

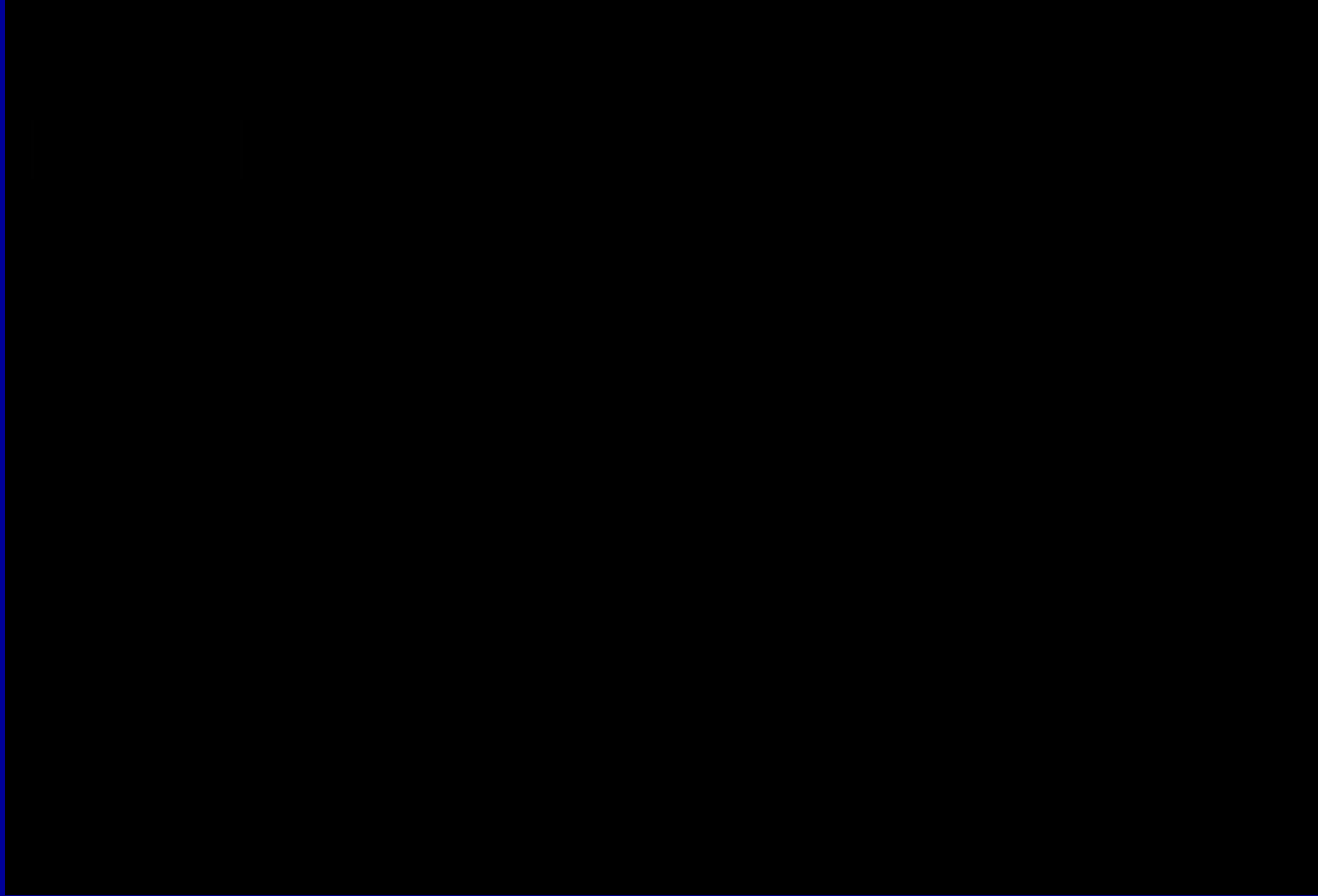
Allergy and Immunology

Kraig W. Jacobson, M.D. Feb. 9, 2017

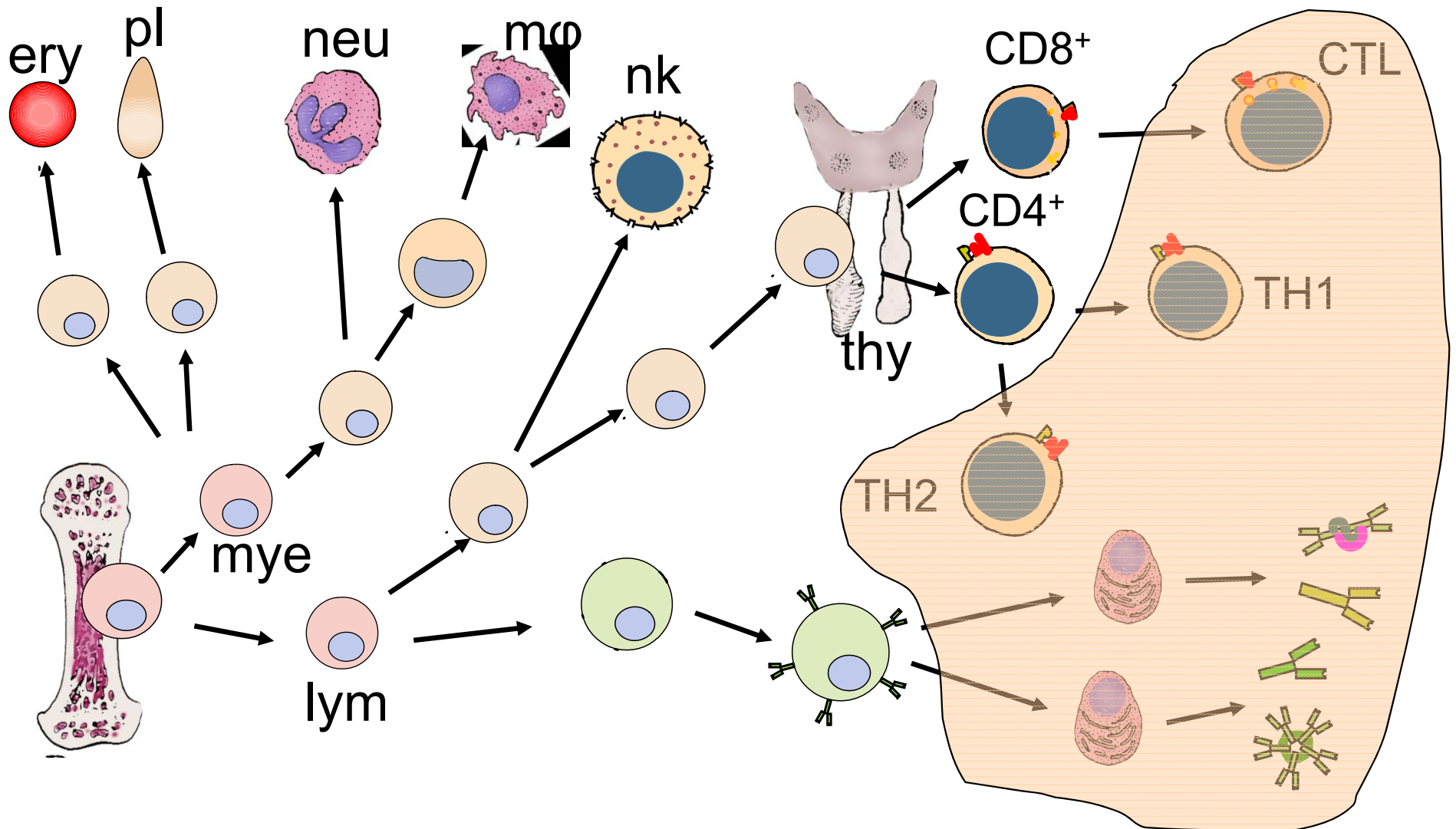




Why do you need immunity?



Development of the Immune System



The Immune System

Innate

physical barriers
natural killer cells
macrophages
Toll-like receptors
Complement

Acquired

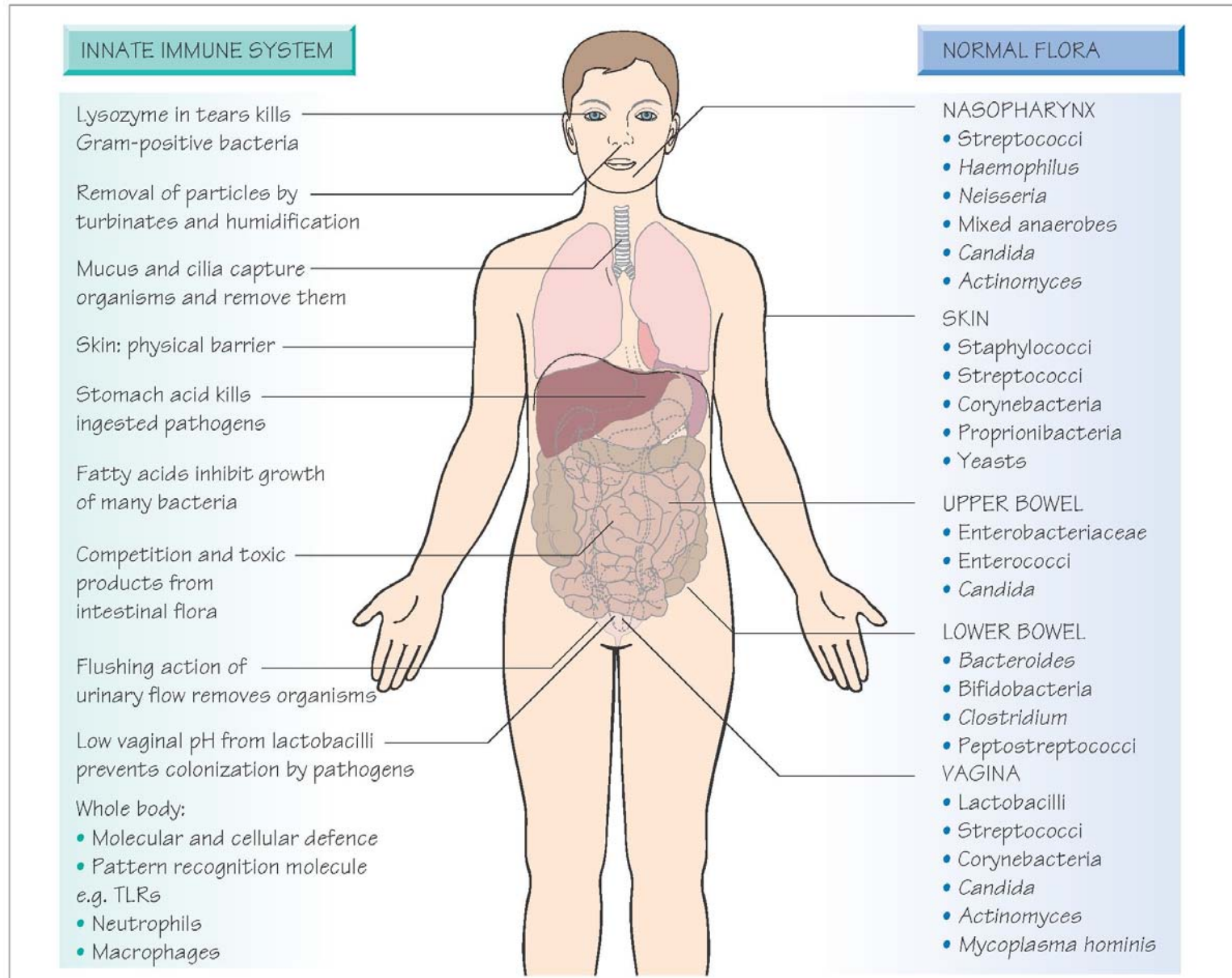
Cell-mediated

T & B cells

Humoral

antibody-mediated

Innate Immune System



Innate Immunity
Non-specific, general
Immediate response
No immunological memory

Adaptive Immunity
Specific to antigen
Lag time from exposure to response **
Immunological memory after exposure

Humoral
Pattern Receptors
Complement
Enzymes
Cytokines

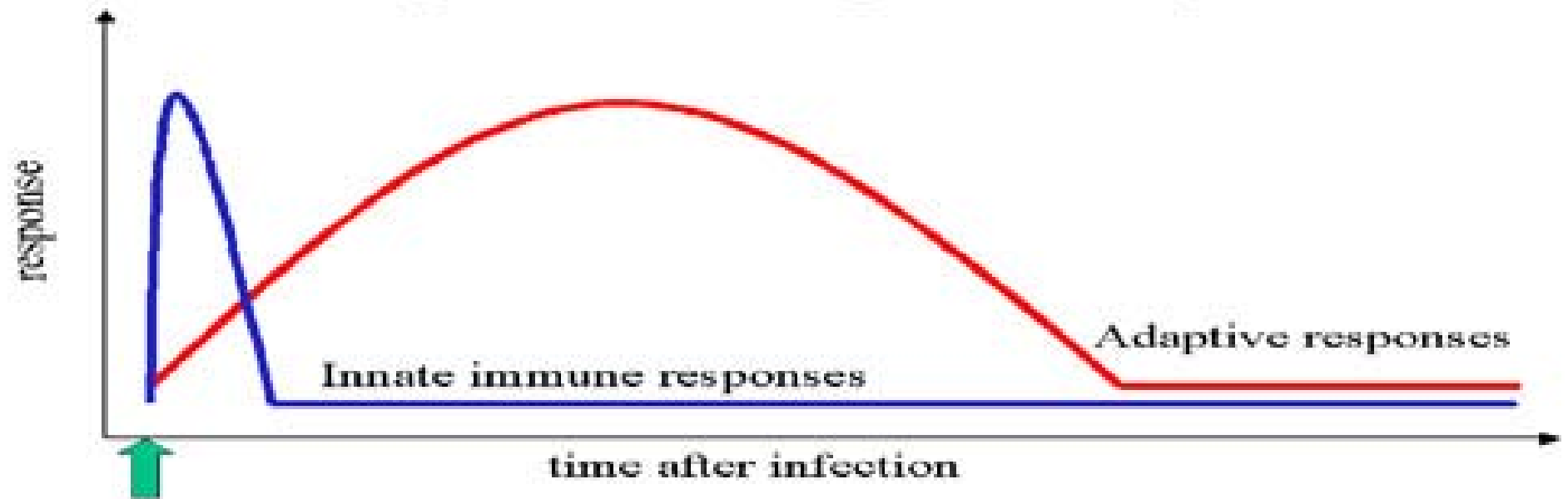
Cellular
Phagocytes
Natural Killer Cells

Humoral
Antibodies
Cytokines

Cellular
T Cells
B Cells

****Except for IgE allergic reactions**

Model of Immune Responses: Speed and Specificity



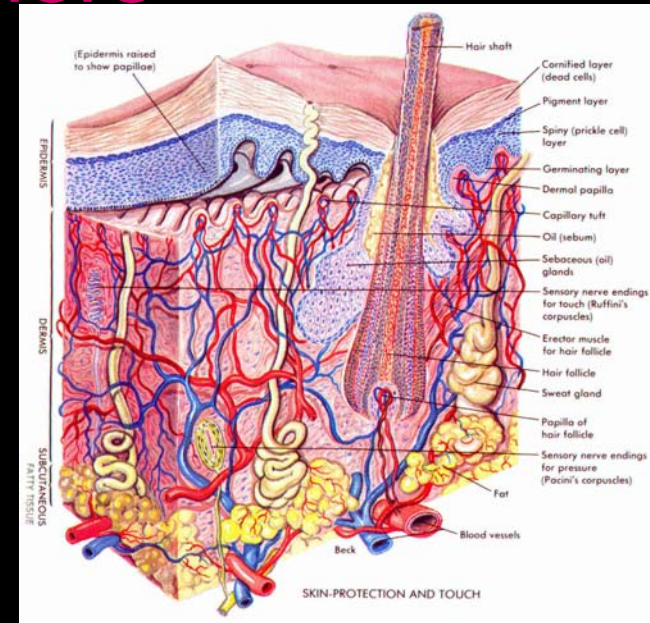
INNATE IMMUNITY

Physical Barriers

–skin

–hair

–mucous







prurigo nodularis

INNATE IMMUNITY

Chemical Barriers

- sweat
- tears
- saliva
- stomach acid
- urine







Filaggrin null mutation

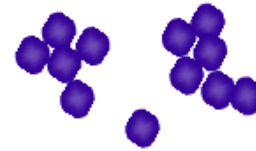


Complement

Classical



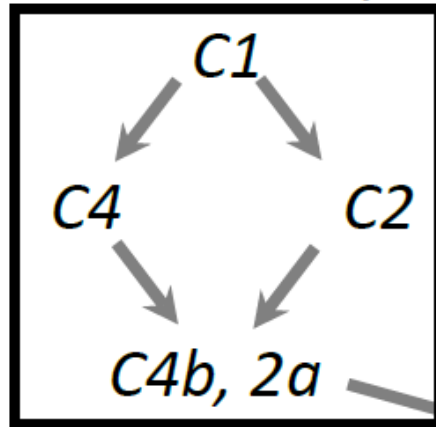
Immune Complex



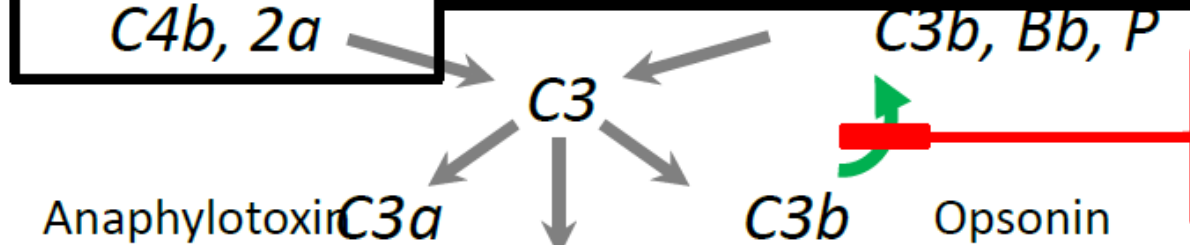
Alternative

Microbes

C3(H₂O), Bb



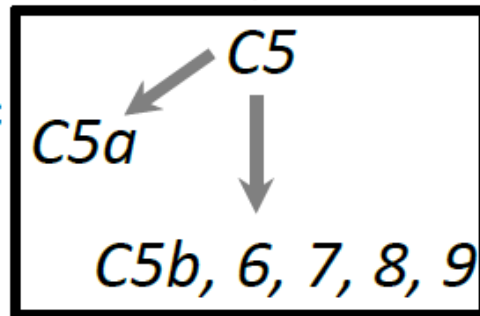
- Recurrent pyogenic infections (*Strep. pneumoniae*)
- Glomerulonephritis, SLE



*Factor I
Factor
H*

- Familial HUS
- Age-related Macular Degeneration

- Recurrent *Neisserial* infections



Membrane Attack Complex Bactericidal Activity

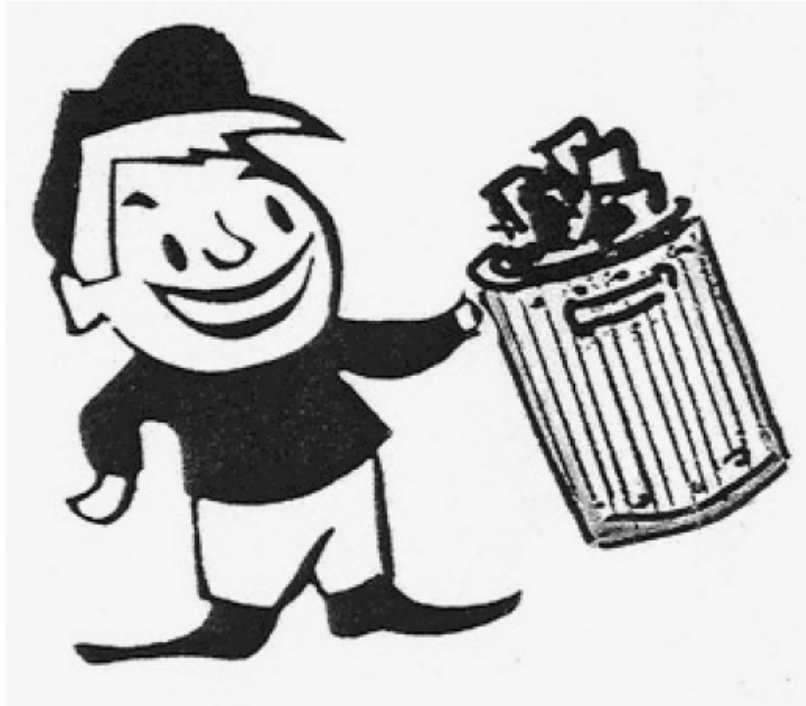




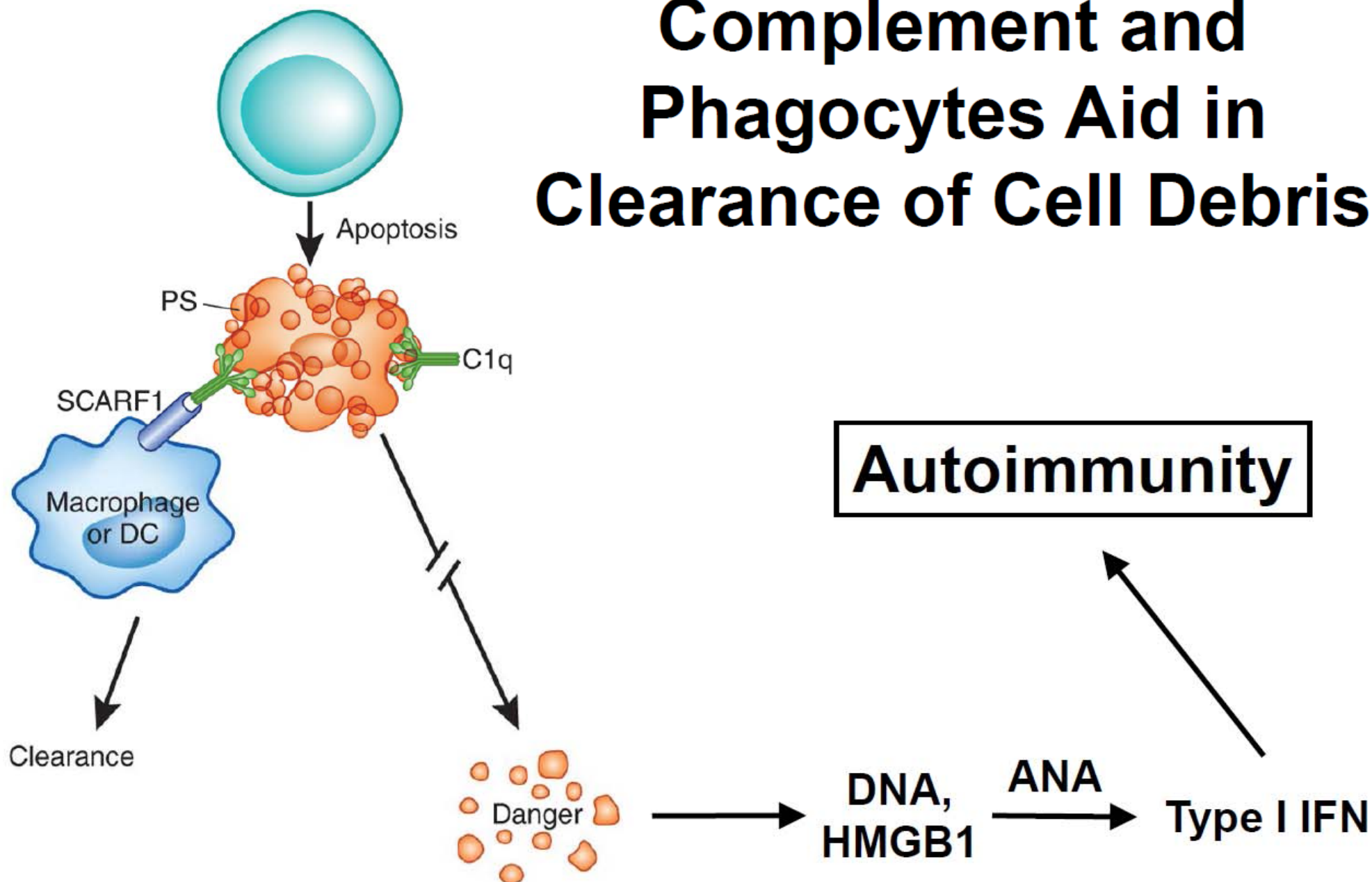




Immune System – Garbage Disposal is Important



Complement and Phagocytes Aid in Clearance of Cell Debris



Complement Deficiency

- **C1q/r/s Deficiency** – ~90% of homozygotes develop SLE or GN, usually <20 y/o.
- **C4 Deficiency** - ~75% of homozygotes develop SLE or GN.
- **C2 Deficiency** – Most common homozygous complement deficiency. ~40% of homozygotes develop SLE or GN .

Arthritis Rheum. 1989 Jul;32(7):906-13.

Successful plasma infusion treatment of a patient with C2 deficiency and systemic lupus erythematosus: clinical experience over forty-five months.

Steinsson K1, Erlendsson K, Valdimarsson H.

45 cycles, 22 infusions 6-8 weeks apart

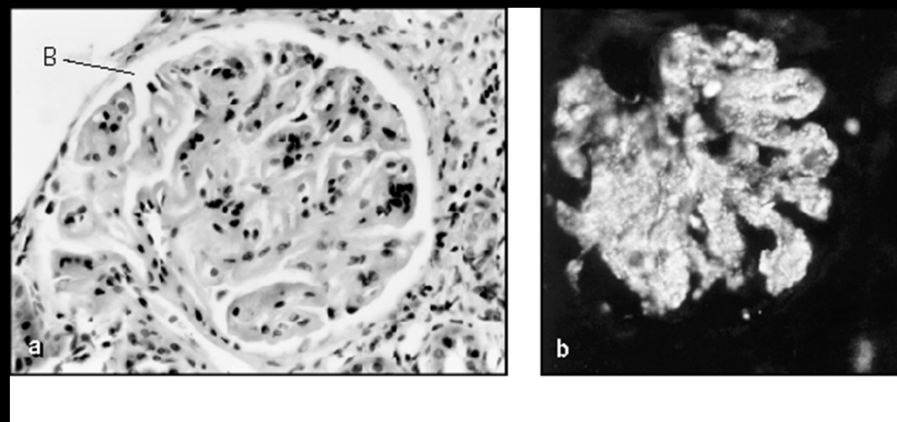
Systemic Lupus Erythematosus (SLE)

- **A chronic systemic autoimmune disease.**
 - Complexes of anti-self antibodies and antigen deposit in, and cause tissue damage.
- **1 million sufferers in the U.S.**
 - SLE strikes women nine times more often than men.
- Symptoms may include a butterfly-shaped rash on face, fatigue, and headaches.
- Triggered by environmental effects in persons who are genetically susceptible.



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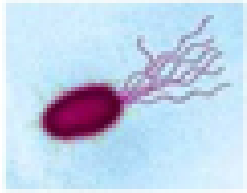
Lupus “butterfly” rash



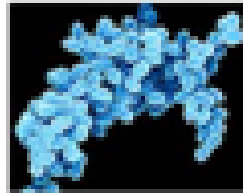
Damaged kidney (left) caused by immunoglobulin deposits (right)

The Human Toll-like Receptor Family

Gm- Bacteria



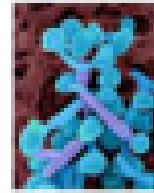
Gm+ Bacteria



Mycobacteria



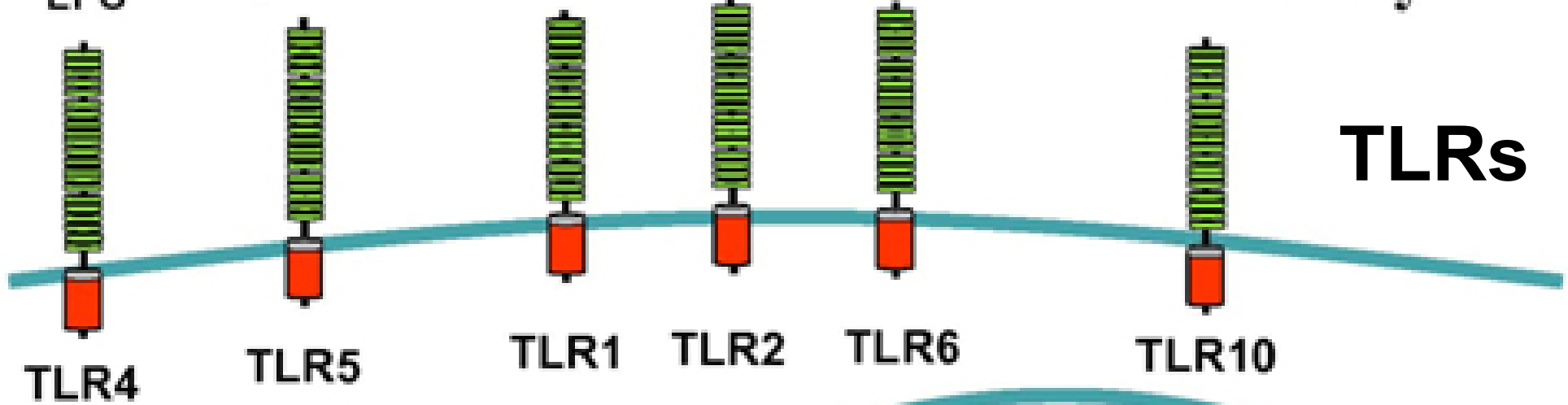
Yeast



Various Membrane/Wall Components

LPS

Flagellin



TLRs

ENDOSOME

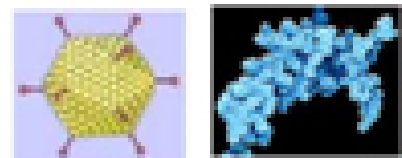
TLR3 dsRNA

Viral and Bacterial Nucleic Acids

TLR7 ssRNA

TLR8 ssRNA

TLR9 dsDNA



INNATE IMMUNE RESPONSE

TLRs in Treatment


Imiquimod (Aldara) activates immune cells through the [toll-like receptor 7](#) (TLR7), commonly involved in pathogen recognition. Cells activated by imiquimod via TLR-7 secrete [cytokines](#) (primarily [interferon- \$\alpha\$](#) (INF- α), [interleukin-6](#) (IL-6), and [tumor necrosis factor- \$\alpha\$](#) (TNF- α)). There is evidence that imiquimod, when applied to skin, can lead to the activation of [Langerhans cells](#), which subsequently migrate to local lymph nodes to activate the adaptive immune system.^[9] Other cell types activated by imiquimod include [natural killer cells](#), [macrophages](#) and [B-lymphocytes](#)



4 Compartments of the Immune System


Innate Immunity

Complement
“Land Mines”



A collection of various pink and red geometric shapes including a crescent moon, a cross, a pentagon, a triangle, and a lightning bolt, representing different complement proteins.

Phagocytes
“The Marines”



Two types of phagocytes: a Neutrophil (orange circle with pink granules) and a Macrophage (green starburst shape with a purple nucleus).

Neutrophils Macrophages


Adaptive Immunity

B Cells
“Air Force – Make & Deploy Cruise Missiles”

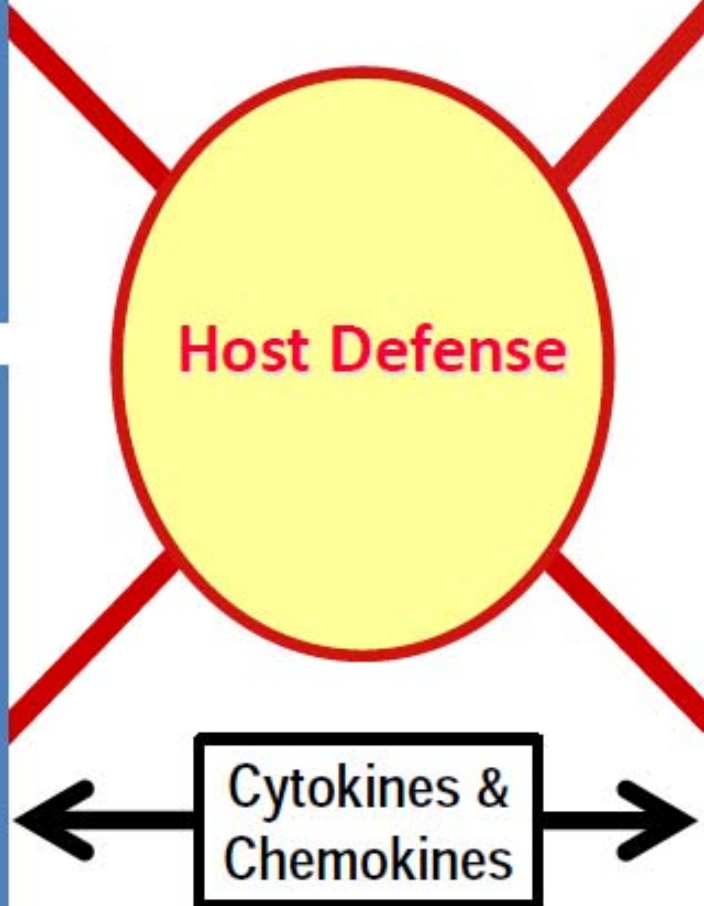


A yellow circle with a red nucleus and several Y-shaped antibodies extending from its surface.

T Cells
“The Generals”
“The Assassins”
“The Psychologists”



A purple circle with a green nucleus.



Innate Immunity

- Antigen independent
- No time lag
- Not antigen specific
- No Immunologic memory

Adaptive Immunity

- Antigen dependent
- A lag period (except IgE)
- Antigen specific
- Development of memory

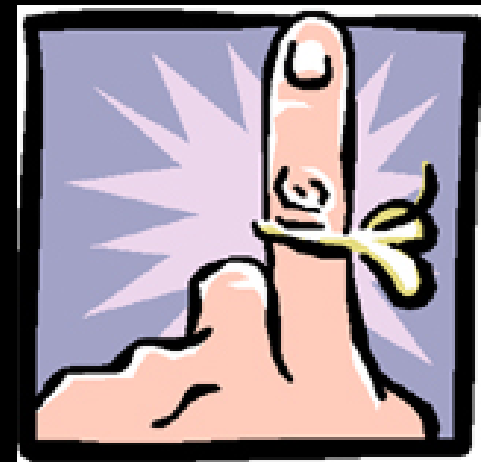
Primary Function of the Adaptive Immune System

- Protect self from non-self;



and ...

- Remember it!

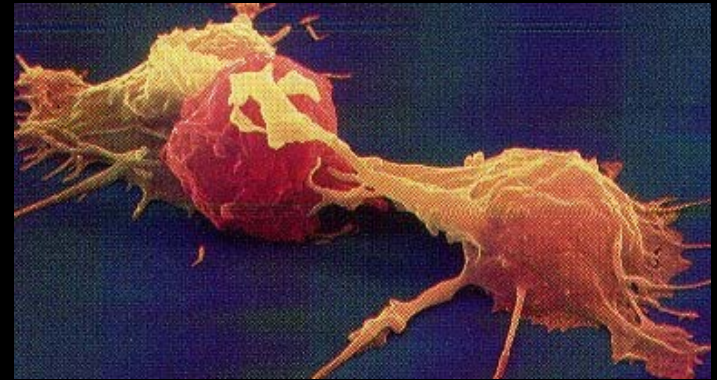






T and B Lymphocytes

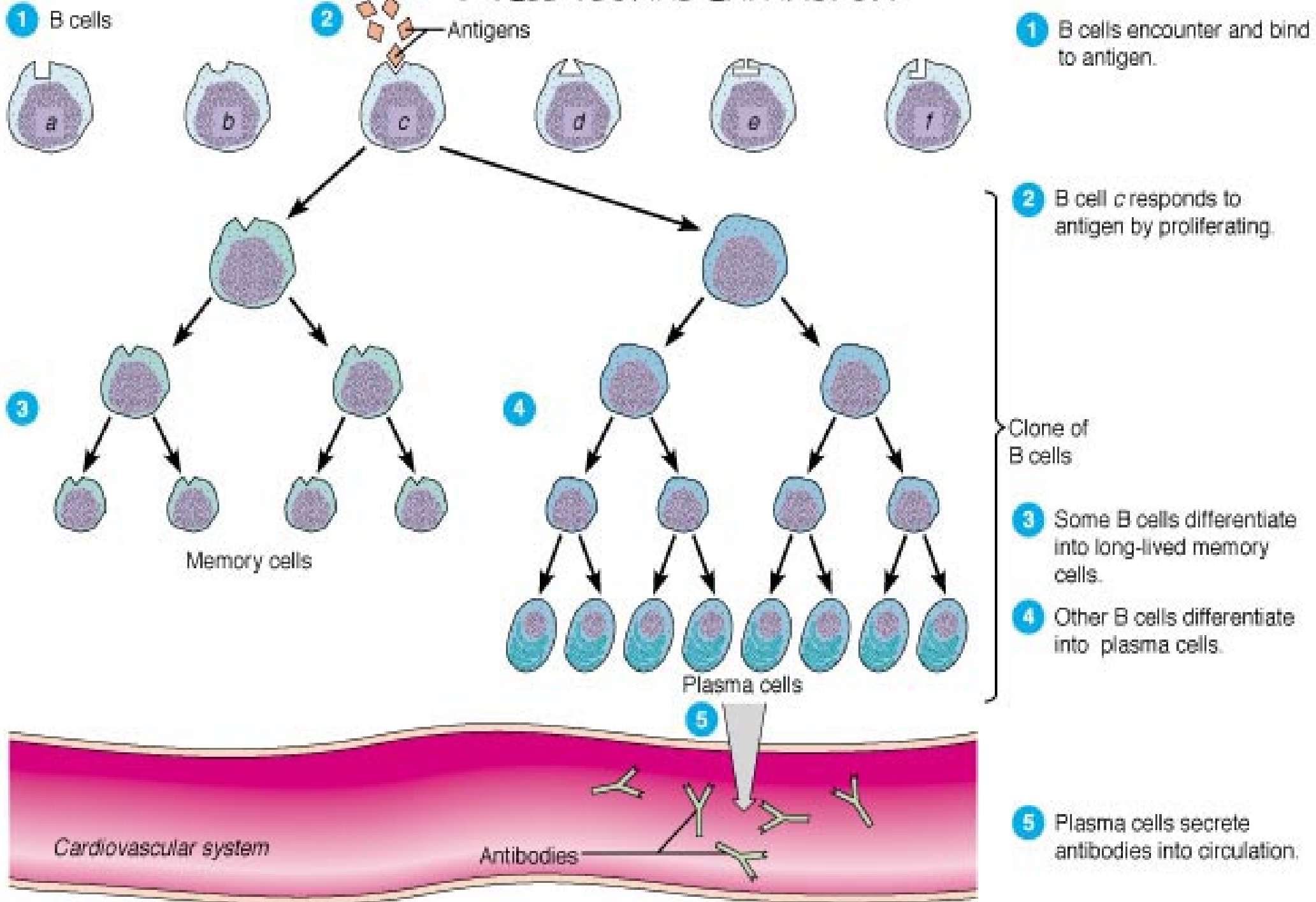
- T cells originate from the **Thymus** and may be Helper (CD4), Suppressor (CD8) or Cytotoxic.
- B cells originate from the **“Bursa”**. Their major function is to produce antibodies in response to foreign proteins including bacteria, viruses, and tumor cells.



Bursa of Fabricius



B CELL CLONAL EXPANSION



Function of the Immune System (Self / Non-self Discrimination)

- To protect from pathogens
 - Intracellular (*e.g.* viruses and some bacteria and parasites)
 - Extracellular (*e.g.* most bacteria, fungi and parasites)
- To eliminate modified or altered self

Hypersensitivity

There are four different responses of the immune system:

Type I: Immediate hypersensitivity

- onset within minutes of antigen challenge
- examples are allergies to molds, insect bites

Type II: Cytotoxic hypersensitivity

- onset within minutes or a few hours of antigen challenge
- examples are adult hemolytic anemia and drug allergies

Type III: Immune complex-mediated hypersensitivity

- onset usually within 2 - 6 hours
- examples include serum sickness and systemic lupus erythematosus

Type IV: Delayed hypersensitivity

- inflammation by 2- 6 hours; peaks by 24 - 48 hours
- examples include poison ivy and chronic asthma

Two Sides of the Adaptive Immune System

Humoral = Immediate sensitivity

Antibodies (Type I, II, III)





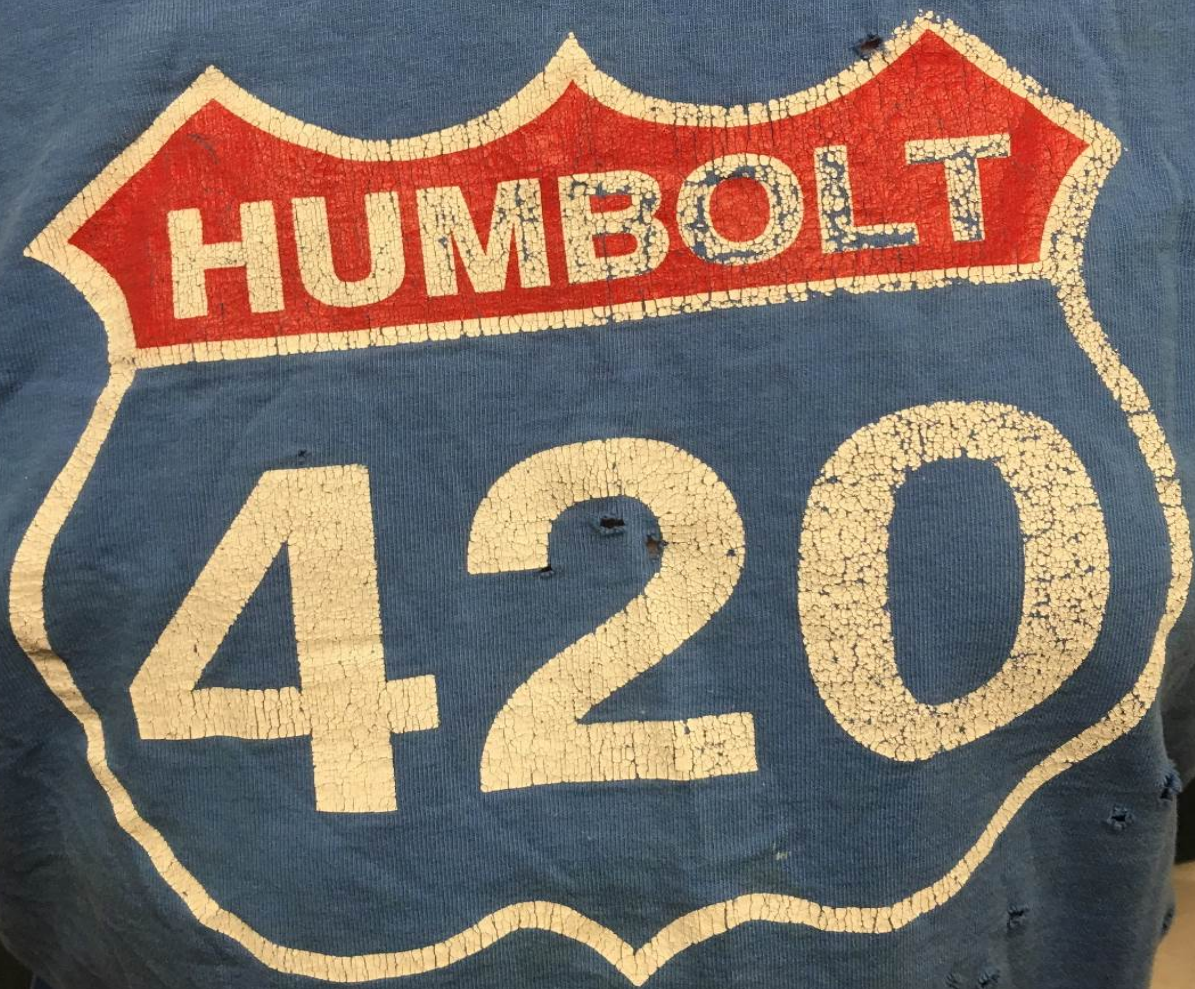
Two Sides of the Adaptive Immune System

Cellular = Delayed sensitivity (Type IV)



24 - 48 hours after exposure
CONTACT DERMATITIS



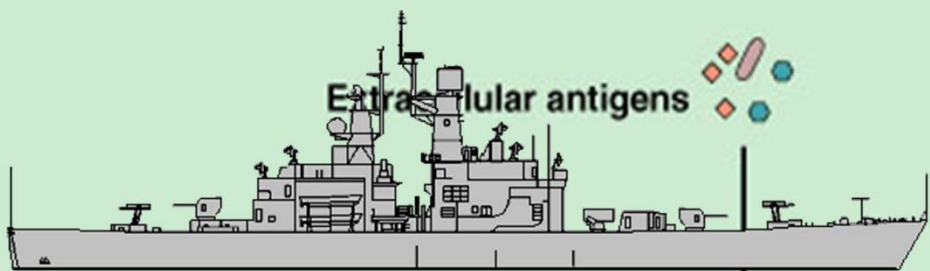


HUMBOLT

420

HUMORAL (ANTIBODY-MEDIATED) IMMUNE SYSTEM

Control of freely circulating pathogens

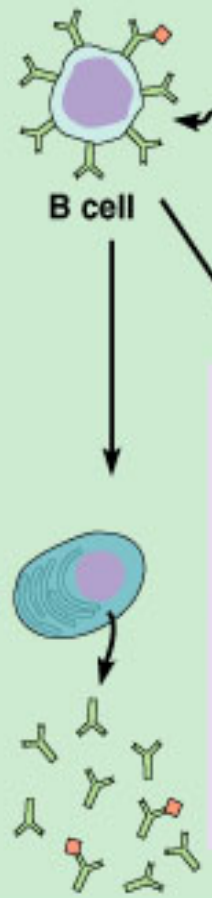


1 A B cell binds to the antigen for which it is specific. Usually requires cooperation from helper T cell.

2 The B cell, often with stimulation from a helper T cell, differentiates into a plasma cell.



3 Plasma cells proliferate and produce antibodies against the antigen.



CELL-MEDIATED IMMUNE SYSTEM

Control of intracellular pathogens

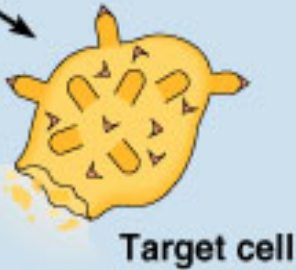
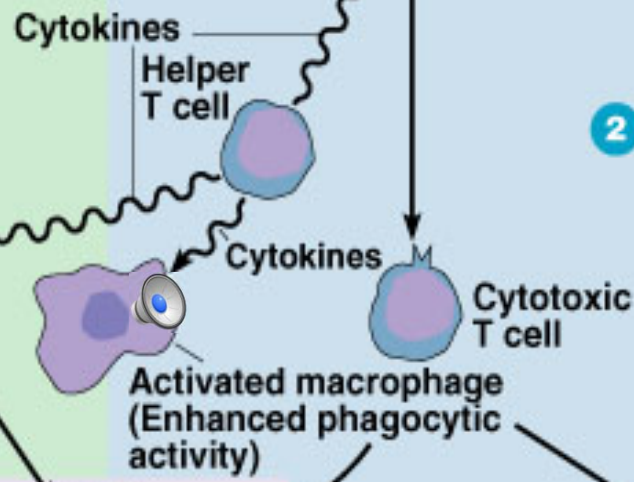


Intracellular antigens expressed on the surface of a cell infected by a virus, bacterium, or parasite. (Also may be expressed on surface of an APC).

1 A T cell binds to MHC-antigen complexes on the surface of the infected cell, activating the T cell (with its cytokine receptors).

2 A helper T cell produces cytokines that cause the activated T cell to differentiate into a cytotoxic T cell. These cytokines also influence the formation of plasma cells and activated macrophages.

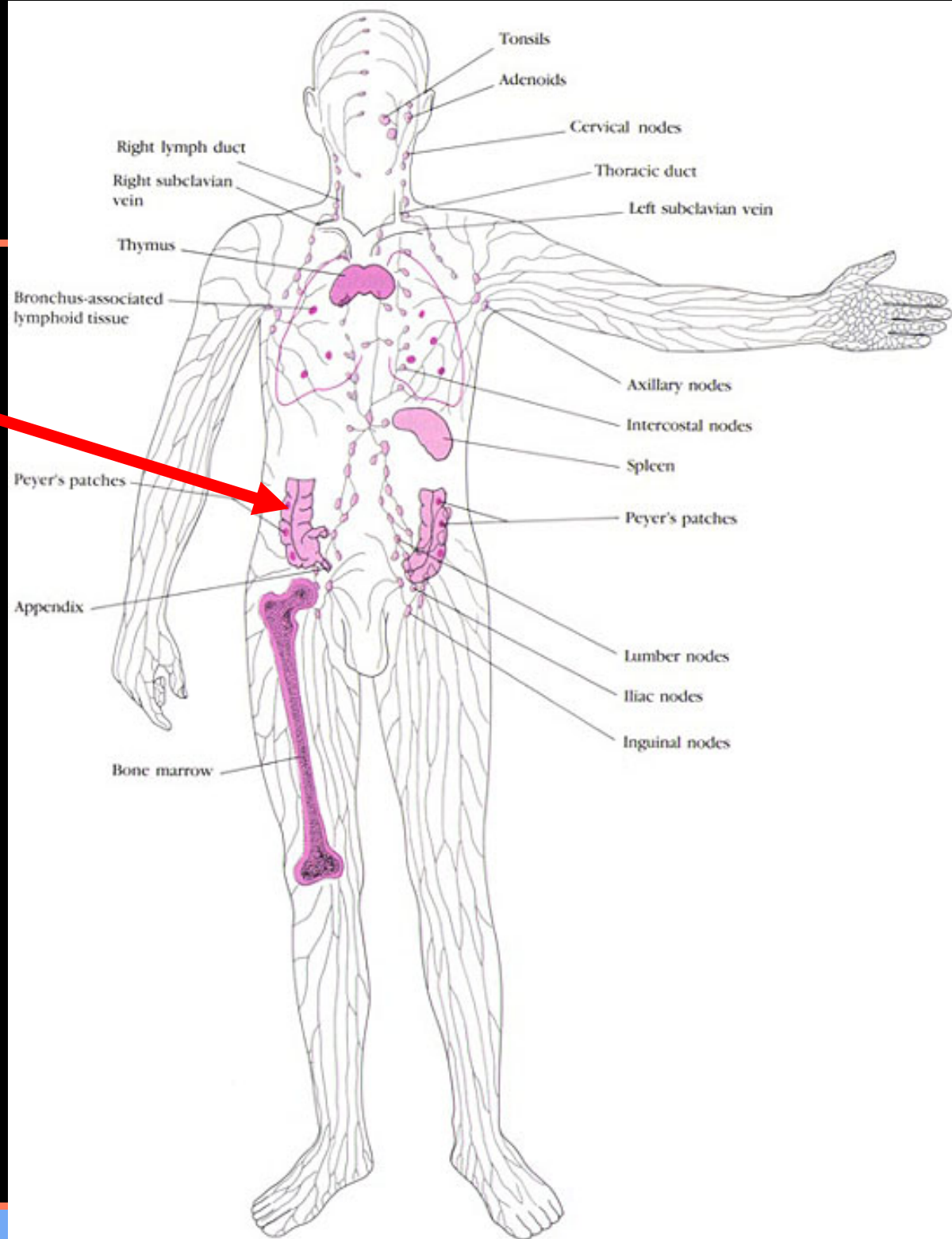
3 The infected target cell is lysed by the cytotoxic T cell.



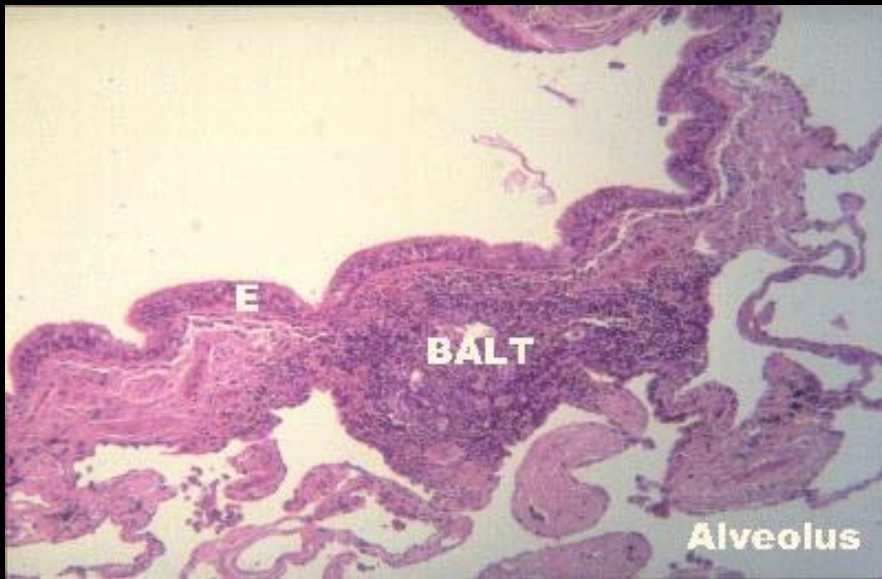
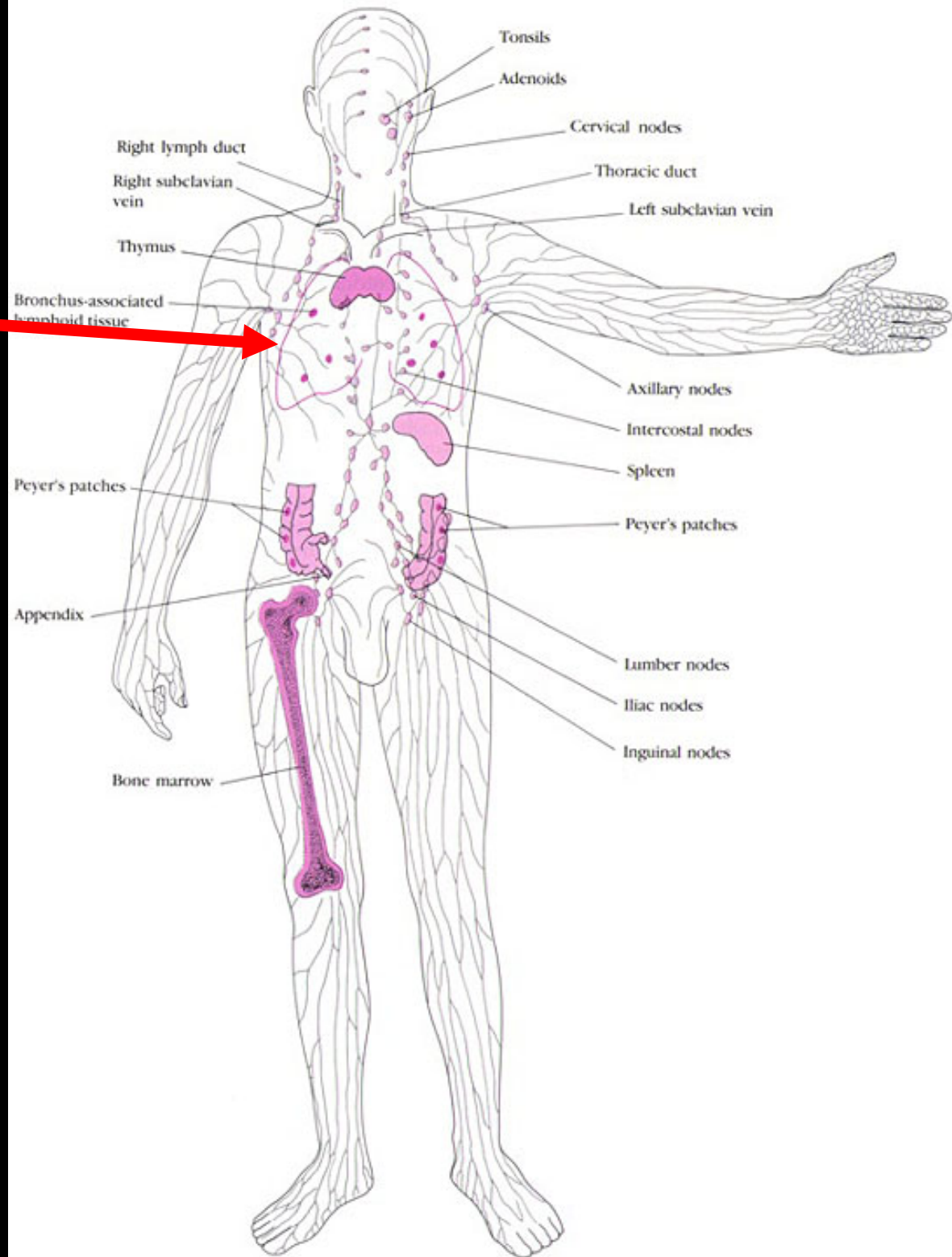
Memory cell

Some T and B cells differentiate into memory cells that respond rapidly to any secondary encounter with an antigen.

GALT = Gut Associated Lymphoid Tissue

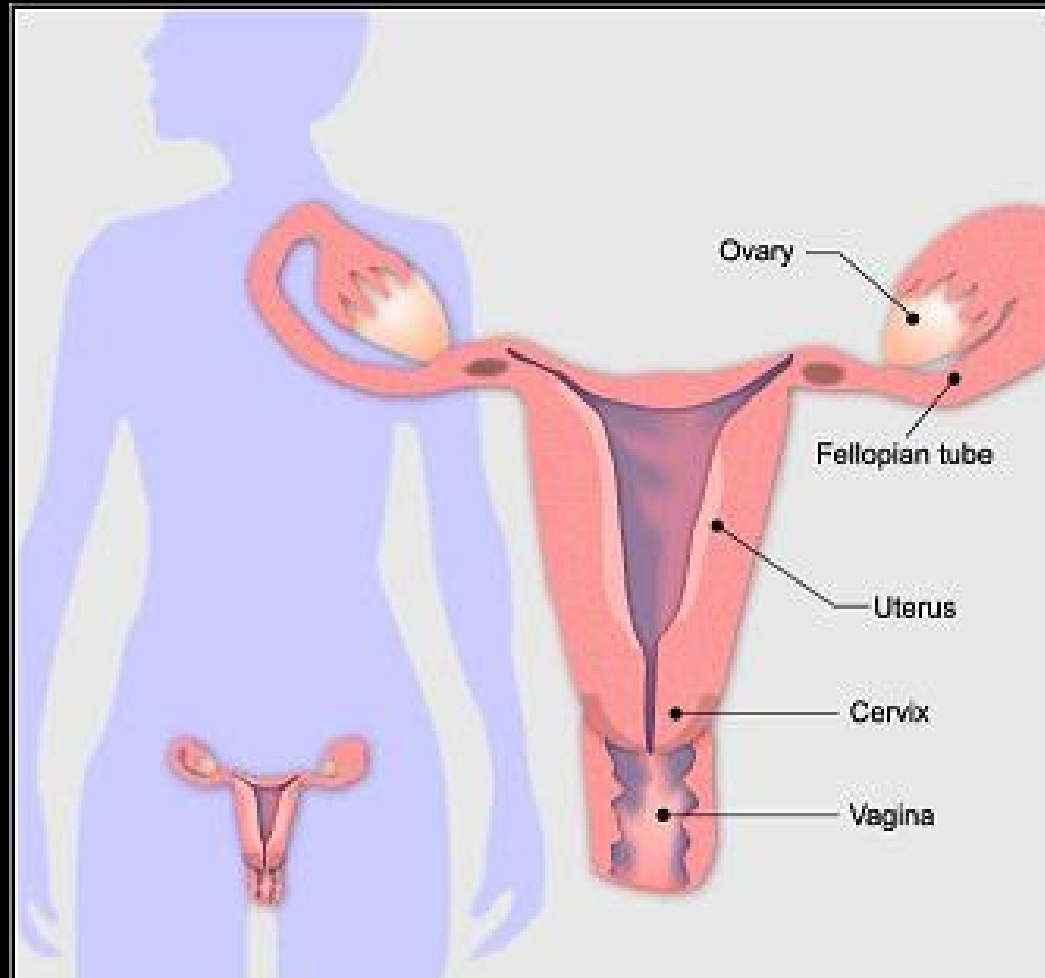


BALT = Bronchial Associated Lymphoid Tissue



GENITAL TRACT

- no associated lymphoid tissue
- no clear site of immunologic priming

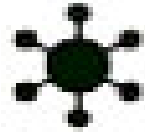


Exposure to Pathogens

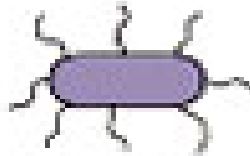
Antigens



Foreign proteins



Viruses



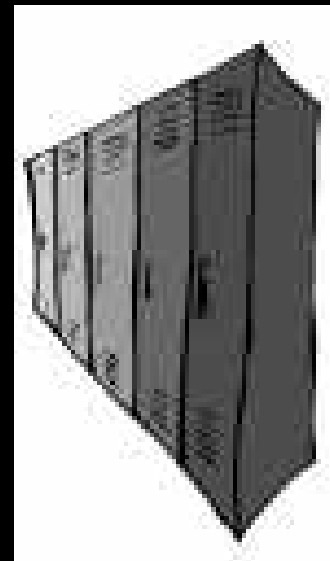
Bacteria



Parasites



Fungi



Antigen Processing



Remember the 5 Classes of Antibodies

- Ig = Immunoglobulin

G – A – M – E – D

- Ig**G** = “Good” major antibody class
- Ig**A** = “Appetite” to “A” hole, orifices
- Ig**M** = Macroglobulin, first one out
- Ig**E** = “Evil”, causes allergies
- Ig**D** = “Dumb class”, does nothing

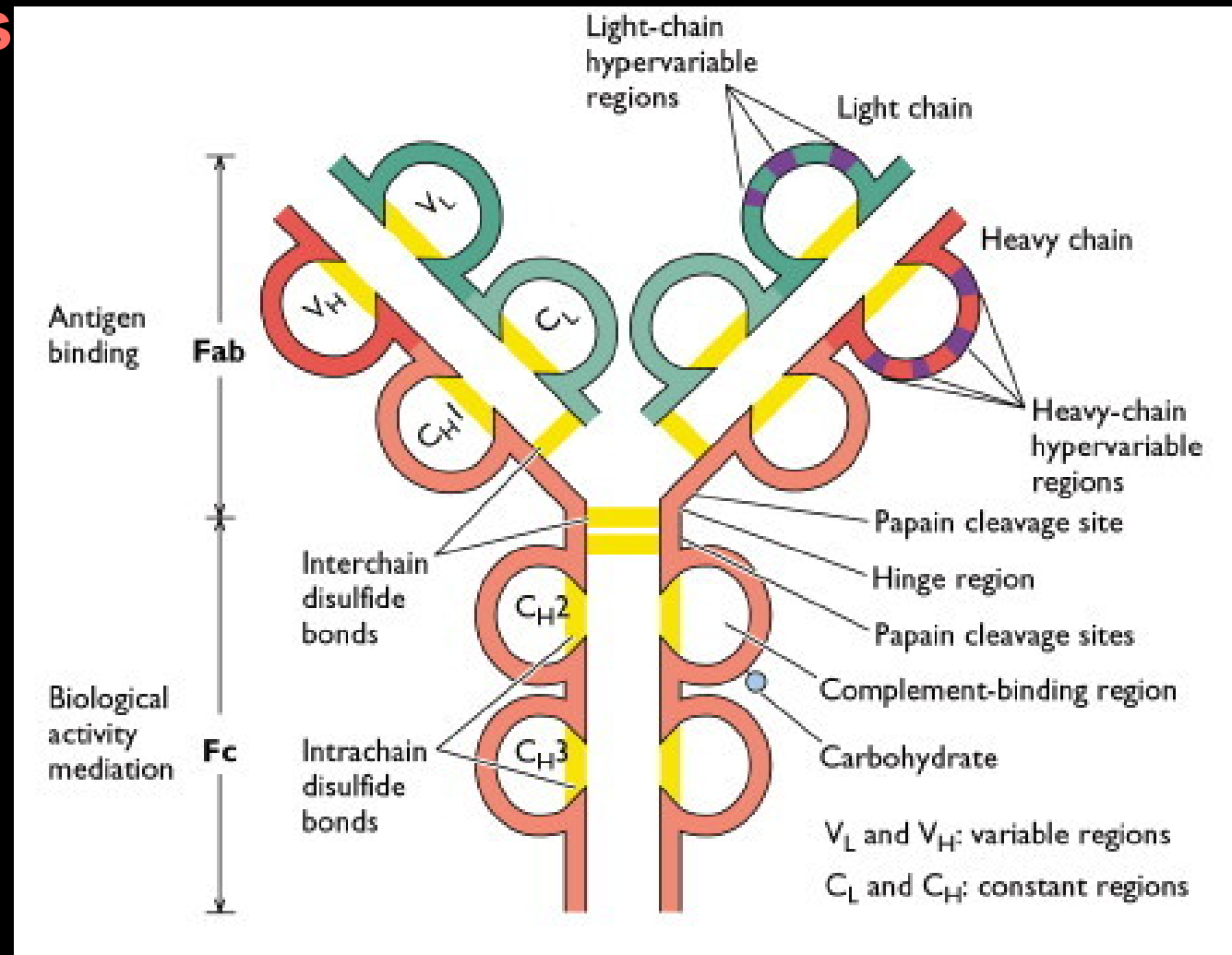
Antibody Structure

- **Two Heavy Chains**

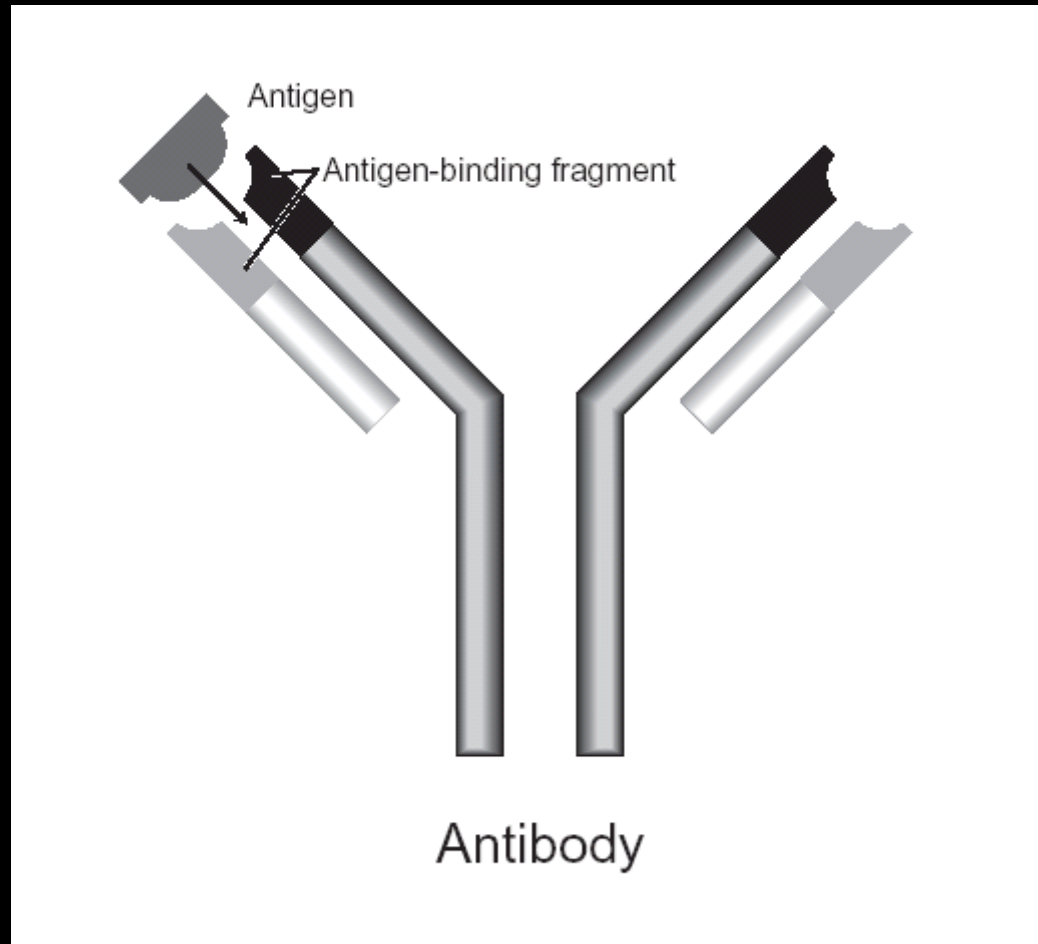
- IgA = α Alpha
- IgD = δ Delta
- IgM = μ Mu
- IgE = ϵ Epsilon
- IgG = γ Gamma

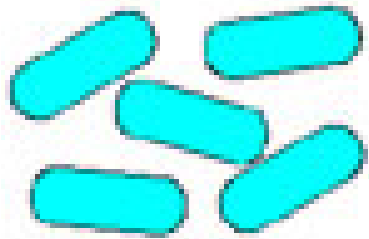
- **Two Light Chains**

- Kappa κ
- Lambda λ

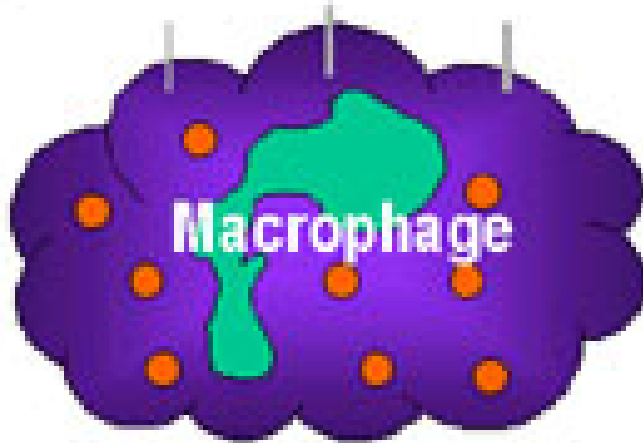


Antibody Drawing



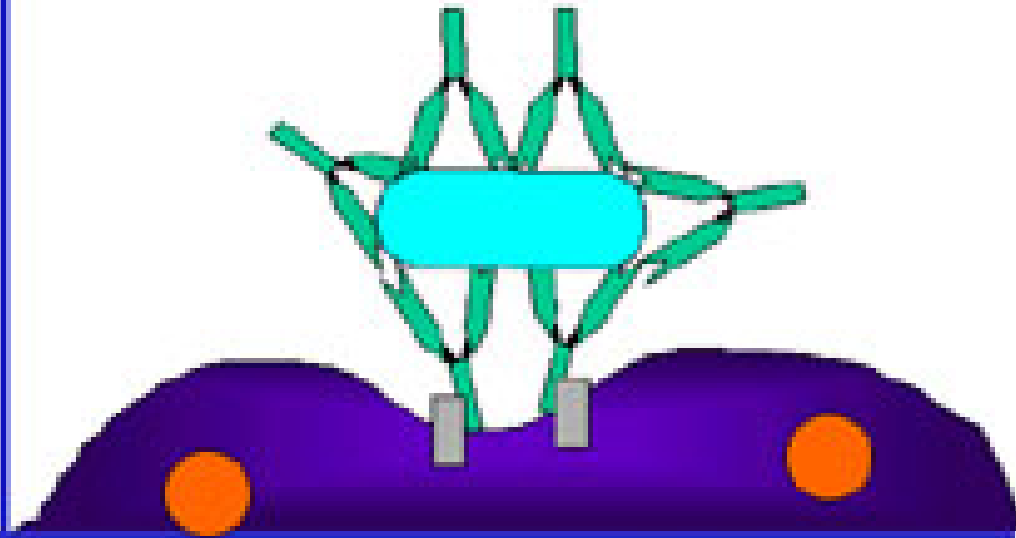


Extracellular
bacteria



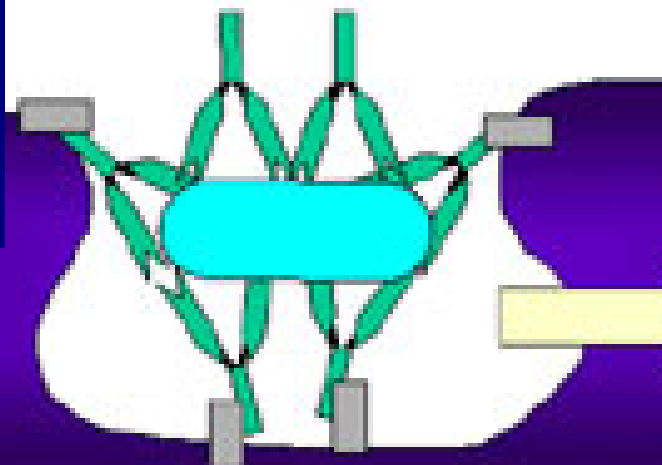
Macrophage

Opsonization



BACTERIAL CAPSULE:
The slippery capsule of
Streptococcus pneumoniae
enables these bacteria to
avoid being eaten by
neutrophils

Opsonization by macrophage



BACTERIAL CAPSULE:
The slippery capsule of
Streptococcus pneumoniae
enables these bacteria to
avoid being eaten by
neutrophils

Digestion in lysosome

HIV

An infection of T Helper or CD4 Cells

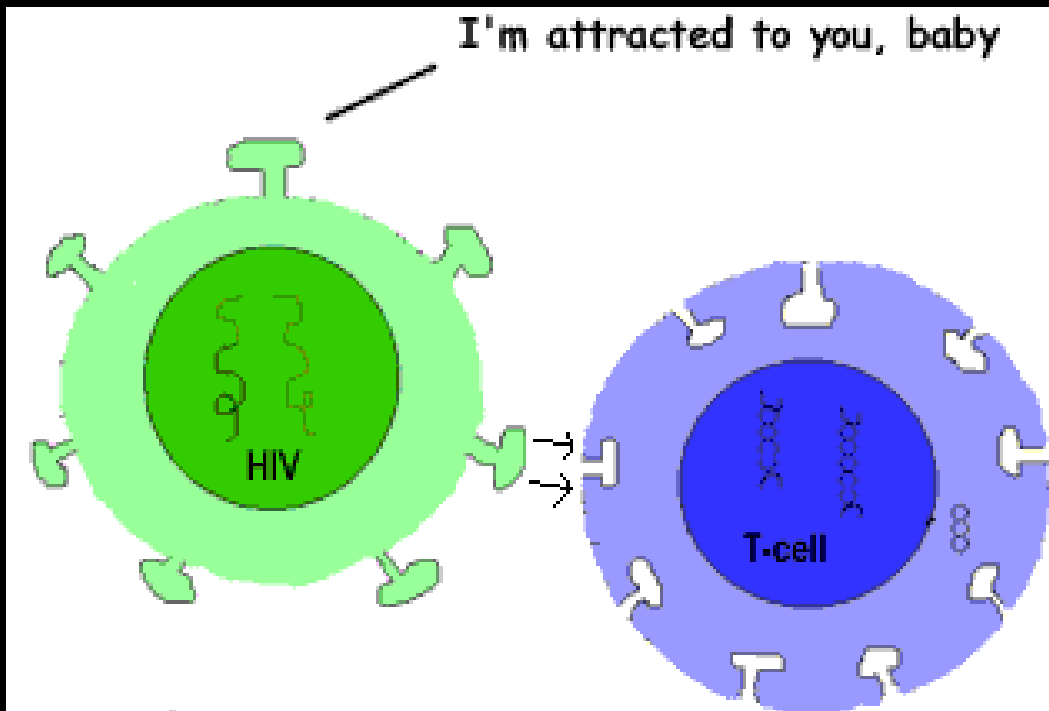


Figure 4
Virus attaches to healthy T-cell

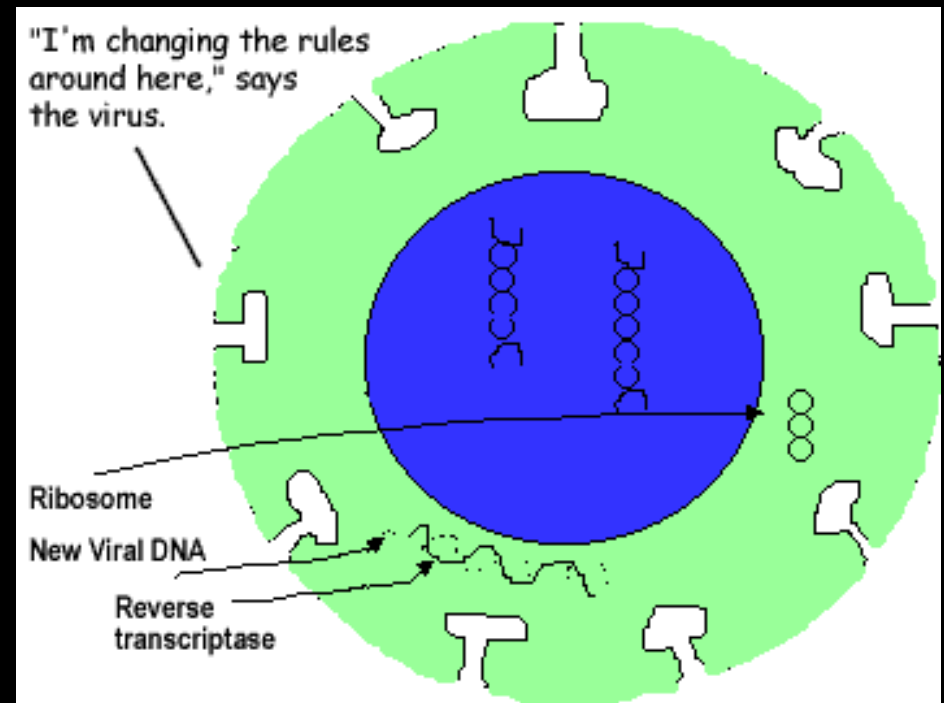


Figure 6
The viral RNA and the reverse transcriptase change the T-cell, giving it a new set of codes/info

ALLERGIES?

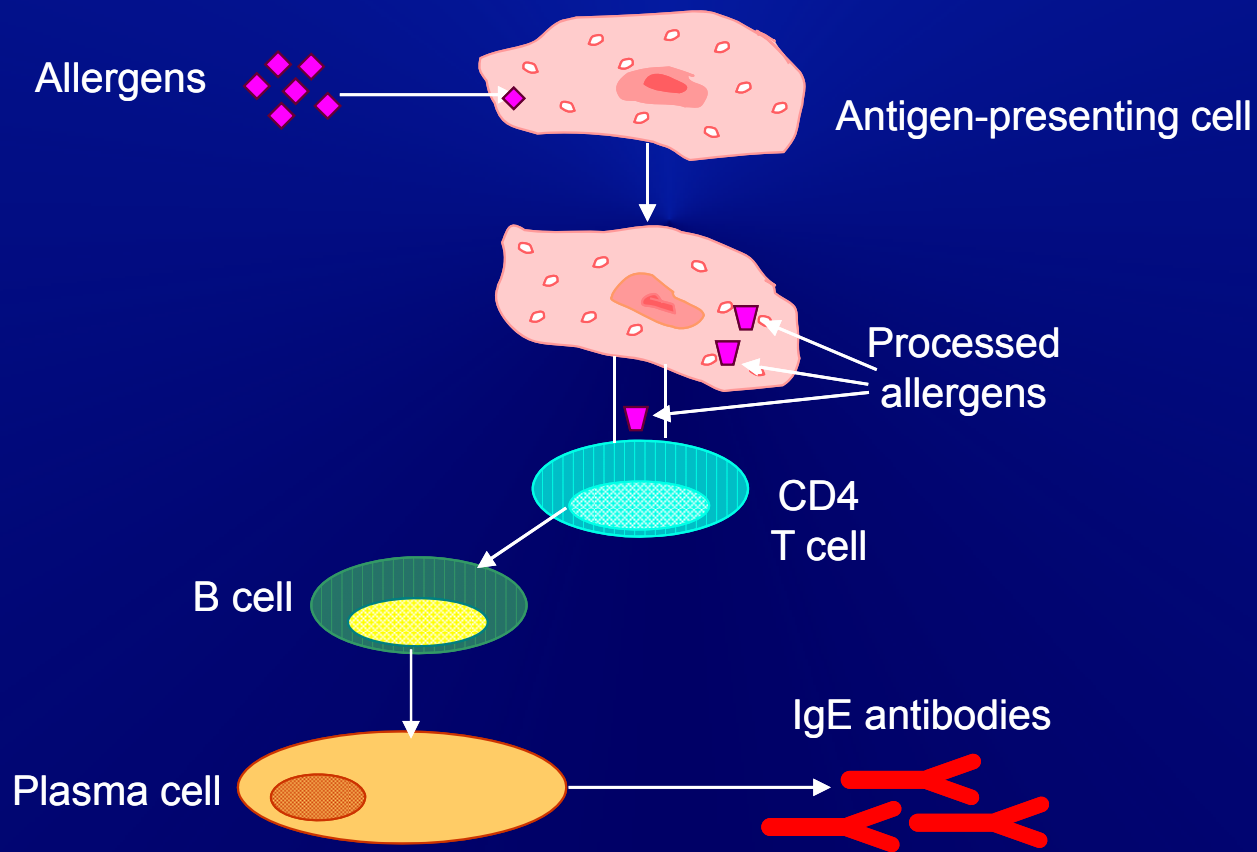


(C) WWW.OHMYGOODNESS.COM



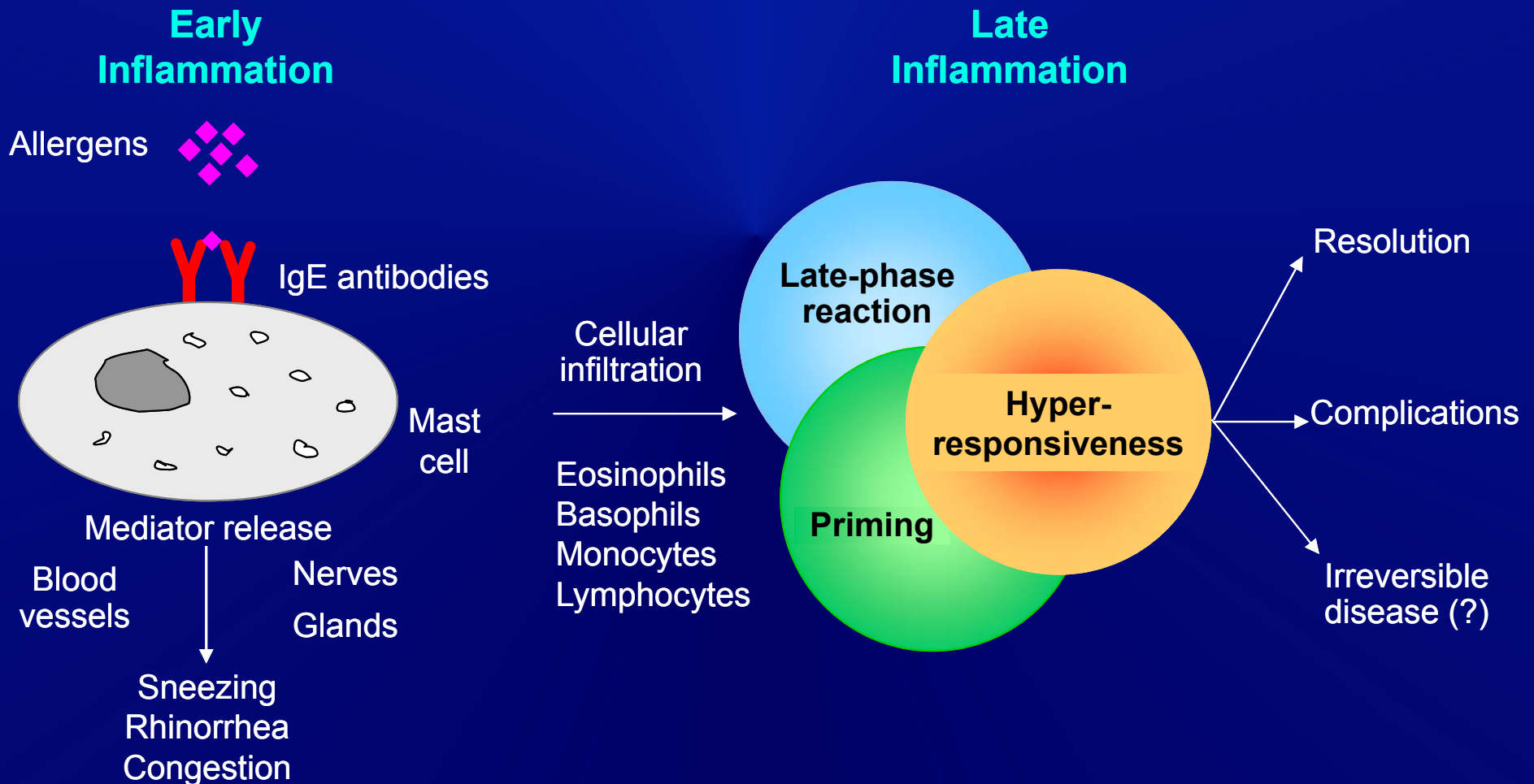
Pathophysiology of Allergic Inflammation: Sensitization

Phase 1: Sensitization



Pathophysiology of Allergic Inflammation: Clinical Disease

Phase 2: Clinical Disease







CLOSE TO HOME By John McPherson

McPHERSON

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In the midst of final exams, Noreen developed an allergic reaction to algebra.



N Drive, Research, Patient Photos, Skin tests



ST DOB: 04-09-1995

Skin Tests 12-28-2001 Weeds, Trees, Mixed Grass, Cat Pelt

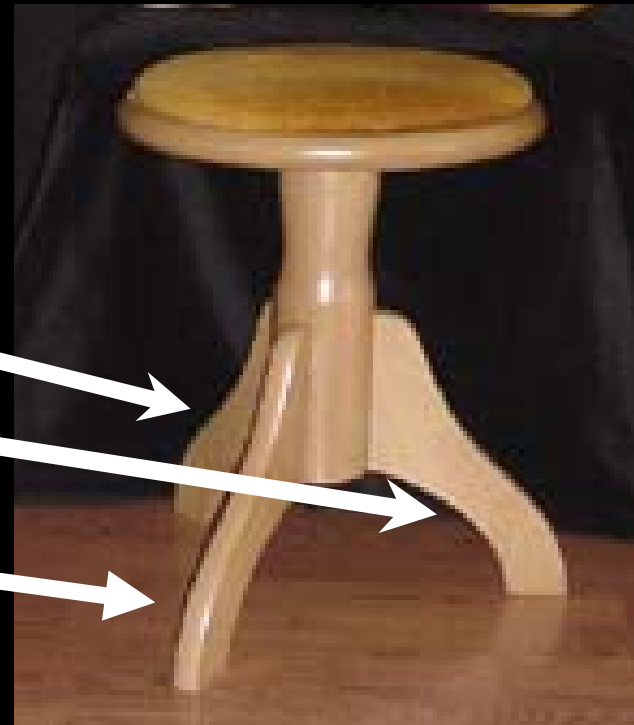






Three Legged Stool of Allergy Treatment

1. Avoidance
2. Medications
3. Immunotherapy



Avoidance



Medications





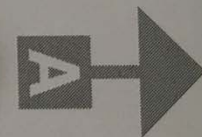
Immunotherapy



Oralair

300 IR

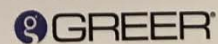
(eet vernal, orchard, perennial rye, timothy, and kentucky blue grass
mixed pollens allergen extract) TABLET FOR SUBLINGUAL USE



Manufactured by:
Stallergenes SA
92183 Antony France
US License # 1893



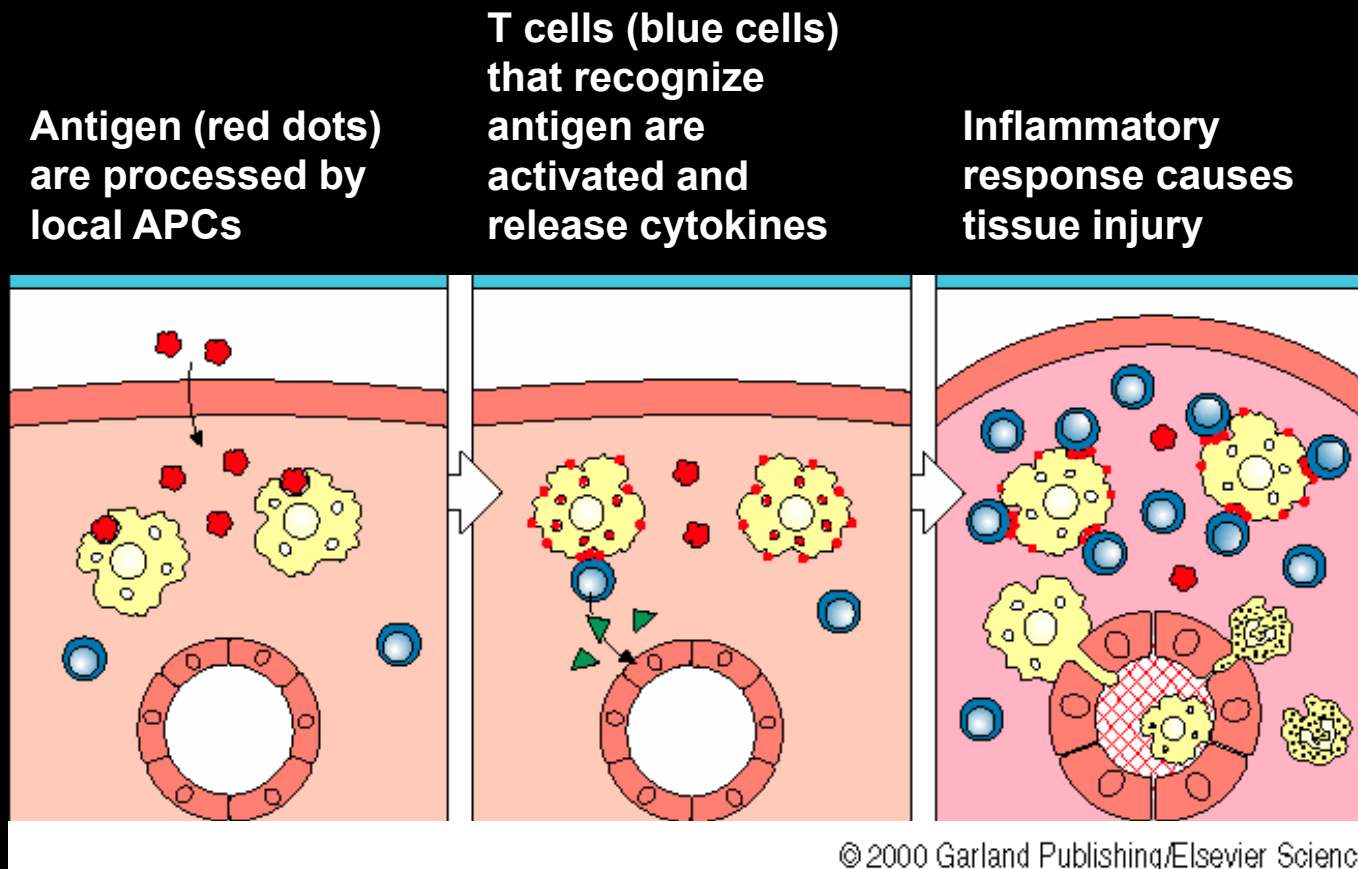
Distributed by:
GREER Laboratories, Inc.
Lenoir, NC 28645



Rx only

Type IV Hypersensitivity - A Delayed Reaction

CONTACT DERMATITIS

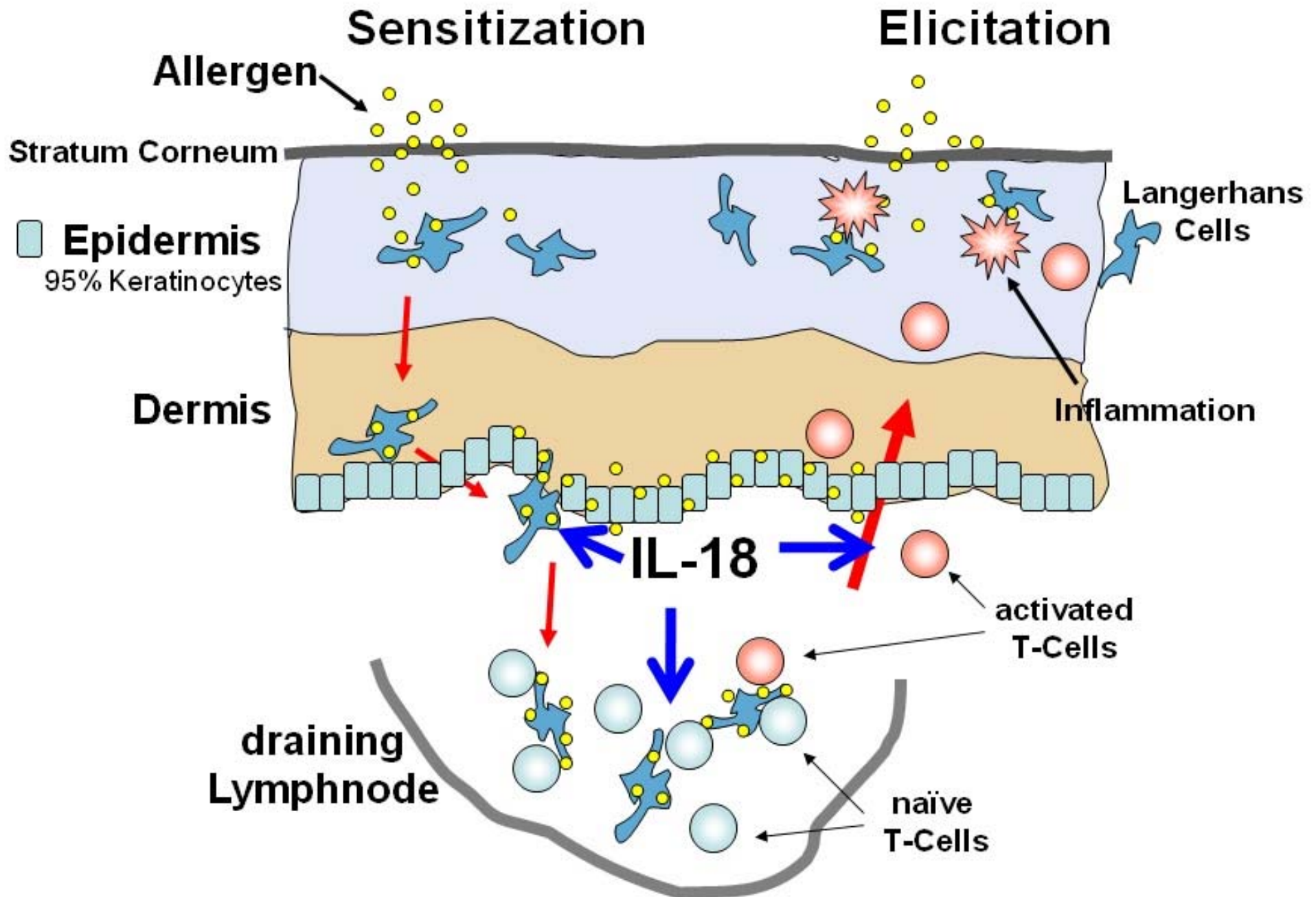


Antigen is presented by APC's to antigen-specific memory T cells.

They become activated and produce chemicals that cause inflammatory cells to move into the area, leading to tissue injury.

Inflammation by 2 - 6 hours with peak in 24 - 48 hours.

ALLERGIC CONTACT DERMATITIS

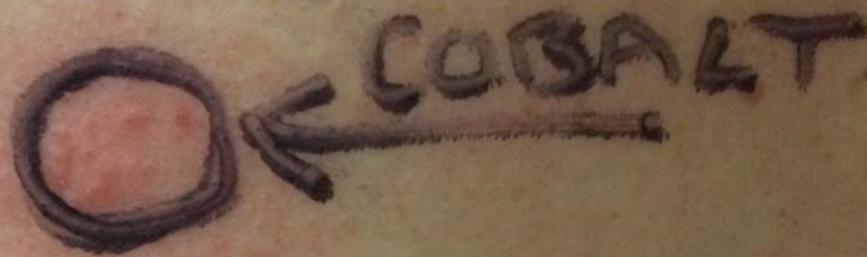








COBALT



NICKEL





STEVENS-JOHNSON SYNDROME

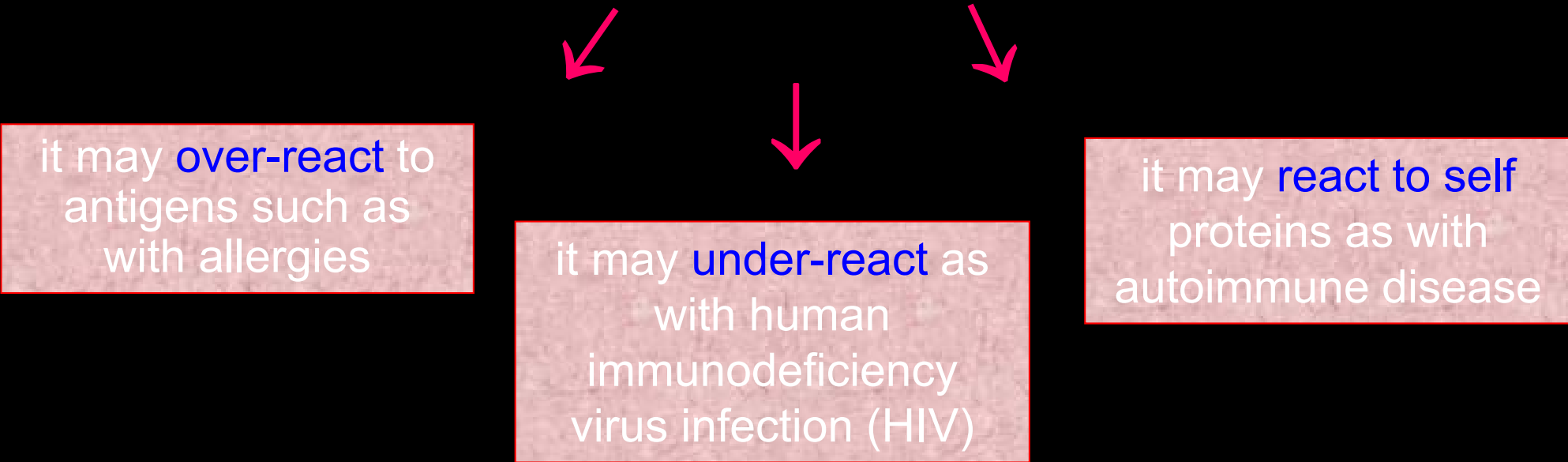


TOXIC EPIDERMAL NECROLYSIS (TEN)



What Makes us Sick?

- “Enemies” in the environment like microbes and chemicals are constantly attacking our bodies, disrupting homeostasis.
- Sometimes immune system homeostasis is disrupted on its own.



it may **over-react** to antigens such as with allergies

it may **under-react** as with human immunodeficiency virus infection (HIV)

it may **react to self** proteins as with autoimmune disease





Auto-Immune Diseases

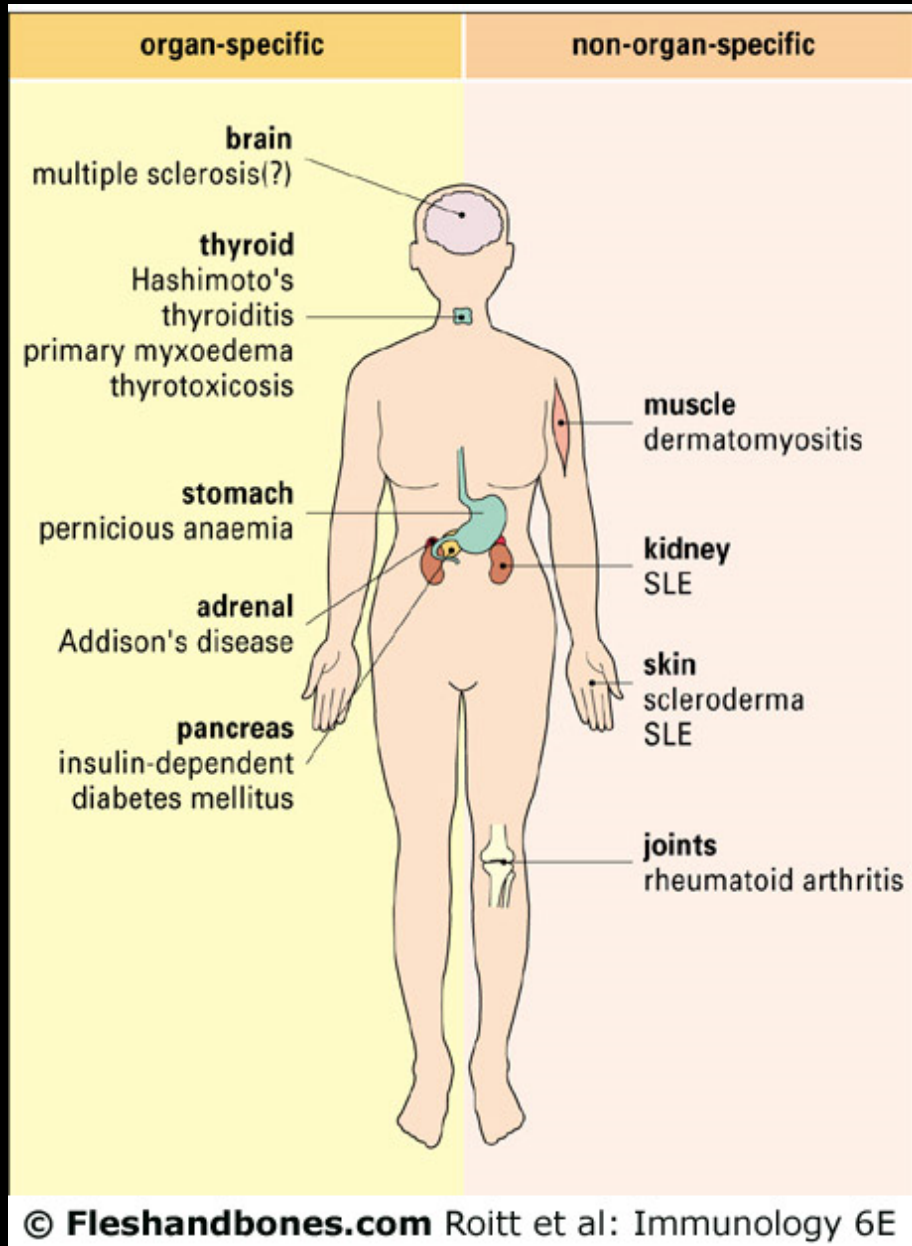
The immune system sees “self” antigens as “non-self”.

- The autoimmune response results in tissue damage;
 - Some damage occurs in only one or a few organs;
 - In other cases it may be body-wide (systemic).
- ~ 3.5 % of people have autoimmune diseases;
On average, women are 2.7 times more likely to develop these diseases than men.
- The cause may be due to genetic factors, infectious agents, gender, and age.
Most auto-immune diseases have no known cause or cure - treatment is aimed at controlling symptoms.

Why Does the Immune System Attack What it's Supposed to Protect?

- **Failure to recognize some cells as “self”**
 - In rheumatic fever, the streptococcus antigen is very similar to a protein in heart tissue, so the body mistakenly identifies heart tissues as foreign.
- **Cells seen as foreign are attacked and destroyed**
 - May be organ-specific, targeting a few select cells or organs;
 - May be systemic.

Auto-Immune Diseases



- Organ-Specific

- Multiple Sclerosis
- Juvenile Diabetes

- Systemic

- Systemic Lupus Erythematosus
- Rheumatoid Arthritis





BECHETS DISEASE

Rheumatoid Arthritis (RA)

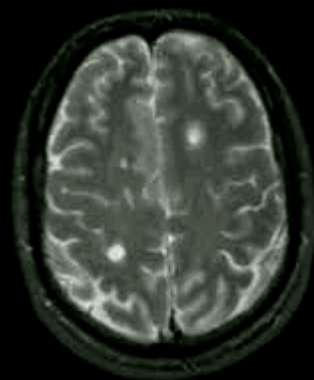
- **A chronic systemic autoimmune disease.**
 - **Anti-self antibodies that react with the constant regions of other antibodies (rheumatoid factor).**
- **Disease onset occurs most often between the ages of 25 – 55.**
 - **Women are 3 times more likely to develop this than men.**
- **Symptoms include weakness, fatigue, and joint pain.**
- **Infections, hormones and genetic factors may be involved.**



X-ray shows severe arthritis affecting the joints and limiting mobility

Multiple Sclerosis (MS)

- A chronic organ-specific disease - may be mild or severe.
 - MS involves the destruction of the myelin sheath that covers cells of the spinal cord and brain.
- Affects ~ 1 in 1,600 people.
 - 60% of the cases occur in women.
- Symptoms include weakness, tremors or paralysis of one or more extremities, numbness, decreased memory and attention span and may disappear and recur over time.
- Infections, hormones and genetic factors may be involved.

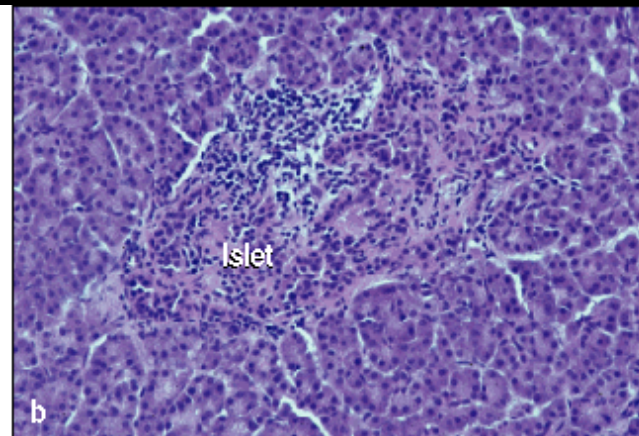
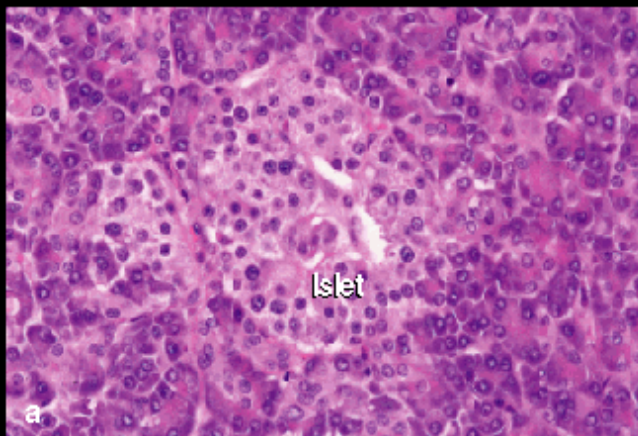


Magnetic resonance image of brain of patient with chronic form of multiple sclerosis, showing characteristic lesions of MS (white spots)

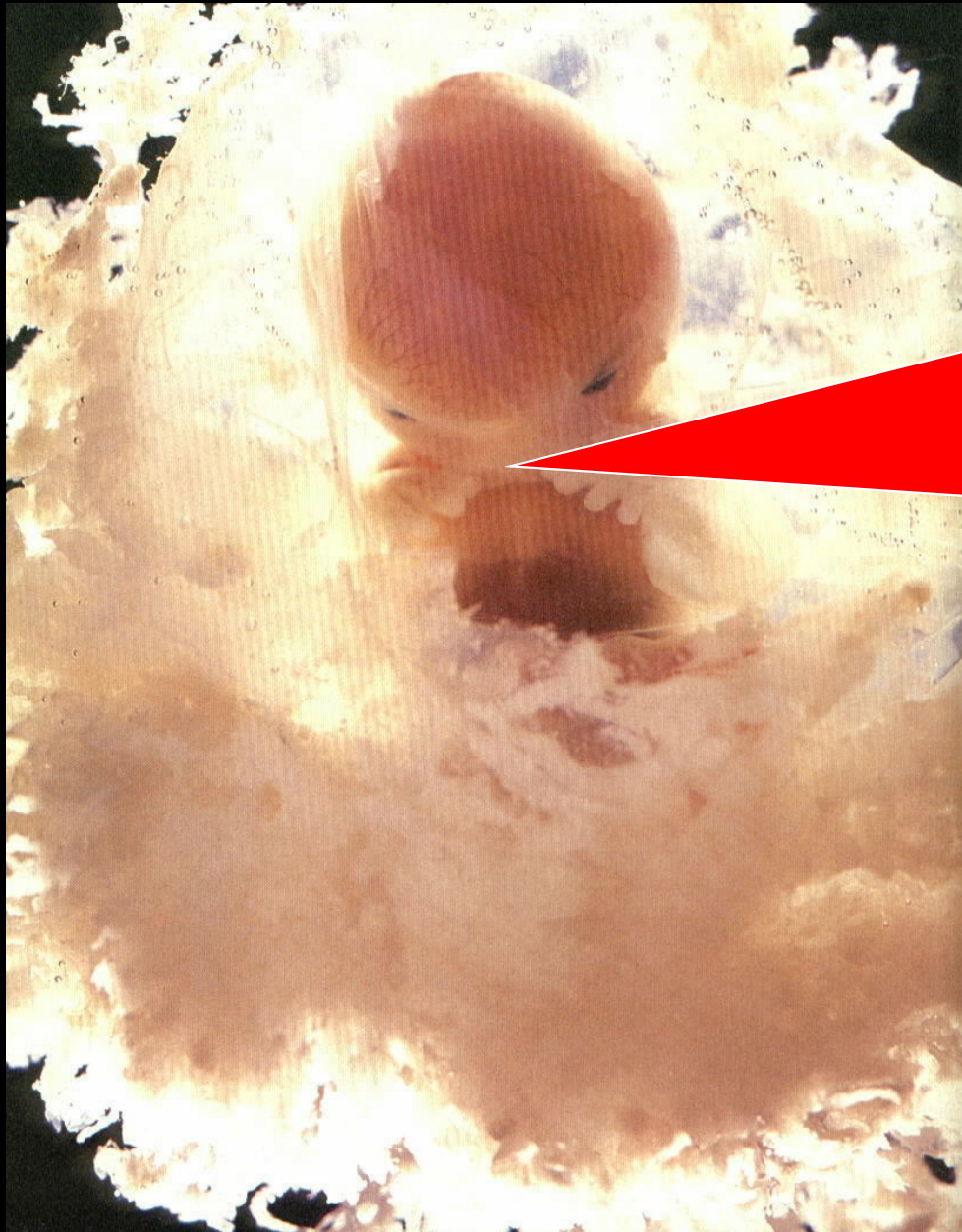
Juvenile Diabetes

- Also known as Type - I diabetes or insulin-dependent.
 - Beta-cells in the pancreas produce little or no insulin.
- Usually occurs before the age of 30.
 - Occurs in 1 in 7,000 children each year.
 - The incidence decreases after the age of 20.
- Symptoms include increased thirst and urination, weight loss, nausea, and fatigue.
- Cause is linked to genetic, viral, and autoimmune factors.

**Normal
pancreas**

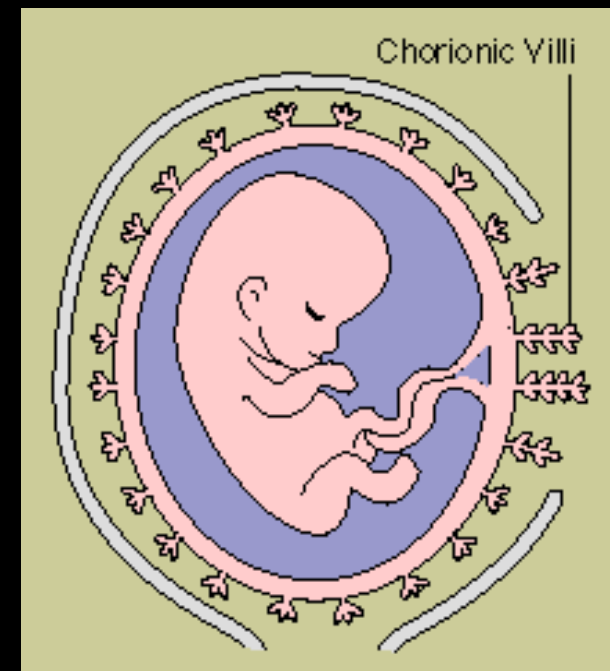


**Diabetic
pancreas**

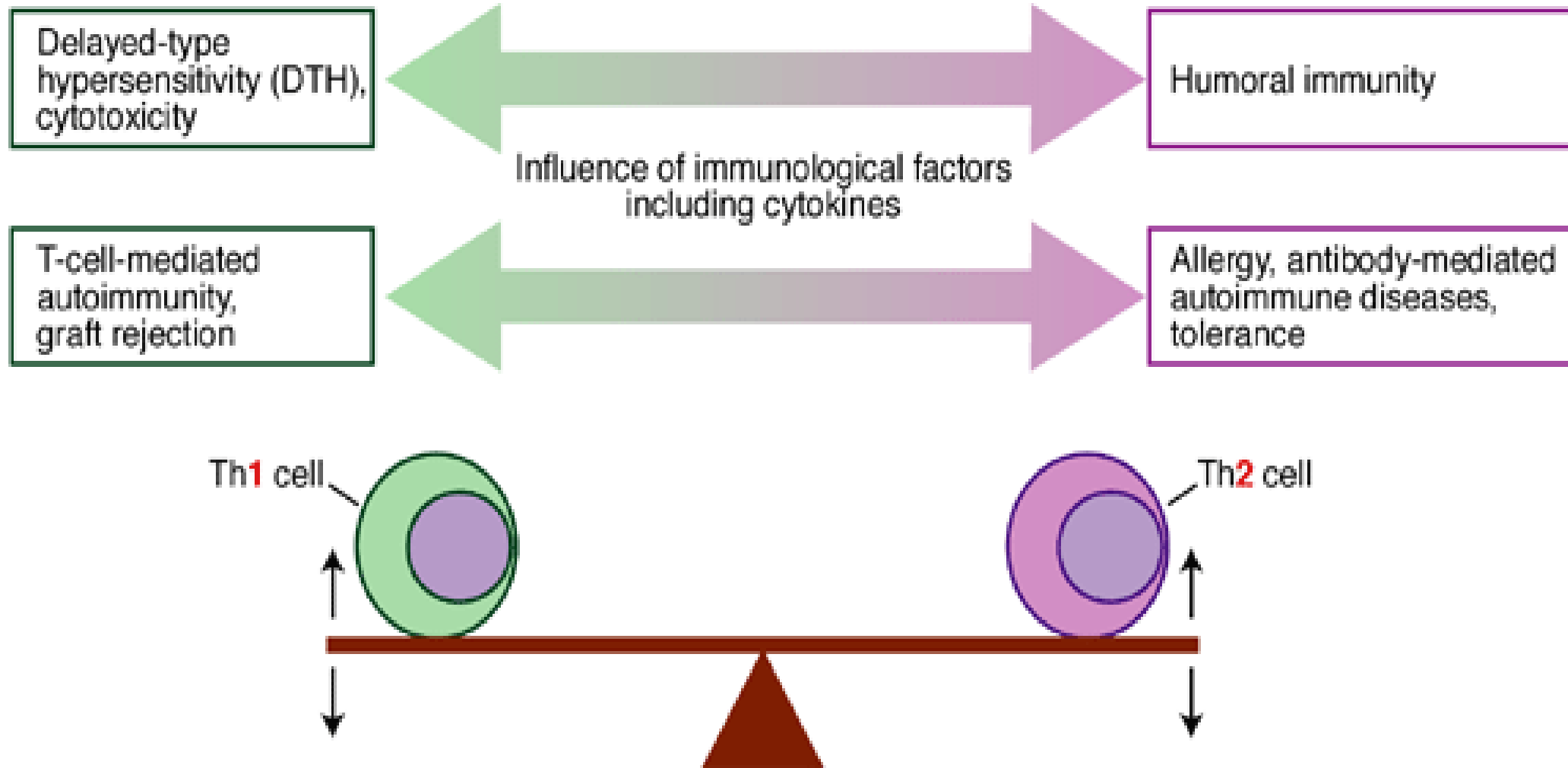


**I am only
half my mom!**

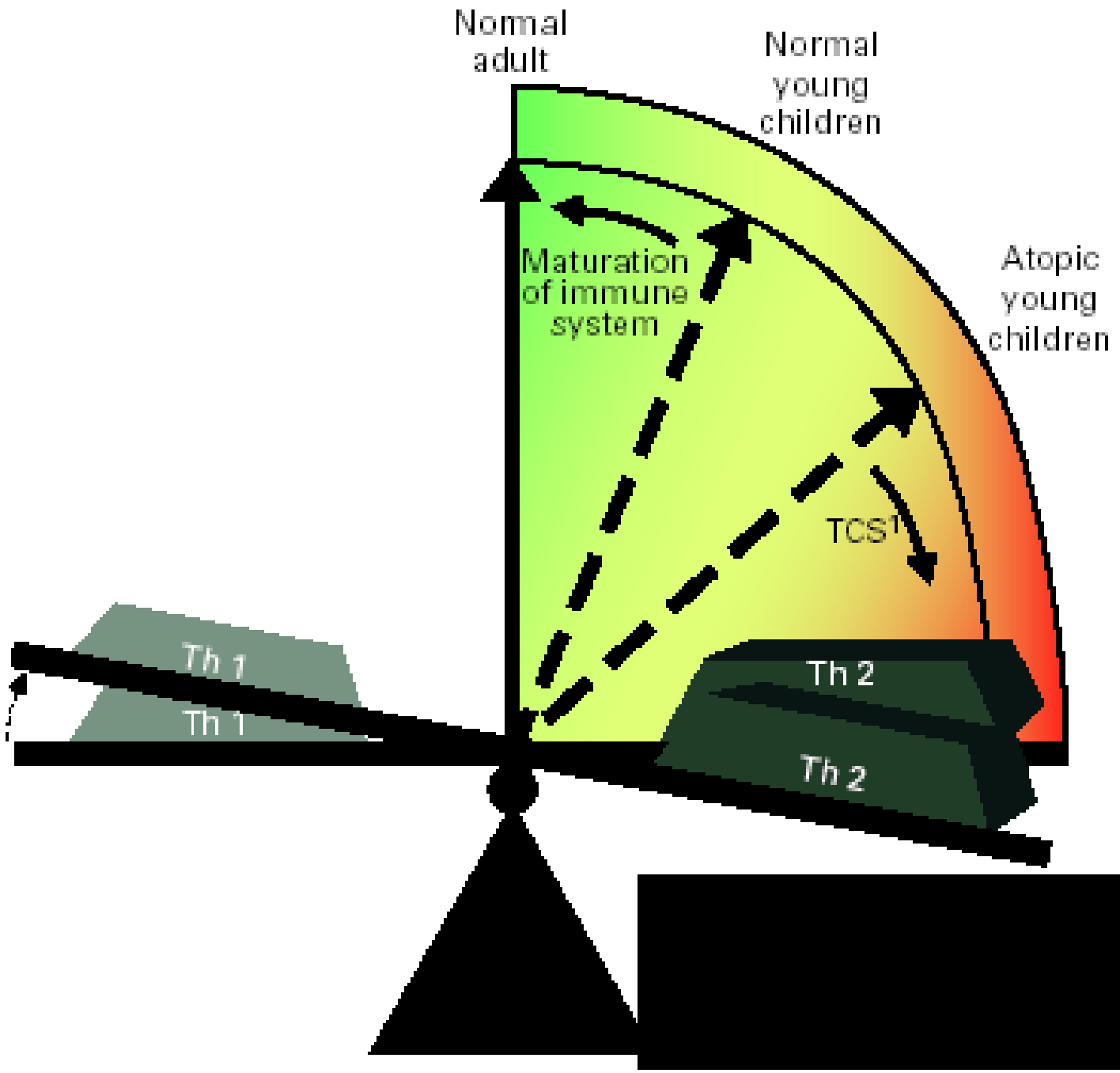
**How does
mom's
immune
system
tolerate me?**



TH1 and TH2 Balance



A model to illustrate the complex balance between T helper 1 (Th1) and Th2 cells



Questions?

