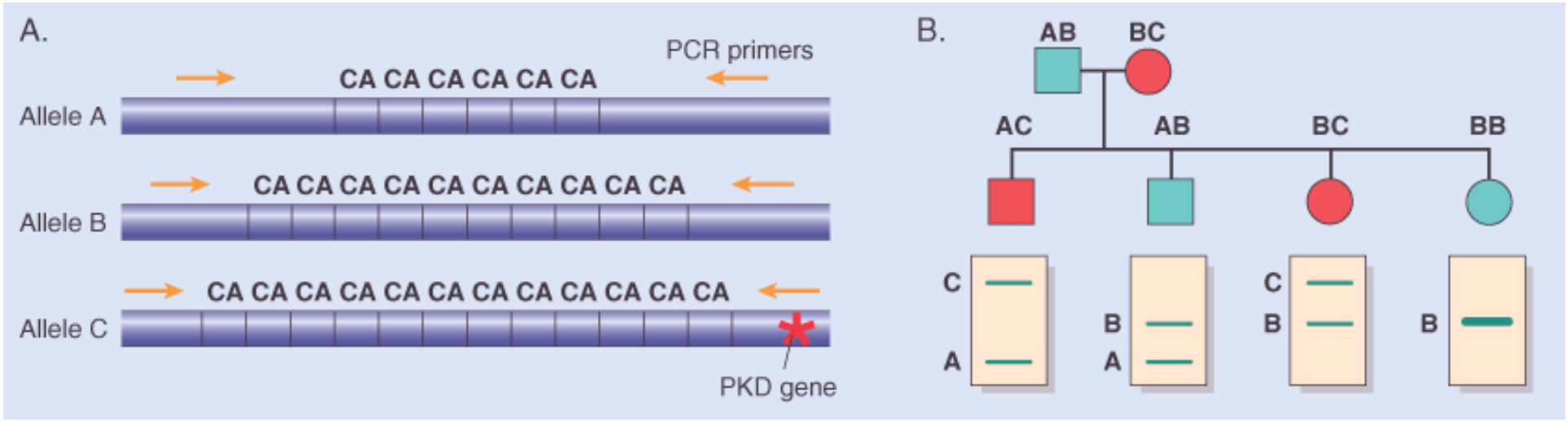


Figure 5-40 Schematic diagram of DNA polymorphisms resulting from a variable number of CA repeats. The three alleles produce PCR products of different sizes, thus identifying their origins from specific chromosomes. In the example depicted, allele C is linked to a mutation responsible for autosomal dominant polycystic kidney disease (PKD). Application of this to detect progeny carrying the disease gene is illustrated in one hypothetical pedigree.



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Chapter 6 - Diseases of Immunity

Abul K. Abbas MD

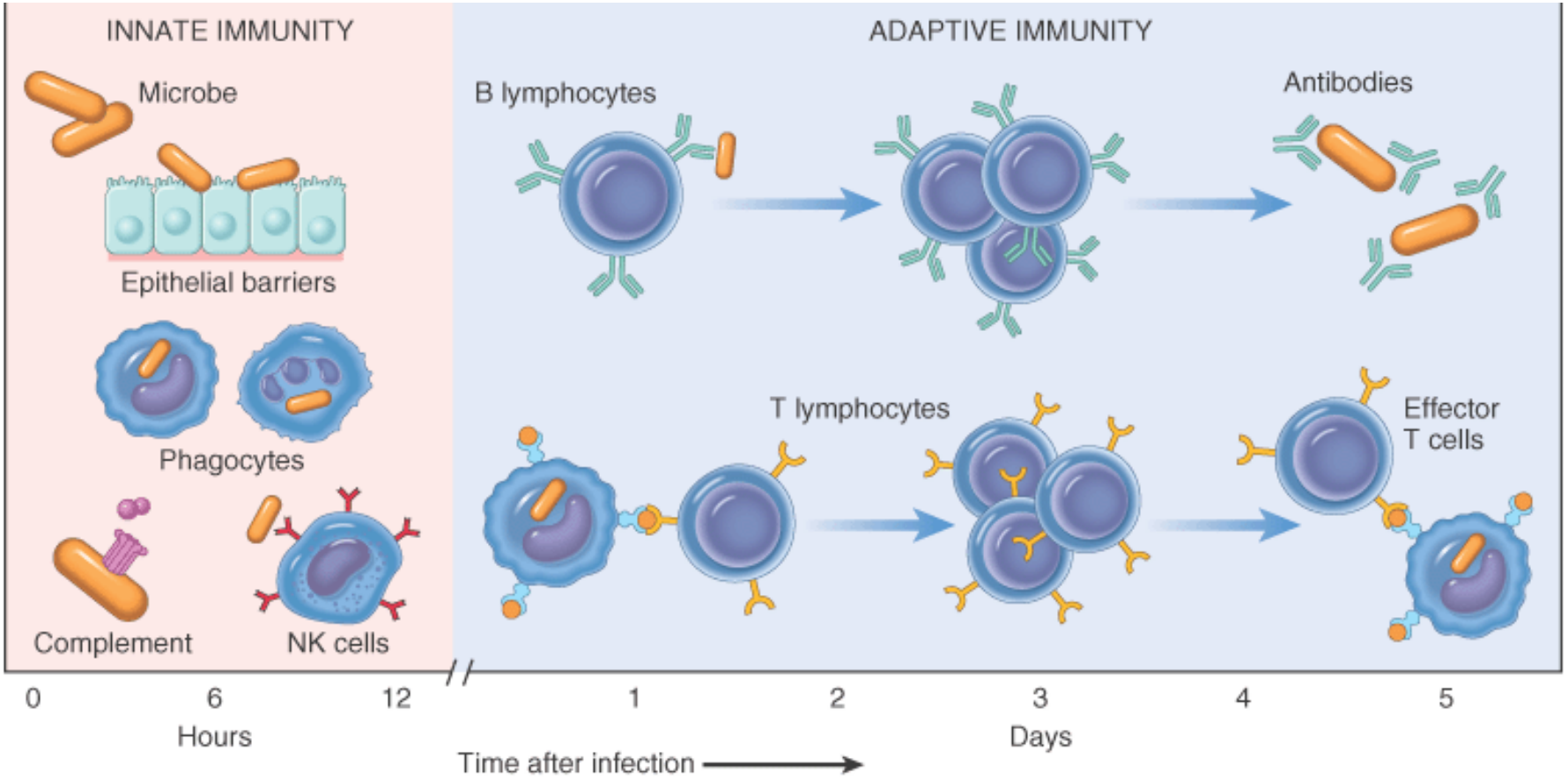
General Features of the Immune System

Although vital to survival, the immune system is similar to the proverbial two-edged sword. On the one hand, immunodeficiency states render humans easy prey to infections and possibly tumors; on the other hand, a hyperactive immune system may cause fatal disease, as in the case of an overwhelming allergic reaction to the sting of a bee. In yet another series of derangements, the immune system may lose its normal capacity to distinguish self from non-self, resulting in immune reactions against one's own tissues and cells (*autoimmunity*). This chapter considers diseases caused by too little immunity as well as those resulting from too much immunologic reactivity. We also consider amyloidosis, a disease in which an abnormal protein, derived in some cases from fragments of immunoglobulins, is deposited in tissues. First, we review some advances in the understanding of innate and adaptive immunity and lymphocyte biology, then give a brief description of the histocompatibility genes because their products are relevant to several immunologically mediated diseases and to the rejection of transplants.

INNATE AND ADAPTIVE IMMUNITY

The physiologic function of the immune system is to protect individuals from infectious pathogens. The mechanisms that are responsible for this protection fall into two broad categories (Fig. 6-1). *Innate immunity* (also called natural, or native, immunity) refers to defense mechanisms that are present even before infection and have evolved to specifically recognize microbes and protect multicellular organisms against infections. *Adaptive immunity* (also called acquired, or specific, immunity) consists of mechanisms that are stimulated by (adapt to) microbes and are capable of also recognizing nonmicrobial substances, called *antigens*. Innate immunity is the first line of defense, because it is always ready

Figure 6-1 Innate and adaptive immunity. The principal mechanisms of innate immunity and adaptive immunity are shown.



Box 6-1. Toll-like Receptors

The Toll-like receptors (TLRs) are membrane proteins that recognize a variety of microbe-derived molecules and stimulate innate immune responses against the microbes. The first protein to be identified in this family was the *Drosophila* Toll protein, which is involved in establishing the dorsal-ventral axis during embryogenesis of the fly, as well as mediating antimicrobial responses. Ten different mammalian TLRs have been identified based on sequence homology to *Drosophila* Toll, and they are named TLR1-10. All these receptors contain leucine-rich repeats flanked by characteristic cysteine-rich motifs in their extracellular regions, and a conserved signaling domain in their cytoplasmic region that is also found in the cytoplasmic tails of the IL-1 and IL-18 receptors and is called the Toll/IL-1 receptor (TIR) domain. The TLRs are expressed on many different cell types that participate in innate immune responses, including macrophages, dendritic cells, neutrophils, NK cells, mucosal epithelial cells, and endothelial cells.

Mammalian TLRs are involved in responses to widely divergent types of molecules that are commonly expressed by microbial but not mammalian cells (see Figure). Some of the microbial products that stimulate TLRs include Gram-negative bacterial lipopolysaccharide (LPS), Gram-positive bacterial peptidoglycan, bacterial lipoproteins, the bacterial flagellar protein flagellin, heat shock protein 60, unmethylated CpG DNA motifs (found in many bacteria), and double-stranded RNA (found in RNA viruses). The specificity of TLRs for microbial products is dependent on associations between different TLRs and non-TLR adapter molecules. For instance, LPS first binds to soluble LPS-binding protein (LBP) in the blood or extracellular fluid, and this complex serves to facilitate LPS binding to CD14, which exists as both a soluble plasma protein and a glycophosphatidylinositol-linked membrane protein on most cells. Once LPS binds to CD14, LBP dissociates, and the LPS-CD14 complex physically associates with TLR4. An additional extracellular accessory protein, called MD2, also binds to the complex with CD14. LPS, CD14, and MD2 are all required for efficient LPS-induced signaling, but it is not yet clear if direct physical interaction of LPS with TLR4 is necessary.

Signaling by TLRs results in the activation of transcription factors, notably NF-κB (see Figure). Ligand binding to the TLR at the cell surface leads to recruitment of cytoplasmic signaling molecules, the first of which is the adapter protein MyD88. A kinase called IL-1 receptor associated kinase (IRAK) is recruited into the signaling complex. IRAK undergoes autophosphorylation, dissociates from MyD88, and activates another signaling molecule, called TNF-receptor (TNF-R) associated factor-6 (TRAF-6). TRAF-6 then activates the I-κB kinase cascade, leading to activation of the NF-κB transcription factor. In some cell types certain TLRs also engage other signaling pathways, such as the MAP kinase cascade, leading to activation of the AP-1 transcription factor. Some TLRs may use adapter proteins other than MyD88. The relative importance of these various pathways of TLR signaling, and the way the "choice" of pathways is made, are not well understood.

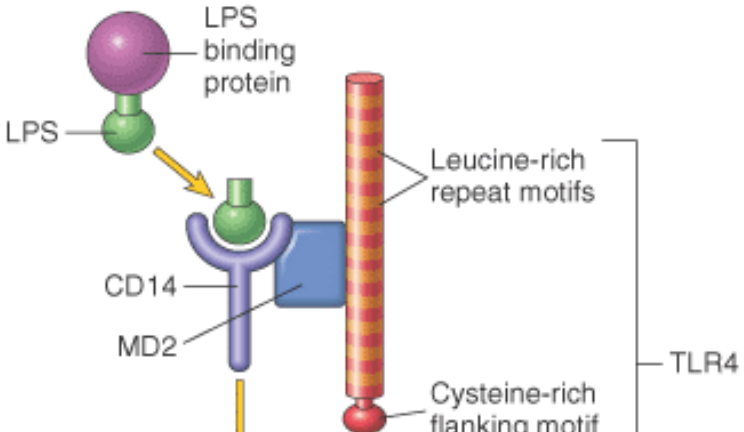
The genes that are expressed in response to TLR signaling encode proteins important in many different components of innate immune responses. These include inflammatory cytokines (TNF, IL-1, and IL-12), endothelial adhesion molecules (E-selectin), and proteins involved in microbial killing mechanisms (inducible nitric oxide synthase). The particular genes expressed will depend on the responding cell type.

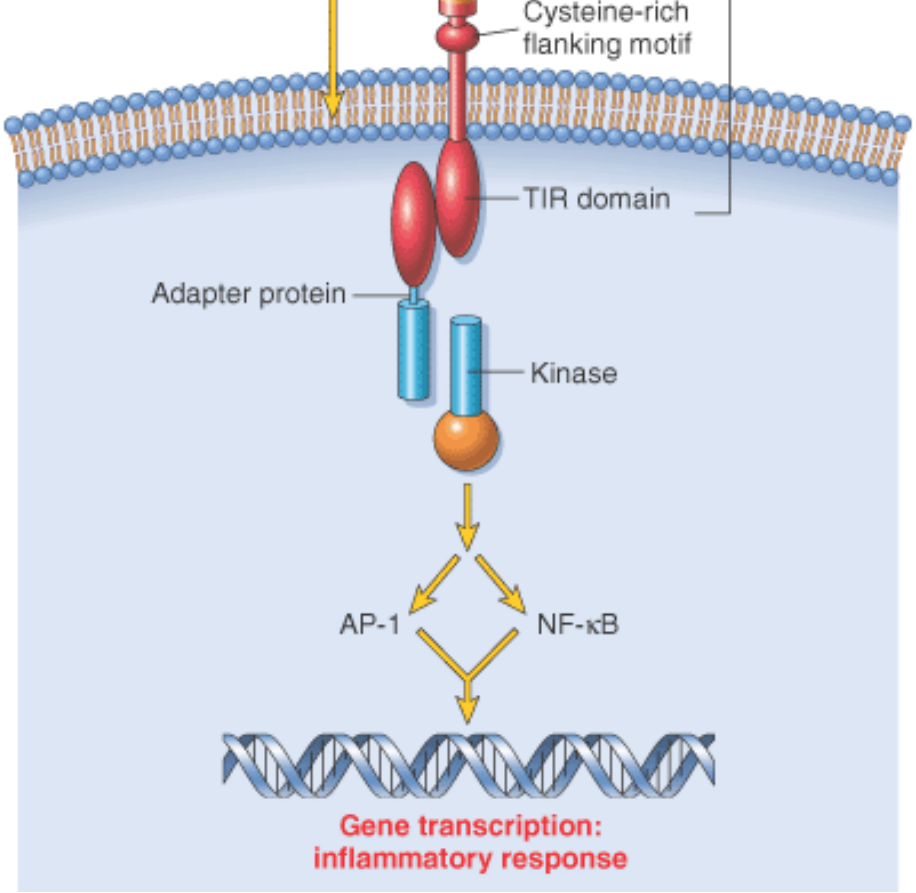
Figure 6- *A*, Different TLRs are involved in responses to different microbial products. *B*, Signaling by a prototypic TLR, TLR4, in response to bacterial LPS. An adapter protein links the TLR to a kinase, which activates transcription factors such as NF-κB and AP-1. TIR, Toll/IL-1 receptor domain.

A

TLR	Ligand	Microbial source
TLR2	Lipoproteins Peptidoglycan Zymosan LPS GPI anchor Lipoarabinomannan Phosphatidylinositol dimannoside	Bacteria Gram positive bacteria Fungi Leptospira Trypanosomes Mycobacteria Mycobacteria
TLR3	Double-stranded RNA	Viruses
TLR4	LPS HSF00	Gram negative bacteria Chlamydia
TLR5	Flagellin	Various bacteria
TLR6	CpG DNA	Bacteria, protozoans

B





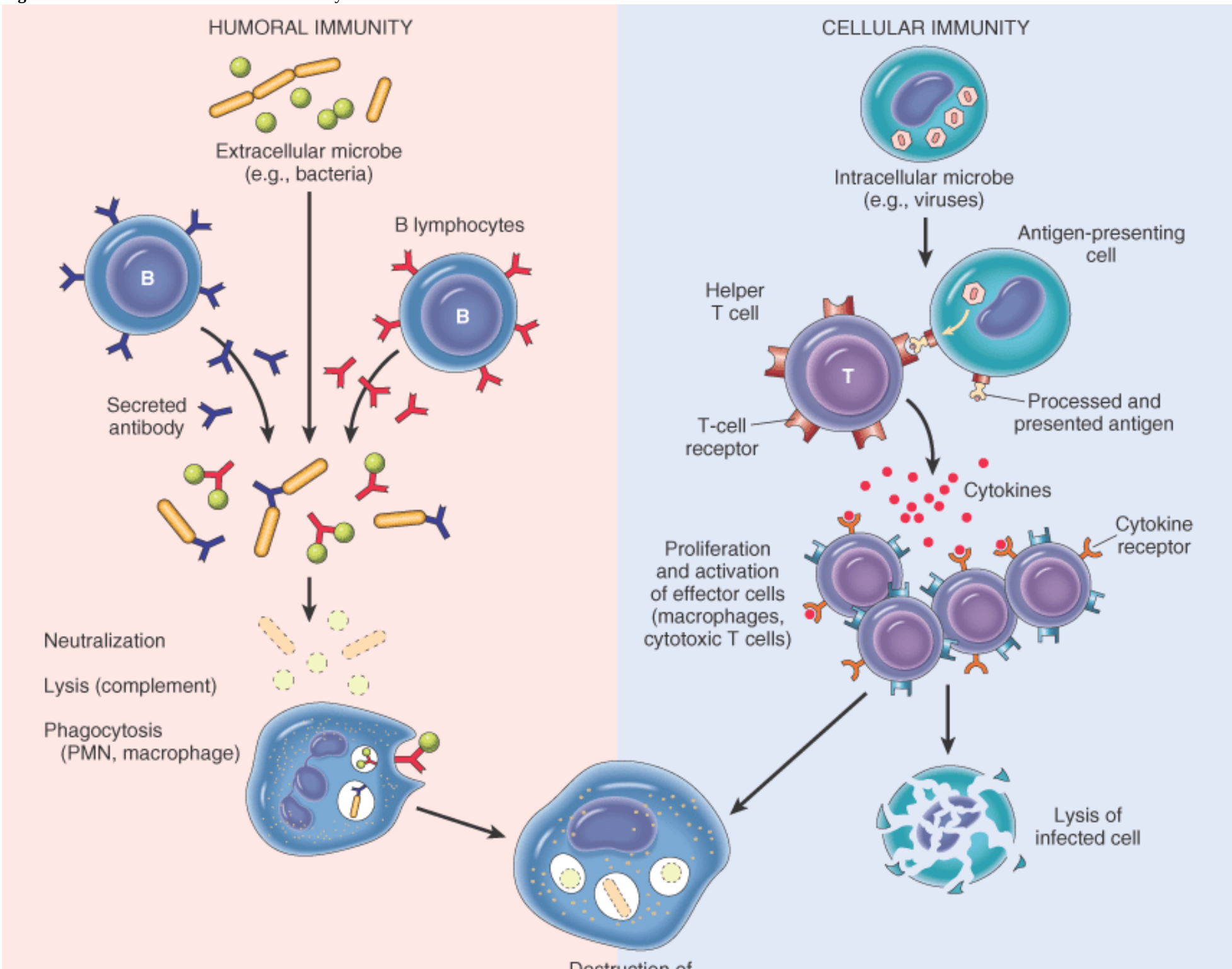
of innate immunity, providing protection against inhaled microbes.

The adaptive immune system consists of lymphocytes and their products, including antibodies. The receptors of lymphocytes are much more diverse than those of the innate immune system, but lymphocytes are not inherently specific for microbes, and they are capable of recognizing a vast array of foreign substances. In the remainder of this introductory section we focus on lymphocytes and the reactions of the adaptive immune system.

CELLS AND TISSUES OF THE IMMUNE SYSTEM

There are two main types of adaptive immunity—cell-mediated (or cellular) immunity, which is responsible for defense against intracellular microbes, and humoral immunity, which protects against extracellular microbes and their toxins (Fig. 6-2). Cellular immunity is mediated by T (thymus-derived) lymphocytes, and humoral immunity is mediated by B (bone marrow-derived) lymphocytes and their secreted products,

Figure 6-2 Humoral and cell-mediated immunity.



Destruction of
phagocytosed microbes

Figure 6-3 Histology of a lymph node. *A,* The organization of the lymph node, with an outer cortex containing follicles and an inner medulla. *B,* The location of B cells (stained green, using the immunofluorescence technique) and T cells (stained red) in a lymph node. *C,* A germinal center.

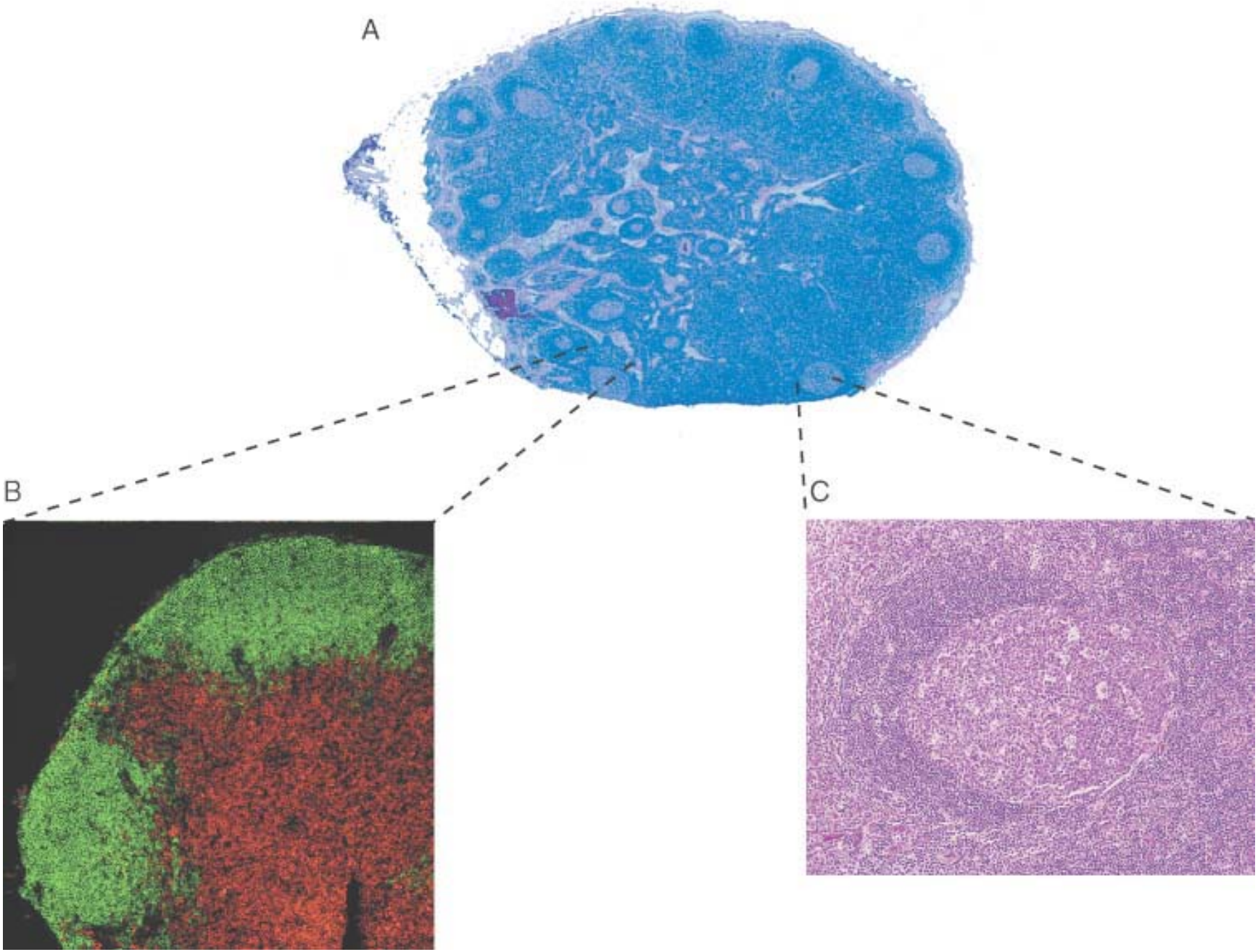
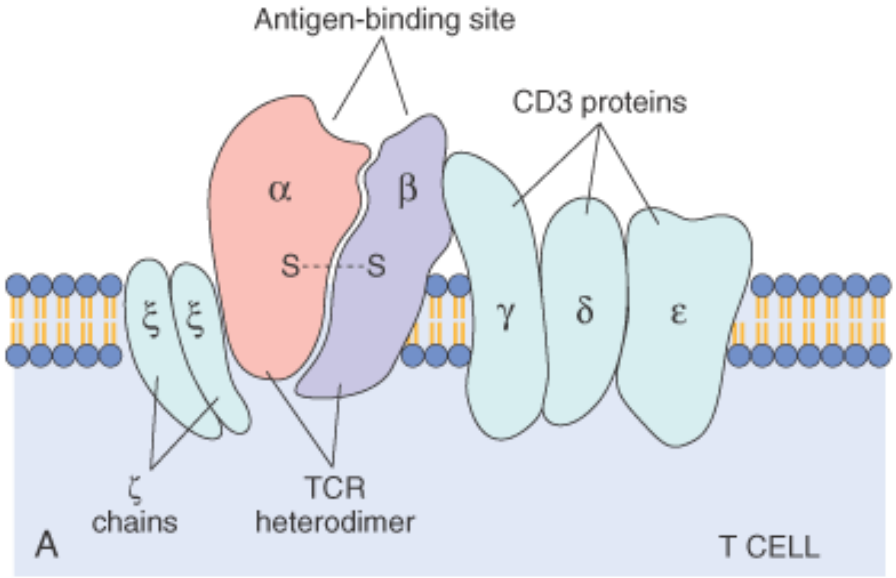
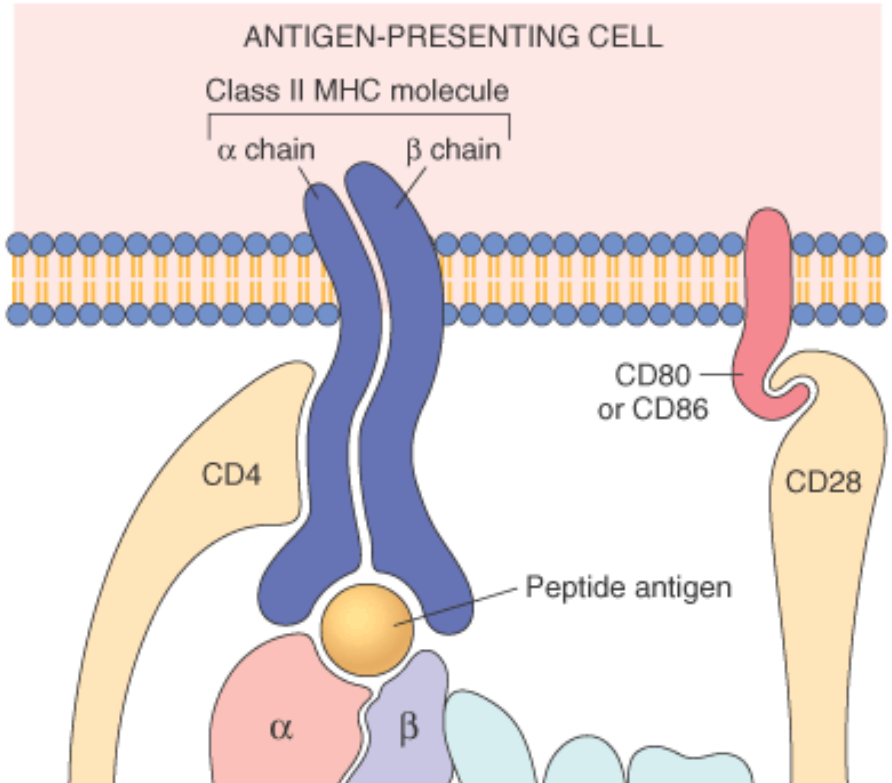


Figure 6-4 The T-cell receptor (TCR) complex. *A,* Schematic illustration of TCRα and TCRβ chains linked to the CD3 complex. *B,* Recognition of MHC-associated peptide displayed on an antigen-presenting cell (top) by the TCR. Note that the TCR-associated ζ chains and CD3 complex deliver signals (signal 1) upon antigen recognition, and CD28 delivers signals (signal 2) upon recognition of costimulators (B7 molecules).





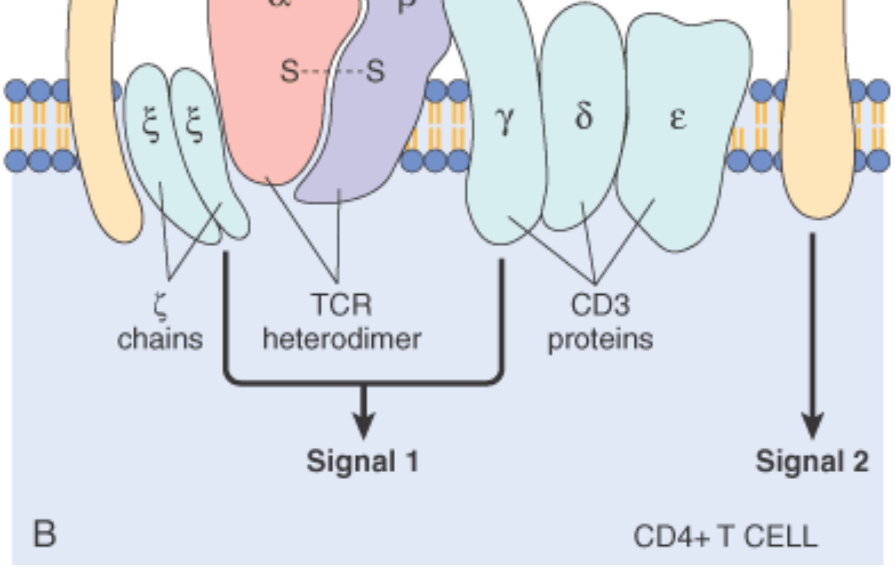
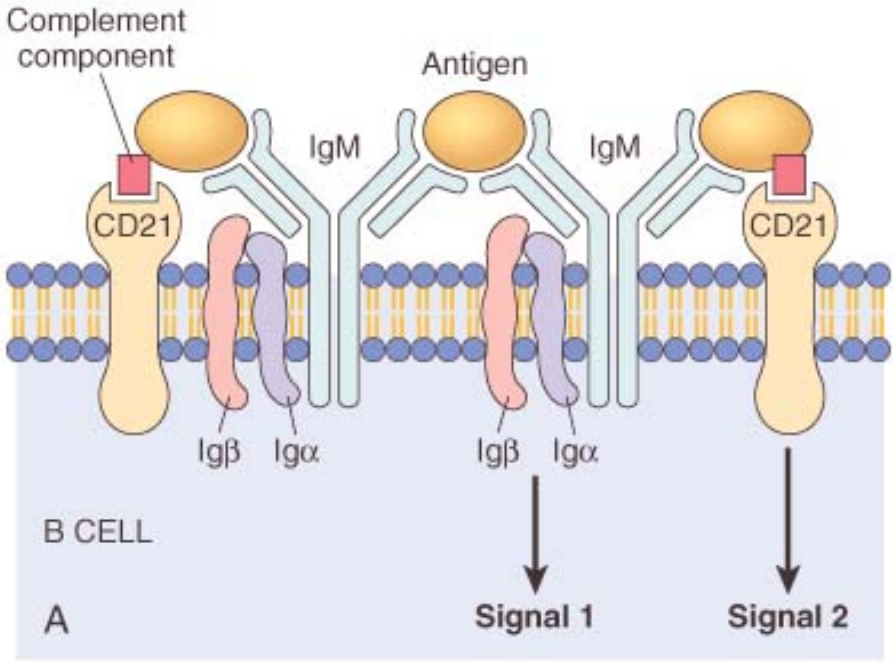


Figure 6-5 Structure of antibodies and the B-cell antigen receptor. *A*, The B-cell receptor complex composed of membrane IgM (or IgD, not shown) and the associated signaling proteins Igα and Igβ. CD21 is a receptor for a complement component that also promotes B-cell activation. *B*, Crystal structure of a secreted IgG molecule, showing the arrangement of the variable (V) and constant (C) regions of the heavy (H) and light (L) chains. *(Courtesy of Dr. Alex McPherson, University of California, Irvine, CA.)*



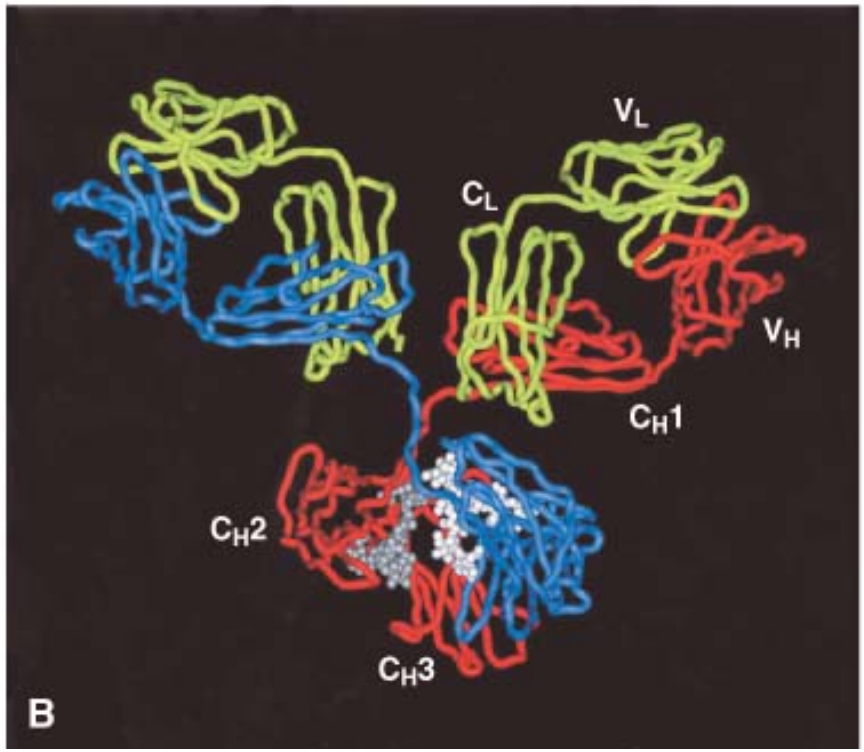
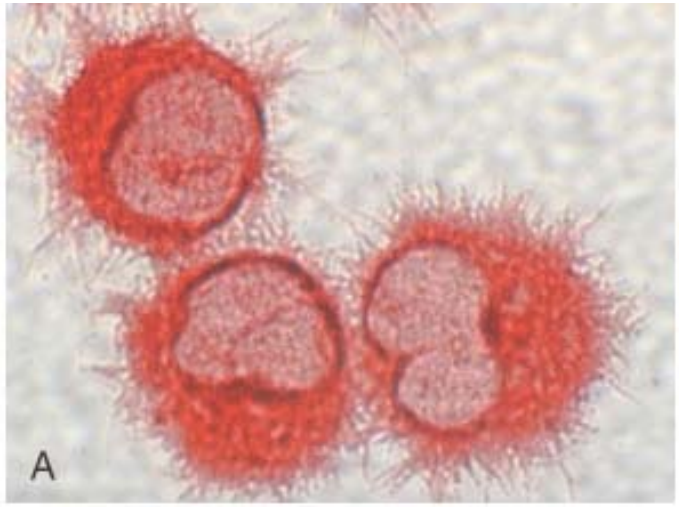
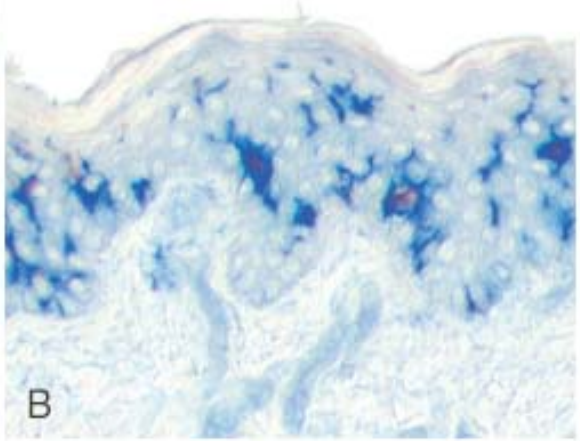
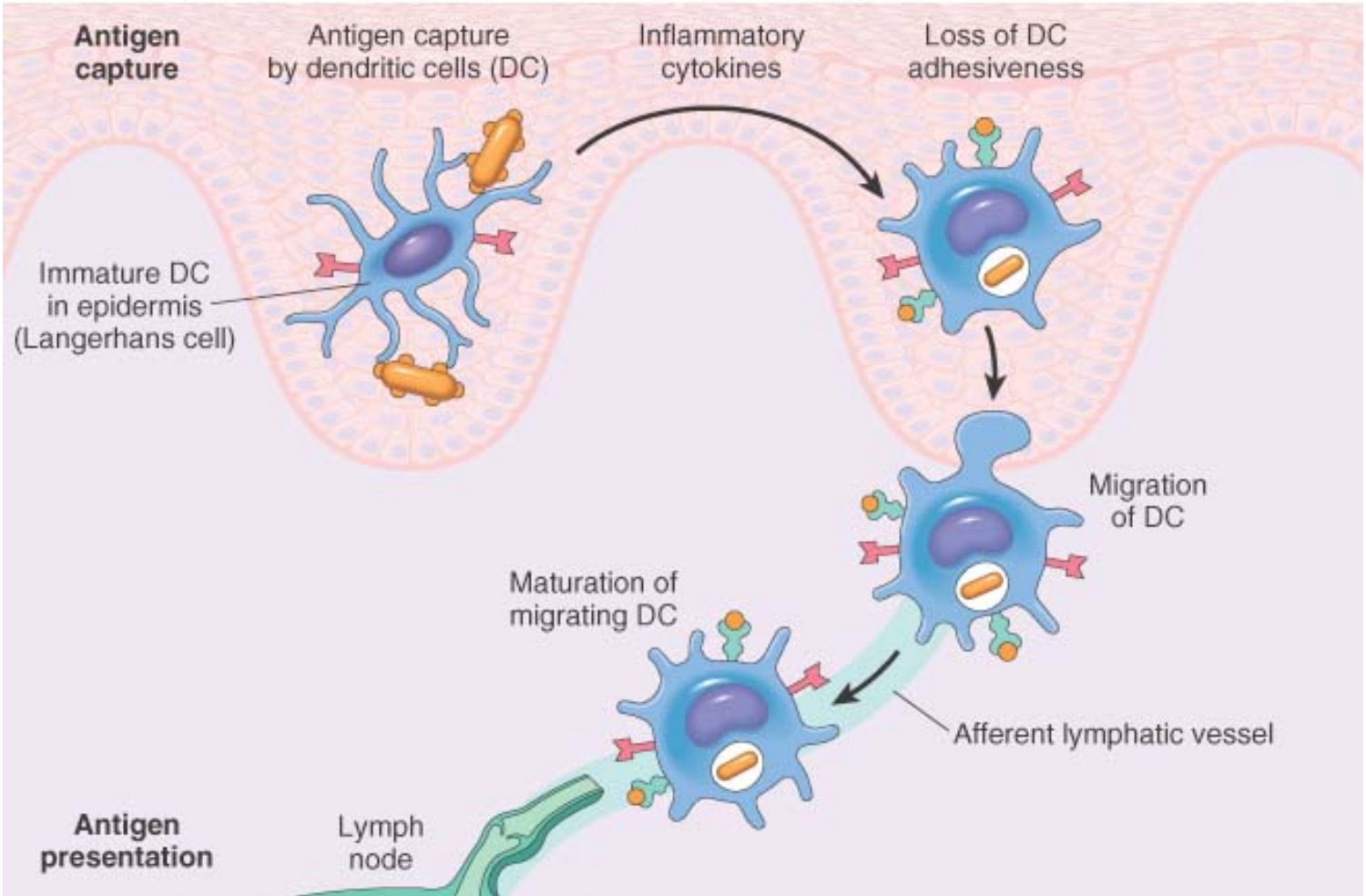


Figure 6-6 The morphology and functions of dendritic cells (DC). *A,* The morphology of cultured dendritic cells. *(Courtesy of Dr. Y-J. Liu, M. D. Anderson Cancer Center, Houston.) B,*

The location of dendritic cells (Langerhans cells) in the epidermis. *(Courtesy of Dr. Y-J. Liu, M. D. Anderson Cancer Center, Houston.) C*, The role of dendritic cells in capturing microbial antigens from epithelia and transporting them to regional lymph nodes.







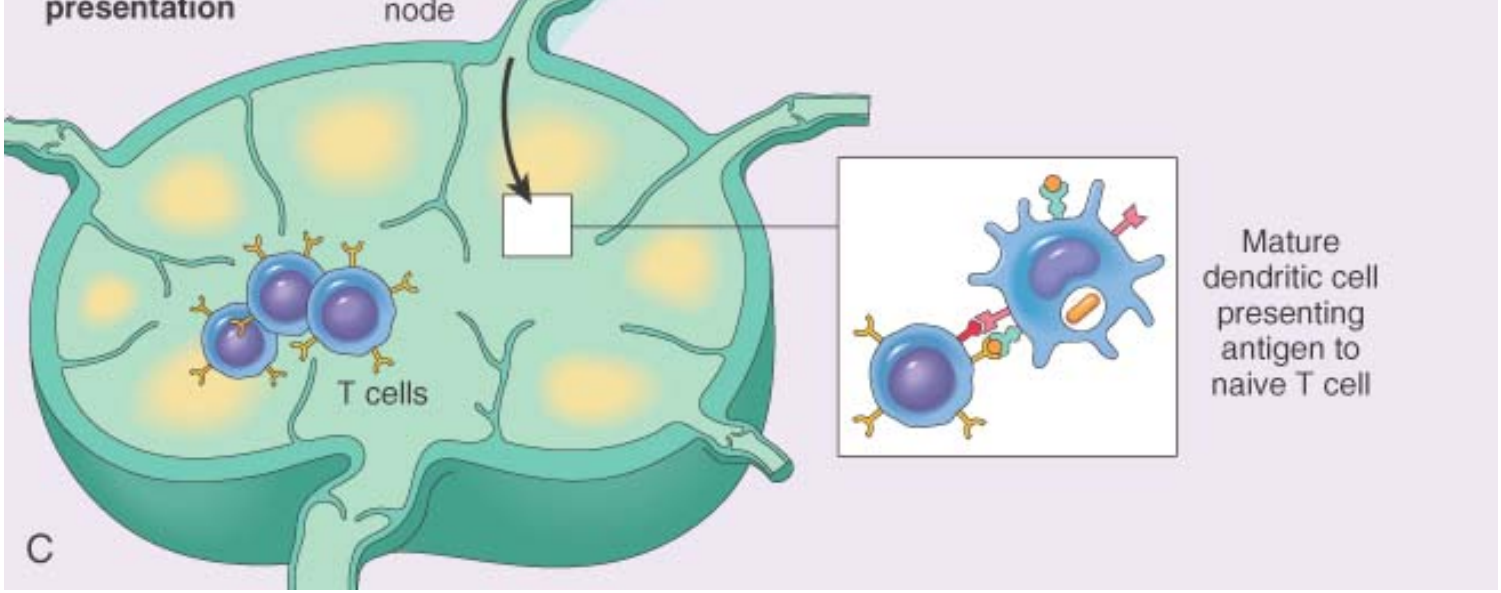


Figure 6-7 A highly activated natural killer cell with abundant cytoplasmic granules. *(Courtesy of Dr. Noelle Williams, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

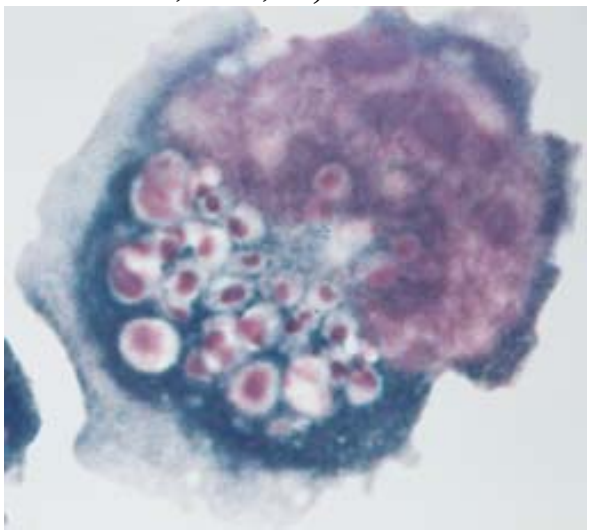
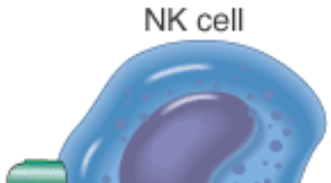


Figure 6-8 Schematic representation of NK-cell receptors and killing. NK cells express activating and inhibitory receptors; some examples of each are indicated. Normal cells are not killed because inhibitory signals from normal MHC class I molecules override activating signals. In tumor cells or virus-infected cells, there is increased expression of ligands for activating receptors, and reduced expression or alteration of MHC molecules, which interrupts the inhibitory signals, allowing activation of NK cells and lysis of target cells. KIR, killer cell Ig-like recepors.



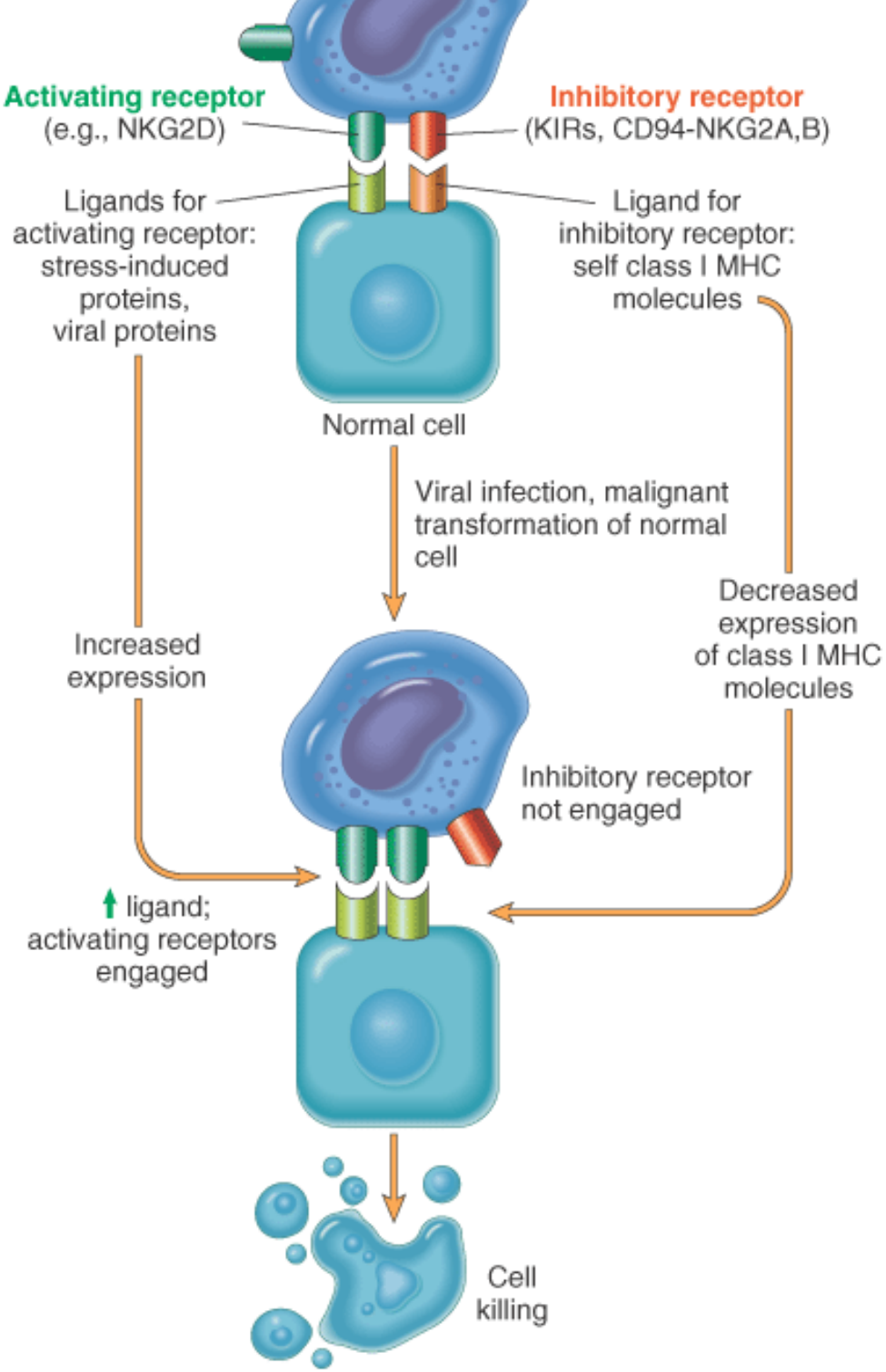

Activating receptor
(e.g., NKG2D)
Inhibitory receptor
(KIRs, CD94-NKG2A,B)
Ligands for activating receptor: stress-induced proteins, viral proteins
Ligand for inhibitory receptor: self class I MHC molecules
Normal cell
Viral infection, malignant transformation of normal cell
Increased expression
Decreased expression of class I MHC molecules
Inhibitory receptor not engaged
↑ ligand; activating receptors engaged
Cell killing

Figure 6-9 The HLA complex and the structure of HLA molecules. *A,* The location of genes in the HLA complex is shown. The sizes and distances between genes are not to scale. *B,* Schematic diagrams and crystal structures of class I and class II HLA molecules. *(Crystal structures are courtesy of Dr. P. Bjorkman, California Institute of Technology, Pasadena, CA.)*

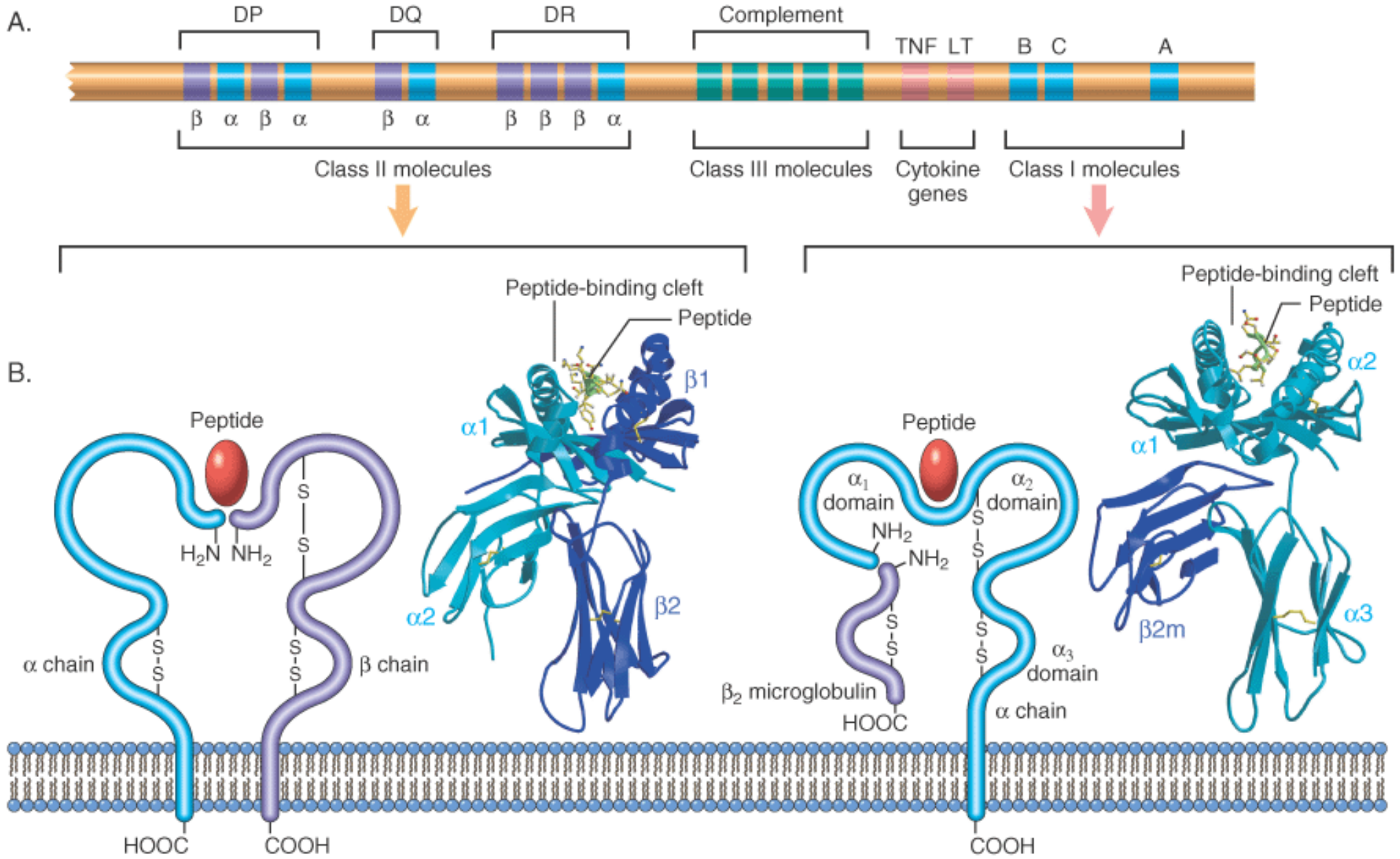
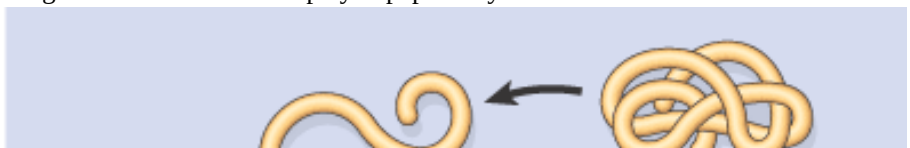


Figure 6-10 Antigen processing and recognition. The sequence of events in the processing of a cytoplasmic protein antigen and its display by class I MHC molecules are shown at the top. The recognition of this MHC-displayed peptide by a CD8+ T cell is shown at the bottom.



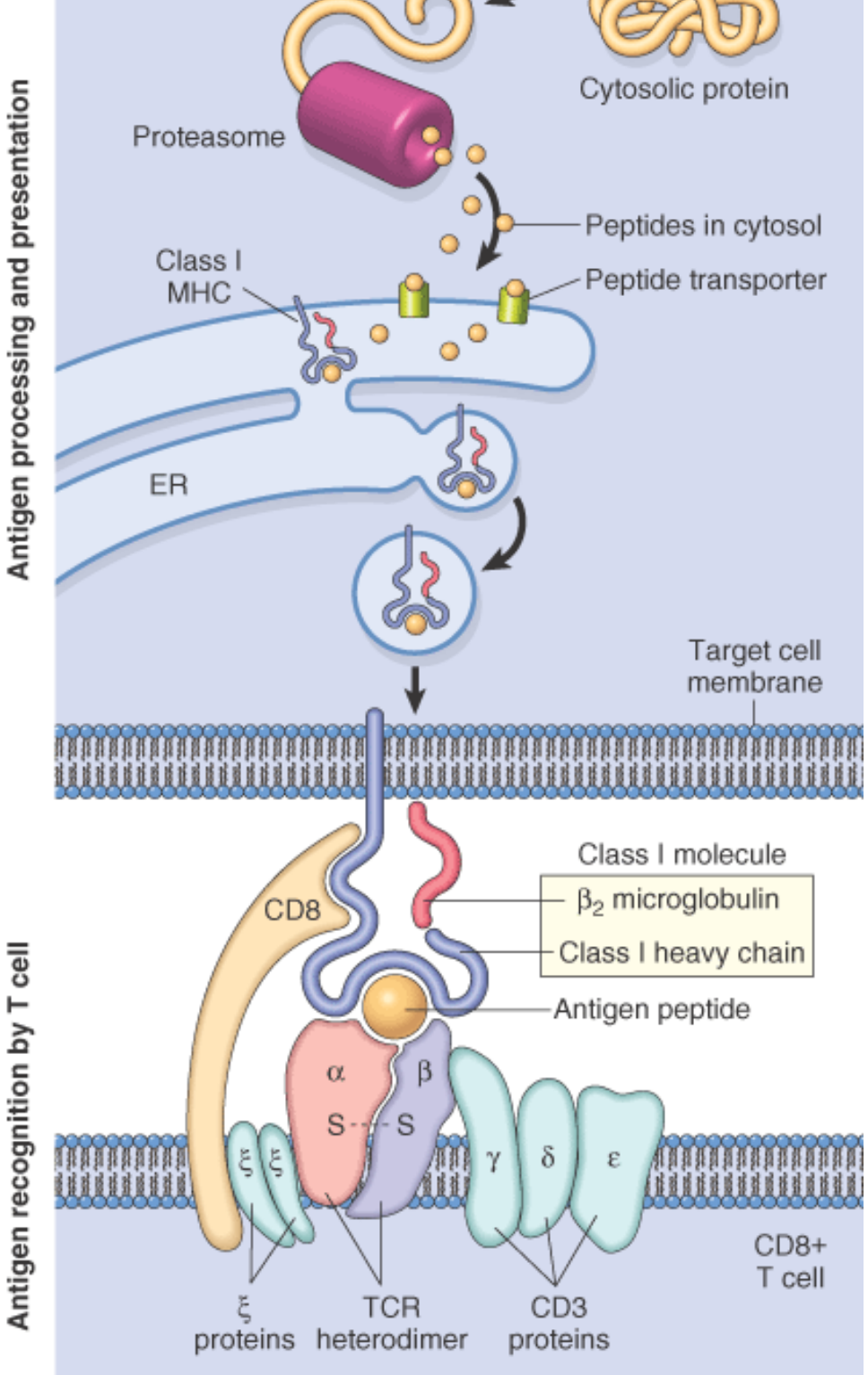

Antigen processing and presentation
Cytosolic protein
Proteasome
Peptides in cytosol
Class I
MHC
Peptide transporter
ER
Target cell
membrane
Antigen recognition by T cell
Class I molecule
CD8
β2 microglobulin
Class I heavy chain
Antigen peptide
α
β
S
S
ξ
ξ
γ
δ
ε
CD8+
T cell
ξ
proteins
TCR
heterodimer
CD3
proteins

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

MECHANISMS OF HYPERSENSITIVITY REACTIONS

Humans live in an environment teeming with substances capable of producing immunologic responses. Contact with antigen leads not only to induction of a protective immune response, but also to reactions that can be damaging to tissues. Exogenous antigens occur in dust, pollens, foods, drugs, microbiologic agents, chemicals, and many blood products used in clinical practice. The immune responses that may result from such exogenous antigens take a variety of forms, ranging from annoying but trivial discomforts, such as itching of the skin, to potentially fatal diseases, such as bronchial asthma. The various reactions produced are called *hypersensitivity reactions*, and tissue injury in these reactions may be caused by humoral or cell-mediated immune mechanisms.

Injurious immune reactions may be evoked not only by exogenous environmental antigens, but also by endogenous tissue antigens. Some of these immune reactions are triggered by homologous antigens that differ among individuals with different genetic backgrounds. Transfusion reactions and graft rejection are examples of immunologic disorders evoked by homologous antigens. Another category of disorders, those incited by self-, or autologous, antigens, constitutes the important group of autoimmune diseases (discussed later). These diseases arise because of the emergence of immune responses against self-antigens.

Hypersensitivity diseases can be classified on the basis of the immunologic mechanism that mediates the disease (Table 6-2). This classification is of value in distinguishing the manner in which the immune response ultimately causes tissue injury and disease, and the accompanying pathologic alterations. Prototypes of each of these immune mechanisms are presented in the subsequent sections.

- In *immediate hypersensitivity (type I hypersensitivity)*, the immune response releases vasoactive and spasmogenic substances that act on vessels and smooth muscle and pro-inflammatory cytokines that recruit inflammatory cells.
- In *antibody-mediated disorders (type II hypersensitivity)*, secreted antibodies participate directly in injury to cells by promoting their phagocytosis or lysis and injury to tissues by inducing inflammation. Antibodies may also interfere with cellular functions and cause disease without tissue injury.
- In *immune complex-mediated disorders (type III hypersensitivity)*, antibodies bind antigens and then induce inflammation directly or by activating complement. The leukocytes that are recruited (neutrophils and monocytes) produce tissue damage by release of lysosomal enzymes and generation of toxic free radicals.
- In *cell-mediated immune disorders (type IV hypersensitivity)*, sensitized T lymphocytes are the cause of the cellular and tissue injury.

Most hypersensitivity diseases show a genetic predisposition. Modern methods of mapping disease-associated susceptibility

TABLE 6-2 -- Mechanisms of Immunologically Mediated Diseases

Type	Prototype Disorder	Immune Mechanisms	Pathologic Lesions
Immediate (type I) hypersensitivity	Anaphylaxis; allergies; bronchial asthma (atopic forms)	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; recruitment of inflammatory cells (late-phase reaction)	Vascular dilation, edema, smooth muscle contraction, mucus production, inflammation
Antibody-mediated (type II) hypersensitivity	Autoimmune hemolytic anemia; Goodpasture syndrome	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	Cell lysis; inflammation
Immune complex-mediated (type III) hypersensitivity	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules	Necrotizing vasculitis (fibrinoid necrosis); inflammation
Cell-mediated (type IV) hypersensitivity	Contact dermatitis; multiple sclerosis; type I, diabetes; transplant rejection; tuberculosis	Activated T lymphocytes → i) release of cytokines and macrophage activation; ii) T cell-mediated cytotoxicity	Perivascular cellular infiltrates; edema; cell destruction; granuloma formation

genes are revealing the complex nature of these genetic influences. Many susceptibility loci have been identified in different diseases. Among the genes known to be associated with hypersensitivity diseases are MHC genes, but many non-MHC genes also play a role.

Immediate (Type I) Hypersensitivity

Immediate, or type I, hypersensitivity is a rapidly developing immunologic reaction occurring within minutes after the combination of an antigen with antibody bound to mast cells in individuals previously sensitized to the antigen.[20] [21] These reactions are often called allergy, and the antigens that elicit them are allergens. Immediate hypersensitivity may occur as a systemic disorder or as a local reaction. The systemic reaction usually follows injection of an antigen to which the host has become sensitized. Often within minutes, a state of shock is produced, which is sometimes fatal. The nature of local reactions varies depending on the portal of entry of the allergen and may take the form of localized cutaneous swellings (skin allergy, hives), nasal and conjunctival discharge (allergic rhinitis and conjunctivitis), hay fever, bronchial asthma, or allergic gastroenteritis (food allergy). Many local type I hypersensitivity reactions have two well-defined phases (Fig. 6-11). The *immediate, or initial, response* is characterized by vasodilation, vascular leakage, and depending on the location, smooth muscle spasm or glandular secretions. These changes usually become evident within 5 to 30 minutes after exposure to an allergen and tend to subside in 60 minutes. In many instances (e.g., allergic rhinitis and bronchial asthma), a *second, late-phase* reaction sets in 2 to 24 hours later without additional exposure to antigen and may last for several days. This late-phase reaction is characterized by infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells as well as tissue destruction, typically in the form of mucosal epithelial cell damage.

Because mast cells are central to the development of immediate hypersensitivity, we first review some of their salient characteristics and then discuss the immune mechanisms that underlie this form of hypersensitivity.[22] *Mast cells* are bone

Figure 6-11 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. *(Courtesy of Dr. Daniel Friend, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

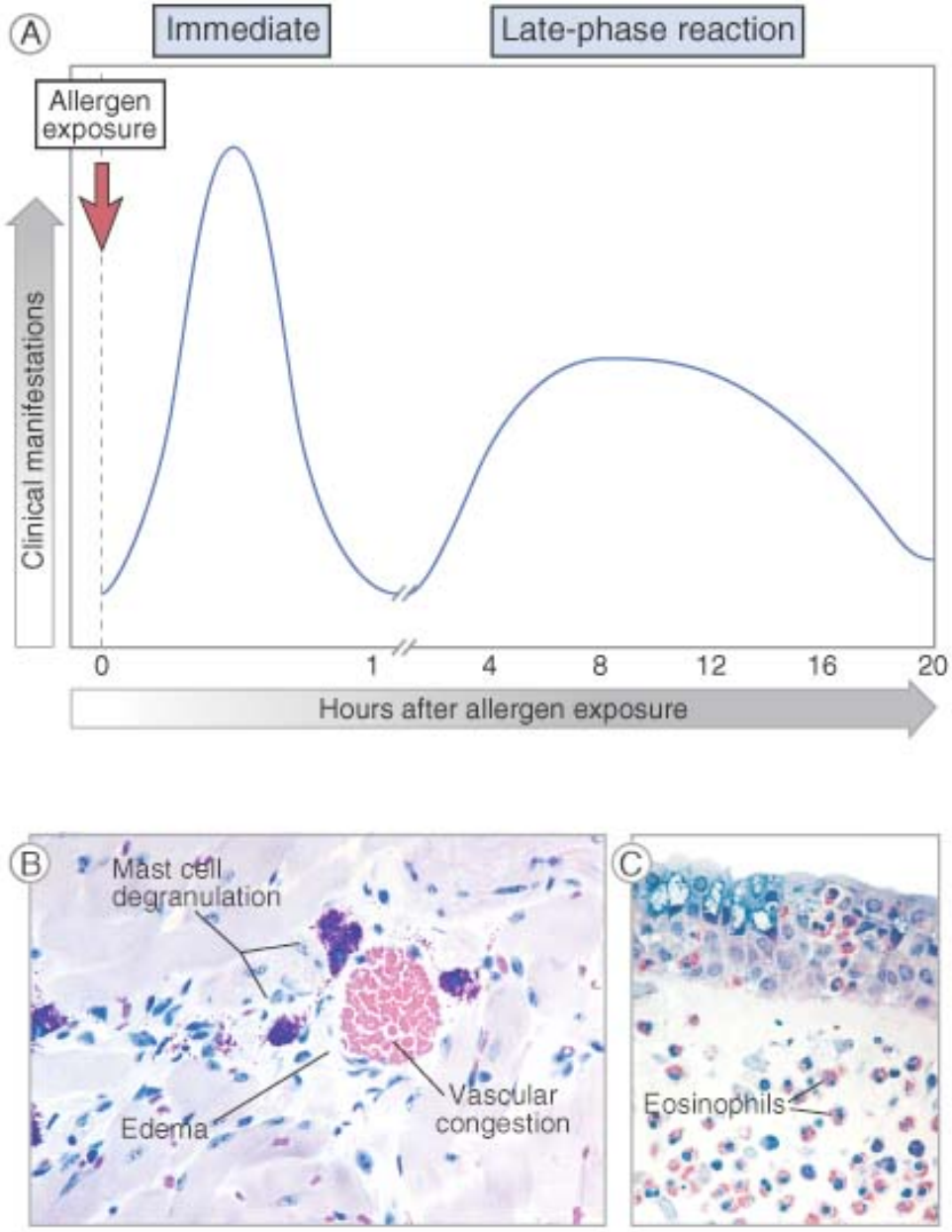
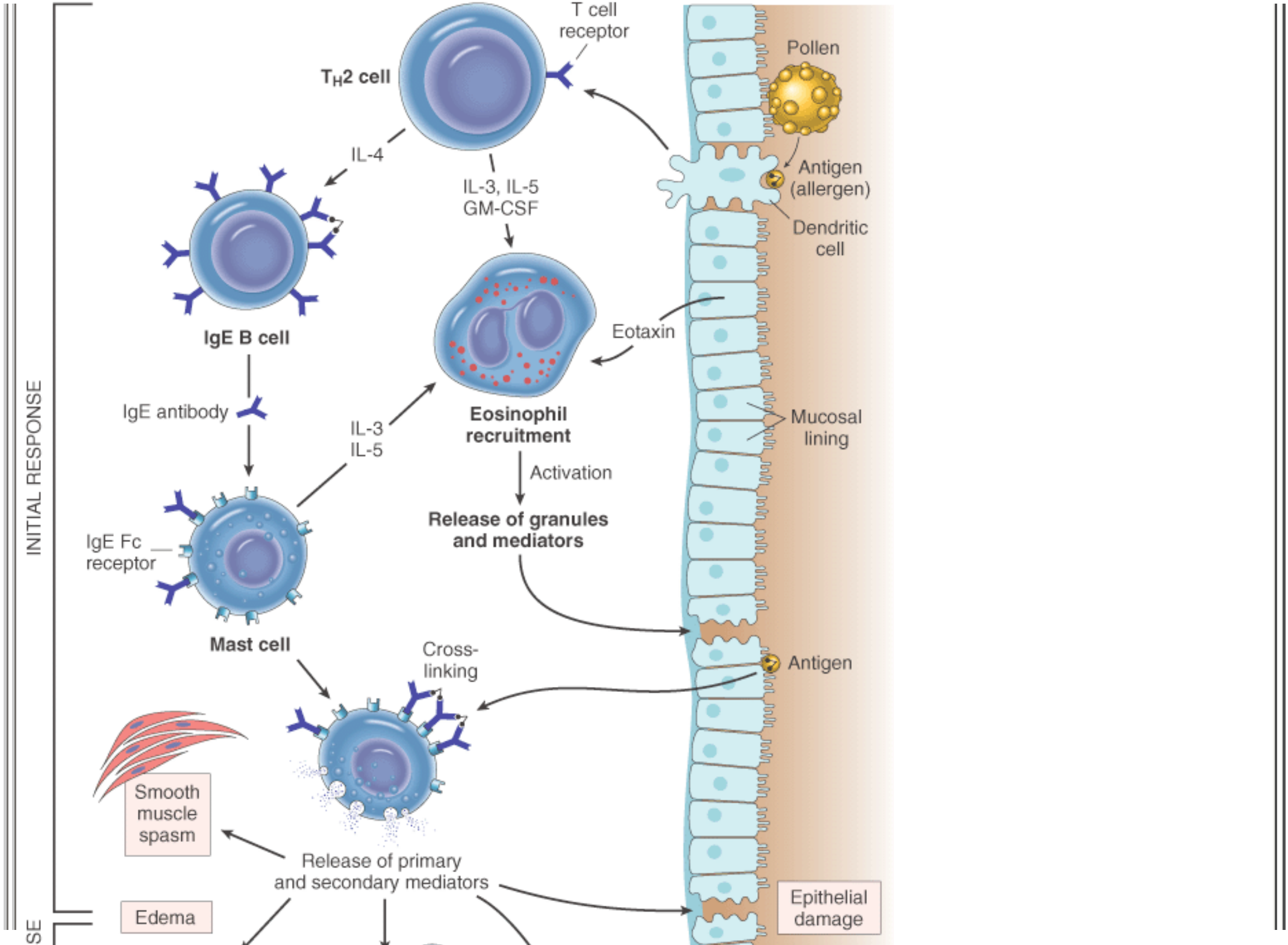


Figure 6-12 Pathogenesis of immediate (type I) hypersensitivity reaction. The late-phase reaction is dominated by leukocyte infiltration and tissue injury. T_H 2, T-helper type 2 CD4 cells.


INITIAL RESPONSE
T cell receptor
T_H2 cell
Pollen
IL-4
IL-3, IL-5
GM-CSF
Antigen (allergen)
Dendritic cell
IgE B cell
Eotaxin
IgE antibody
IL-3
IL-5
Eosinophil recruitment
Mucosal lining
Activation
IgE Fc receptor
Release of granules and mediators
Mast cell
Cross-linking
Antigen
Smooth muscle spasm
Release of primary and secondary mediators
Edema
Epithelial damage

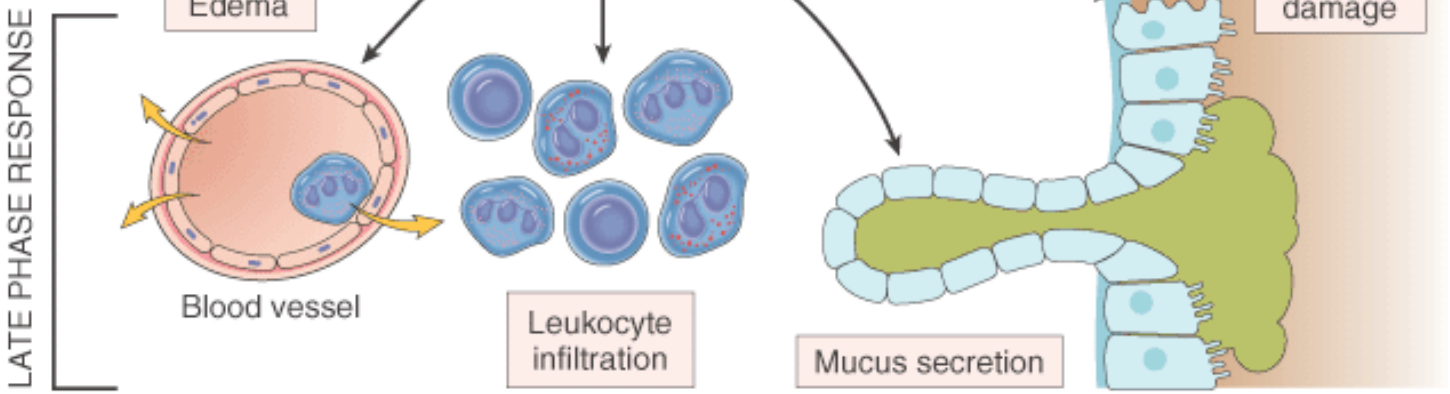
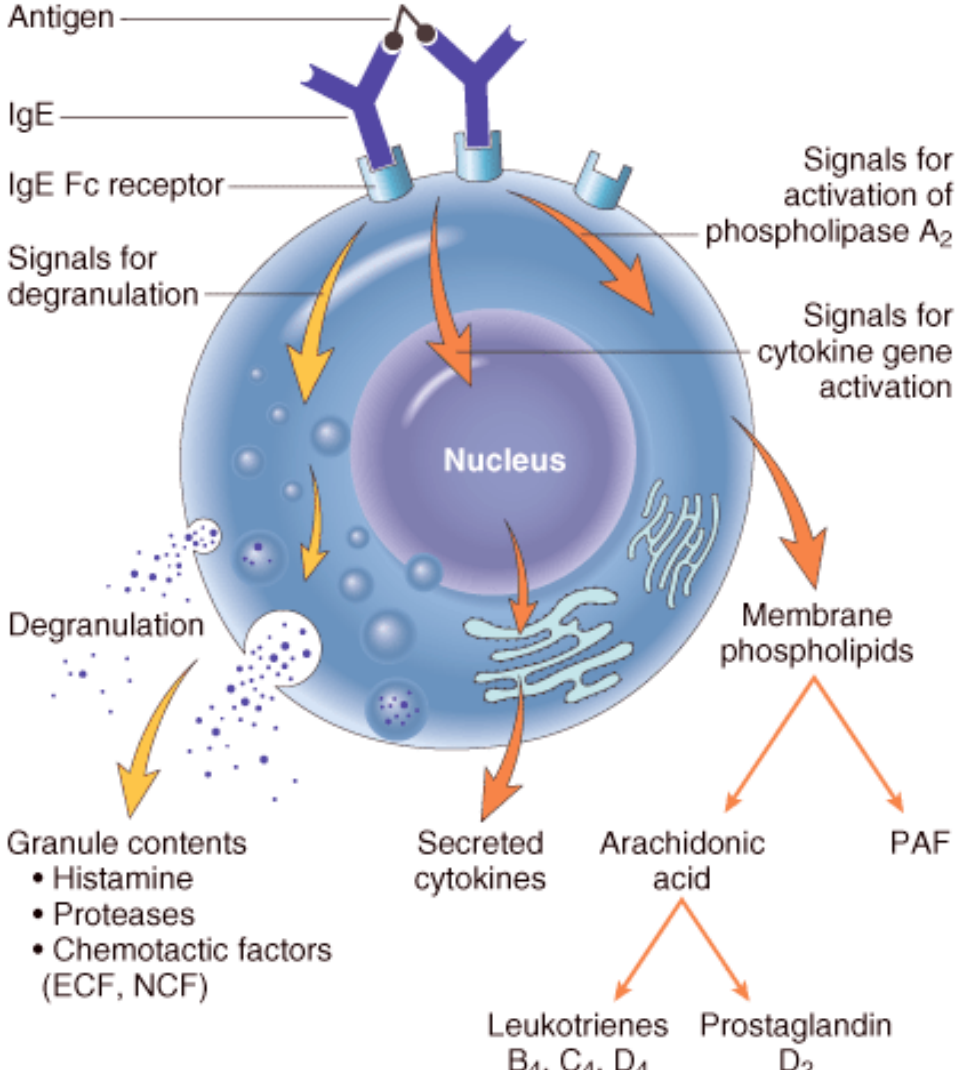


Figure 6-13 Activation of mast cells in immediate hypersensitivity and release of their mediators. ECF, eosinophil chemotactic factor; NCF, neutrophil chemotactic factor; PAF, platelet-activating factor.



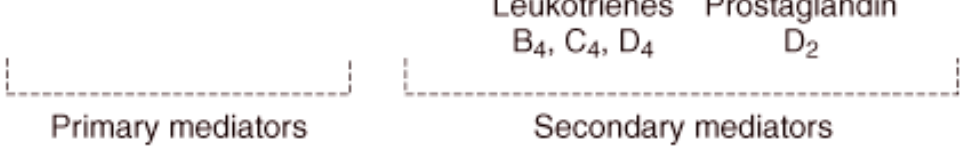


TABLE 6-3 -- Summary of the Action of Mast Cell Mediators in Immediate (Type I) Hypersensitivity

Action	Mediator
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., TNF
	Leukotriene B_4
	Eosinophil and neutrophil chemotactic factors (not defined biochemically)
	PAF

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

produce leukotriene C_4 and PAF and directly activate mast cells to release mediators. Thus, *the recruited cells amplify and sustain the inflammatory response without additional exposure to the triggering antigen*. It is now believed that this late-phase inflammatory response is a major cause of symptoms in some type I hypersensitivity disorders, such as allergic asthma. Therefore, treatment of these diseases requires the use of broad-spectrum anti-inflammatory drugs, such as steroids.

A final point that should be mentioned in this general discussion of immediate hypersensitivity is that *susceptibility to these reactions is genetically determined*. The term *atopy* refers to a predisposition to develop localized immediate hypersensitivity reactions to a variety of inhaled and ingested allergens. Atopic individuals tend to have higher serum IgE levels, and more IL-4-producing T_H 2 cells, compared with the general population. A positive family history of allergy is found in 50% of atopic individuals. The basis of familial predisposition is not clear, but studies in patients with asthma reveal linkage to several gene loci.[27] Candidate genes have been mapped to 5q31, where genes for the cytokines IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF are located, consistent with the idea that these cytokines are involved in the reactions. Linkage has also been noted to 6p, close to the HLA complex, suggesting that the inheritance of certain HLA alleles permits reactivity to certain allergens. Another asthma-associated locus is on chromosome 11q13, the location of the gene encoding the β chain of the high-affinity IgE receptor, but many studies have failed to establish a linkage of atopy with the FcepsilonRI β chain chain or even this chromosomal region.

To summarize, immediate (type I) hypersensitivity is a complex disorder resulting from an IgE-mediated triggering of mast cells and subsequent accumulation of inflammatory cells at sites of antigen deposition. These events are regulated in large part by the induction of T_H 2-type helper T cells that promote synthesis of IgE and accumulation of inflammatory cells, particularly eosinophils. The clinical features result from release of mast-cell mediators as well as the accumulation of an eosinophilrich inflammatory exudate. With this consideration of the basic mechanisms of type I hypersensitivity, we turn to some conditions that are important examples of IgE-mediated disease.

Systemic Anaphylaxis

Systemic anaphylaxis is characterized by vascular shock, widespread edema, and difficulty in breathing. In humans, systemic anaphylaxis may occur after administration of foreign proteins (e.g., antisera), hormones, enzymes, polysaccharides, and drugs (such as the antibiotic penicillin).[28] The severity of the disorder varies with the level of sensitization. Extremely small doses of antigen may trigger anaphylaxis, for example, the tiny amounts used in ordinary skin testing for various forms of allergies. Within minutes after exposure, itching, hives, and skin erythema appear, followed shortly thereafter by a striking contraction of respiratory bronchioles and respiratory distress. Laryngeal edema results in hoarseness. Vomiting, abdominal cramps, diarrhea, and laryngeal obstruction follow, and the patient may go into shock and even die within the hour. The risk of anaphylaxis must be borne in mind when certain therapeutic agents are administered. Although patients at risk can generally be identified by a previous history of some form of allergy, the absence of such

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a history does not preclude the possibility of an anaphylactic reaction.

Local Immediate Hypersensitivity Reactions

Local immediate hypersensitivity, or allergic, reactions are exemplified by so-called atopic allergy. About 10% of the population suffers from allergies involving localized reactions to common environmental allergens, such as pollen, animal dander, house dust, foods, and the like. Specific diseases include urticaria, angioedema, allergic rhinitis (hay fever), and some forms of asthma, all discussed elsewhere in this book. The familial predisposition to the development of this type of allergy has been mentioned earlier.

Antibody-Mediated (Type II) Hypersensitivity

Type II hypersensitivity is mediated by antibodies directed toward antigens present on cell surfaces or extracellular matrix. The antigenic determinants may be intrinsic to the cell membrane or matrix, or they may take the form of an exogenous antigen, such as a drug metabolite, that is adsorbed on a cell surface or matrix. In either case, the hypersensitivity reaction results from the binding of antibodies to normal or altered cell-surface antigens. Three different antibody-dependent mechanisms involved in this type of reaction are depicted in Figure 6-14 and described next. Most of these reactions involve the effector mechanisms that are used by antibodies, namely the complement system and phagocytes.

Opsonization and Complement- and Fc Receptor-Mediated Phagocytosis

The depletion of cells targeted by antibodies is, to a large extent, because the cells are coated (opsonized) with molecules that make them attractive for phagocytes. When antibodies are deposited on the surfaces of cells, they may activate the complement system (if the antibodies are of the IgM or IgG class). Complement activation generates byproducts, mainly C3b and C4b, which are deposited on the surfaces of the cells and recognized by phagocytes that express receptors for these proteins. In addition, cells opsonized by IgG antibodies are recognized by phagocyte Fc receptors, which are specific for the Fc portions of some IgG subclasses. The net result is the phagocytosis of the opsonized cells and their destruction (Fig. 6-14*A*). Complement activation on cells also leads to the formation of the membrane attack complex, which disrupts membrane integrity by "drilling holes" through the lipid bilayer, thereby causing osmotic lysis of the cells.

Antibody-mediated destruction of cells may occur by another process called *antibody-dependent cellular cytotoxicity (ADCC).* This form of antibody-mediated cell injury does not involve

fixation of complement but instead requires the cooperation of leukocytes. Cells that are coated with low concentrations of IgG antibody are killed by a variety of effector cells, which bind to the target by their receptors for the Fc fragment of IgG, and cell lysis proceeds without phagocytosis. ADCC may be mediated by monocytes, neutrophils, eosinophils, and NK cells. Although, in most instances, IgG antibodies are involved in ADCC, in certain cases (e.g., eosinophil-mediated cytotoxicity against parasites), IgE antibodies are used. The role of ADCC in hypersensitivity diseases is uncertain.

Clinically, antibody-mediated cell destruction and phagocytosis occur in the following situations: (1) *transfusion reactions*, in which cells from an incompatible donor react with and are opsonized by preformed antibody in the host; (2) *erythroblastosis fetalis*, in which there is an antigenic difference between the mother and the fetus, and antibodies (of the IgG class) from the mother cross the placenta and cause destruction of fetal red cells; (3) *autoimmune hemolytic anemia*, *agranulocytosis*, and *thrombocytopenia*, in which individuals produce antibodies to their own blood cells, which are then destroyed; and (4) *certain drug reactions*, in which antibodies are produced that react with the drug, which may be attached to the surface of erythrocytes or other cells.

Complement- and Fc Receptor-Mediated Inflammation

When antibodies deposit in extracellular tissues, such as basement membranes and matrix, the resultant injury is because of inflammation and not because of phagocytosis or lysis of cells. The deposited antibodies activate complement, generating byproducts, such as C5a (and to a lesser extent C4a and C3a), that recruit neutrophils and monocytes. The same cells also bind to the deposited antibodies via their Fc receptors. The leukocytes are activated, they release injurious substances, such as enzymes and reactive oxygen intermediates, and the result is damage to the tissues (Fig. 6-14*B*). It was once thought that complement was the major mediator of antibody-induced inflammation, but knockout mice lacking Fc receptors also show striking reduction in these reactions. It is now believed that inflammation in antibody-mediated (and immune complex-mediated) diseases is because of both complement and Fc receptor-dependent reactions.[29]

Antibody-mediated inflammation is the mechanism responsible for tissue injury in some forms of *glomerulonephritis*, *vascular rejection* in organ grafts, and other diseases (Table 6-4). As we shall discuss in more detail below, the same reaction is involved in immune complex-mediated diseases.

Antibody-Mediated Cellular Dysfunction

In some cases, antibodies directed against cell-surface receptors impair or dysregulate function without causing cell injury or inflammation. For example, in *myasthenia gravis*, antibodies reactive with acetylcholine receptors in the motor end-plates of skeletal muscles impair neuromuscular transmission and therefore cause muscle weakness (Fig. 6-14*C*). In *pemphigus vulgaris*, antibodies against desmosomes disrupt intercellular junctions in epidermis, leading to the formation of skin vesicles. The converse (i.e., antibody-mediated stimulation of cell function) is noted in *Graves disease*. In this disorder, antibodies against the thyroid-stimulating hormone receptor on thyroid epithelial cells stimulate the cells, resulting in hyperthyroidism.

Immune Complex-Mediated (Type III) Hypersensitivity

Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition. The toxic

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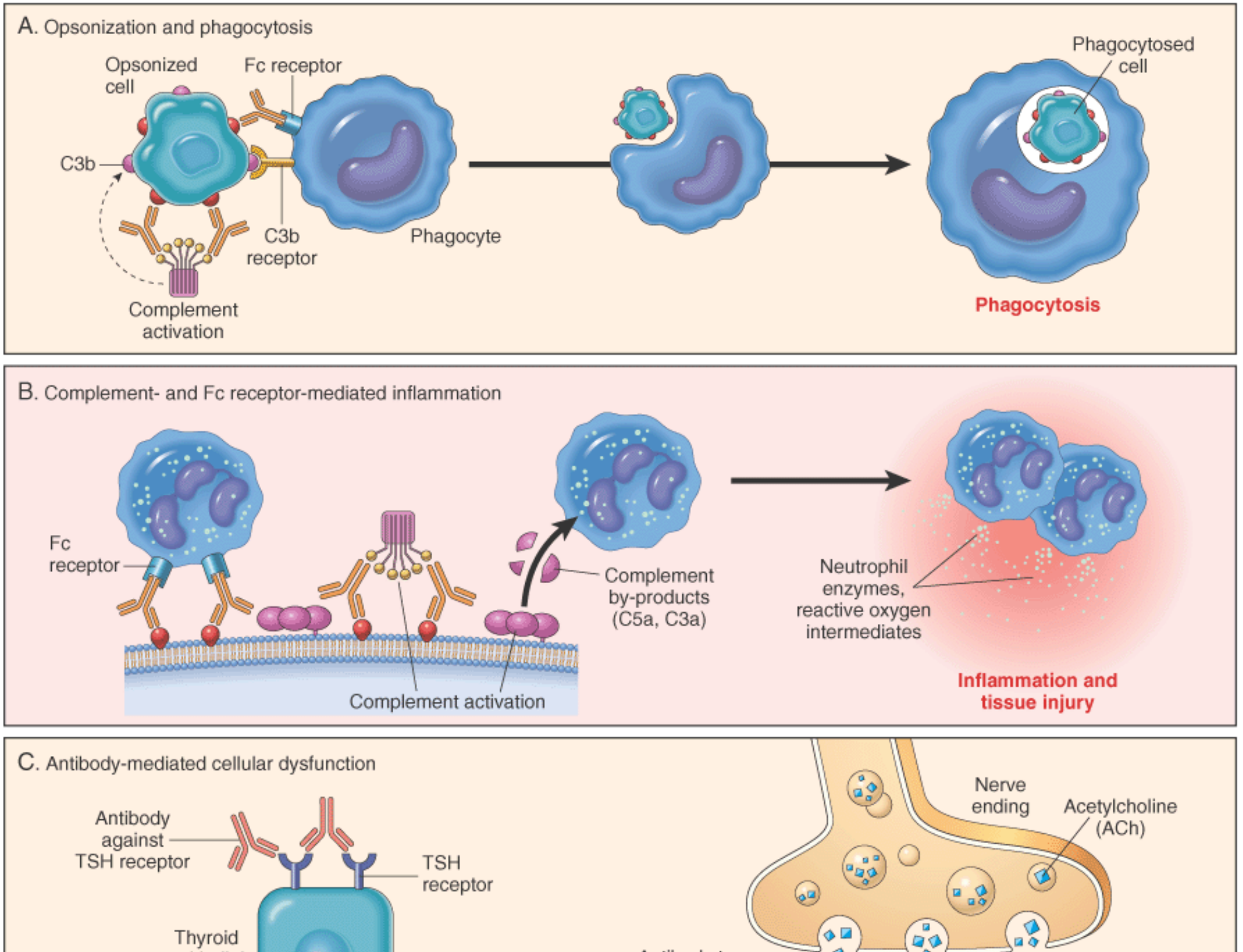
Figure 6-14 Schematic illustration of the three major mechanisms of antibody-mediated injury. *A*, Opsonization of cells by antibodies and complement components and ingestion by phagocytes. *B*, Inflammation induced by antibody binding to Fc receptors of leukocytes and by complement breakdown products. *C*, Antireceptor 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.


A. Opsonization and phagocytosis
Opsonized cell
Fc receptor
C3b
C3b receptor
Phagocyte
Complement activation
Phagocytosed cell
Phagocytosis
B. Complement- and Fc receptor-mediated inflammation
Fc receptor
Complement activation
Complement by-products (C5a, C3a)
Neutrophil enzymes, reactive oxygen intermediates
Inflammation and tissue injury
C. Antibody-mediated cellular dysfunction
Antibody against TSH receptor
TSH receptor
Thyroid
Nerve ending
Acetylcholine (ACh)

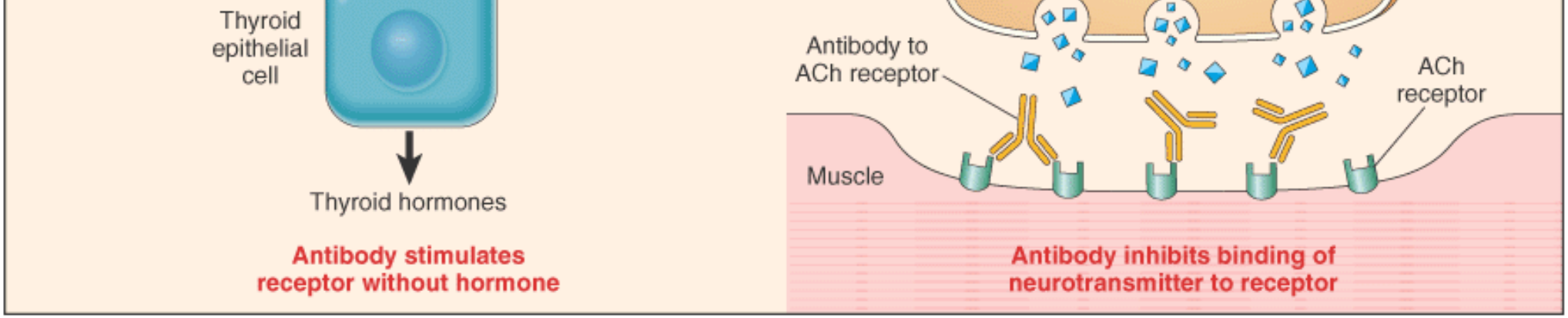


TABLE 6-4 -- Examples of Antibody-Mediated Diseases (Type II Hypersensitivity)

Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpllb:Illa intergrin)	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	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

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

From Abbas AK, Lichtman H: Cellular and Molecular Immunology. 5th edition. WB Saunders Company, Philadelphia, 2003.

Examples of immune complex disorders and the antigens involved are listed in Table 6-5 . Immune complex-mediated diseases can be *generalized*, if immune complexes are formed in the

circulation and are deposited in many organs, or *localized* to particular organs, such as the kidney (glomerulonephritis), joints (arthritis), or the small blood vessels of the skin if the complexes are formed and deposited locally. These two patterns are considered separately.

Systemic Immune Complex Disease

Acute serum sickness is the prototype of a systemic immune complex disease; it was at one time a frequent sequela to the administration of large amounts of foreign serum (e.g., immune serum from horses used for passive immunization.) The

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 *(Treponema)*; parasite antigens (malaria, schistosomes); tumor antigens	Nephritis
Reactive arthritis	Bacterial antigens *(Yersinia)*	Acute arthritis
Arthus reaction	Various foreign proteins	Cutaneous vasculitis
Serum sickness	Various proteins, e.g., foreign serum (anti-thymocyte globulin)	Arthritis, vasculitis, nephritis

occurrence of diseases caused by immune complexes was suspected in the early 1900s by a physician named Clemens von Pirquet. Patients with diphtheria infection were being treated with serum from horses immunized with the diphtheria toxin. Von Pirquet noted that some of these patients developed arthritis, skin rash, and fever, and the symptoms appeared more rapidly with repeated injection of the serum. Von Pirquet concluded that the treated patients made antibodies to horse serum proteins, these antibodies formed complexes with the injected proteins, and the disease was due to the antibodies or immune complexes. He called this disease "serum disease"; it is now known as serum sickness. In modern times the disease is infrequent, but it is an informative model that has taught us a great deal about systemic immune complex disorders.

For the sake of discussion, the pathogenesis of systemic immune complex disease can be divided into three phases: (1) formation of antigen-antibody complexes in the circulation; (2) deposition of the immune complexes in various tissues, thus initiating; and (3) an inflammatory reaction at the sites of immune complex deposition (Fig. 6-15). The *first phase* is initiated by the introduction of antigen, usually a protein, and its interaction with immunocompetent cells, resulting in the formation of antibodies approximately a week after the injection of the protein. These antibodies are secreted into the blood, where they react with the antigen still present in the circulation to form antigen-antibody complexes. In the *second phase*, the circulating antigen-antibody complexes are deposited in various tissues.

The factors that determine whether immune complex formation will lead to tissue deposition and disease are not fully understood, but two possible influences are the size of the immune complexes and the functional status of the mononuclear phagocyte system:

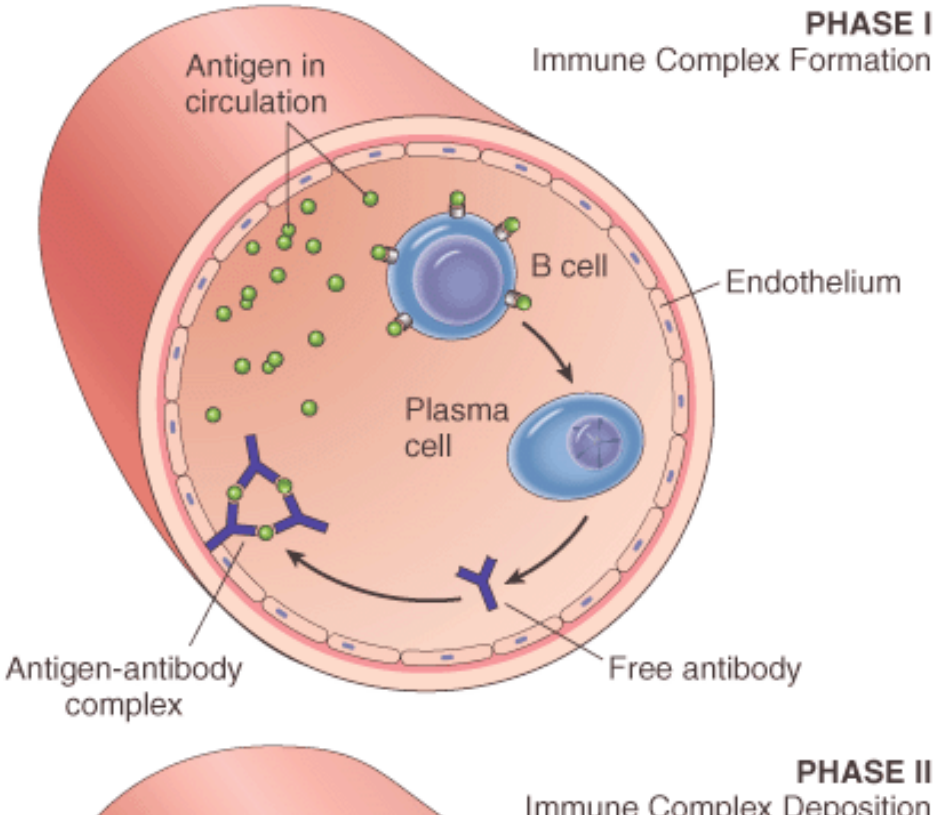
• Large complexes formed in great antibody excess are rapidly removed from the circulation by the mononuclear phagocyte system and are therefore relatively harmless. The most pathogenic complexes are of small or intermediate size (formed in slight antigen excess), which bind less avidly to phagocytic cells and therefore circulate longer.
• Because the mononuclear phagocyte system normally filters out the circulating immune complexes, its overload or intrinsic dysfunction increases the probability of persistence of immune complexes in circulation and tissue deposition.

In addition, several other factors, such as charge of the immune complexes (anionic versus cationic), valency of the antigen, avidity of the antibody, affinity of the antigen to various tissue components, three-dimensional (lattice) structure of the complexes, and hemodynamic factors, influence the tissue deposition of complexes. Because most of these influences have been investigated with reference to deposition of immune complexes in the glomeruli, they are discussed further in Chapter 20 . In addition to the renal glomeruli, the favored sites of immune complex deposition are joints, skin, heart, serosal surfaces, and small blood vessels. For complexes to leave the microcirculation and deposit in the vessel wall, an increase in vascular permeability must occur. This is believed to occur when immune complexes bind to inflammatory cells through their Fc or C3b receptors and trigger release of vasoactive mediators as well as permeability-enhancing cytokines. Mast cells may also be involved in this phase of the reaction.

Once complexes are deposited in the tissues, they initiate an acute inflammatory reaction *(third phase)*. During this phase (approximately 10 days after antigen administration), clinical features such as fever, urticaria, arthralgias, lymph node enlargement, and proteinuria appear.

Wherever complexes deposit, the tissue damage is similar. Two mechanisms are believed to cause *inflammation* at the sites of deposition (Fig. 6-16): (1) activation of the complement cascade, and (2) activation of neutrophils and macrophages through their Fc receptors. As discussed in Chapter 2 , *complement activation* promotes inflammation mainly by production of chemotactic factors, which direct the migration of polymorphonuclear leukocytes and monocytes

Figure 6-15 Schematic illustration of the three sequential phases in the induction of systemic immune complex-mediated disease (type III hypersensitivity).



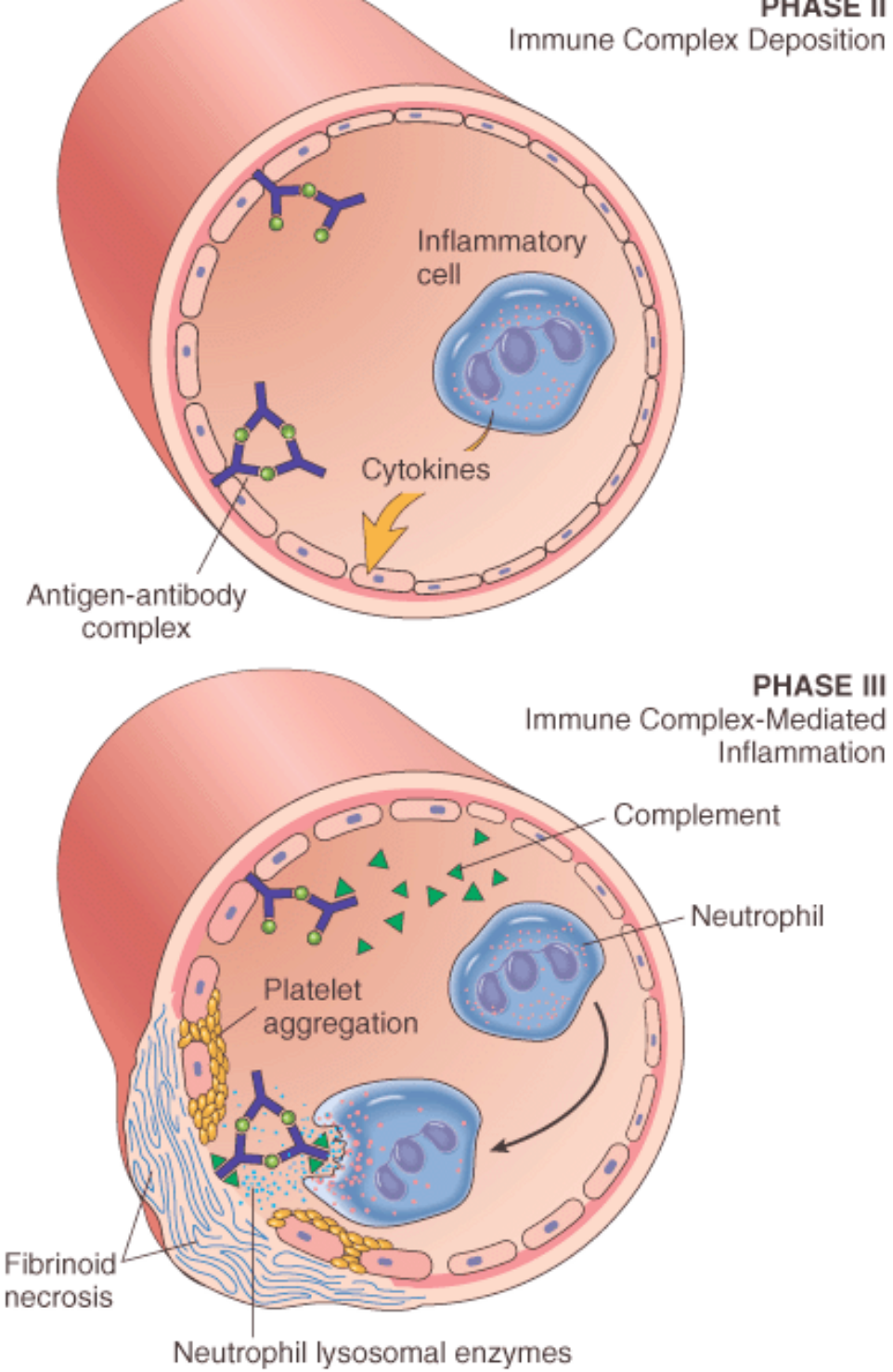


Figure 6-16 Pathogenesis of immune complex-mediated tissue injury. The morphologic consequences are depicted as boxed areas.

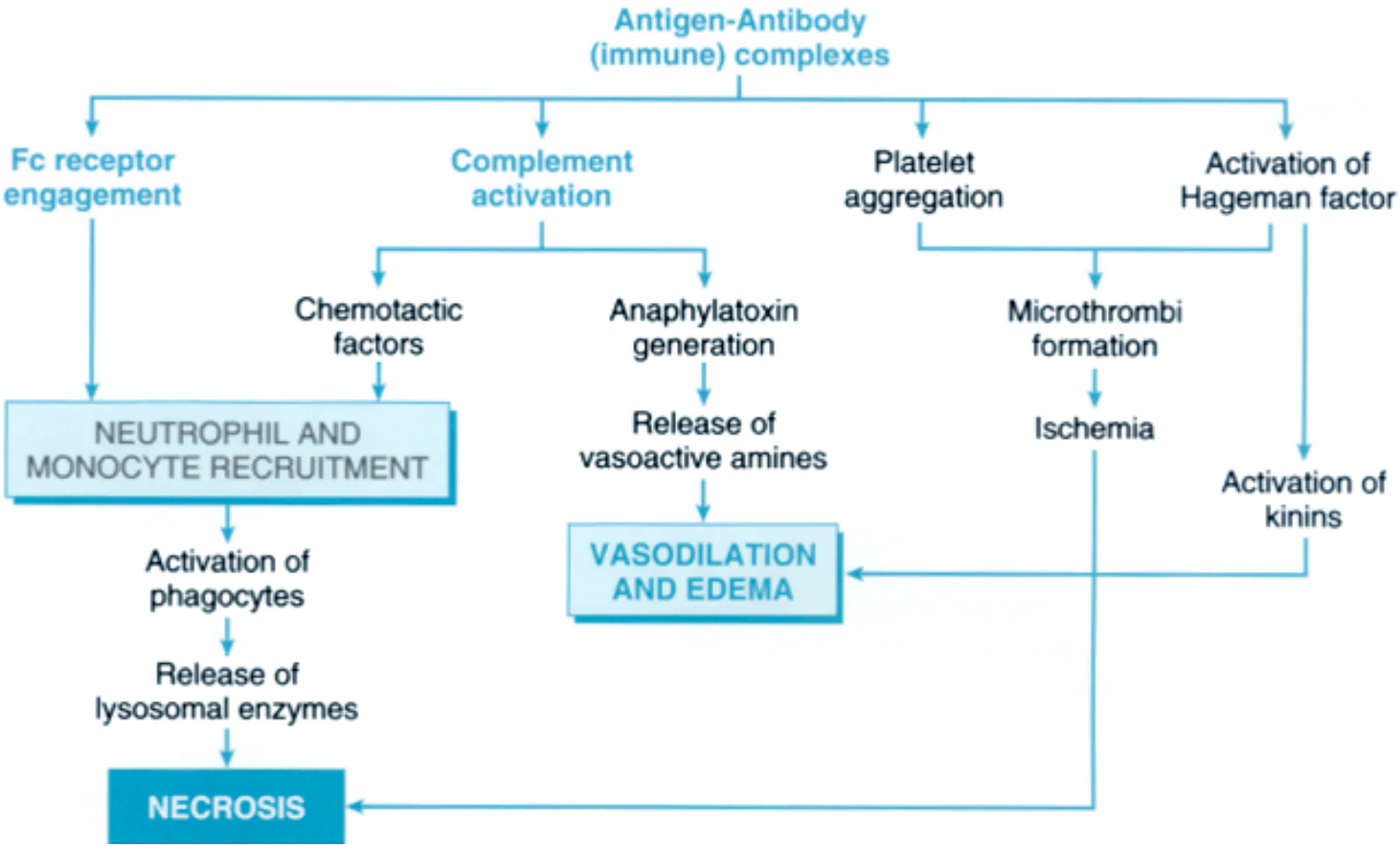


Figure 6-17 Immune complex vasculitis. The necrotic vessel wall is replaced by smudgy, pink "fibrinoid" material. *(Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

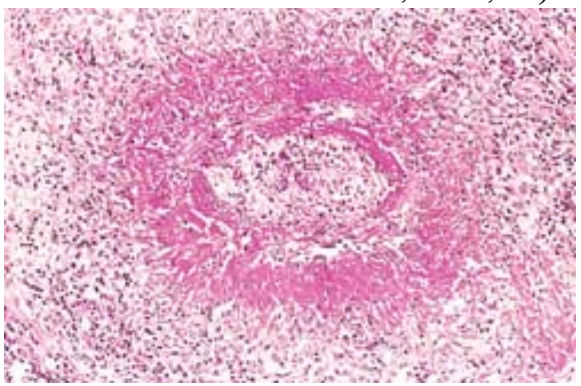


Figure 6-18 Mechanisms of T cell-mediated (type IV) hypersensitivity reactions. *A*, In delayed type hypersensitivity reactions, CD4+ T cells (and sometimes CD8+ cells) respond to tissue antigens by secreting cytokines that stimulate inflammation and activate phagocytes, leading to tissue injury. *B*, In some diseases, CD8+ cytolytic T lymphocytes (CTLs) directly kill tissue cells. APC, antigenpresenting cell.

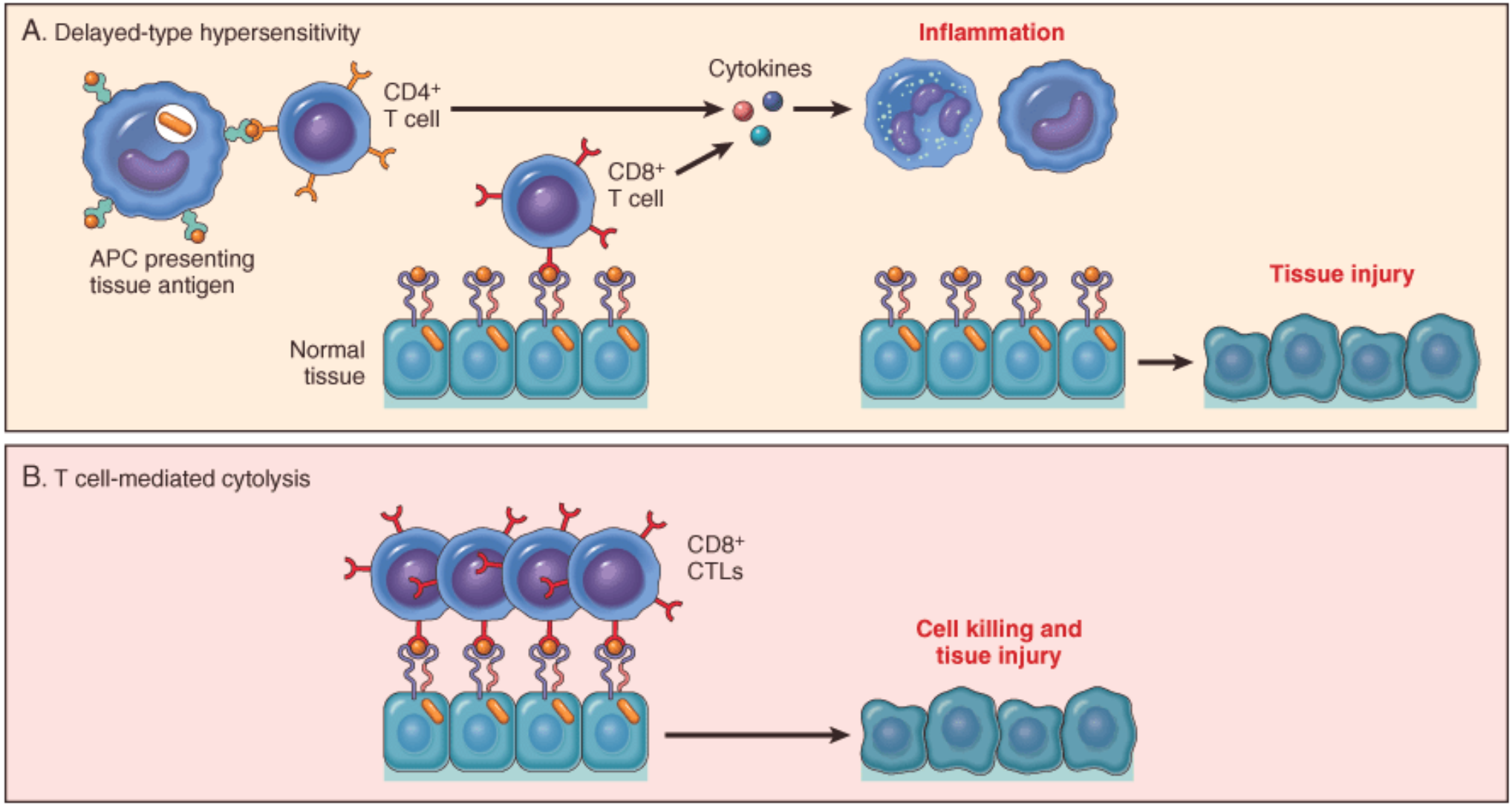


TABLE 6-6 -- Examples of T Cell-Mediated (Type IV) Hypersensitivity

Disease	Specificity of Pathogenic T Cells	Clinicopathologic Manifestations
Type 1 diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	Insulitis (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

and inflammation (Fig. 6-17). Thrombi are formed in the vessels, resulting in local ischemic injury.

Cell-Mediated (Type IV) Hypersensitivity

The cell-mediated type of hypersensitivity is initiated by antigen-activated (sensitized) T lymphocytes. It includes the *delayed type hypersensitivity reactions* mediated by CD4+ T cells, and *direct cell cytotoxicity* mediated by CD8+ T cells (Fig. 6-18). It is the principal pattern of immunologic response not only to a variety of intracellular microbiologic agents, such as *Mycobacterium tuberculosis*, but also to many viruses, fungi, protozoa, and parasites. So-called contact skin sensitivity to chemical agents and graft rejection are other instances of cell-mediated reactions. In addition, many autoimmune diseases are now known to be caused by T cell-mediated reactions (Table 6-6). The two forms of T cell-mediated hypersensitivity are described next.

Figure 6-19 Delayed hypersensitivity in the skin. *A*, Perivascular infiltration by T cells and mononuclear phagocytes. *B*, Immunoperoxidase staining reveals a predominantly perivascular cellular infiltrate that marks positively with anti-CD4 antibodies. *(Courtesy of Dr. Louis Picker, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

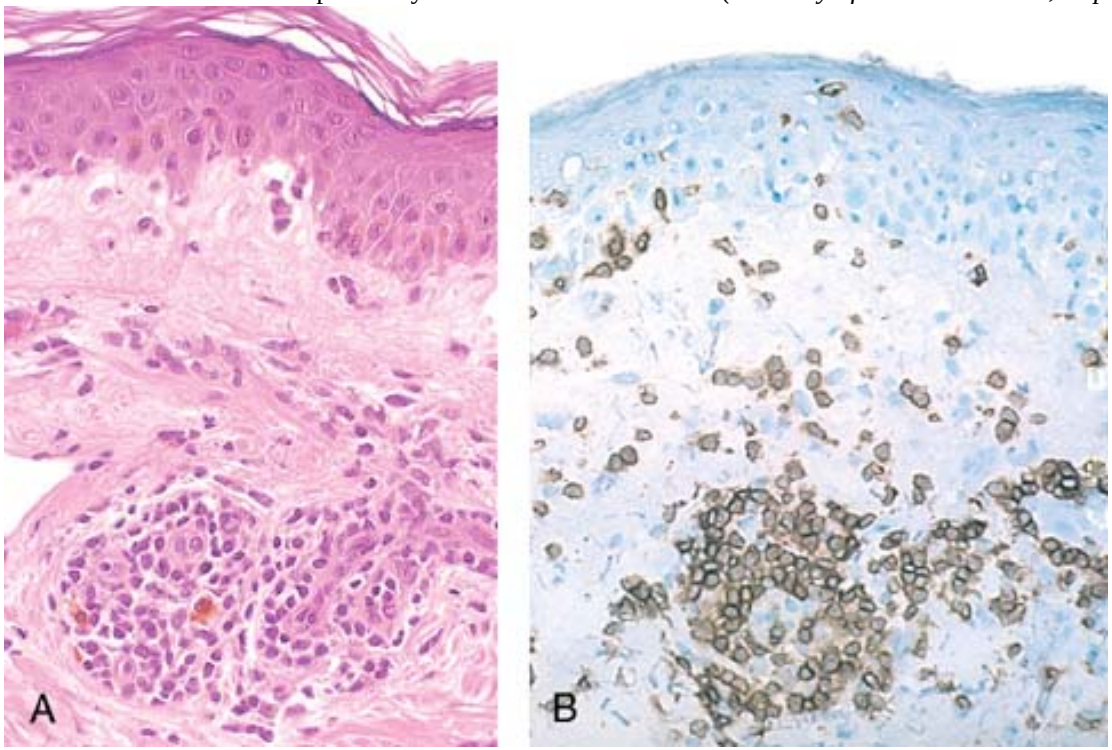


Figure 6-20 A section of a lymph node shows several granulomas, each made up of an aggregate of epithelioid cells and surrounded by lymphocytes. The granuloma in the center shows

several multinucleate giant cells. *(Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

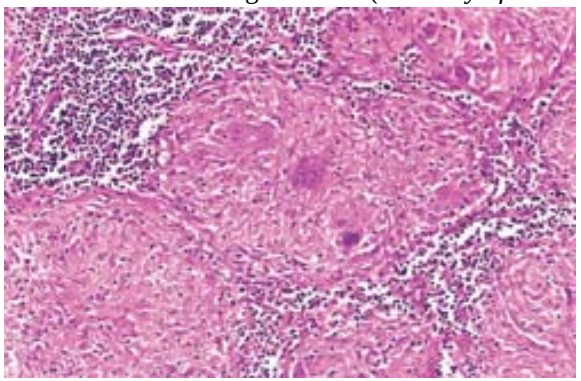


Figure 6-21 Schematic illustration of the events that give rise to the formation of granulomas in cell-mediated (type IV) hypersensitivity reactions. Note the role played by T cell-derived cytokines.

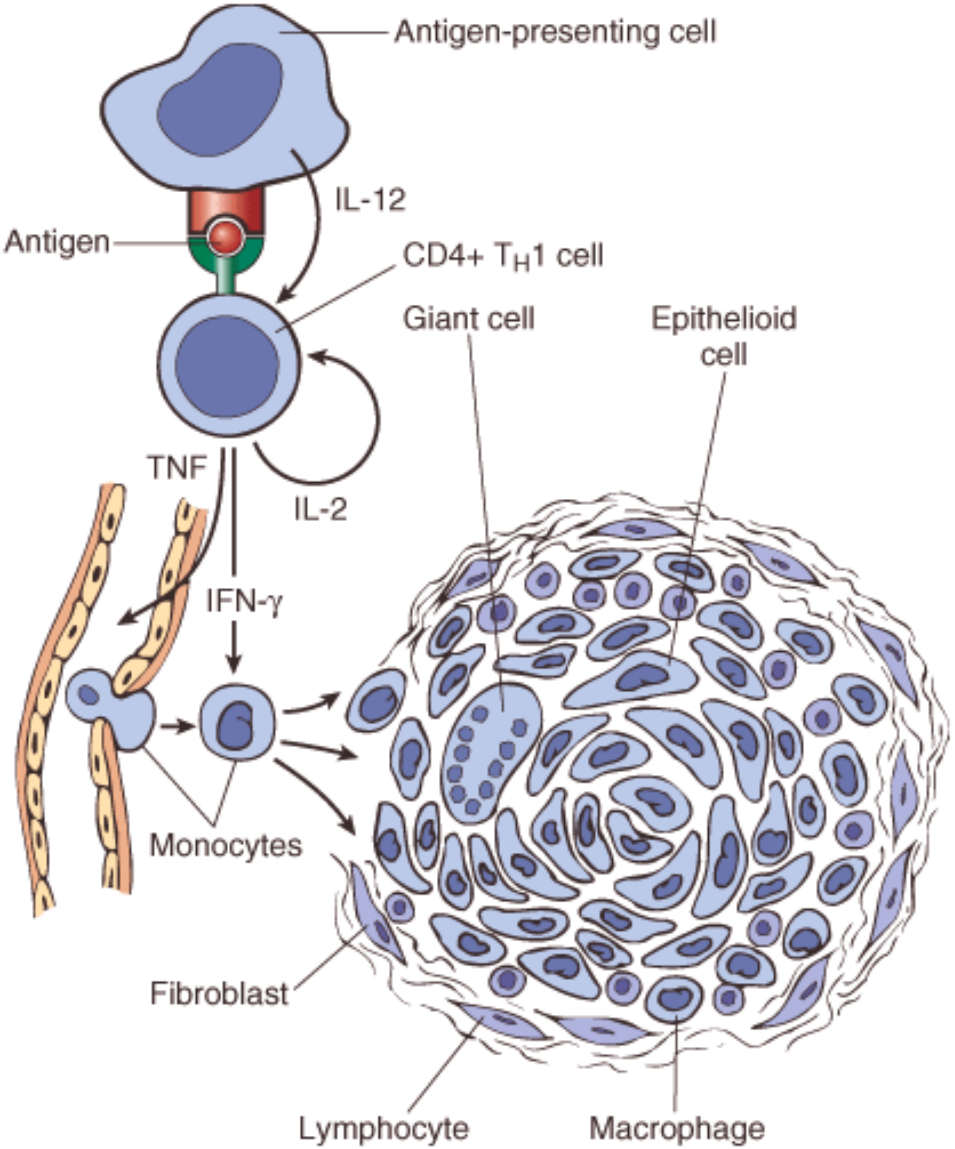


Figure 6-22 Contact dermatitis showing an epidermal blister (vesicle) with dermal and epidermal mononuclear infiltrates. *(Courtesy of Dr. Louis Picker, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

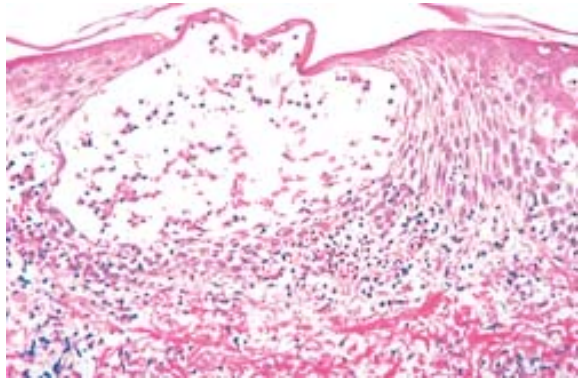
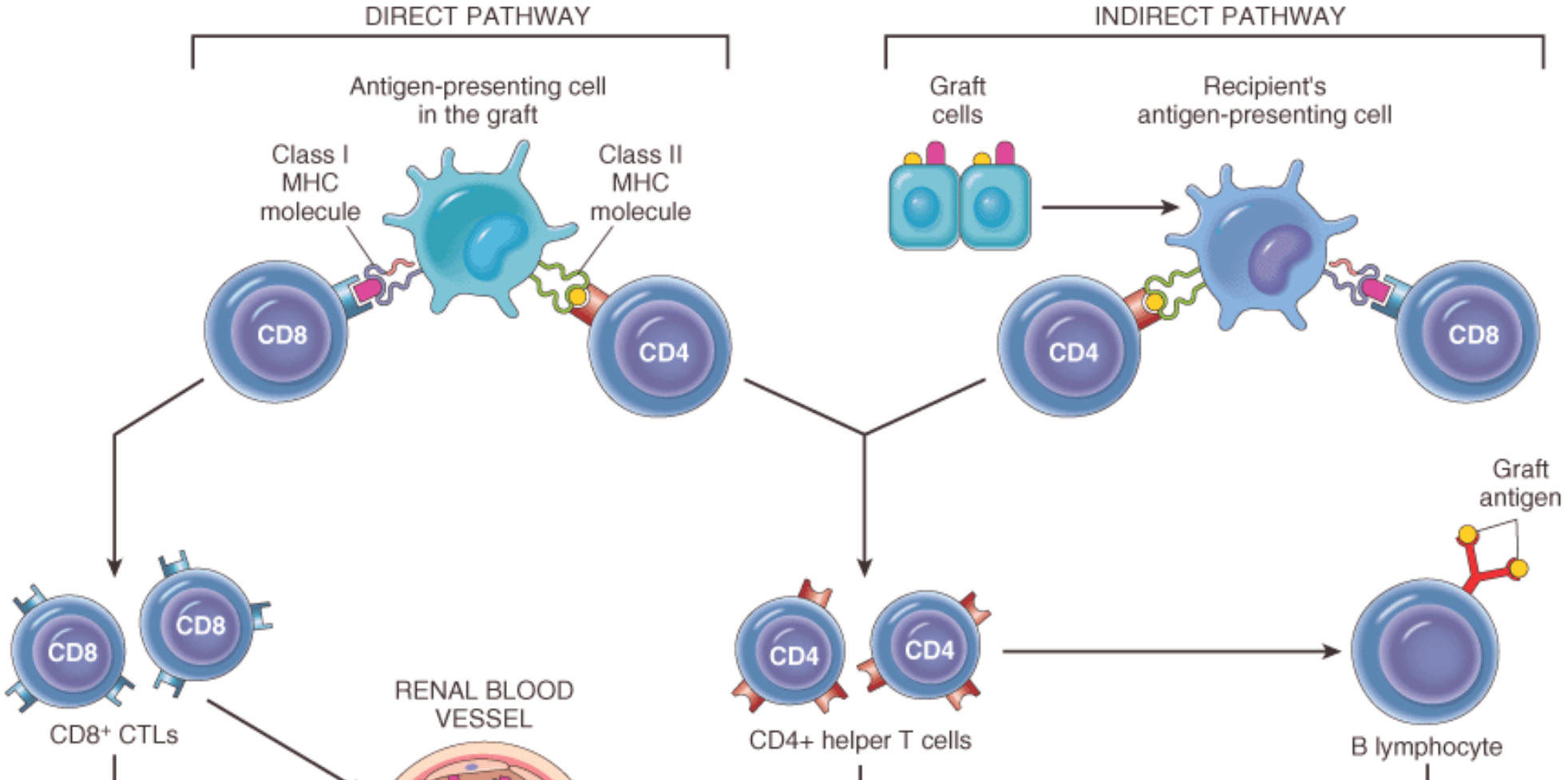


Figure 6-23 Schematic representation of the events that lead to the destruction of histoincompatible grafts. In the direct pathway, donor class I and class II antigens on antigen-presenting cells in the graft (along with B7 molecules, not shown) are recognized by CD8+ cytotoxic T cells and CD4+ helper T cells, respectively, of the host. CD4+ cells proliferate and produce cytokines that induce tissue damage by a local delayed hypersensitivity reaction and stimulate B cells and CD8+ T cells. CD8+ T cells responding to graft antigens differentiate into cytotoxic T lymphocytes that kill graft cells. In the indirect pathway, graft antigens are displayed by host APCs and activate CD4+ cells, which damage the graft by a local delayed hypersensitivity reaction. The example shown is of a kidney allograft.



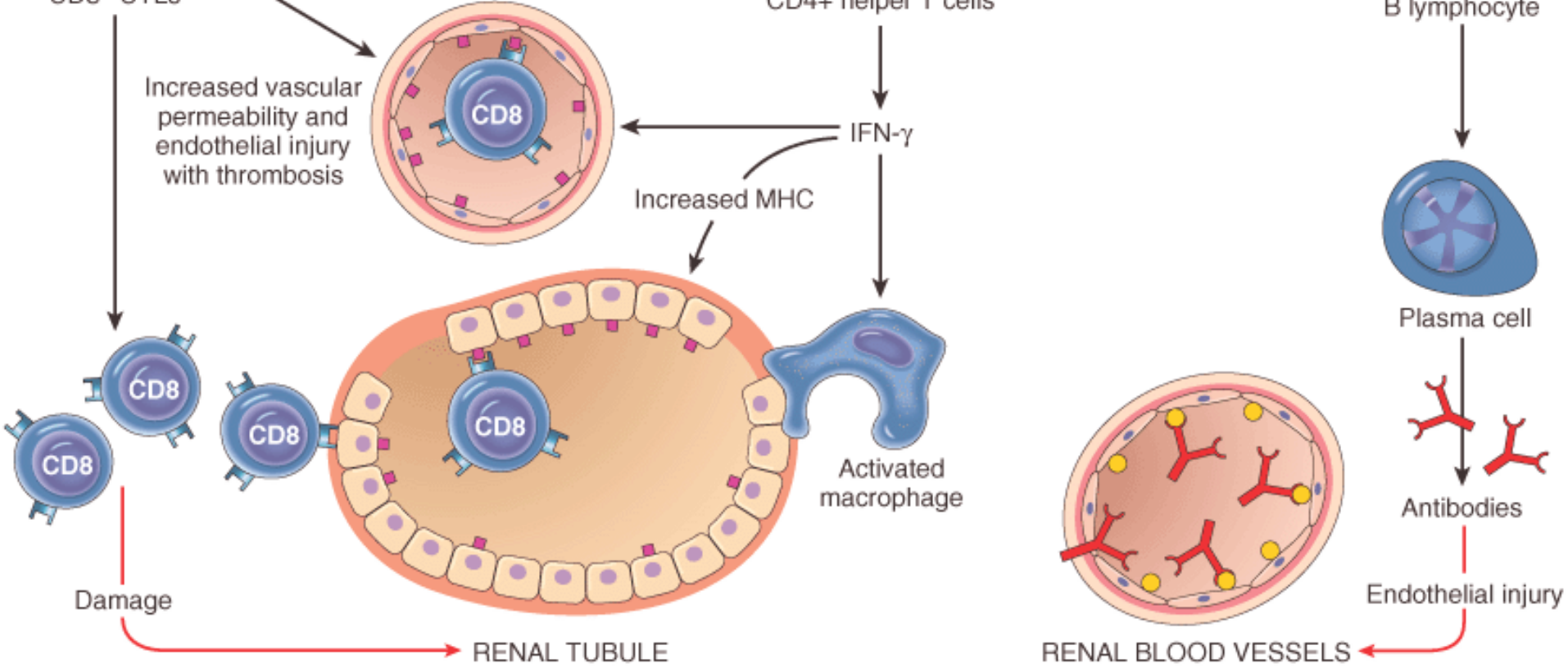


Figure 6-24 Acute cellular rejection of a renal allograft. *A,* An intense mononuclear cell infiltrate occupies the space between the tubules. *B,* T cells (stained brown by the immunoperoxidase technique) are abundant in the interstitium and infiltrating a tubule. *(Courtesy of Dr. Robert Colvin, Department of Pathology, Massachusetts General Hospital, Boston, MA.)*

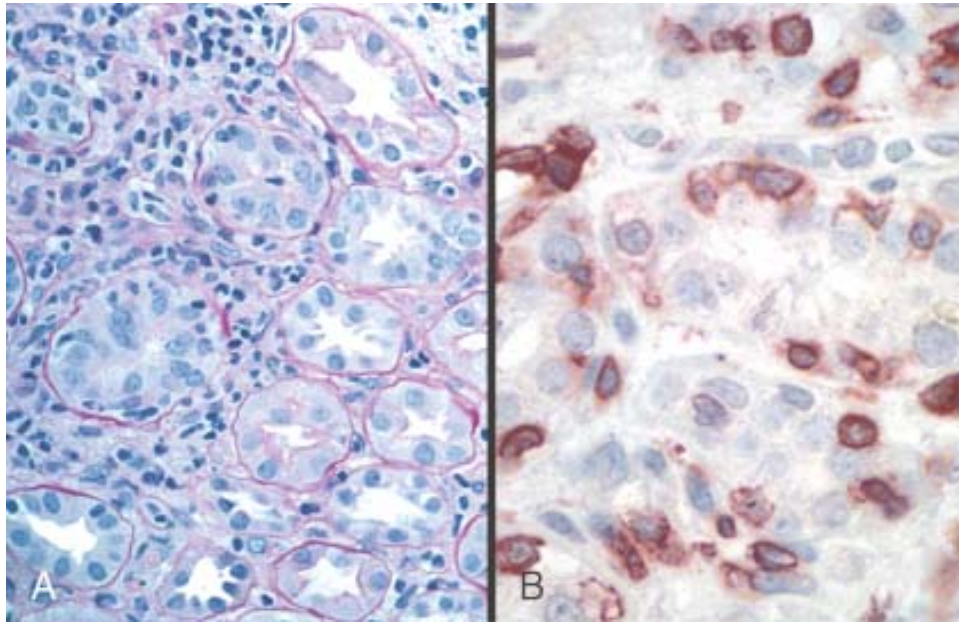


Figure 6-25 Antibody-mediated damage to the blood vessel in a renal allograft. The blood vessel is markedly thickened, and the lumen is obstructed by proliferating fibroblasts and foamy macrophages. *(Courtesy of Dr. Ihsan Housini, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

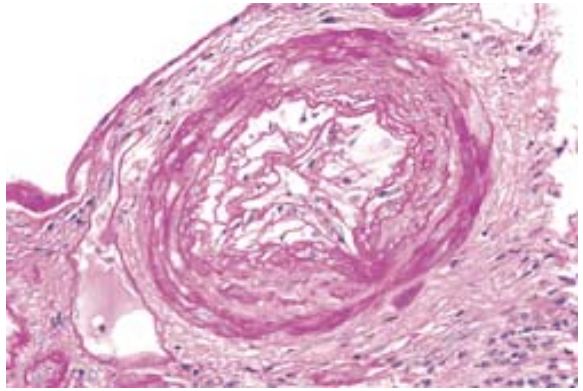


Figure 6-26 Chronic rejection in a kidney allograft. *A,* Changes in the kidney in chronic rejection. *B,* Graft arteriosclerosis. The vascular lumen is replaced by an accumulation of smooth muscle cells and connective tissue in the vessel intima. *(Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.)*

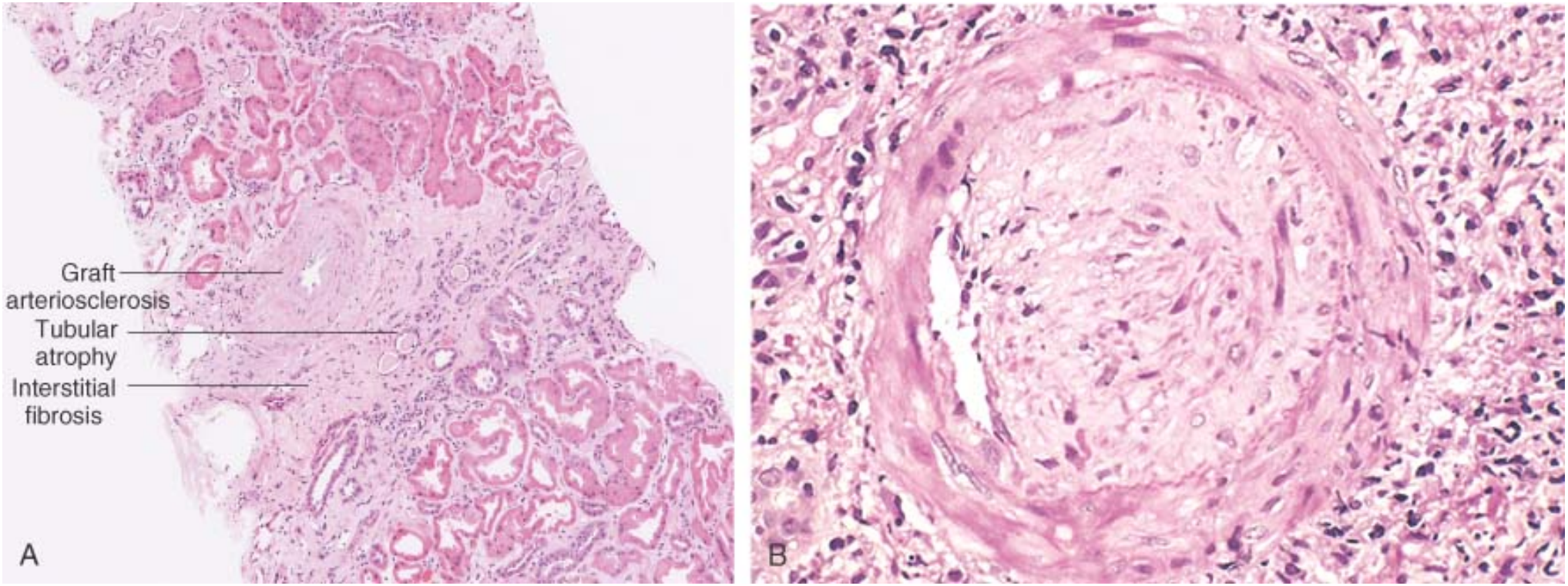


TABLE 6-7 -- Autoimmune Diseases

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 *	

*The evidence supporting an autoimmune basis of these disorders is not strong.

autoimmunity are type I diabetes mellitus, in which the autoreactive T cells and antibodies are specific for β cells of the pancreatic islets, and multiple sclerosis, in which autoreactive T cells react against central nervous system myelin. An example of systemic autoimmune disease is SLE, in which a diversity of antibodies directed against DNA, platelets, red cells, and protein-phospholipid complexes result in widespread lesions throughout the body. In the middle of the spectrum falls Goodpasture syndrome, in which antibodies to basement membranes of lung and kidney induce lesions in these organs.

It is obvious that autoimmunity results from the loss of self-tolerance, and the question arises as to how this happens. Before we look for answers to this question, we review the mechanisms of immunologic tolerance to self-antigens.

Immunologic Tolerance

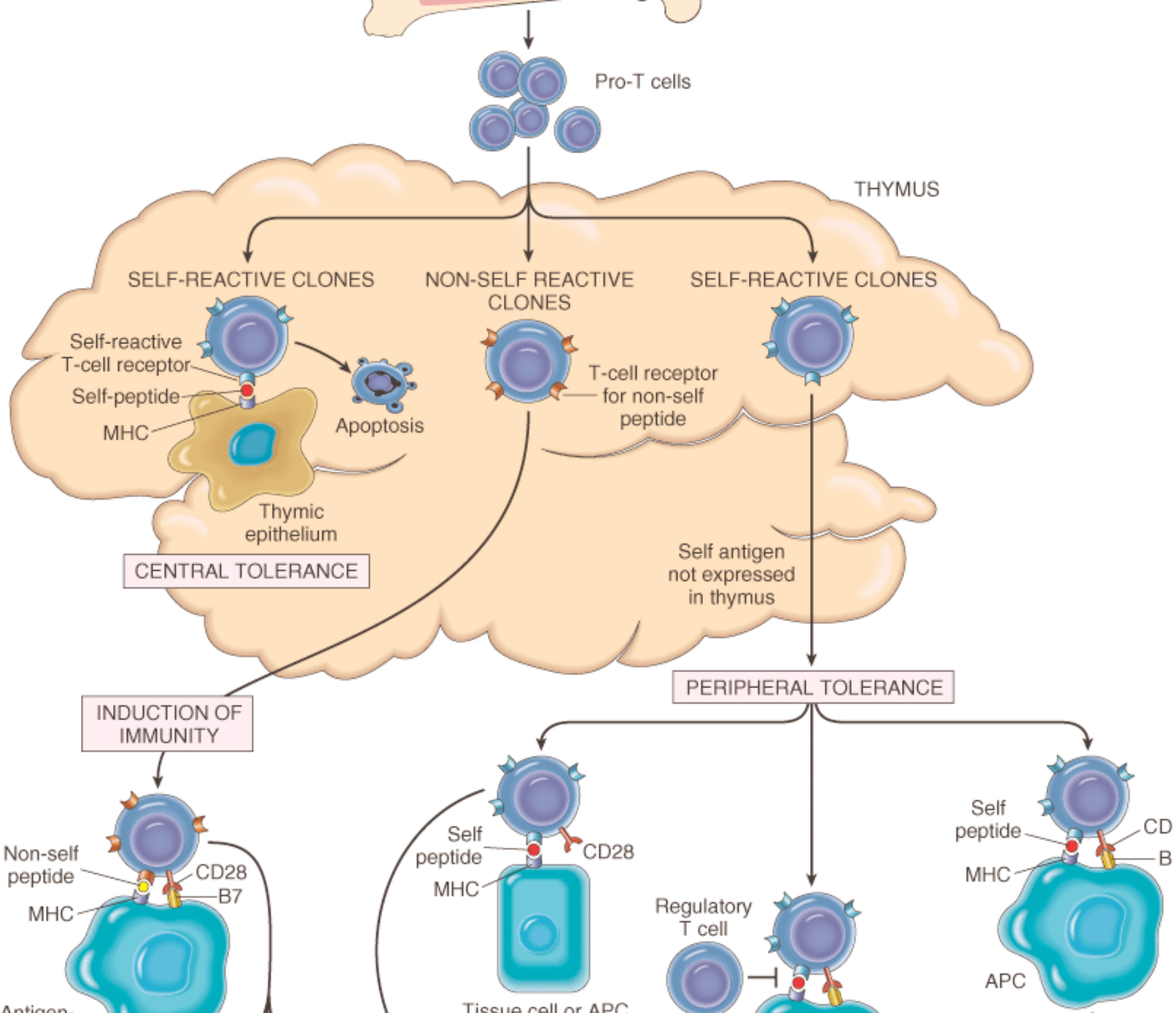
Immunologic tolerance is a state in which the individual is incapable of developing an immune response to a specific antigen. Self-tolerance refers to lack of responsiveness to an individual's own antigens, and it underlies our ability to live in harmony with our cells and tissues. Several mechanisms, albeit not well understood, have been postulated to explain the tolerant state. They can be broadly classified into two groups: *central tolerance* and *peripheral tolerance*.[37] [38] [39] [40] Each of these is considered briefly.

Central Tolerance.

This refers to death (deletion) of self-reactive T- and B-lymphocyte clones during their maturation in the central lymphoid organs (the thymus for T cells and the bone marrow for B cells). Deletion of developing intrathymic T cells has been extensively investigated. Experiments with transgenic mice provide abundant evidence that T lymphocytes that bear receptors for self-antigens undergo apoptosis within the thymus during the process of T-cell maturation. It

is proposed that many autologous protein antigens, including antigens thought to be restricted to peripheral tissues, are processed and presented by thymic antigen-presenting cells in association with self-MHC molecules.[37] A protein called AIRE (autoimmune regulator) is thought to stimulate expression of many "peripheral" self-antigens in the thymus and is thus critical for deletion of immature self-reactive T cells.[38] Mutations in the *AIRE* gene (either spontaneous in humans or created in knockout mice) are the cause of an autoimmune polyendocrinopathy (Chapter 24). The

Figure 6-27 Schematic illustration of the mechanisms involved in central and peripheral tolerance. The principal mechanisms of tolerance in CD4+ T cells are shown. APC, antigen-presenting cell.


Pro-T cells
THYMUS
SELF-REACTIVE CLONES
NON-SELF REACTIVE CLONES
SELF-REACTIVE CLONES
Self-reactive T-cell receptor
Self-peptide
MHC
Apoptosis
T-cell receptor for non-self peptide
Thymic epithelium
CENTRAL TOLERANCE
Self antigen not expressed in thymus
PERIPHERAL TOLERANCE
INDUCTION OF IMMUNITY
Non-self peptide
CD28
B7
MHC
Self peptide
CD28
MHC
Regulatory T cell
Self peptide
CD
B
MHC
APC
Tissue cell or APC

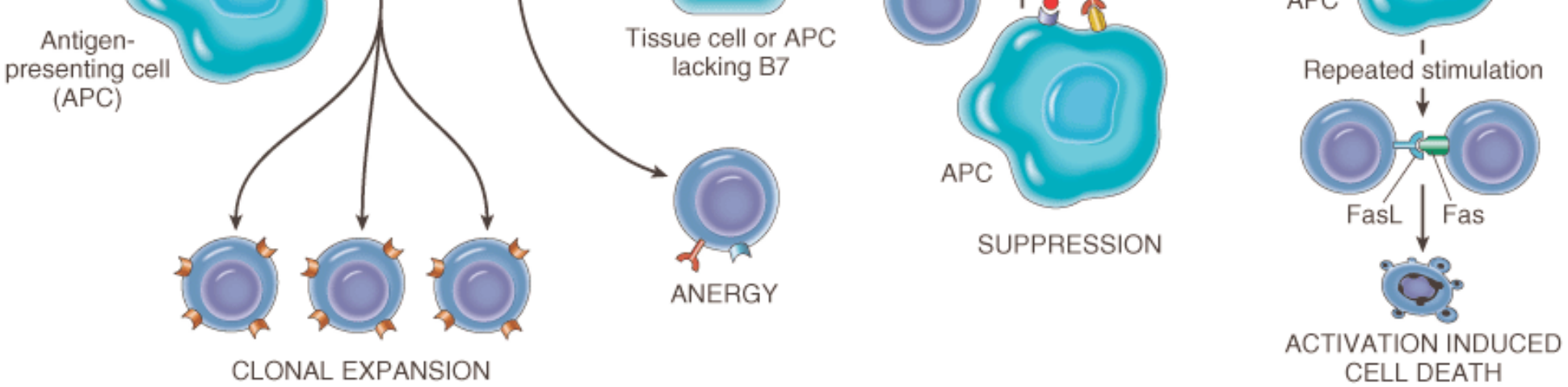


Figure 6-28 Pathogenesis of autoimmunity. Autoimmunity results from multiple factors, including susceptibility genes that may interfere with self-tolerance and environmental triggers (inflammation, other inflammatory stimuli) that promote lymphocyte entry into tissues, activation of lymphocytes, and tissue injury.

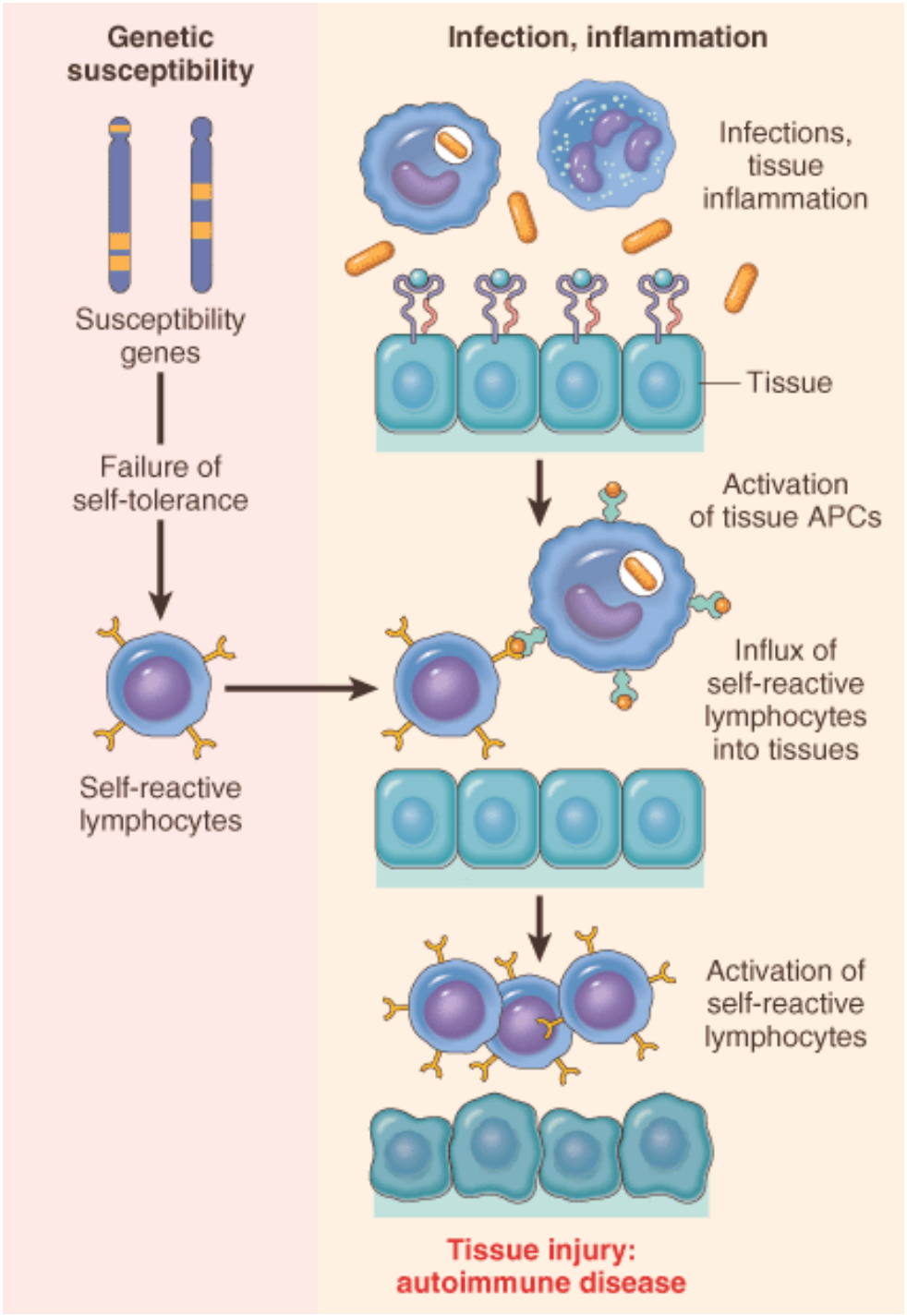


Figure 6-29 Role of infections in autoimmunity. Infections may promote activation of self-reactive lymphocytes by inducing the expression of costimulators (*A*), or microbial antigens may mimic self-antigens and activate self-reactive lymphocytes as a cross-reaction (*B*).

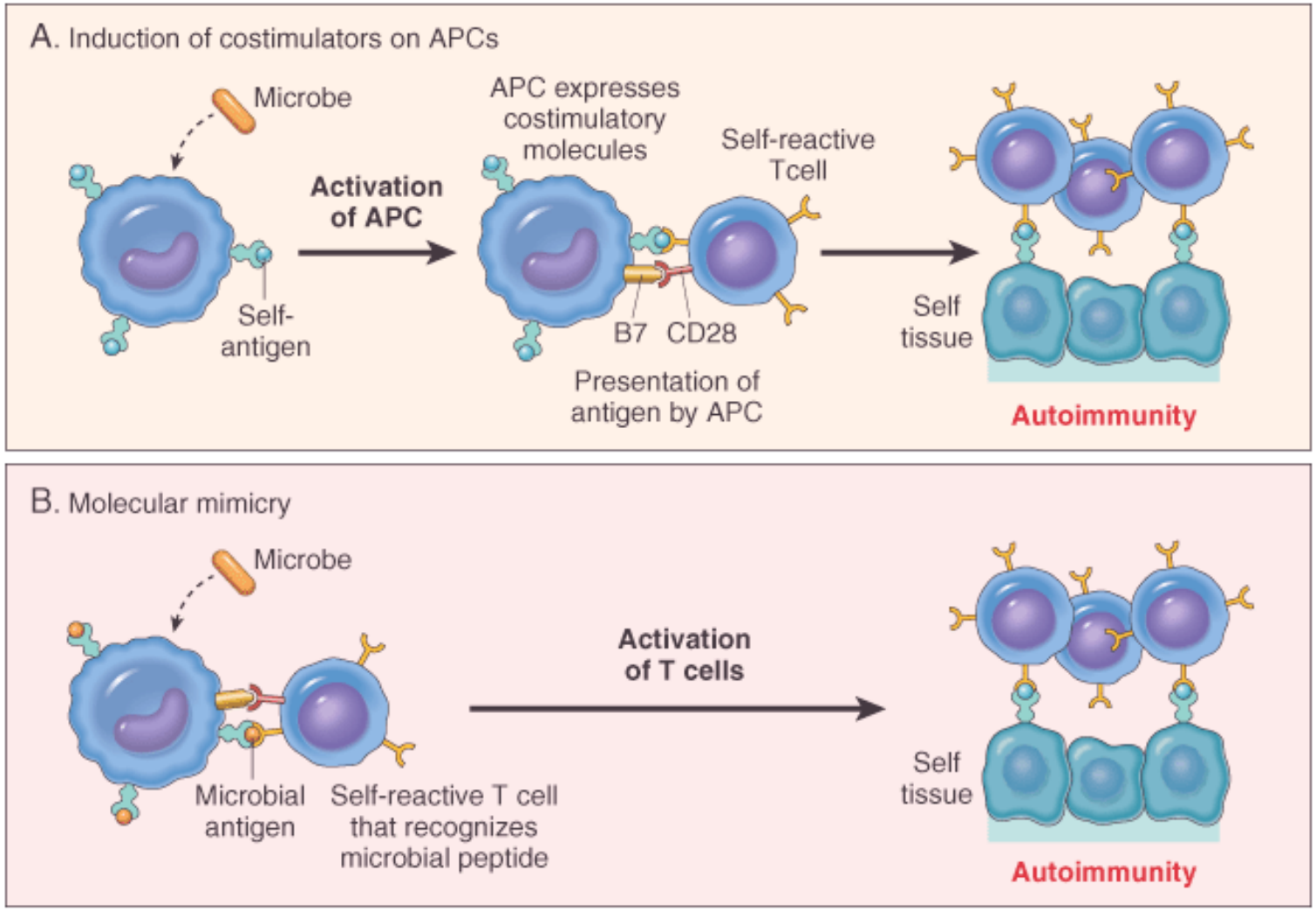


TABLE 6-8 -- 1997 Revised Criteria for Classification of Systemic Lupus Erythematosus

(Not Available)

Data from Tan EM, 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.

mechanisms that maintain self-tolerance. Antibodies have been identified against an array of nuclear and cytoplasmic components of the cell that are neither organ nor species specific. In addition, a third group of antibodies is directed against cell-surface antigens of blood cells. Apart from their value in the diagnosis and management of patients with SLE, these antibodies are of major pathogenetic significance, as, for example, in the immune complex-mediated glomerulonephritis so typical of this disease.[56]

ANAs are directed against several nuclear antigens and can be grouped into four categories:[56] (1) antibodies to DNA, (2) antibodies to histones, (3) antibodies to nonhistone proteins bound to RNA, and (4) antibodies to nucleolar antigens. Table 6-9 lists several ANAs and their association with SLE as well as with other autoimmune diseases to be discussed later.

Several techniques are used to detect ANAs. Clinically the most commonly used method is indirect immunofluorescence, which detects a variety of nuclear antigens, including DNA, RNA, and proteins (collectively called *generic ANAs*). The pattern of nuclear fluorescence suggests the type of antibody present in the patient's serum. Four basic patterns are recognized:

- *Homogeneous or diffuse nuclear staining* usually reflects antibodies to chromatin, histones and, occasionally, double-stranded DNA.
- *Rim or peripheral staining* patterns are most commonly indicative of antibodies to double-stranded DNA.
- *Speckled pattern* refers to the presence of uniform or variable-sized speckles. This is one of the most commonly observed patterns of fluorescence and therefore the least specific. It reflects the presence of antibodies to non-DNA nuclear constituents. Examples include Sm antigen, ribonucleoprotein, and SS-A and SS-B reactive antigens (Table 6-9).
- *Nucleolar pattern* refers to the presence of a few discrete spots of fluorescence within the nucleus and represents antibodies to nucleolar RNA. This pattern is reported most often in patients with systemic sclerosis.

The fluorescence patterns are not absolutely specific for the type of antibody, and because many autoantibodies may be present, combinations of patterns are frequent. *The immunofluorescence test for ANA is positive in virtually every patient with SLE; hence this test is sensitive, but it is not specific because patients with other autoimmune diseases also frequently score positive* (see Table 6-9). *Furthermore, approximately 5% to 15% of normal individuals have low titers of these antibodies.* The incidence increases with age.

Detection of antibodies to specific nuclear antigens requires specialized techniques. Of the numerous nuclear antigen-antibody systems,[57] some that are clinically useful are listed in Table 6-9 . *Antibodies to double-stranded DNA and the so-called Smith (Sm) antigen are virtually diagnostic of SLE.*

There is some, albeit imperfect, correlation between the presence or absence of certain ANAs and clinical manifestations. For example, high titers of double-stranded DNA antibodies are usually associated with active renal disease. Conversely the risk of nephritis is low if anti-SS-B antibodies are present.[56]

TABLE 6-9 -- Antinuclear Antibodies in Various Autoimmune Diseases

		Disease, % Positive					
Nature of Antigen	**Antibody System**	***SLE***	***Drug-Induced LE***	***Systemic Sclerosis—Diffuse***	***Limited Scleroderma—CREST***	***Sjögren 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	Antihistone	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	Anticentromere	<5	<5	22–36	90	<5	<5
Histidyl-t-RNA synthetase	Jo-1	<5	<5	<5	<5	<5	25
Boxed entries indicate high correlation.							
SLE, systemic lupus erythematosus; LE, lupus erythematosus; ANA, antinuclear antibodies; RNP, ribonucleoprotein.							

In addition to ANAs, lupus patients have a host of other autoantibodies. Some are directed against elements of the blood, such as red cells, platelets, and lymphocytes; others are directed against proteins complexed to phospholipids. In recent years, there has been much interest in these so-called antiphospholipid antibodies. [58] They are present in 40% to 50% of lupus patients. Although initially believed to be directed against anionic phospholipids, they are actually directed against epitopes of plasma proteins that are revealed when the proteins are complexed to phospholipids. A variety of protein substrates have been implicated, including prothrombin, annexin V, β_2 -glycoprotein I, protein S, and protein C.[59] *Antibodies against the phospholipid-β_2 -glycoprotein complex also bind to cardiolipin antigen, used in syphilis serology, and therefore lupus patients may have a false-positive test result for syphilis*. Some of these antibodies interfere with in vitro clotting tests, such as partial thromboplastin time. Therefore, these antibodies are sometimes referred to as *lupus anticoagulant*. Despite having a circulating anticoagulant that delays clotting in vitro, these patients have complications associated with a *hypercoagulable state*.[60] They have venous and arterial thromboses, which may be associated with recurrent spontaneous miscarriages and focal cerebral or ocular ischemia. This constellation of clinical features, in association with lupus, is referred to as the *secondary antiphospholipid antibody syndrome*. The pathogenesis of thrombosis in these patients is unknown; possible mechanisms are discussed in Chapter 4 . Some patients develop these autoantibodies and the clinical syndrome without associated SLE. They are said to have the primary antiphospholipid syndrome (Chapter 4).

Given the presence of all these autoantibodies, we still know little about the mechanism of their emergence. Three converging lines of investigation hold center stage today: genetic predisposition, some nongenetic (environmental) factors, and a fundamental abnormality in the immune system.

Genetic Factors.

SLE is a complex genetic trait with contribution from MHC and multiple non-MHC genes. Many lines of evidence support a genetic predisposition. [51] [61]

- Family members of patients have an increased risk of developing SLE. Up to 20% of clinically unaffected first-degree relatives of SLE patients reveal autoantibodies and other immunoregulatory abnormalities.
- There is a higher rate of concordance (>20%) in monozygotic twins when compared with dizygotic twins (1% to 3%). Monozygotic twins who are discordant for SLE have similar patterns and titers of autoantibodies.[62] These data suggest that the genetic makeup regulates the formation of autoantibodies, but the expression of the disease (i.e., tissue injury) is influenced by non-genetic (possibly environmental) factors.
- Studies of HLA associations further support the concept that MHC genes regulate production of specific autoantibodies, rather than conferring a generalized predisposition to SLE. Specific alleles of the HLA-DQ locus have been linked to the production of anti-double-stranded DNA, anti-Sm, and antiphospholipid antibodies.
- Some lupus patients (approximately 6%) have inherited deficiencies of early complement components, such as C2, C4, or C1q. Lack of complement may impair removal of circulating immune complexes by the mononuclear phagocyte system, thus favoring tissue deposition. Knockout mice lacking C4 or certain complement receptors are also prone to develop lupus-like autoimmunity. Various mechanisms have been invoked, including failure to clear immune complexes and loss of B-cell self-tolerance. It has also been proposed that deficiency of C1q results in failure of phagocytic

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clearance of apoptotic cells.[63]Such cells are produced normally, and if they are not cleared their nuclear components may elicit immune responses.

- In animal models of SLE, several non-MHC susceptibility loci have been identified. The best-known animal model is the (NZBxNZW)F1 mouse strain. In different versions of this strain, up to 20 loci are believed to be associated with the disease. [51]

Environmental Factors.

There are many indications that, in addition to genetic factors, several *environmental* or non-genetic factors must be involved in the pathogenesis of SLE. The clearest example comes from the observation that *drugs* such as hydralazine, procainamide, and D-penicillamine can induce an SLE-like response in humans.[64] Exposure to *ultraviolet light* is another environmental factor that exacerbates the disease in many individuals. How ultraviolet light acts is not entirely clear, but it is suspected of modulating the immune response. For example, it induces keratinocytes to produce IL-1, a factor known to influence the immune response. In addition, UV irradiation may induce apoptosis in cells, and alter the DNA in such a way that it becomes immunogenic. [65] *Sex hormones* seem to exert an important influence on the occurrence and manifestations of SLE. During the reproductive years, the frequency of SLE is 10 times greater in women than in men, and exacerbation has been noted during normal menses and pregnancy.

Immunologic Factors.

With all the immunologic findings in SLE patients, there can be little doubt that some fundamental derangement of the immune system is involved in the pathogenesis of SLE. Although a variety of immunologic abnormalities affecting both T cells and B cells have been detected in patients with SLE, it has been difficult to relate any one of them to the causation of this disease. For years, it had been thought that an intrinsic B-cell hyperactivity is fundamental to the pathogenesis of SLE. Polyclonal B-cell activation can be readily demonstrated in patients with SLE and in murine models of this disease. Molecular analyses of anti-double-stranded DNA antibodies, however, strongly suggest that pathogenic autoantibodies are not derived from polyclonally activated B cells. Instead, it appears that the production of tissue-damaging antibodies is driven by self-antigens and results from an antigen-specific helper T cell-dependent B-cell response with many characteristics of responses to foreign antigens.[66] These observations have shifted the onus of driving the autoimmune response squarely on helper T cells.[66A] Based on these findings, a model for the pathogenesis of SLE has been proposed (Fig. 6-30). Other contributing factors include defective clearance of apoptotic cells, mentioned above, and dysregulation of cytokines, notably interferons.[61] SLE is a heterogeneous disease, however, and as mentioned earlier, the production of different autoantibodies is regulated by

distinct genetic factors. Hence, there may well be distinct immunoregulatory disturbances in patients with different genetic backgrounds and autoantibody profiles.[67]

Regardless of the exact sequence by which autoantibodies are formed, they are clearly the mediators of tissue injury. *Most of the visceral lesions are mediated by immune complexes (type III hypersensitivity).* DNA-anti-DNA complexes can be detected in the glomeruli and small blood vessels. Low levels of serum complement and granular deposits of complement

Figure 6-30 Model for the pathogenesis of systemic lupus erythematosus. *(Modified from Kotzin BL: Systemic lupus erythematosus. Cell 65:303, 1996. Copyright 1996, Cell Press.)*

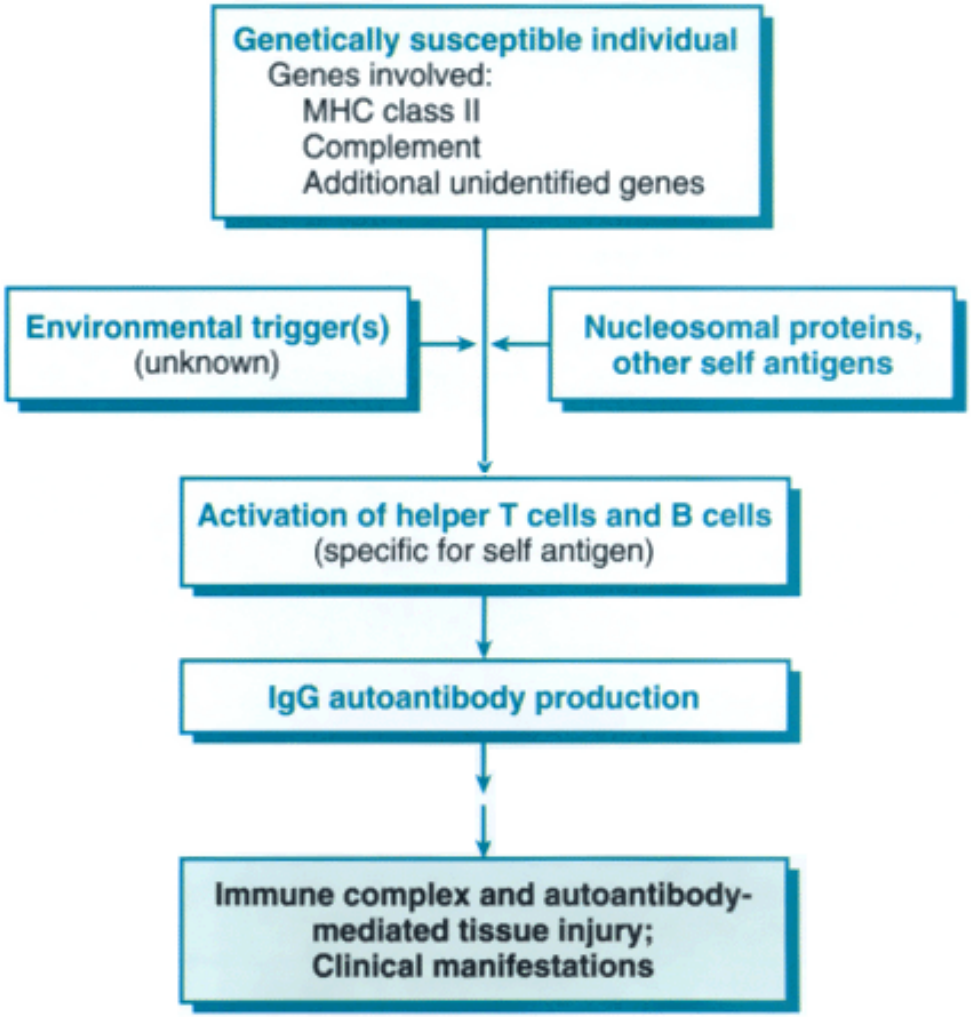


TABLE 6-10 -- Clinical and Pathologic Manifestations of Systemic Lupus Erythematosus

Clinical Manifestation	Prevalence in Patients, %
Hematologic	100
Arthritis	•90

Skin	•85
Fever	•83
Fatigue	•81
Weight loss	•63
Renal	•50
Central nervous system	•50
Pleuritis	•46
Myalgia	•33
Pericarditis	•25
Gastrointestinal	•21
Paynaud phenomenon	•20
Ocular	•15
Peripheral neuropathy	•14

lesions result from the deposition of immune complexes and are found in the blood vessels, kidneys, connective tissue, and skin.

An acute necrotizing vasculitis involving small arteries and arterioles may be present in any tissue.[68] The arteritis is characterized by fibrinoid deposits in the vessel walls. In chronic stages, vessels undergo fibrous thickening with luminal narrowing.

Kidney.

The kidney is a frequent target of injury in SLE. The principal mechanism of injury is immune complex deposition in renal structures, including glomeruli, tubular and peritubular capillary basement membranes, and larger blood vessels. Other forms of injury may include a thrombotic process involving the glomerular capillaries and extraglomerular vasculature, thought to be caused by antiphospholipid antibodies.

A morphologic classification of the patterns of immune complex-mediated glomerular injury in SLE has proven to be clinically useful.[69] There are several versions of the World Health Organization (WHO) classification of lupus nephritis, but in all, five patterns are recognized: (1) minimal or no detectable abnormalities (class I), which is rare, seen in renal biopsies from less than 5% of SLE patients; (2) mesangial lupus glomerulonephritis (class II); (3) focal proliferative glomerulonephritis (class III); (4) diffuse proliferative glomerulonephritis (class IV); and (5) membranous glomerulonephritis (class V). None of these patterns is specific for lupus.

Mesangial lupus glomerulonephritis is characterized by mesangial cell proliferation and lack of involvement of glomerular capillary walls. It is seen in 10% to 25% of patients, most of whom have minimal clinical manifestations, such as mild hematuria or transient proteinuria. There is a slight to moderate increase in the intercapillary mesangial matrix as well as in the number of mesangial cells. Despite the mild histologic changes, **granular mesangial deposits of immunoglobulin and complement are always present**. Such deposits presumably reflect the earliest change because filtered immune complexes accumulate primarily in the mesangium. The other changes to be described are usually superimposed on the mesangial changes.

Focal proliferative glomerulonephritis is seen in 20% to 35% of patients. It is a focal lesion, affecting fewer than 50% of the glomeruli and generally only portions of each glomerulus.

Typically, one or two tufts in an otherwise normal glomerulus exhibit swelling and proliferation of endothelial and mesangial cells, infiltration with neutrophils, and sometimes fibrinoid deposits and intracapillary thrombi (Fig. 6-31). Occasionally, affected glomeruli exhibit global injury. Focal lesions are associated with hematuria and proteinuria. In some patients, the nephritis progresses to diffuse proliferative disease.

Diffuse proliferative glomerulonephritis is the most serious of the renal lesions in SLE, occurring in 35% to 60% of patients who undergo biopsy. Anatomic changes are dominated by proliferation of endothelial, mesangial and, sometimes, epithelial cells (Fig. 6-32), producing in some cases epithelial crescents that fill the Bowman space (Chapter 20). The presence of fibrinoid necrosis, crescents, prominent infiltration by leukocytes, cell death as indicated by apoptotic bodies, and hyaline thrombi indicates active disease. Most or all glomeruli are involved in both kidneys, and the entire glomerulus is frequently affected. Patients with diffuse lesions are usually overtly symptomatic, showing microscopic or gross hematuria as well as proteinuria that is severe enough to cause the nephrotic syndrome in more than 50% of patients. Hypertension and mild to severe renal insufficiency are also common.

Membranous glomerulonephritis is a designation given to glomerular disease in which the principal histologic change consists of widespread thickening of the capillary walls. The lesions are similar to those encountered in idiopathic membranous glomerulonephritis, described more fully in Chapter 20 . This type of lesion is seen in 10% to 15% of patients with

Figure 6-31 Lupus nephritis. There are two focal necrotizing lesions in the glomerulus *(arrowheads)*. *(Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

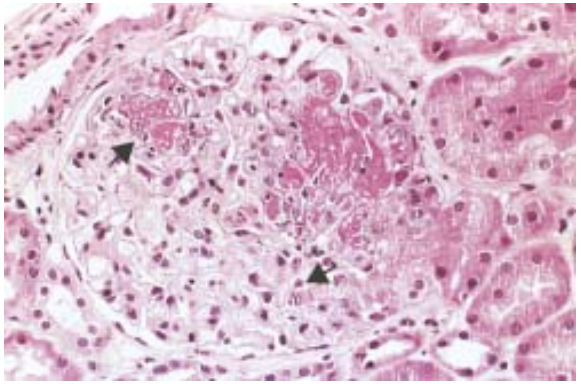


Figure 6-32 Lupus nephritis, diffuse proliferative type. Note the marked increase in cellularity throughout the glomerulus. *(Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

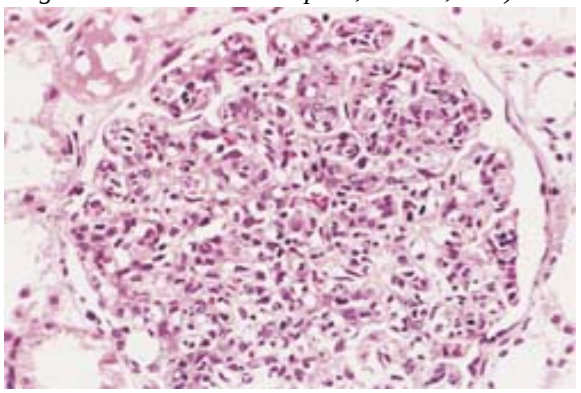


Figure 6-33 Immunofluorescence micrograph stained with fluorescent anti-IgG from a patient with diffuse proliferative lupus nephritis. One complete glomerulus and part of another one are seen. Note the mesangial and capillary wall deposits of IgG. *(Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

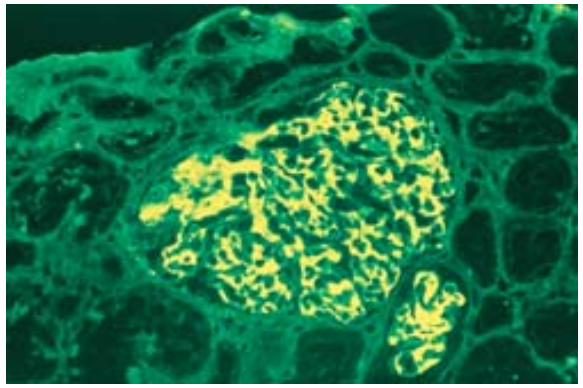


Figure 6-34 Electron micrograph of a renal glomerular capillary loop from a patient with systemic lupus erythematosus nephritis. Subendothelial dense deposits correspond to "wire loops" seen by light microscopy. Deposits are also present in the mesangium. *(Courtesy of Dr. Jean Olson, Department of Pathology, University of California San Francisco, San Francisco, CA.)*

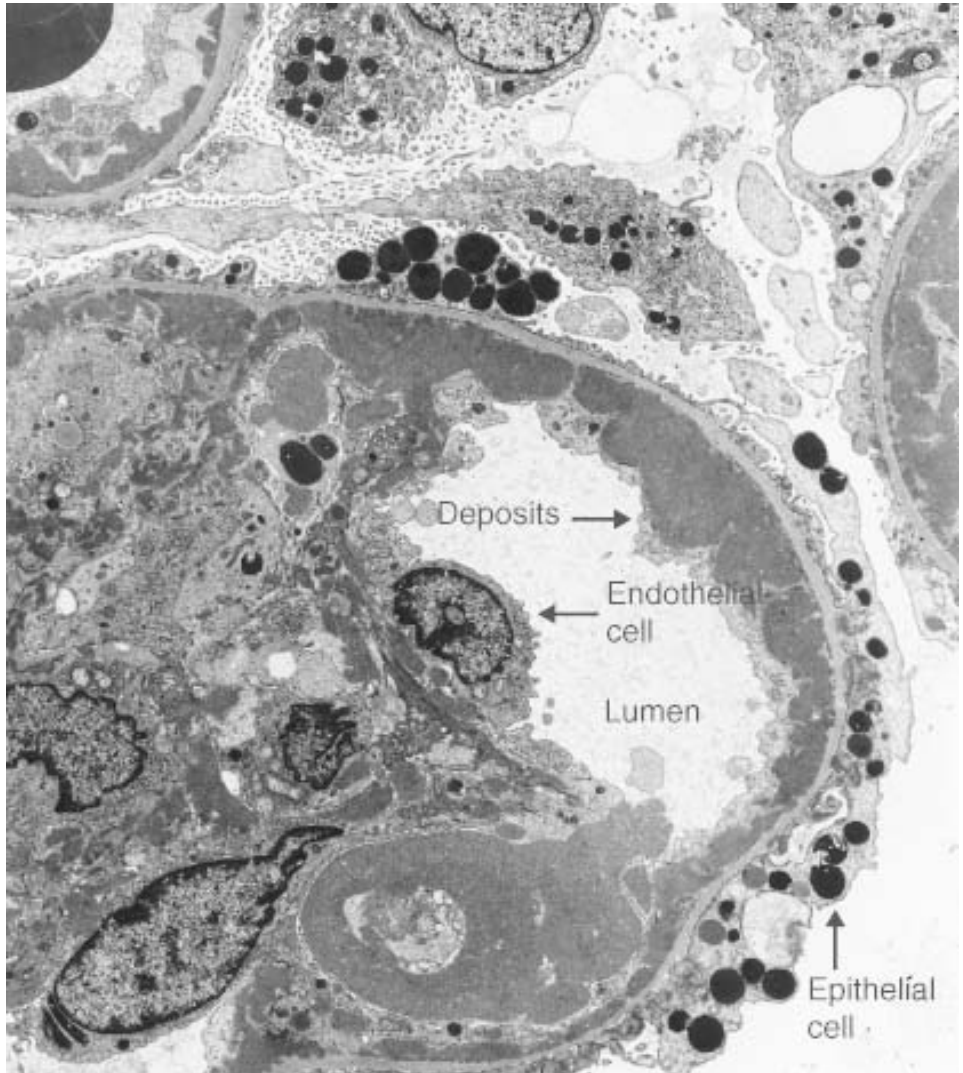


Figure 6-35 Lupus nephritis showing a glomerulus with several "wire loop" lesions representing extensive subendothelial deposits of immune complexes. (Periodic acid-Schiff [PAS] stain.) *(Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

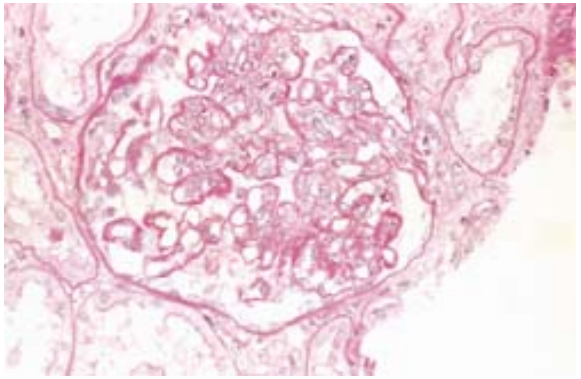


Figure 6-36 Systemic lupus erythematosus involving the skin. *A,* An H&E-stained section shows liquefactive degeneration of the basal layer of the epidermis and edema at the dermoepidermal junction. *(Courtesy of Dr. Jag Bhawan, Boston University School of Medicine, Boston, MA.) B,* An immunofluorescence micrograph stained for IgG reveals deposits of immunoglobulin along the dermal-epidermal junction. *(Courtesy of Dr. Richard Sontheimer, Department of Dermatology, University of Texas Southwestern Medical School, Dallas, TX.)*

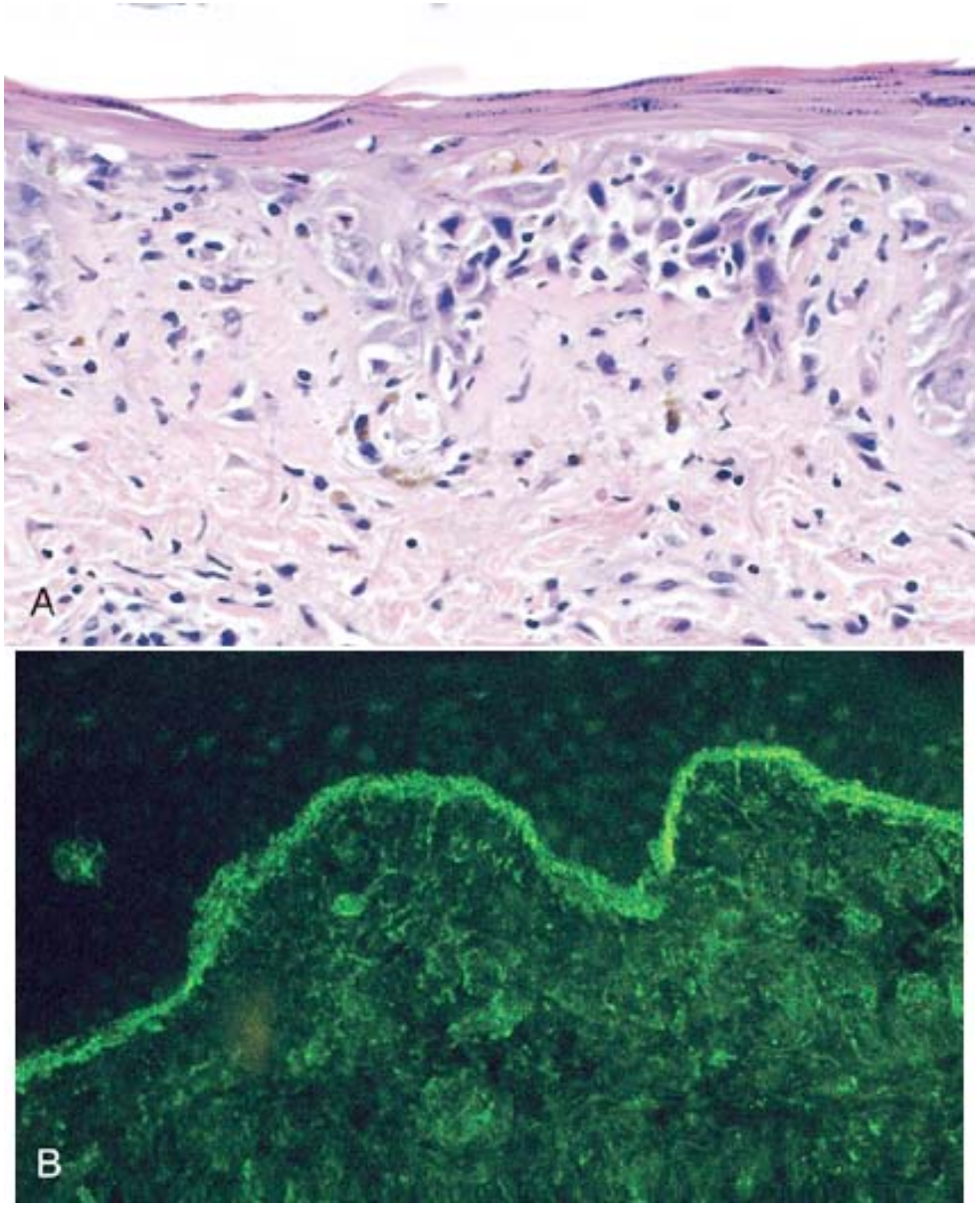


Figure 6-37 Libman-Sacks endocarditis of the mitral valve in lupus erythematosus. The vegetations attached to the margin of the thickened valve leaflet are indicated by *arrows*. *(Courtesy of Dr. Fred Schoen, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

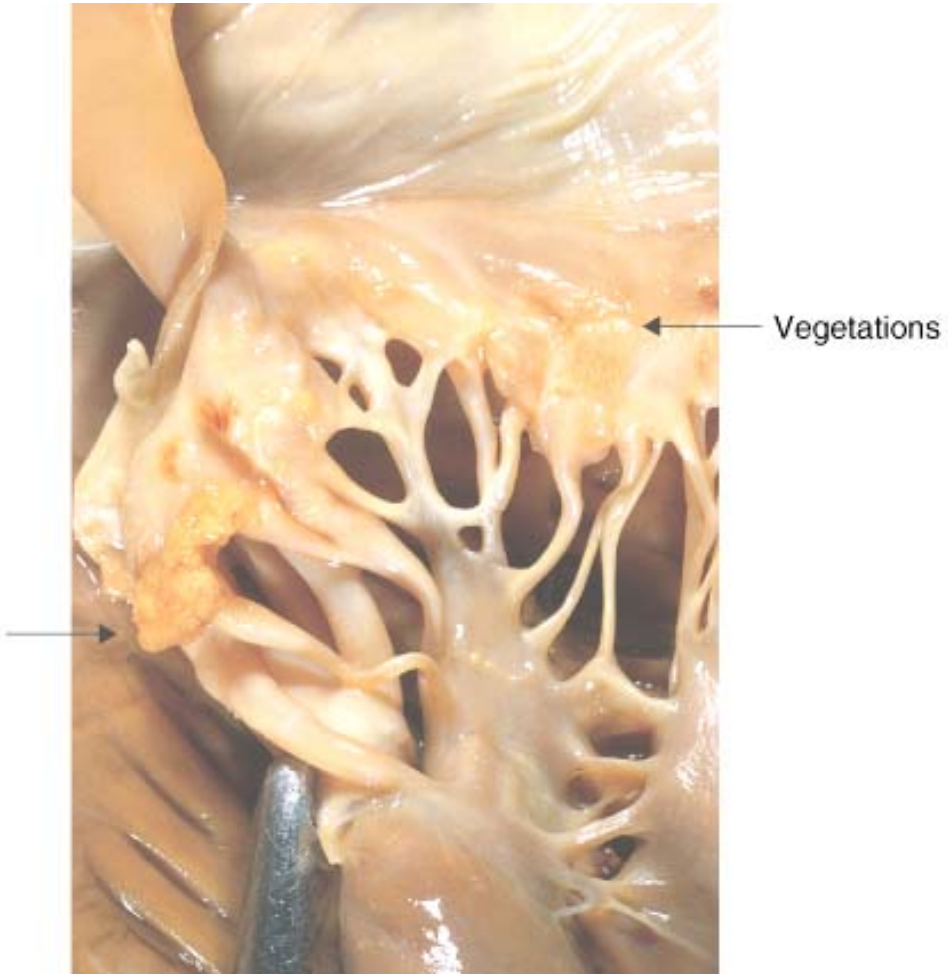


Figure 6-38 Sjögren syndrome. *A*, Enlargement of the salivary gland. *(Courtesy of Dr. Richard Sontheimer, Department of Dermatology, University of Texas Southwestern Medical School, Dallas, TX.) B*, Intense lymphocytic and plasma cell infiltration with ductal epithelial hyperplasia in a salivary gland. *(Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

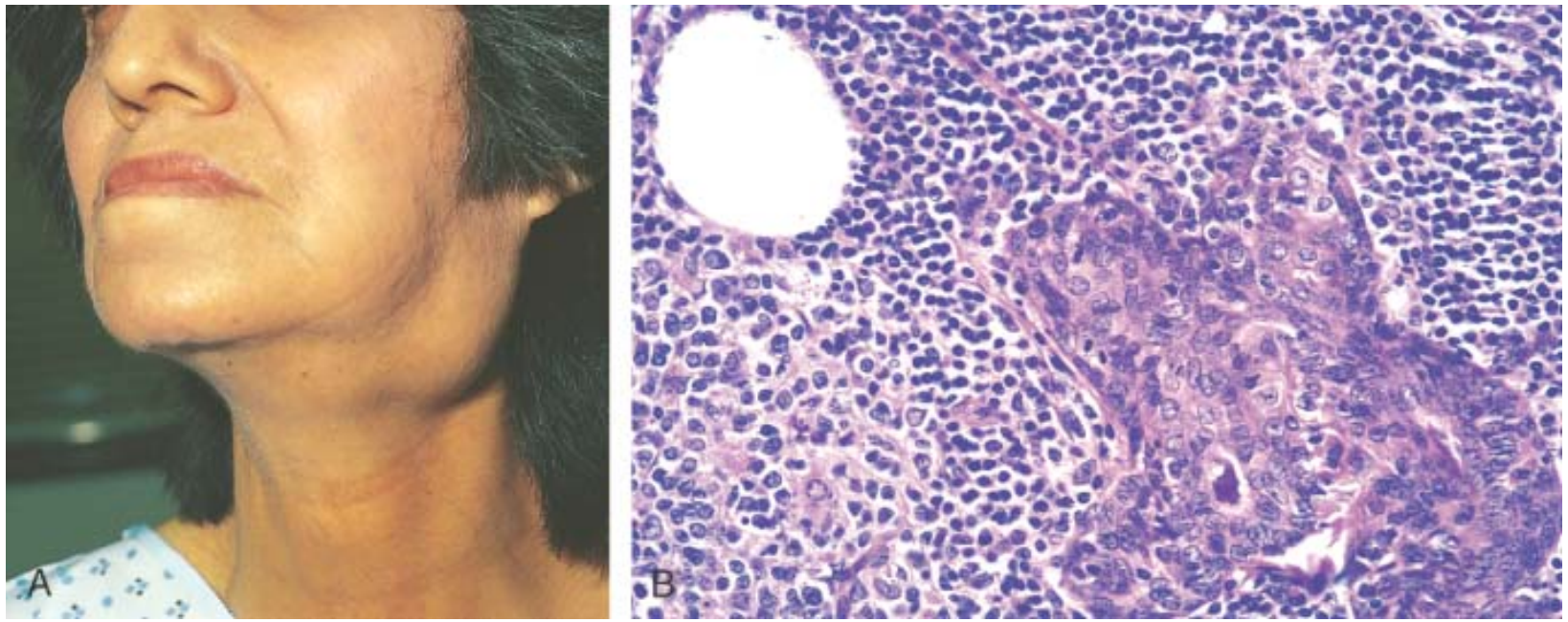


Figure 6-39 Schematic illustration of the possible mechanisms leading to systemic sclerosis.

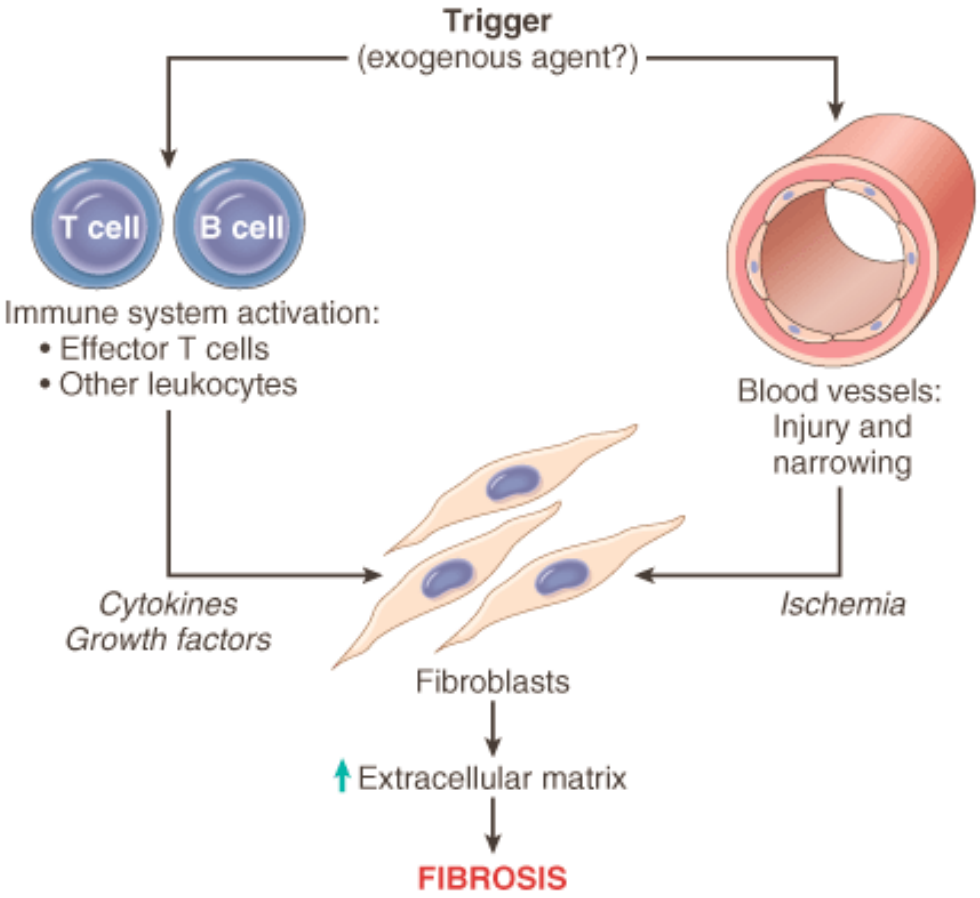


Figure 6-40 Systemic sclerosis. *A*, Normal skin. *B*, Skin biopsy from a patient with systemic sclerosis. Note the extensive deposition of dense collagen in the dermis with virtual absence of appendages (e.g. hair follicles) and foci of inflammation *(arrow)*.

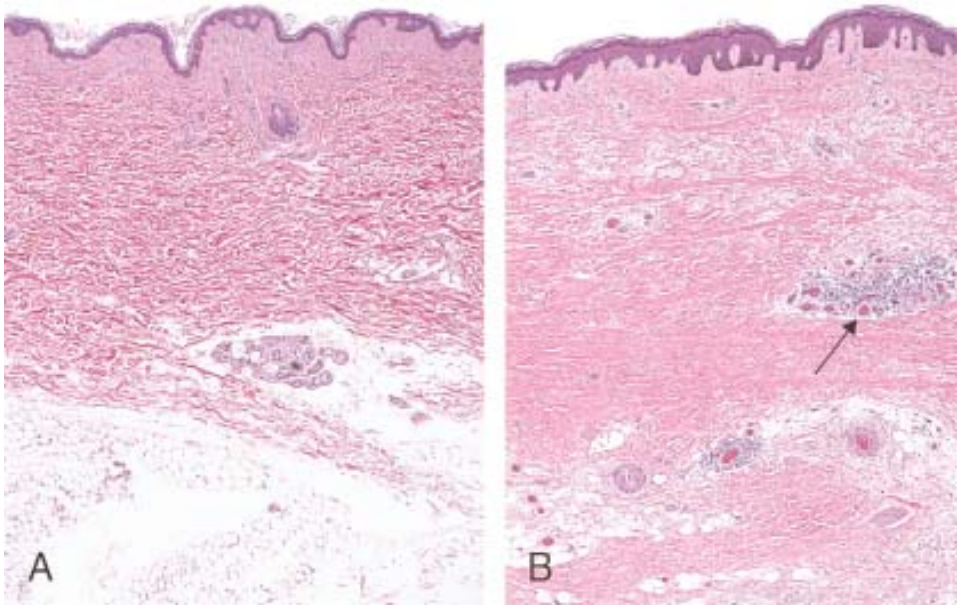


Figure 6-41 Advanced systemic sclerosis. The extensive subcutaneous fibrosis has virtually immobilized the fingers, creating a clawlike flexion deformity. Loss of blood supply has led to cutaneous ulcerations. *(Courtesy of Dr. Richard Sontheimer, Department of Dermatology, University of Texas Southwestern Medical School, Dallas, TX.)*

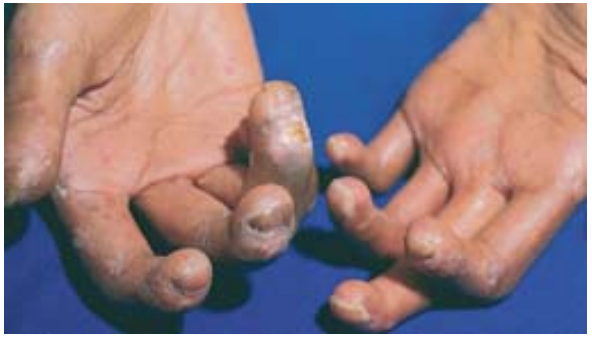


TABLE 6-11 -- Examples of Infections in Immunodeficiencies

Pathogen Type	T-Cell-Defect	B-Cell Defect	Granulocyte Defect	Complement Defect
Bacteria	Bacterial sepsis	Streptococci, staphylococci, *Haemophilus*	Staphylococci, *Pseudomonas*	Neisserial infections, other pyogenic bacterial infections
Viruses	Cytomegalovirus, Epstein-Barr virus, severe varicella, chronic infections with respiratory and intestinal viruses	Enteroviral encephalitis		
Fungi and parasites	*Candida, Pneumocystis carinii*	Severe intestinal giardiasis	*Candida, Nocardia, Aspergillus*	

Special features	Aggressive disease with opportunistic pathogens, failure to clear infections	Recurrent sinopulmonary infections, sepsis, chronic meningitis		

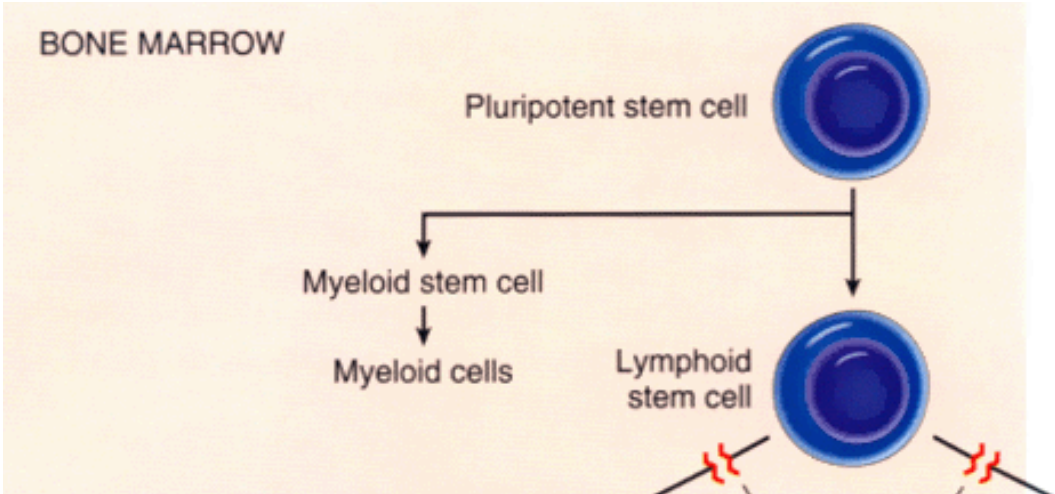
From Puck JM: Primary immunodeficiency diseases. JAMA 278:1835, 1997. Copyright 1997, American Medical Association.

of T cells are often indistinguishable clinically from combined deficiencies of T and B cells. Although originally thought to be quite rare, some forms, such as IgA deficiency, are common, and collectively they are a significant health problem, especially in children. Most primary immunodeficiencies manifest themselves in infancy, between 6 months and 2 years of life, and they are detected because the affected infants are susceptible to recurrent infections. The nature of infecting organisms depends to some extent on the nature of the underlying defect, as summarized in Table 6-11 . Detailed classification of the primary immunodeficiencies according to the suggested cellular defect may be found in the WHO report on immunodeficiency.[92] Defects of phagocytes were discussed in Chapter 2 . Here we present selected examples of other immunodeficiencies. We begin with isolated defects in B cells, followed by a discussion of combined immunodeficiencies and defects in complement proteins. Finally, Wiskott-Aldrich syndrome, a complex disorder affecting lymphocytes as well as platelets, is presented. With rapid advances in genetic analyses, in the past ten years the mutations responsible for many primary immunodeficiencies have been identified.[93]

X-Linked Agammaglobulinemia of Bruton

X-linked agammaglobulinemia is one of the more common forms of primary immunodeficiency.[94] It is *characterized by the failure of B-cell precursors (pro-B cells and pre-B cells) to mature into B cells*. During normal B-cell maturation in the bone marrow, the immunoglobulin heavy-chain genes are rearranged first, followed by rearrangement of the light chain genes. In X-linked agammaglobulinemia, B-cell maturation stops after the rearrangement of heavy chain genes. Because light chains are not produced, the complete immunoglobulin molecule (which contains heavy and light chains) cannot be assembled and transported to the cell membrane. Free heavy chains can be found in the cytoplasm. This block in differentiation is due to mutations in a cytoplasmic tyrosine kinase, called *B-cell tyrosine kinase (Btk)*.[95] Btk is a protein tyrosine kinase associated with the antigen receptor complex of pre-B and mature B cells. It is needed to transduce signals from the antigen receptor that are critical for driving maturation. When it is mutated, the pre-B cell receptor cannot deliver signals, and maturation stops at this stage. The *BTK* gene maps to the long arm of the X chromosome at Xq21.22.

Figure 6-42 Scheme of lymphocyte development and sites of block in primary immunodeficiency diseases. The affected genes are indicated in parentheses for some of the disorders. ADA, adenosine deaminase; CD40L, CD40 ligand; SCID, severe combined immunodeficiency.



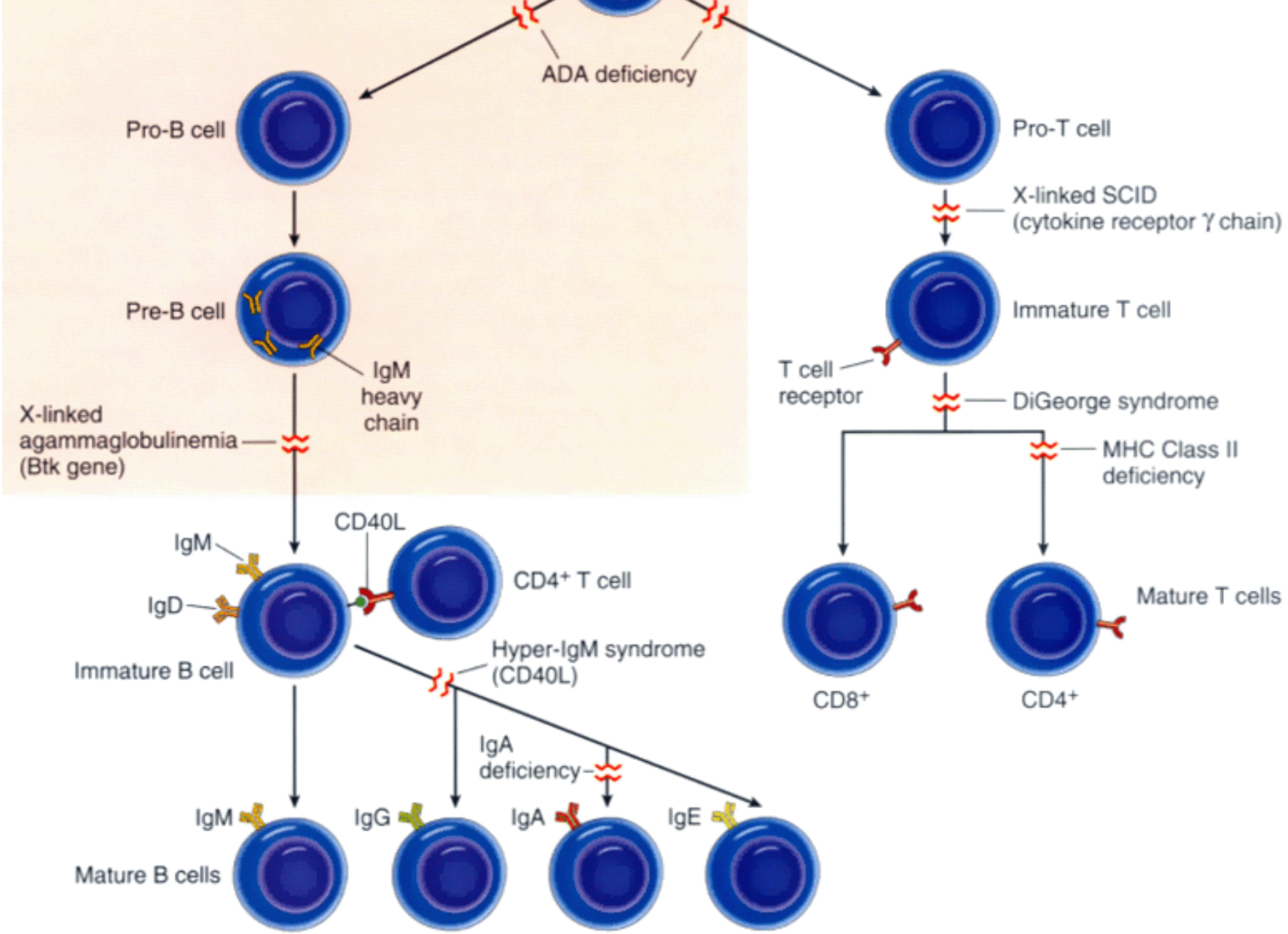


Figure 6-43 Schematic illustration of an HIV-1 virion. The viral particle is covered by a lipid bilayer that is derived from the host cell.

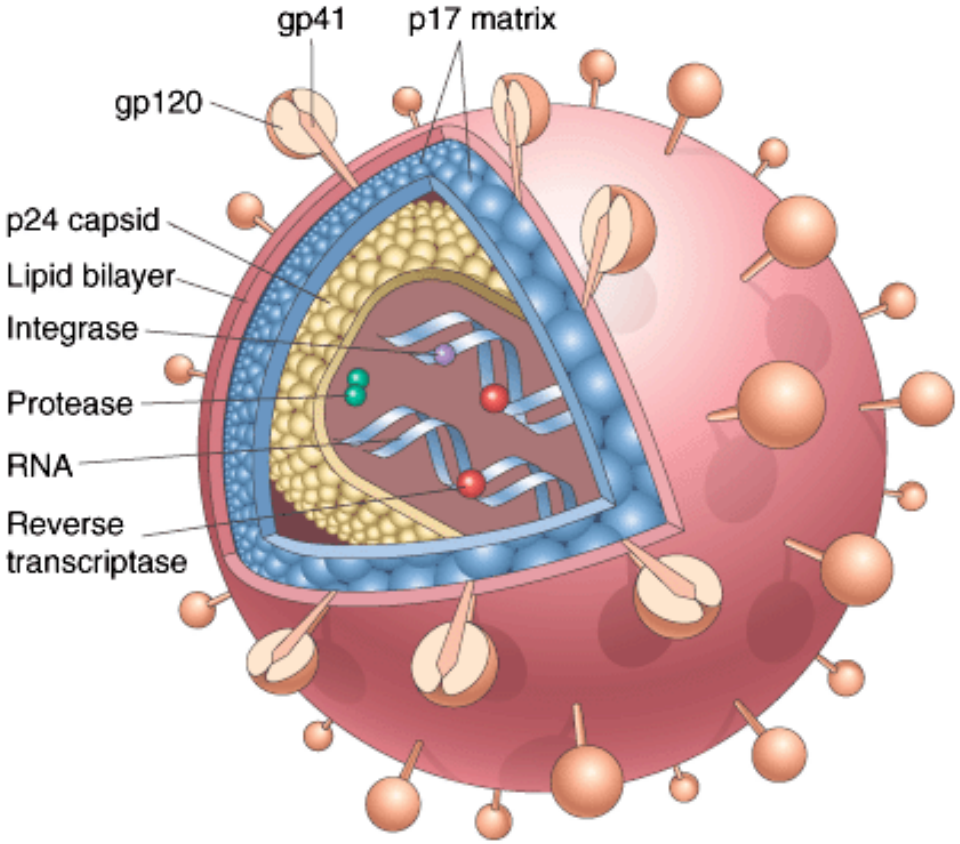


Figure 6-44 HIV proviral genome. Several viral genes and their corresponding functions are illustrated. The genes outlined in red are unique to HIV; others are shared by all retroviruses.

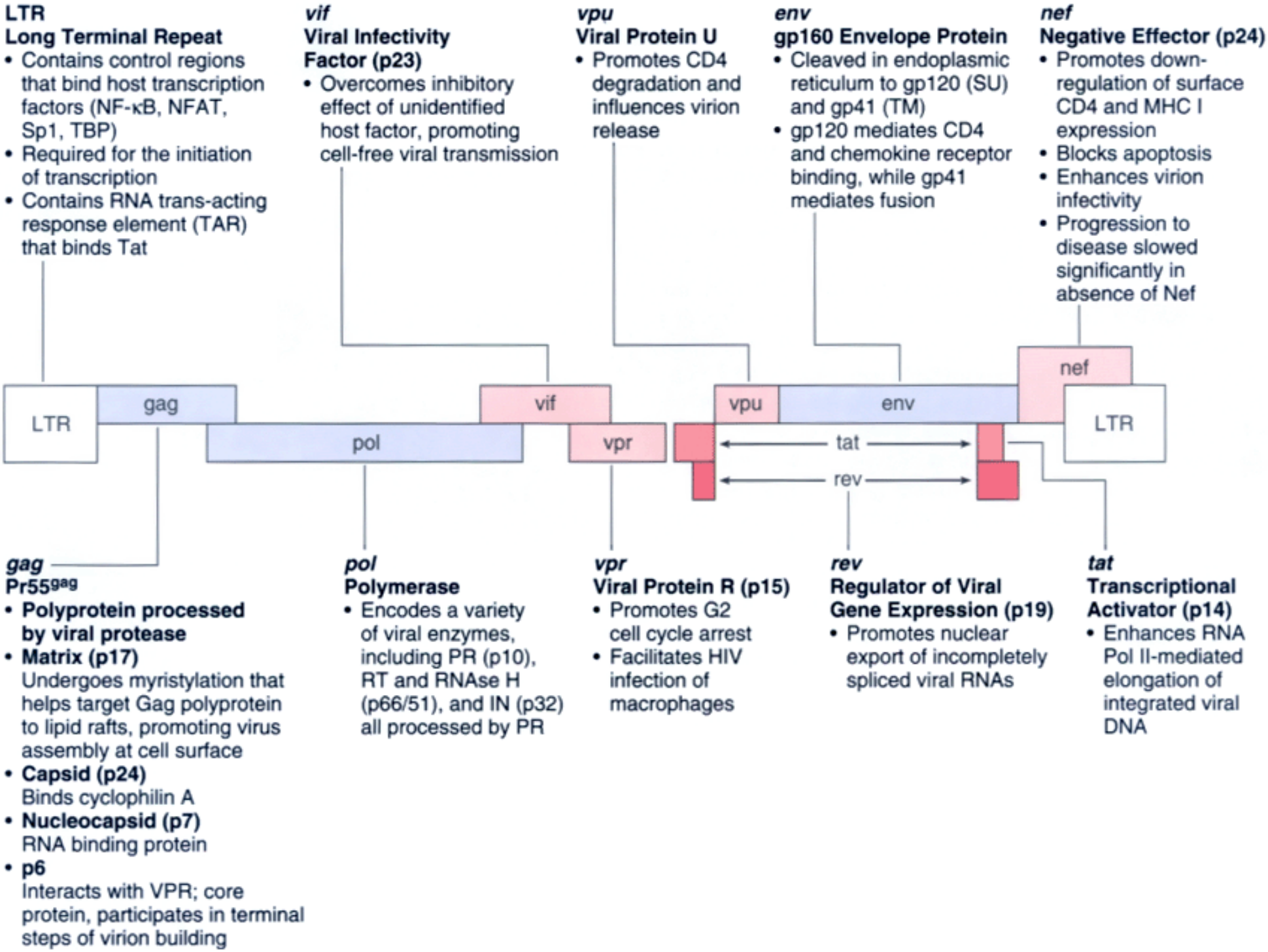
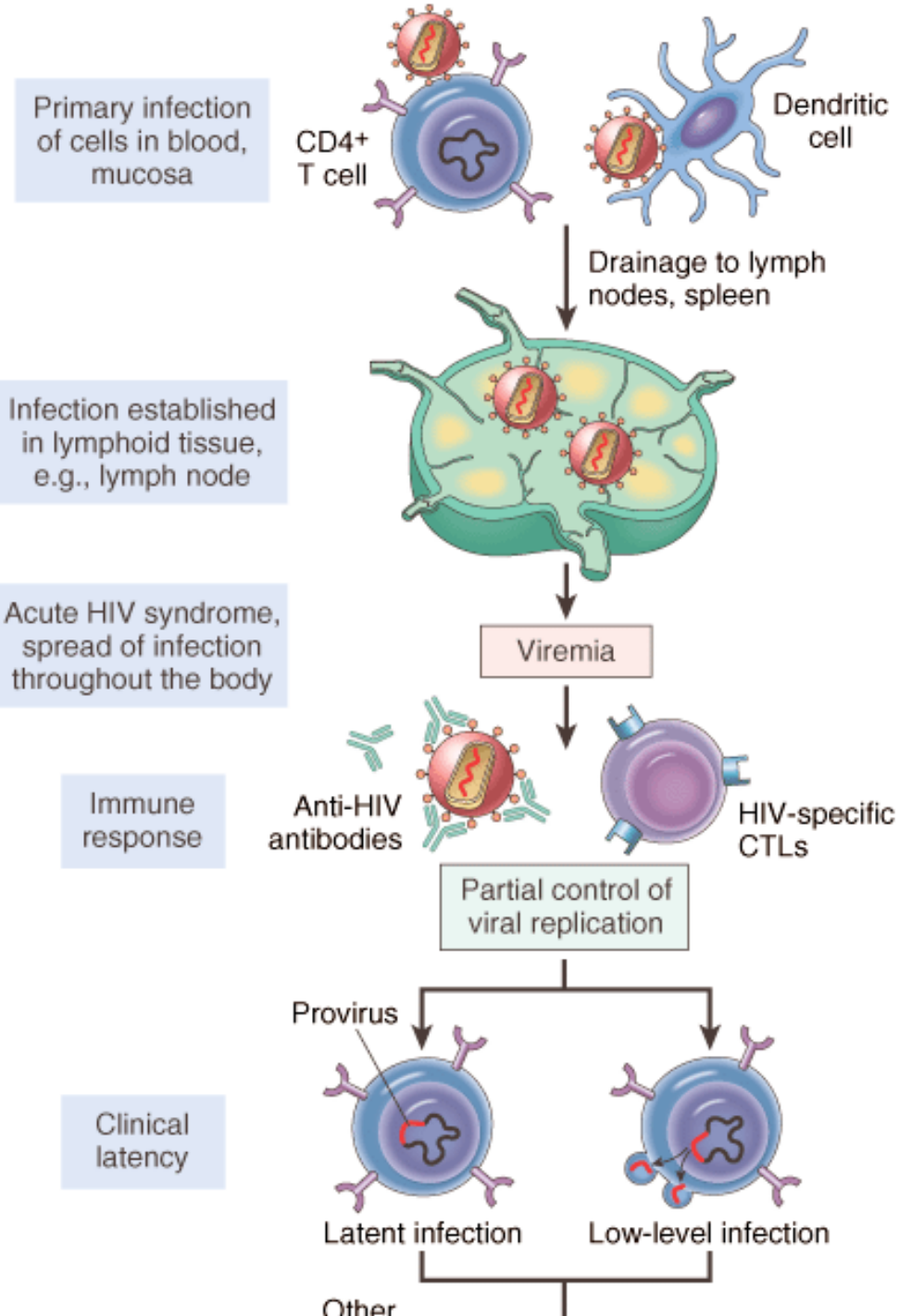


Figure 6-45 Pathogenesis of HIV-1 infection. Initially, HIV-1 infects T cells and macrophages directly or is carried to these cells by Langerhans cells. Viral replication in the regional

lymph nodes leads to viremia and widespread seeding of lymphoid tissue. The viremia is controlled by the host immune response *(not shown)*, and the patient then enters a phase of clinical latency. During this phase, viral replication in both T cells and macrophages continues unabated, but there is some immune containment of virus *(not illustrated)*. There continues a gradual erosion of CD4+ cells by productive infection (or other mechanisms, *not shown*). Ultimately, CD4+ cell numbers decline, and the patient develops clinical symptoms of full-blown AIDS. Macrophages are also parasitized by the virus early; they are not lysed by HIV-1, and they may transport the virus to tissues, particularly the brain.



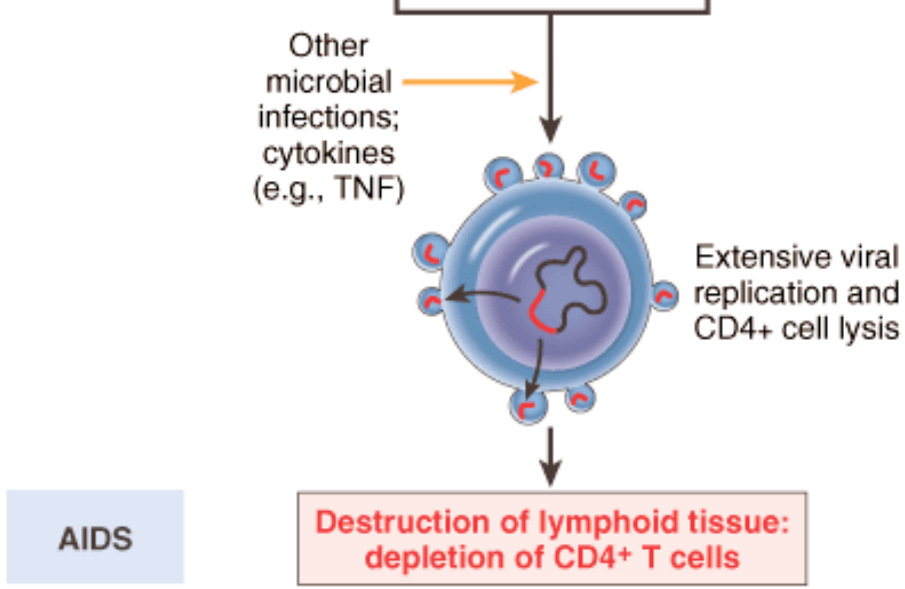


Figure 6-46 Mechanism of HIV entry into host cells. Interactions with CD4 and CCR5 coreceptor are illustrated. *(Adapted with permission from Wain-Hobson S: HIV. One on one meets two. Nature 384:117, 1996. Copyright 1996, Macmillam Magazines Limited.)*

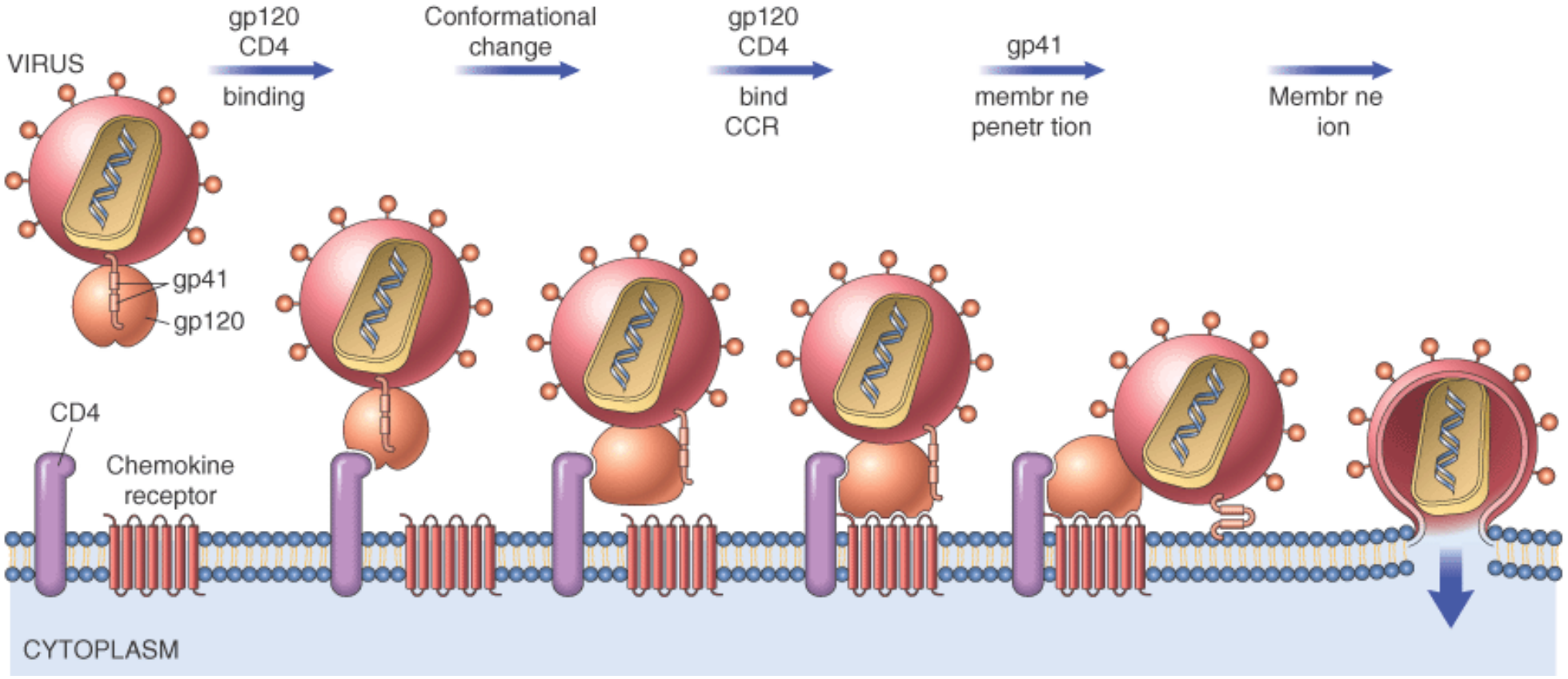


Figure 6-47 The life cycle of HIV. The steps from viral entry to production of infectious virions are illustrated.

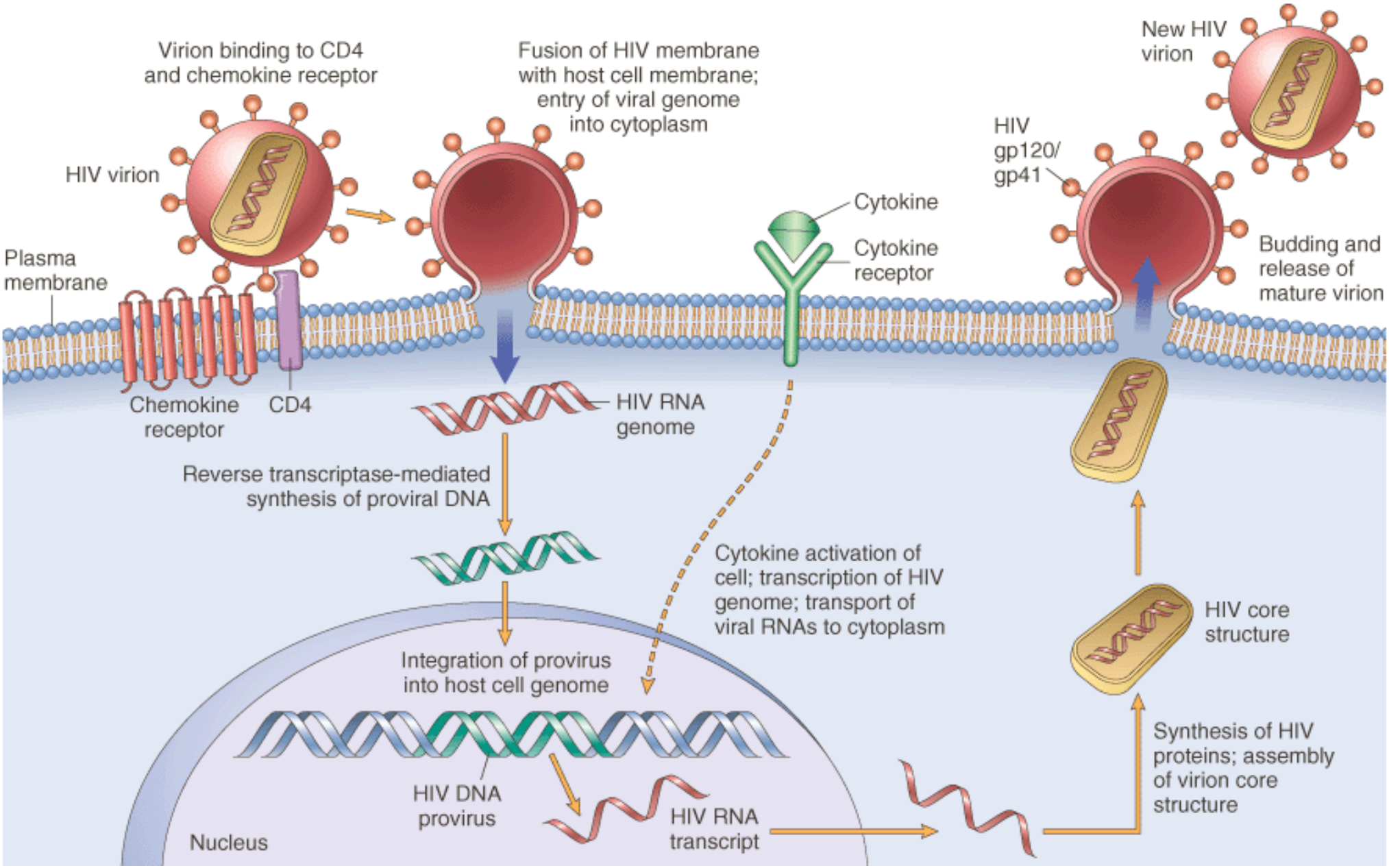


Figure 6-48 Mechanisms of CD4 cell loss in HIV infection.

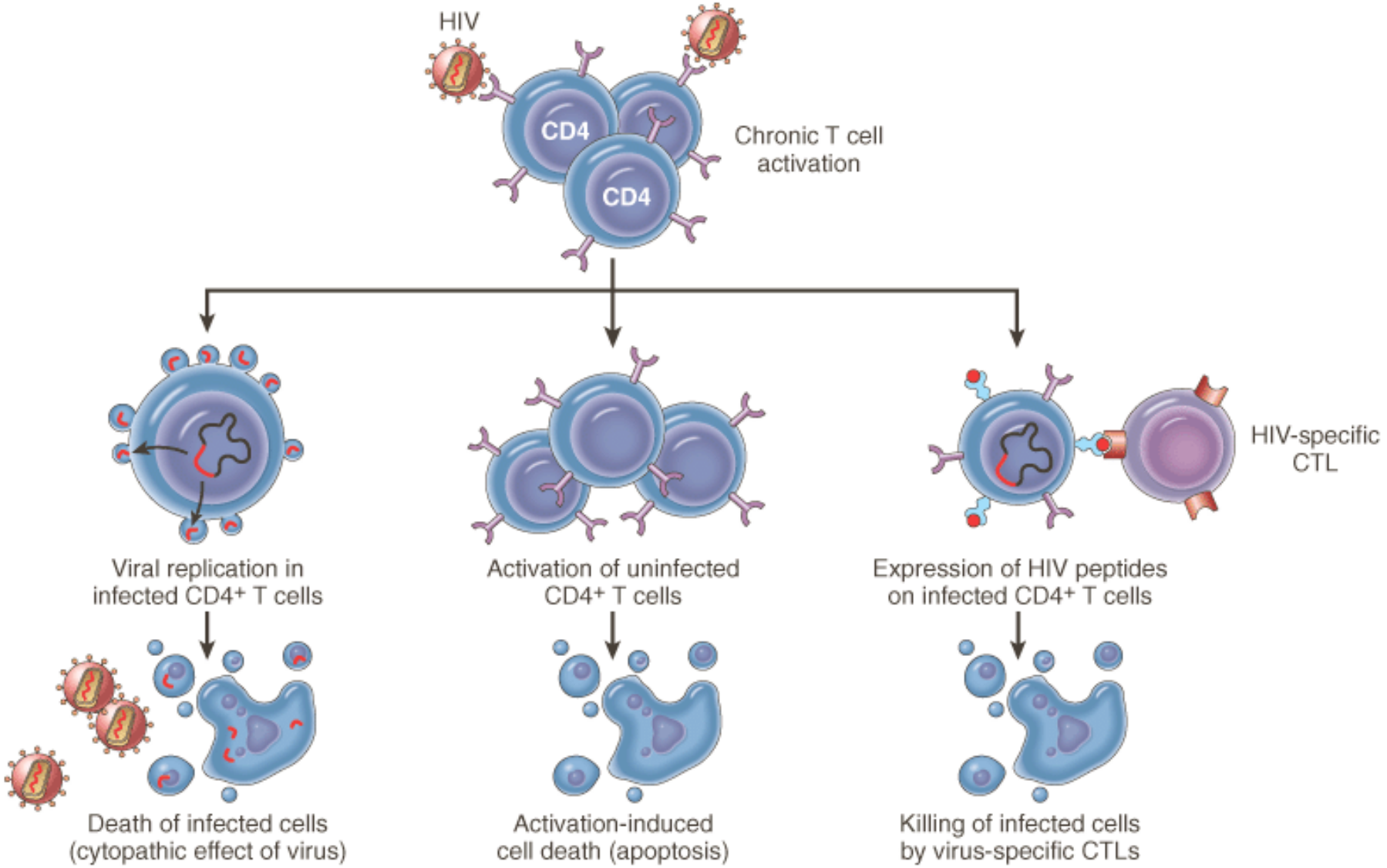


Figure 6-49 HIV infection showing the formation of giant cells in the brain. *(Courtesy of Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

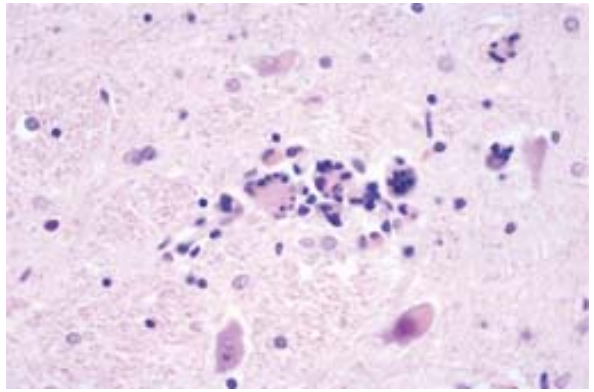


TABLE 6-12 -- Major Abnormalities of Immune Function in AIDS

Lymphopenia
Predominantly due to selective loss of the CD4+ helper-inducer T-cell subset; inversion of CD4:CD8 ratio
Decreased T-Cell Function In Vivo
Preferential loss of memory T cells
Susceptibility to opportunistic infections
Susceptibility to neoplasms
Decreased delayed-type hypersensitivity
Altered T-Cell Function In Vitro
Decreased proliferative response to mitogens, alloantigens, and soluble antigens
Decreased specific cytotoxicity
Decreased helper function for pokeweed mitogen-induced B-cell immunoglobulin production
Decreased IL-2 and TFN-γ production
Polyclonal B-Cell Activation
Hypergammaglobulinemia and circulating immune complexes
Inability to mount de novo antibody response to a new antigen or vaccine
Refractoriness to the 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 IL-1, TNF, IL-6

HIV infection of macrophages has three important implications. First, monocytes and macrophages represent a veritable virus factory and reservoir, whose output remains largely protected from host defenses. Second, macrophages provide a safe vehicle for HIV to be transported to various parts of the body, including the nervous system. Third, in late stages of HIV infection, when the CD4+ T-cell numbers decline greatly, macrophages may be an important site of continued viral replication.[135]

In contrast to tissue macrophages, the number of monocytes in circulation infected by HIV is low, yet there are unexplained functional defects that have important consequences for host defense. These defects include impaired microbicidal activity, decreased chemotaxis, decreased secretion of IL-1, inappropriate secretion of TNF, and, most important, poor capacity to present antigens to T cells.

Studies have documented that, in addition to macrophages, two types of *dendritic cells* are also important targets for the initiation and maintenance of HIV infection: mucosal and follicular dendritic cells. It is thought that *mucosal dendritic cells are infected by the virus and transport it to regional lymph*

---

nodes, where CD4+ T cells are infected.[136] Dendritic cells also express a lectin-like receptor that specifically binds HIV and displays it in an intact, infectious form to T cells, thus promoting infection of the T cells.[137] *Follicular dendritic cells in the germinal centers of lymph nodes are, similar to macrophages, important reservoirs of HIV.*[138] Although some follicular dendritic cells may be susceptible to HIV infection, most virus particles are found on the surface of their dendritic processes. Follicular dendritic cells have receptors for the Fc portion of immunoglobulins, and hence they trap HIV virions coated with anti-HIV antibodies. The antibody-coated virions localized to follicular dendritic cells retain the ability to infect CD4+ T cells as they traverse the intricate meshwork formed by the dendritic processes of the follicular dendritic cells. *To summarize, CD4+ T cells, macrophages, and follicular dendritic cells contained in the lymphoid tissues are the major sites of HIV infection and persistence.*

Although much attention has been focused on T cells, macrophages, and dendritic cells because they can be infected by HIV, patients with AIDS also display profound abnormalities of B-cell function. Paradoxically, these patients have hypergammaglobulinemia and circulating immune complexes owing to polyclonal B-cell activation. This may result from multiple interacting factors: reactivation of or reinfection with cytomegalovirus and EBV, both of which are polyclonal B-cell activators, can occur; gp41 itself can promote B-cell growth and differentiation; and HIV-infected macrophages produce increased amounts of IL-6, which stimulates proliferation of B cells. *Despite the presence of spontaneously activated B cells, patients with AIDS are unable to mount antibody responses to new antigens.* This could be due, in part, to lack of T-cell help, but antibody responses against T-independent antigens are also suppressed, and hence there may be other defects in B cells as well. Impaired humoral immunity renders these patients prey to disseminated infections caused by encapsulated bacteria, such as *S. pneumoniae* and *H. influenzae*, both of which require antibodies for effective opsonization and clearance.

Pathogenesis of Central Nervous System Involvement.

The pathogenesis of neurologic manifestations deserves special mention because, in addition to the lymphoid system, the nervous system is a major target of HIV infection.[139] [140] Macrophages and microglia, cells in the central nervous system that belong to the monocyte and macrophage lineage, are the predominant cell types in the brain that are infected with HIV. It is widely believed that HIV is carried into the brain by infected monocytes. In keeping with this, the HIV isolates from the brain are almost exclusively M-tropic. The mechanism of HIV-induced damage of the brain, however, remains obscure. Because neurons are not infected by HIV, and the extent of neuropathologic changes is often less than might be expected from the severity of neurologic symptoms, most workers believe that neurologic deficit is caused indirectly by viral products and by soluble factors produced by infected microglia. Included among the soluble factors are the usual culprits, such as IL-1, TNF, and IL-6. In addition, nitric oxide induced in neuronal cells by gp41 has been implicated. Direct damage of neurons by soluble HIV gp120 has also been postulated. According to some investigators, these diverse soluble neurotoxins act by triggering excessive entry of Ca^{2+} into the neurons through their action on glutamate-activated ion channels that regulate intracellular calcium.

Natural History of HIV Infection

The course of HIV infection can be best understood in terms of an interplay between HIV and the immune system. Three phases reflecting the dynamics of virus-host interaction can be recognized: (1) an acute retroviral syndrome; (2) a middle, chronic phase; and (3) full-blown AIDS (see Fig. 6-45 ; also Fig. 6-50). [141] We first present the cardinal features of the phases of HIV infection and their associated clinical syndromes then recount the sequential virologic and immunologic findings during the course of HIV infection.

The *acute retroviral syndrome* represents the initial or primary response of an immunocompetent adult to HIV infection. [142] It is characterized initially by a high level of virus production, viremia, and *widespread seeding of the lymphoid tissues*. The initial infection, however, is readily controlled by the development of an antiviral immune response. It is estimated that 40% to 90% of individuals who acquire a primary infection develop the viral syndrome 3 to 6 weeks after infection, and this resolves spontaneously in 2 to 4 weeks. Clinically, this phase is associated with a self-limited acute illness with nonspecific symptoms, including sore throat, myalgias, fever, rash, weight loss, and fatigue, resembling a flulike syndrome. Other clinical features, such as rash, cervical adenopathy, diarrhea, and vomiting, may also occur.

The middle *chronic phase* represents a stage of relative containment of the virus, associated with a period of clinical latency. The immune system is largely intact, but *there is continuous HIV replication, predominantly in the lymphoid tissues, which may last for several years*. Patients are either asymptomatic or develop persistent generalized lymphadenopathy. In addition, many patients have minor opportunistic infections, such as thrush and herpes zoster. Thrombocytopenia may also be noted (Chapter 13). Persistent lymphadenopathy with significant constitutional symptoms (fever, rash, fatigue) reflects the onset of immune system decompensation, escalation of viral replication, and onset of the *crisis* phase.

The final phase is *progression to AIDS*. It is characterized by a breakdown of host defense, a dramatic increase in plasma virus, and clinical disease. Typically the patient presents with long-lasting fever (>1 month), fatigue, weight loss, and diarrhea. After a variable period, serious opportunistic infections, secondary neoplasms, or clinical neurologic disease (grouped under the rubric *AIDS indicator diseases*, discussed below) supervene, and the patient is said to have developed AIDS.

In the absence of treatment, most but not all patients with HIV infection progress to AIDS after a chronic phase lasting from 7 to 10 years. Exceptions to this typical course are exemplified by long-term nonprogressors and by rapid progressors. Nonprogressors are defined as untreated HIV-1-infected individuals who remain asymptomatic for 10 years or more, with stable CD4 + counts and low levels of plasma viremia. In rapid progressors, the middle, chronic phase is telescoped to 2 to 3 years after primary infection. The possible basis for these variant outcomes is discussed later.

With this overview of the phases of HIV disease, we can consider some details of host-parasite relationships during the course of a typical HIV infection. The initial entry of the virus may be through a mucosal surface, as in sexual intercourse (via rectal or cervical mucosa) or via blood exposure (e.g., after intravenous drug use). From the mucosal portal, the virus is carried to the regional lymph nodes by dendritic cells.

Figure 6-50 Typical course of HIV infection. *A*, During the early period after primary infection, there is widespread dissemination of virus and a sharp decrease in the number of CD4+ T cells in peripheral blood. An immune response to HIV ensues, with a decrease in viremia followed by a prolonged period of clinical latency. During this period, viral replication continues. The CD4+ T-cell count gradually decreases during the following years, until it reaches a critical level below which there is a substantial risk of opportunistic diseases. *(Redrawn from Fauci AS, Lane HC: Human immunodeficiency virus disease: AIDS and related conditions. In Fauci AS, et al (eds): Harrison's Principles of Internal Medicine, 14th ed. New York, McGraw-Hill, 1997, p 1791.) B*, Immune response to HIV infection. A cytolytic T lymphocyte (CTL) response to HIV is detectable by 2 to 3 weeks after the initial infection and peaks by 9 to 12 weeks. Marked expansion of virus-specific CD8+ T cell clones occurs during this time, and up to 10% of a patient's CTLs may be HIV specific at 12 weeks. The humoral immune response to HIV peaks at about 12 weeks.

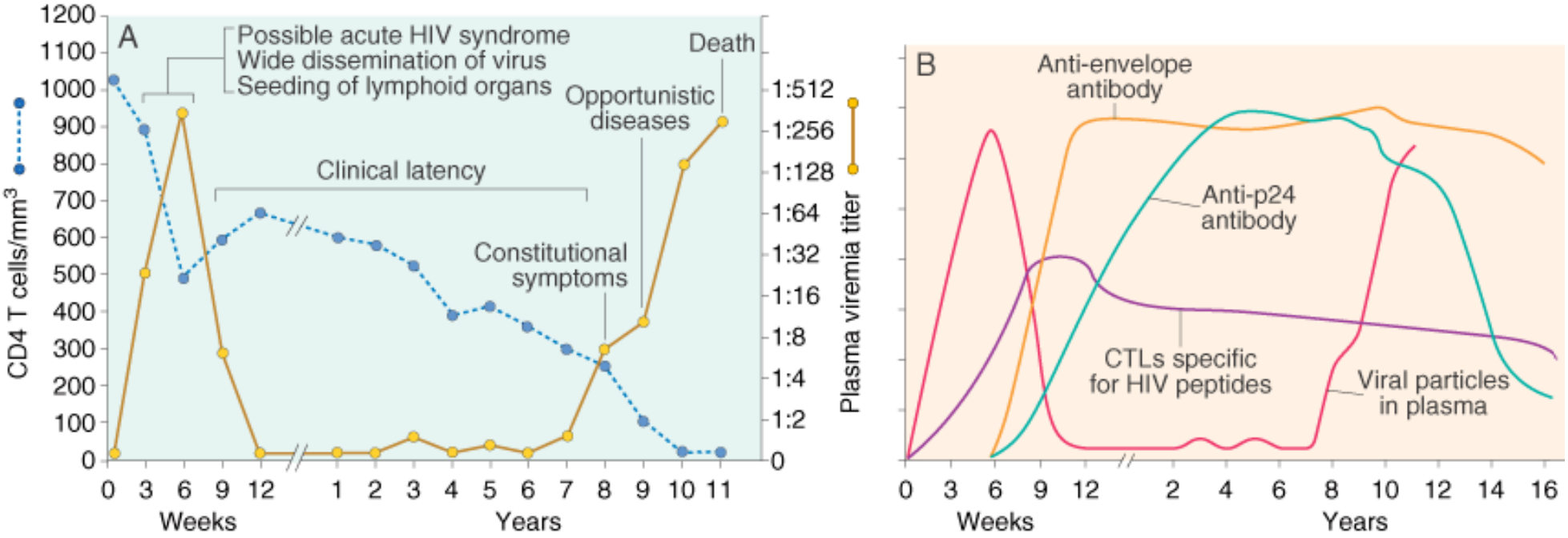


TABLE 6-13 -- CDC Classification Categories of HIV Infection

	CD4+ T-Cell Categories		
Clinical Categories	**1. ≥500/µL**	**2. 200–499/µL**	**3. ≤200/µL**
A. Asymptomatic, acute (primary) HIV, or persistent generalized lymphadenopathy	A1	A2	A3
B. Symptomatic, not A or C conditions	B1	B2	B3
C. AIDS indicator conditions: including constitutional disease, neurologic disease, or secondary infection or neoplasm			

Data from CDC. Centers for Disease Control and Prevention: 1993 revised classification system and expanded surveillance definition for AIDS among adolescents and adults. MMWR 41 (RR-17): 1, 1992.

CD4+ cell count and the development of AIDS, there is extensive turnover of the virus. In other words, *HIV infection lacks a phase of true microbiologic latency*, that is, a phase during which *all* the HIV is in the form of proviral DNA, and no cell is productively infected.

Before this discussion of the virus-host relationships is ended, some comments on those patients who are considered long-term nonprogressors are in order. Individuals in this group remain asymptomatic for long periods of time (10 years or more), have low levels of viremia, and have stable CD4+ cell counts. People with such an uncommon clinical course have attracted great attention in the hope that studying them may shed light on host and viral factors that influence disease progression. Studies to date suggest that this group is heterogeneous with respect to the factors that influence the course of the disease. In a small subset of nonprogressors, the infecting HIV had deletions or mutations in the *nef* gene, suggesting that Nef proteins are critical to disease progression. In most cases, the viral isolates do not show any qualitative abnormalities. In all cases, there is evidence of a vigorous anti-HIV immune response, but the immune correlates of protection are still unknown. Some of these patients have high levels of HIV-specific CD8+ cells, and these levels are maintained over the course of infection. It is not clear whether the robust CD8+ cell response is the cause or consequence of the slow progression. Further studies, it is hoped, will provide the answers to this and other questions critical to

disease progression.

Clinical Features of AIDS

The clinical manifestations of HIV infection can be readily surmised from the foregoing discussion. They range from a mild acute illness to severe disease. Because the salient clinical features of the acute early and chronic middle phases of HIV infection were described earlier, here we summarize the clinical manifestations of the terminal phase, AIDS. At the outset it should be pointed out that the clinical manifestations and opportunistic infections associated with HIV infection may differ in different parts of the world. Typically, HIV-infected individuals in Africa show a more rapid progression of the disease and a shorter survival time than in other geographic areas. Importantly, the clinical course of the disease has been greatly modified by new anti-retroviral therapies, and many complications that were once devestating are now infrequent.

In the United States, the typical adult patient with AIDS presents with fever, weight loss, diarrhea, generalized lymphadenopathy, multiple opportunistic infections, neurologic disease and, in many cases, secondary neoplasms. The infections and neoplasms listed in Table 6-14 are included in the surveillance definition of AIDS.[149]

Opportunistic infections account for the majority of deaths in patients with AIDS. The actual frequency of infections varies in different regions of the world, and has been greatly reduced by the advent of HAART.[150] A brief summary of selected opportunistic infections is provided here. Extensive reviews on the subject are available.[151] [152]

Approximately 15% to 30% of HIV-infected people develop pneumonia caused by the opportunistic fungus *P. carinii* (representing reactivation of a prior latent infection), despite prophylaxis. Prior to HAART, this infection was the presenting feature in about 20% of cases, but the incidence is much less in patients who respond to HAART. The risk of developing this infection is extremely high in individuals with fewer than 200 CD4+ cells/µL. Even in these patients there has been a substantial decline in the incidence of this infection because of effective prophylaxis.

An increasing number of patients present with an opportunistic infection other than *P. carinii* pneumonia. Among the most common pathogens are *Candida*, cytomegalovirus,

TABLE 6-14 -- AIDS-Defining Opportunistic Infections and Neoplasms Found in Patients with HIV Infection

INFECTIONS
Protozoal and Helminthic Infections
Cryptosporidiosis or isosporidiosis (enteritis)
Pneumocytosis (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., *M. avium-intracellulare*, disseminated or extrapulmonary; *M. 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)
Varicella-zoster virus (localized or disseminated)
Progressive multifocal leukoencephalopathy)
NEOPLASMS
Kaposi sarcoma
B-cell non-Hodgkin lymphomas
Primary lymphoma of the brain
Invasive cancer of uterine cervix
CNS, central nervous system.

atypical and typical mycobacteria, *Cryptococcus neoformans*, *Toxoplasma gondii*, *Cryptosporidium*, herpes simplex virus, papovaviruses, and *Histoplasma capsulatum*.

Candidiasis is the most common fungal infection in patients with AIDS. *Candida* infection of the oral cavity (thrush) and esophagus are the two most common clinical manifestations of candidiasis in HIV-infected patients. In asymptomatic HIV-infected individuals, oral candidiasis is a sign of immunologic decompensation, and it often heralds the transition to AIDS. Invasive candidiasis is not common in patients with AIDS, and it usually occurs when there is drug-induced neutropenia or use of indwelling catheters. *Cytomegalovirus* may cause disseminated disease, although, more commonly, it affects the eye and gastrointestinal tract. Chorioretinitis was seen in approximately 25% of patients pre-HAART, but this has decreased by over 50% after the intiation of HAART. Cytomegalovirus retinitis occurs almost exclusively in patients with CD4+ cell counts below 50/µl. Gastrointestinal disease, seen in 5% to 10% of cases, manifests as esophagitis and colitis, the latter associated with multiple mucosal ulcerations. Disseminated bacterial infection with *atypical mycobacteria* (mainly *M. avium-intracellulare*) also occurs late, in the setting of severe immunosuppression. Coincident with the AIDS epidemic, the incidence of tuberculosis has risen dramatically. [153] Worldwide, almost a third of all deaths in AIDS patients are attributable to tuberculosis; in the United states, about 5% of patients with AIDS develop active tuberculosis. Patients with AIDS have reactivation of latent pulmonary disease as well as outbreaks of primary infection. In contrast to infection with atypical mycobacteria, *M. tuberculosis* manifests itself early in the course of AIDS. As with tuberculosis in other settings, the infection may be confined to lungs or may involve multiple organs. The pattern of expression depends on the degree of immunosuppression; dissemination is more common in patients with very low CD4+ cell counts. Most worrisome are reports indicating that a growing number of isolates are resistant to multiple drugs.

Cryptococcosis occurs in about 10% of AIDS patients. Among fungal infections that prey on HIV-infected individuals, it is second only to candidiasis. As in other settings with immunosuppression, meningitis is the major clinical manifestation of cryptococcosis. In contrast to *Cryptococcus, T. gondii*, another frequent invader of the central nervous system in AIDS, causes encephalitis and is responsible for 50% of all mass lesions in the central nervous system. JC virus, a human papovavirus, is another important cause of central nervous system infections in HIV-infected patients. It causes progressive multifocal leukoencephalopathy (Chapter 28). *Herpes simplex virus infection* is manifested by mucocutaneous ulcerations involving the mouth, esophagus, external genitalia, and perianal region. *Persistent diarrhea*, so common in patients with AIDS, is often caused by infections with protozoans such as

Cryptosporidium, Isospora belli, or microsporidia. These patients have chronic, profuse, watery diarrhea with massive fluid loss. Diarrhea may also result from infection with enteric bacteria, such as *Salmonella* and *Shigella*, as well as *M. avium-intracellulare*. Depressed humoral immunity renders AIDS patients susceptible to severe, recurrent bacterial pneumonias.

Patients with AIDS have a high incidence of certain tumors, especially *Kaposi sarcoma (KS)*, non-Hodgkin B-cell lymphoma, cervical cancer in women, and anal cancer in men.[154] [155] It is estimated that 25% to 40% of HIV-infected individuals will eventually develop a malignancy. A common feature of these tumors is that they are all believed to be caused by oncogenic DNA viruses, that is, Kaposi sarcoma herpesvirus (Kaposi sarcoma), EBV (B-cell lymphoma), human papillomavirus (cervical and anal carcinoma). The increased risk of malignancy is thus mainly a consequence of increased susceptibility to infections by these viruses and decreased immunity against the tumors.

KS, a vascular tumor that is otherwise rare in the United States, is the most common neoplasm in patients with AIDS. The morphology of KS and its occurrence in patients not infected with HIV are discussed in Chapter 11 . At the onset of the AIDS epidemic, up to 30% of infected homosexual or bisexual men had KS, but in recent years, with use of HAART there has been a marked decline in its incidence, from 15 cases per 1000 person years to less than 5 cases.

The lesions of KS are characterized by the proliferation of spindle-shaped cells that express markers of both endothelial (vascular or lymphatic) and smooth muscle lineages. There is also a profusion of slit-like vascular spaces, suggesting that the lesions may arise from primitive mesenchymal precursors of vascular channels. In addition, KS lesions display chronic inflammatory cell infiltrates. There is still some debate about whether the lesions represent an exuberant hyperplasia or a malignant neoplasm, but the weight of evidence favors the former. For instance, spindle cells in many KS lesions are polyclonal or oligoclonal, although more advanced lesions occasionally show monoclonality.[156] Moreover, spindle cells in many KS lesions are diploid, dependent on growth factors for their proliferation, and do not form tumors in immunodeficient mice.[157] When KS cells are implanted subcutaneously in such mice, they transiently induce slit-like new blood vessels and inflammatory infiltrates in the surrounding tissue; these elements recall features of human KS, but interestingly are of murine origin. When the human KS cells involute, these elements also regress. These observations suggest that KS pathogenesis involves a complex web of paracrine signaling interactions among different types of cells, no one of which is fully autonomous. One popular view envisions that spindle cells produce pro-inflammatory and angiogenic factors, recruiting the inflammatory and neovascular components of the lesion, while the latter components supply signals that aid in spindle cell survival or growth[157] (Fig. 6-51).

But what initiates this cycle of events? Clues to this came from the observation that not all HIV patients are at equal risk for KS development. AIDS-related KS is twenty times more frequent in individuals who acquire HIV by sexual routes compared to those who acquire it parenterally. This observation suggested that a sexually transmitted agent other than HIV might be implicated in KS etiology and prompted a search for new viruses in KS. This search yielded a novel herpesvirus, aptly labeled *KS herpesvirus* (KSHV), or *human herpesvirus 8*.[158] Epidemiologic studies strongly link KSHV to KS development. Infection is uncommon in the general population and strikingly increased in prevalence in groups in which KS is common. In individual patients, KSHV infection precedes KS development and is highly correlated with increased KS risk. KSHV DNA is found in virtually all KS lesions, including those that occur in HIV-negative populations. In the lesions, KSHV is strikingly localized to the spindle cells, which display predominantly latent infection.[159] Thus,

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Figure 6-51 Proposed role of HIV, KSHV (HHV8), and cytokines in the pathogenesis of Kaposi sarcoma. Cytokines are produced by the mesenchymal cells infected by KSHV, or by HIV-infected CD4+ cells. B cells may also be infected by KSHV; their role in the disease is unclear.

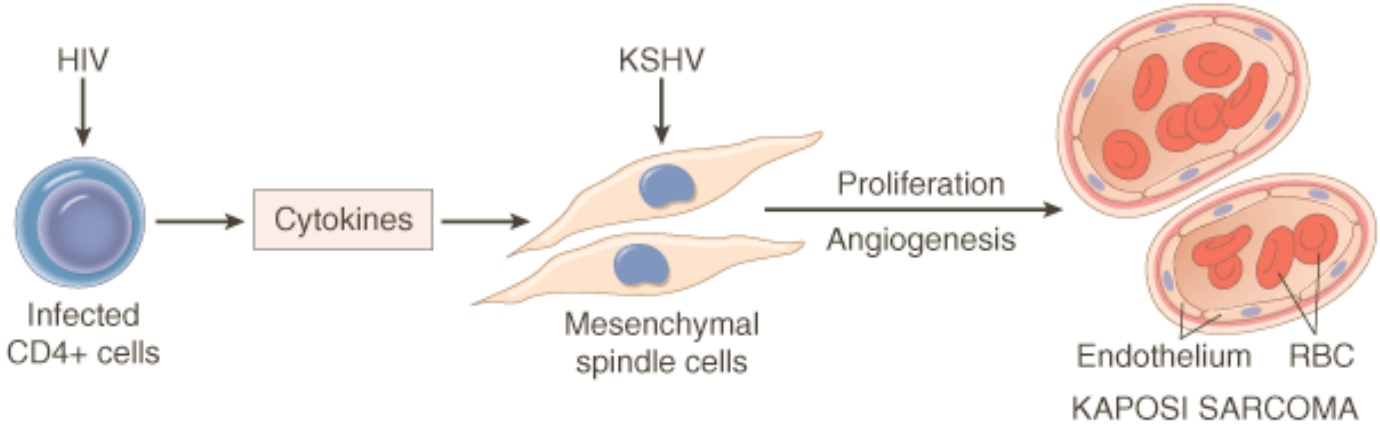

Figure 6-52 Amyloidosis. *A*, A section of the liver stained with Congo red reveals pink-red deposits of amyloid in the walls of blood vessels and along sinusoids. *B*, Note the yellow-green birefringence of the deposits when observed by polarizing microscope. *(Courtesy of Dr. Trace Worrell and Sandy Hinton, Department of Pathology, University of Texas Southwestern Medical School, Dallas TX.)*

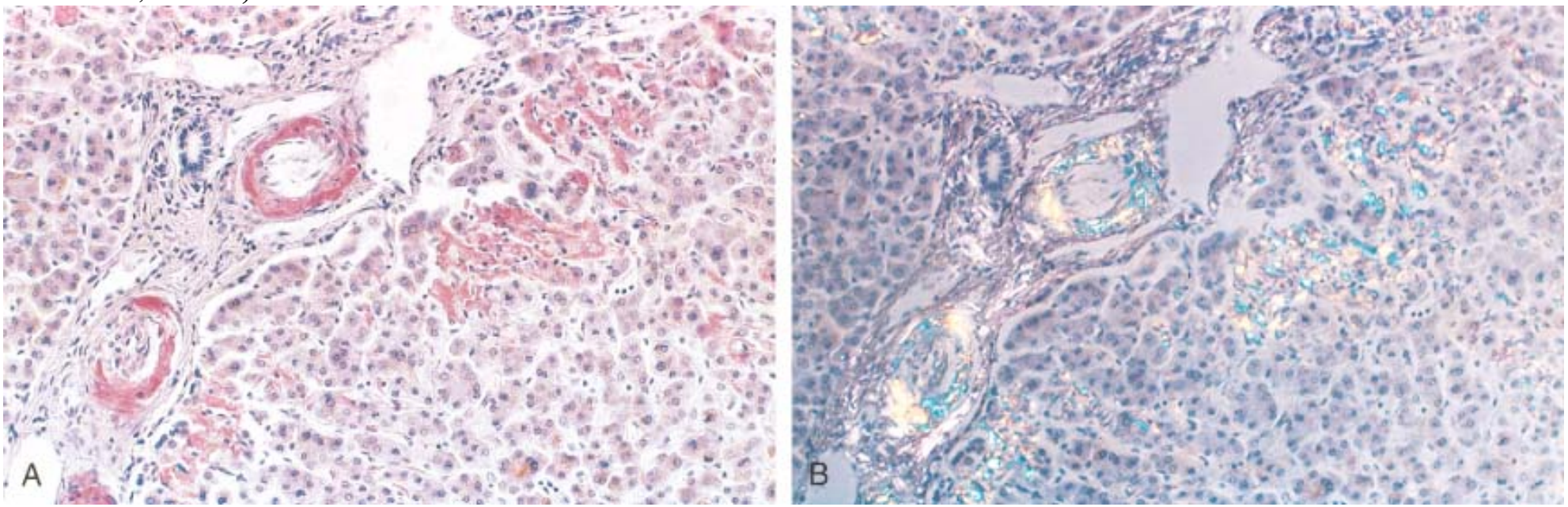

Figure 6-53 Structure of an amyloid fibril, depicting the β-pleated sheet structure and binding sites for the Congo red dye, which is used for diagnosis of amyloidosis. *(Modified from Glenner GG: Amyloid deposit and amyloidosis. The β-fibrilloses. N Engl J Med 52:148, 1980. By permission of The New England Journal of Medicine.)*

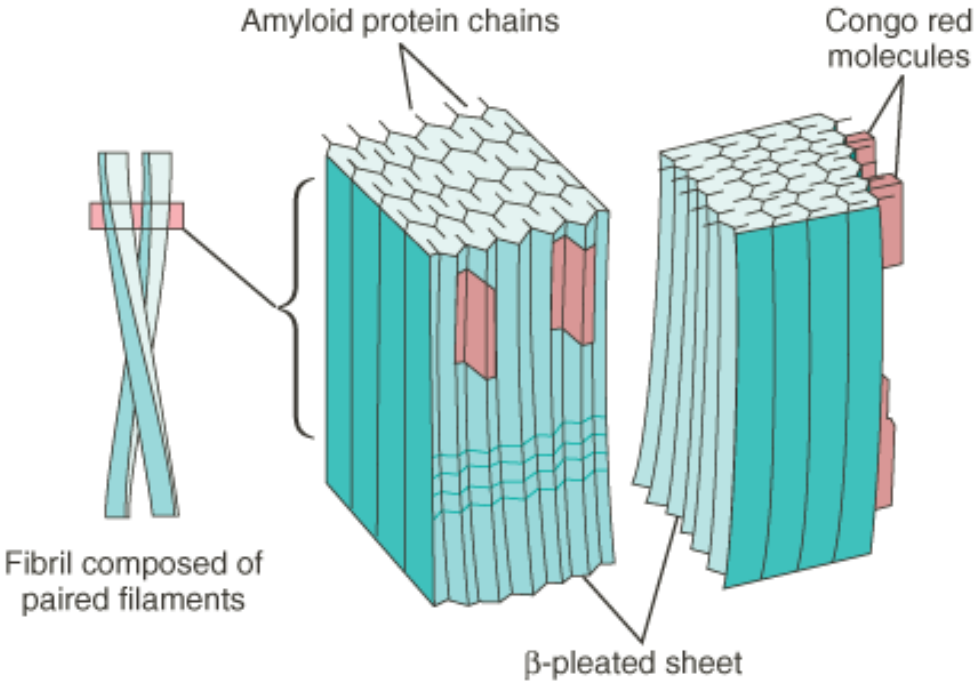

TABLE 6-15 -- Classification of Amyloidosis

Clinicopathologic Category	Associated Diseases	Major Fibril Protein	Chemically Related Precursor Protein
Systemic (Generalized) Amyloidosis			
Immunocyte dyscrasias with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal B-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	$A\beta_2$ m	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
••Islet of Langerhans	Type II diabetes	AIAPP	Islet amyloid peptide
Isolated atrial amyloidosis	—	AANF	Atrial natriuretic factor
Prion diseases	Various prion diseases of the CNS	Misfolded prion protein (PrP^{SC})	Normal prion protein PrP

In addition, other minor components are always present in amyloid. These include serum amyloid P component, proteoglycans, and highly sulfated glycosaminoglycans. Serum amyloid P protein may contribute to amyloid deposition by stabilizing the fibrils and decreasing their clearance.

Classification of Amyloidosis.

According to devoted "amyloidologists," who congregate every few years to discuss their favorite protein, amyloid should be classified based on its constituent chemical fibrils into categories such as AL, AA, and ATTR and not based on clinical syndromes.[170] Because a given biochemical form of amyloid (e.g., AA) may be associated with amyloid deposition in diverse clinical settings, we follow a combined biochemical-clinical classification for our discussion (Table 6-15). Amyloid may be *systemic* (generalized), involving several organ systems, or it may be *localized*, when deposits are limited to a single organ, such as the heart. As should become evident, several different biochemical forms of amyloid are encompassed by such segregation.

On clinical grounds, the systemic, or generalized, pattern is subclassified into *primary amyloidosis*, when associated with some immunocyte dyscrasia, or *secondary amyloidosis*, when it occurs as a complication of an underlying chronic inflammatory or tissue destructive process. *Hereditary* or *familial amyloidosis* constitutes a separate, albeit heterogeneous group, with several distinctive patterns of organ involvement.

Immunocyte Dyscrasias with Amyloidosis (Primary Amyloidosis).

Amyloid in this category is usually systemic in distribution

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and is of the AL type. With approximately 1275 to 3200 new cases every year in the United States, this is the most common form of amyloidosis. In many of these cases, the patients have some form of plasma cell dyscrasia. Best defined is the occurrence of systemic amyloidosis in 5% to 15% of patients with multiple myeloma, a plasma-cell tumor characterized by multiple osteolytic lesions throughout the skeletal system (Chapter 14). The malignant B cells characteristically synthesize abnormal amounts of a single specific immunoglobulin (monoclonal gammopathy), producing an M (myeloma) protein spike on serum electrophoresis. In addition to the synthesis of whole immunoglobulin molecules, only the light chains (referred to as *Bence Jones protein*) of either the λ or the κ variety may be elaborated and found in the serum. By virtue of the small molecular size of the Bence Jones protein, it is frequently excreted in the urine. The amyloid deposits contain the same light chain protein. Almost all the patients with myeloma who develop amyloidosis have Bence Jones proteins in the serum or urine, or both, but a great majority of myeloma patients who have free light chains do not develop amyloidosis. Clearly, therefore, *the presence of Bence Jones proteins, although necessary, is by itself not enough to produce amyloidosis*. We discuss later the other factors, such as the type of light chain produced (*amyloidogenic potential*) and the subsequent handling (possibly degradation) that may have a bearing on whether Bence Jones proteins are deposited as amyloid.

The great majority of patients with AL amyloid do not have classic multiple myeloma or any other overt B-cell neoplasm; such cases have been traditionally classified as primary amyloidosis because their clinical features derive from the effects of amyloid deposition without any other associated disease. In virtually all such cases, however, monoclonal immunoglobulins or free light chains, or both, can be found in the serum or urine. Most of these patients also have a modest increase in the number of plasma cells in the bone marrow,

which presumably secrete the precursors of AL protein. Clearly, these patients have an underlying B-cell dyscrasia in which production of an abnormal protein, rather than production of tumor masses, is the predominant manifestation. Recent studies have revealed chromosomal translocations in many of these patients, suggesting the presence of neoplastic clones.[171] Whether most of these clones would evolve into myeloma if the patients lived long enough can only be a matter for speculation.

Reactive Systemic Amyloidosis.

The amyloid deposits in this pattern are systemic in distribution and are composed of AA protein. This category was previously referred to as *secondary amyloidosis* because it is secondary to an associated inflammatory condition. The feature common to most of the conditions associated with reactive systemic amyloidosis is protracted breakdown of cells resulting from a wide variety of infectious and noninfectious chronic inflammatory conditions. At one time, tuberculosis, bronchiectasis, and chronic osteomyelitis were the most important underlying conditions, but with the advent of effective antimicrobial chemotherapy, the importance of these conditions has diminished. More commonly now, reactive systemic amyloidosis complicates rheumatoid arthritis, other connective tissue disorders such as ankylosing spondylitis, and inflammatory bowel disease, particularly Crohn disease and ulcerative colitis. Among these, the most frequent associated condition is rheumatoid arthritis. Amyloidosis is reported to occur in approximately 3% of patients with rheumatoid arthritis and is clinically significant in one half of those affected. Heroine abusers who inject the drug subcutaneously also have a high occurrence rate of generalized AA amyloidosis. The chronic skin infections associated with "skin-popping" of narcotics seem to be responsible for amyloidosis in this group of patients. Reactive systemic amyloidosis may also occur in association with non-immunocyte-derived tumors, the two most common being renal cell carcinoma and Hodgkin disease.

Hemodialysis-Associated Amyloidosis.

Patients on long-term hemodialysis for renal failure develop amyloidosis owing to deposition of β_2 -microglobulin. This protein is present in high concentrations in the serum of patients with renal disease and is retained in circulation because it cannot be filtered through the cuprophane dialysis membranes. In some series, as many as 60% to 80% of the patients on long-term dialysis developed amyloid deposits in the synovium, joints, and tendon sheaths.

Heredofamilial Amyloidosis.

A variety of familial forms of amyloidosis have been described. Most of them are rare and occur in limited geographic areas. The most common and best studied is an autosomal recessive condition called *familial Mediterranean fever*.[172] This is a febrile disorder of unknown cause characterized by attacks of fever accompanied by inflammation of serosal surfaces, including peritoneum, pleura, and synovial membrane. This disorder is encountered largely in individuals of Armenian, Sephardic Jewish, and Arabic origins. It is associated with widespread tissue involvement indistinguishable from reactive systemic amyloidosis. The amyloid fibril proteins are made up of AA proteins, suggesting that this form of amyloidosis is related to the recurrent bouts of inflammation that characterize this disease. The gene for familial Mediterranean fever has been cloned, and its product is called *pyrin* (for its relation to fever). Although its exact function is not known, it has been suggested that pyrin is responsible for regulating acute inflammation, presumably by inhibiting the function of neutrophils.[173] The relationship of this mutation to the disease is not understood.

In contrast to familial Mediterranean fever, a group of autosomal dominant familial disorders is characterized by deposition of amyloid predominantly in the nerves—peripheral and autonomic. These familial amyloidotic polyneuropathies have been described in different parts of the world. As mentioned previously, in all of these genetic disorders, the fibrils are made up of mutant transthyretins (ATTR).

Localized Amyloidosis.

Sometimes, amyloid deposits are limited to a single organ or tissue without involvement of any other site in the body. The deposits may produce grossly detectable nodular masses or be evident only on microscopic examination. Nodular (tumor-forming) deposits of amyloid are most often encountered in the lung, larynx, skin, urinary bladder, tongue, and the region about the eye. Frequently, there are infiltrates of lymphocytes and plasma cells in the periphery of these amyloid masses, raising the question of whether the mononuclear infiltrate is a response to the deposition of amyloid or instead is responsible for it. At least in some cases, the amyloid consists of AL protein and may therefore represent a localized form of immunocyte-derived amyloid.

Endocrine Amyloid.

Microscopic deposits of localized amyloid may be found in certain endocrine tumors, such as

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medullary carcinoma of the thyroid gland, islet tumors of the pancreas, pheochromocytomas, and undifferentiated carcinomas of the stomach, and in the islets of Langerhans in patients with type II diabetes mellitus. In these settings, the amyloidogenic proteins seem to be derived either from polypeptide hormones (e.g., medullary carcinoma) or from unique proteins (e.g., islet amyloid polypeptide).

Amyloid of Aging.

Several well-documented forms of amyloid deposition occur with aging.[174] *Senile systemic amyloidosis* refers to the systemic deposition of amyloid in elderly patients (usually in their seventies and eighties). Because of the dominant involvement and related dysfunction of the heart, this form was previously called *senile cardiac amyloidosis*. Those who are symptomatic present with a restrictive cardiomyopathy and arrhythmias. The amyloid in this form is composed of the normal TTR molecule. In addition to the sporadic senile systemic amyloidosis, another form, affecting predominantly the heart, that results from the deposition of a mutant form of TTR has also been recognized. Approximately 4% of the black population in the United States is a carrier of the mutant allele, and cardiomyopathy has been identified in both homozygous and heterozygous patients. The precise prevalance of patients with this mutation who develop clinically manifest cardiac disease is not known.

Pathogenesis.

Amyloidosis results from abnormal folding of proteins, which are deposited as fibrils in extracellular tissues and disrupt normal function. Misfolded proteins are often unstable and self-associate, ultimately leading to the formation of oligomers and fibrils that are deposited in tissues. The reason diverse conditions are associated with amyloidosis may be that each of these conditions results in excessive production of proteins that are prone to misfolding. The proteins that form amyloid fall into two general categories: (1) normal proteins that have an inherent tendency to fold improperly, associate and form fibrils, and do so when they are produced in

Figure 6-54 Proposed schema of the pathogenesis of the major forms of amyloid fibrils.

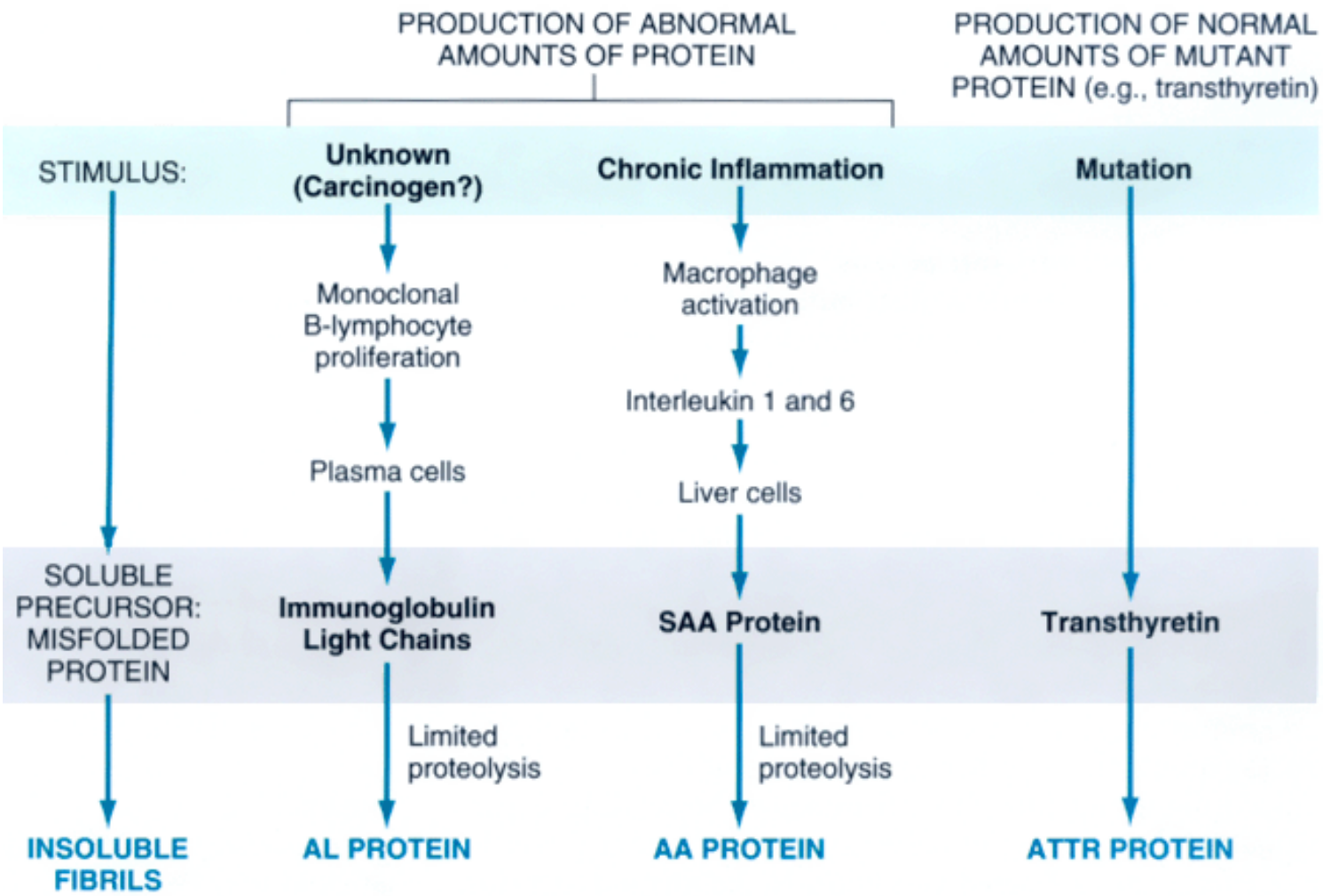


Figure 6-55 Amyloidosis of the kidney. The glomerular architecture is almost totally obliterated by the massive accumulation of amyloid.

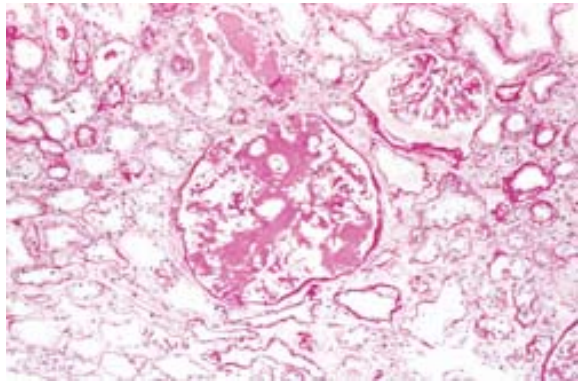
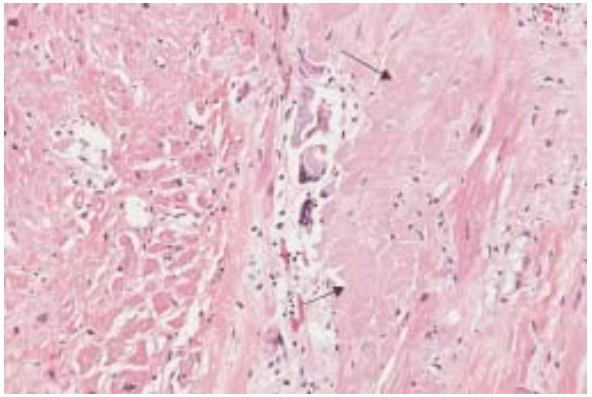


Figure 6-56 Cardiac amyloidosis. The atrophic myocardial fibers are separated by structureless, pink-staining amyloid *(arrows)*.



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