6 Oct 2023,
BT 304
Lecture 24

"Horror Autotoxicus"

- Literally, the **horror** of self-toxicity.
- A term coined by the great German bacteriologist and immunologist **Paul Ehrlich** (1854-1915) to describe the body's innate aversion to immunological self-destruction.
- Later it was accepted that: Failure of host's humoral and cellular immune systems to distinguish self from non-self
  - Autoimmunity
  - Can result in tissue and organ damage, can be fatal
- Autoimmunity results from a failure of the mechanisms of self-tolerance in T or B cells, which may lead to an imbalance between lymphocyte activation and control mechanisms.

TABLE 16-1 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_H1 cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_H1 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 DISEASES	
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_H1 cells and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjögren's syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes

Table 16-1
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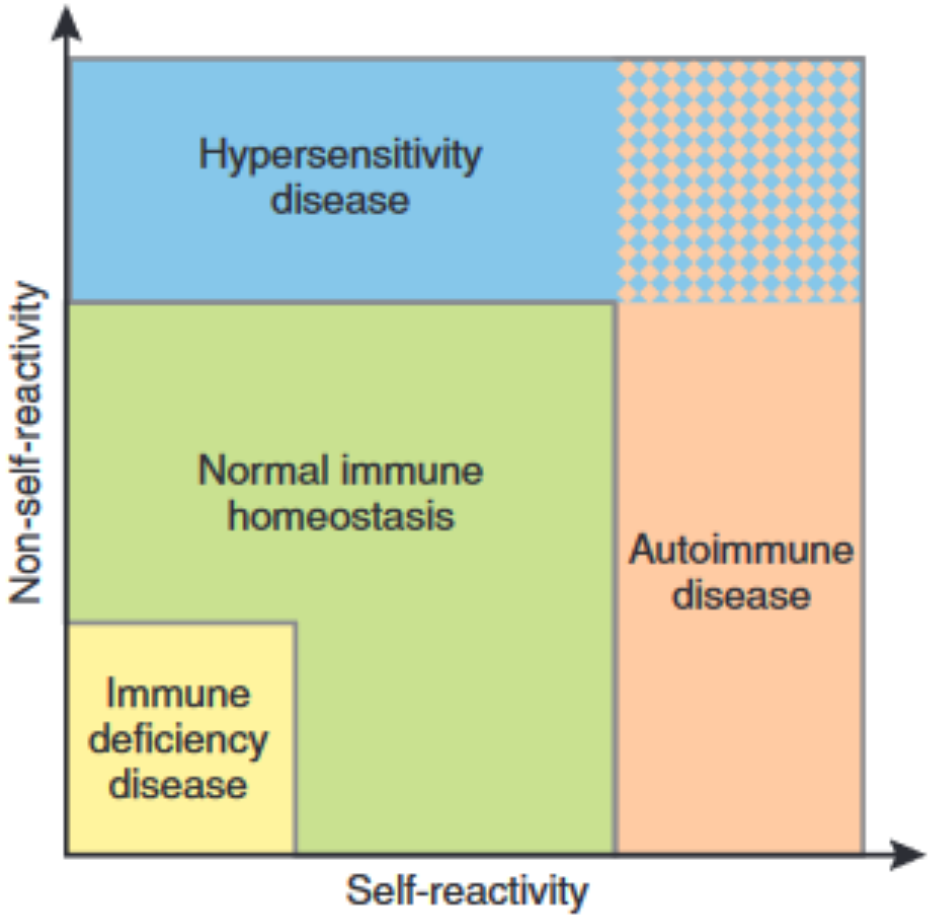
- Normal immune homeostasis involves a balance between T cells, B cells, and antibodies that are reactive with self, non-self, or both.

- Disease results when there is an imbalance of immune responsivity with either too little immune defense against foreign pathogens (immune deficiency disease), more immune response to non-self antigens than is beneficial (allergic or hypersensitivity disease), or more immune response to self antigens than is beneficial (autoimmune disease).



Tolerance

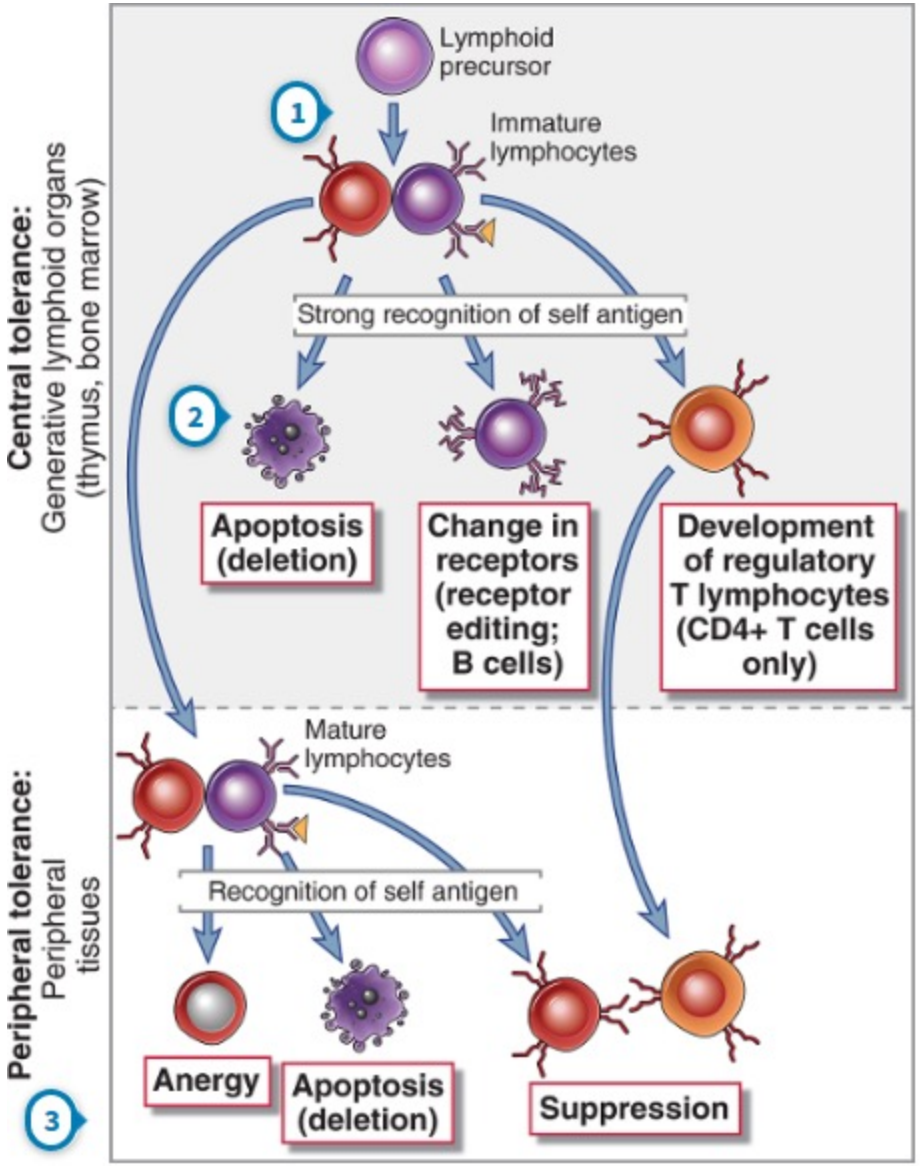
- **Immune tolerance**, or **immunological tolerance**, or **immunotolerance**, is a state of unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response in a given organism.

- # of mechanisms are in place to protect individual from self-reactive lymphocytes
  - Central tolerance – deleting T or B clones before maturity if they have receptors that recognize self-antigens with great affinity
  - Peripheral tolerance – kills lymphocytes in secondary lymphoid tissue
    - Also, life span of lymphocytes regulated by apoptosis
    - *central tolerance is not perfect, and it cannot account for unresponsiveness to antigens that are expressed only in peripheral tissues.*

1. Immature lymphocytes specific for self antigens may encounter these antigens in the generative lymphoid organs.

2. Self-reactive immature cells are deleted, change their specificity (B cells only), or (in the case of $CD4^+$ T cells) develop into regulatory lymphocytes (central tolerance).

3. Some self-reactive lymphocytes may mature and enter peripheral tissues and may be inactivated or deleted by encounter with self antigens in these tissues, or are suppressed by the regulatory T cells (peripheral tolerance).



Central tolerance

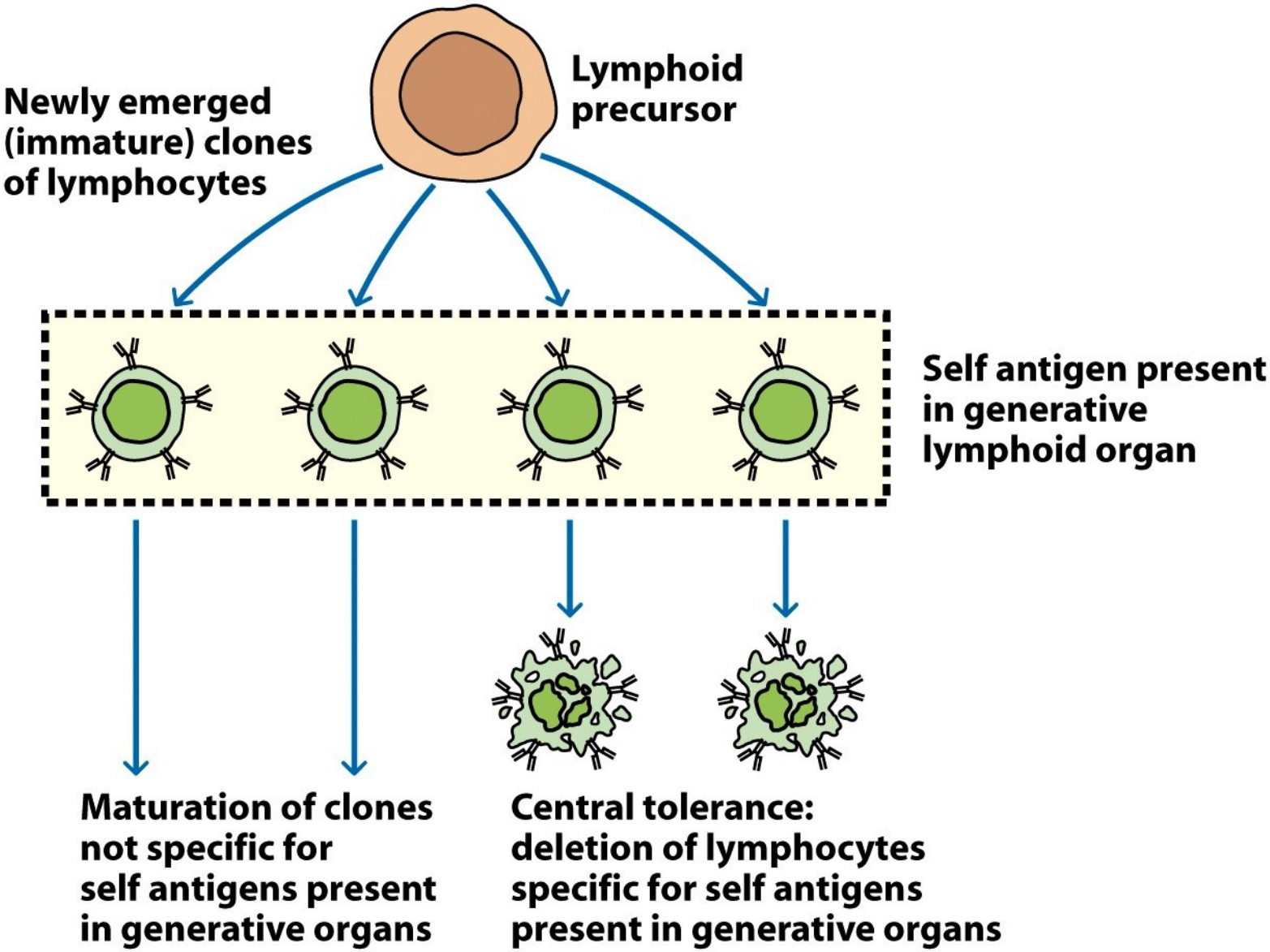


Figure 16-1a
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Peripheral tolerance

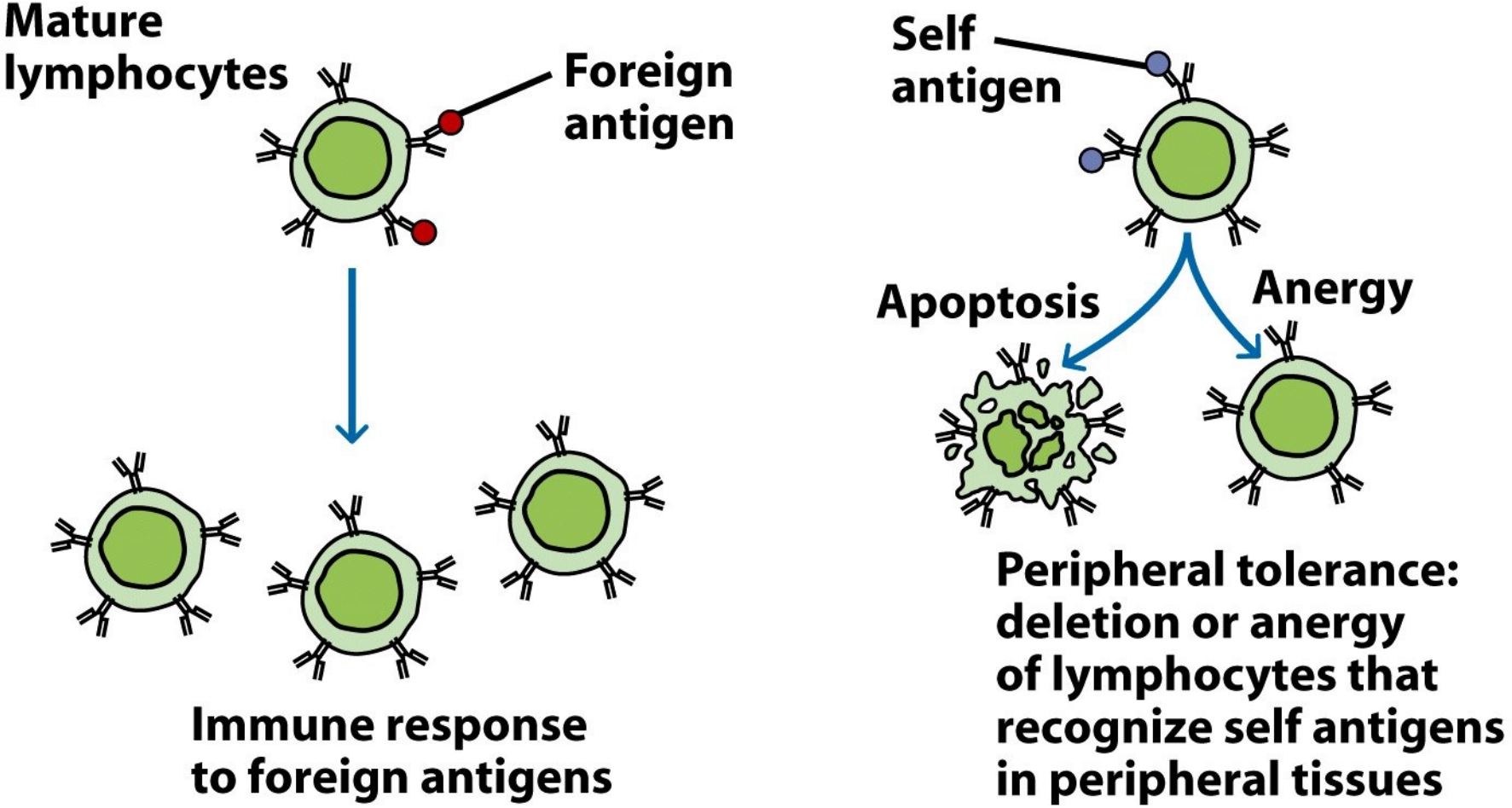

Figure 16-1b
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- Some antigens can produce tolerance
  - Termed tolerogens rather than immunogens
    - High dosages of antigen
    - Persistence of antigen in host
    - IV (intravenous) or oral introduction
    - Absence of adjuvants
    - Low levels of costimulators
      - CD28 will bind to B7 and provide activating signals; however, it was discovered that another receptor, CTLA-4 will bind to B7 and inhibit

- Anergy
  - Unresponsiveness to antigenic stimulus

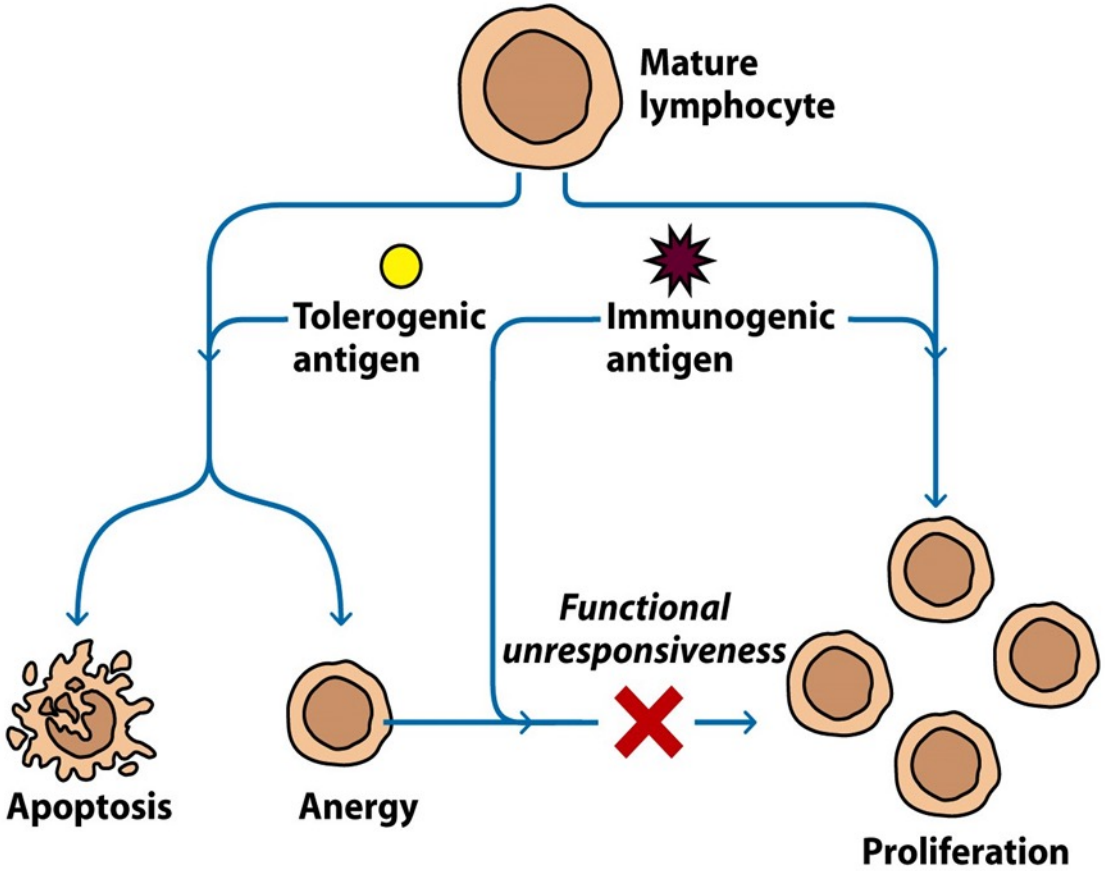

Figure 16-2
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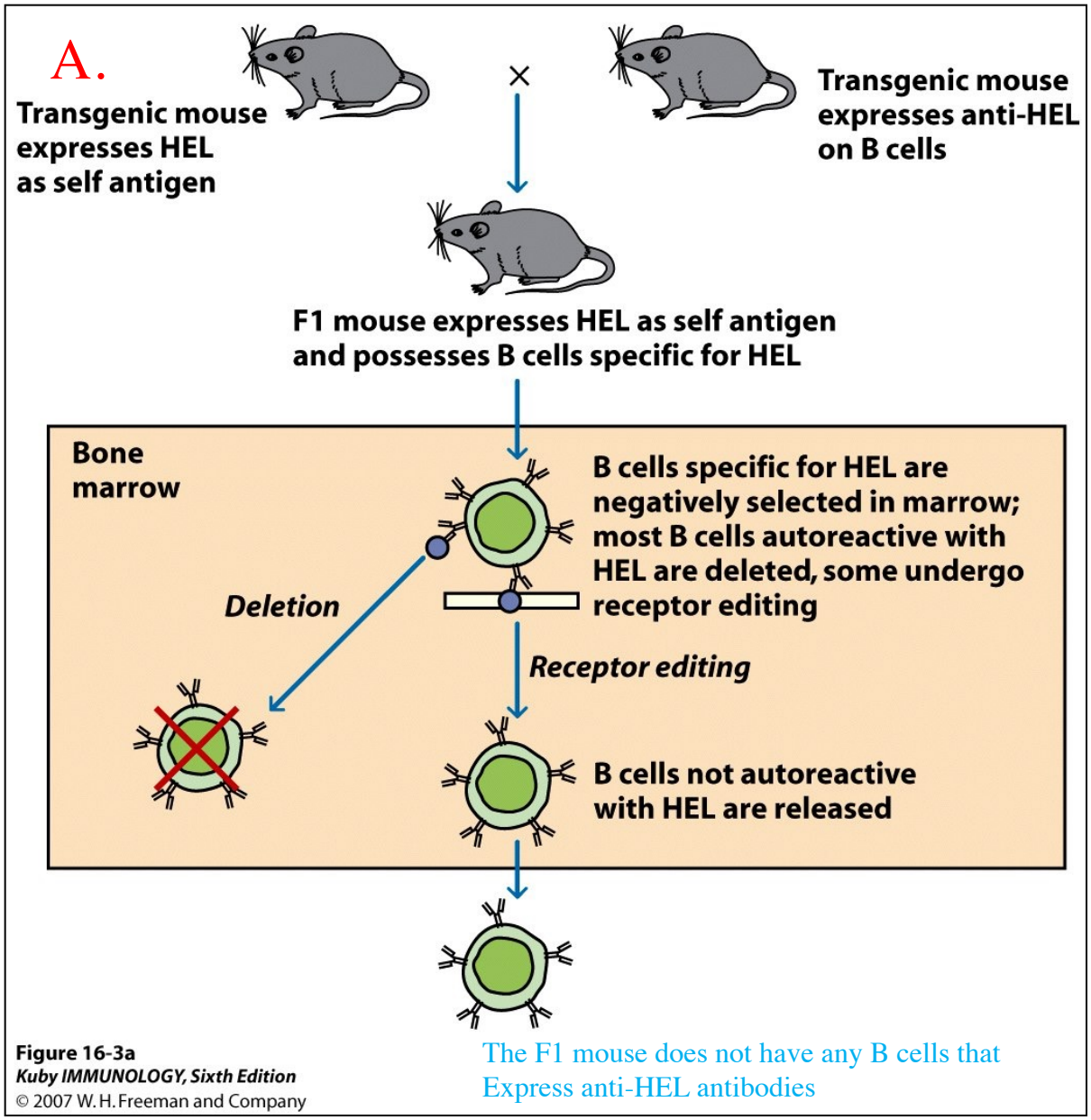
Experimental evidence for central and peripheral tolerance

A. Mouse experiment demonstrating existence of central tolerance



The F1 mouse does not have any B cells that Express anti-HEL antibodies