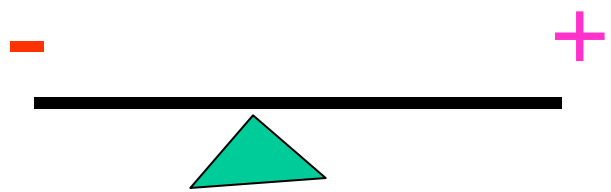
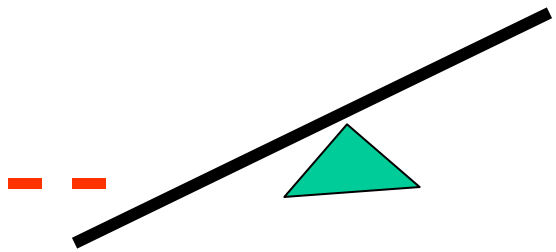
Tolerance and Autoimmunity

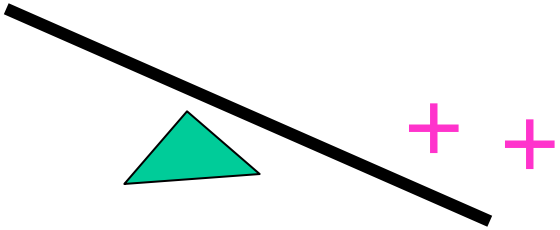
Lecture 19 April 20, 2009 Dr. Raveche

- **Pathways : Deletion/Anergy**
- **Central v.s. Peripheral Tolerance**
- **Factors Involved in Induction of Tolerance**
- **Define mechanisms that lead to Autoimmunity**





Tolerance



Autoimmunity

- **Tolerance means the inability to make a positive immune response to a specific antigen**

- **Tolerance is not global unresponsiveness to all antigens (ie immunodeficient patient or patient receiving immunosuppressive drugs)**

- **Tolerance is usually achieved by prior exposure to specific antigens**

- **Normally we are tolerant to self antigens**

Antigen	Effect of response to antigen	
	Normal response	Deficient response
Infectious agent	Protective immunity	Recurrent infection
Innocuous substance	Allergy	No response
Grafted organ	Rejection	Acceptance
Self organ	Autoimmunity	Self tolerance
Tumor	Tumor immunity	Cancer

Fig 1.32

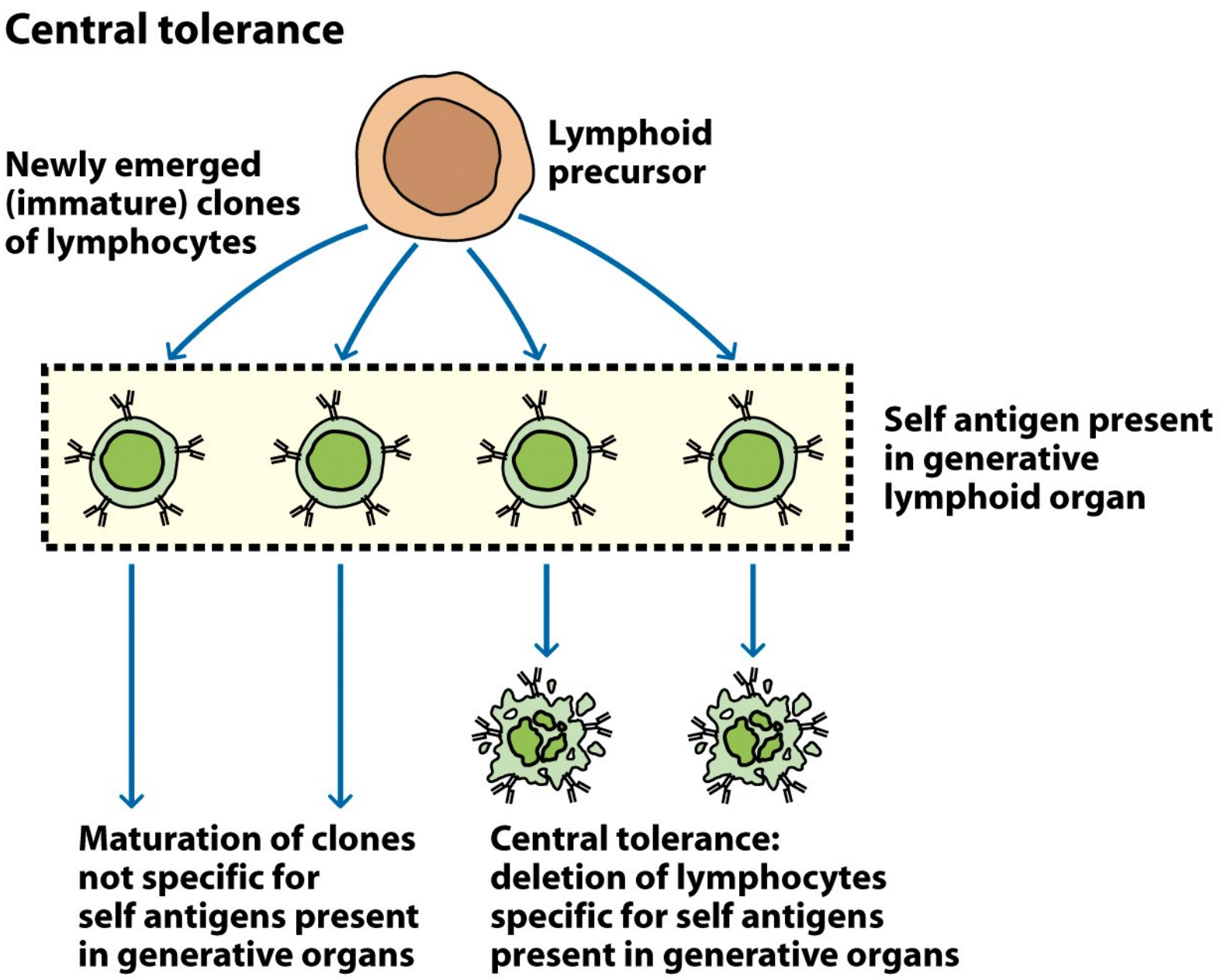


Figure 16-1a
Kuby IMMUNOLOGY, Sixth Edition

Central Tolerance is Maintained by

Clonal Deletion--removal of antigen reactive cells

Main mechanism is apoptosis: programmed cell death

Consequence of immature self-reactive lymphocytes recognizing self-antigen

Peripheral tolerance

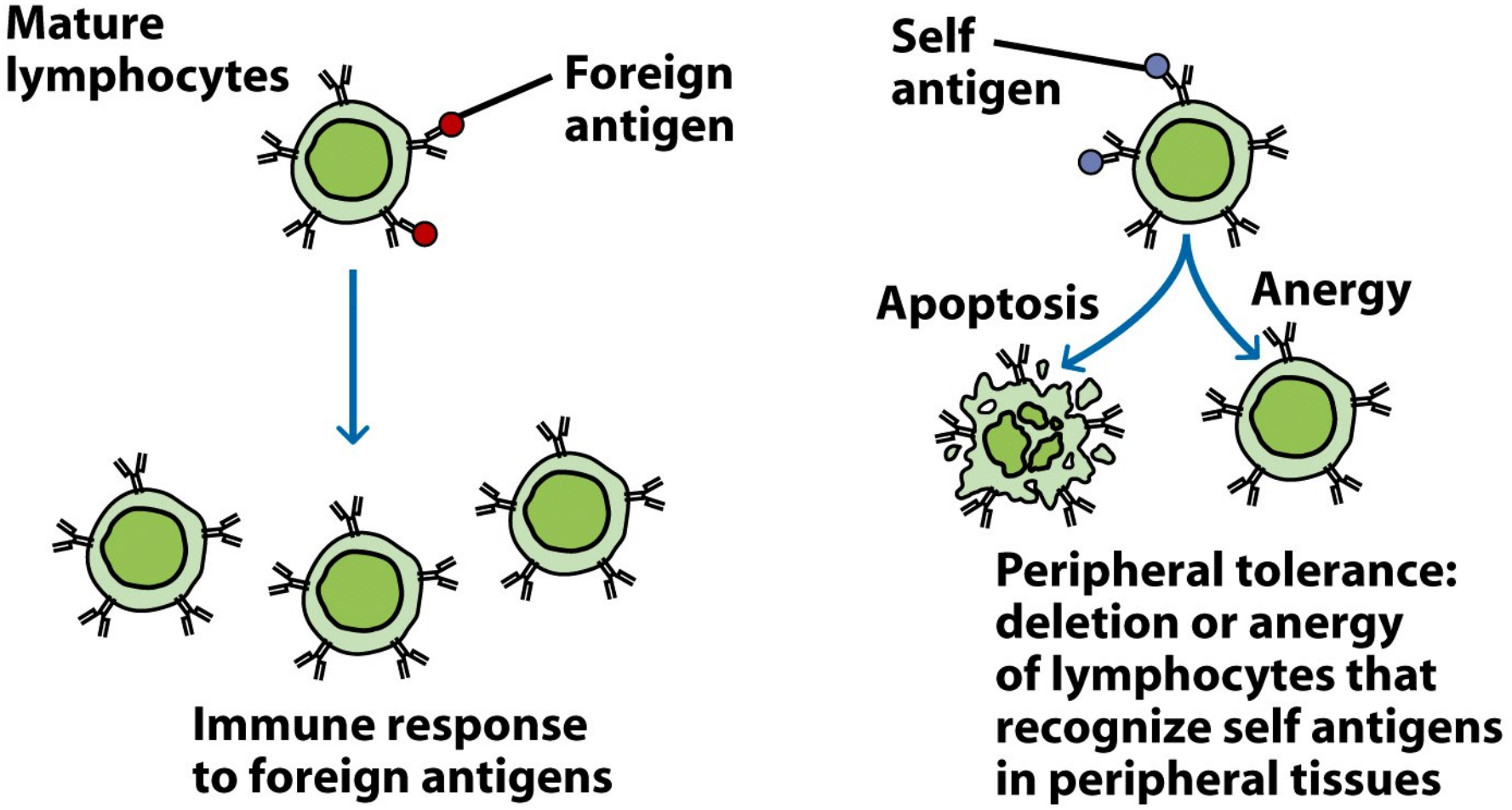


Figure 16-1b
Kuby IMMUNOLOGY, Sixth Edition

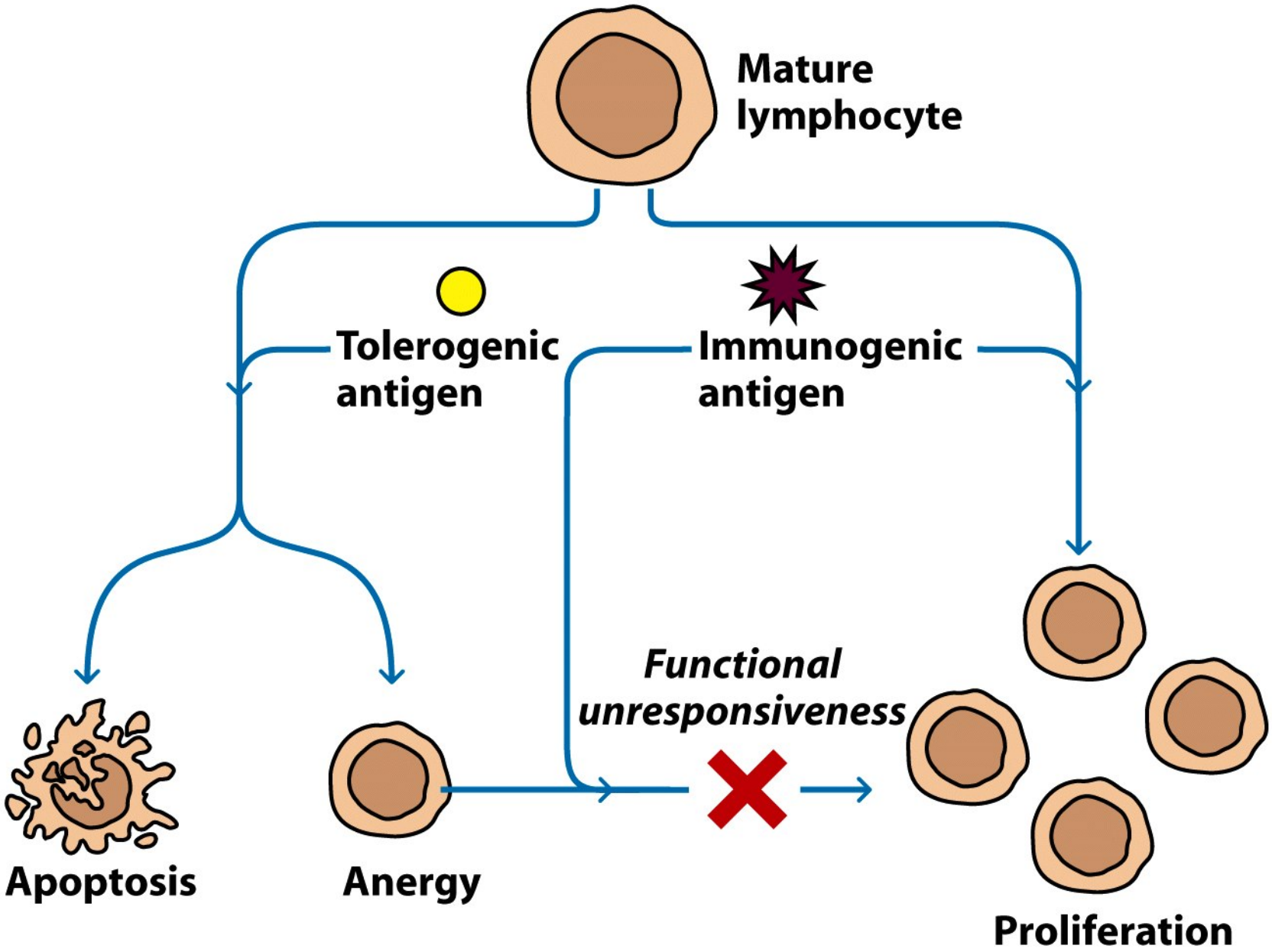


Figure 16-2
Kuby IMMUNOLOGY, Sixth Edition

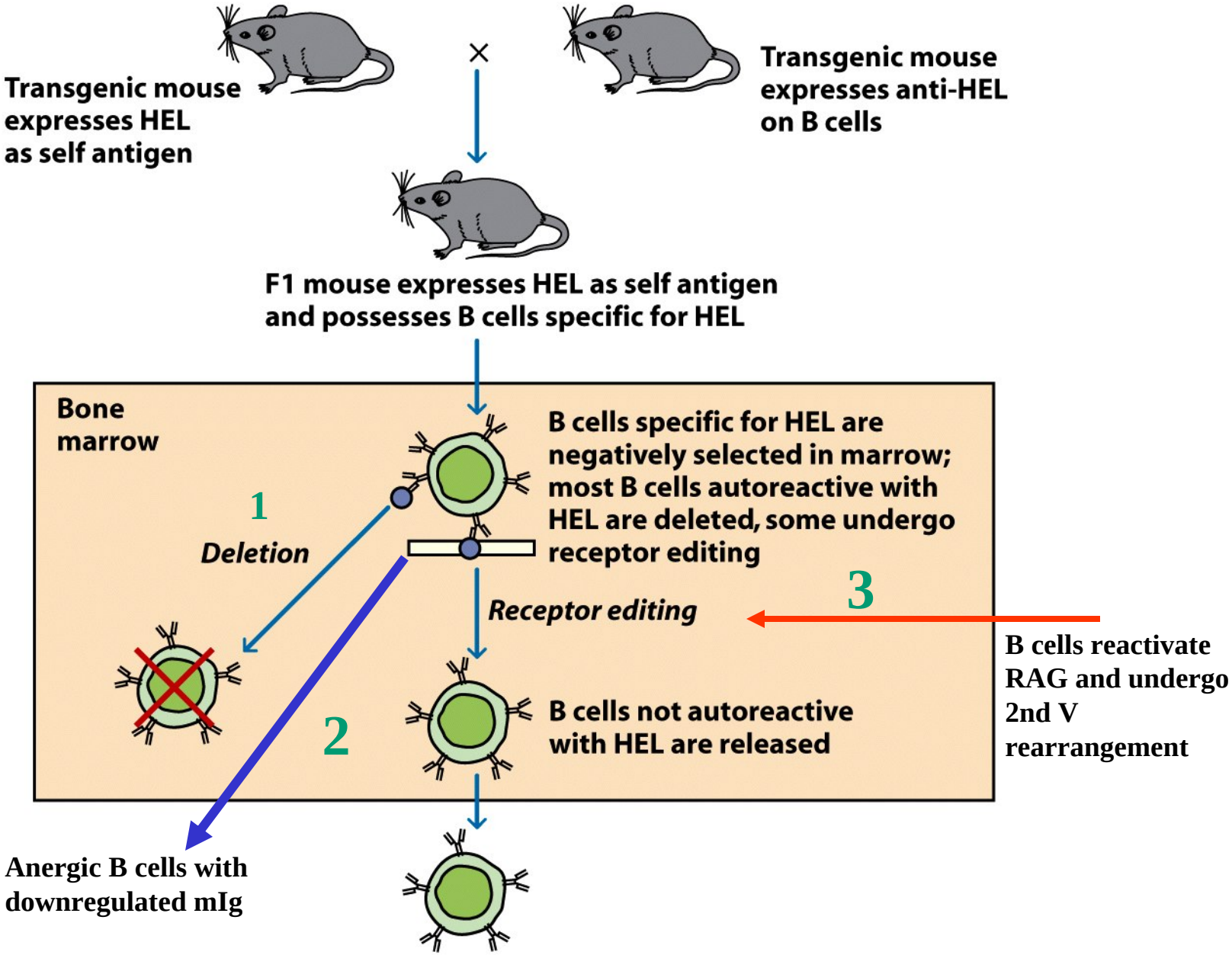


Figure 16-3a
Kuby IMMUNOLOGY, Sixth Edition

Central

= Mean Fluorescence Intensity, green shaded area are cells with no reactivity to HEL

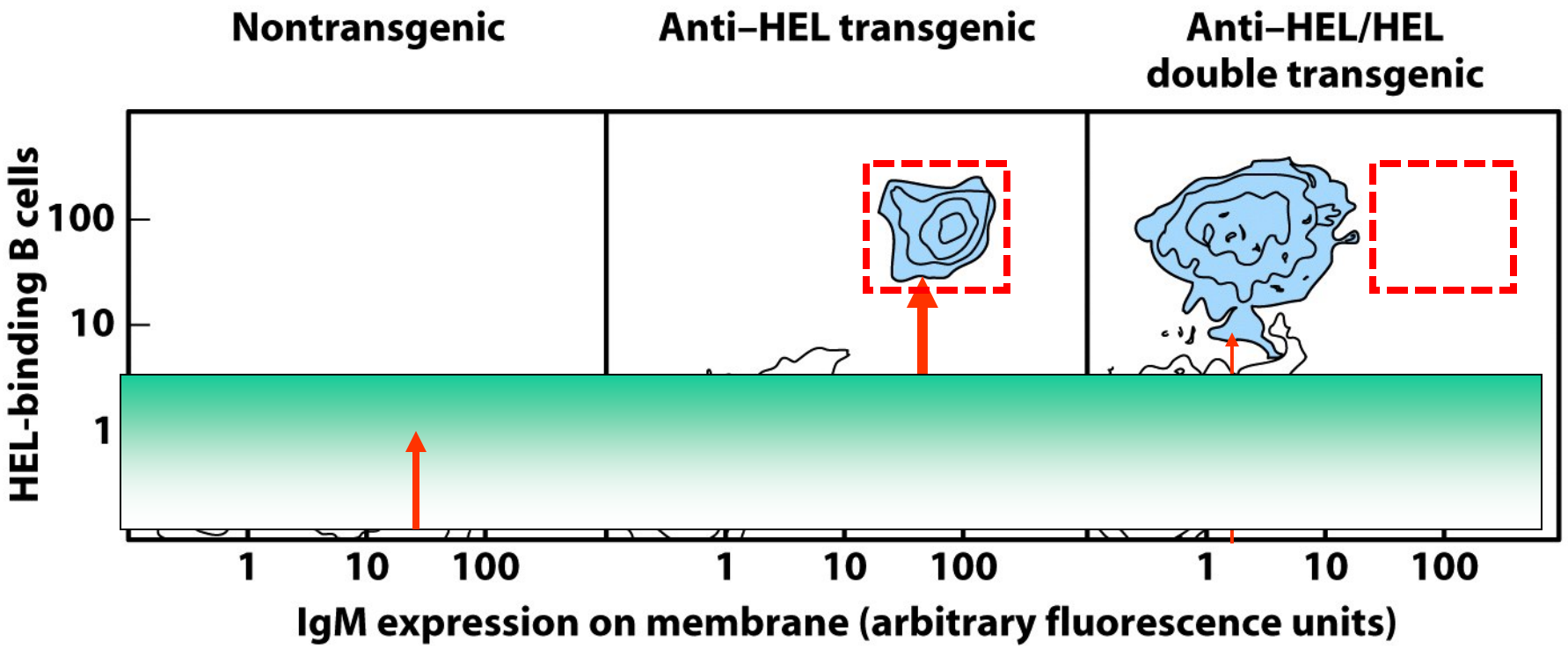


Figure 11-14b
Kuby IMMUNOLOGY, Sixth Edition

• Normal mice do not have detectable numbers of B cells reactive to hen egg lysozyme (naïve B cells have different BCRs with no exposure to Ag, no clonality)

2.Single transgenic >90% of anti-HEL transgenic mice have mIgM reactive with HEL (no Ag injection required these are naïve B cells)

3. Double transgenic: All B (except those that undergo receptor editing) react to HEL, however HEL Ag is also present in periphery--anergy occurs by downregulation of membrane IgM expression

Immature B cells Undergo Receptor Edi

Immature B cells that encounter Ag in bone marrow undergo apoptosis *UNLESS*

- **RAG genes are reactivated**
- **Additional light chain VJ recombination**
- **New light chain produced**
- **Different Ig receptor which does not react with Ag present in bone marrow**

TABLE 11-3 Expression of anti-HEL transgene by mature peripheral B cells in single- and double-transgenic mice

Experimental group	HEL level	Membrane anti-HEL	Anti-HEL PFC/spleen*	Anti-HEL serum titer*
Anti-HEL single transgenics	None	+	High	High
Anti-HEL/HEL double transgenics (group 1)	10^{-9} M	+	Low	Low

*Experimental animals were immunized with hen egg-white lysozyme (HEL). Several days later, hemolytic plaque assays for the number of plasma cells secreting anti-HEL antibody were performed and the serum anti-HEL titers were determined. PFC = plaque-forming cells.

SOURCE: Adapted from C. C. Goodnow, 1992, *Annual Review of Immunology* **10**:489.

Table 11-3
Kuby IMMUNOLOGY, Sixth Edition

T Cells Undergo Peripheral Tolerance of CD4+T due to:

Regulatory T cells: mediated by cytokines

Clonal Anergy

Activation Induced Cell Death:

Passive: no survival Stimuli

Active: FasL (priviledged site)

Thymic Selection deletes HEL reactive T cells (HEL now self-antigen)

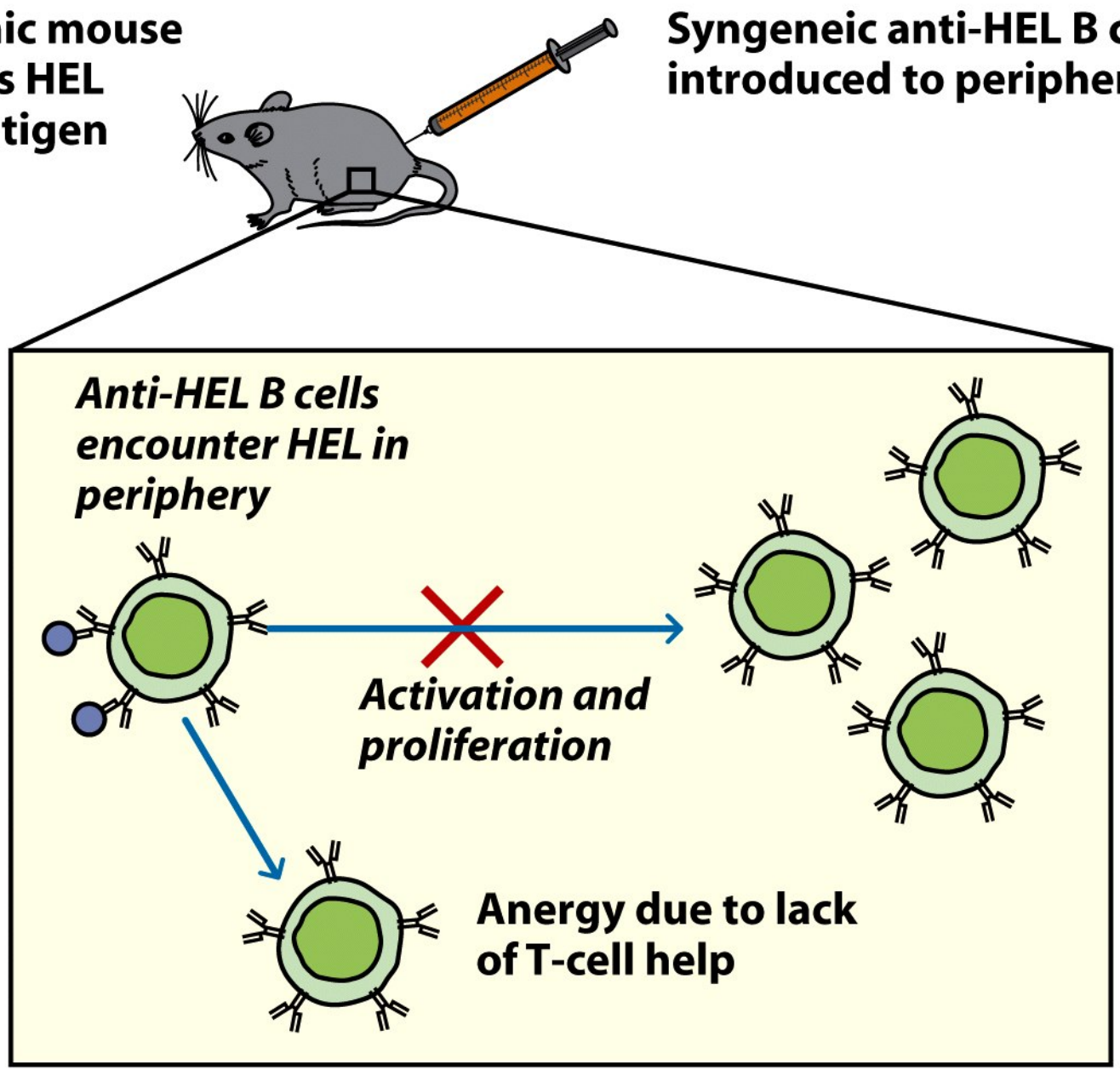
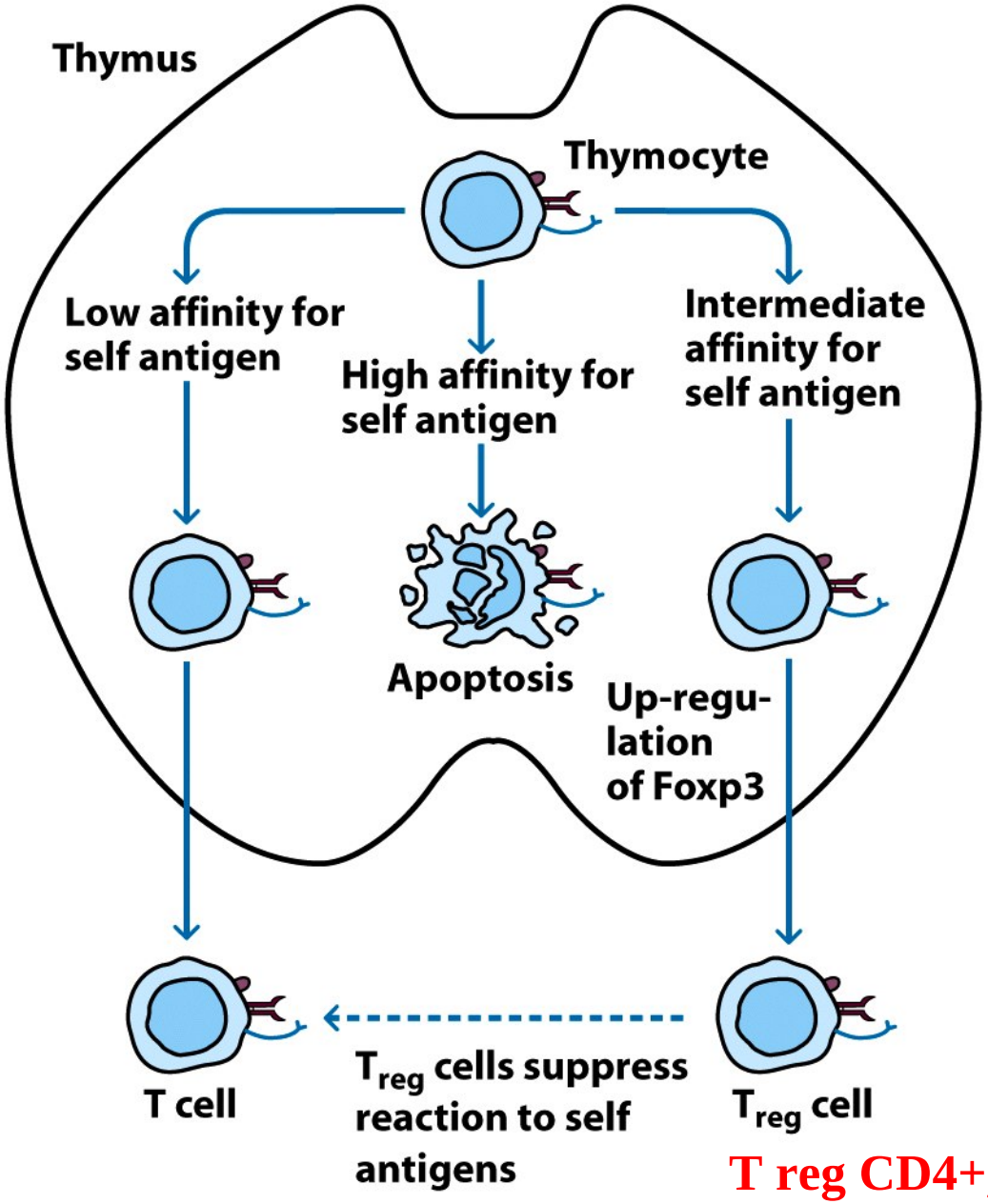


Figure 16-3b
Kuby IMMUNOLOGY, Sixth Edition



T reg CD4+, CD25+, FOXP3+

Figure 16-4
Kuby IMMUNOLOGY, Sixth Edition

Regulatory T cells

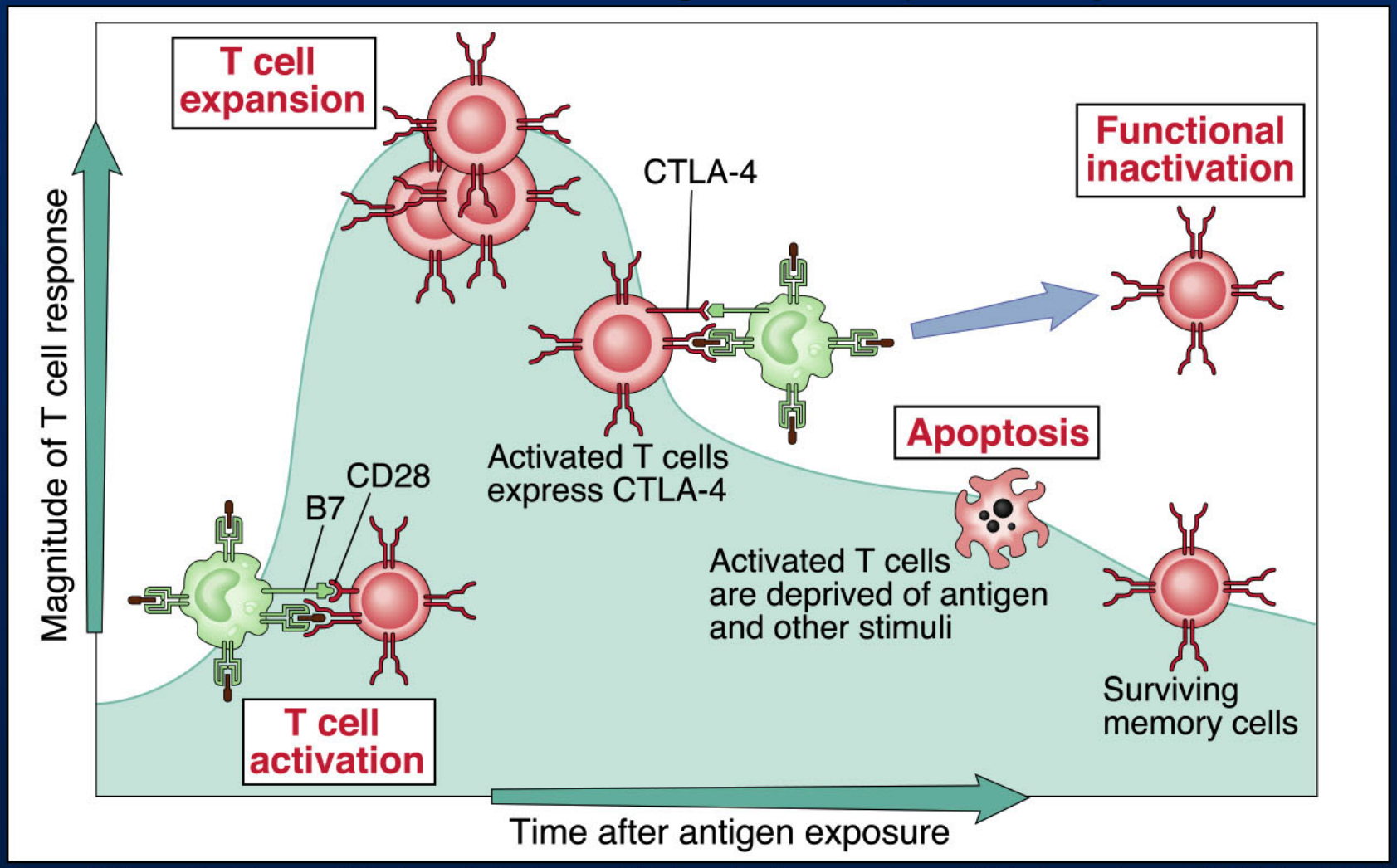
$CD4^{+}$, $CD25^{+(bright)}$

Treg: Develop in thymus
express CTLA-4
express FoxP3 (transcription factor)
PRODUCE: IL-10 AND TGF

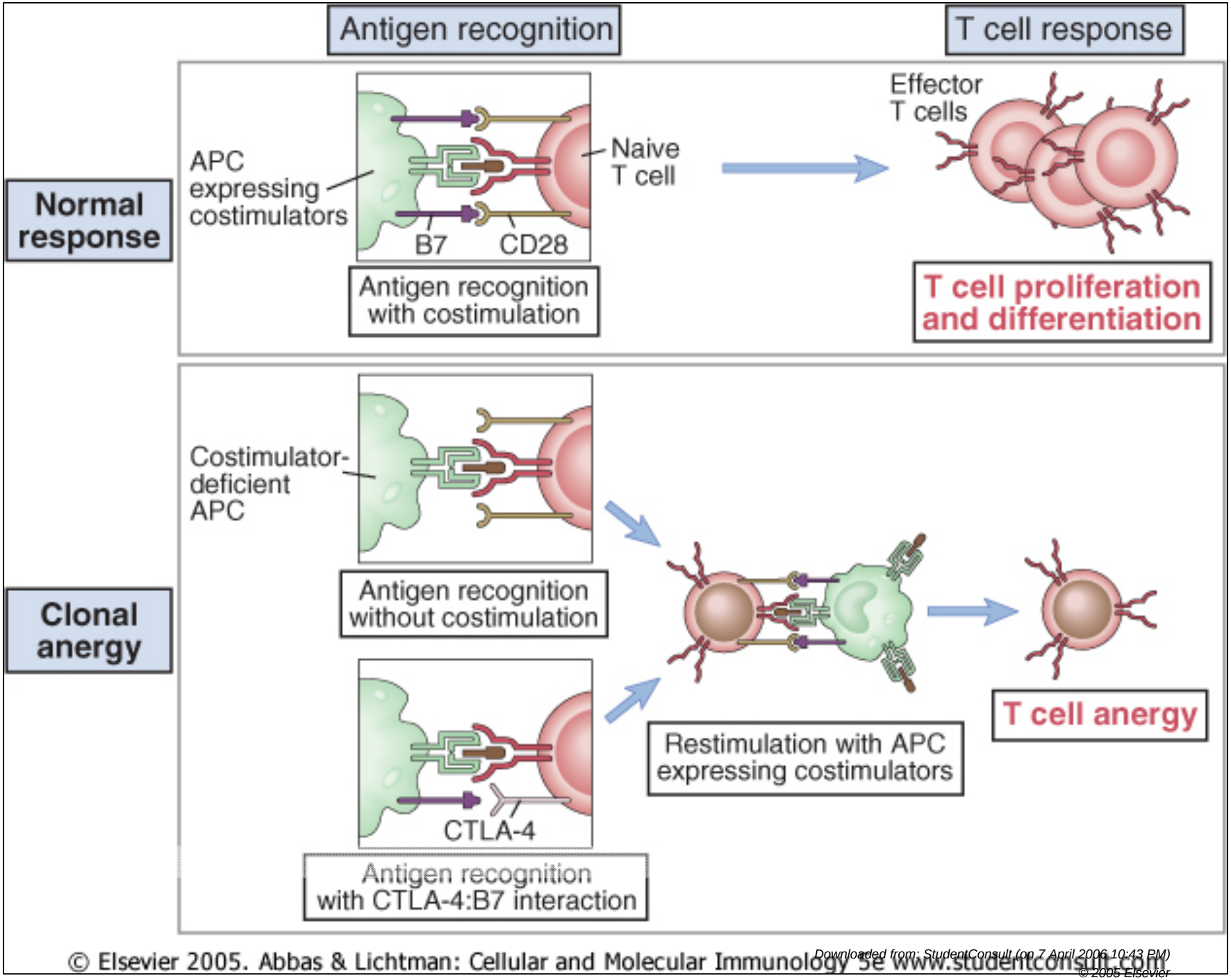
Tr1 : Suppress Th1 (are antigen specific)
Usually IL-10 cytokine mediated (TGF-β too)
Ag in periphery

Th3: Suppression UsuallyTGF beta cytokine mediated

Mechanisms of homeostasis in immune responses (T cells)



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 10-14



B7 Costimulatory Pathways

- B7-2 on APC (constitutive), B7-1 appears later
- Receptors…
    - CD28 (low affinity-constitutive on T cells, surface expression
    - CTLA-4 CD152 (high affinity cytoplasmic and upon stimulation becomes surface

CD28 mediates:

- T cell proliferation
- Induction of bcl-xl
- Increase in CD40L (CD154
- Differentiation of CD8+CTL
- Cytokine production

CTLA-4 (CD152

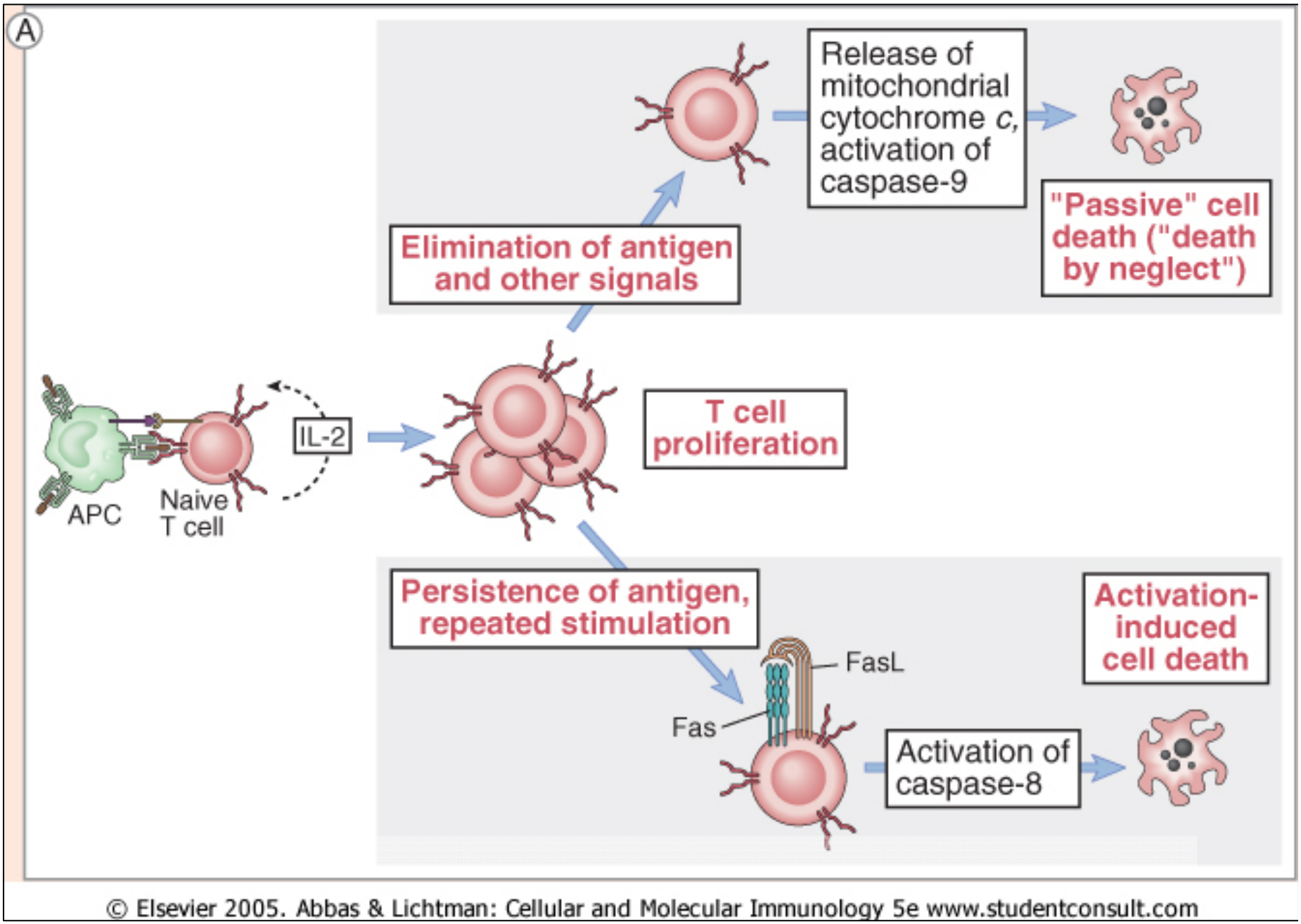
- Induces apoptosis
- KO mice have LPD

T Cells Undergo Peripheral Tolerance of CD4+T due to:

Activation-Induced Cell Death

Apoptosis: Activation of cysteine proteases, caspases

Not Necrosis
Triggered by ligand binding to receptors (Fas, TNFR)
Characterized by DNA cleavage
Nuclear fragmentation
plasma membrane blebbing
phagocytosis of apoptotic bodies
Prevented by inhibitors of caspases (FLIP)
activation of Bcl family



Factors Involved in Tolerance

Tolerance is easier to achieve in newborns

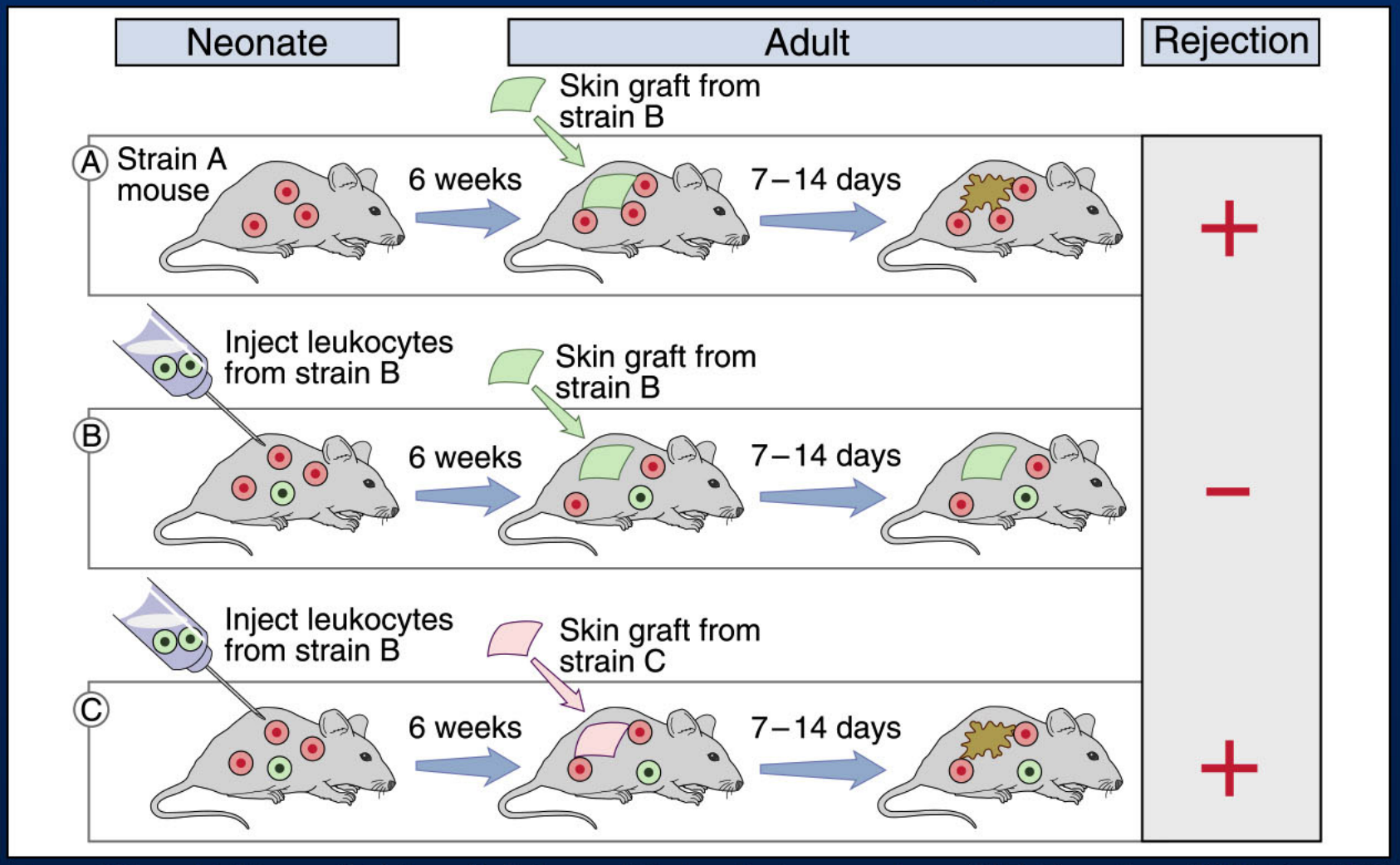
Nature of antigen- soluble antigens are better tolerogens

Route of antigen administration--oral good for tolerance

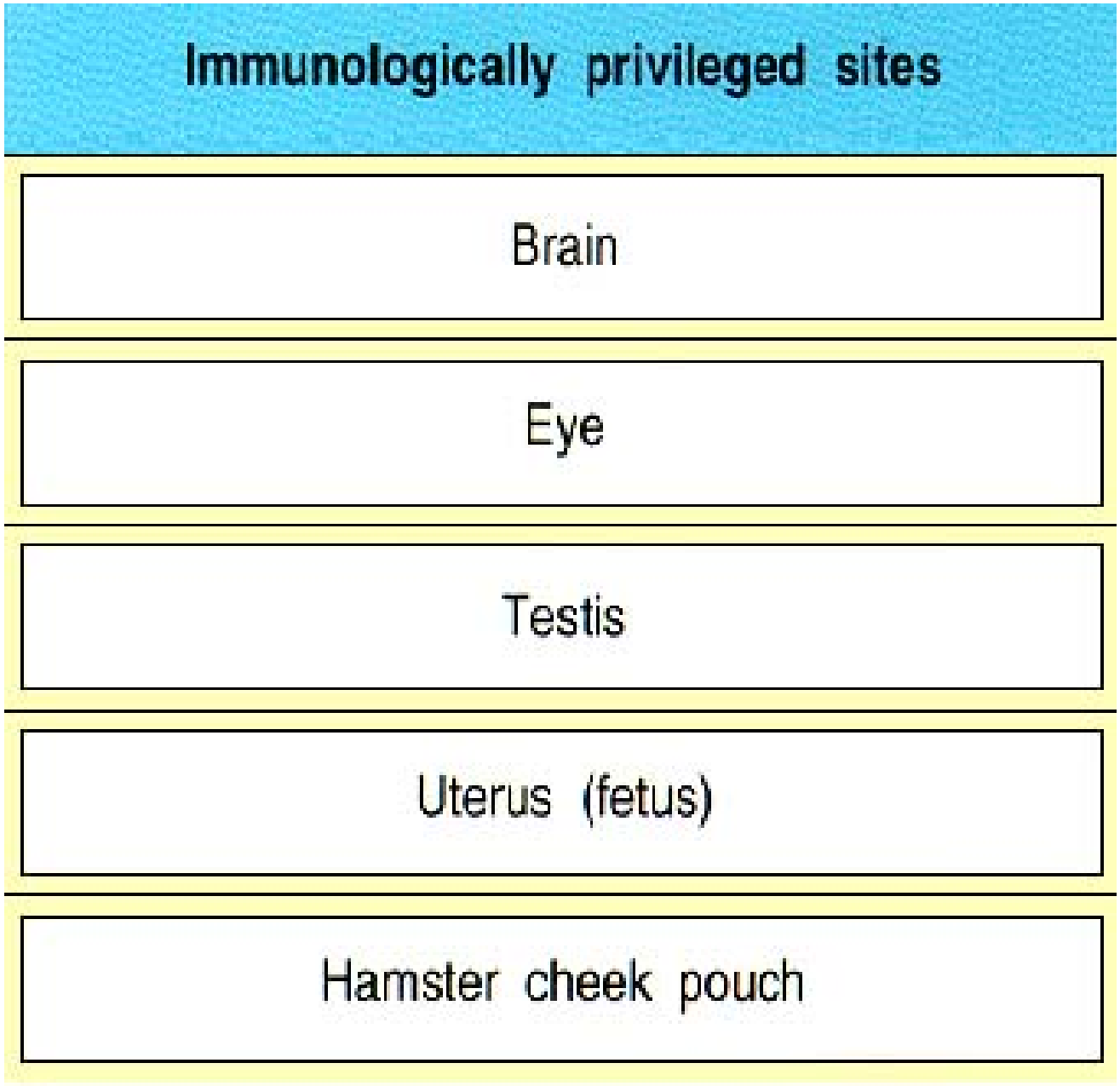
Dose of antigen

Inefficient antigen presentation leads to T cell tolerance

Neonatal tolerance to allografts



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 10-2



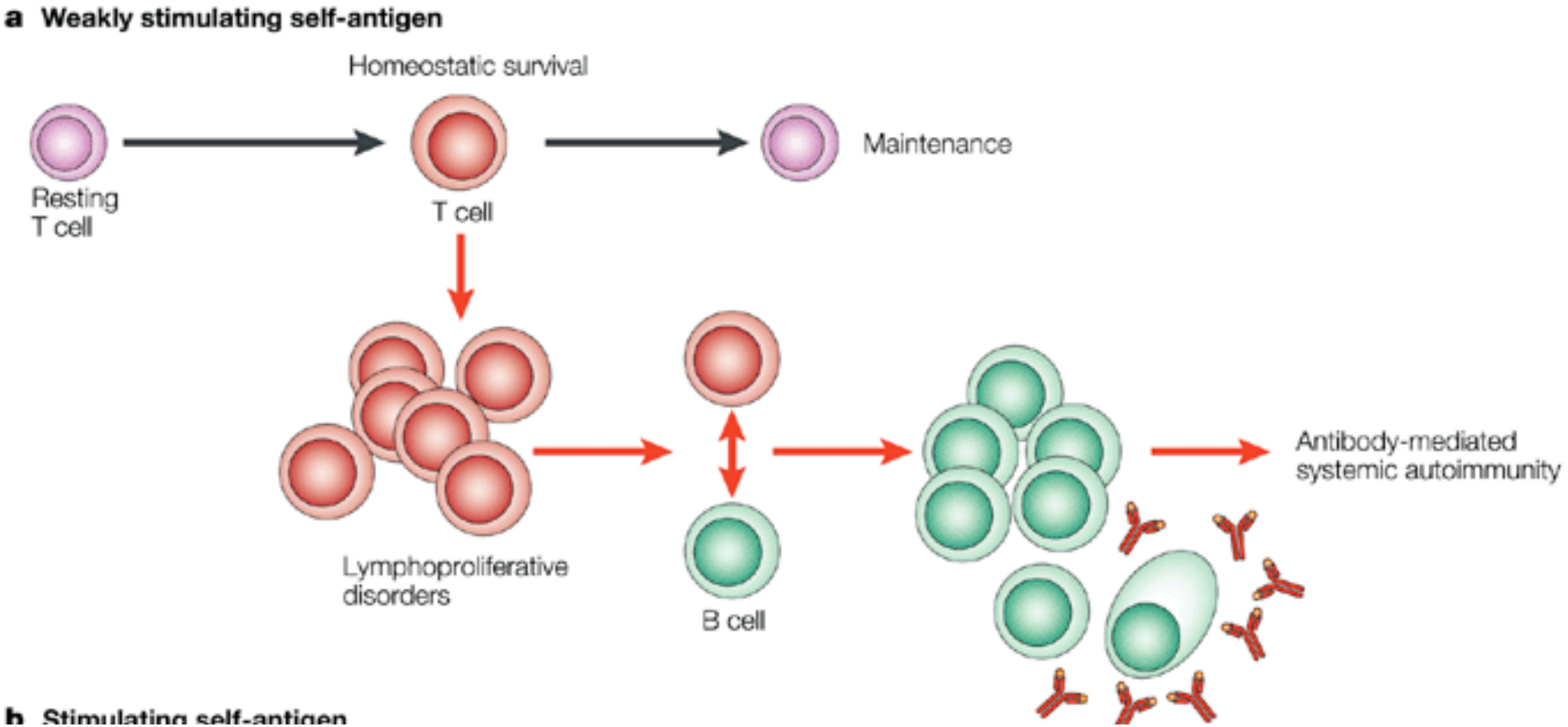
Autoimmunity

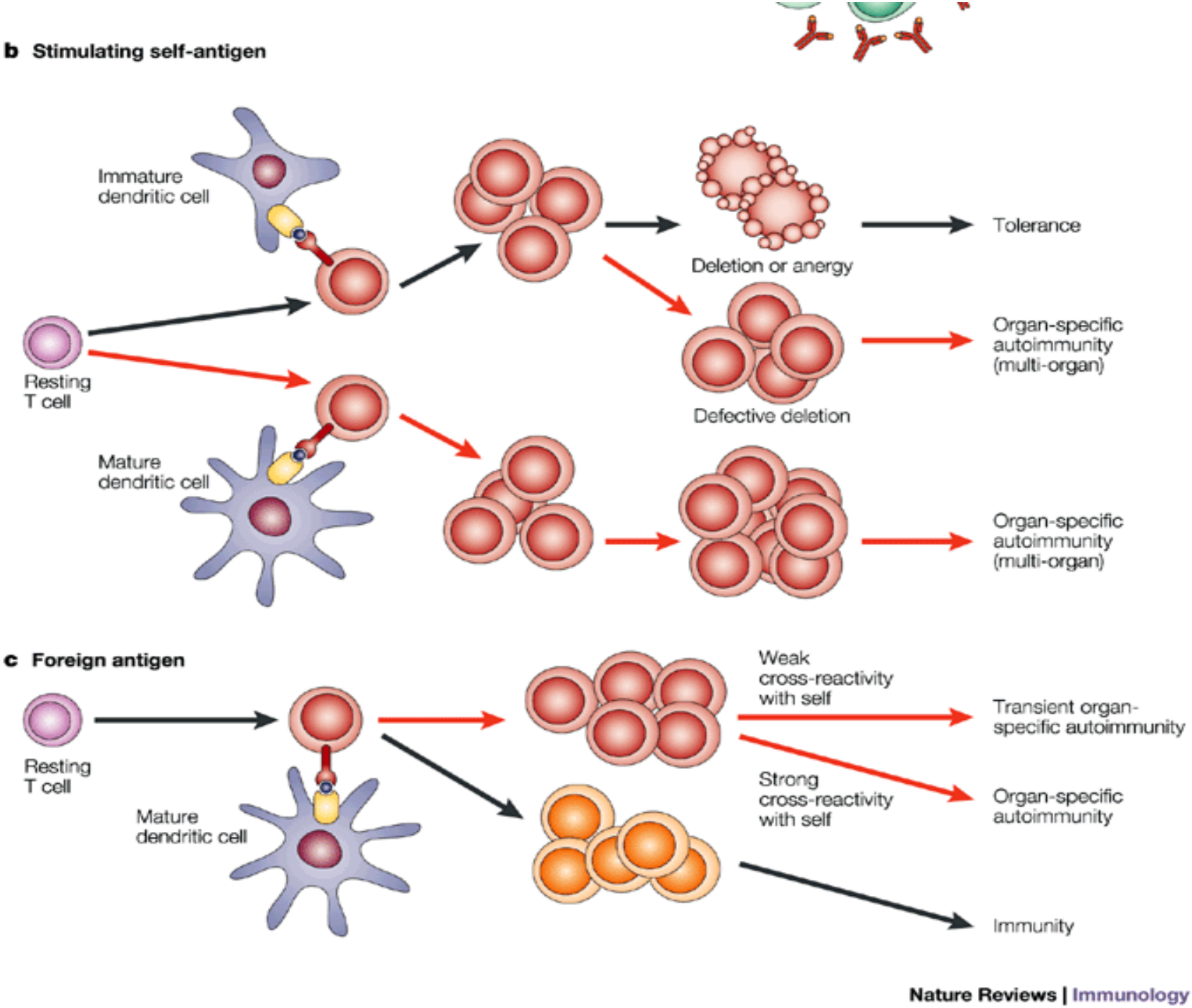
→ → **Describe Mechanisms responsible for autoimmune damage**

→ → **Name autoimmune diseases and major self-antigen**

Autoimmunity is a breakdown in tolerance
Immune hyperactivity, self recognition
Normally, tolerant to self antigens

Autoimmune Diseases can by Systemic or Organ-Specific




b Stimulating self-antigen
Immature dendritic cell
Resting T cell
Mature dendritic cell
Deletion or anergy
Tolerance
Defective deletion
Organ-specific autoimmunity (multi-organ)
Organ-specific autoimmunity (multi-organ)
c Foreign antigen
Resting T cell
Mature dendritic cell
Weak cross-reactivity with self
Transient organ-specific autoimmunity
Strong cross-reactivity with self
Organ-specific autoimmunity
Immunity

Overall Mechanism

- Autoimmune diseases results from breakdown of self-tolerance in B cells, or T cells, or both.
- Genetic, hormonal and environmental factors or infectious agents may contribute to the development of autoimmune diseases.
- Damage may be due to immune complexes, circulating autoantibodies, and/or autoreactive T
- Once initiated, autoimmune reactions may injure tissues and cause the release and alteration of other tissue antigens resulting in activation of lymphocytes specific for these other antigens.

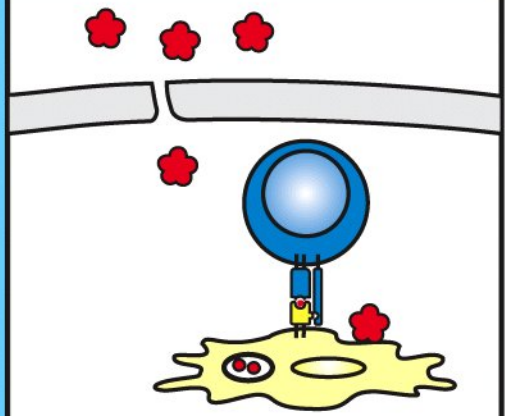
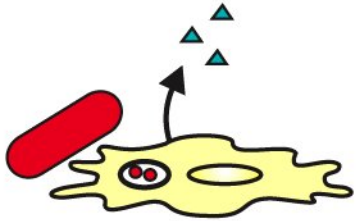
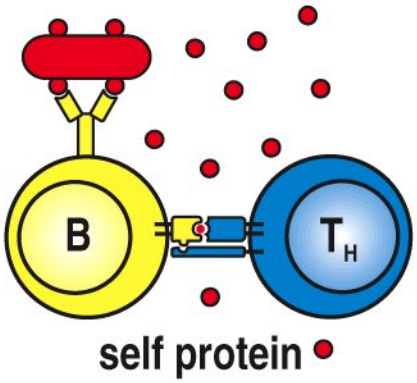
Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell	Binding of pathogen to self protein
Effect	Release of sequestered self antigen; activation of nontolerized cells	Release of inflammatory mediators, notably IFN-α	Pathogen acts as carrier to allow anti-self response
Example	Sympathetic ophthalmia	? SLE	? Interstitial nephritis ? SLE
			

Figure 13-26 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

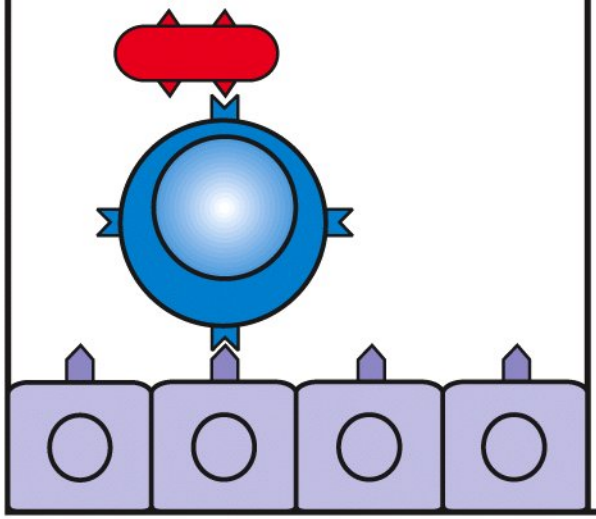
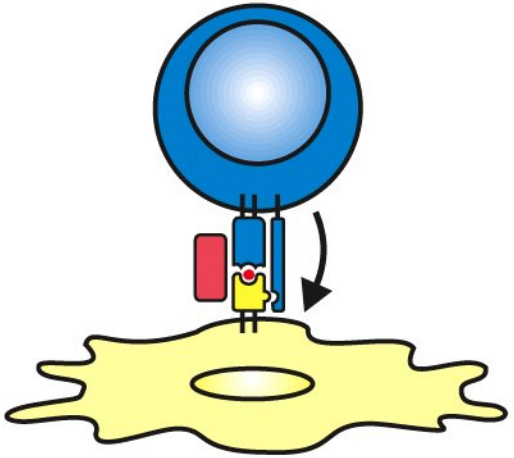
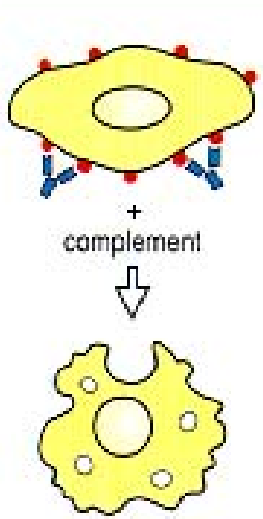
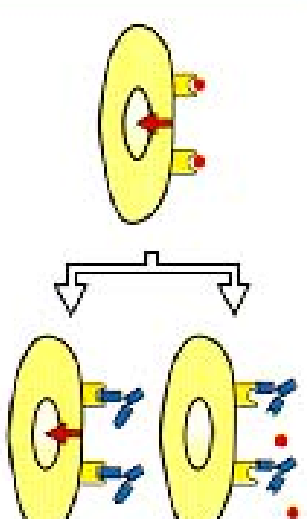
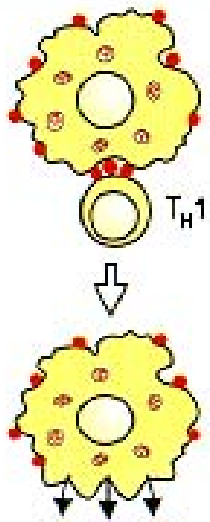
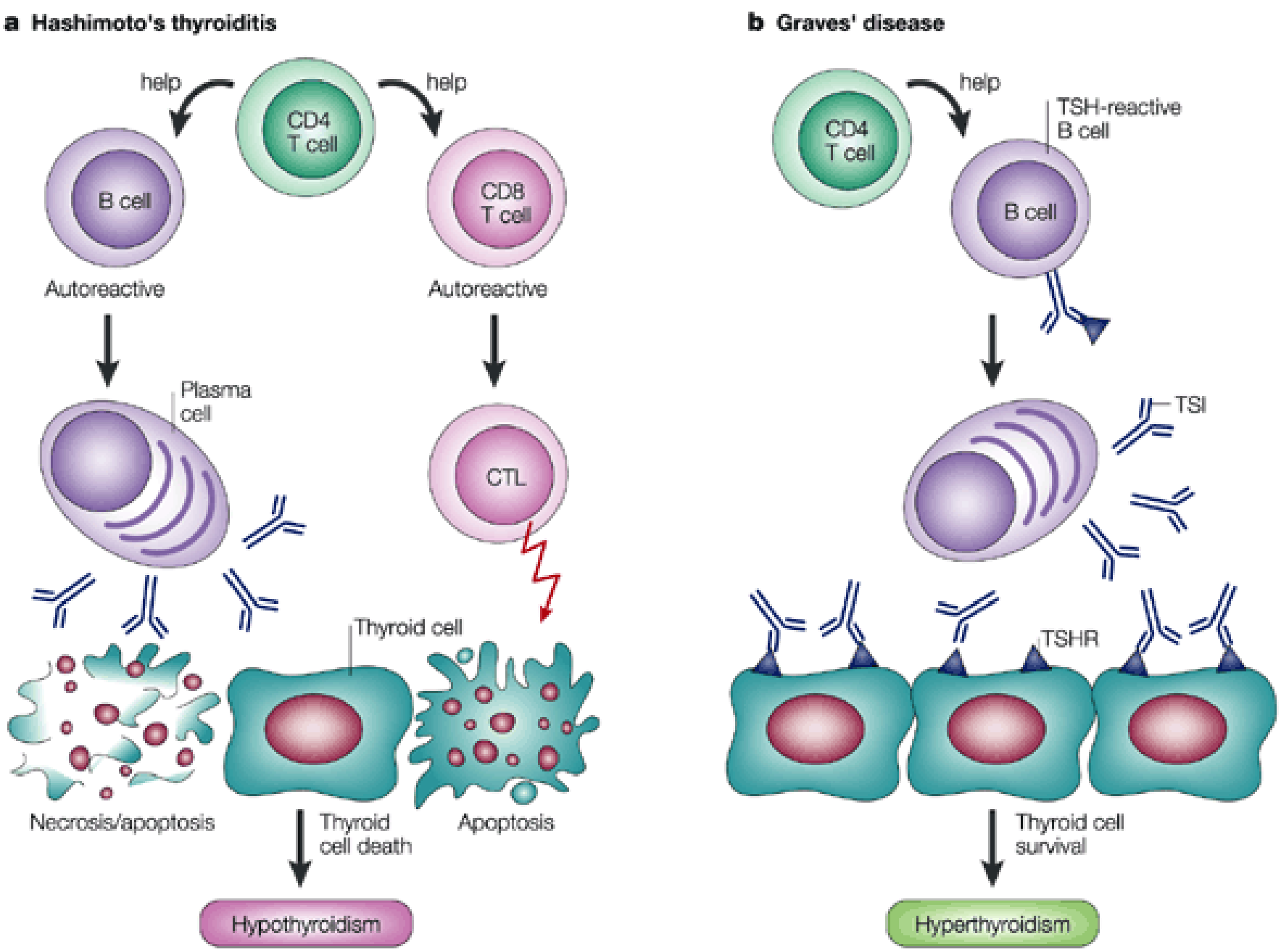
Mechanism	**Molecular mimicry**	**Superantigen**
Effect	**Production of cross-reactive antibodies or T cells**	**Polyclonal activation of autoreactive T cells**
Example	**Rheumatic fever ? Diabetes ? Multiple sclerosis**	**? Rheumatoid arthritis**
		

Figure 13-26 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Type II		Type III	Type IV Typ
IgG antibody		IgG antibody	T
Cell- or matrix-associated antigen	Cell-surface receptors	Soluble antigen	Soluble antigen
Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement Phagocytes	Macrophage activation
			
Some drug allergies (eg penicillin), transfusion reaction, autoimmune hemolytic anemia	Graves' disease (agonist) Myasthenia gravis (antagonist)	Serum sickness, Systemic lupus erythematosus	Contact dermatitis, graft rejection, rheumatoid arthritis

ing


a Hashimoto's thyroiditis
help
CD4 T cell
help
B cell
CD8 T cell
Autoreactive
Autoreactive
Plasma cell
CTL
Thyroid cell
Necrosis/apoptosis
Thyroid cell death
Apoptosis
Hypothyroidism
b Graves' disease
help
CD4 T cell
TSH-reactive B cell
B cell
TSI
TSHR
Thyroid cell survival
Hyperthyroidism

STIMULATING AUTO-ANTIBODIES (Graves' disease)

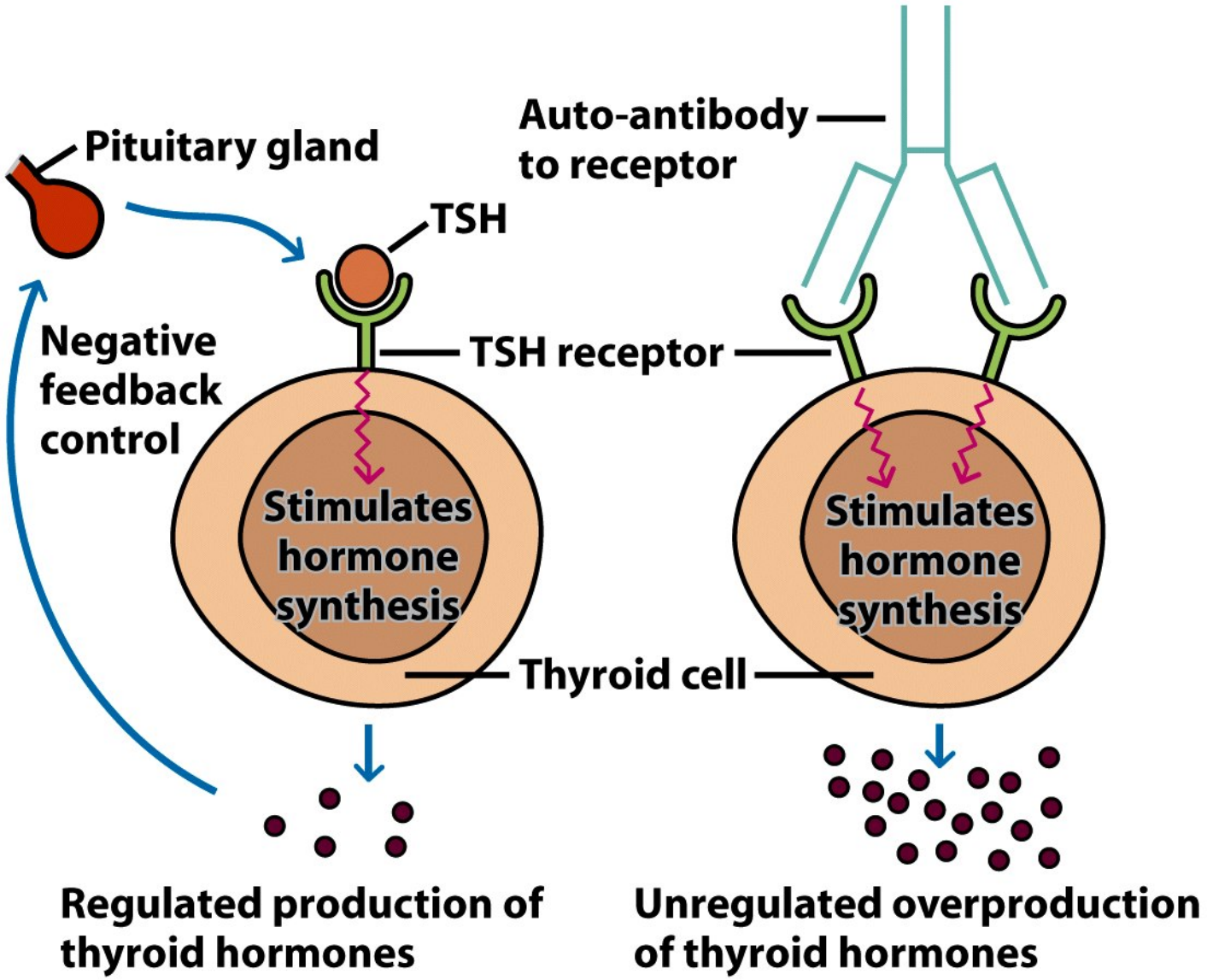


Figure 16-8
Kuby IMMUNOLOGY, Sixth Edition

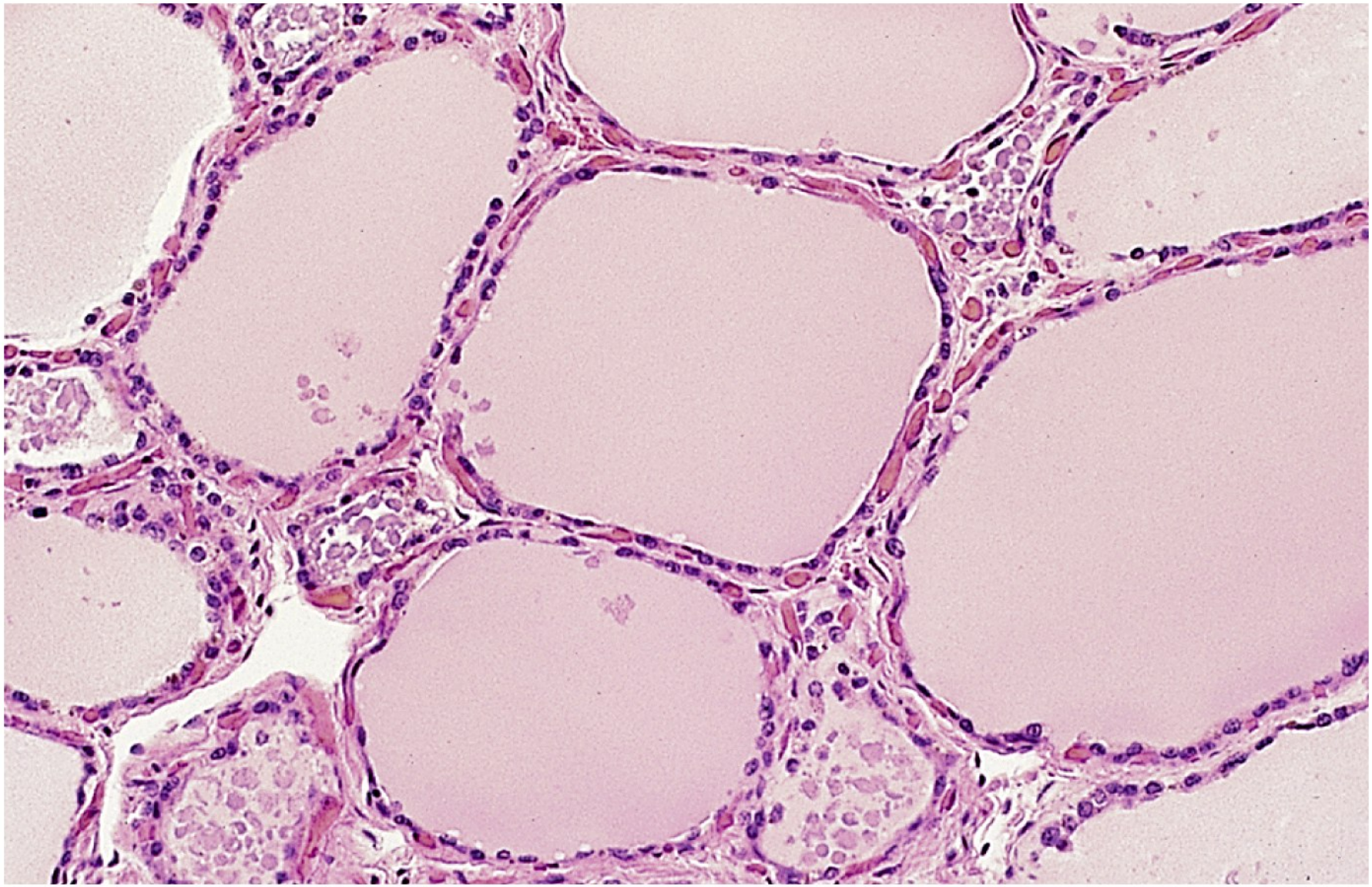


Figure 16-5a
Kuby IMMUNOLOGY, Sixth Edition

Normal thyroid follicle lined with

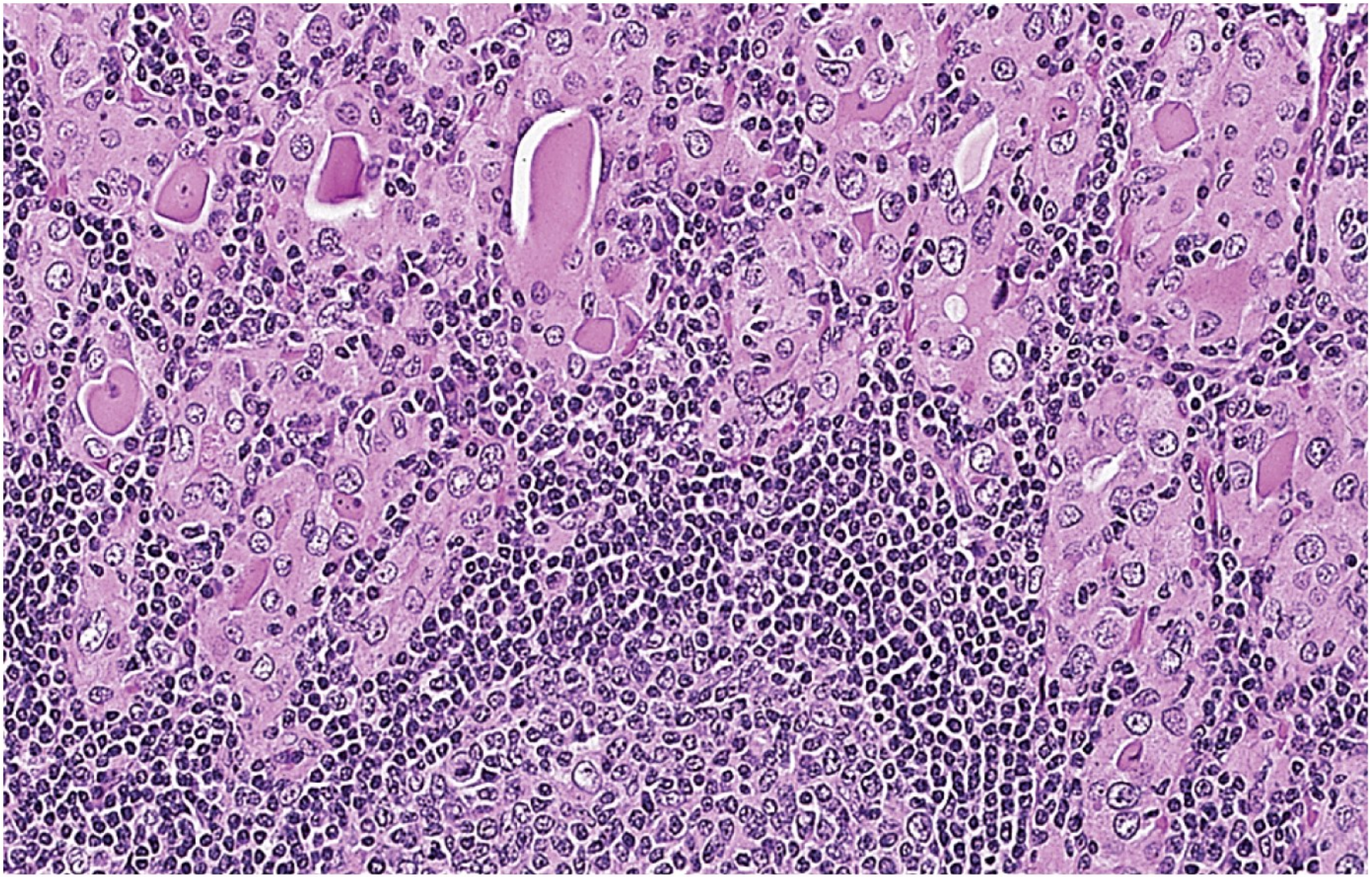


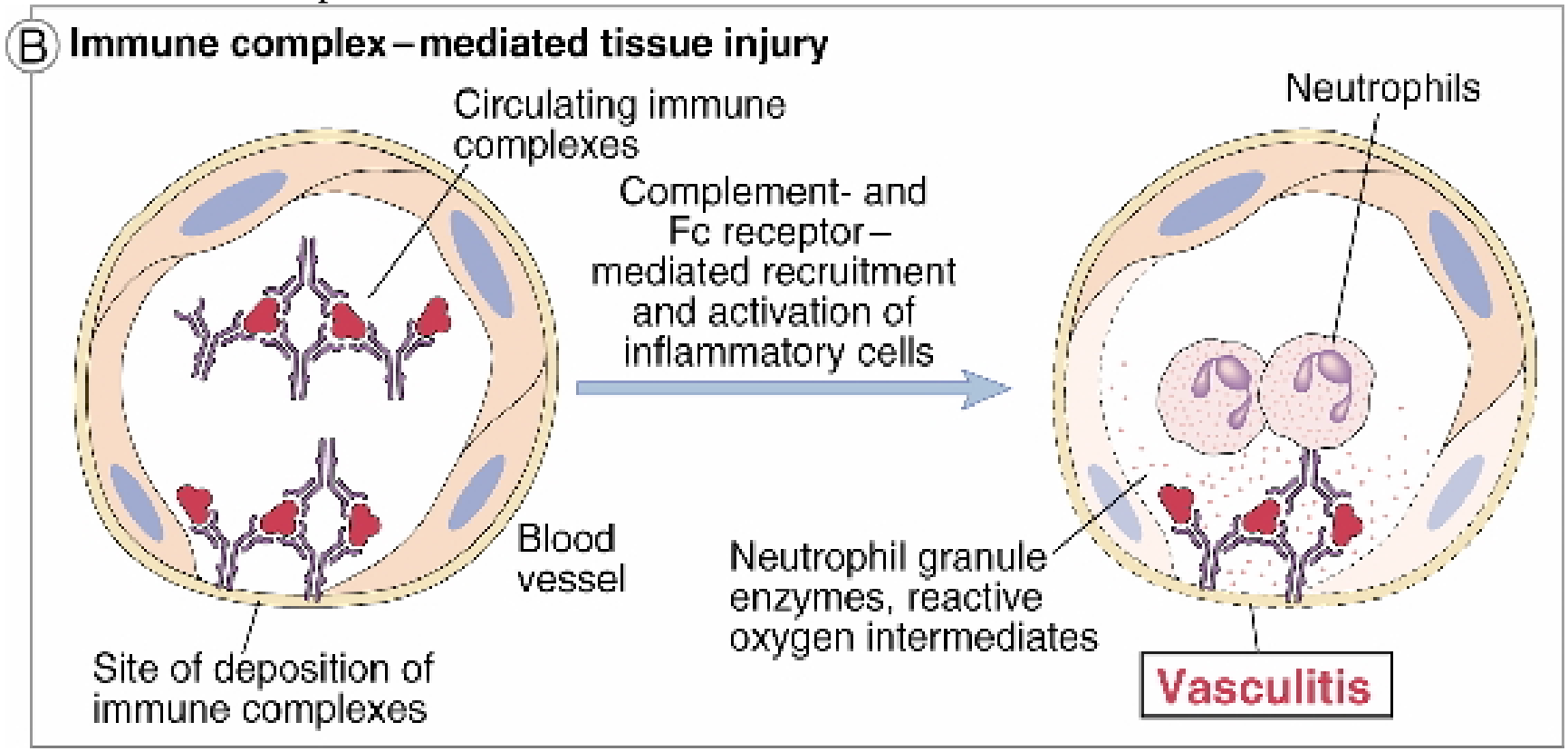
Figure 16-5b
Kuby IMMUNOLOGY, Sixth Edition

Thyroid follicle in Hashimoto's thyroiditis with

Type III hypersensitivity

Mechanisms of
Ab deposition

Effector mechanisms
of tissue injury



Abbas 18-1B

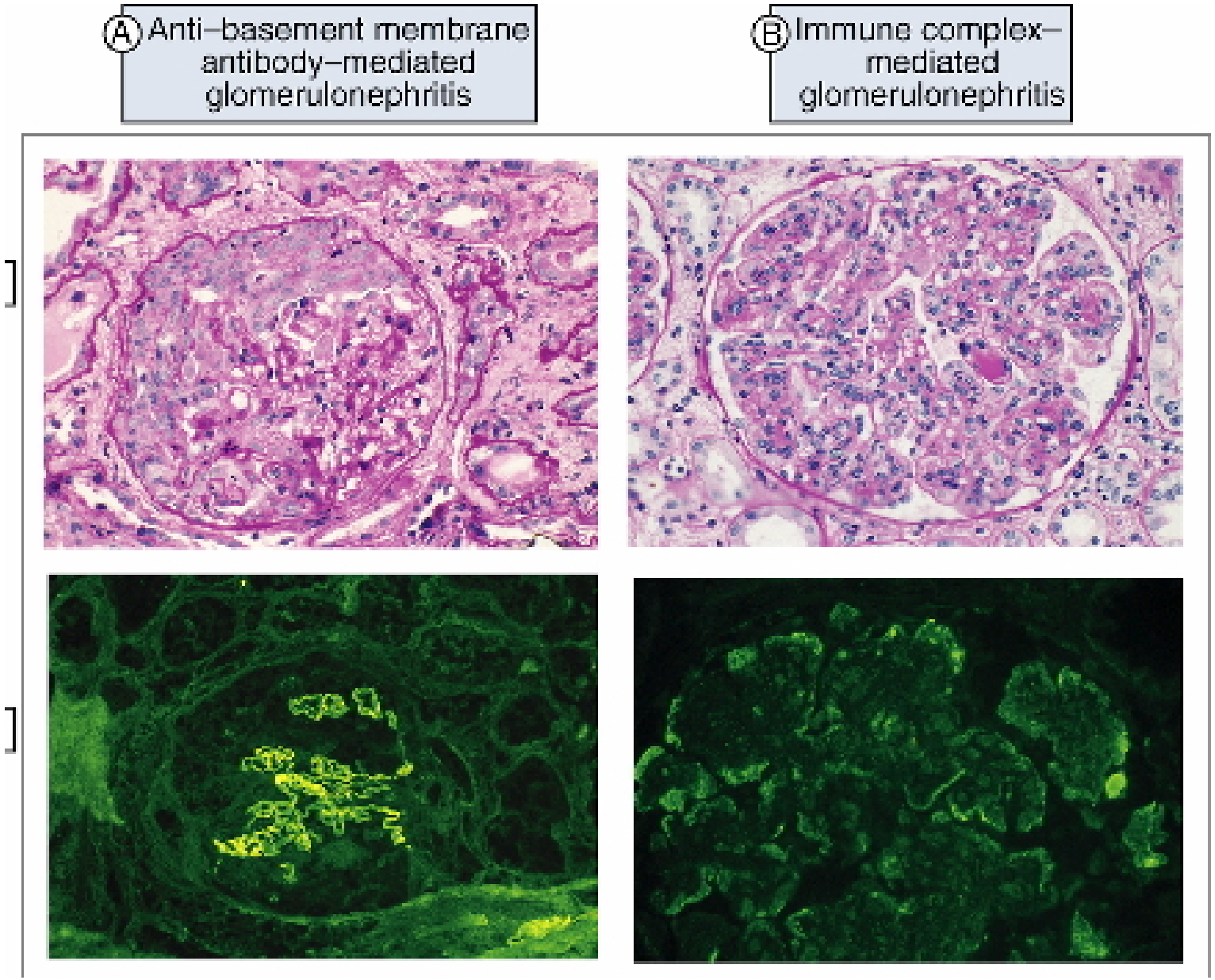
Table 18–3. Examples of Human Immune Complex–Mediated Diseases

Disease	Antigen involved	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Serum sickness	Various proteins	Arthritis,vasculitis, nephritis

Possible Causes of Immune Complex Deposition

- Size of complex - small complexes are not always phagocytosed & can be deposited in vessels.
- Charge - cationic antigens bind to negatively charged components of the basement membranes of blood vessels and kidney glomeruli.
- Sites of high hydrostatic pressure (kidney).
- Following activation of inflammatory cells and mast cells - cytokines & vasoactive mediators are released leading to increased adhesion of leukocytes to endothelium, increased vascular permeability and enlarged interendothelial spaces allowing deposition of complexes.

Pathologic features of antibody-mediated glomerulonephritis



Goodpasture's **Systemic Lupus Erythematosus (SLE)**

Some proteins implicated in the etiology of SLE		
Candidate activity	**Role**	**Deficiency in SLE**
Antigen clearance	Binding and clearance of autoantigens and immune complexes	Complement proteins: C1q, C1r, and C1s, C4>>C2 Serum IgM
	Masking or digestion of DNA and chromatin	Serum amyloid P component DNase 1
Tolerance induction	Threshold for lymphocyte activation	Lyn SHP-1 CD22 FcγRIIB
	Deletion of autoreactive lymphocytes	Fas and Fas ligand Cell-cycle inhibitor p21
Organ-specific manifestations of autoimmunity	Renal disease	FcγRIIB polymorphism FcγRIII polymorphism

Fig 13.7 © 2001 Garland Science

Associations of HLA serotype with susceptibility to autoimmune disease

Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Associations of infection with immune-mediated tissue damage

Infection	HLA association	Consequence
Group A streptococcus	?	Rheumatic fever (carditis, polyarthritis)
Chlamydia trachomatis	HLA-B27	Reiter's syndrome (arthritis)
Shigella flexneri, *Salmonella typhimurium*, *S. enteritidis*, *Yersinia enterocolitica*, *Campylobacter jejuni*	HLA-B27	Reactive arthritis
Borrelia burgdorferi	HLA-DR2, DR4	Chronic arthritis in Lyme disease

TABLE 16-3 Molecular mimicry between proteins of infectious organisms and human host proteins

Protein*	Sequence†
Human cytomegalovirus IE2	79 P D P L G R P D E D
HLA-DR molecule	60 V T E L G R P D A E
Poliovirus VP2	70 S T T K E S R G T T
Acetylcholine receptor	176 T V I K E S R G T K
Papilloma virus E2	76 S L H L E S L K D S
Insulin receptor	66 V Y G L E S L K D L
Rabies virus glycoprotein	147 T K E S L V I I S
Insulin receptor	764 N K E S L V I S E
Klebsiella pneumoniae nitrogenase	186 S R Q T D R E D E
HLA-B27 molecule	70 K A Q T D R E D L
Adenovirus 12 E1B	384 L R R G M F R P S Q C N
α-Gliadin	206 L G Q G S F R P S Q Q N
Human immunodeficiency virus p24	160 G V E T T T P S
Human IgG constant region	466 G V E T T T P S
Measles virus P3	13 L E C I R A L K
Corticotropin	18 L E C I R A C K
Measles virus P3	31 E I S D N L G Q E
Myelin basic protein	61 E I S F K L G Q E

Cell 50:819 (1987)

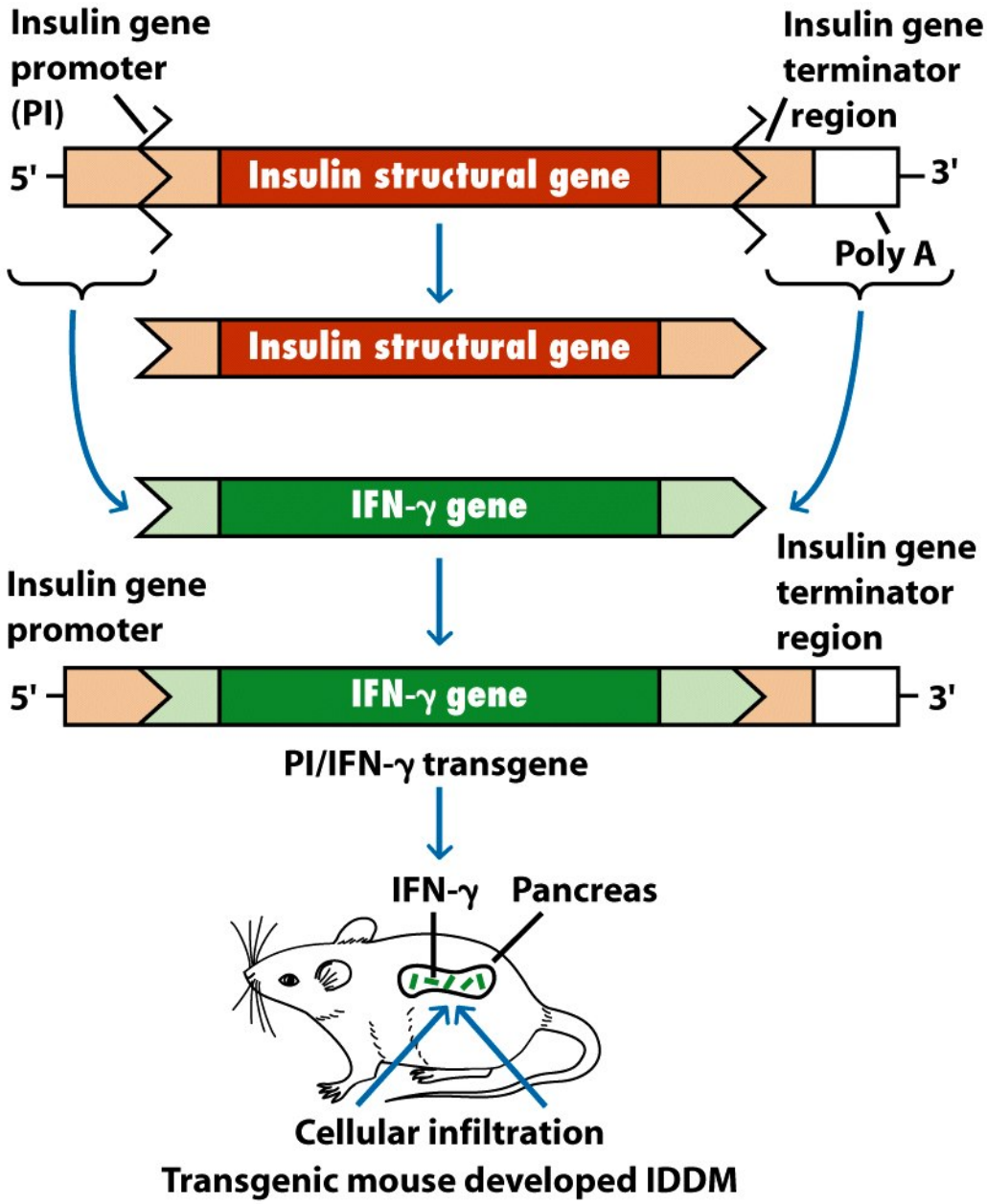
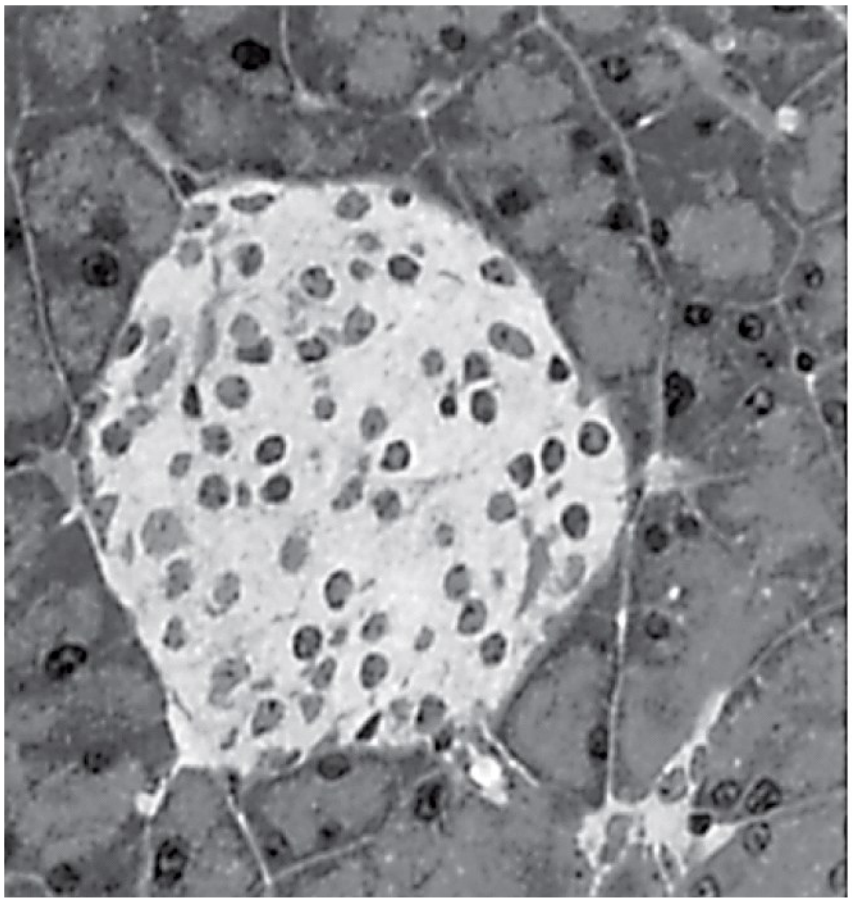


Figure 16-13a
Kuby IMMUNOLOGY, Sixth Edition



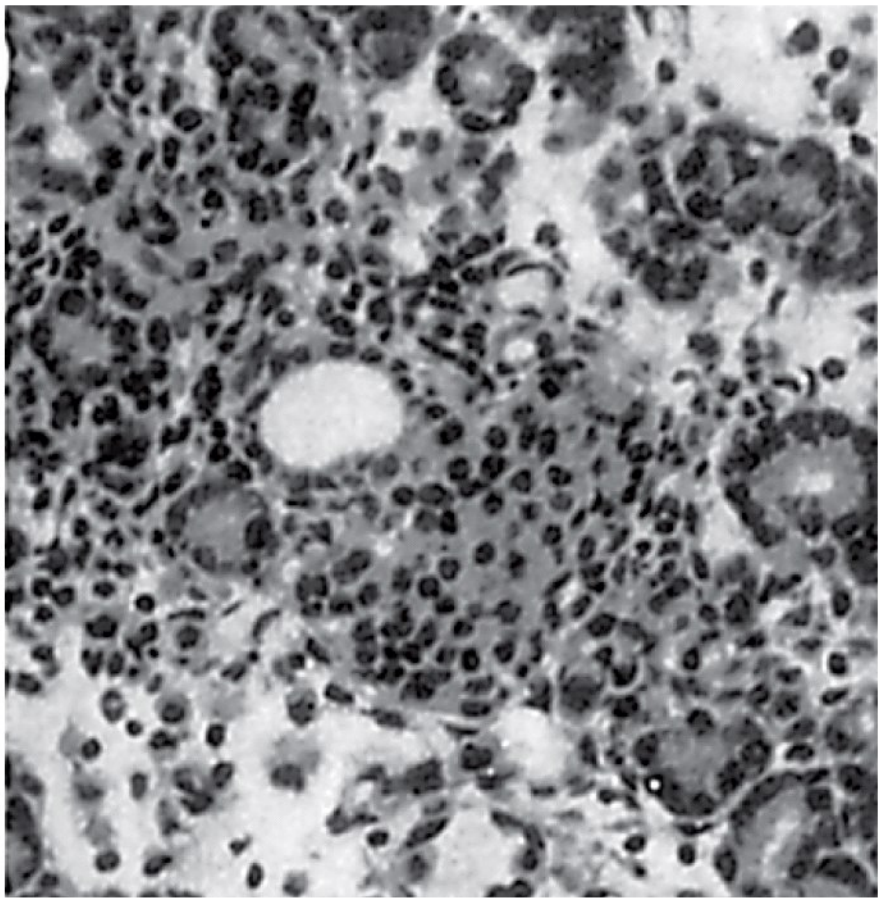


Figure 16-13b
Kuby IMMUNOLOGY, Sixth Edition

Mechanism of Autoimmunity

Failure of Central Tolerance

- **Thymic Selection is Flawed**

Peripheral Tolerance Defective

- **Failure of activation induced Cell death --AICD**

Hyper Immune response

- **Cytokine Imbalance**
- **Abnormal expression of co-stimulatory molecules**

Cross-Reactivity

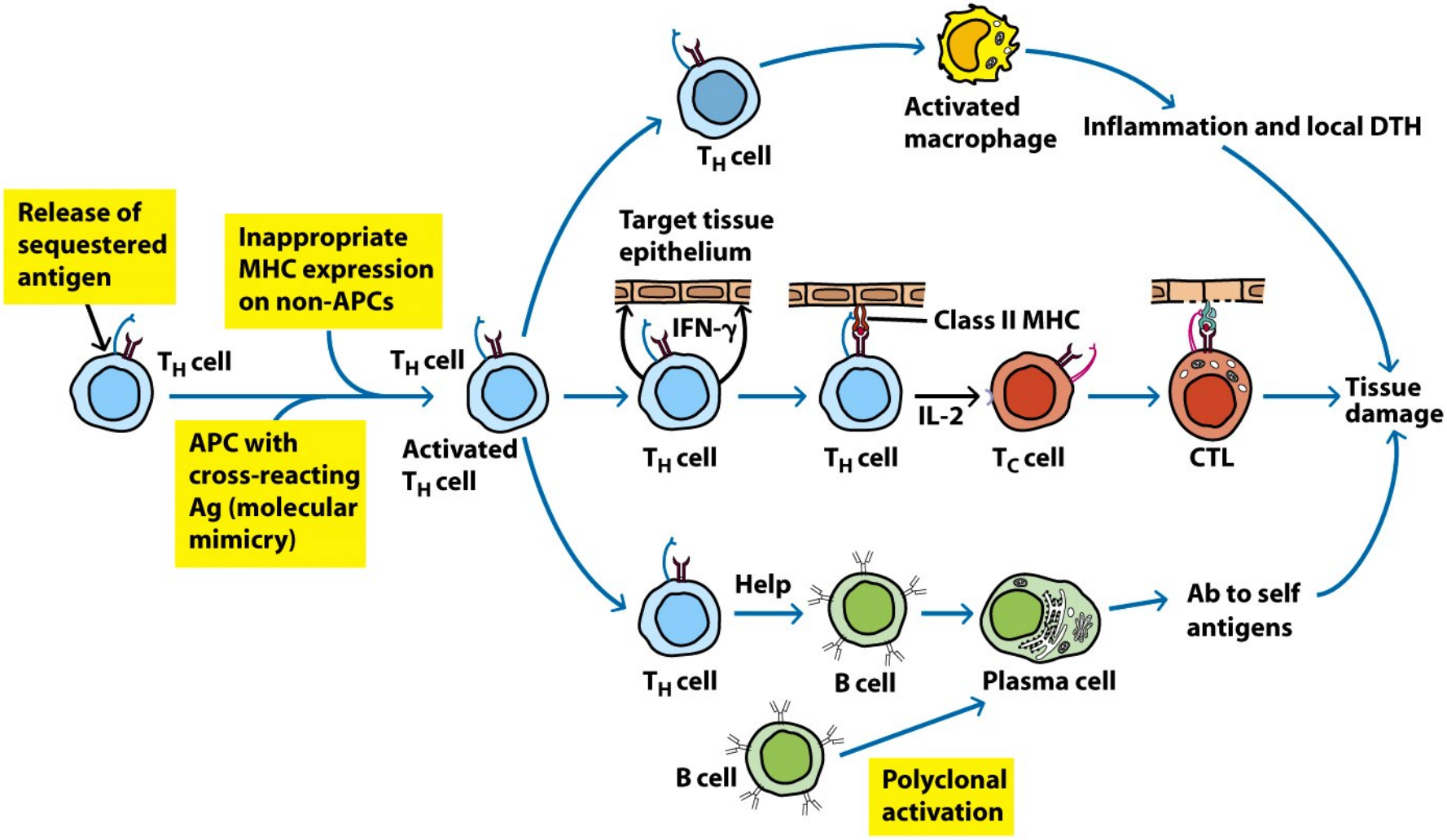
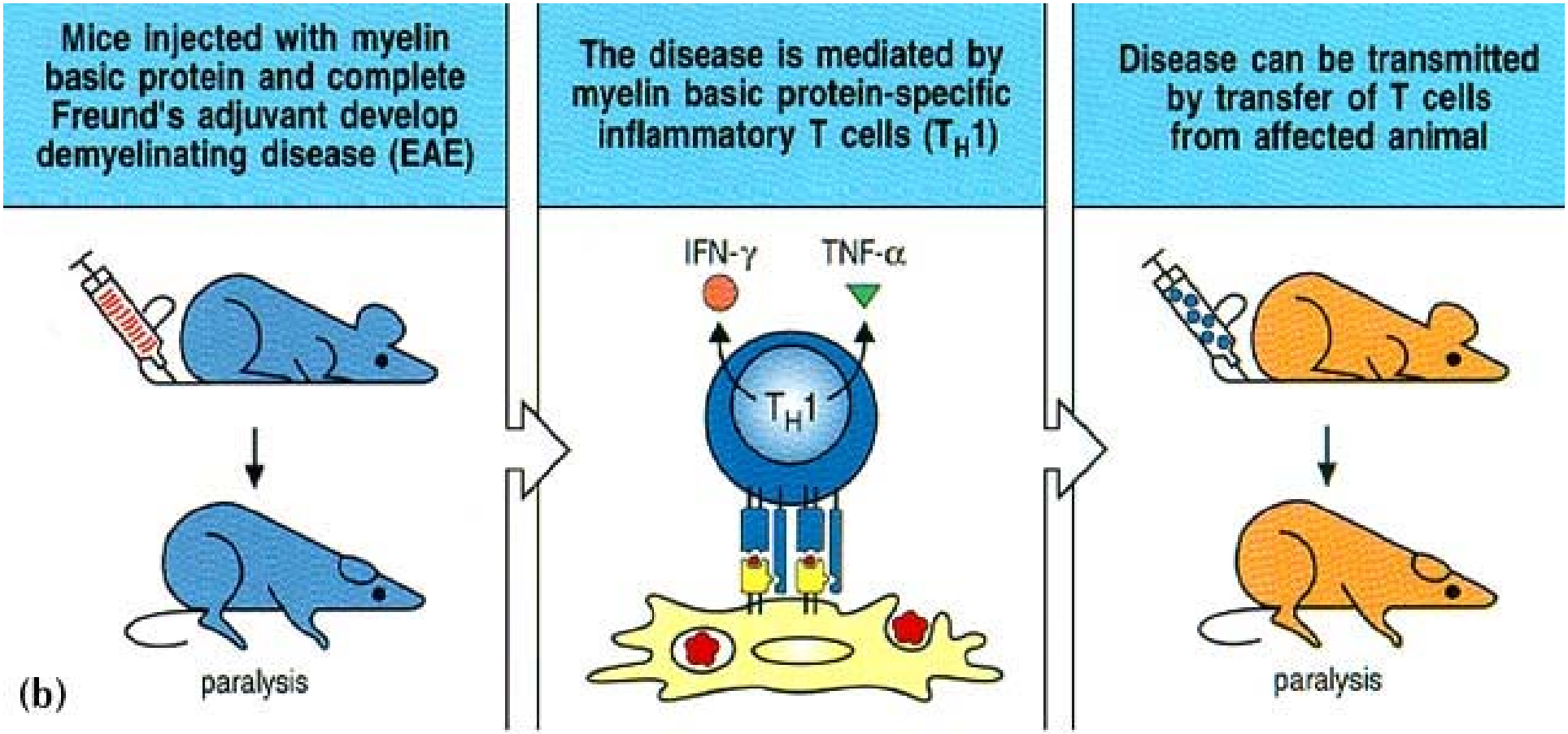


Figure 16-12
Kuby IMMUNOLOGY, Sixth Edition

TABLE 16-2 Experimental animal models of autoimmune diseases

Animal model	Possible human disease counterpart	Inducing antigen	Disease transferred by T cells
SPONTANEOUS AUTOIMMUNE DISEASES			
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 DISEASES*			
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.



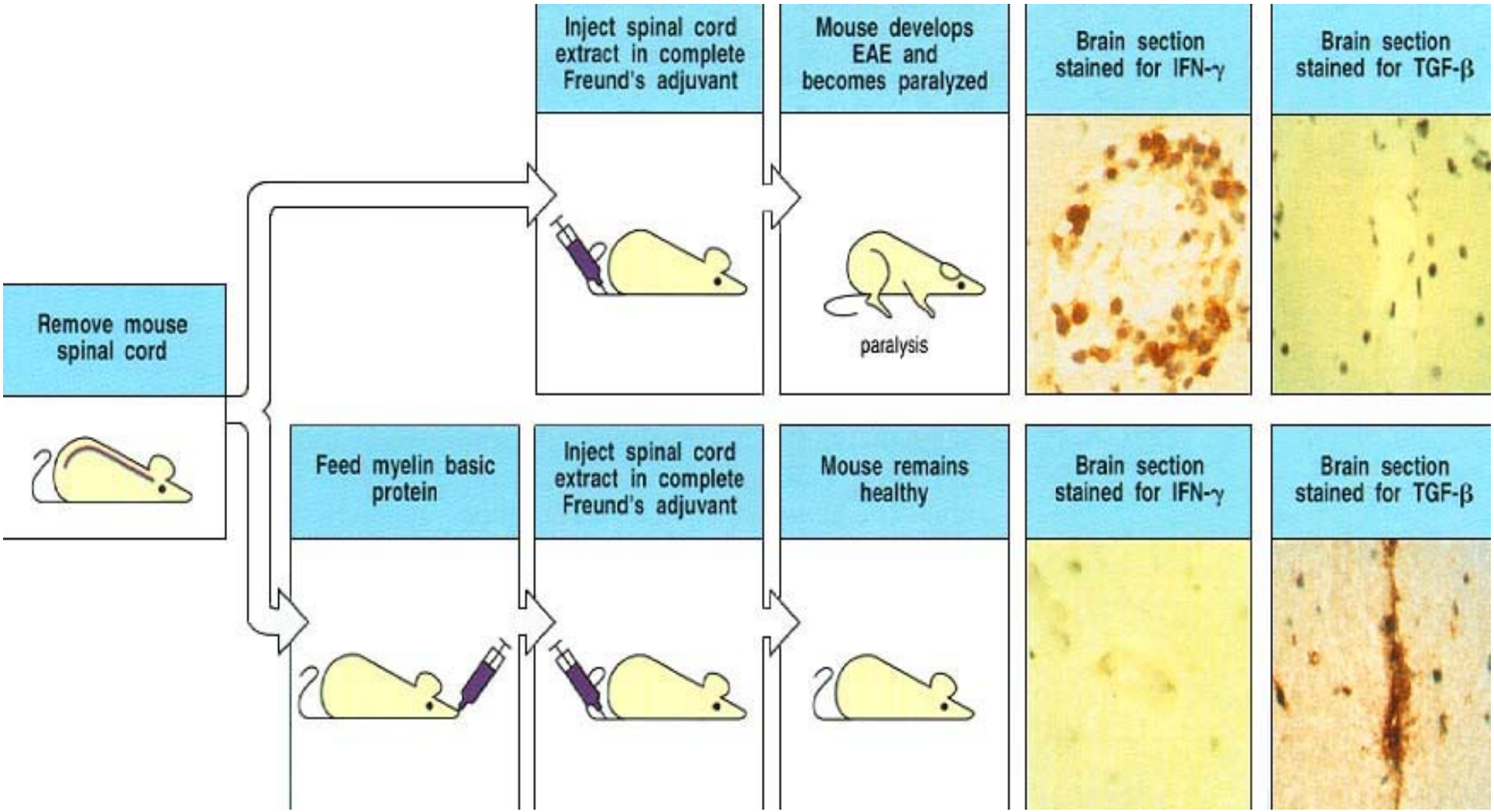
New Therapies

- **Induce Tolerance--oral feeding of self-proteins**

- **Remove T cells--inject TCR peptides use anti-CD4**

- **Decoys (altered peptide) -make analogs of self peptide that bind to MHC Class II with high affinity but do not stimulate T cells**

- **Anti-inflammatory cytokines (anti-TNF)= Engineered EMBREL TNFR/IgG FC - binds TNF and removes it**


Remove mouse spinal cord
Inject spinal cord extract in complete Freund's adjuvant
Mouse develops EAE and becomes paralyzed
paralysis
Brain section stained for IFN-γ
Brain section stained for TGF-β
Feed myelin basic protein
Inject spinal cord extract in complete Freund's adjuvant
Mouse remains healthy
Brain section stained for IFN-γ
Brain section stained for TGF-β

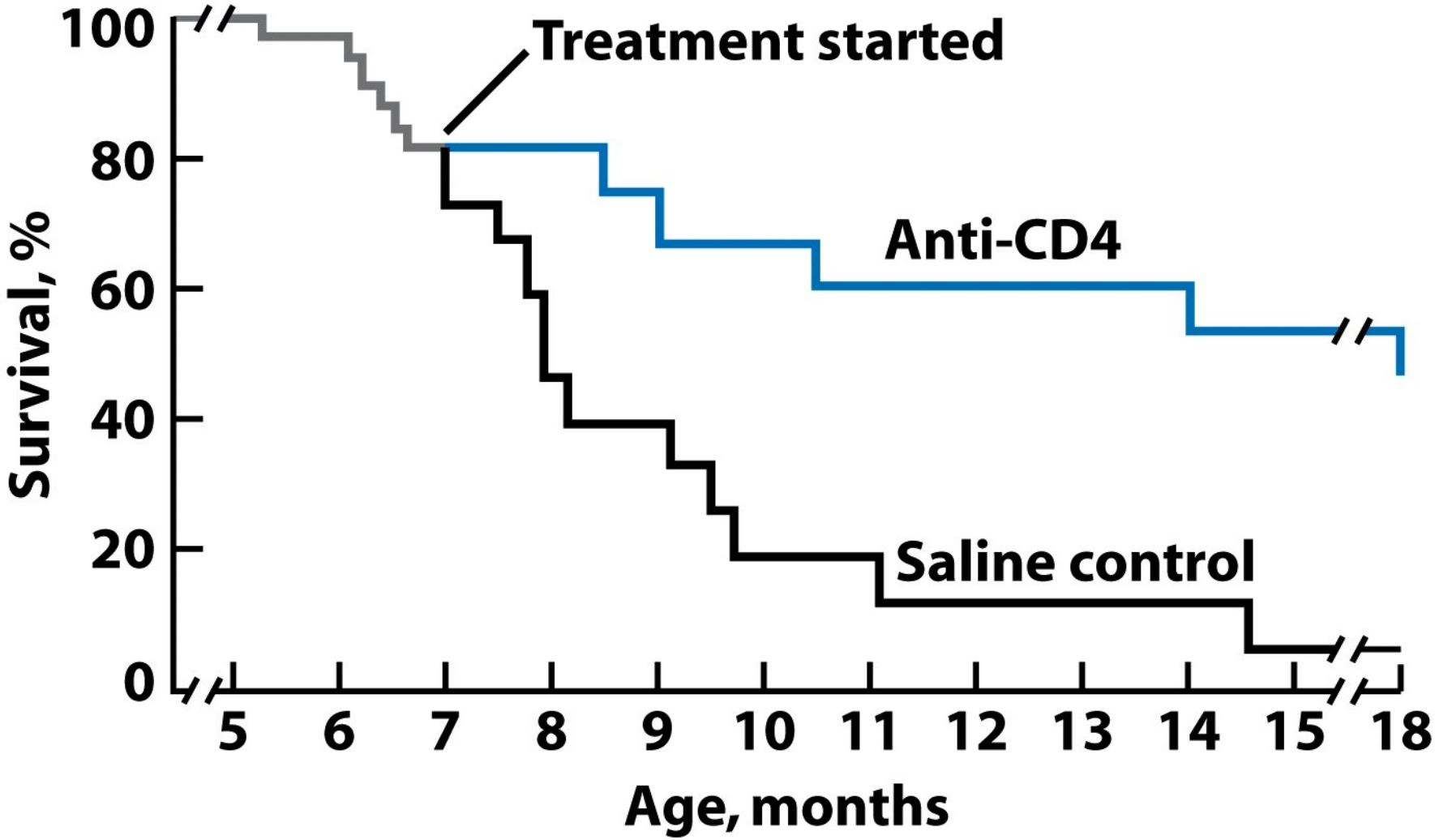


Figure 16-14
Kuby IMMUNOLOGY, Sixth Edition

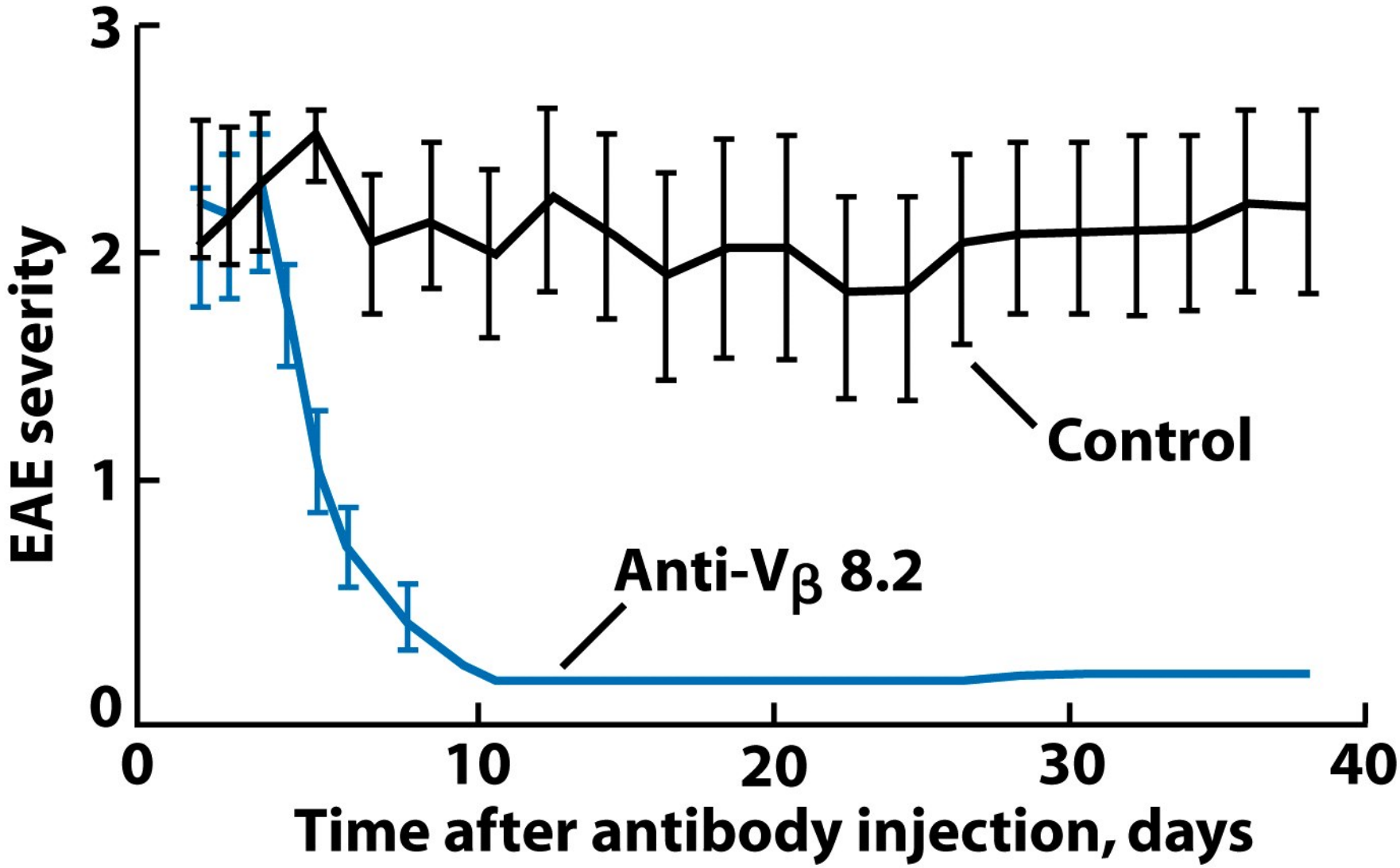
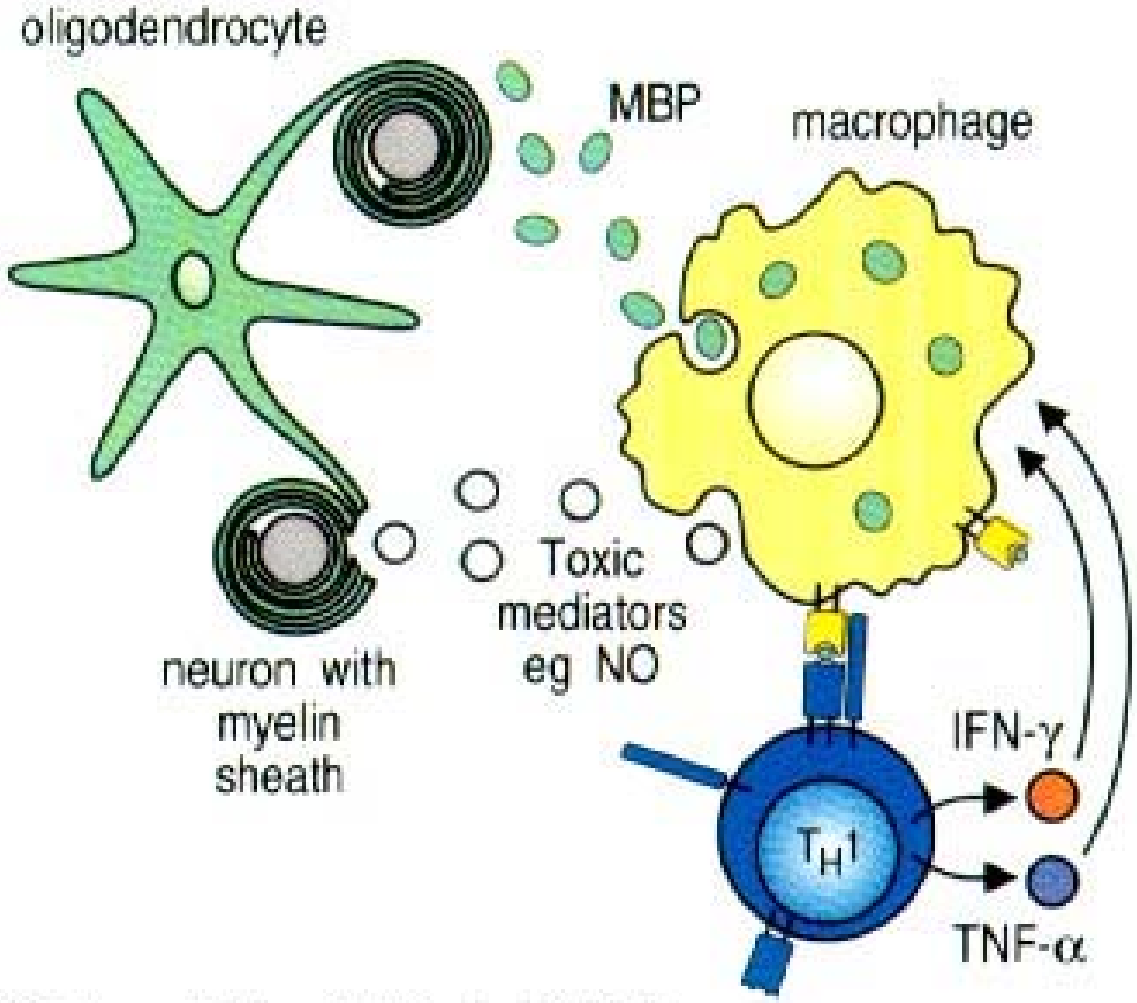


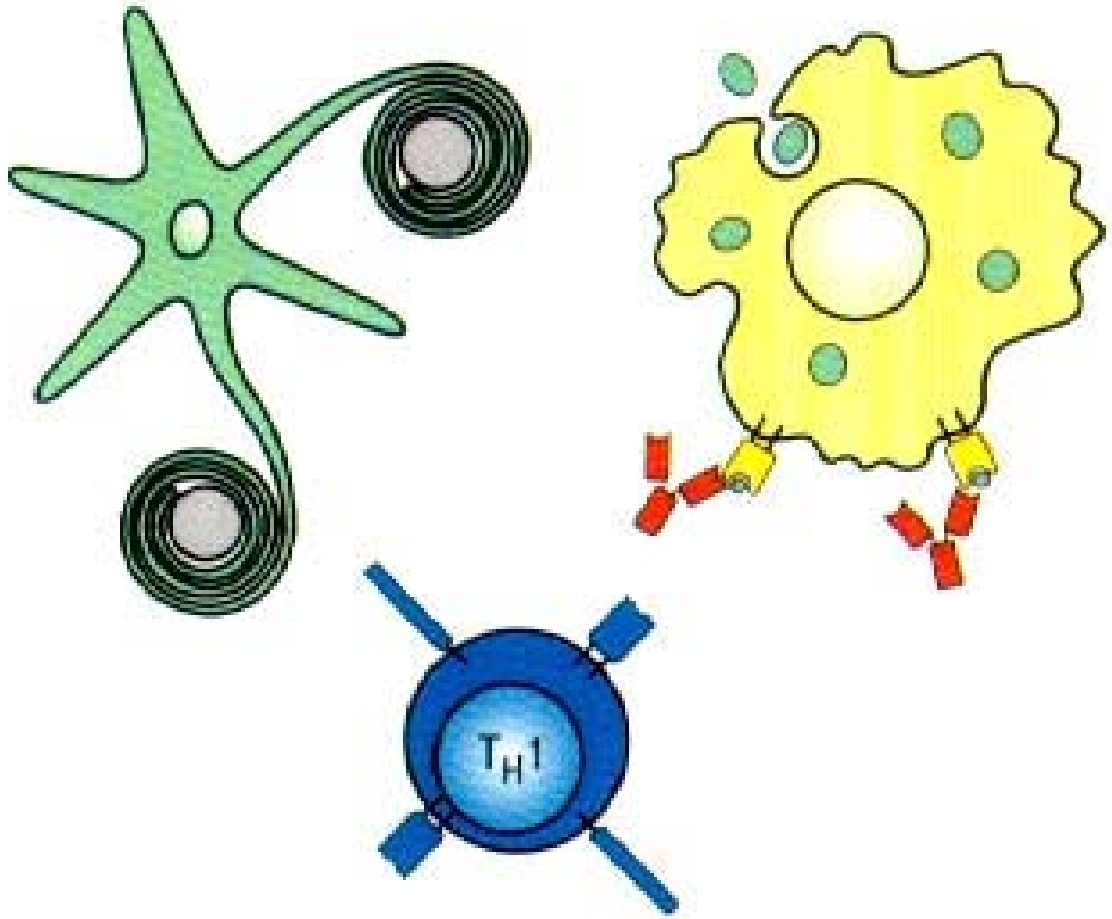
Figure 16-15
Kuby IMMUNOLOGY, Sixth Edition

(a) **Activation of MBP-specific T_H1 cells activates macrophages. Activated macrophages damage oligodendrocytes, causing demyelination of neurons**



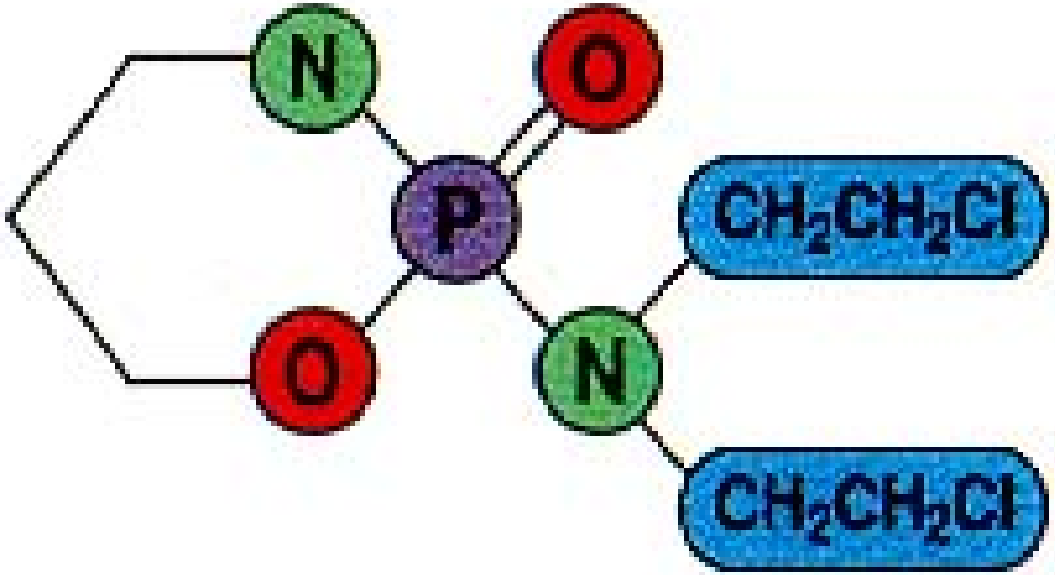
(b)

Antibodies to MHC class II molecules block T-cell activation and inhibit demyelination



(b) Immunosuppressive drugs kill dividing cells or inhibit inflammation

Cyclophosphamide



(c) Immunosuppressive drugs kill dividing cells or inhibit inflammation

Prednisone