Autoimmunity & Immunodeficiency

Jun Dou(窦骏)

njdoujun@seu.edu.cn

Building 1, Room 507

Department of Pathogenic biology and Immunology,
School of Medicine, Southeast University

Autoimmunity

The Universe of Antigens

- The number of potential pathogens is essentially infinite.
- Contact with most of them is not predictable.
- The immune system uses a clever mechanism that has evolved to solve these problems. The cells of
- the adaptive immune system (B and T cells) have ***randomized*** antigen receptors (via **VDJ** and hypermutation).

- **The strategy is that a few (among billions) of naive B and T cells will recognize antigen and will expand in response to it. This is called *clonal selection* theory.**
- **The strategy carries with it a potential danger. Since antigen receptors on B and T cells are randomized, they have the potential to recognize self as well as non-self (pathogens).**
- **Reaction against self is called *autoimmunity*.**

Autoimmune Disease

TABLE 20-1 SOME AUTOIMMUNE DISEASES IN HUMANS

Disease	Self-antigen	Immune response
Organ-specific autoimmune diseases		
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_{DTH} cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_{DTH} cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
Systemic autoimmune disease		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_{DTH} and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjogren's syndrome	Salivary gland, liver, kidney, thryoid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antobidies, immune complexes

Disease	Disease mechanism	Consequence
Graves' disease	Autoantibodies against the thyroid-stimulating-hormone receptor	Hyperthyroidism: overproduction of thyroid hormones
Rheumatoid arthritis	Autoreactive T cells against antigens of joint synovium	Joint inflammation and destruction causing arthritis
Hashimoto's thyroiditis	Autoantibodies and autoreactive T cells against thyroid antigens	Destruction of thyroid tissue leading to hypothyroidism: underproduction of thyroid hormones
Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM)	Autoreactive T cells against pancreatic islet cell antigens	Destruction of pancreatic islet β cells leading to non-production of insulin
Multiple sclerosis	Autoreactive T cells against brain antigens	Formation of sclerotic plaques in brain with destruction of myelin sheaths surrounding nerve cell axons, leading to muscle weakness, ataxia, and other symptoms
Systemic lupus erythematosus	Autoantibodies and autoreactive T cells against DNA, chromatin proteins, and ubiquitous ribonucleoprotein antigens	Glomerulonephritis, vasculitis, rash
Sjögren's syndrome	Autoantibodies and autoreactive T cells against ribonucleoprotein antigens	Lymphocyte infiltration of exocrine glands, leading to dry eyes and/or dry mouth; other organs may be involved, leading to systemic disease

Figure 14-1 Immunobiology, 7ed. (© Garland Science 2008)

Mechanisms of Tolerance Induction

- **Organisms that employ the randomization strategy and do nothing to reduce the number of autoreactive cells in the immune repertoire would be reckless and would be unlikely to survive in the Darwinian sense.**

- **Two classes of tolerance induction mechanisms are used by both B and T cells.**

- ***Central tolerance*** **operates on <u>immature</u> T and B cells**
  - **Thymus for T cells**
  - **Bone marrow for B cells**
- ***Peripheral tolerance*** **provides a backup to central tolerance and operates on mature lymphocytes.**
- **Existence of autoimmune reactions shows that tolerance induction is not perfect**

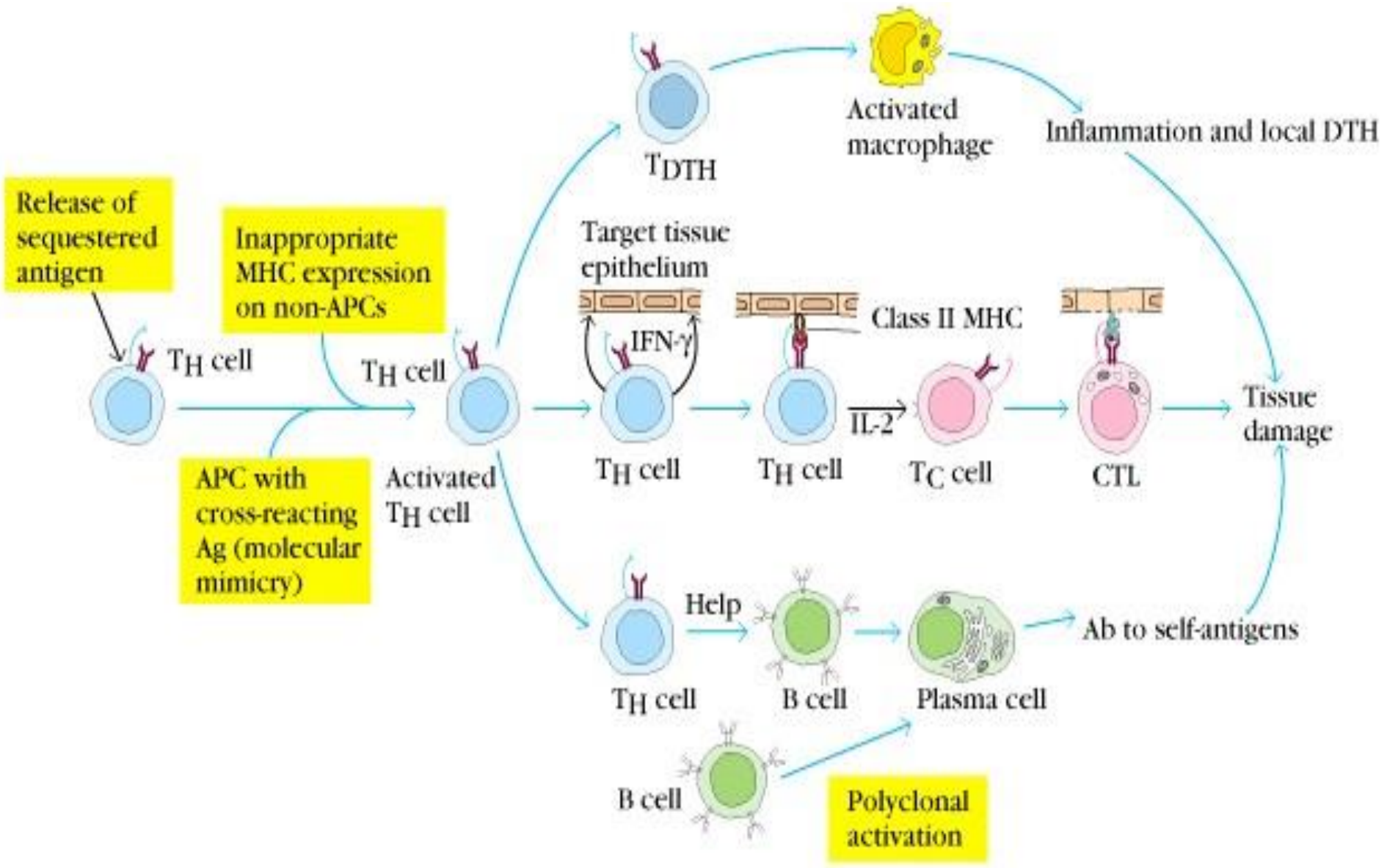
Layers of self-tolerance

Type of tolerance	Mechanism	Site of action
Central tolerance	Deletion Editing	Thymus Bone marrow
Antigen segregation	Physical barrier to self-antigen access to lymphoid system	Peripheral organs (e.g. thyroid, pancreas)
Peripheral anergy	Cellular inactivation by weak signaling without co-stimulus	Secondary lymphoid tissue
Regulatory cells	Suppression by cytokines, intercellular signals	Secondary lymphoid tissue and sites of inflammation
Cytokine deviation	Differentiation to T_H2 cells, limiting inflammatory cytokine secretion	Secondary lymphoid tissue and sites of inflammation
Clonal deletion	Apoptosis post-activation	Secondary lymphoid tissue and sites of inflammation

Susceptibility to Autoimmune Diseases: Contribution of MHC and Gender

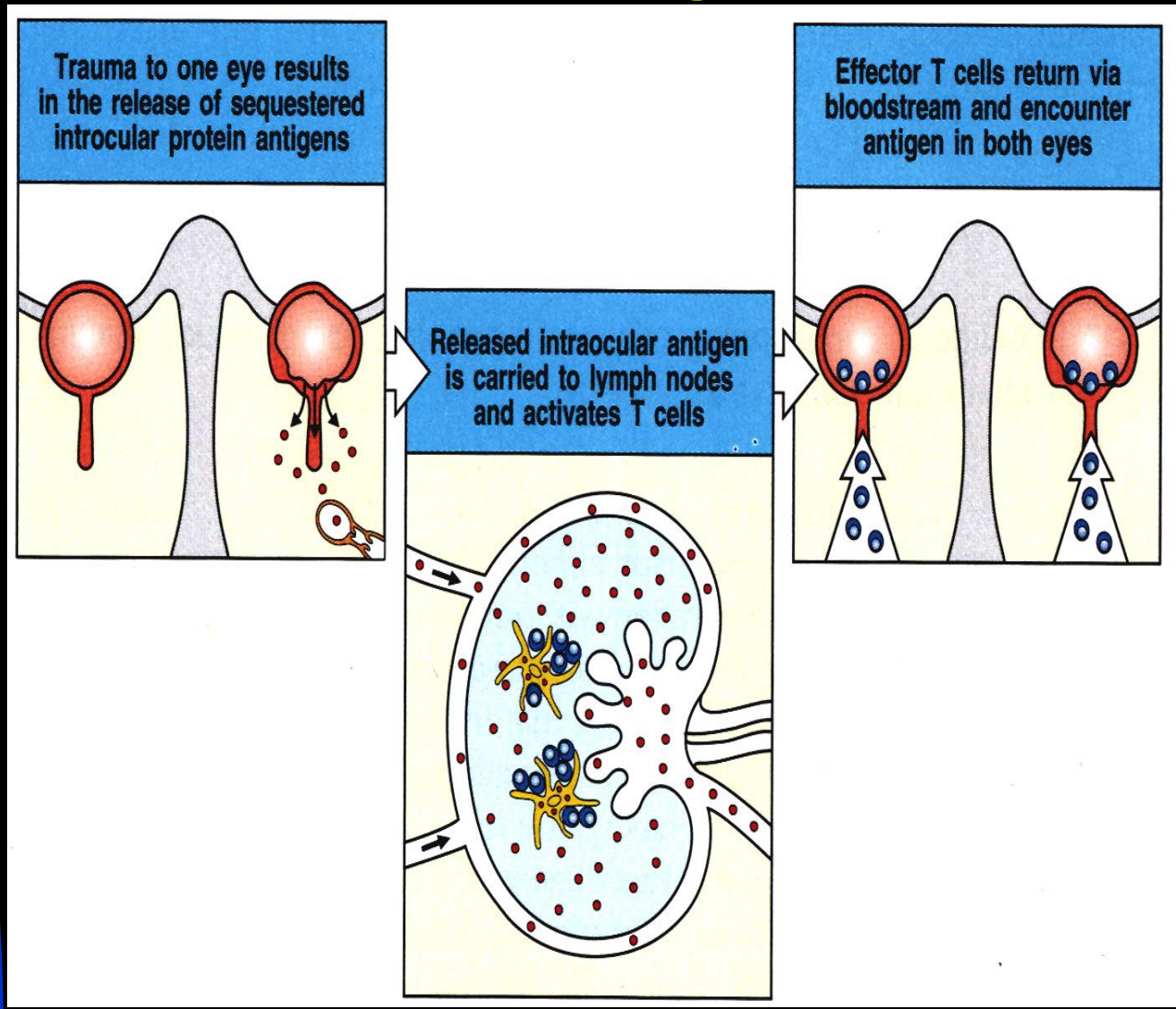
Disease	*HLA allele*	*Relative Risk*	*Sex Ratio (F/M)*
Ankyloi ng spondyliti s	B27	87.4	0.3
Acute anterior uvei tis	B27	10.04	<0.5
Goodpasture抯 Syndrome	DR2	15.9	?
Multi ple Sclerosis	DR2	4.8	10
Grave s?Dise ase	DR3	3.7	4-5
Myast henia gravis	DR3	2.5	~1
Lupus (SLE)	DR3	5.8	10-20
IDDM	DR3 and DR4	3.2	~1
Rhumatoi d arthritis	DR4	4.2	3
Pemphi gus vulgaris	DR4	14.4	?
Hashimoto抯 thyroditis	DR5	3.2	~1

Mechanisms for inducing autoimmune responses.



- Sympathetic opthalmia
- The eye is not normally “sampled” by T cells
- Trauma to the eye can release antigens unique to the eye (not presented in the thymus)
- These antigens can be brought to lymph nodes where they activate T cells.
- Primed T cells can traffic through privileged sites and cause tissue damage if they recognize antigen

Release of Sequestered Antigen from Immunoprivileged Site



Type II Autoimmune Diseases: Antibodies to cell surface or matrix proteins

Syndrome	*Autoantigen*	*Consequence*
Hemolytic Anemia	Rh blood group, I antigen	Destruction of RBC by complement and phagocytes; anemia
Thrombocytopenia purpura	Platelet integrin gpIIb:IIIa	Abnormal bleeding
Goodpasture指 Syndrome	Non-collagenous domain of basement membrane collagen type IV	Vasculitis, renal failure
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Acute rheumatic fever	Streptococcal cell wall antigens, antibodies cross-react with cardiac muscle	Arthritis, myocarditis, scarring of heart valves

Type III - Immune Complex Disease

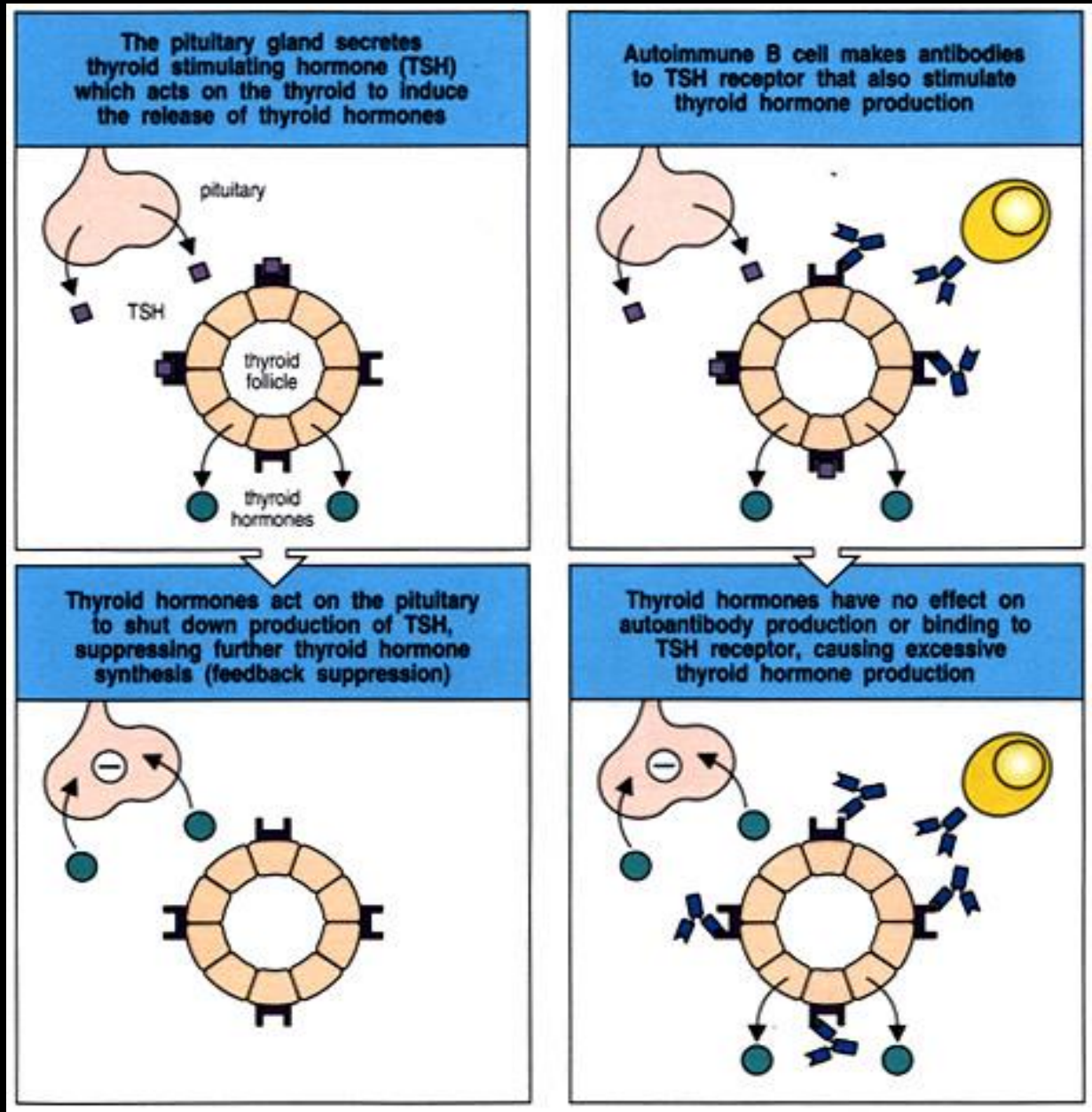
Syndrome	*Autoantigen*	*Consequence*
Post-streptococcal glomerulonephritis	Streptococcal antigen	Transient nephrotic syndrome
Polyarteritis nodosa	Hepatitis B surface antigen	Systemic vasculitis
Systemic lupus erythematosus (SLE)	DNA, histones, ribosomes, etc.	Glomerulonephritis, vasculitis, arthritis

Type IV - T cell mediated disease

Syndrome	Autoantigen	Consequence
Insulin-dependent diabetes mellitus	Unknown pancreatic β cell antigen (GAD?)	β-cell destruction
Rheumatoid arthritis	Unknown synovial joint antigen	Joint inflammation and destruction
Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis	Mylein basic protein (MBP), proteolipid protein (PLP)	Brain invasion by CD4 T cells, paralysis

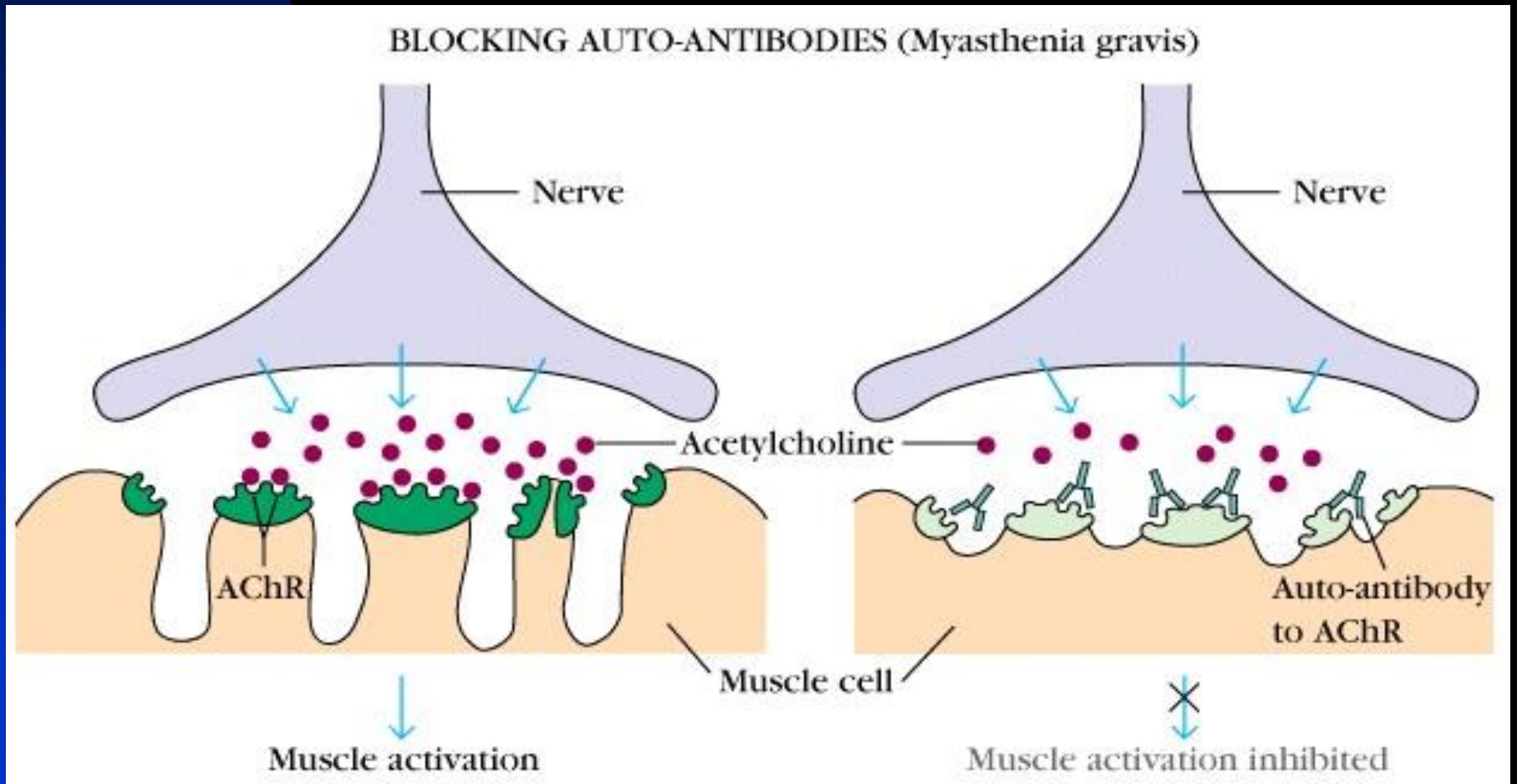
Graves' Disease:A type II hypersensitivity reaction involving receptor binding

- Antibodies to thyroid stimulating hormone receptor stimulate thyroid hormone production. Block of TSH feedback inhibition
- Result is excessive thyroid hormone production



Myasthenia Gravis:A type II hypersensitivity reaction involving receptor binding

- Autoantibodies to chain of acetylcholine receptor found at neuromuscular junction block neuromuscular transmission. Antibodies also drive degradation of AChR. Patients develop progressive weakness and eventually die.



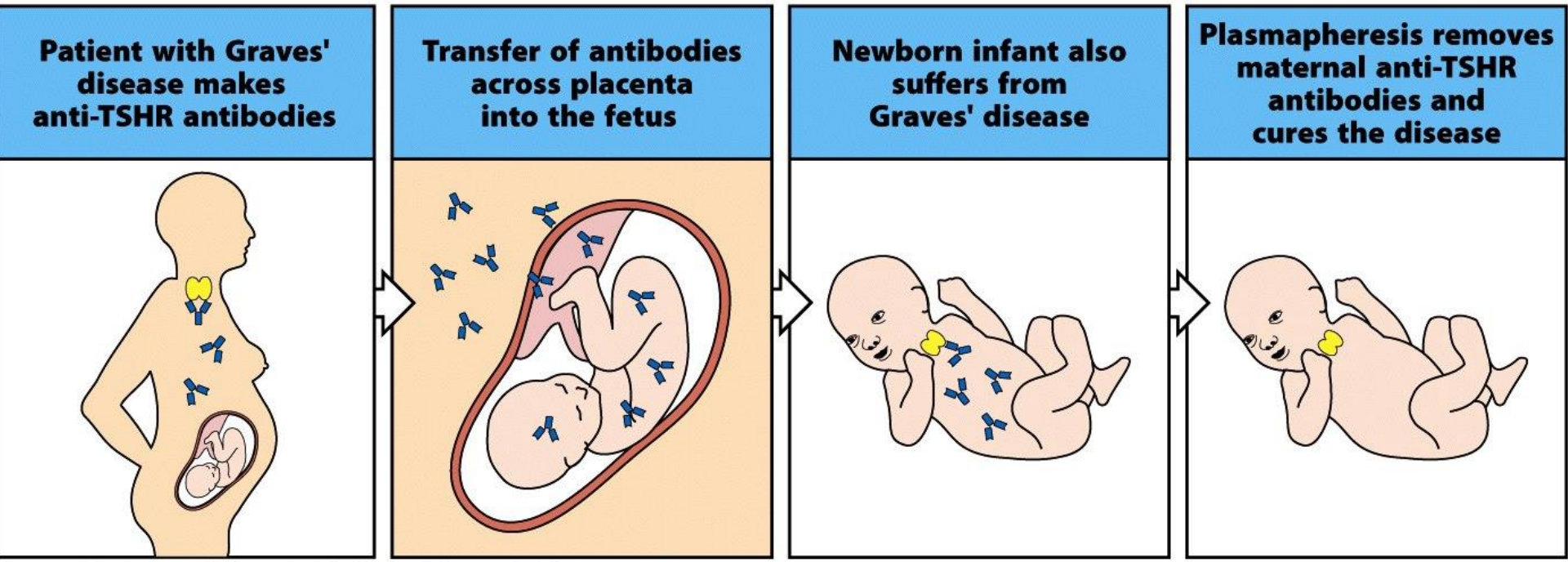


Figure 14-15 Immunobiology, 7ed. (© Garland Science 2008)

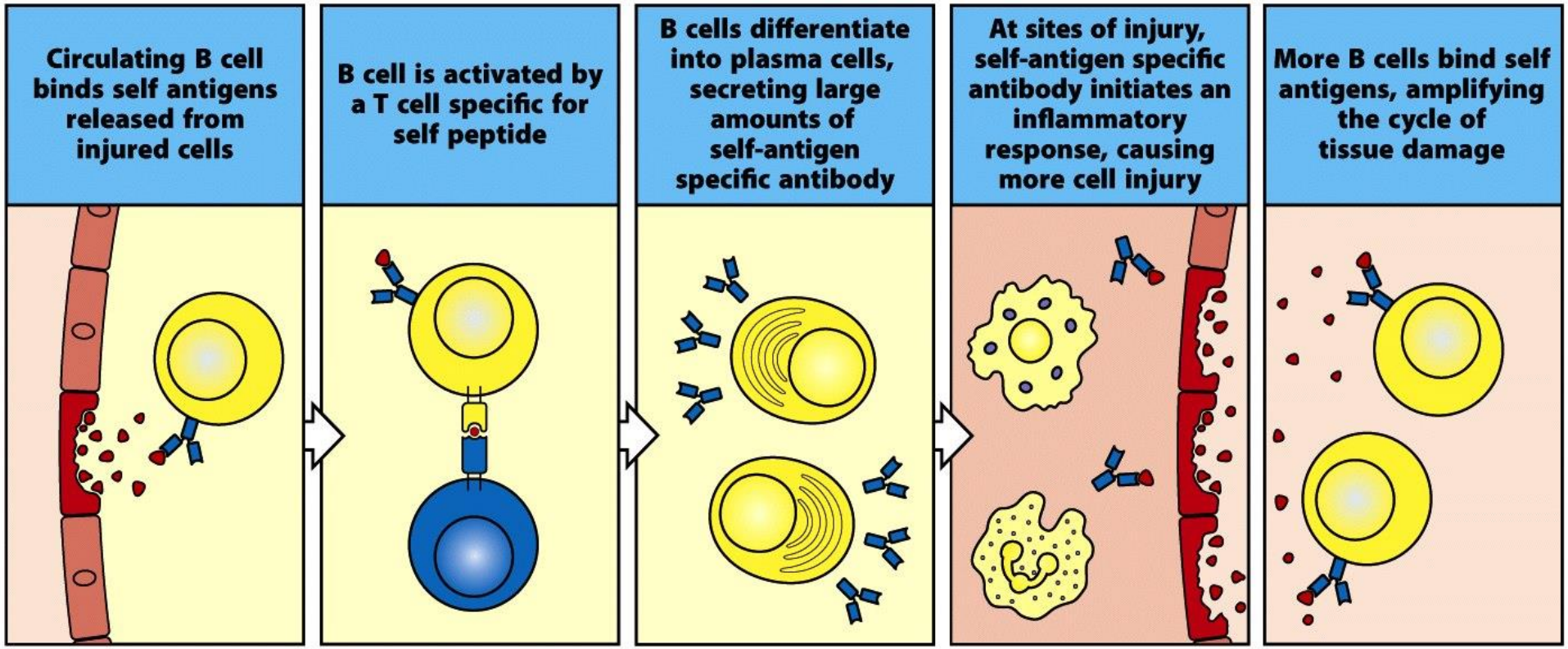
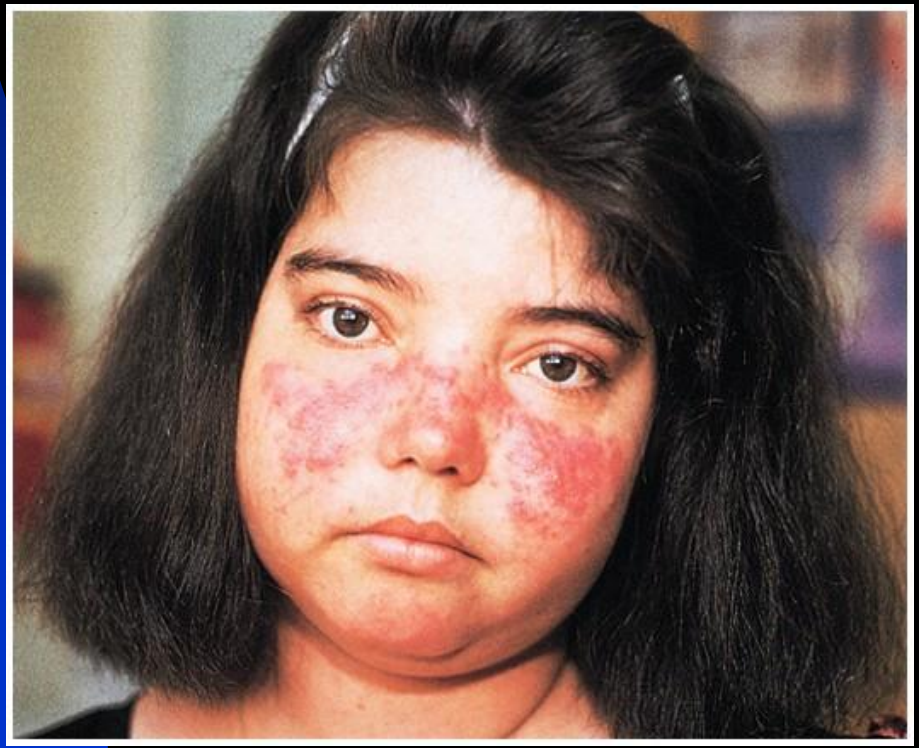
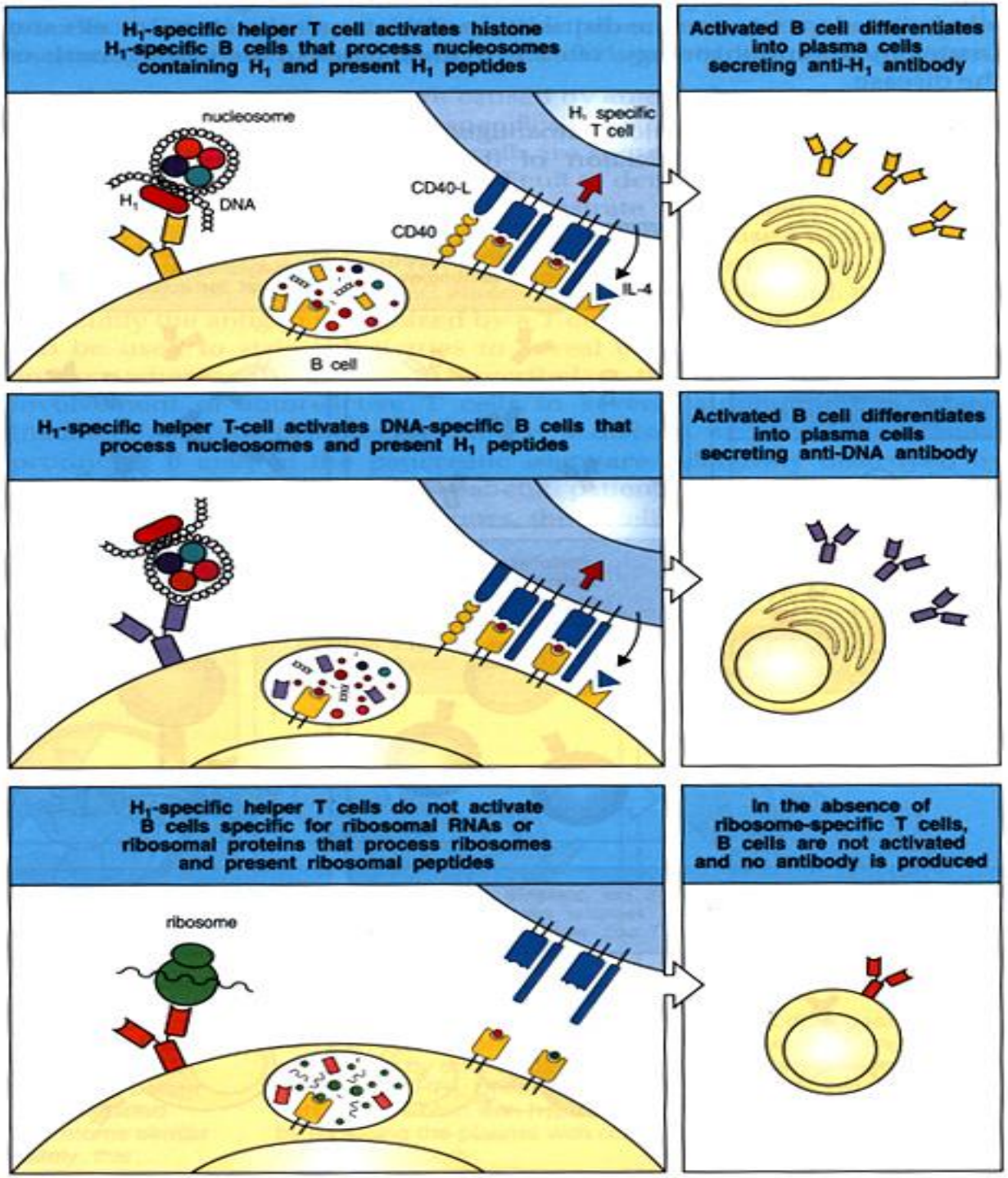


Figure 14-17 Immunobiology, 7ed. (© Garland Science 2008)

Systemic Lupus Erythematosus (SLE)

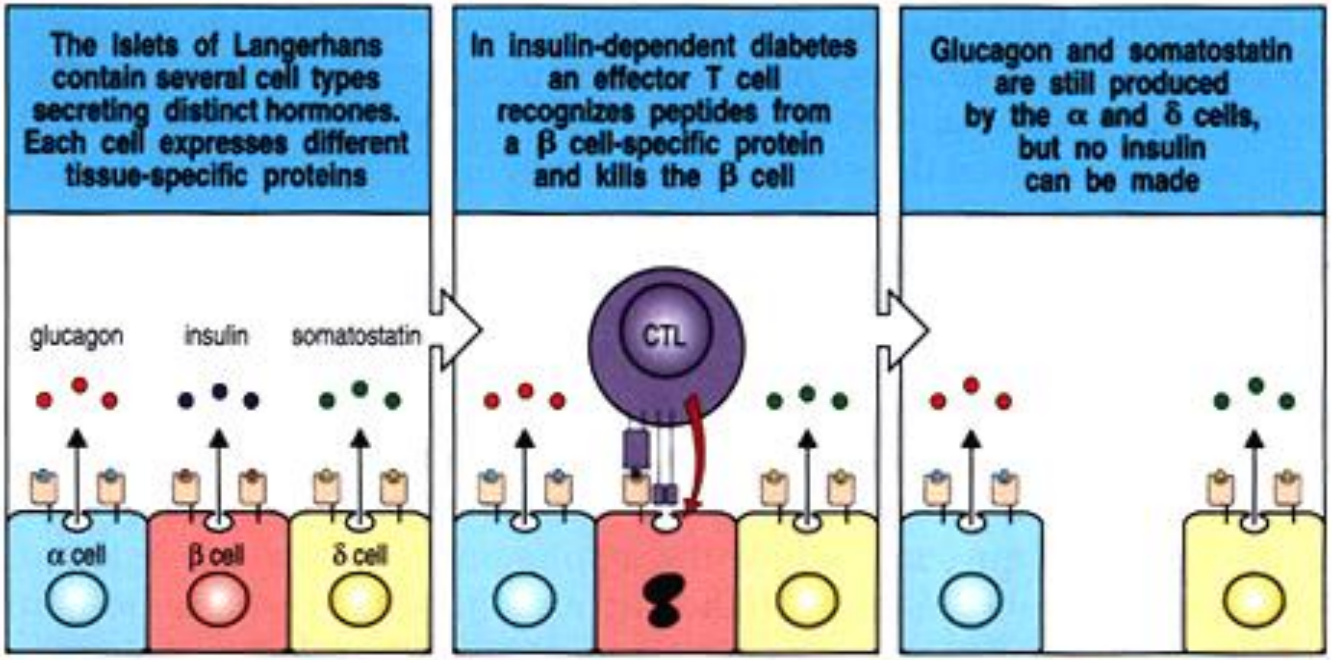
- **Multiple B cells with different specificities can receive help from a single autoreactive T cell when the B cells recognize constituents of large complexes.**

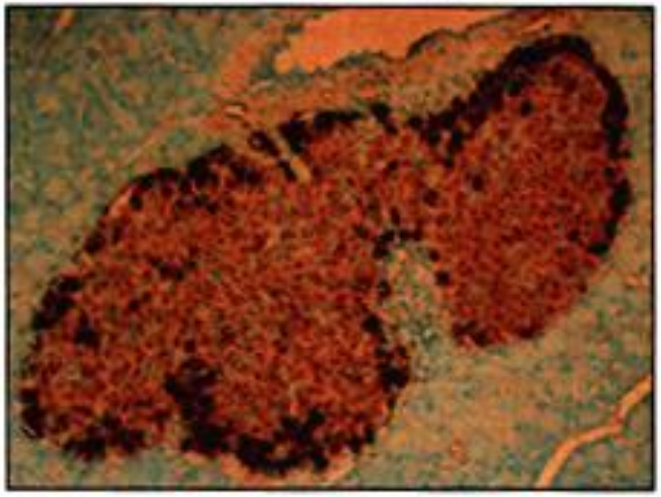


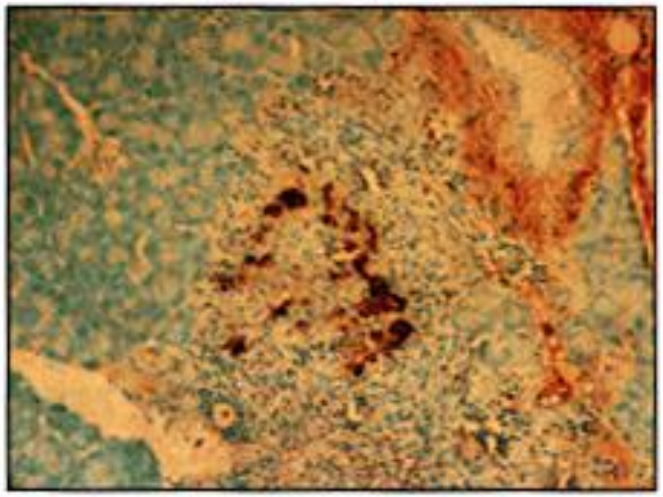

H1-specific helper T cell activates histone H1-specific B cells that process nucleosomes containing H1 and present H1 peptides
nucleosome
H1
DNA
H1 specific T cell
CD40-L
CD40
IL-4
B cell
Activated B cell differentiates into plasma cells secreting anti-H1 antibody
H1-specific helper T-cell activates DNA-specific B cells that process nucleosomes and present H1 peptides
Activated B cell differentiates into plasma cells secreting anti-DNA antibody
H1-specific helper T cells do not activate B cells specific for ribosomal RNAs or ribosomal proteins that process ribosomes and present ribosomal peptides
ribosome
In the absence of ribosome-specific T cells, B cells are not activated and no antibody is produced

Insulin Dependent Diabetes Mellitus

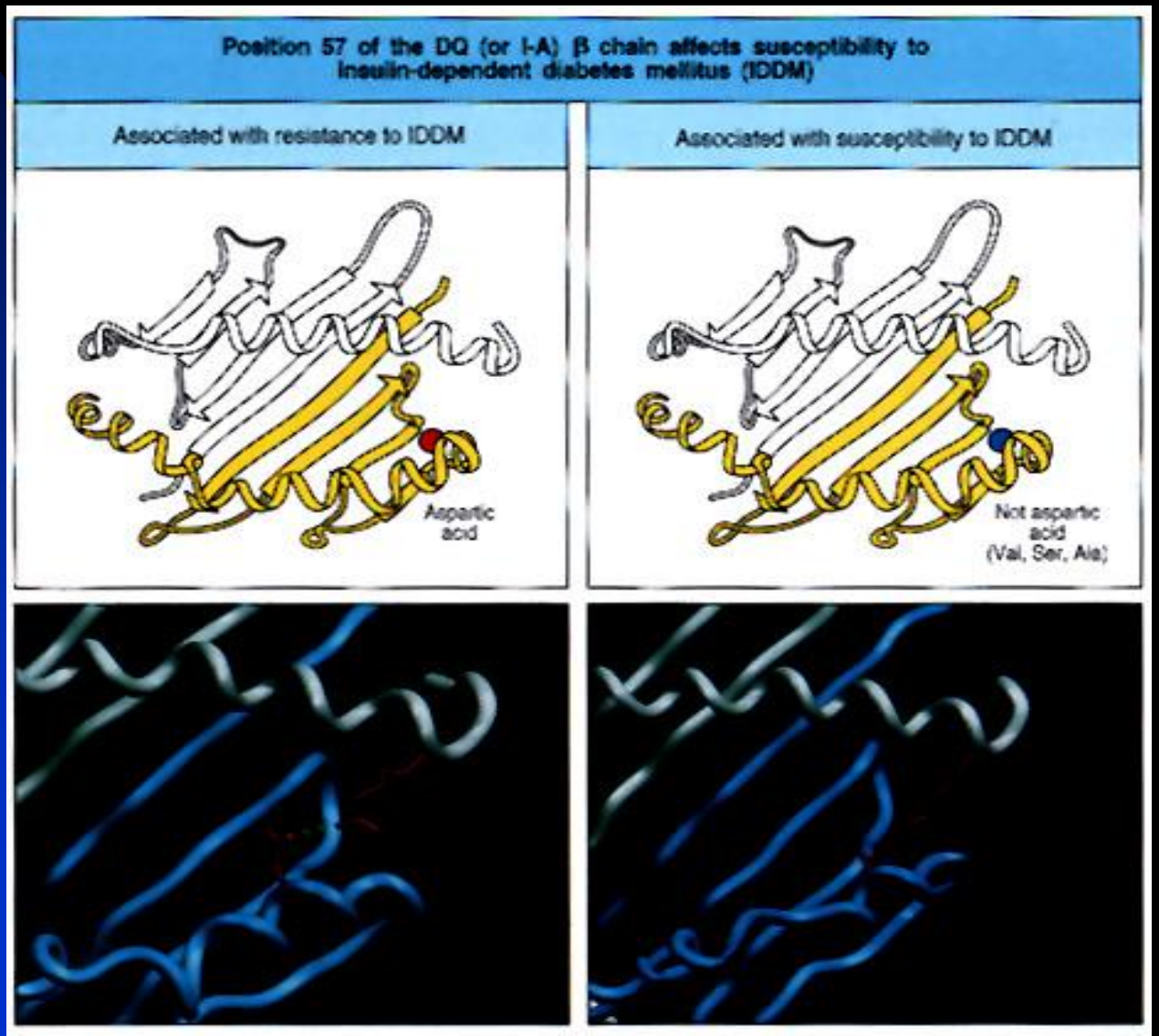
- T cell mediated destruction of cells in Islets of Langerhans in pancreas
- Staining for insulin and glucagon
- T cell infiltrates CD4 and CD8 cells involved antigens not known



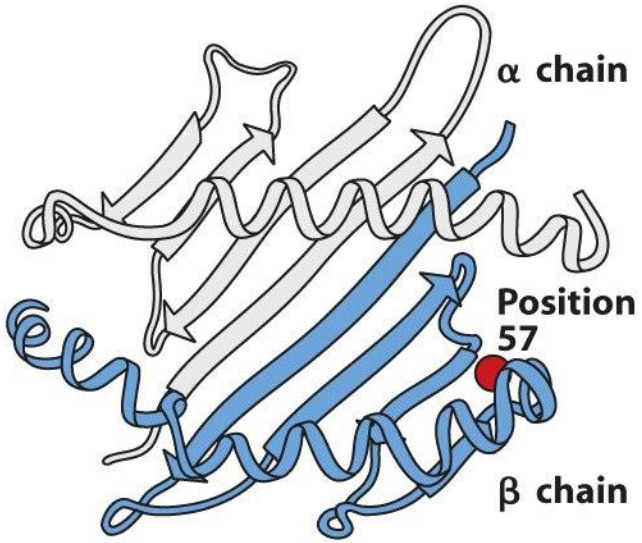




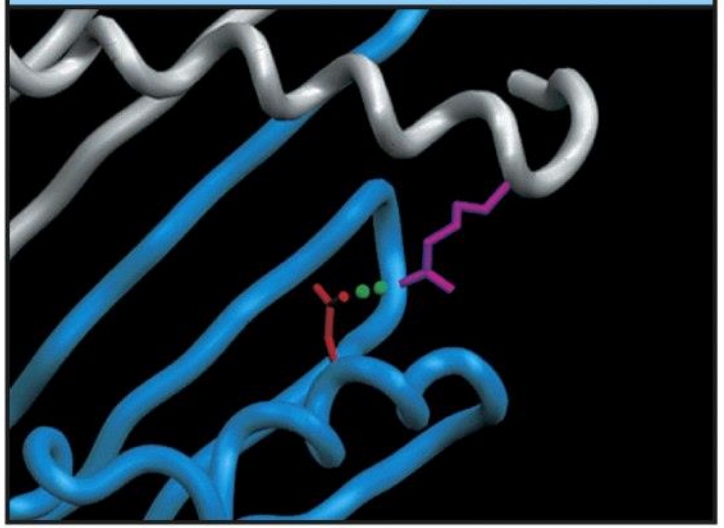
Susceptibility to IDDM is Associated with Single Amino Acid in HLA-DQ1



Position 57 of the DQβ chain affects susceptibility to type 1 diabetes mellitus



Associated with resistance to IDDM



Associated with susceptibility to IDDM

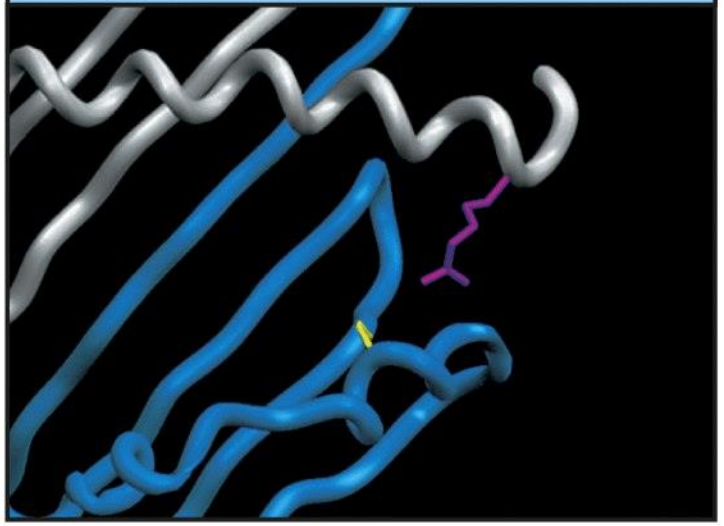
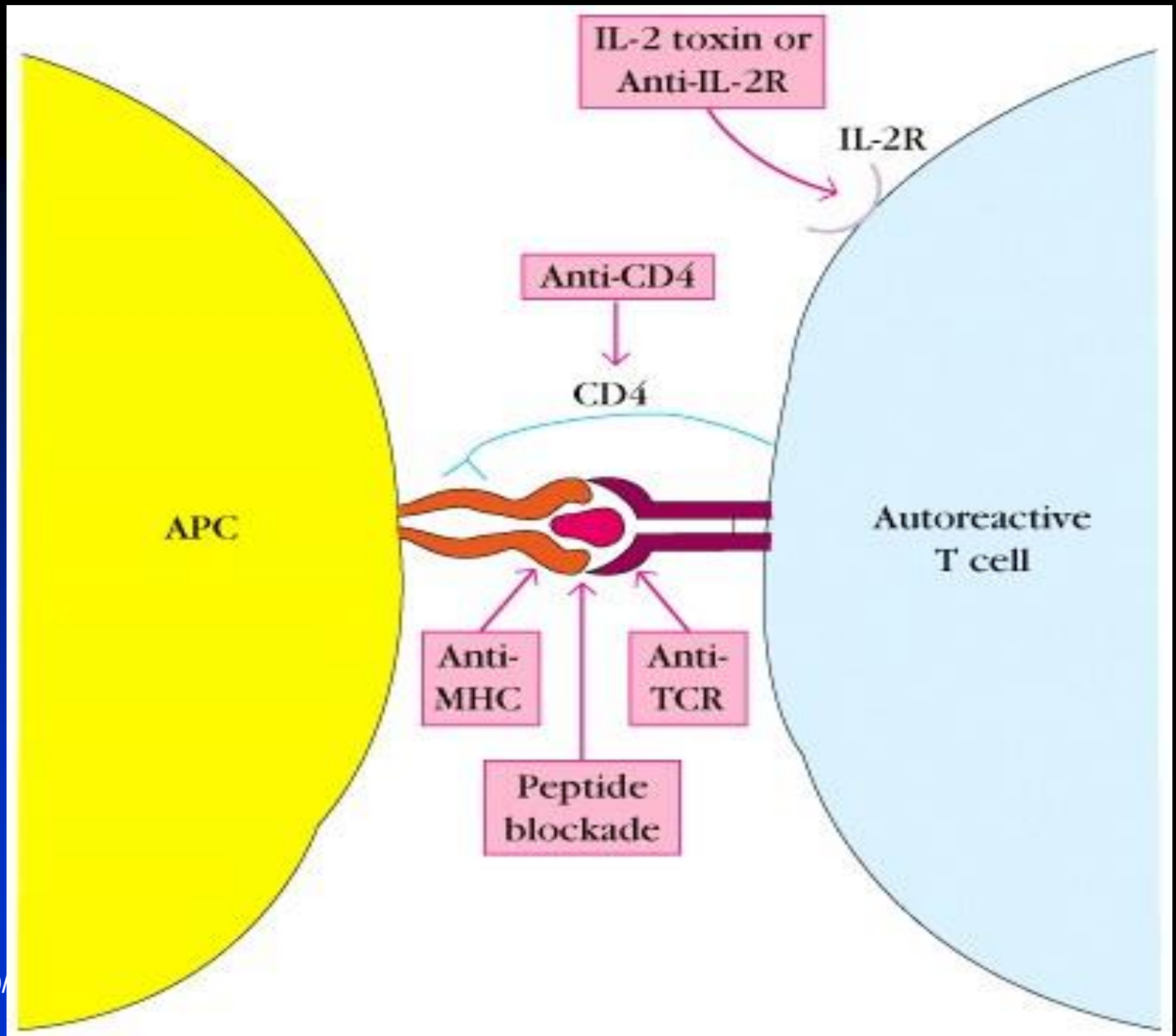


Figure 14-36 Immunobiology, 7ed. (© Garland Science 2008)

Treatment of Autoimmune Disease

- **Nonspecific suppression of Immune system**
  - Corticosteroids, etc.
  - cyclosporin etc.
  - Removal of thymus,
  - Plasma pheresis
- **Experimental approaches**
  - T cell vaccination
  - Peptide blockade of MHC
  - Monoclonal antibody treatment (e.g. anti-CD4, Anti-TCR)
  - Tolerance induction by oral tolerance
  - Cytokines e.g. IFN-beta for MS


IL-2 toxin or
Anti-IL-2R
IL-2R
Anti-CD4
CD4
APC
Autoreactive
T cell
Anti-
MHC
Anti-
TCR
Peptide
blockade

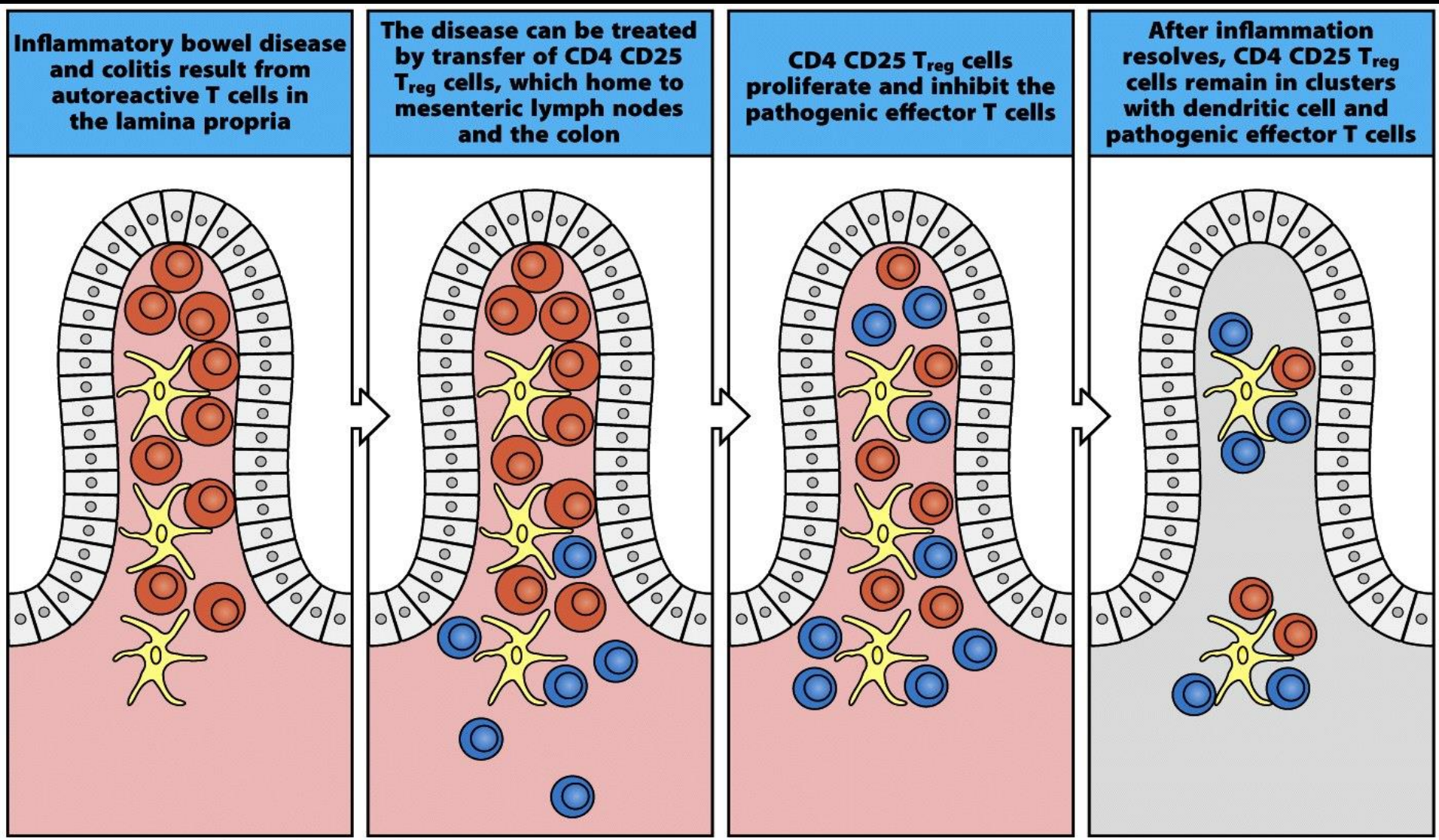


Figure 14-10 Immunobiology, 7ed. (© Garland Science 2008)

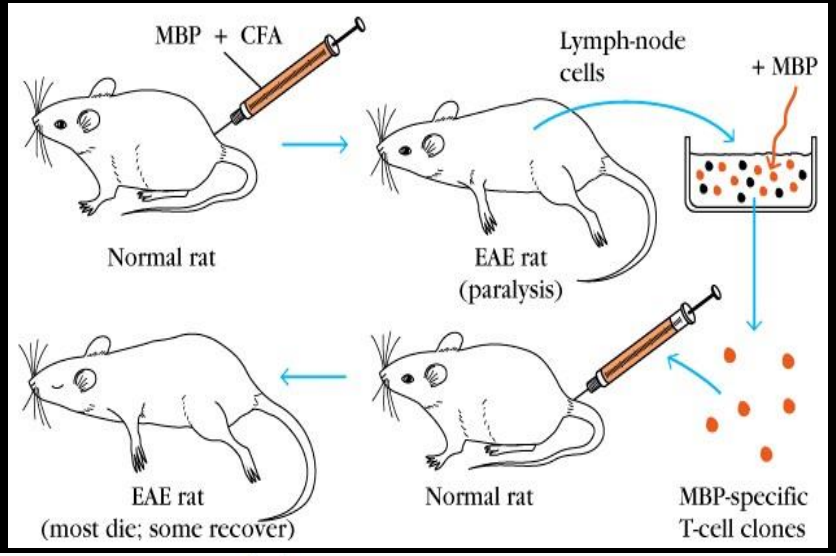
TABLE 20-2 EXPERIMENTAL ANIMAL MODELS OF AUTOIMMUNE DISEASES

Animal model	Possible human disease counterpart	Inducing antigen	Disease transferred by T cells
Spontaneous autoimmune disease			
Nonobese diabetic (NOD) mouse	Insulin-dependent diabetes mellitus (IDDM)	Unknown	Yes
(NZB × NZW) F_1 mouse	Systemic lupus erythematosus (SLE)	Unknown	Yes
Obese-strain chicken	Hashimoto's thyroiditis	Thyroglobulin	Yes
Experimentally induced autoimmune disease*			
Experimental autoimmune myasthenia gravis (EAMG)	Myasthenia gravis	Acetylcholine receptor	Yes
Experimental autoimmune encephalomyelitis (EAE)	Multiple sclerosis (MS)	Myelin basic protein (MBP); proteolipid protein (PLP)	Yes
Autoimmune arthritis (AA)	Rheumatoid arthritis	*M. tuberculosis* (proteoglycans)	Yes
Experimental autoimmune thyroiditis (EAT)	Hashimoto's thyroiditis	Thyroglobulin	Yes

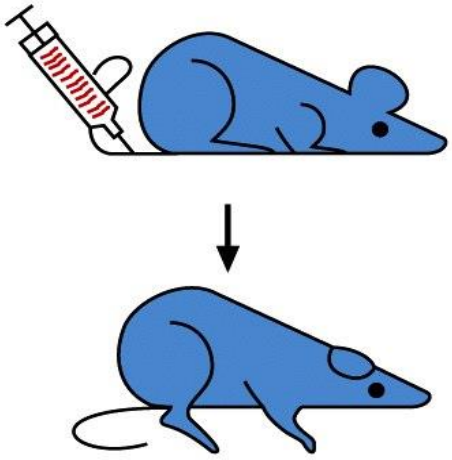
*These diseases can be induced by injecting appropriate animals with the indicated antigen in complete Freund's adjuvant. Except for autoimmune arthritis, the antigens used correspond to the self-antigens associated with the human-disease counterpart. Rheumatoid arthritis involves reaction to proteoglycans, which are self-antigens associated with connective tissue.

Mouse after induction of EAE (left), compared with normal healthy mouse

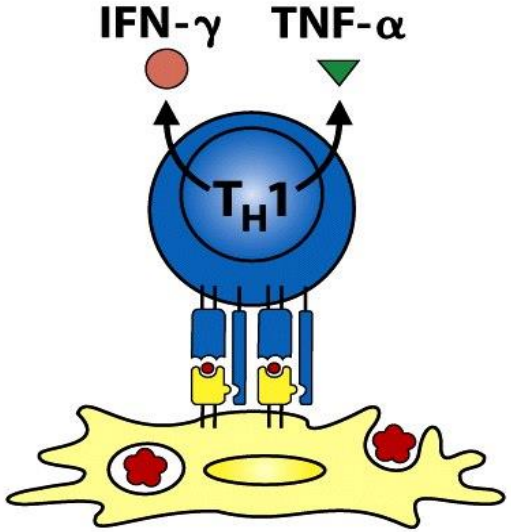
Figure 14-13 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)



Mice injected with myelin basic protein and complete Freund's adjuvant develop EAE and are paralyzed



The disease is mediated by T_H1 cells specific for myelin basic protein



Disease can be transmitted by transfer of T cells from affected animal

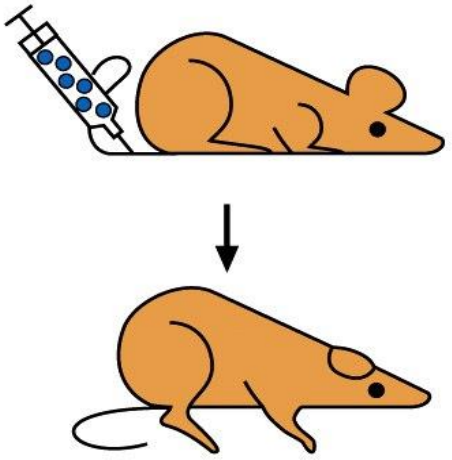


Figure 14-13 part 2 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Summary

1. Human autoimmune diseases can be divided into organ-specific and systemic diseases. The organ-specific diseases involve an autoimmune response directed primarily against a single organ or gland. In contrast, the systemic diseases are directed against a broad spectrum of tissues and have manifestations in a variety of organs.

2. There are both spontaneous and experimental animal models for autoimmune diseases. Spontaneous models include a disease in NZB and (NZB × NZW) F_1 mice that parallels systemic lupus erythematosus, a thyroiditis seen in Obese-strain chickens that parallels Hashimoto's thyroiditis, and a diabetes in NOD mice that resembles human insulin-dependent diabetes mellitus. Several experimental animal models have been developed by immunizing animals with self-antigens in the presence of adjuvant. In experimental autoimmune myasthenia gravis (EAMG), the antigen is the acetylcholine receptor; in experimental autoimmune encephalomyelitis (EAE), the antigen is myelin basic protein; in experimental autoimmune thyroiditis (EAT), the antigen is thyroglobulin.

3. The experimental autoimmune animal models have revealed a central role for the $CD4^+$ T_H cell in the development of autoimmunity. In each of the experimentally induced autoimmune diseases, autoimmune T-cell clones can be isolated that induce the autoimmune disease in normal animals. The MHC haplotype of the experimental animal determines the ability to present various autoantigens to T_H cells. In addition, some autoimmune animals utilize a restricted repertoire of TCR genes, which may predispose the animal toward T-cell activity in response to a given self-antigen.

4. A variety of mechanisms have been proposed for autoimmunity, including release of sequestered antigens, molecular mimicry, inappropriate class II MHC expression on cells, a cytokine imbalance, a dysfunction of the idiotype network, a dysfunction of T-cell–mediated suppression, and polyclonal activation of lymphocytes. Evidence exists for each of these mechanisms, reflecting the many different pathways leading to autoimmune reactions.

5. Current therapies for autoimmune diseases include treatment with immunosuppressive drugs, thymectomy, and plasmapheresis for diseases involving immune complexes. These therapies, which are relatively nonspecific, may have significant side effects. Several more specific approaches have shown some success in various animal models for autoimmune diseases. These include vaccination with T cells specific for a given autoantigen, administration of synthetic blocking peptides that compete with autoantigen for binding to MHC molecules, treatment with monoclonal antibodies that react with some component specifically involved in an autoimmune reaction, and induction of tolerance to autoantigens by administering them orally.

Concepts:

1. Graves disease and Myasthenia Gravis
2. Goodpasture's syndrome
3. System lupus erythematosus (SLE)
4. Rheumatoid arthritis (RA)
5. Multiple sclerosis (MS)
6. Insuline-dependent diabetes mellitus (IDDM)

Questions:

1. Define autoimmunity. Discuss the postulation that could explain autoimmune responses, please !
2. What is autoimmune disease? Discuss the orgain-specific autoimmune disease, please !

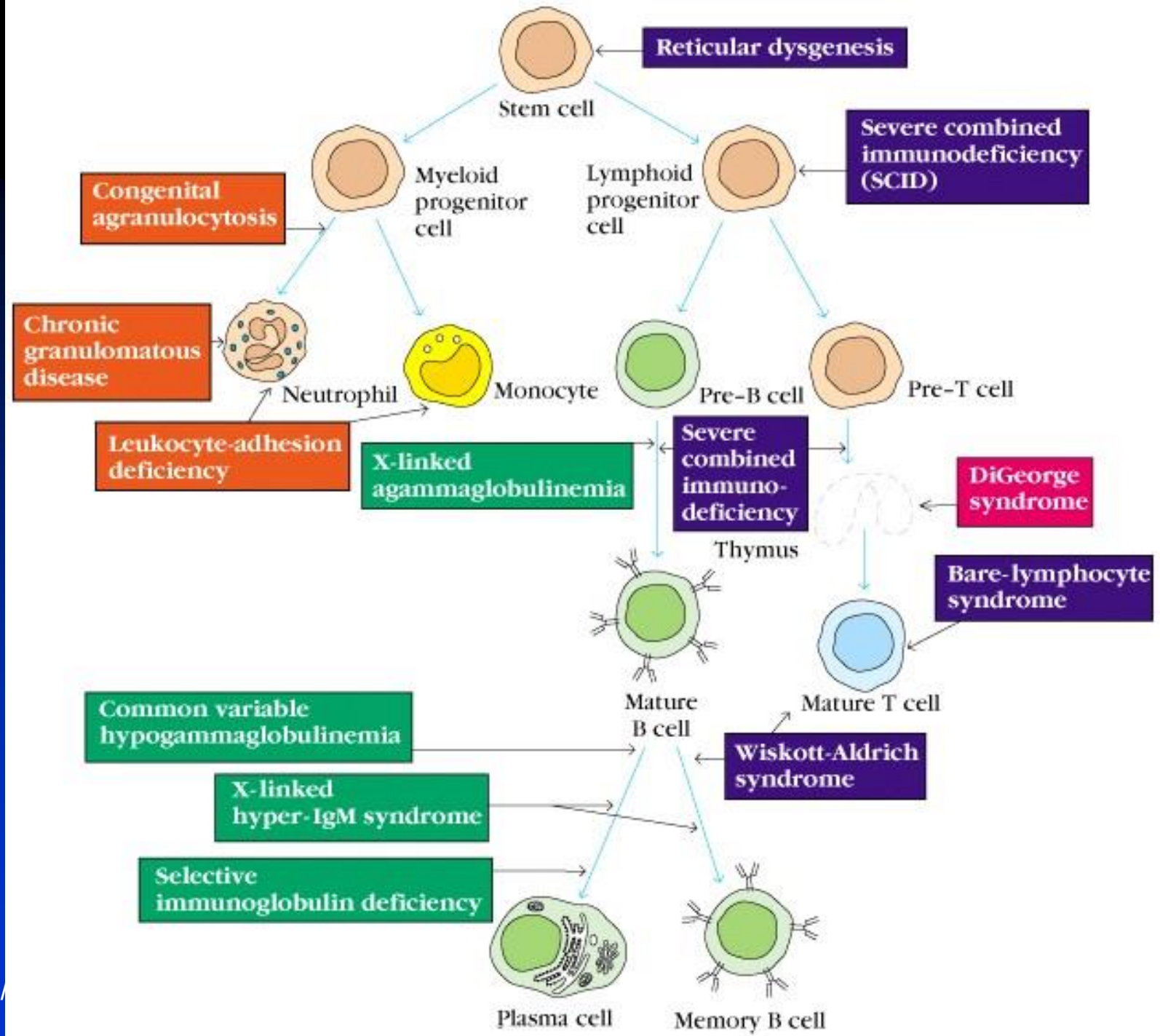

Reticular dysgenesis
Stem cell
Severe combined immunodeficiency (SCID)
Congenital agranulocytosis
Myeloid progenitor cell
Lymphoid progenitor cell
Chronic granulomatous disease
Neutrophil
Monocyte
Pre-B cell
Pre-T cell
Leukocyte-adhesion deficiency
X-linked agammaglobulinemia
Severe combined immuno-deficiency
DiGeorge syndrome
Thymus
Bare-lymphocyte syndrome
Mature B cell
Mature T cell
Common variable hypogammaglobulinemia
Wiskott-Aldrich syndrome
X-linked hyper-IgM syndrome
Selective immunoglobulin deficiency
Plasma cell
Memory B cell

TABLE 19-1 SOME PRIMARY HUMAN IMMUNODEFICIENCY DISEASES AND UNDERLYING GENETIC DEFECTS

Immunodeficiency disease	Specific defect	Impaired function	Inheritance mode*	Chromosomal defect
Severe combined immunodeficiency (SCID)	RAG-1/RAG-2 deficiency	No TCR or Ig gene rearrangement	AR	11p13
	ADA deficiency	Toxic metabolite in T and B cells	AR	20q13
	PNP deficiency		AR	14q13
	JAK-3 deficiency	Defective signals from IL-2, 4, 7, 9, 15	AR	19p13
	IL-2Rγ-deficiency		XL	Xq13
	ZAP-70 deficiency	Defective signal from TCR	AR	2q12
Bare lymphocyte syndrome	Defect in MHC class II gene promoter	No class II MHC molecules	AR	16p13
Wiskott-Aldrich syndrome (WAS)	Cytoskeletal protein (CD43)	Defective T cells and platelets	XL	Xp11
Interferon gamma receptor	IFN-γ–receptor defect	Impaired immunity to mycobacteria	AR	6q23
DiGeorge syndrome	Thymic aplasia	T- and B-cell development	AD	22q11
Ataxia telangiectasia	Defective cell-cycle kinase	Low IgA, IgE	AR	11q22
Gammaglobulinemias	X-linked agammaglobulinemia	Bruton's tyrosine kinase (Btk); no mature B cells	XL	Xq21
	X-linked hyper-IgM syndrome	Defective CD40 ligand	XL	Xq26
	Common variable immunodeficiency	Low IgG, IgA; variable IgM	Complex	
	Selective IgA deficiency	Low or no IgA	Complex	
Chronic granulomatous disease	Cyt $p91^{phox}$	No oxidative burst for bacterial killing	XL	Xp21
	Cyt $p67^{phox}$		AR	1q25
	Cyt $p22^{phox}$		AR	16q24
Chediak-Higashi syndrome	Defective intracellular transport protein (LYST)	Inability to lyse bacteria	AR	1q42
Leukocyte-adhesion defect	Defective integrin β2 (CD18)	Leukocyte extravasation	AR	21q22

TABLE 19-2 PROPERTIES OF INTEGRIN MOLECULES THAT ARE ABSENT IN LEUKOCYTE-ADHESION DEFICIENCY

	Integrin molecules*		
Property	LFA-1	CR3	CR4
CD designation	CD11a/CD18	CD11b/CD18	CD11c/CD18
Subunit composition	αLβ2	αMβ2	αXβ2
Subunit molecular mass (kDa)			
α chain	175,000	165,000	150,000
β chain	95,000	95,000	95,000
Cellular expression	Lymphocytes Monocytes Macrophages Granulocytes Natural killer cells	Monocytes Macrophages Granulocytes Natural killer cells	Monocytes Macrophages Granulocytes
Ligand	ICAM-1 ICAM-2	C3bi	C3bi
Functions inhibited with monoclonal antibody	Extravasation CTL killing T-B conjugate formation ADCC	Opsonization Granulocyte adherence, aggregation, and chemotaxis ADCC	Granulocyte adherence and aggregation

*CR3 = type 3 complement receptor, also known as Mac-1; CR4 = type 4 complement receptor, also known as gp150/90. LFA-1, CR3, and CR4 are heterodimers containing a common β chain but different α chains designated L, M, and X, respectively.

	Evaluation of the cellular components of the human immune system		
	B cells	**T cells**	**Phagocytes**
Normal numbers ($\times 10^9$ per liter of blood)	Approximately 0.3	Total 1.0–2.5 CD4 0.5–1.6 CD8 0.3–0.9	Monocytes 0.15–0.6 Polymorphonuclear leukocytes Neutrophils 3.00–5.5 Eosinophils 0.05–0.25 Basophils 0.02
Measurement of function *in vivo*	Serum Ig levels Specific antibody levels	Skin test	—
Measurement of function *in vitro*	Induced antibody production in response to pokeweed mitogen	T-cell proliferation in response to phytohemagglutinin or to tetanus toxoid	Phagocytosis Nitro blue tetrazolium uptake Intracellular killing of bacteria
Specific defects	See Fig. 11.8	See Fig. 11.8	See Fig. 11.8

	Evaluation of the humoral components of the human immune system				
	Immunoglobulins				**Complement**
Component	IgG	IgM	IgA	IgE	
Normal levels	600–1400 $mg\,dl^{-1}$	40–345 $mg\,dl^{-1}$	60–380 $mg\,dl^{-1}$	0–200 $IU\,ml^{-1}$	CH_{50} of 125–300 $IU\,ml^{-1}$

Immunoglobulin Deficiencies: B cell defects

- X-linked agammaglobulinemia (XLA)
  Mutation in btk; progression through pre-B development (Bruton's Agammaglobulinemia)

- IgA deficiency
  - Frequency 1:800
  - Increase frequency in patients with chronic lung disease;

- Consistent with role of IgA at surfaces
- No know specific susceptibilities

- **Common variable immunodeficiency**
  - Deficiency in IgA, IgG
  - Susceptible to extracellular bacterial infections
    - Treatment with antibiotics, passive Ig transfer

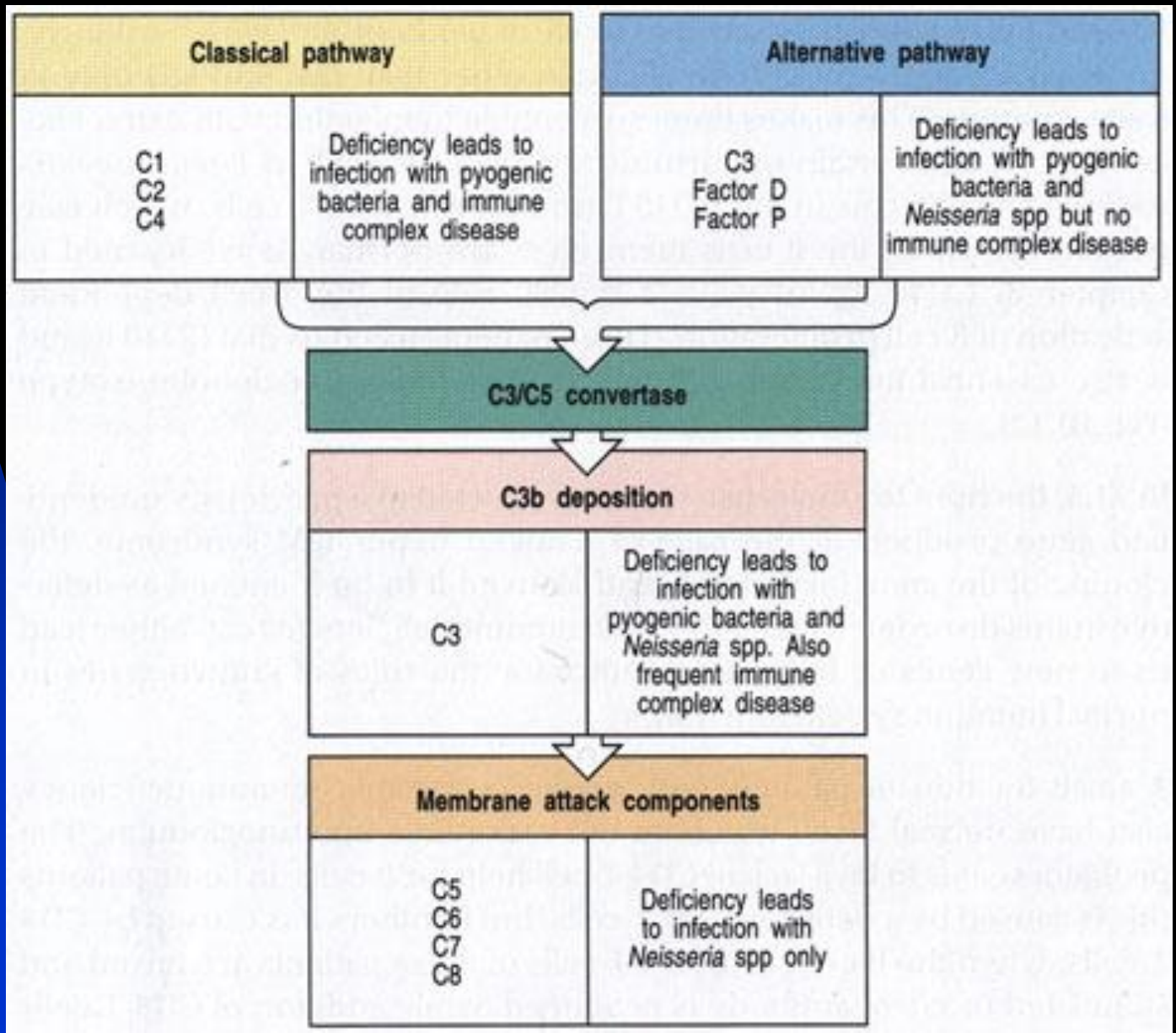
Immunoglobulin Deficiencies: T cell defects

- X-linked hyper IgM syndrome
  - Normal B cell development
  - High serum levels of IgM
  - Limited IgM responses against T-dependent antigens
- Extremely limited production of classes other
- than IgM, IgD; susceptible to extracellular bacteria such as *Pneumocystis carinii.*
- Defect in CD40L on activated T cells
  - CD40L essential for class switch

- **Phagocytic cell defects**
- **Adhesion molecule defects**
  - **Integrins common 2 subunit (CD18)**
    - **CD11a/CD18 (LFA-1)**
    - **CD11b/CD18 (Mac-1/CR3)**
    - **CD11c/CD18 (CR4)**
  - **Impaired migraiton across blood vessel walls**
    - **Cannot get to sites of infection**
- **Effector mechanism defects**
  - **CGD. chronic granulomatours disease**
  - **Defective superoxide production**
  - **Other enzyme deficiencies**
- **Susceptibility to intra-and extracellular bacterial infections**

Complement Deficiencies

- Defects in several components of complement pathway lead to susceptibility to bacterial infections, especially *Neisseria*, the cause of meningitis and gonorrhea.



SCID: Severe Combined Immunodeficiencies

- **Generally T cell defects**
  - Highlights role of T cells in regulating/coordinating immune responses
- **X-linked**
  - Mutation in IL2R chain
- Nucleotide degradation
  - ADA - adenosine deaminase
  - PNP - purine nucleotide phosphorylase
  - Both give rise to accumulation of nucleotide metabolites that are particularly toxic to T cells

- **Bare lymphocyte syndrome**
  - Defect in class II expression
    - Mutations in one of at least 4 genes regulating class II expression
    - Impaired CD4+ T cell development
    - Normal CD8+ T cell development
  - Illustrates central role of CD4+ T cells
- *Defects of thymic epithelium*
  - DiGeorge syndrome
  - Nude mice

Clinical focus: Primary T-cell Deficiency

DiGeorge syndrome (Angelo DiGeorge, 1965)

* arises from a defect in thymus embryogenesis
* affecting 1-5 per 100, 000 of the population

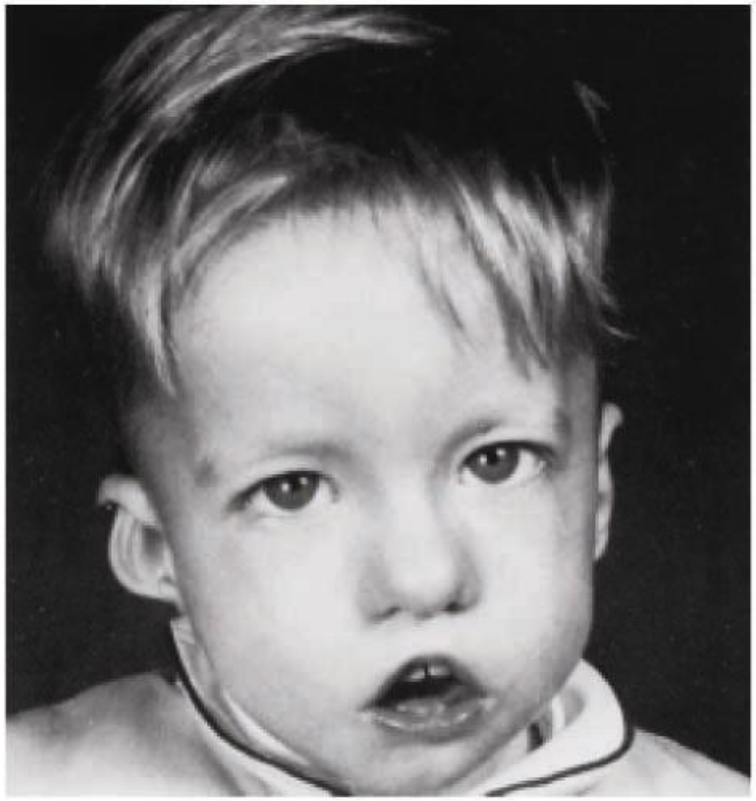


FIGURE 19-4 A child with DiGeorge syndrome showing characteristic dysplasia of ears and mouth and abnormally long distance between the eyes. *[R. Kretschmer et al., 1968,* New Engl. J. Med. ***279:****1295; photograph courtesy of F. S. Rosen.]*

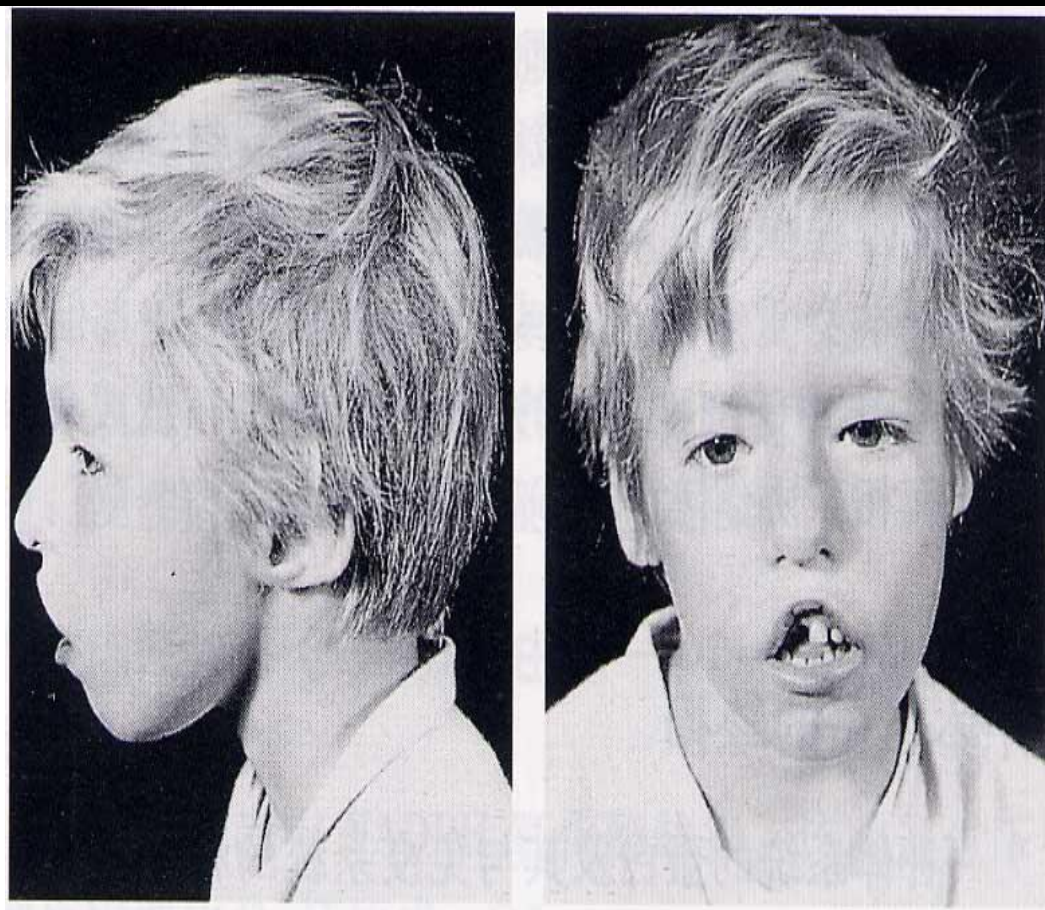


图 19.10 DiGeorge 畸形 注意眼距增宽，双耳下移，鼻唇沟缩短。还可能有先天性心血管系统畸形。

FIGURE 22-3 Chronic cutaneous candidiasis in a boy with defective cell-mediated immunity. [From R. J. Schlegel et al., 1970, *Pediatrics* **45**:926.]

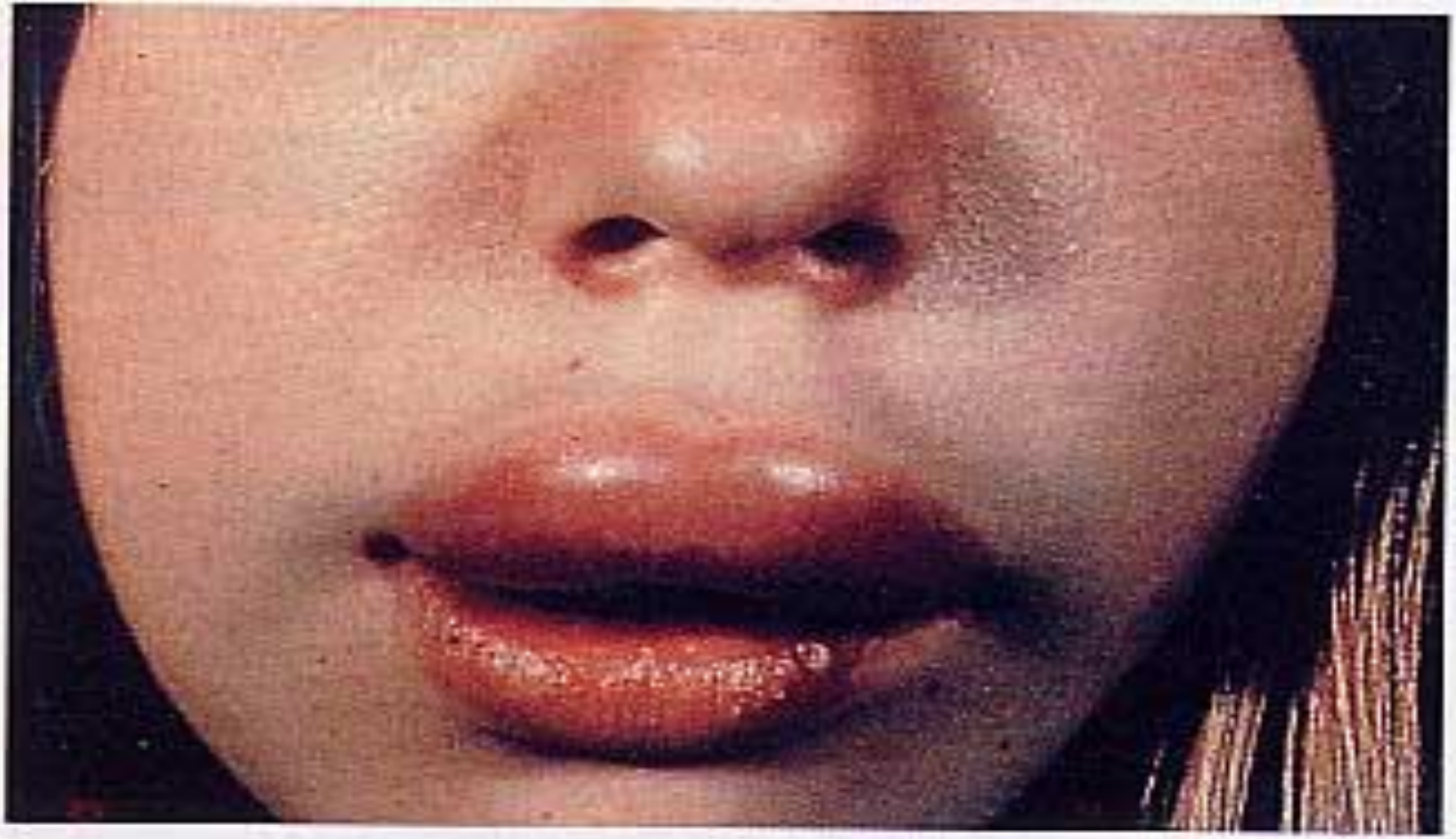


Fig. 19.12 Hereditary angioneurotic oedema. This clinical photograph shows the transient localized swelling which occurs in this condition.

Acquired Immunodeficiency

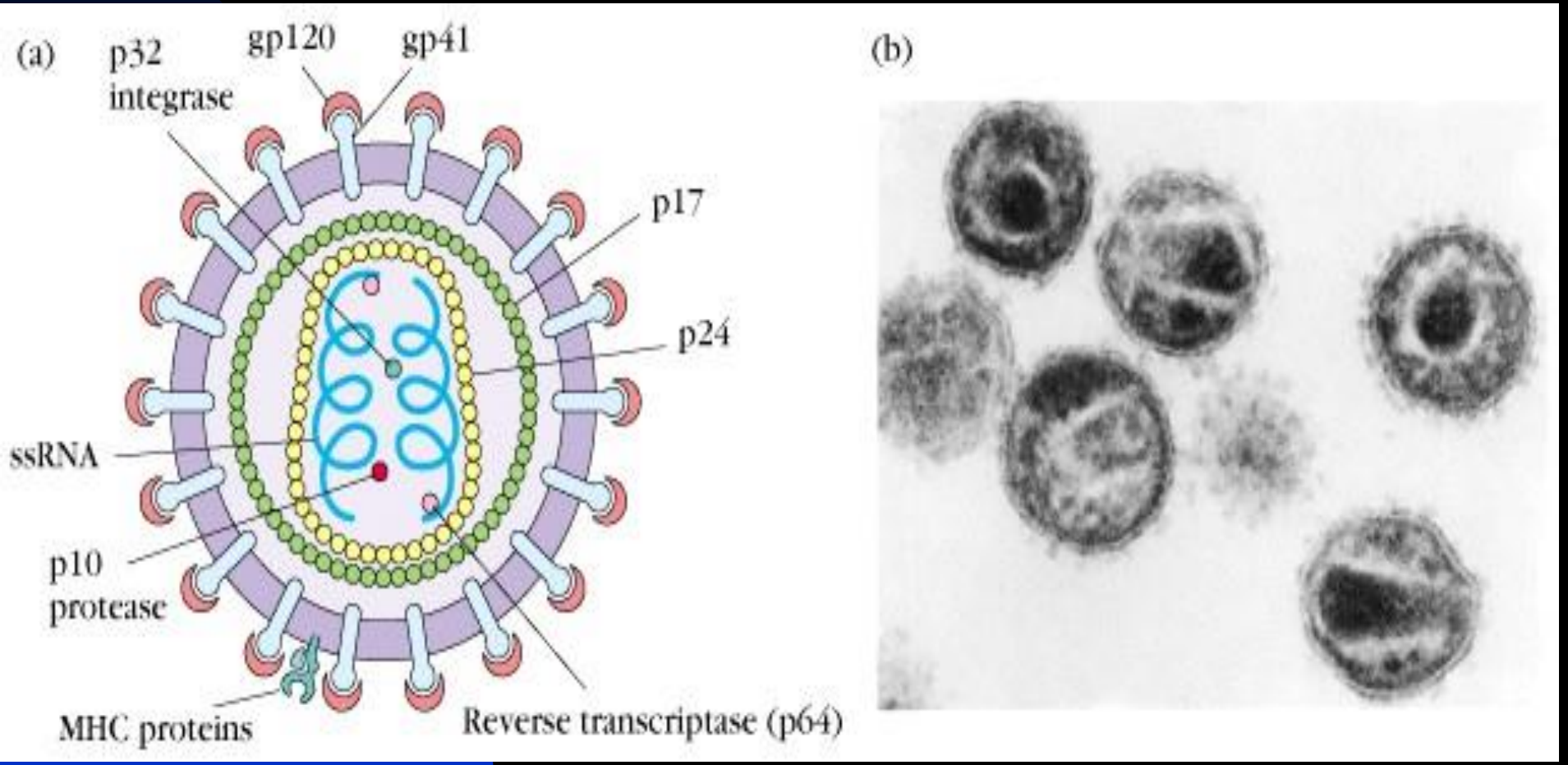
- Nutrition
- Behavior
- Toxins
- Drugs
- Medical practice
- Cancer
- Infectious disease
- Other

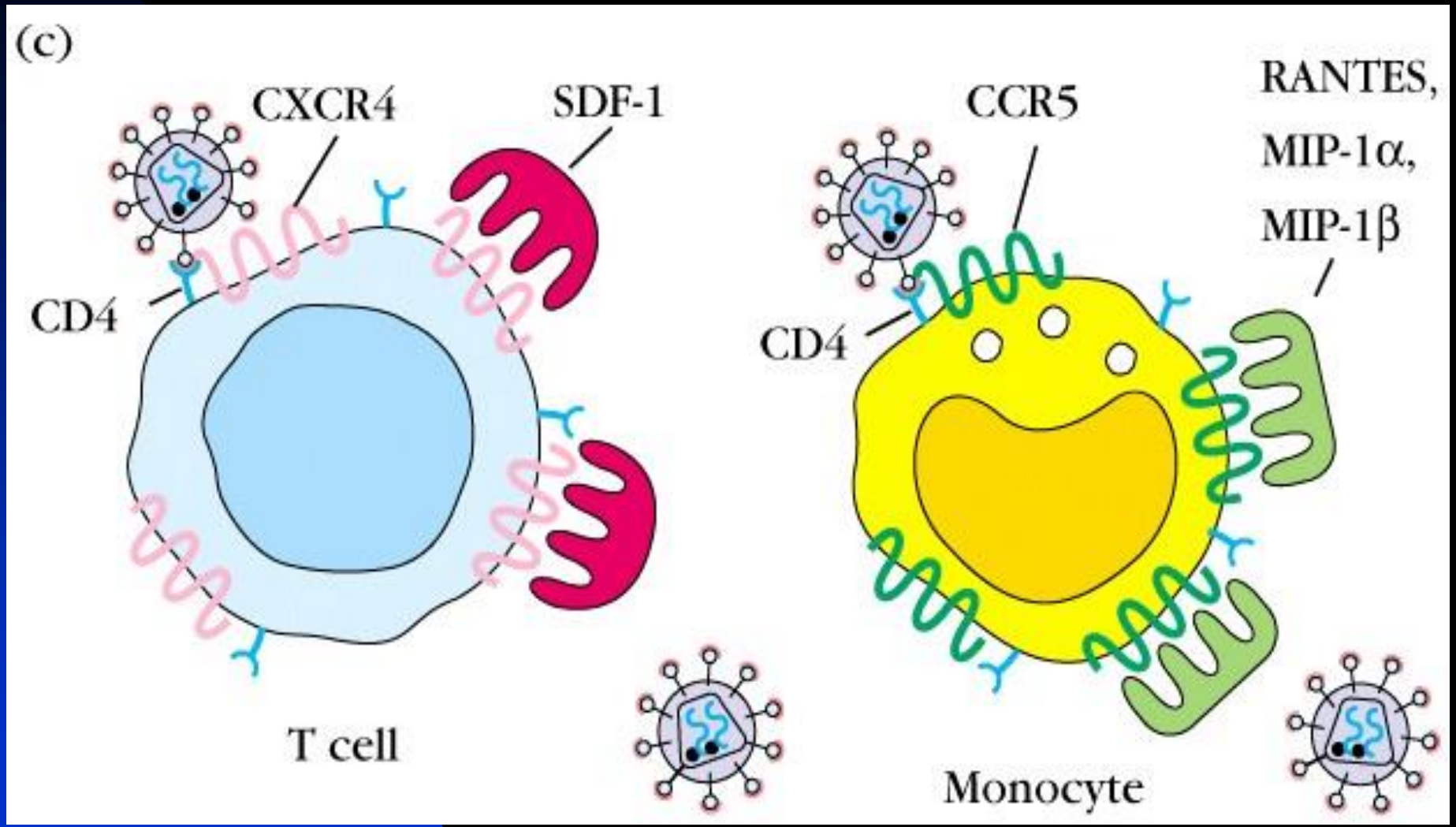
Immunodeficiency and Infectious Disease

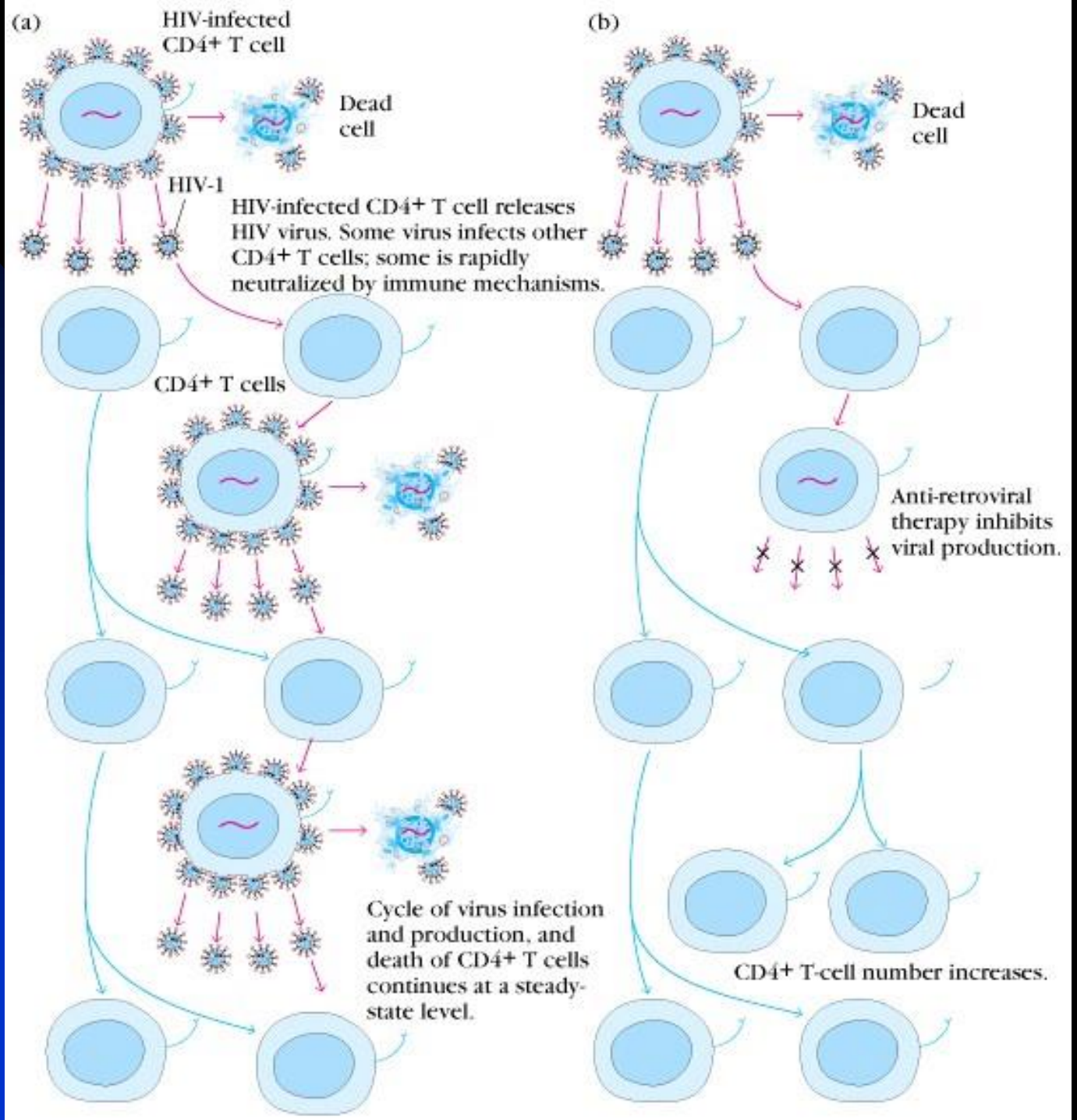
- Infectious disease is (by definition) suppression or subversion of immune response.
- Many pathogens have ways to down regulate immune defense reactions.
- Virulence factors expressed by microbes can suppress immune responses.

- **Just a few Examples:**
  - **HIV kills $CD4^+$ cells that participate in immune response.**
  - **EBV expresses a cytokine-like molecule that disregulates.**
  - **Measle virus depresses IL-12 production.**
  - **Adenovirus and others inhibit MHC expression.**
  - **Toxins produced by bacteria such as Listeria inhibit antigen processing.**
  - **Herpes virus hides in DNA.**
  - **Streptococcus inhibits phagocytosis.**

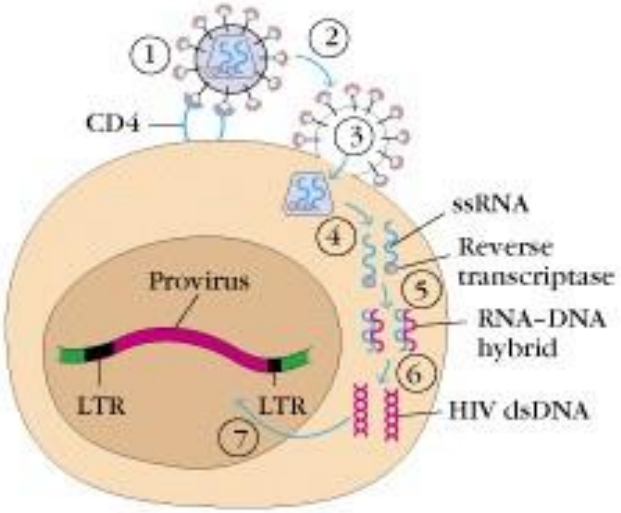
Human immunodeficiency virus (HIV)



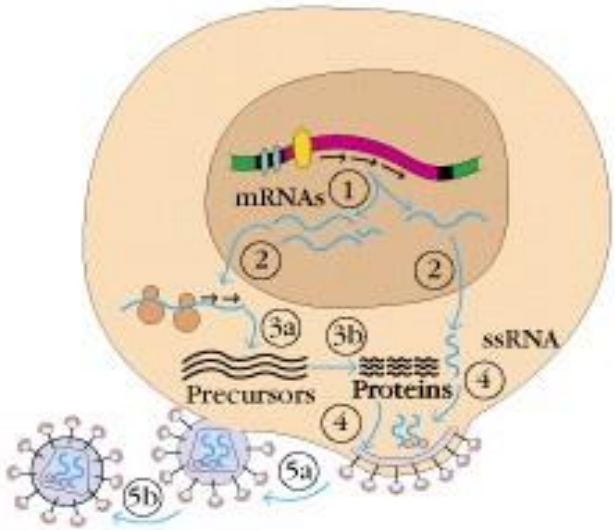

(c)
CXCR4
SDF-1
CD4
T cell
CCR5
RANTES,
MIP-1α,
MIP-1β
CD4
Monocyte


(a)
HIV-infected CD4+ T cell
Dead cell
HIV-1
HIV-infected CD4+ T cell releases HIV virus. Some virus infects other CD4+ T cells; some is rapidly neutralized by immune mechanisms.
CD4+ T cells
Cycle of virus infection and production, and death of CD4+ T cells continues at a steady-state level.
(b)
Dead cell
Anti-retroviral therapy inhibits viral production.
CD4+ T-cell number increases.

(a) Infection of target cell



(b) Activation of provirus



1. HIV gp120 binds to CD4 on target cell.
2. Fusogenic domain in gp41 and CXCR4, a G-protein–linked receptor in the target-cell membrane, mediate fusion.
3. Nucleocapsid containing viral genome and enzymes enters cells.
4. Viral genome and enzymes are released following removal of core proteins.
5. Viral reverse transcriptase catalyzes reverse transcription of ssRNA, forming RNA–DNA hybrids.
6. Original RNA template is partially degraded by ribonuclease H, followed by synthesis of second DNA strand to yield HIV dsDNA.
7. The viral dsDNA is then translocated to the nucleus and integrated into the host chromosomal DNA by the viral integrase enzyme.

1. Transcription factors stimulate transcription of proviral DNA into genomic ssRNA and, after processing, several mRNAs.
2. Viral RNA is exported to cytoplasm.

3a. Host-cell ribosomes catalyze synthesis of viral precursor proteins.

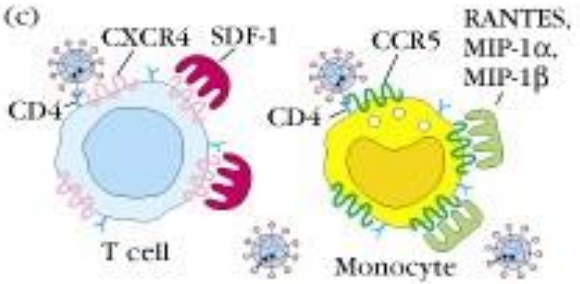
3b. Viral protease cleaves precursors into viral proteins.

4. HIV ssRNA and proteins assemble beneath the host-cell membrane, into which gp41 and gp120 are inserted.

5a. The membrane buds out, forming the viral envelope.

5b. Released viral particles complete maturation; incorporated precursor proteins are cleaved by viral protease present in viral particles.

(c)



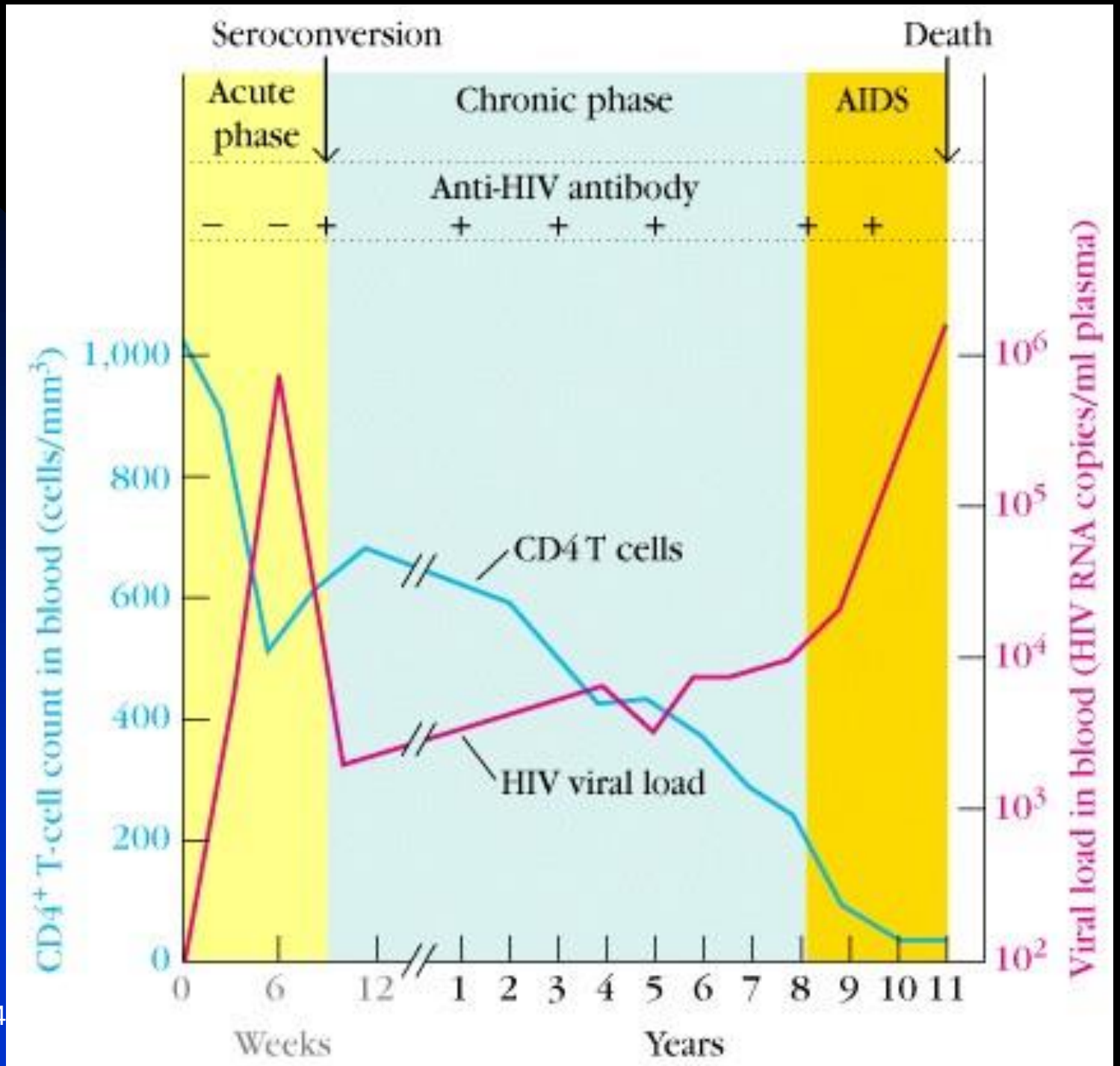

Seroconversion
Death
Acute phase
Chronic phase
AIDS
Anti-HIV antibody
− − + + + + + +
CD4 T cells
HIV viral load
CD4+ T-cell count in blood (cells/mm3)
1,000
800
600
400
200
0
Viral load in blood (HIV RNA copies/ml plasma)
10^6
10^5
10^4
10^3
10^2
0 6 12 1 2 3 4 5 6 7 8 9 10 11
Weeks
Years

TABLE 19-3 CLINICAL DIAGNOSIS OF HIV-INFECTED INDIVIDUALS

CD4⁺ T-cell count	Clinical categories* A	B	C
≥500/μl	A1	B1	**C1**
200–499/μl	A2	B2	**C2**
<200μl	**A3**	**B3**	**C3**

Classification of AIDS indicator disease

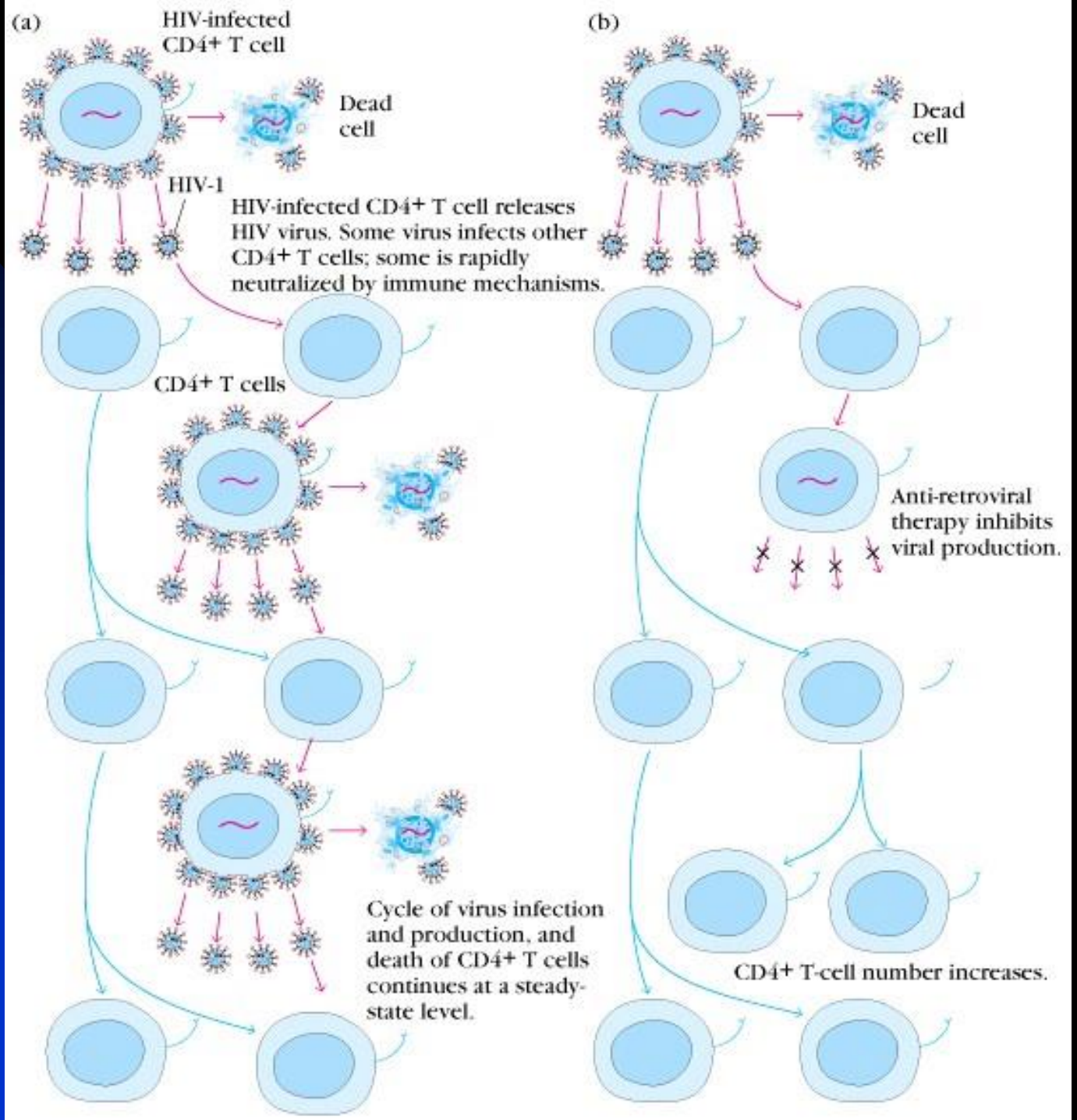
Category A
- Asymptomatic: no symptoms at the time of HIV infection
- Acute primary infection: glandular fever-like illness lasting a few weeks at the time of infection
- Persistent generalized lymphadenopathy (PGL): lymph-node enlargement persisting for 3 or more months with no evidence of infection

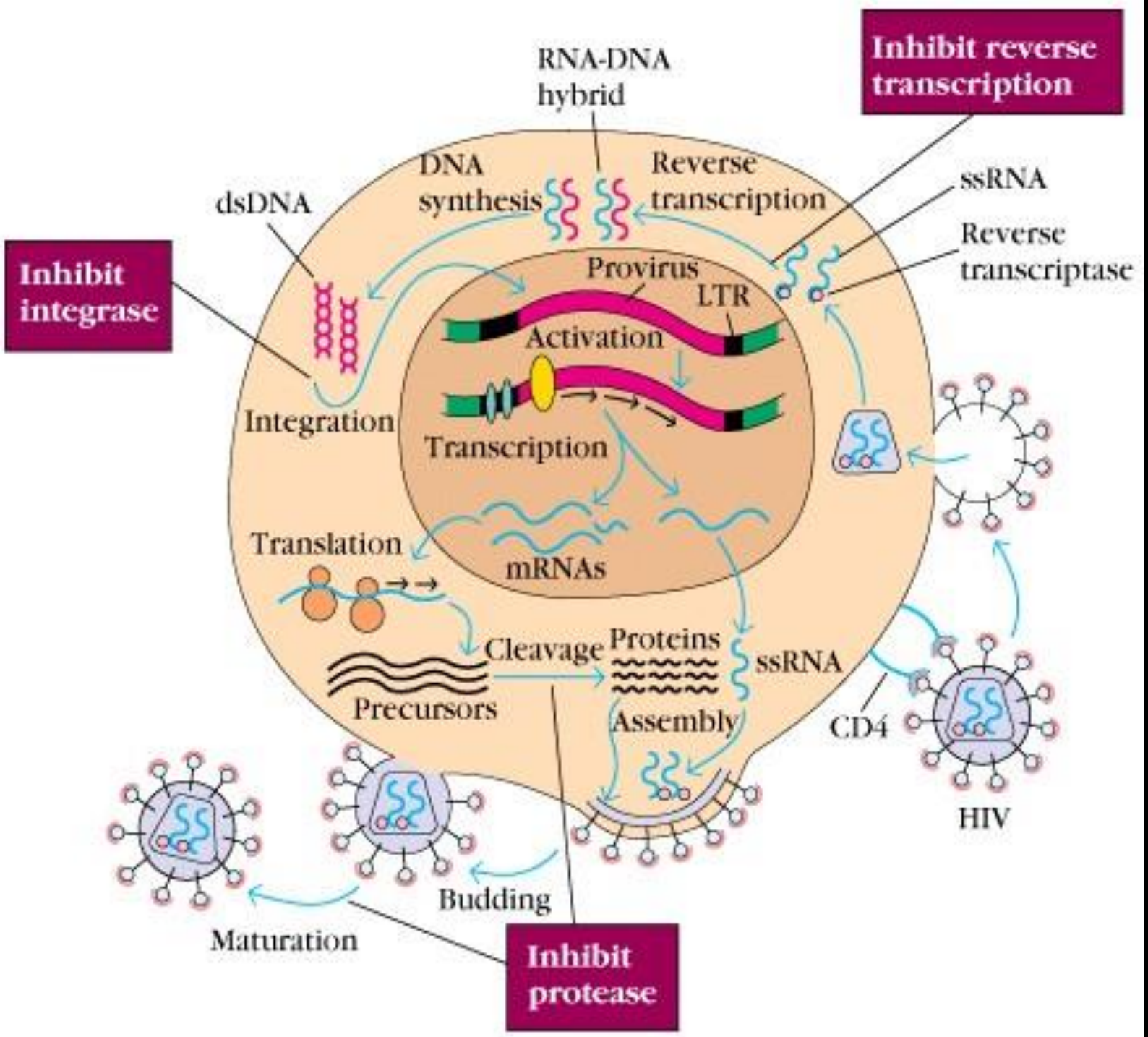
Category B
- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal: persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms such as fever (>38.5°C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly by tubo-ovarian abscess
- Peripheral neuropathy

Category C
- Candidiasis of bronchi, tracheae, or lungs
- Candidiasis, esophageal
- Cervical cancer (invasive)
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month duration), bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's
- Lymphoma, immunoblastic
- Lymphoma, primary of brain
- *Mycobacterium avium* complex or *M. Kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site
- *Mycobacterium*, other or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia (recurrent)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

TABLE 19-4 IMMUNOLOGIC ABNORMALITIES ASSOCIATED WITH HIV INFECTION

Stage of infection	Typical abnormalities observed
	Lymph node structure
Early	Infection and destruction of dendritic cells; some structural disruption
Late	Extensive damage and tissue necrosis; loss of folicular dendritic cells and germinal centers; inability to trap antigens or support activation of T and B cells
	T helper (T_H) cells
Early	No in vitro proliferative response to specific antigen
Late	Decrease in T_H-cell numbers and corresponding helper activities; no response to T-cell mitogens or alloantigens
	Antibody production
Early	Enhanced nonspecific IgG and IgA production but reduced IgM synthesis
Late	No proliferation of B cells specific for HIV-1: no detectable anti-HIV antibodies in some patients
	Cytokine production
Early	Increased levels of some cytokines
Late	Shift in cytokine production from T_H1 subset to T_H2 subset
	Delayed-type hypersensitivity
Early	Highly significant reduction in proliferative capacity of T_{DTH} cells and reduction in skin-test reactivity
Late	Elimination of DTH response; complete absence of skin-test reactivity
	T cytotoxic (T_C) cells
Early	Normal reactivity
Late	Reduction but not elimination of CTL activity due to impaired ability to generate CTLs from T_C cells


(a)
HIV-infected CD4+ T cell
Dead cell
HIV-1
HIV-infected CD4+ T cell releases HIV virus. Some virus infects other CD4+ T cells; some is rapidly neutralized by immune mechanisms.
CD4+ T cells
Cycle of virus infection and production, and death of CD4+ T cells continues at a steady-state level.
(b)
Dead cell
Anti-retroviral therapy inhibits viral production.
CD4+ T-cell number increases.


RNA-DNA hybrid
Inhibit reverse transcription
DNA synthesis
Reverse transcription
dsDNA
ssRNA
Reverse transcriptase
Inhibit integrase
Provirus
LTR
Activation
Integration
Transcription
Translation
mRNAs
Cleavage
Proteins
ssRNA
Precursors
Assembly
CD4
HIV
Budding
Maturation
Inhibit protease

HAART: highly active anti-retroviral therapy.
Two nucleoside analogs and one protease inhibitor.

2020/5/14

TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE

Generic name (other names)	Typical dosage	Some potential side effects
Reverse transcriptase inhibitors: Nucleoside analog		
Didanosine (Videx, ddI)	2 pills, 2 times a day on empty stomach	Nausea, diarrhea, pancreatic inflammation, peripheral neuropathy
Lamivudine (Epivir, 3TC)	1 pill, 2 times a day	Usually none
Stavudine (Zerit, d4T)	1 pill, 2 times a day	Peripheral neuropathy
Zalcitabine (HIVID, ddC)	1 pill, 3 times a day	Peripheral neuropathy, mouth inflammation, pancreatic inflammation
Zidovudine (Retrovir, AZT)	1 pill, 2 times a day	Nausea, headache, anemia, neutropenia (reduced levels of neutrophil white blood cells), weakness, insomnia
Pill containing lamivudine and zidovudine (Combivir)	1 pill, 2 times a day	Same as for zidovudine
Reverse transcriptase inhibitors: Nonnucleoside analogues		
Delavirdine (Rescriptor)	4 pills, 3 times a day (mixed into water); not within an hour of antacids or didanosine	Rash, headache, hepatitis
Nevirapine (Viramune)	1 pill, 2 times a day	Rash, hepatitis
Protease inhibitors		
Indinavir (Crixivan)	2 pills, 3 times a day on empty stomach or with a low-fat snack and not within 2 hours of didanosine	Kidney stones, nausea, headache, blurred vision, dizziness, rash, metallic taste in mouth, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Nelfinavir (Viracept)	3 pills, 3 times a day with some food	Diarrhea, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Ritonavir (Norvir)	6 pills, 2 times a day (or 4 pills, 2 times a day if taken with saquinavir) with food and not within 2 hours of didanosine	Nausea, vomiting, diarrhea, abdominal pain, headache, prickling sensation in skin, hepatitis, weakness, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Saquinavir (Invirase, a hard-gel capsule; Fortovase, a soft-gel capsule)	6 pills, 3 times a day (or 2 pills, 2 times a day if taken with ritonavir) with a large meal	Nausea, diarrhea, headache, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

SOURCE: JG Bartlett and RD Moore, 1998, Improving HIV therapy, *Sci. Am.* **279**(1):87.

Summary

- 1. The immune system makes mistakes.
- 2. Anything that can go wrong will go wrong.
- 3. AIDS is a challenge.

Concepts:

1. Immunodeficiency disease (IDD)
2. Congenital immunodeficiency disease (CIDD)
3. X-linked Agammaglobulinemia (Bruton's Agammaglobulinemia)
4. DiGeorge syndrome
5. Severe Combined Immunodeficiencies(SCID)
6. Human immunodeficiency virus (HIV)

Questions:

1. Discuss the pathogenesis and immune response of HIV infection (AIDS), please !
2. Discuss the mechanism of $CD4^{+}$T cell depletion and dysfunction HIV infection , please !