

GUYTON AND HALL
TEXTBOOK OF **MEDICAL PHYSIOLOGY**
THIRTEENTH EDITION



Resistance of the Body to Infection:
II. Immunity and Allergy; Innate Immunity

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Immunity

- non-specific* *We are born with innate immunity against certain pathogens, especially those that infect animals (and vice versa for the animals)*
- **Innate** - inborn ability to resist damaging organisms and toxins: skin, gastric acids, tissue neutrophils and macrophages, complement, *e.g. Enzymes found in the lysosomes* microbicidal and lytic chemicals in blood and blood cells

- Performed by the lymphocytes*
- **Acquired** = specific
 - Developed after the organism enters the body.* **humoral** → *B cells* circulating antibodies → *Immunoglobulins*
 - cellular** → *T cells* activated cells

Acquired Immunity

→ A must-have
(Its absence at birth leads to death)
Dysfunction

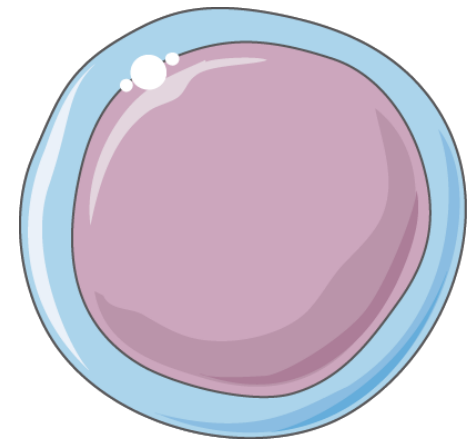
- **Antibodies or activated cells** that specifically **target and destroy invading organisms and toxins**
- **Powerful: can neutralize 100,000 x lethal dose of some toxins** *eg. Botulinum and Tetanus toxins*
- **Two types of acquired immunity:**
 - **Humoral (B cell)**
 - **Cell-mediated (T cell)**

Antigen

- A substance that can elicit an immune response
- Unique to each invading organism
- Usually proteins or large polysaccharides
- Most are large (MW > 8,000) and have recurring molecular groups on their surfaces
 - 1. Easy to recognize
 - 2. Highly specific
- The molecular structures that are specifically recognized in acquired immunity are called “epitopes”
 - Unique like a barcode

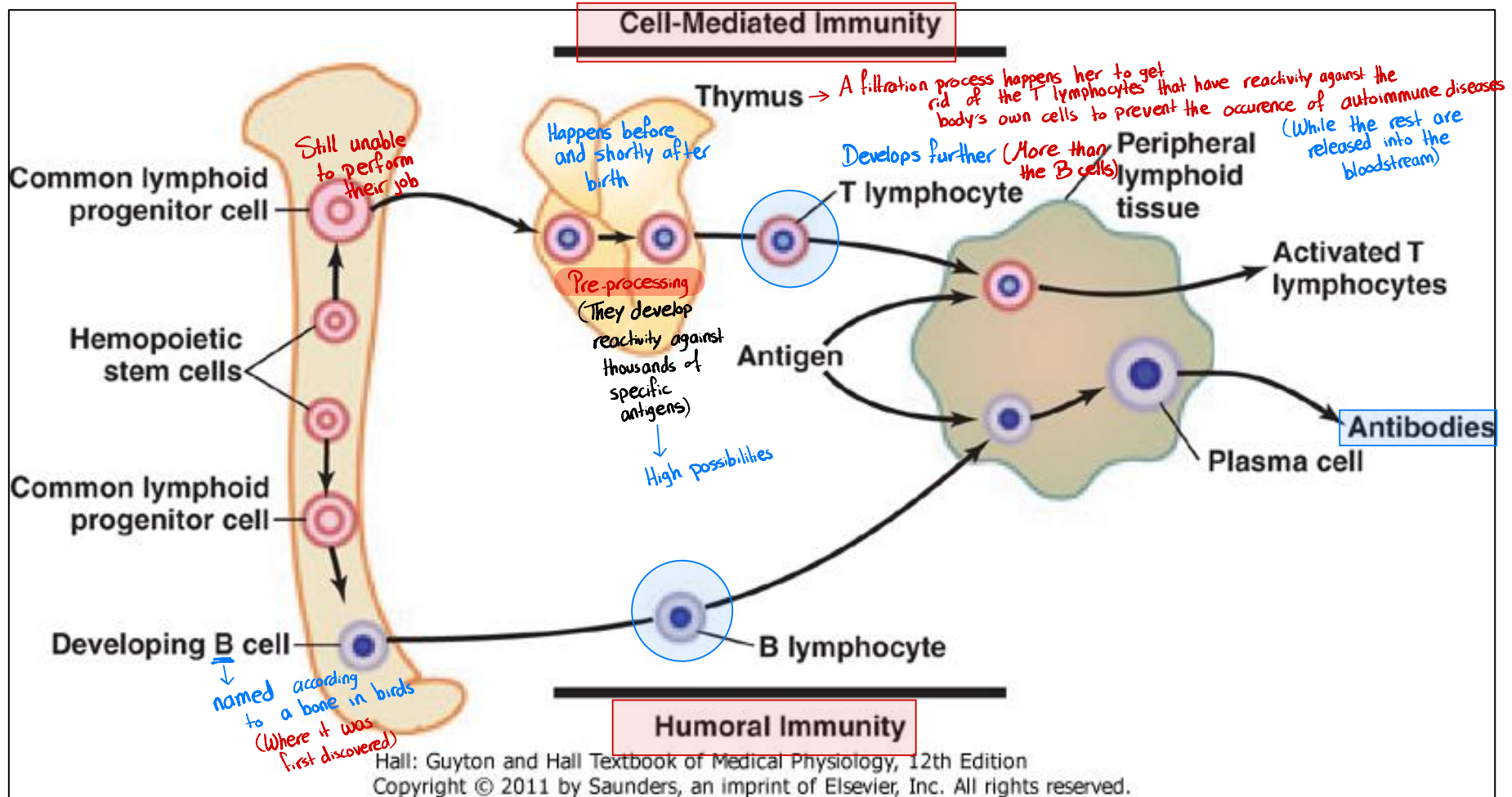
Main player in the acquired immunity

Lymphocytes



- **Mediate acquired immunity**
- **Develop in lymphoid tissues** → *Its origin differs at different pregnancy stage and after birth*
 - **Tonsils / adenoids, Peyer's patches (GI), lymph nodes, spleen, thymus, marrow**
- **Are strategically positioned**

Two types of lymphocytes



Maturation of T cells in the Thymus

Rapid expansion

Each clone is specific for a single antigen

Self-reactive clones are deleted (up to 90%) → Because it is a random process

Migrate to peripheral lymphoid organs

Much of the above occurs just before and shortly after birth

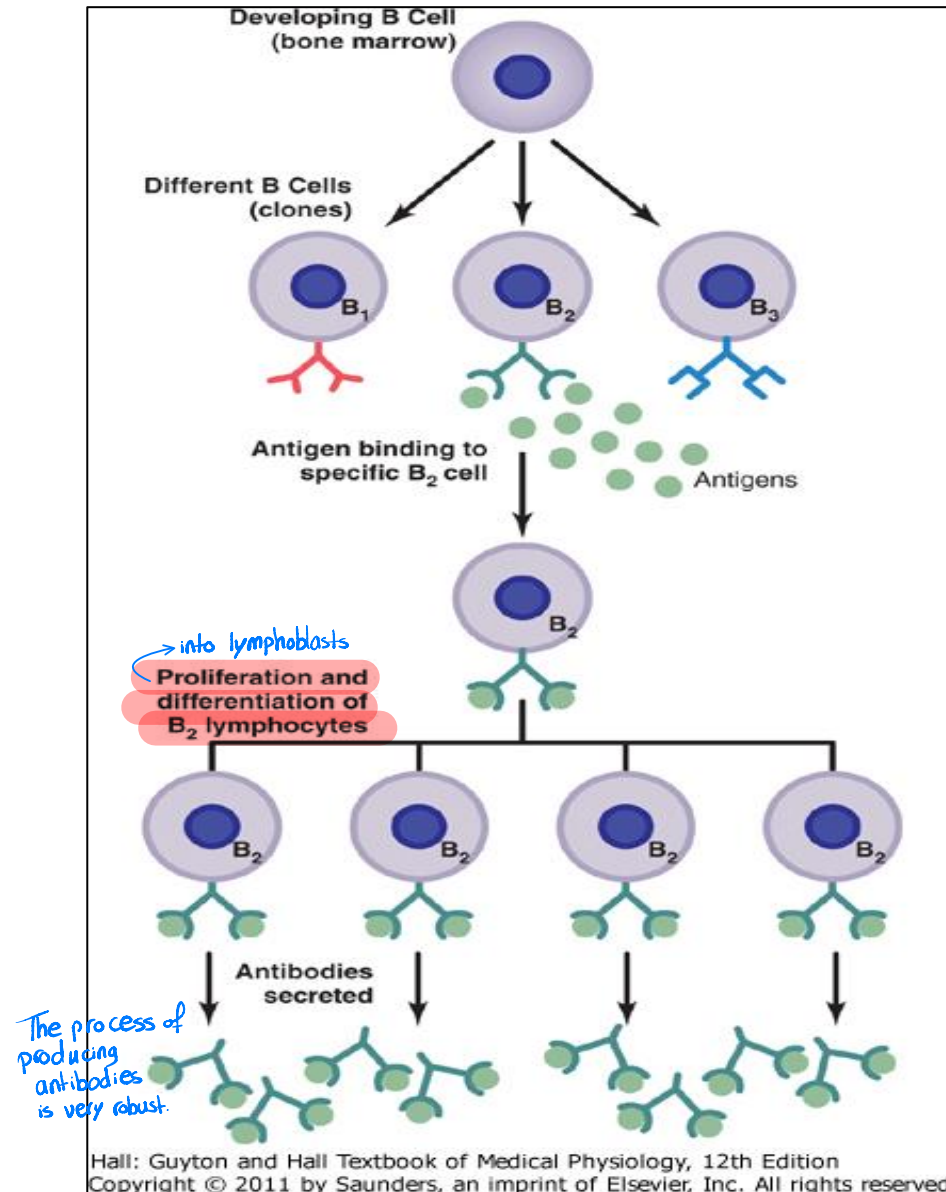
If we removed a baby's thymus shortly after birth, they won't develop acquired immunity (X transplant rejection) → A year later
↓
Removed
Acquired immunity ✓

B cell Development



- Initial growth and differentiation in the liver (fetal) and bone marrow (after birth)
- Migrate to the peripheral lymphoid organs
- Each clone is specific for a single antigen
- Clonal development provides almost limitless antibody specificity
- Secreted antibodies destroy or neutralize molecules or organisms bearing their cognate antigen

B cell proliferation in response to antigen



Immunologic Specificity

- Each B or T cell clone is specific for a single epitope of a single antigen Cross reactivity might occur (Where a single antigen activates more than one type of B cells)
- The genes for B cell receptors (immuno-globulins) and T cell receptors have hundreds of “not a whole gene gene segments” that are used in varying combinations
- Permutations (arrangements) of these cassettes allow specificity for millions of distinct epitopes

Lymphocyte Activation

Help T and B cells recognize antigens.

Macrophages in lymphoid organs...

- ingest antigen and present antigenic peptides to “helper” T cells → Responsible for stimulating all types of immune cells.
- Secrete IL-1, other cytokines that promote lymphocyte growth and differentiation

Strengthens the immune response

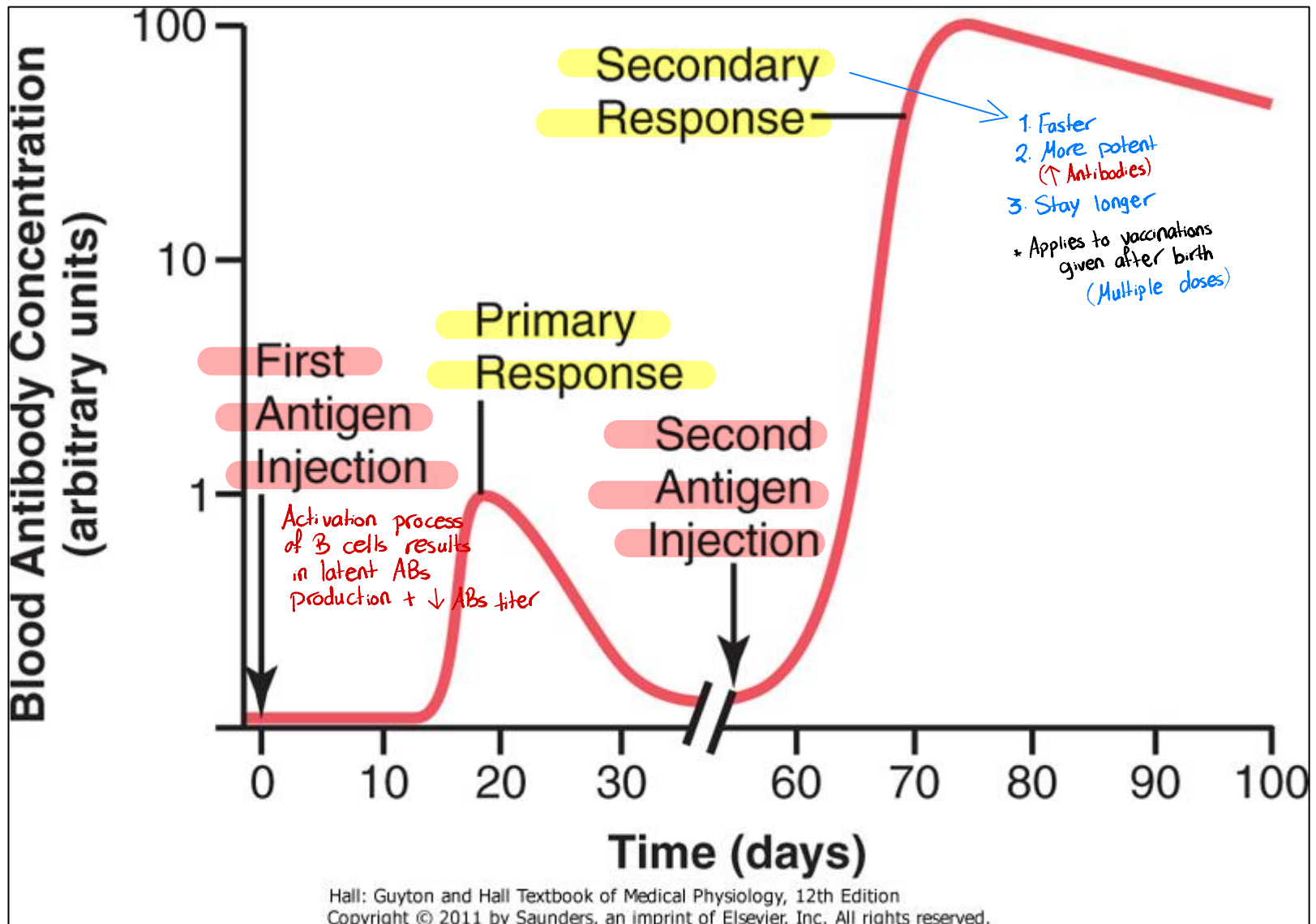
Helper T cells produce additional cytokines that stimulate B and T cell proliferation and differentiation

Both B and T cells require antigenic stimulation to proliferate

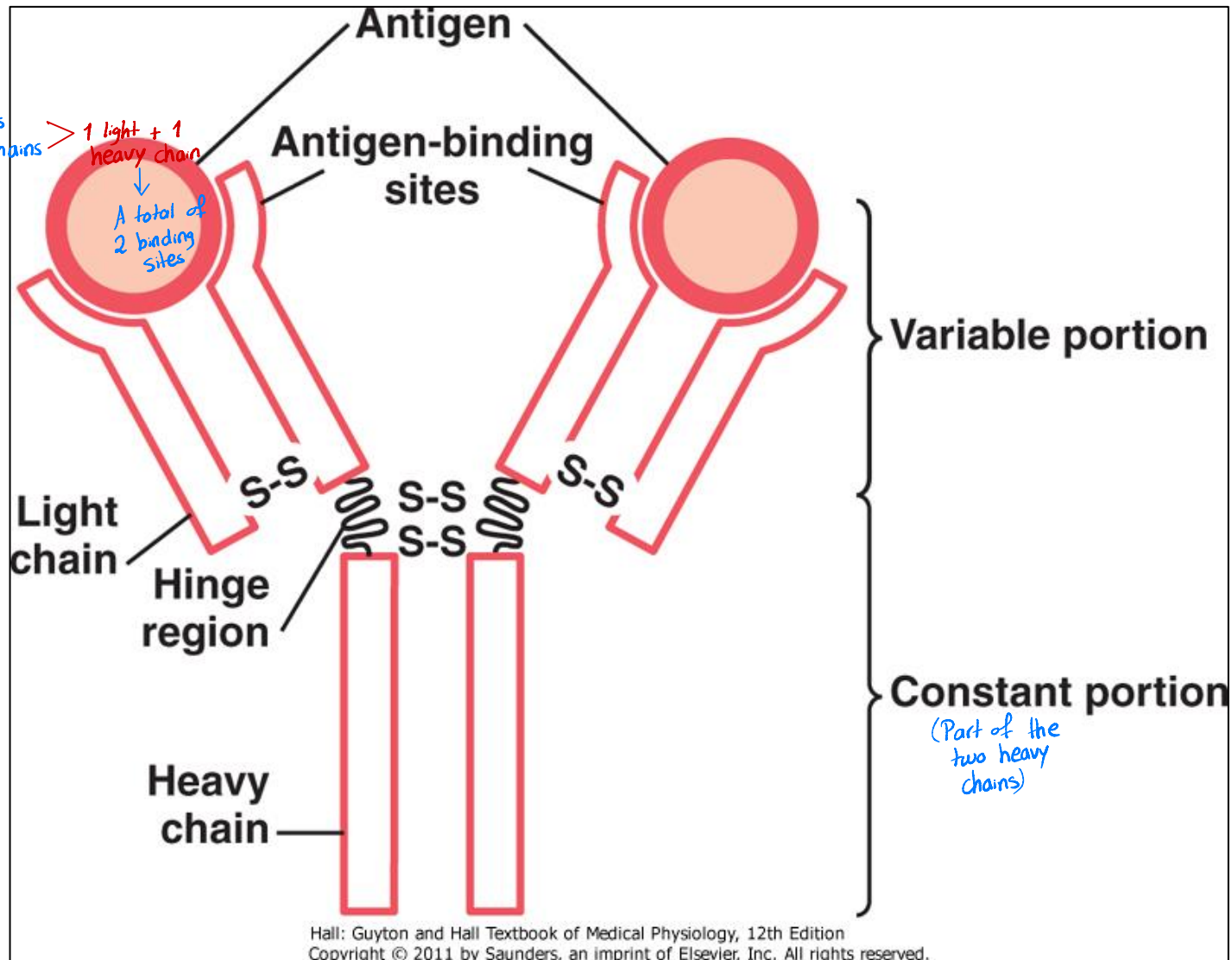
Antibody Production

- B cells bind intact antigen
- T cells bind ^{ONLY} presented ^{i.e. found on APCs} antigenic peptides
- B cells proliferate (with T cell help), developing lymphoblasts and plasmablasts
Without helper T cells, the immune response won't be as strong
- Up to 500 antigen-specific progeny in 4 days, each producing as many as 2,000 Ig molecules/sec
- Can persist for many weeks, if antigenic stimulation persists

Memory B cells and secondary responses



Structure of Immunoglobulins



Antibody Specificity

- Each antibody has a steric configuration specific to its antigen *The longer the binding → the stronger the activation and destruction are.*
- Multiple prosthetic groups of each antigen interact with complementary structures of the antibody, through...
 - hydrophobic bonding
 - hydrogen bonding
 - ionic interactions
 - van der Waals forces
- Antibodies are at least bivalent

Antibody classes (isotypes)

- **IgM (earliest produced, five pairs of heavy chains and light chains)** → *important in the primary response*
 - **IgG (75% of all immunoglobulins)**
 - **IgA**
 - **IgD**
 - **IgE (critically involved in allergic reactions)**
- **Immunoglobulins make up about 20% of all plasma proteins**

Antibodies: mechanisms of action

Agglutination

Each AB binds two antigens
↓
Clumping
↓
Agglutination

Precipitation

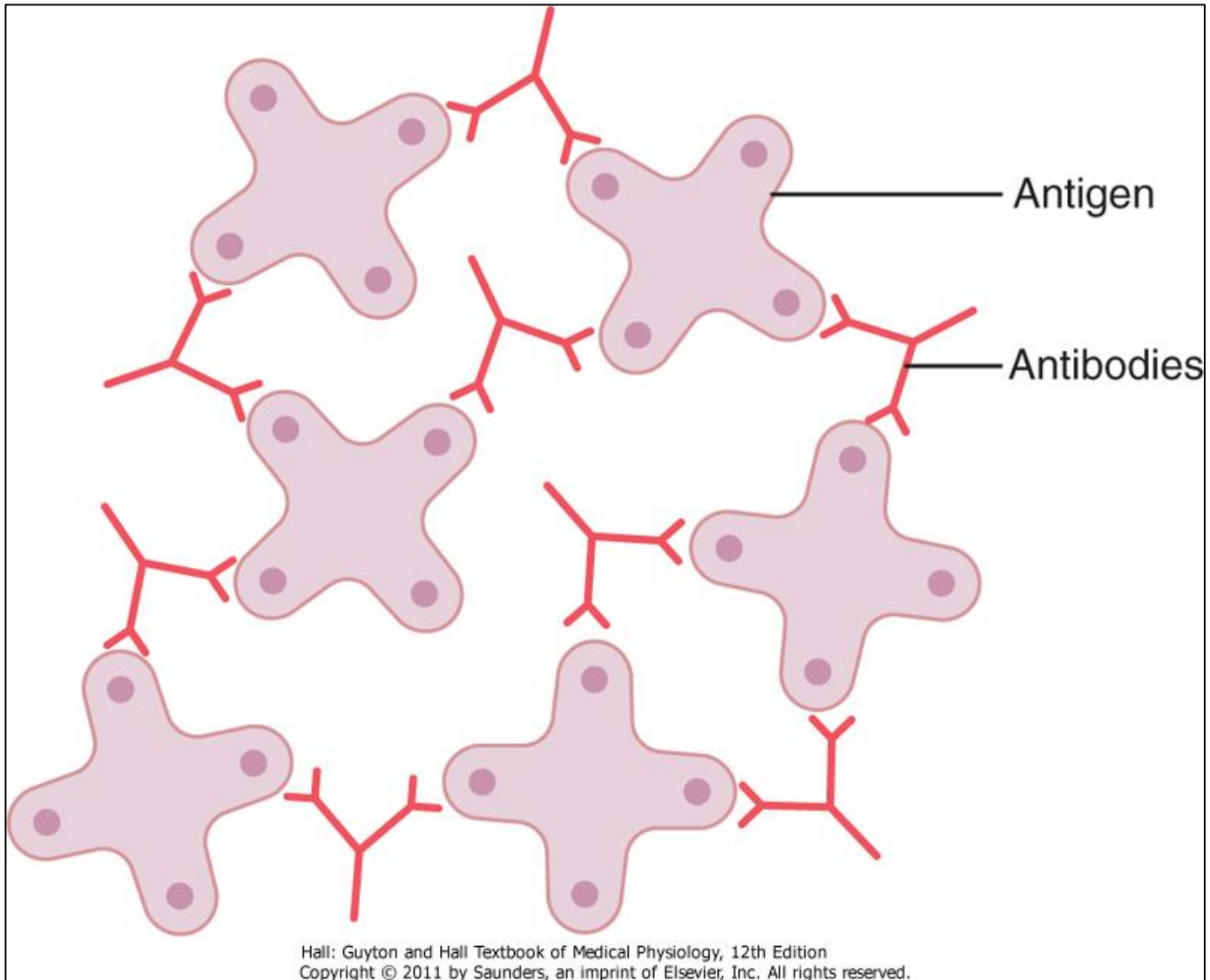
Neutralization → of ABs to block the binding toxins from harming the body.

Lysis

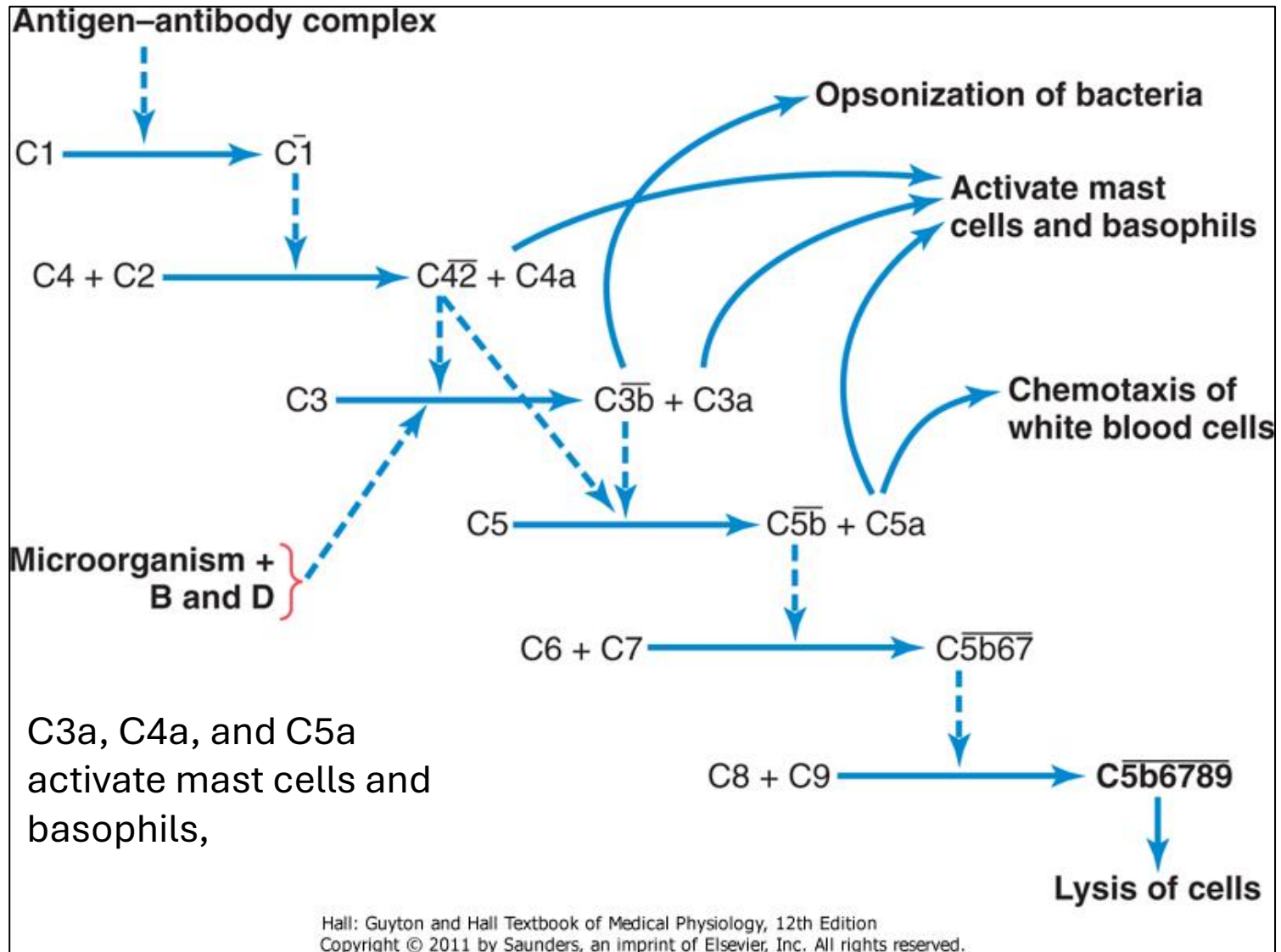
Complement activation

→ Cascade of activation
↙ ↘
Opsonization Chemotaxis
 Activation of other cells eg. mast cells and basophils → Robust inflammatory reaction

Agglutination



The Complement System



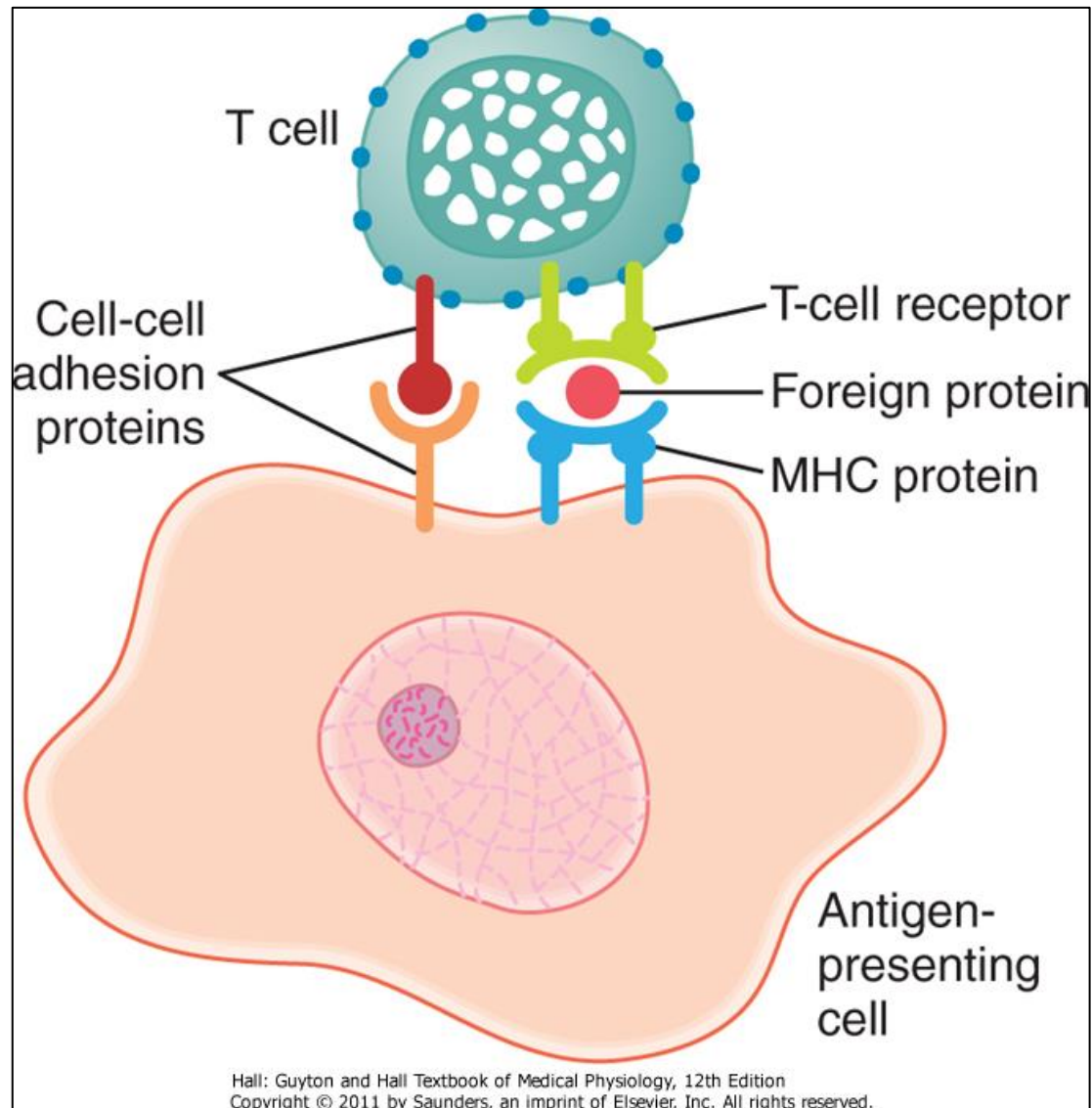
T cell activation

- **Binds to cognate antigen presented by antigen-presenting cell**
- **Rapid expansion of T helper (CD4) cells**
- **T helper cells produce cytokines**
- **Drives expansion of both T helper (CD4) and cytotoxic (CD8) T cells**
- **Both types of cells also generate clonal memory T cells**

MHC Proteins

- **B cell surface and secreted antibodies recognize intact antigen**
- **T cells only recognize antigen fragments that are presented by MHC molecules of antigen presenting cells...**
 - **macrophages**
 - **B lymphocytes**
 - **dendritic cells**

Antigen Presentation



MHC Molecules

- **Encoded by the Major Histocompatibility Complex**
 - **MHC I – Present to cytotoxic T cells (CD8)**
 - **MHC II – Present to helper T cells (CD4)**
- **Antigen in the context of MHC is recognized by as many as 100,000 T cell receptors per cell**

Helper (CD4) T cells

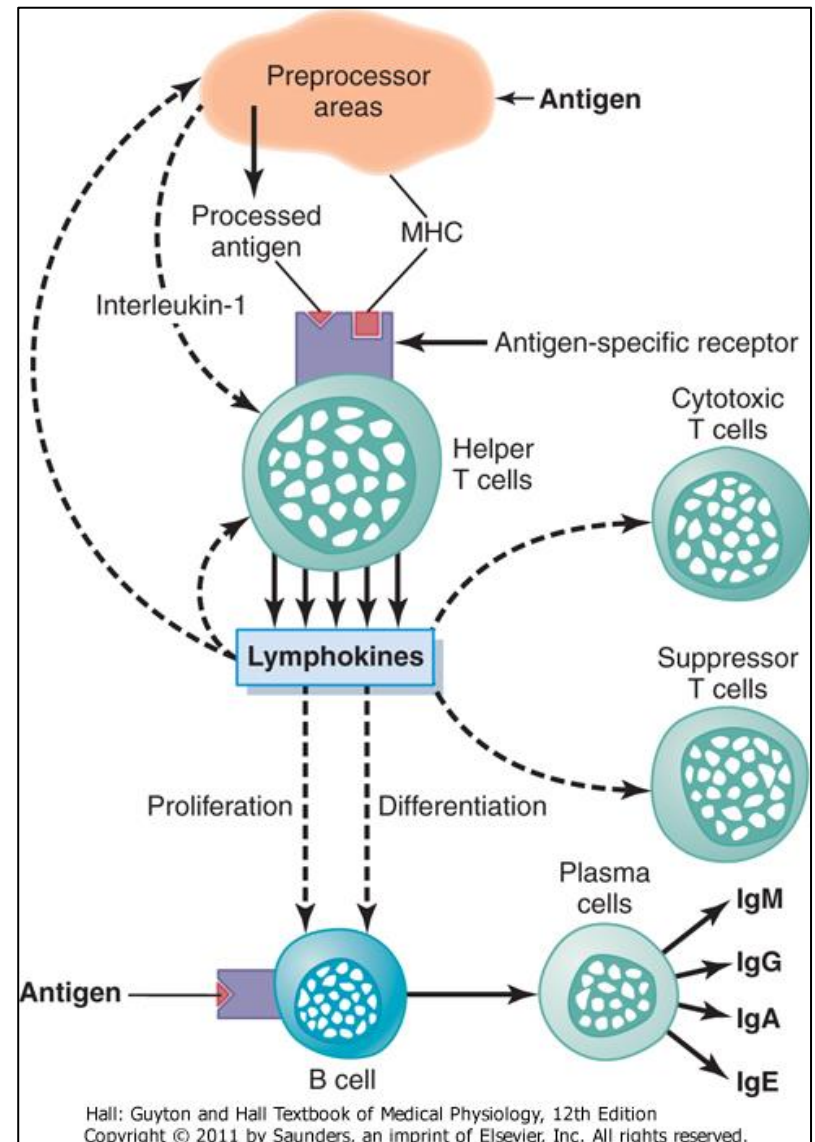
- ~ 75% of all T cells
- Regulate functions of other immunologic cells by producing cytokines...
 - Interleukin (IL-) 2, 3, 4, 5, 6, GM-CSF, Interferon-gamma

Table 35-1 Subsets of T-helper Cells

	T _H 1	T _H 2	T _H 17
Lymphokines that induce subset	IFN- γ , IL-12	IL-4	TGF- β , IL-1, IL-6, IL-23
Major lymphokines/factors produced	IFN- γ , IL-2 TNF- α , GM-CSF	IL-4, IL-5, IL-6, IL-10, IL-13	IL-17, IL-22
Major immune reactions	Macrophage activation, Stimulate IgG antibody production	Stimulate IgE production, Activation of mast cells and eosinophils	Recruitment of neutrophils and monocytes

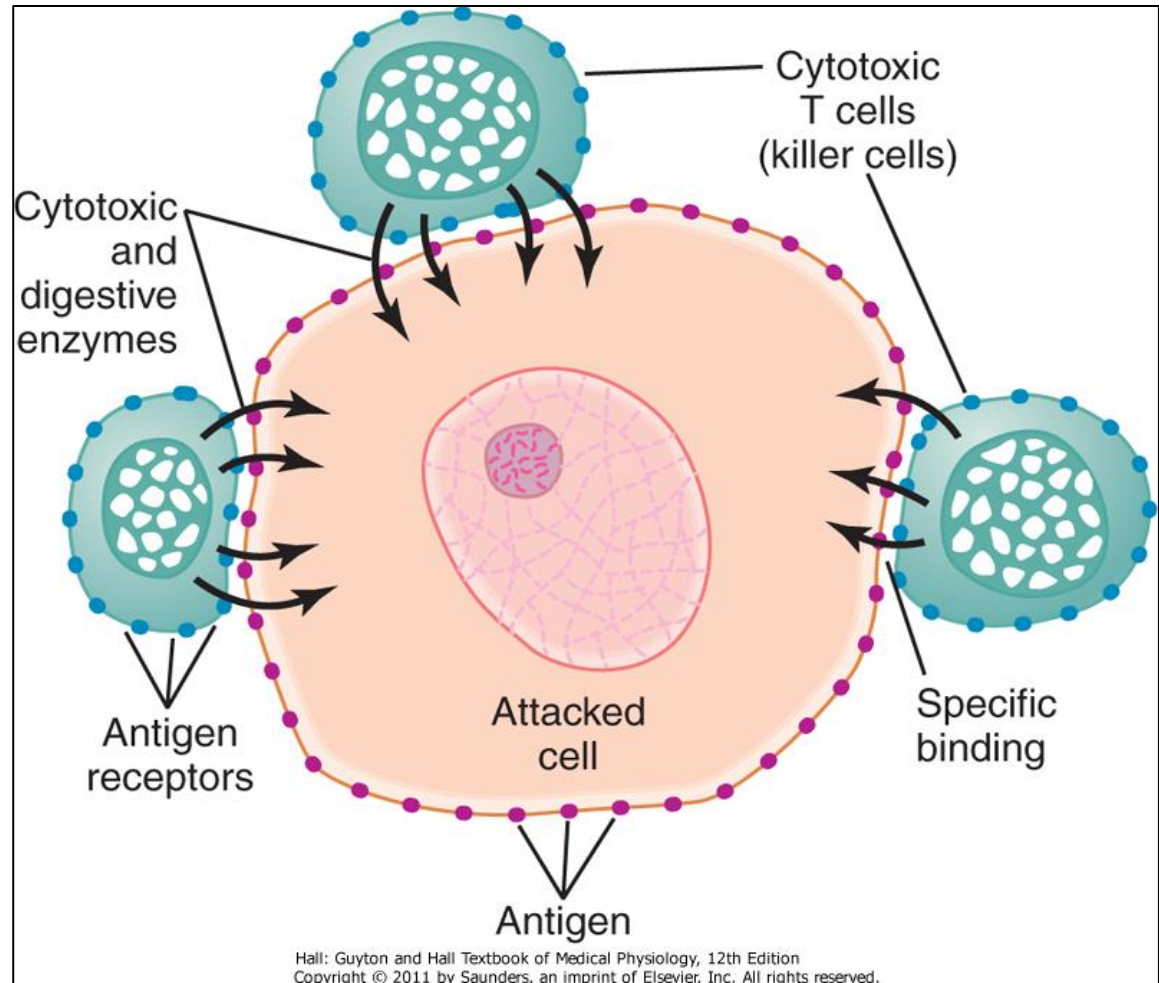
T cell help for immune response

- **Positive feedback for helper T cells (IL-2)**
- **Stimulation of cytotoxic T cells (IL-2, other cytokines)**
- **Stimulation of B cells (IL-4, 5, 6 (BCGFs))**
- **Macrophage accumulation, activation, enhanced killing**



Killing by cytotoxic T cells

- **Virus-infected cells**
- **Cancer cells**
- **Transplanted organs and tissues**



Immunologic Tolerance

- **Host defense employs powerful destructive mechanisms**
- **These must be directed at pathogens while protecting host tissues from damage**
- **“Tolerance” in acquired immunity is achieved mainly by clonal selection of T cells in the thymus and B cells in the bone marrow**
 - **clones that bind host antigens with high affinity are induced to undergo apoptosis, and are deleted**

Failure of tolerance produces autoimmunity

- Rheumatic fever (**cross-reactivity with streptococcal antigens**)
- Post-streptococcal glomerulonephritis
- Myasthenia gravis (**antibodies to acetylcholine receptors**)
- Systemic lupus erythematosus (**auto-immunity to multiple tissues**)

Immunization

- **Injecting killed organisms or their products...**
 - **typhoid, whooping cough, diphtheria, tetanus toxoid**
- **Infection with attenuated organisms...**
 - **Smallpox, yellow fever, polio, measles, herpes zoster, other viral diseases**
- **Passive immunity...**
 - **Infusing antibody or activated T cells from an immune individual (antibodies last 2-3 weeks)**

Allergy and hypersensitivity

- **T cell mediated (delayed)...**
 - **poison ivy, nickel allergies**
 - **usually cutaneous; can occur in lungs with airborne antigens**
- **IgE mediated (immediate)...**
 - **typical allergies**
 - **a single mast cell / basophil can bind 500,000 IgE molecules**

Mast cell / basophil degranulation

- **Histamine**
- **Proteases**
- **Leukotrienes**
- **Eosinophil and neutrophil chemotactic factors**
- **Heparin**
- **Platelet activating factor**

Allergic manifestations

- Anaphylaxis
 - **systemic, potentially fatal**
 - **widespread vasodilatation**
 - **↑↑ capillary permeability, volume loss**
 - **leukotrienes → bronchospasm and wheezing**
Treatment: epinephrine and antihistamines
- Urticaria
 - **localized vasodilatation and red flare**
 - **Increased permeability and swelling (“hives”)**
Treatment: antihistamines

Allergic manifestations (cont'd)

- **Hay fever**

- histamine mediated
- vascular dilatation in the nasal passages and sinuses (and eyes)
- leakage of fluid
- sneezing

Treatment: Anti-histamines, local corticosteroids

- **Asthma**

- mediated largely by leukotrienes
- sustained bronchospasm

Treatment: β agonists, inhaled steroids, leukotriene receptor blockers; treat upper airway component