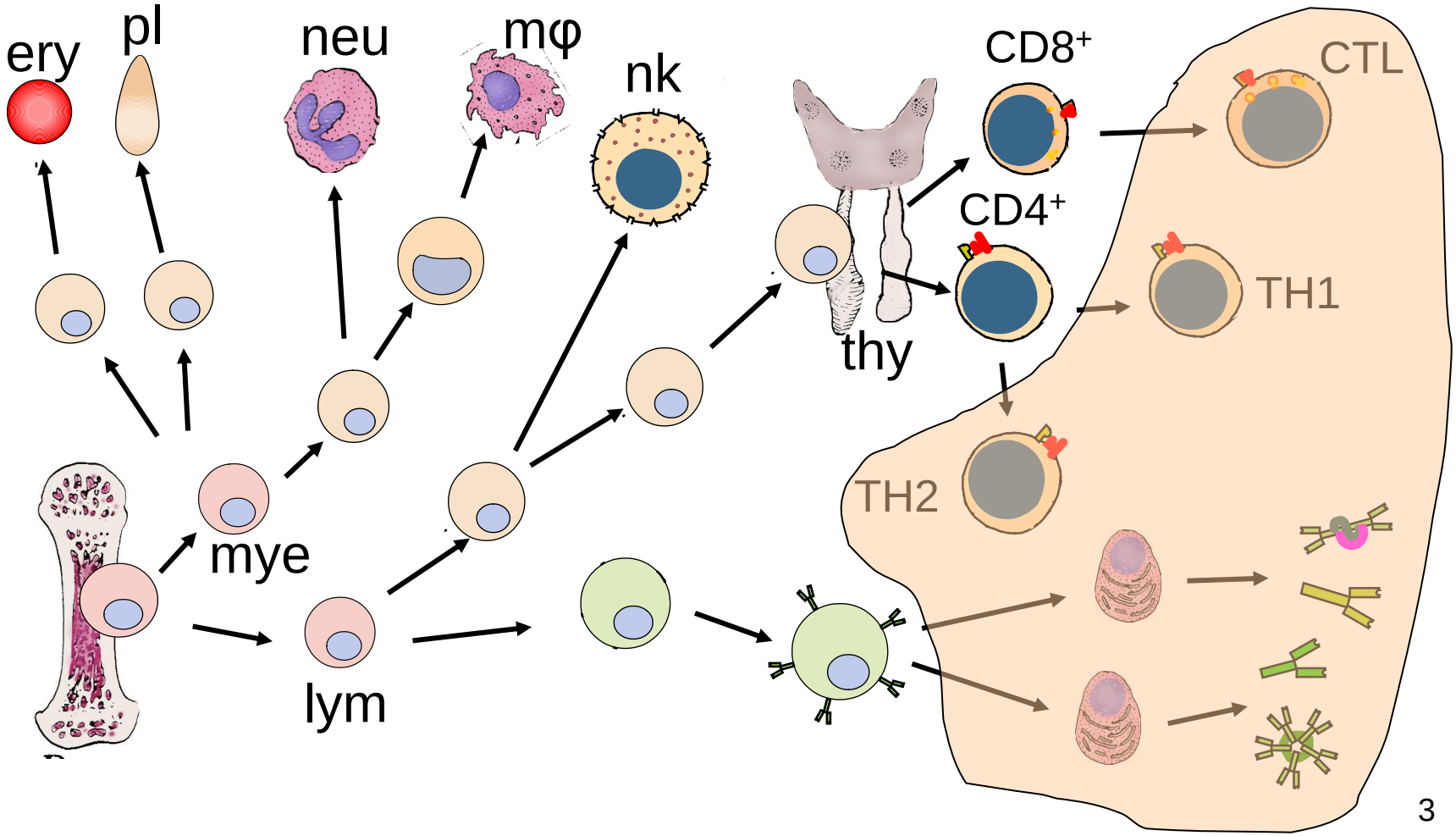
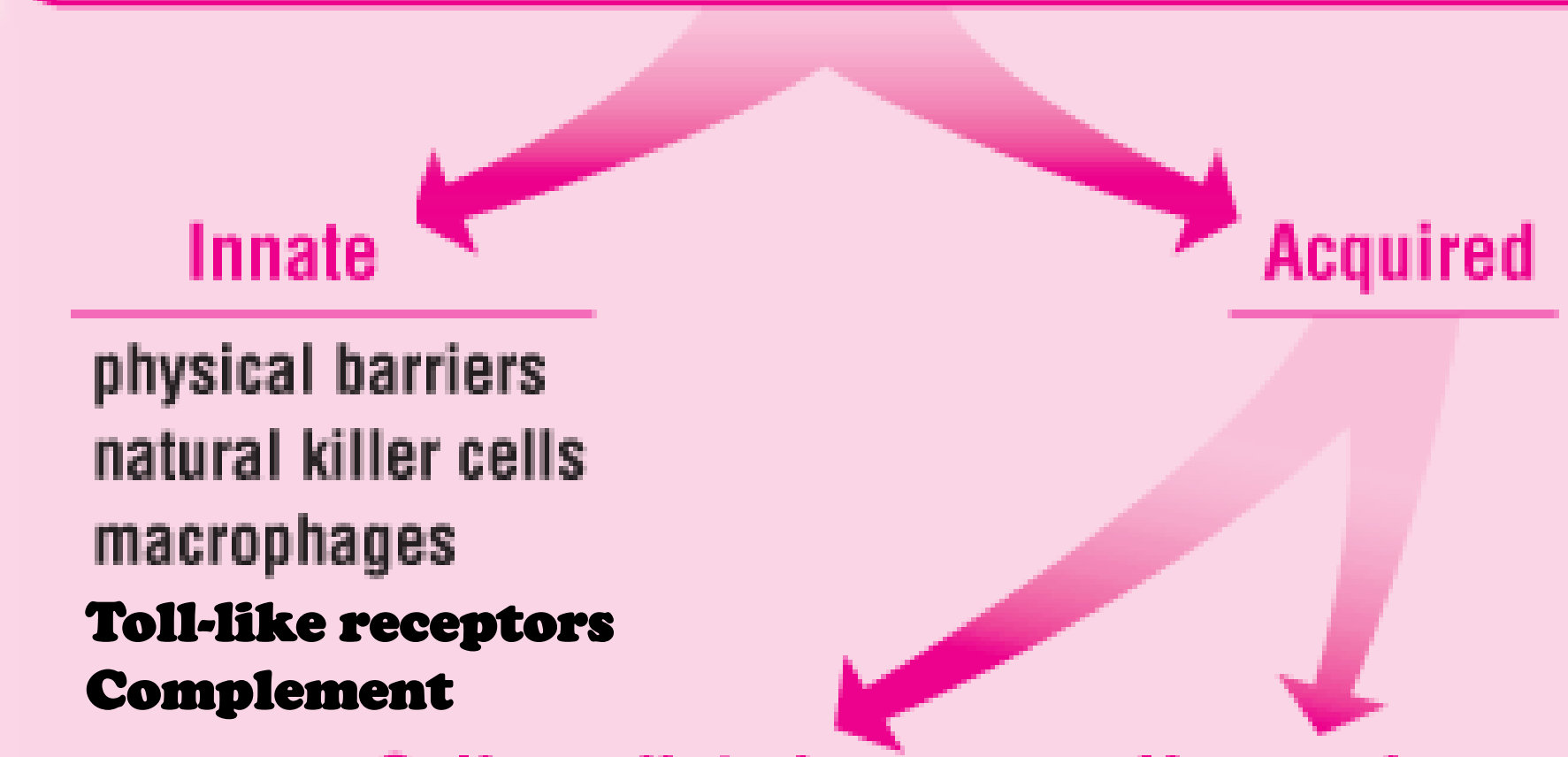
Allergy and Immunology

Kraig W. Jacobson, M.D. Feb. 10, 2015

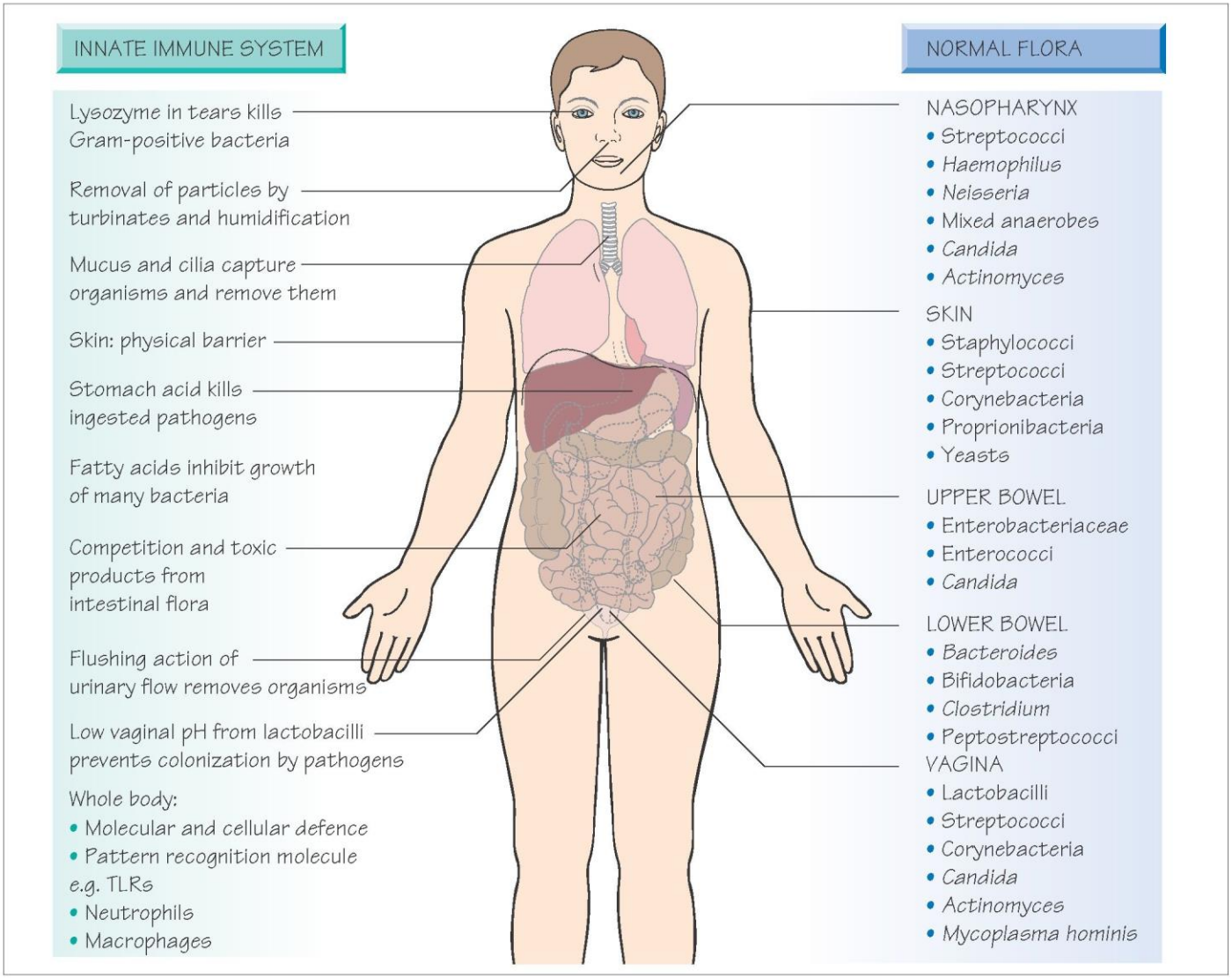
Development of the Immune System

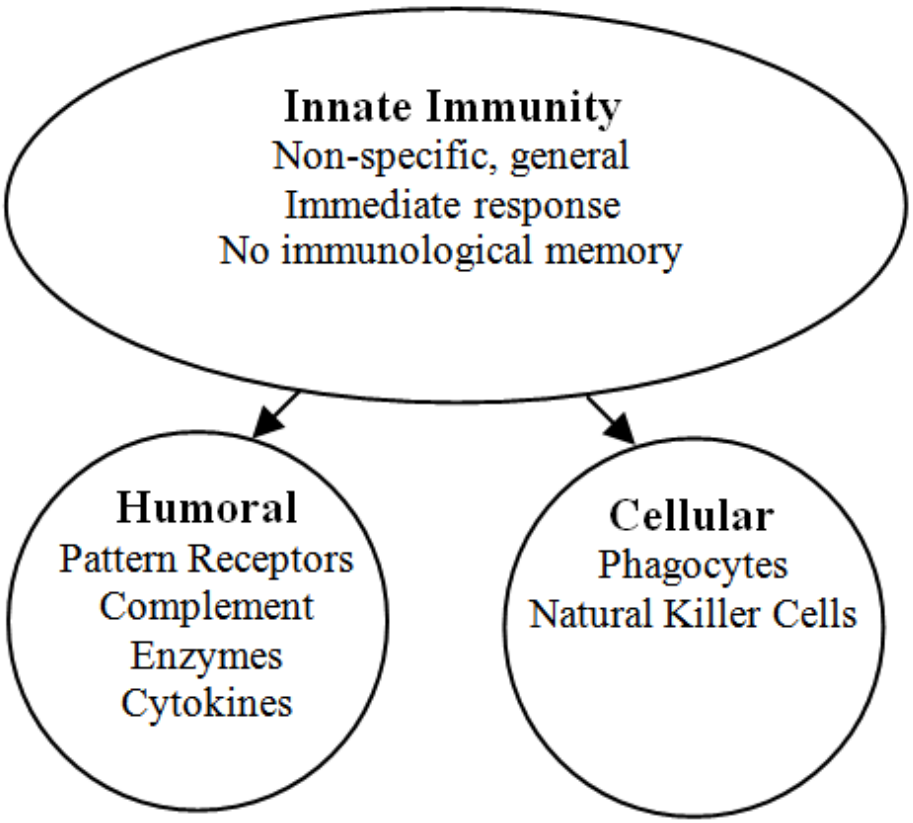


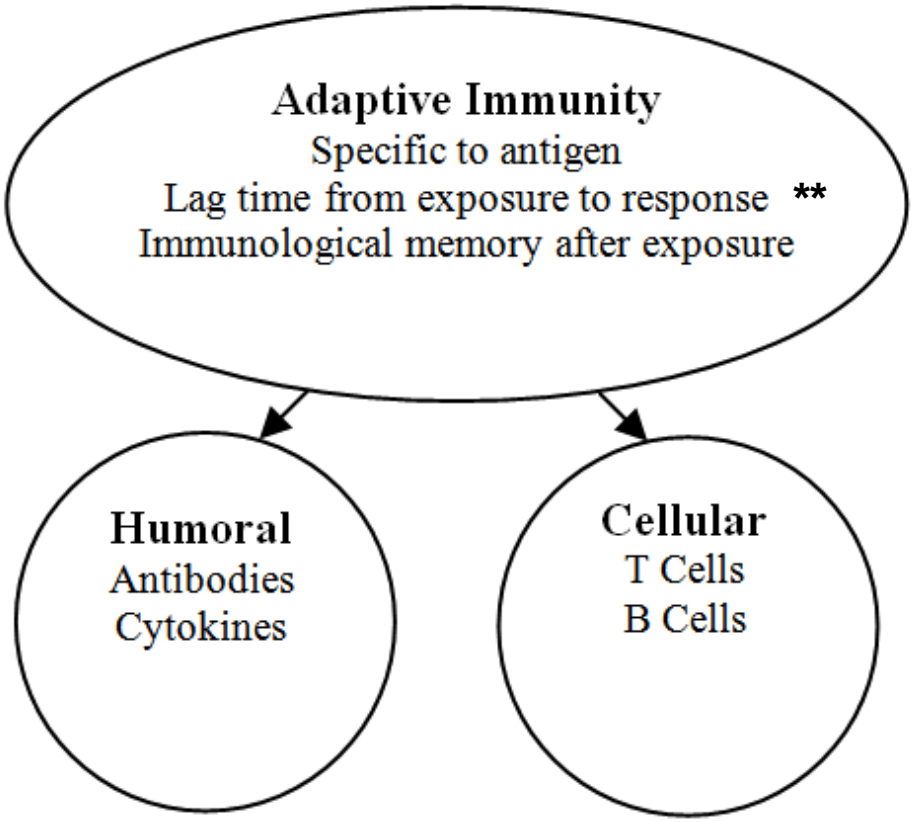
The Immune System



Innate Immune System

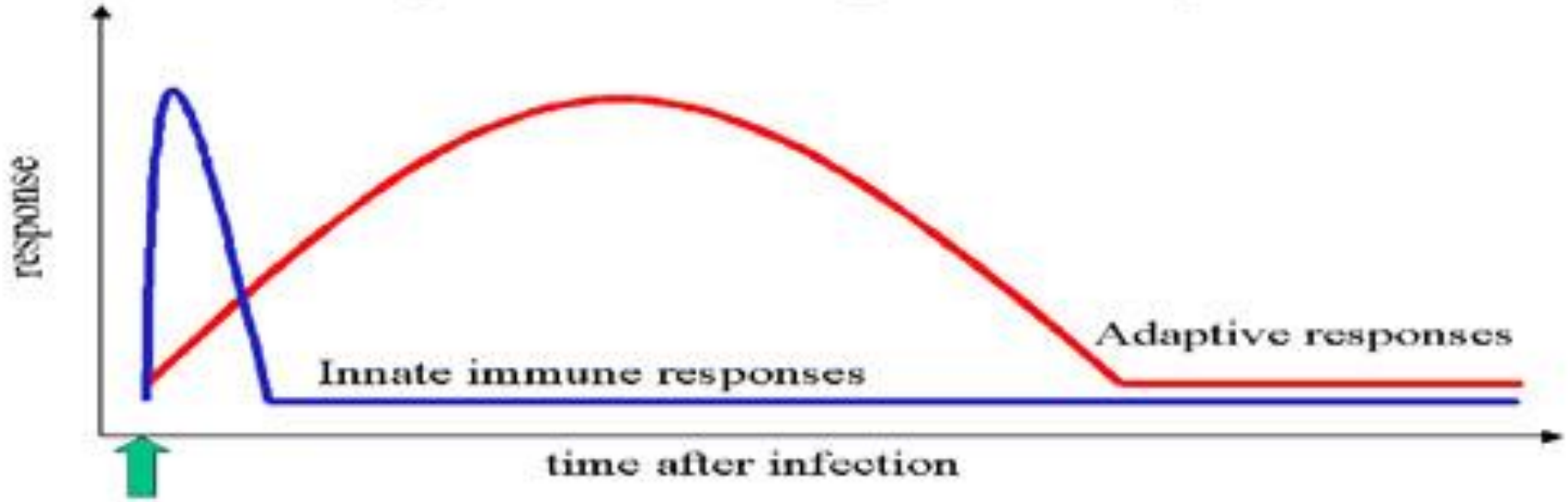






****Except for IgE allergic reactions**

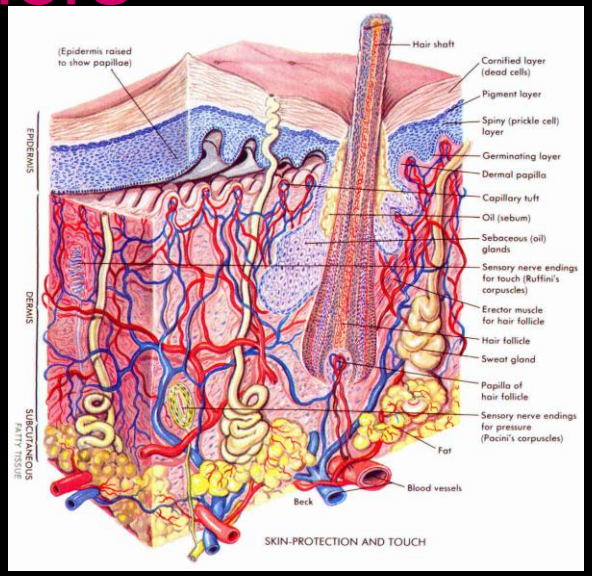
Model of Immune Responses: Speed and Specificity



INNATE IMMUNITY

Physical Barriers

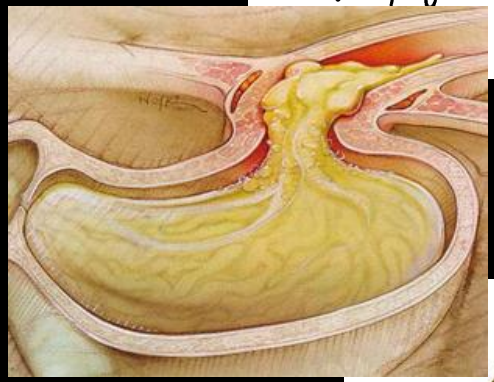
- skin
- hair
- mucous



INNATE IMMUNITY

Chemical Barriers

- sweat
- tears
- saliva
- stomach acid
- urine



Fallagrin null mutation

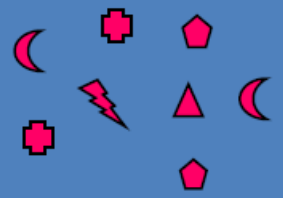
4 Compartments of the Immune System

Innate Immunity

Adaptive Immunity

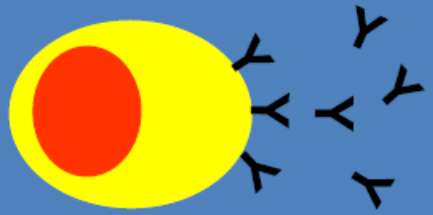
Complement

"Land Mines"



B Cells

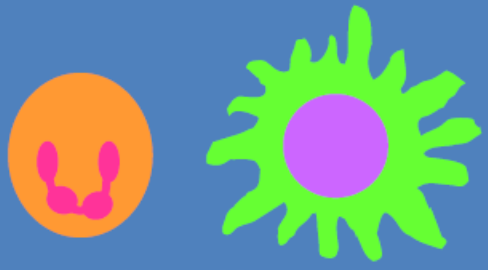
"Air Force – Make & Deploy Cruise Missiles"



Host Defense

Phagocytes

"The Marines"



Neutrophils Macrophages

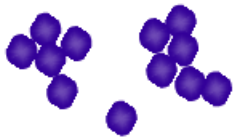
T Cells

"The Generals"
"The Assassins"
"The Psychologists"

Cytokines & Chemokines

Complement

Classical



Alternative

Immune Complex

Microbes

C3(H_2O), Bb

C1

C4 *C2*

C4b, 2a

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

C3b, Bb, P

C3

Anaphylotoxin *C3a* *C3b* Opsonin

Factor I

Factor H

- Familial HUS
- Age-related Macular Degeneration

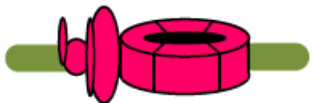
- Recurrent *Neisserial* infections

C5

C5a

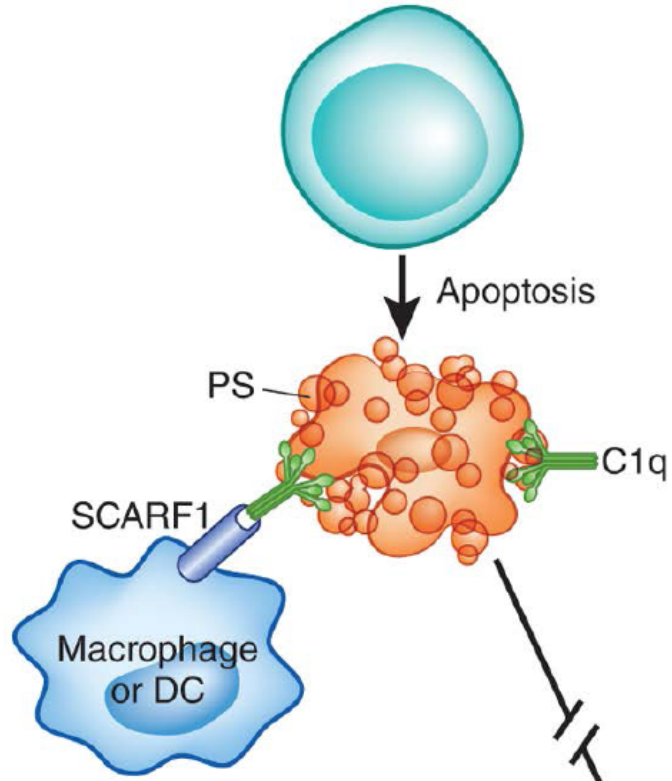
C5b, 6, 7, 8, 9

Membrane Attack Complex Bactericidal Activity



Immune System – Garbage Disposal is Important

Complement and Phagocytes Aid in Clearance of Cell Debris



DNA, HMGB1 → ANA → Type I IFN

Autoimmunity

Complement Deficiency

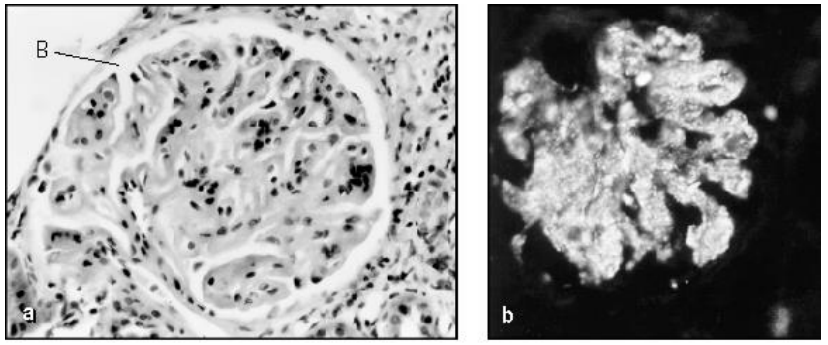
- **C1q/r/s Deficiency** – ~90% of homozygotes develop SLE or GN, usually <20 y/o.
- **C4 Deficiency** - ~75% of homozygotes develop SLE or GN.
- **C2 Deficiency** – Most common homozygous complement deficiency. ~40% of homozygotes develop SLE or GN .

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

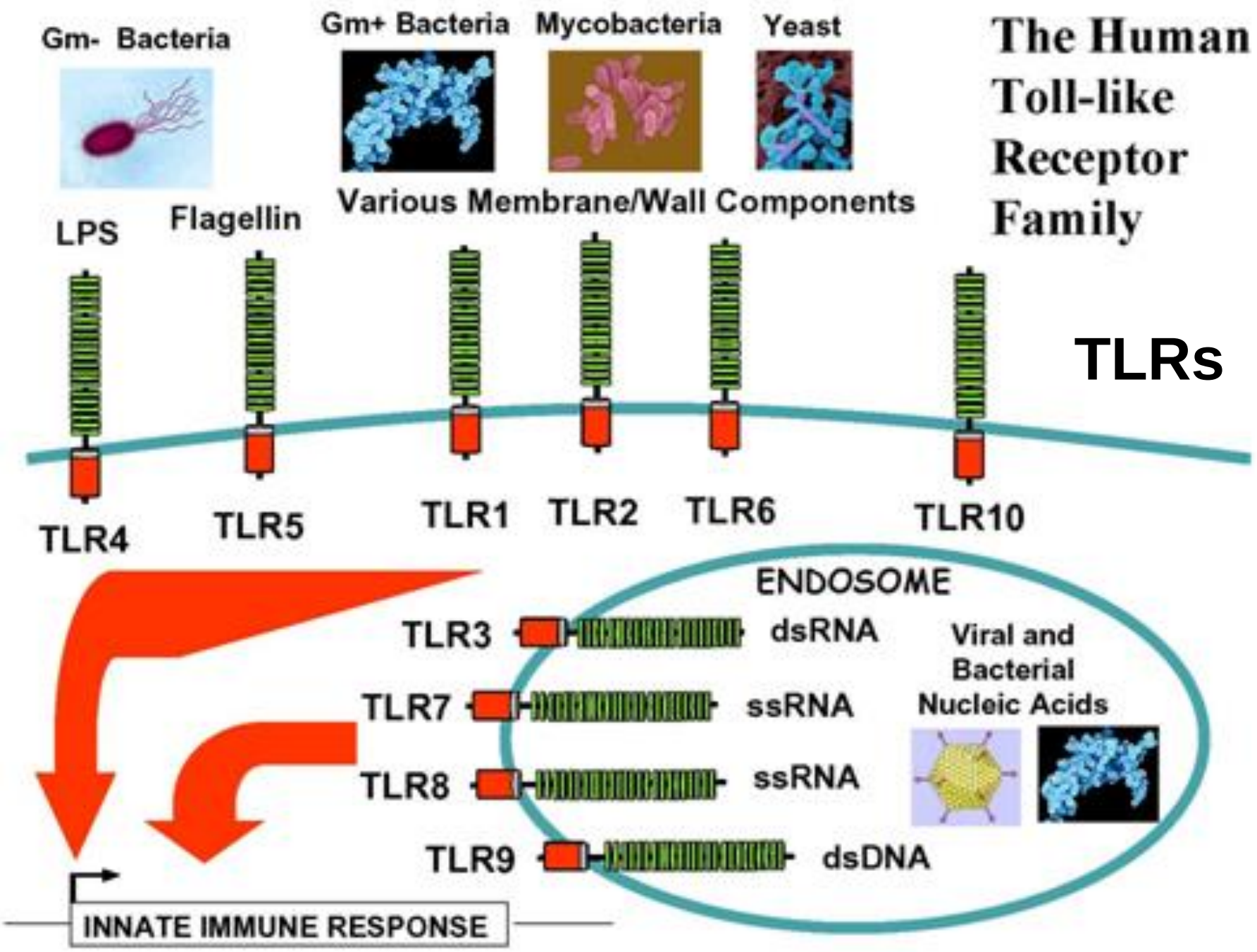
Systemic Lupus Erythematosus (SLE)

- 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.

Lupus “butterfly” rash



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


Gm- Bacteria
Gm+ Bacteria
Mycobacteria
Yeast
The Human Toll-like Receptor Family
Various Membrane/Wall Components
LPS
Flagellin
TLRs
TLR4
TLR5
TLR1
TLR2
TLR6
TLR10
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-α (INF-α), interleukin-6 (IL-6), and tumor necrosis factor-α (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

Adaptive Immunity

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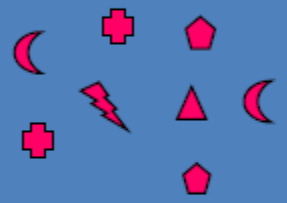
"Land Mines"



B Cells

"Air Force – Make & Deploy Cruise Missiles"

Host Defense

Phagocytes

"The Marines"

Neutrophils Macrophages

Cytokines & Chemokines

T Cells

"The Generals"
"The Assassins"
"The Psychologists

Innate Immunity	Adaptive Immunity
Antigen independent	Antigen dependent
No time lag	A lag period **(except IgE)**
Not antigen specific	Antigen specific
No Immunologic memory	Development of memory

Primary Function of the Adaptive Immune System

- Protect self from non-self;

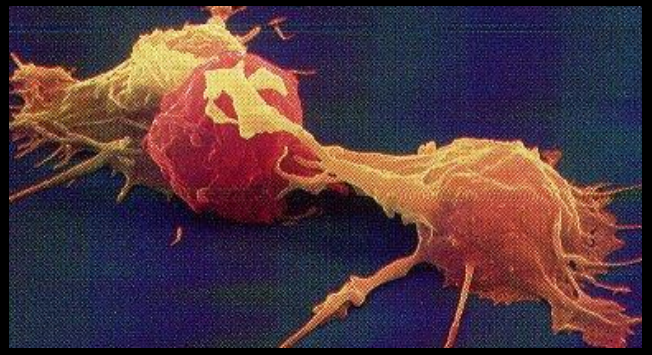
and …

- Remember it!


ASTHMA

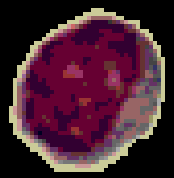
T and B Lymphocytes

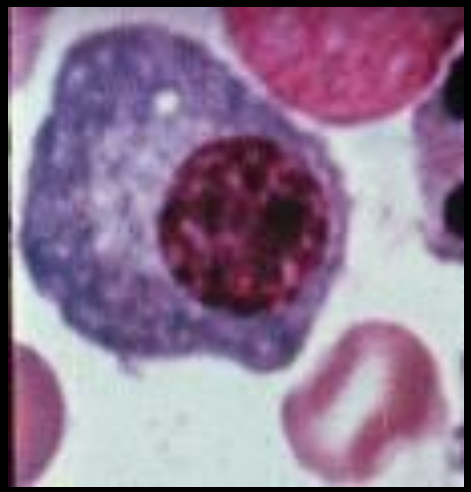
- **T** cells originate from the **Thymus** and may be Helper (CD4), Suppressor (CD8) or Cytotoxic.



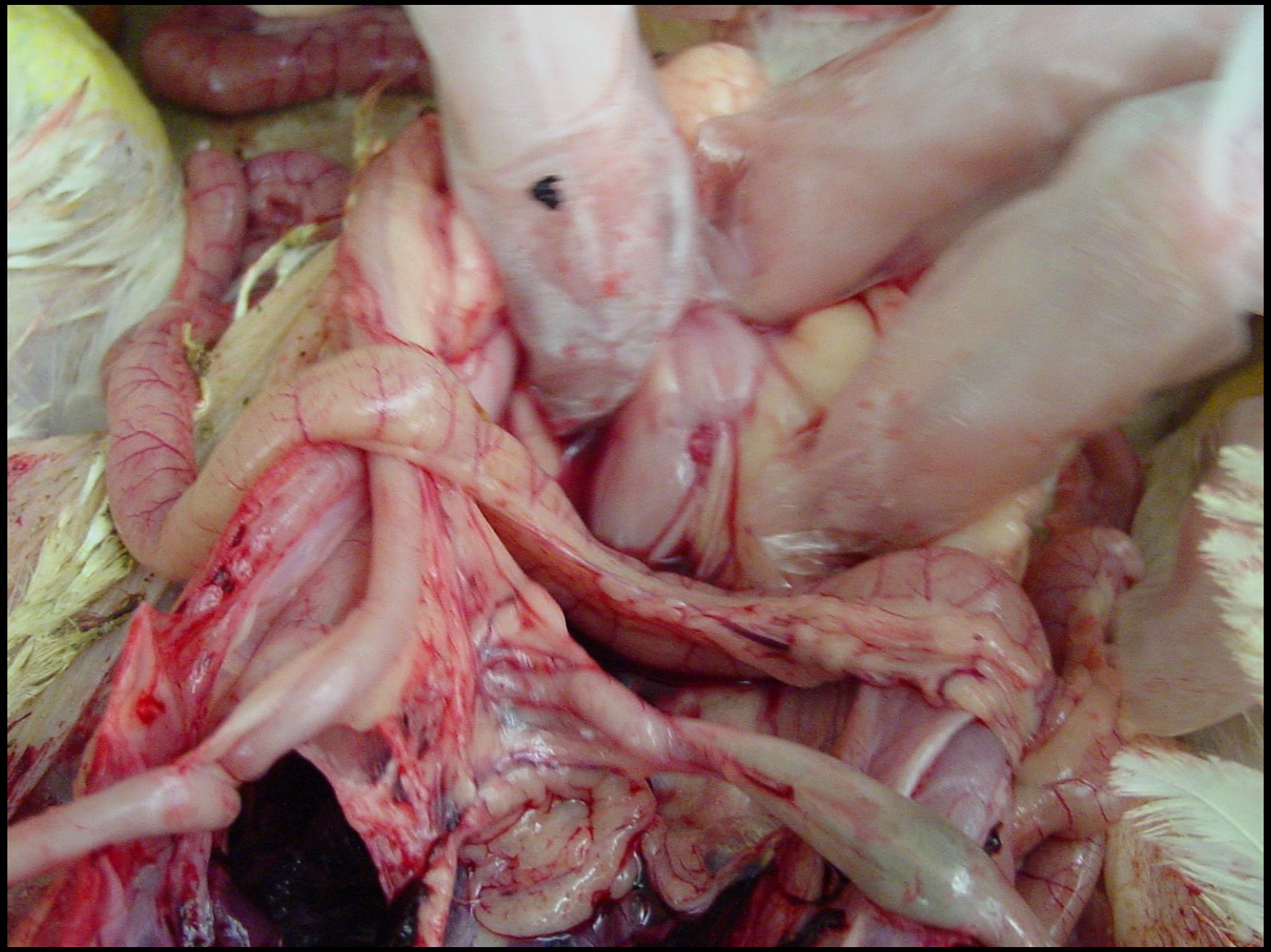
- **B** cells originate from the **"Bursa".**

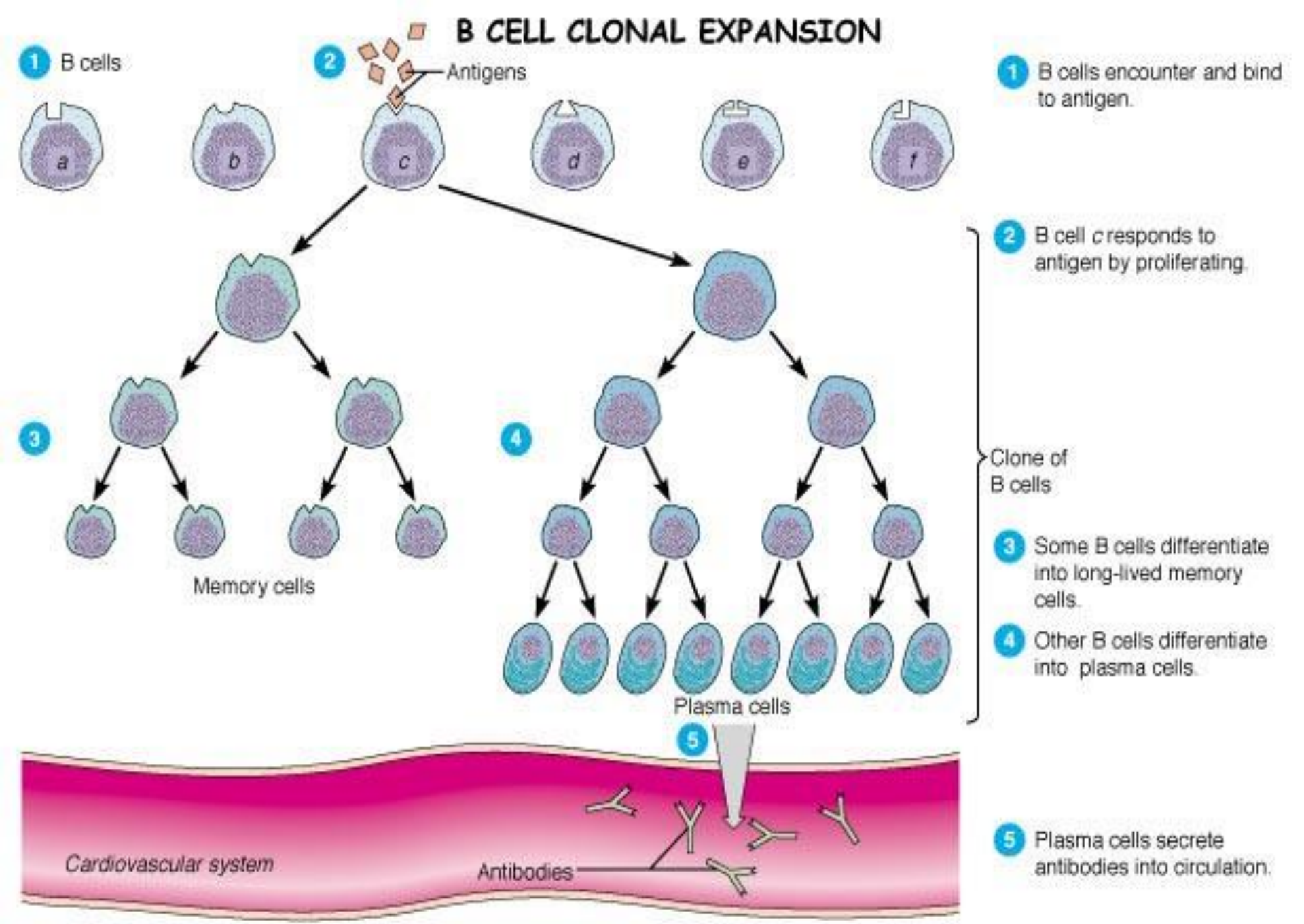
Their major function is to produce antibodies in response to foreign proteins including bacteria, viruses, and tumor cells.





Bursa of Fabricus





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

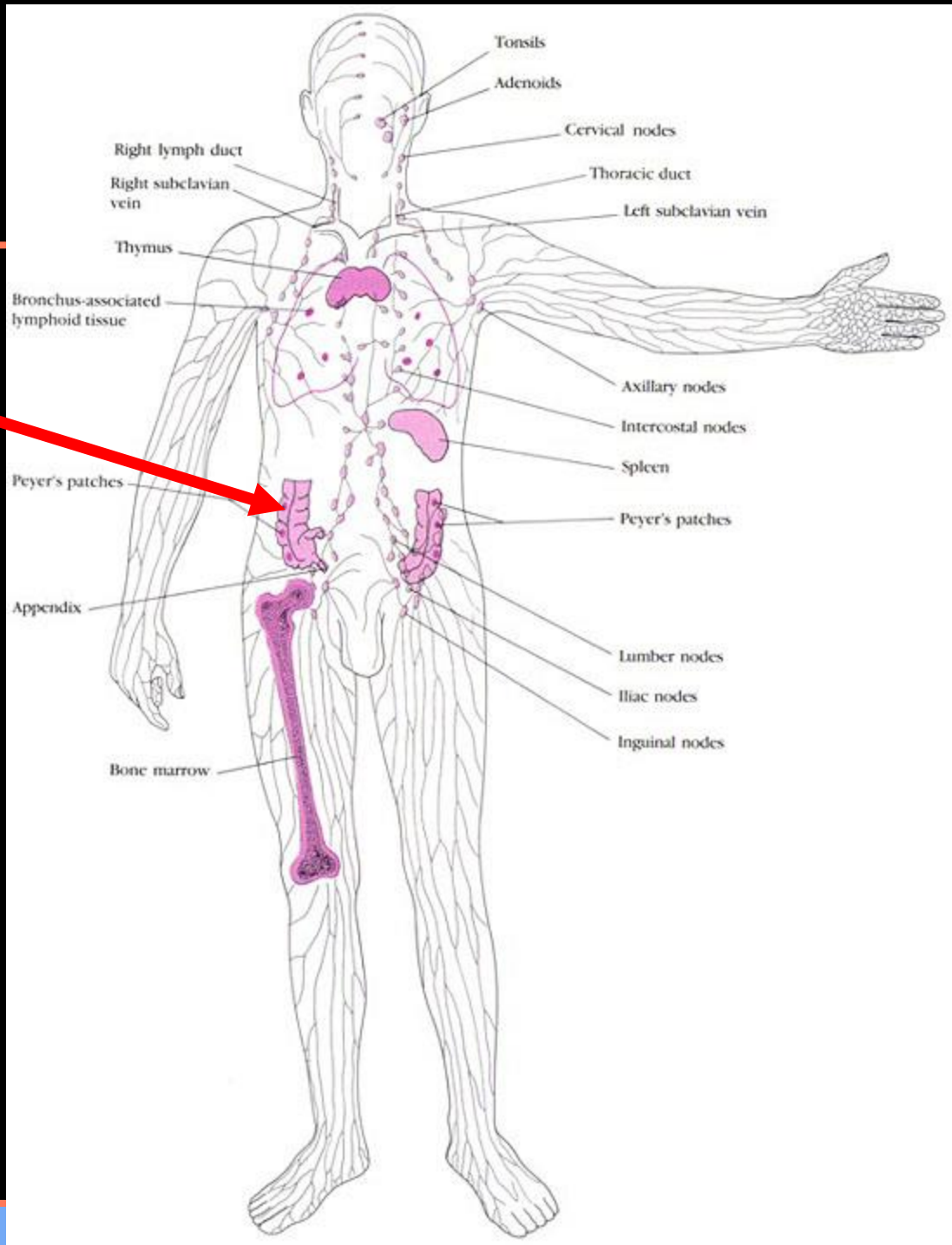
Humoral = Immediate sensitivity
Antibodies (Type I, II, III)

Two Sides of the Adaptive Immune System

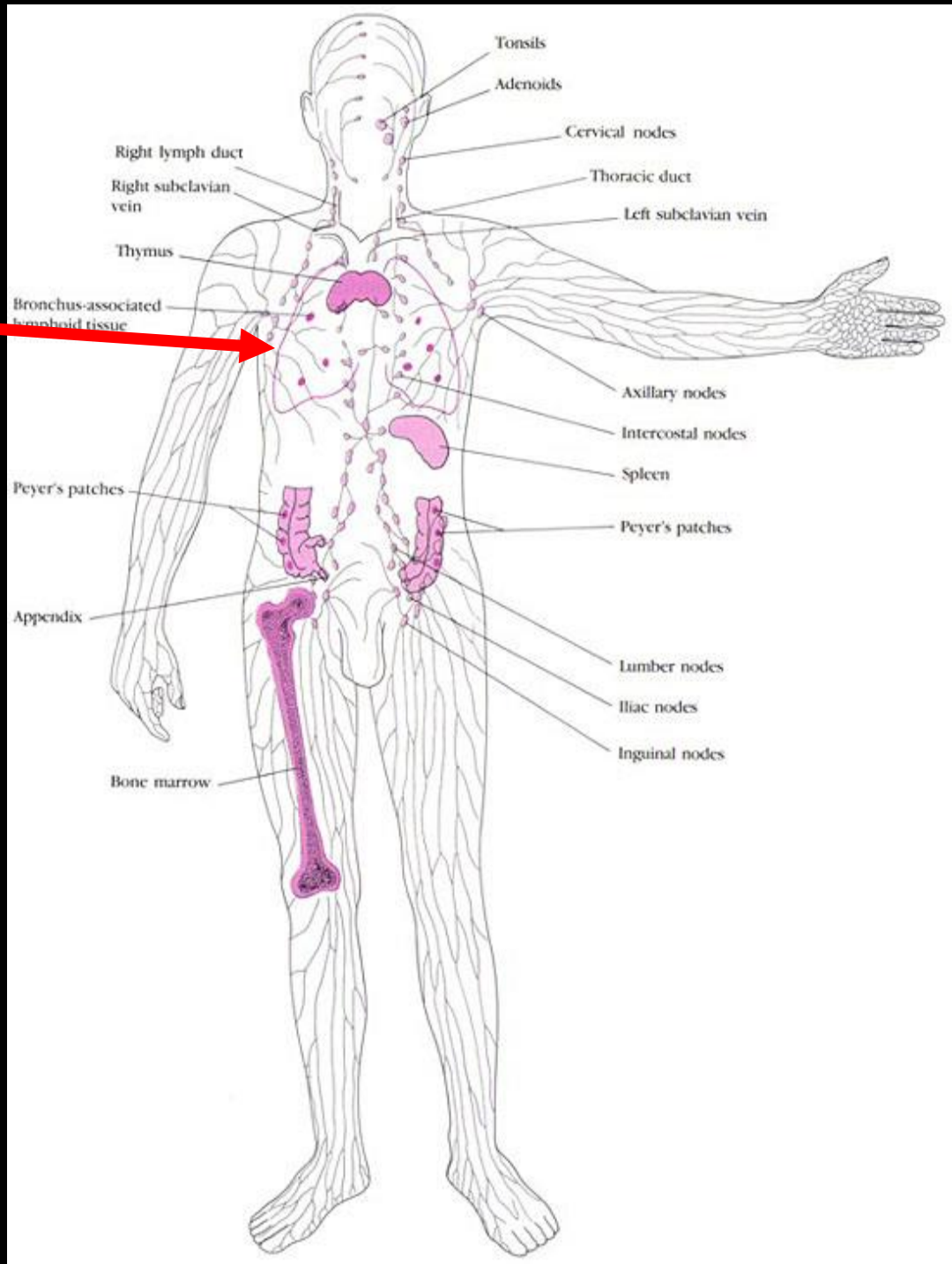
Cellular = Delayed sensitivity (Type IV)

24 - 48 hours after exposure
CONTACT DERMATITIS

GALT = Gut Associated Lymphoid Tissue

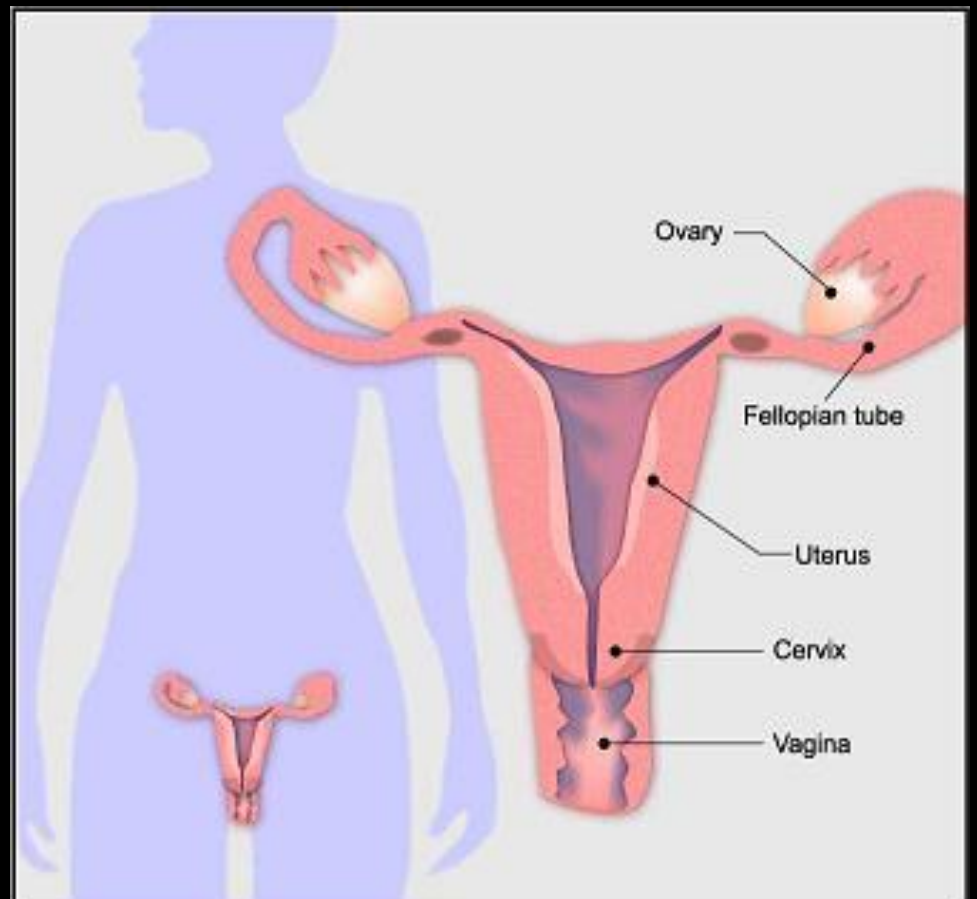


BALT =
Bronchial **A**ssociated
Lymphoid **T**issue

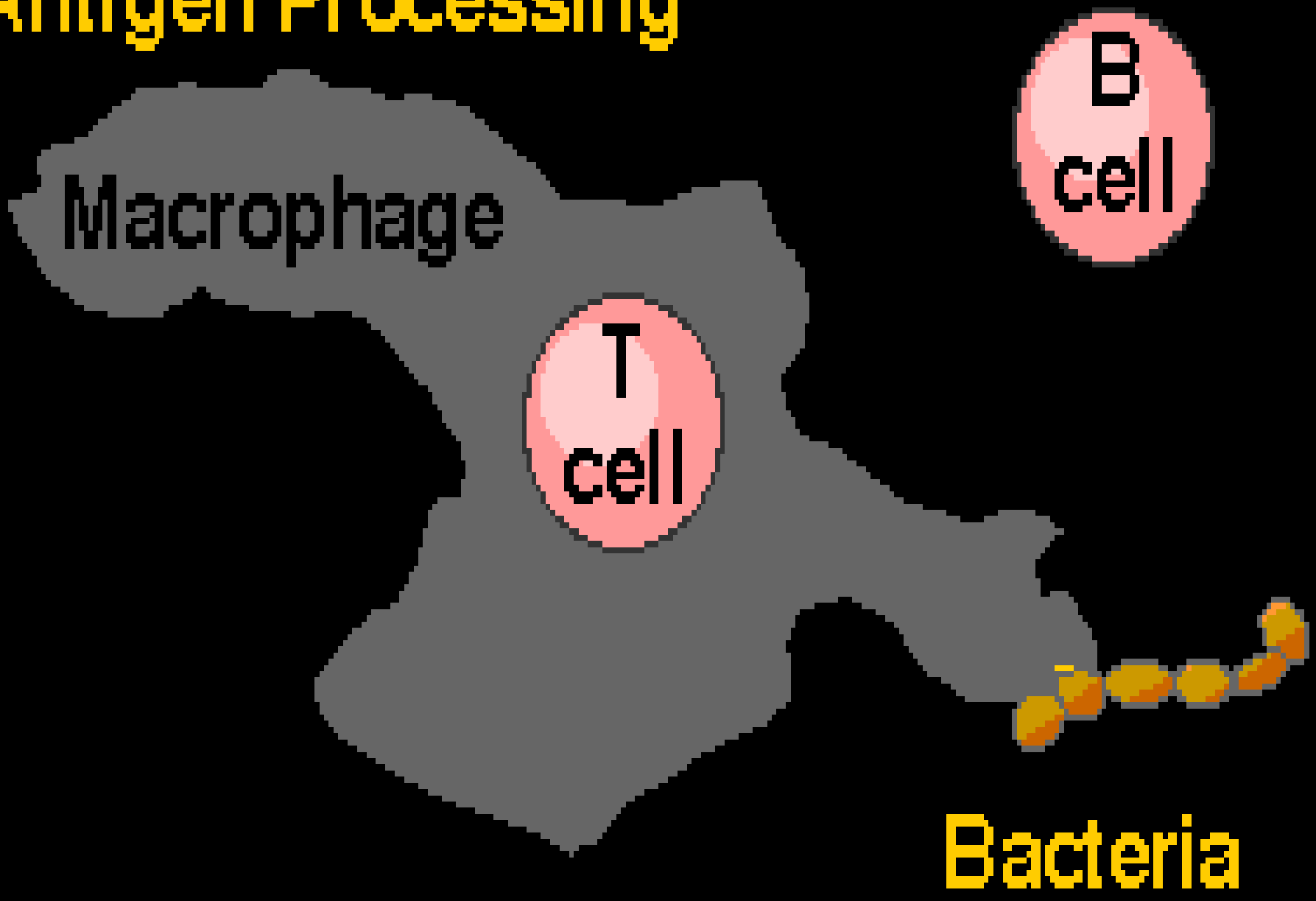


GENITAL TRACT

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



Antigen Processing



Remember the 5 Classes of Antibodies

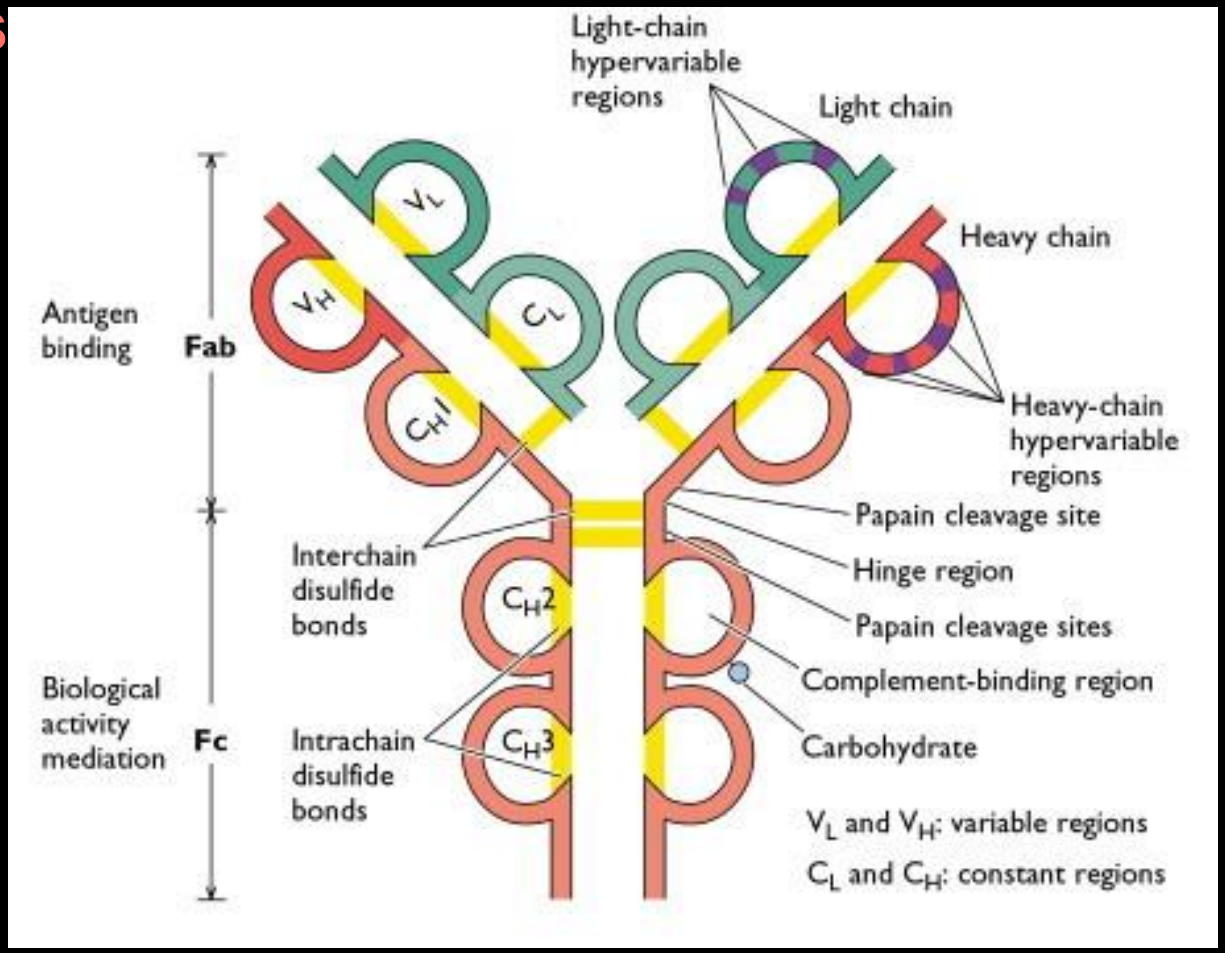
- Ig = Immunoglobulin

G – A – M – E – D

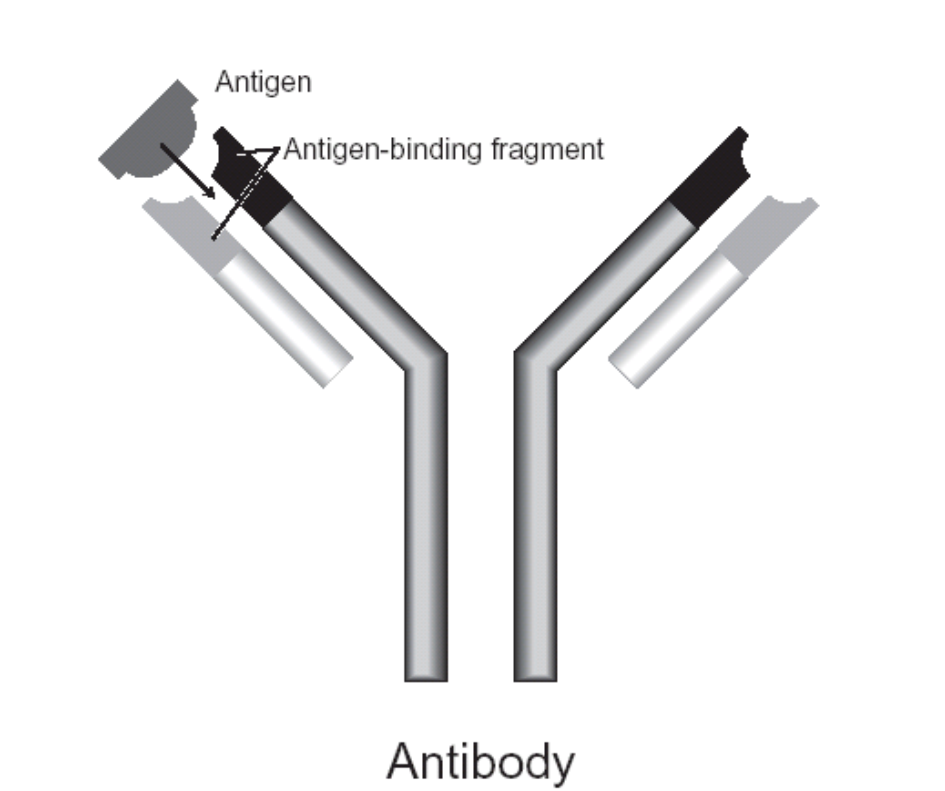
- Ig**G** = “**G**ood” major antibody class
- Ig**A** = “**A**ppetite” to “**A**” hole, orifices
- Ig**M** = **M**acroglobulin, first one out
- Ig**E** = “**E**vil”, causes allergies
- Ig**D** = “**D**umb class”, does nothing

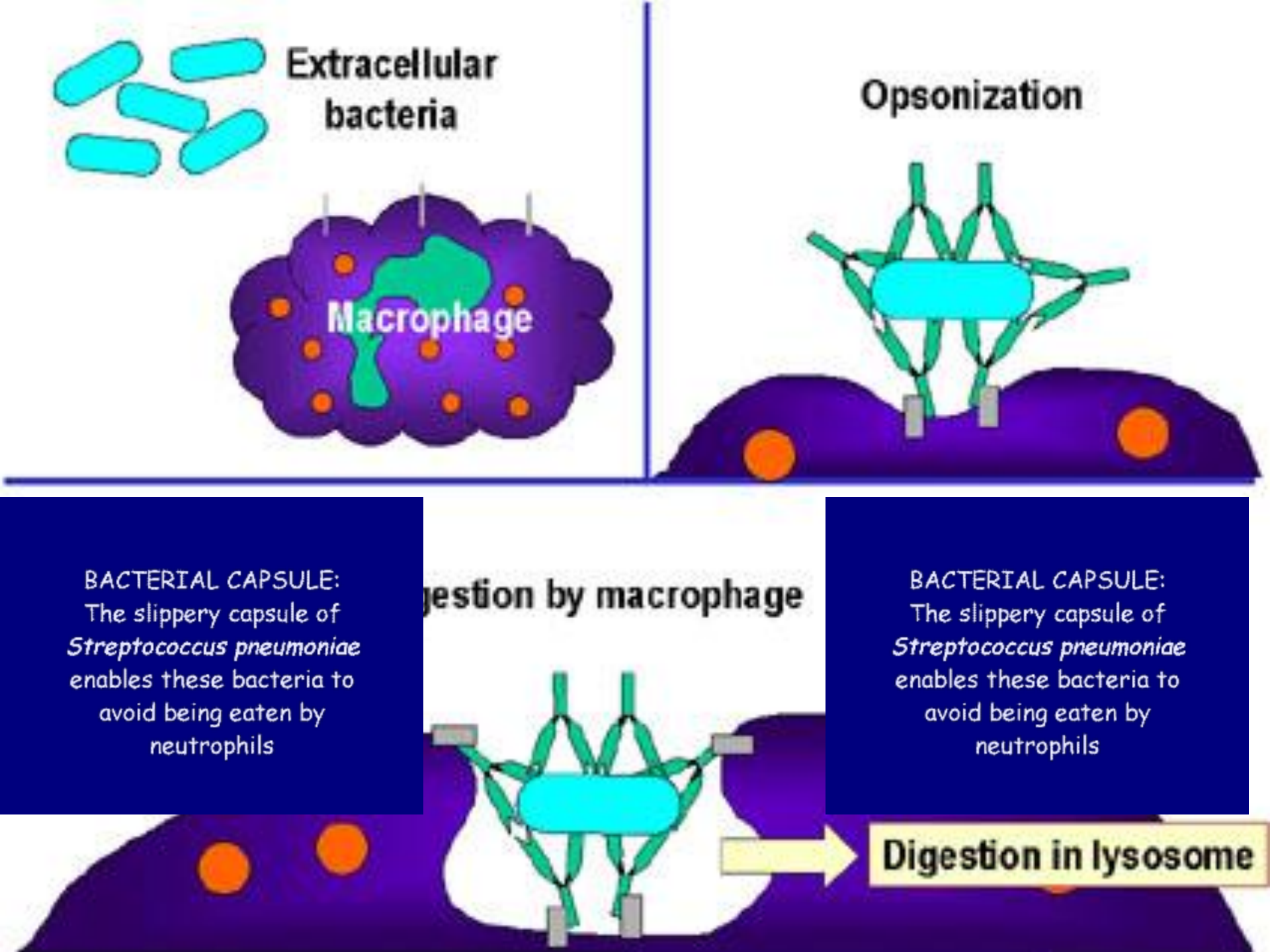
Antibody Structure

- **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
gestion 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

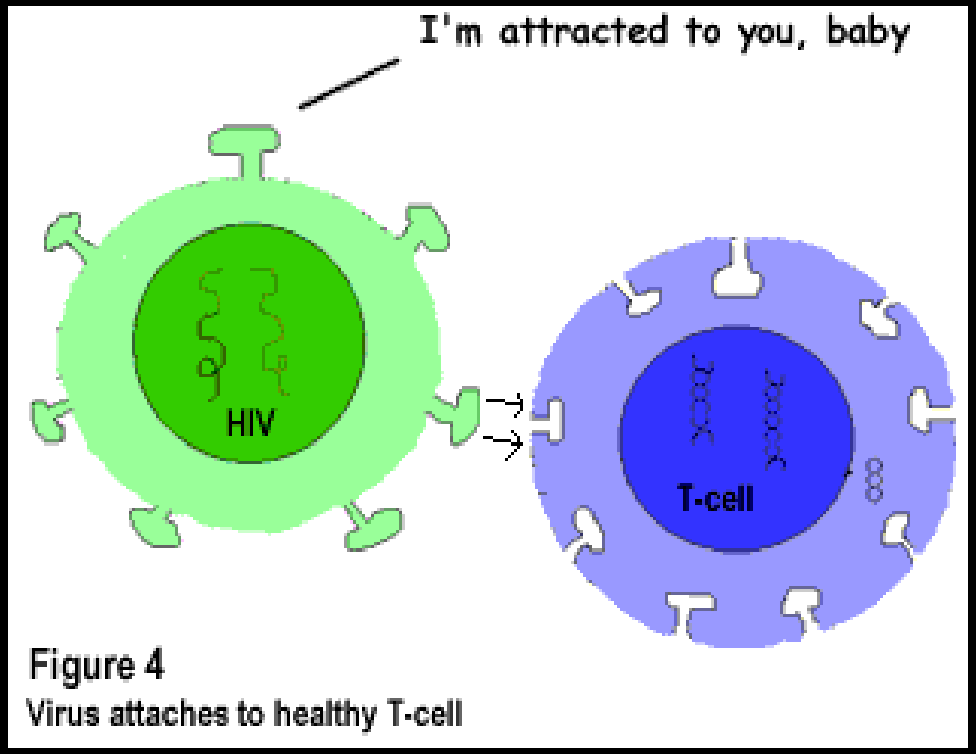


Figure 4
Virus attaches to healthy T-cell

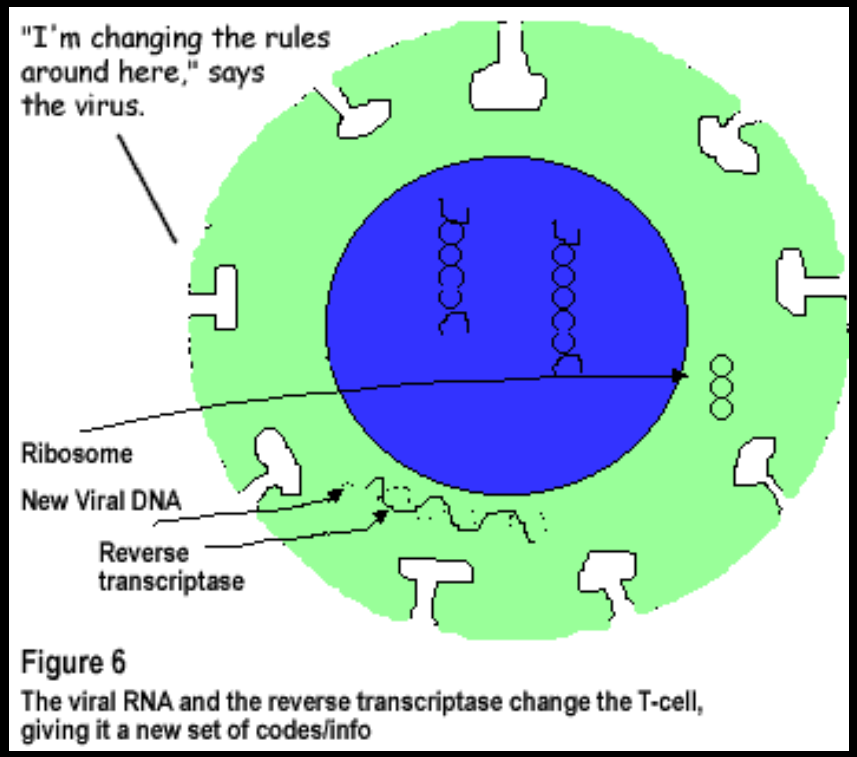
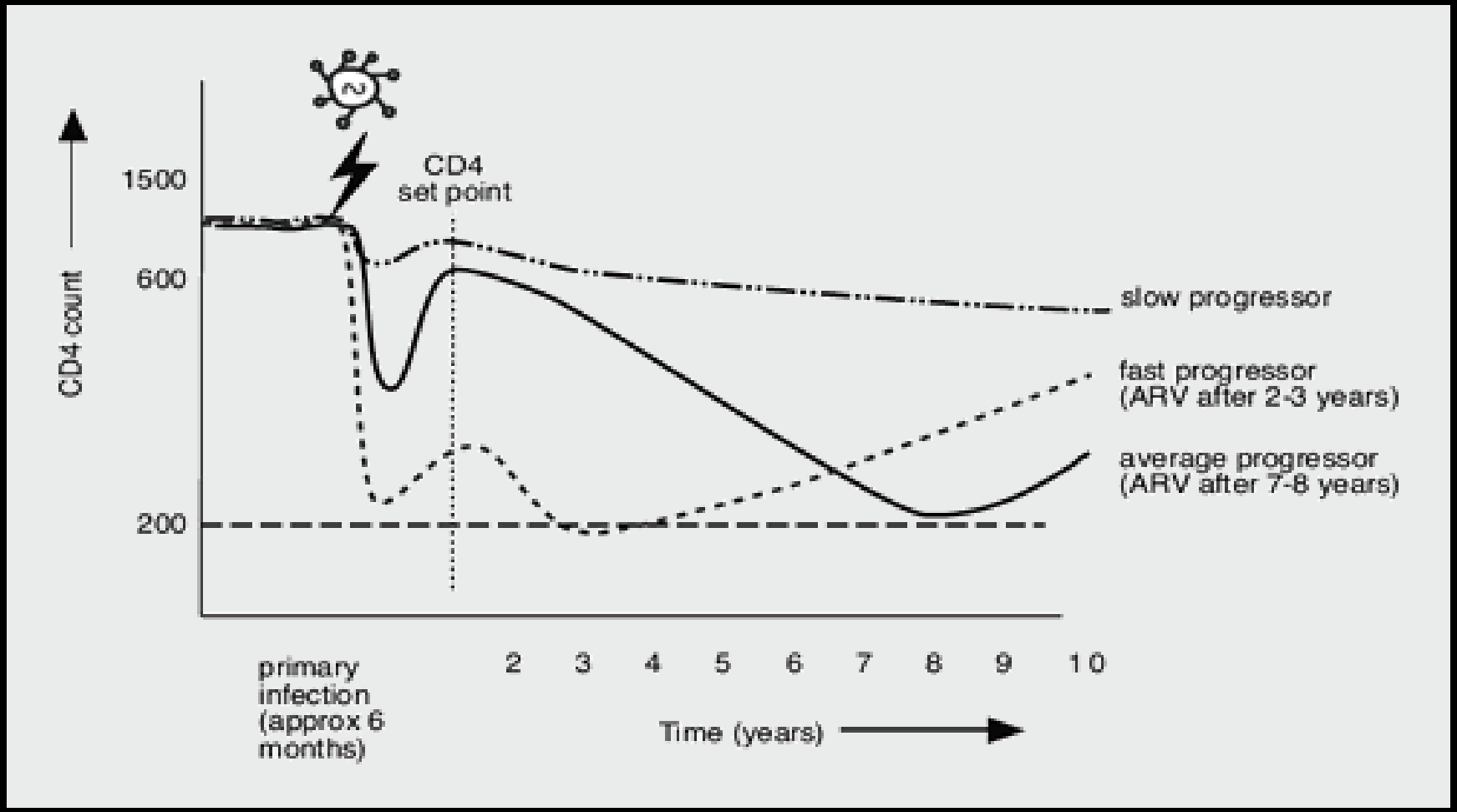


Figure 6
The viral RNA and the reverse transcriptase change the T-cell, giving it a new set of codes/info

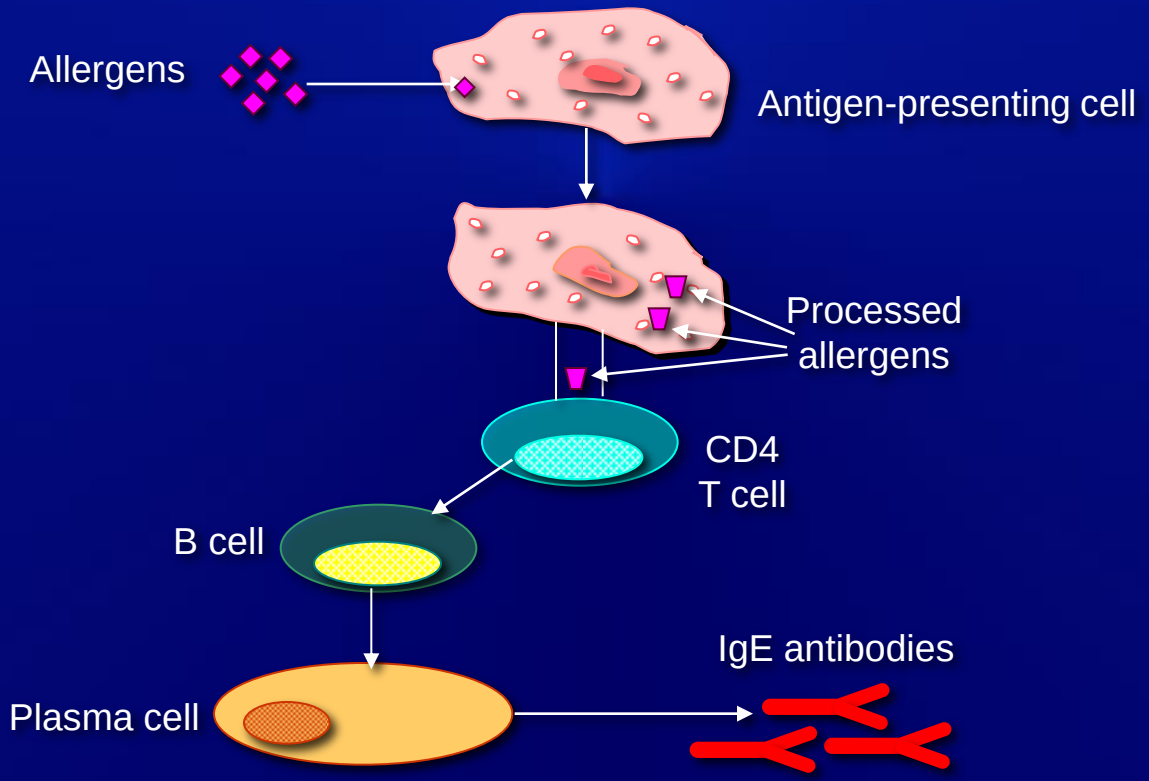
CD4 CELLS with HIV



ALLERGIES?

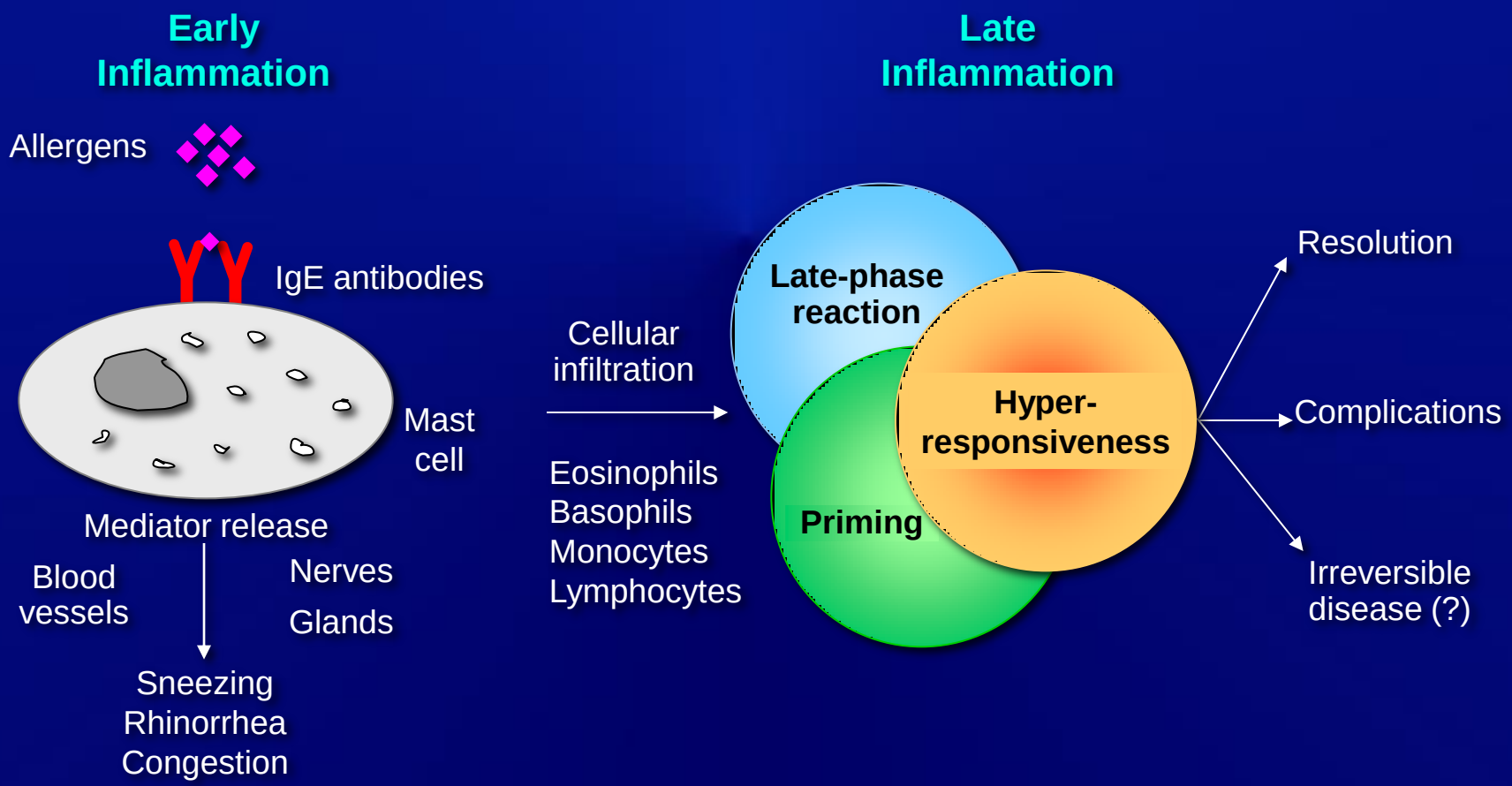
Pathophysiology of Allergic Inflammation: Sensitization

Phase 1: Sensitization



Pathophysiology of Allergic Inflammation: Clinical Disease

Phase 2: Clinical Disease



CLOSE TO HOME By John McPherson

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

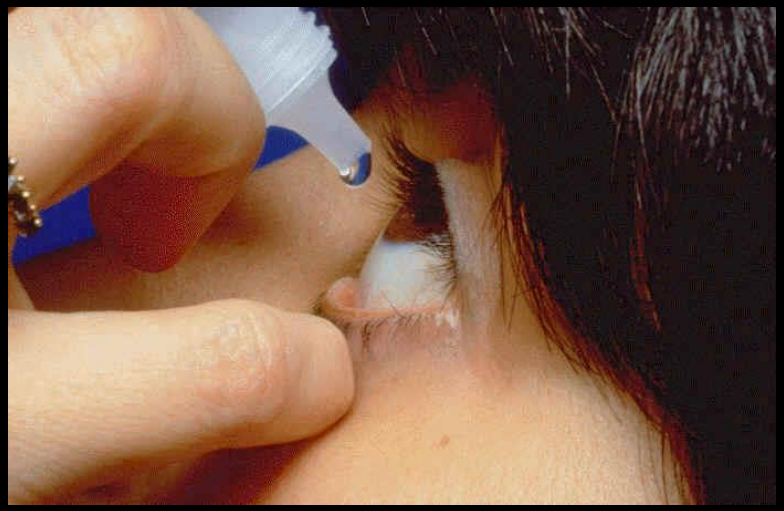
Skin Tests 12-28-2001 Weeds, Trees, Mixed Grass, Cat Pelt

Three Legged Stool of Allergy Treatment

1. Avoidance
2. Medications
3. Immunotherapy

Avoidance

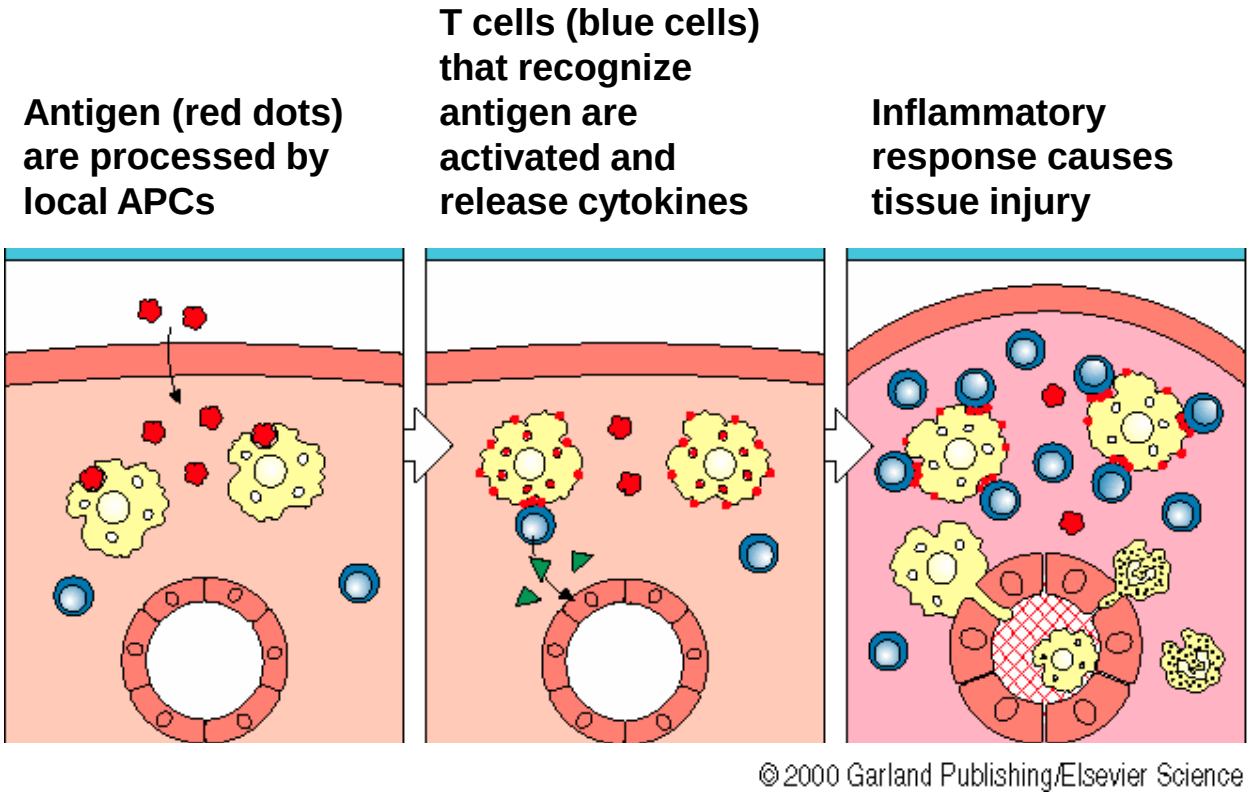
Medications



Immunotherapy

Type IV Hypersensitivity - A Delayed Reaction

CONTACT DERMATITIS

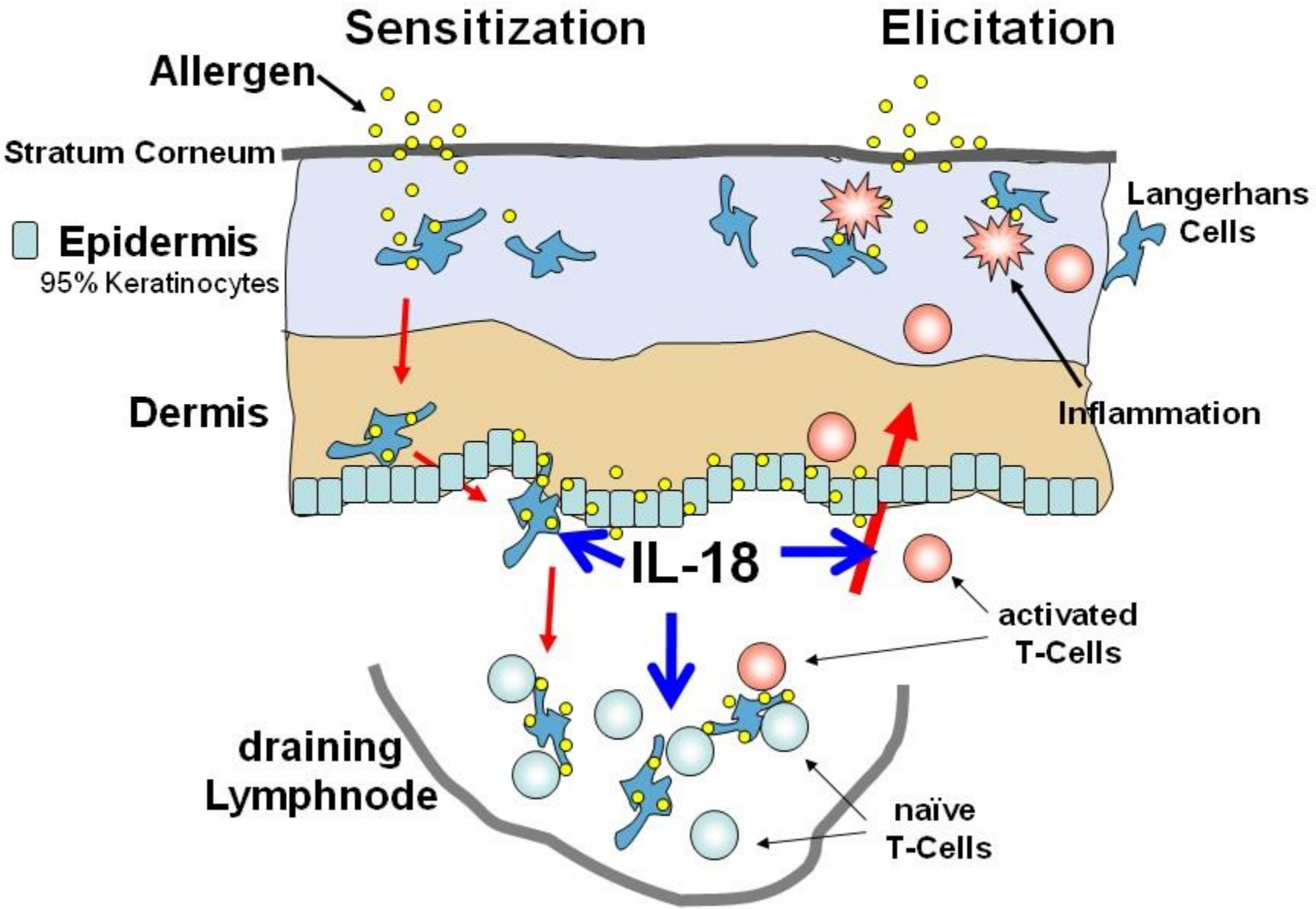


Antigen is presented by APC's to antigen-specific memory T cells.

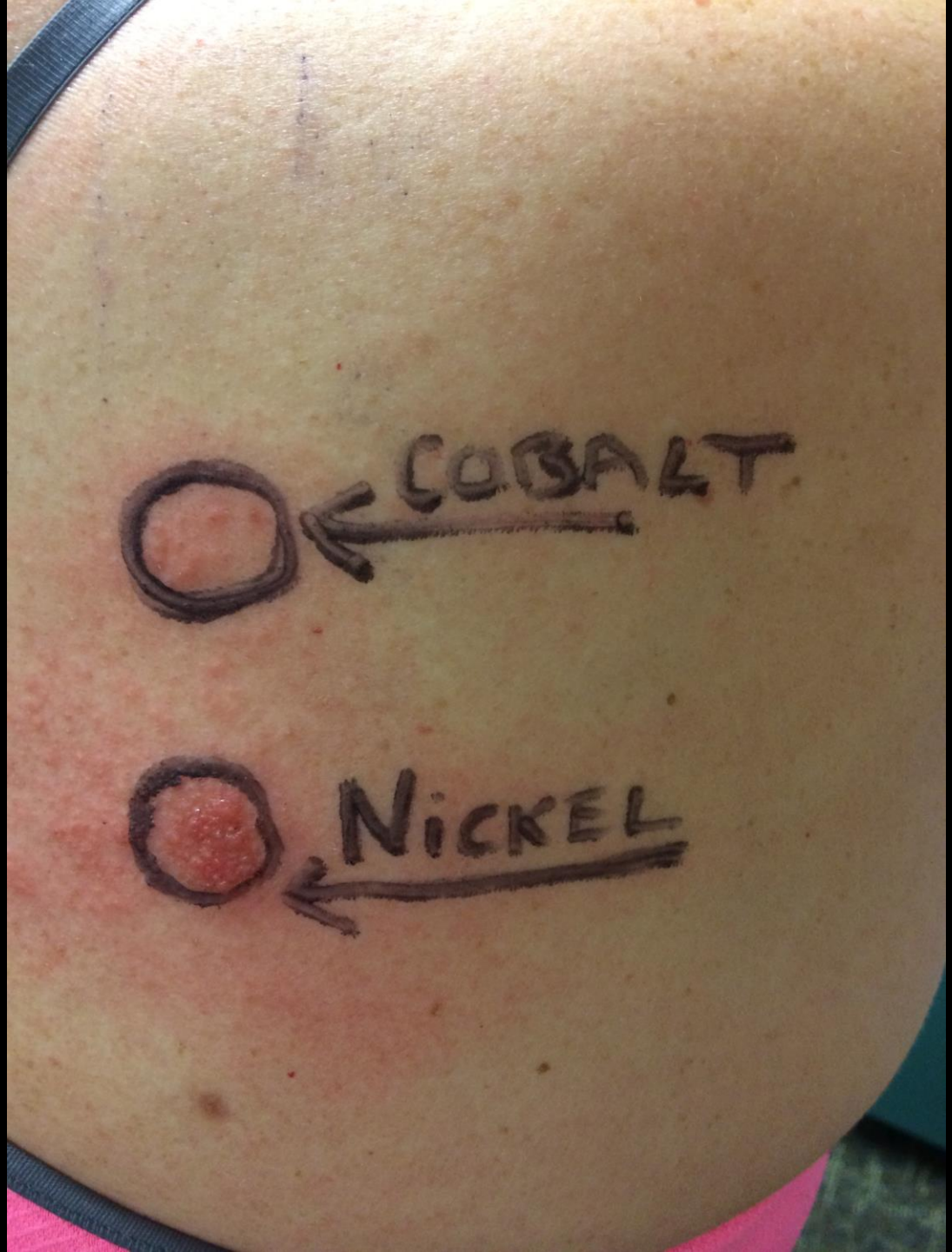
They become activated and produce chemicals that cause inflammatory cells to move into the area, leading to tissue injury.

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

ALLERGIC CONTACT DERMATITIS




4
5
6


COBALT
NICKEL

STEVENS-JOHNSON SYNDROME

TOXIC EPIDERMAL NECROLSIS (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).**

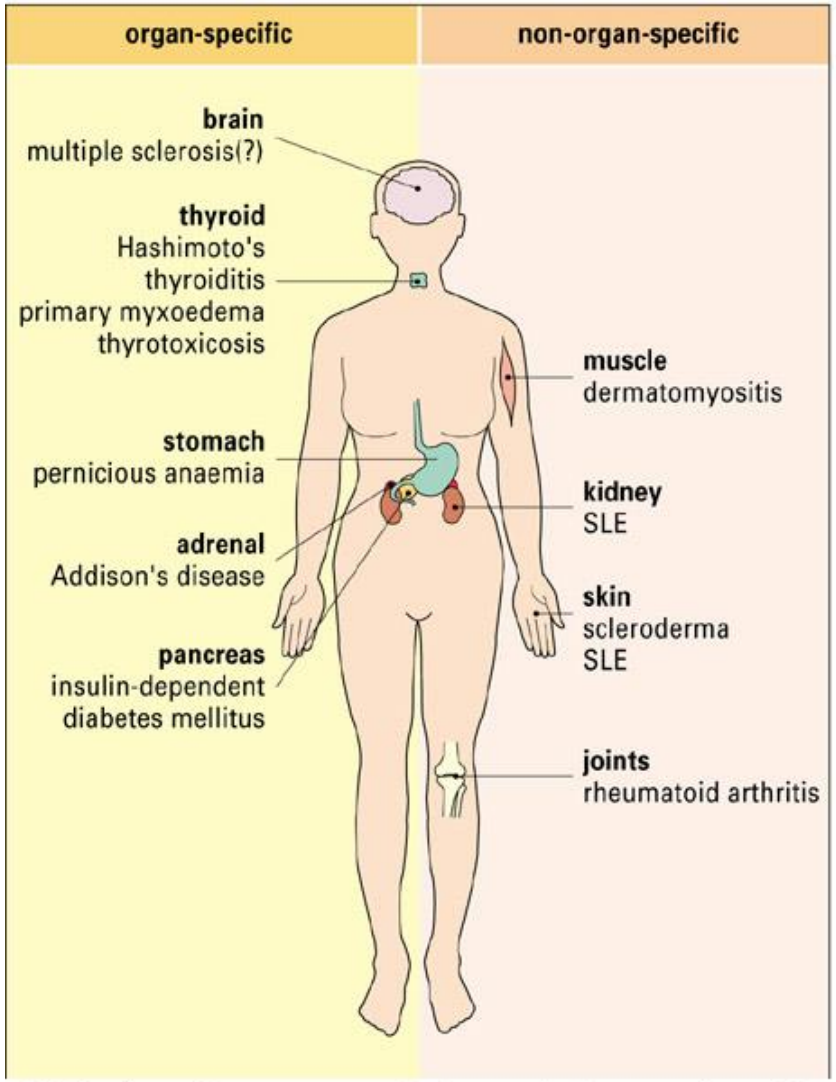
- **~ 3.5 % of people have autoimmune diseases;**
  On average, women are 2.7 times more likely to develop these diseases than men.

- **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**

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)

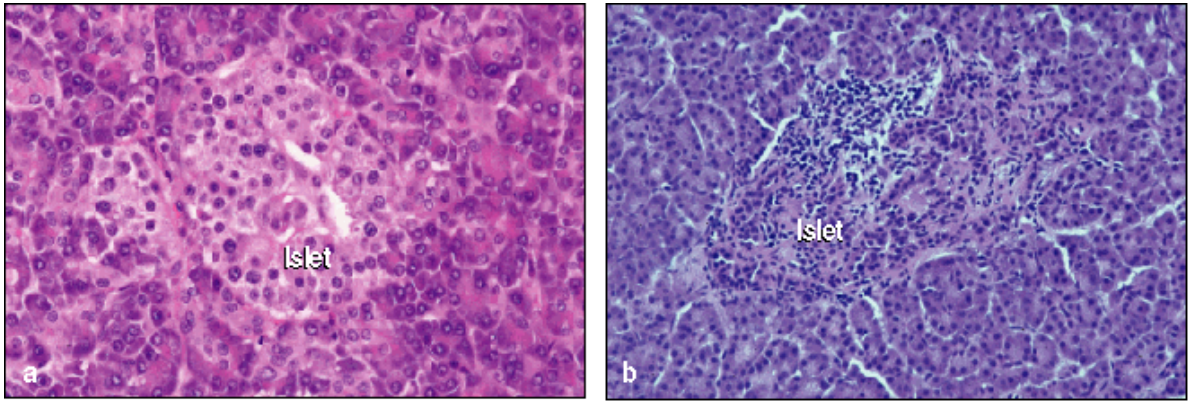
- A chronic organ-specific disease - may be mild or severe.
  - MS involves the destruction of the myelin sheath that covers cells of the spinal cord and brain.
- Affects ~ 1 in 1,600 people.
  - 60% of the cases occur in women.
- Symptoms include weakness, tremors or paralysis of one or more extremities, 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.

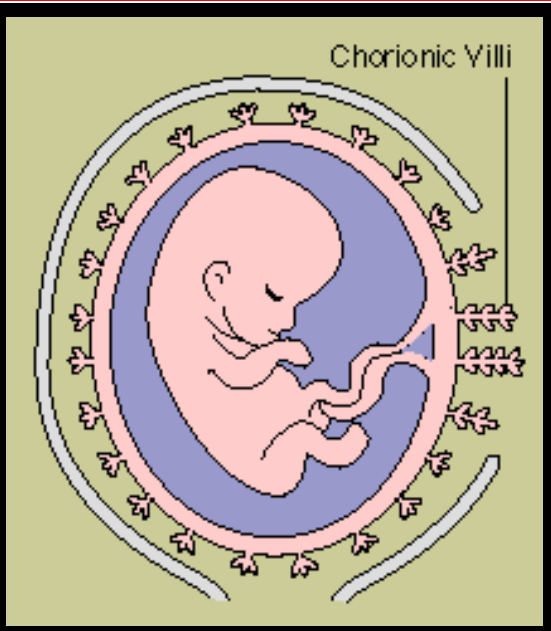
Normal pancreas



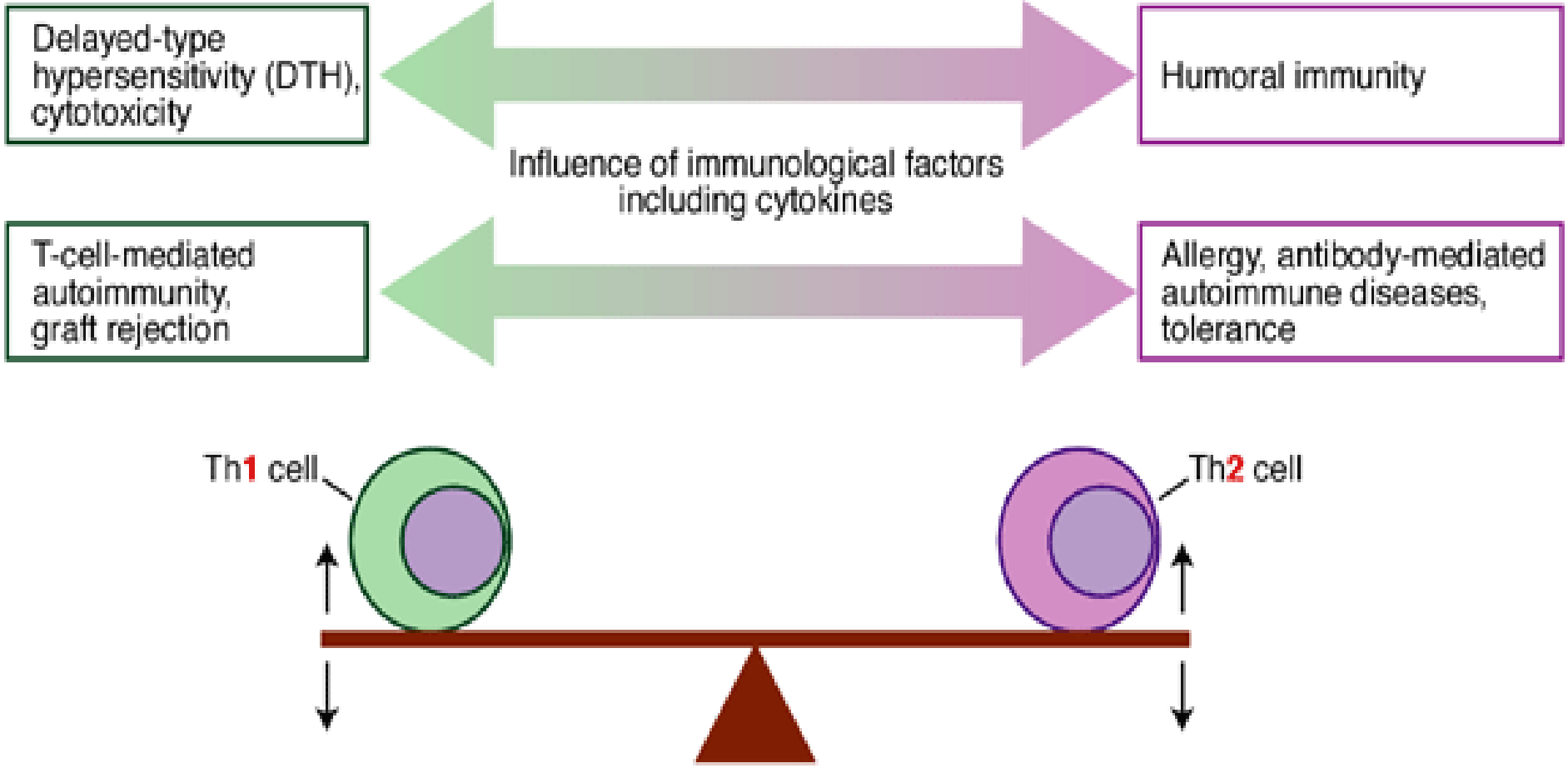
Diabetic pancreas

I am only half my mom!

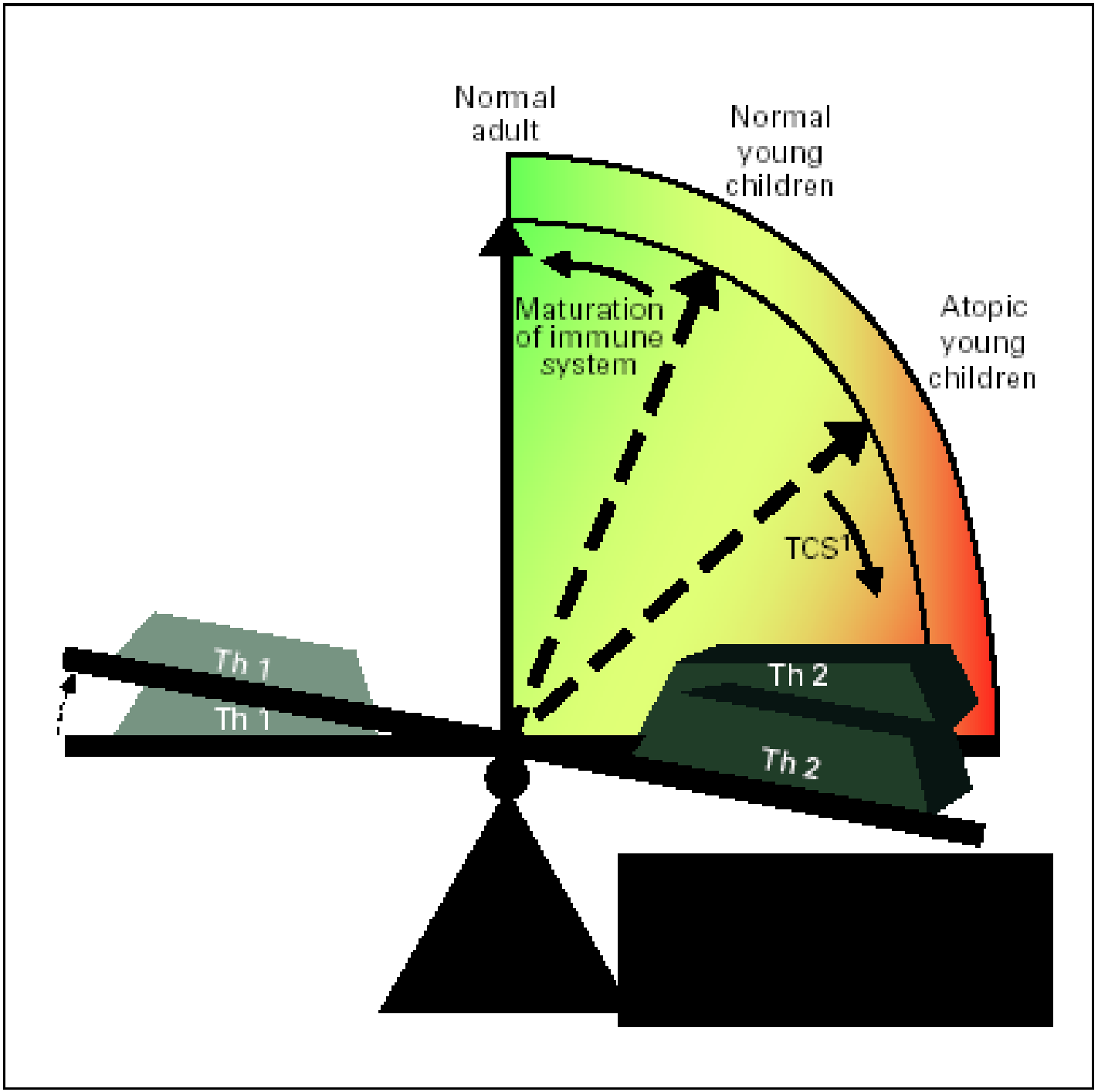
How does mom's immune system tolerate me?



TH1 and TH2 Balance



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


Normal adult
Normal young children
Atopic young children
Maturation of immune system
TCS1
Th 1
Th 1
Th 2
Th 2

WHERE IS THE WORST?

This map shows the four cities with the highest measured one-day readings for seasonal allergens (plus Louisville's highest readings) in the year 2000, as reported by the National Allergy Board.

For comparative readings from other cities, see the chart on Page 2. (Note: Readings are not taken in all cities, and monitoring methods vary.)

Source: National Allergy Board of the American Academy of Allergy, Asthma and Immunology (aaaai.org). Used by permission.

BY JOANNE MESHEW AND KIM KOLARK, THE C-J

WHAT POLLEN COUNTS MEAN

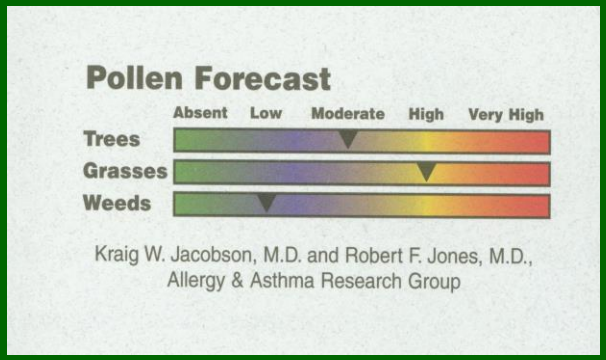
Numbers are grains of pollen or mold spores per cubic meter

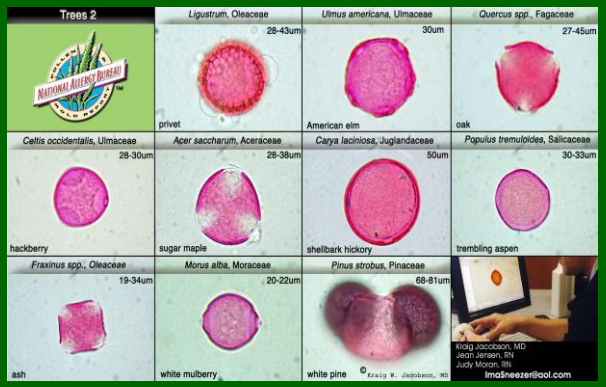
	Weeds	Grasses	Trees	Molds
Low	0-10	0-6	0-15	0-6,500
Moderate	10-50	5-20	15-90	6,500-13,000
High	50-500	20-200	90-1,500	13,000-50,000
Very high	500 +	200 +	1,500 +	50,000 +

Symptoms	
Low	Only individuals extremely sensitive to these pollens and molds will experience symptoms.
Moderate	Many individuals sensitive to these pollens and molds will experience symptoms.
High	Most individuals with any sensitivity to these pollens and molds will experience symptoms.
Very high	Almost all individuals with any sensitivity to these pollens and molds will experience symptoms.

What is in the Air Now?

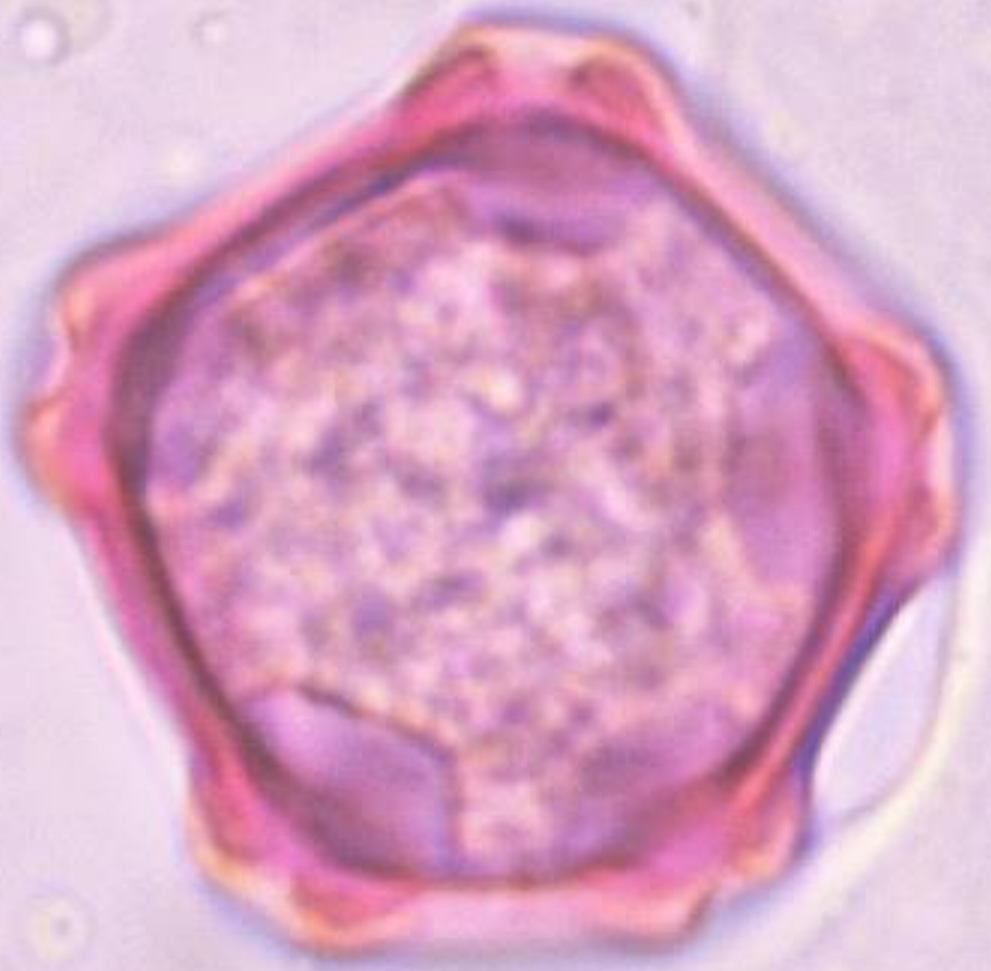
Tree Pollen


Pollen Forecast
Absent
Low
Moderate
High
Very High
Trees
Grasses
Weeds
Kraig W. Jacobson, M.D. and Robert F. Jones, M.D.,
Allergy & Asthma Research Group

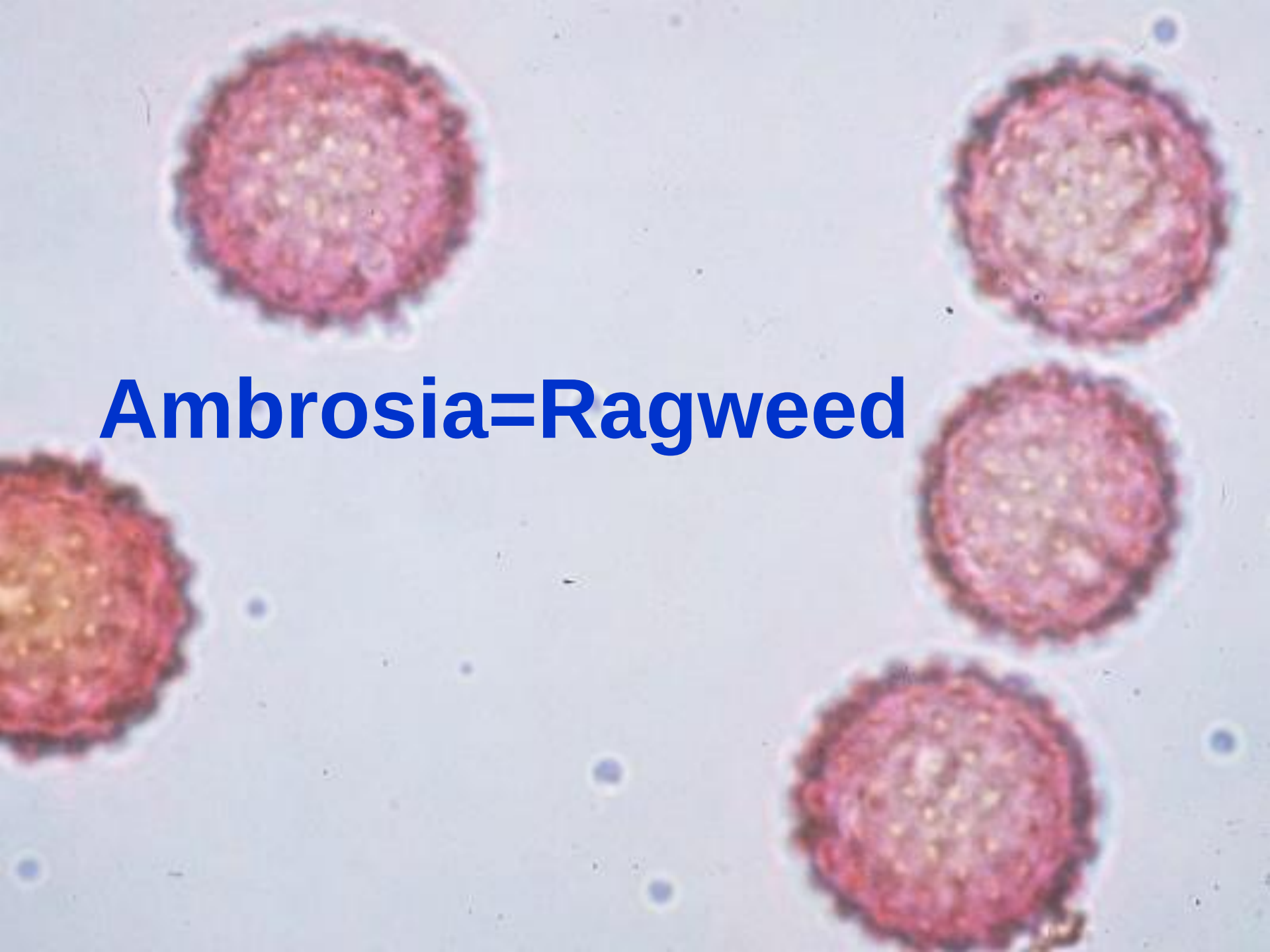

Trees 2
Ligustrum, Oleaceae
28-43um
privet
Ulmus americana, Ulmaceae
30um
American elm
Quercus spp., Fagaceae
27-45um
oak
Celtis occidentalis, Ulmaceae
28-30um
hackberry
Acer saccharum, Aceraceae
28-38um
sugar maple
Carya laciniosa, Juglandaceae
50um
shellbark hickory
Populus tremuloides, Salicaceae
30-33um
trembling aspen
Fraxinus spp., Oleaceae
19-34um
ash
Morus alba, Moraceae
20-22um
white mulberry
Pinus strobus, Pinaceae
68-81um
white pine
© Kraig W. Jacobson, MD
Kraig Jacobson, MD
Jean Jensen, RN
Judy Moran, RN
ImaSneezer@aol.com

Corylus=Hazelnut

Alnus = Alder



Betula = Birch



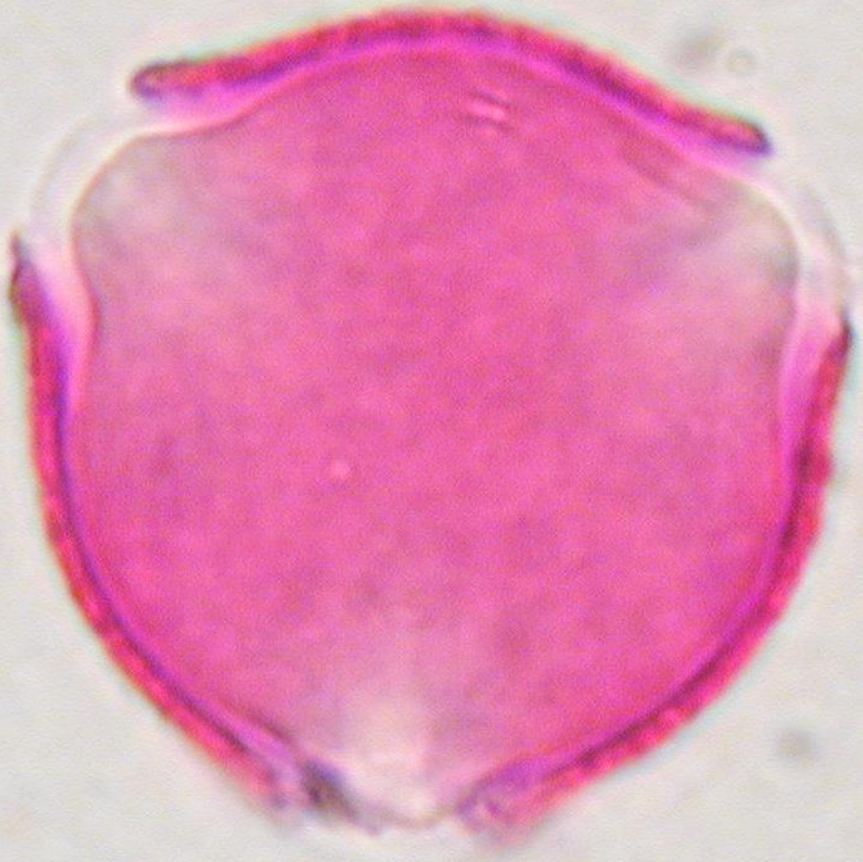
Ambrosia=Ragweed

Gramineae / Poaceae = Grass

Ulmus americana (Ulmaceae) 30um
American Elm

Quercus spp. (Fagaceae) 27-45um

Oak



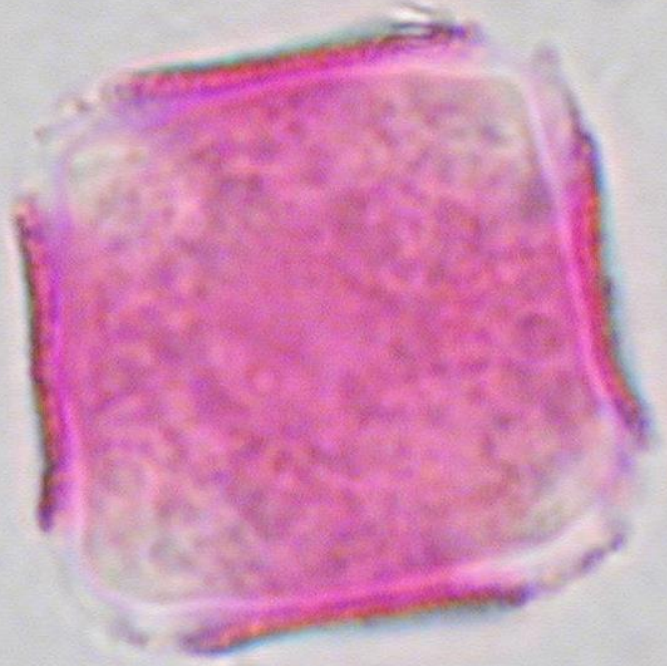
Celtis occidentalis (Ulmaceae) 28-30um

Hackberry

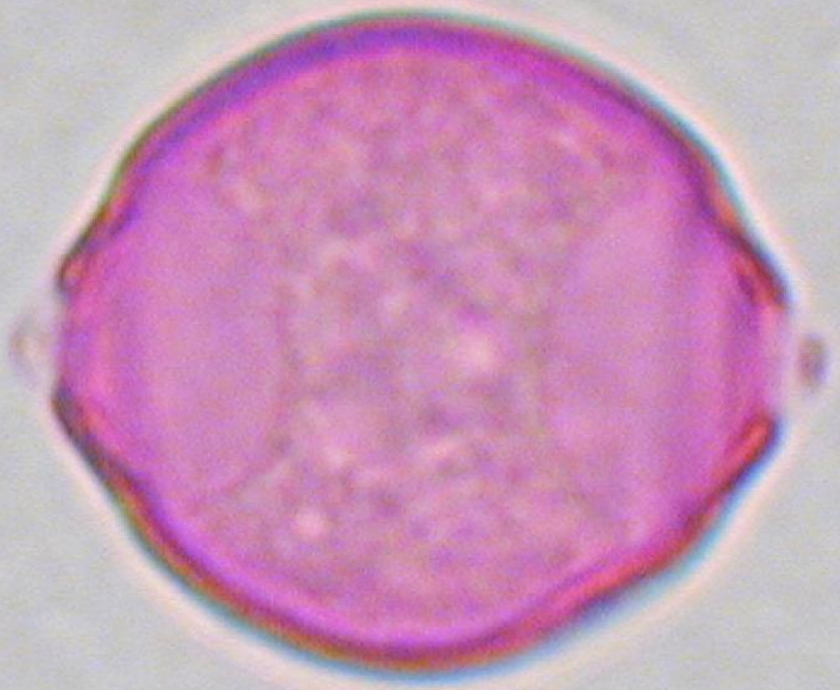

Acer saccharum (Aceraceae) 28-38um
Sugar Maple

Fraxinus spp. (Oleaceae) 19-34um

Ash

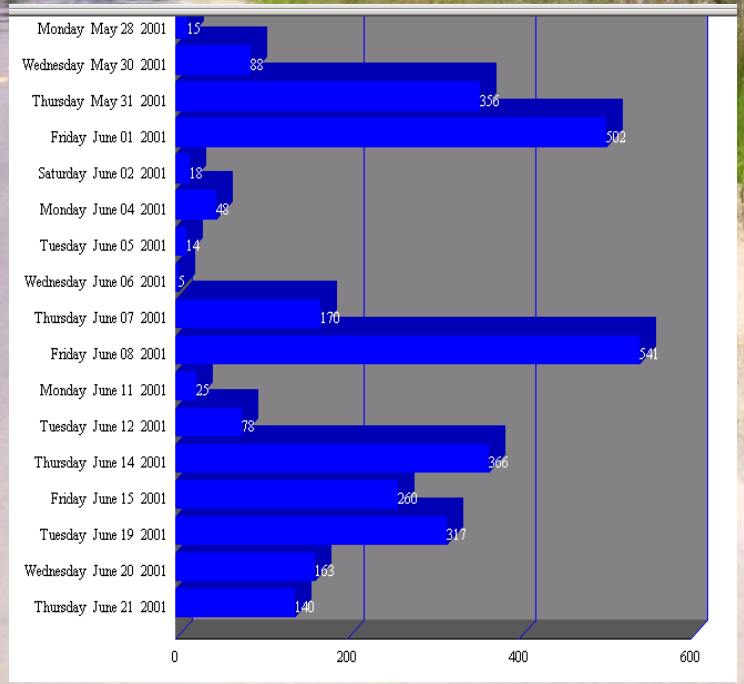


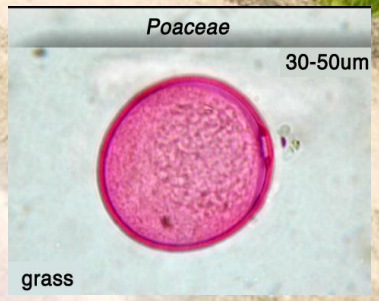
Morus alba (Moraceae) 20-22ug
White Mulberry



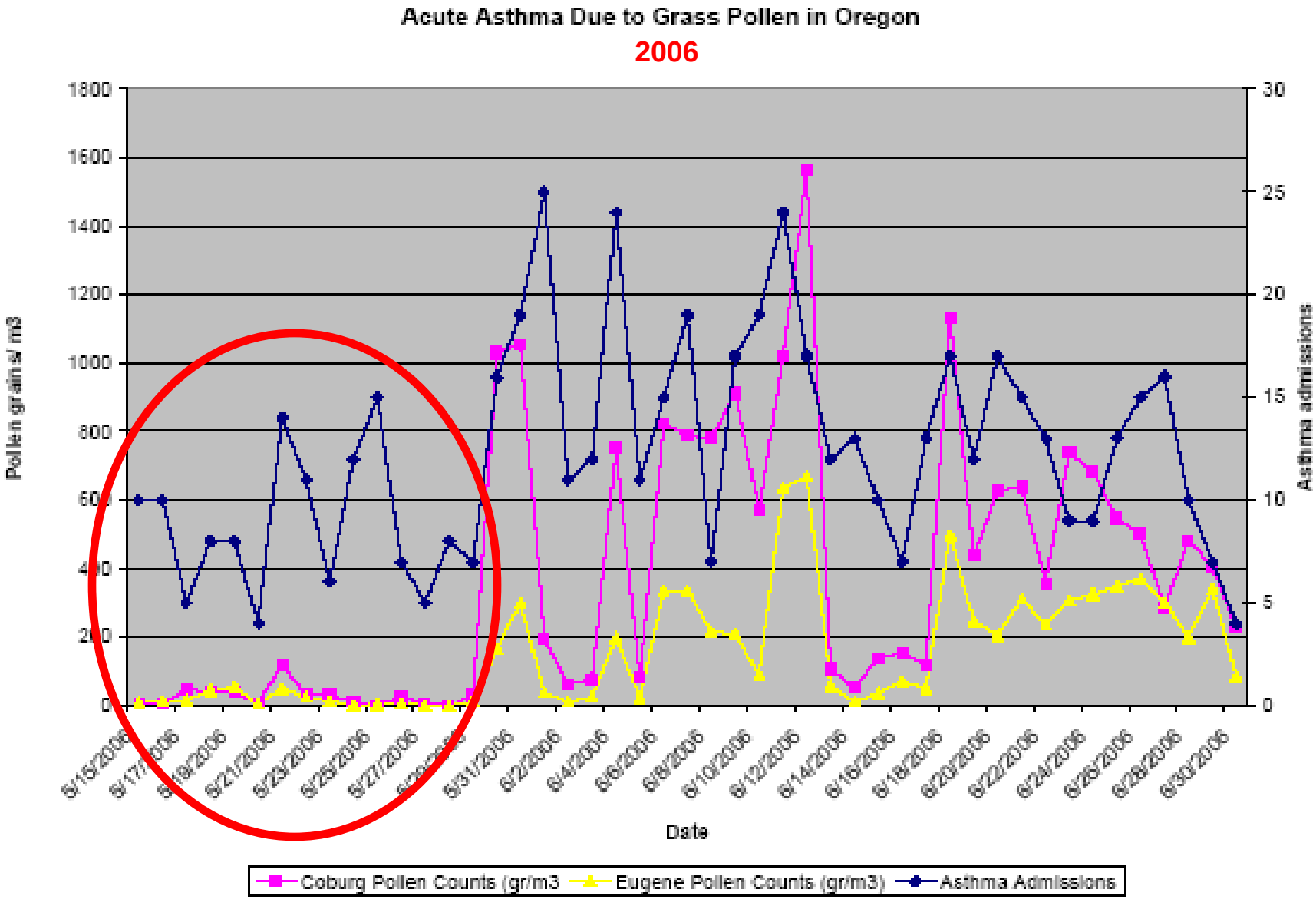

Pinus strobus (Pinaceae) 68-81um
White Pine

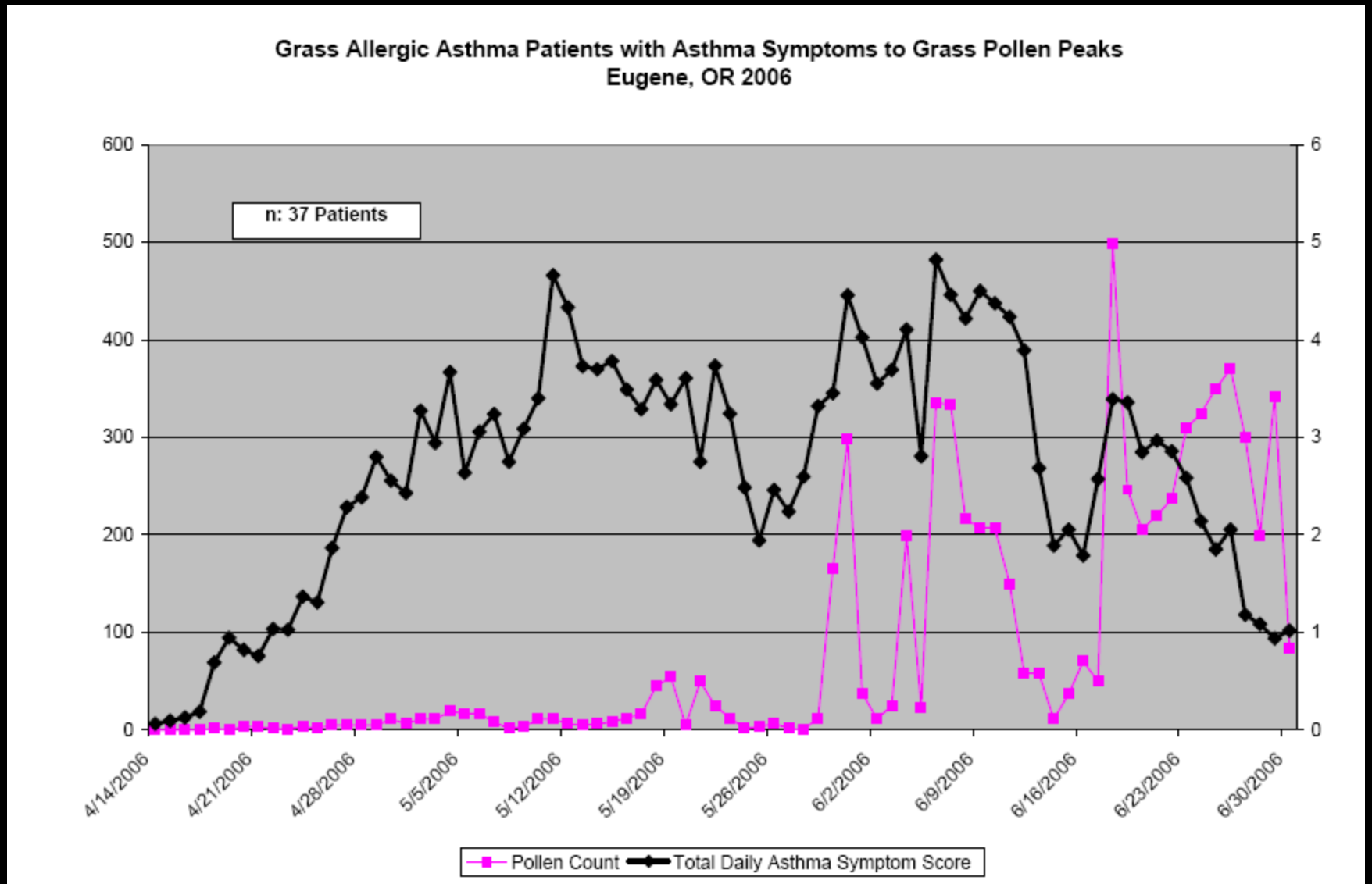
What Makes The Willamette Valley Unique?



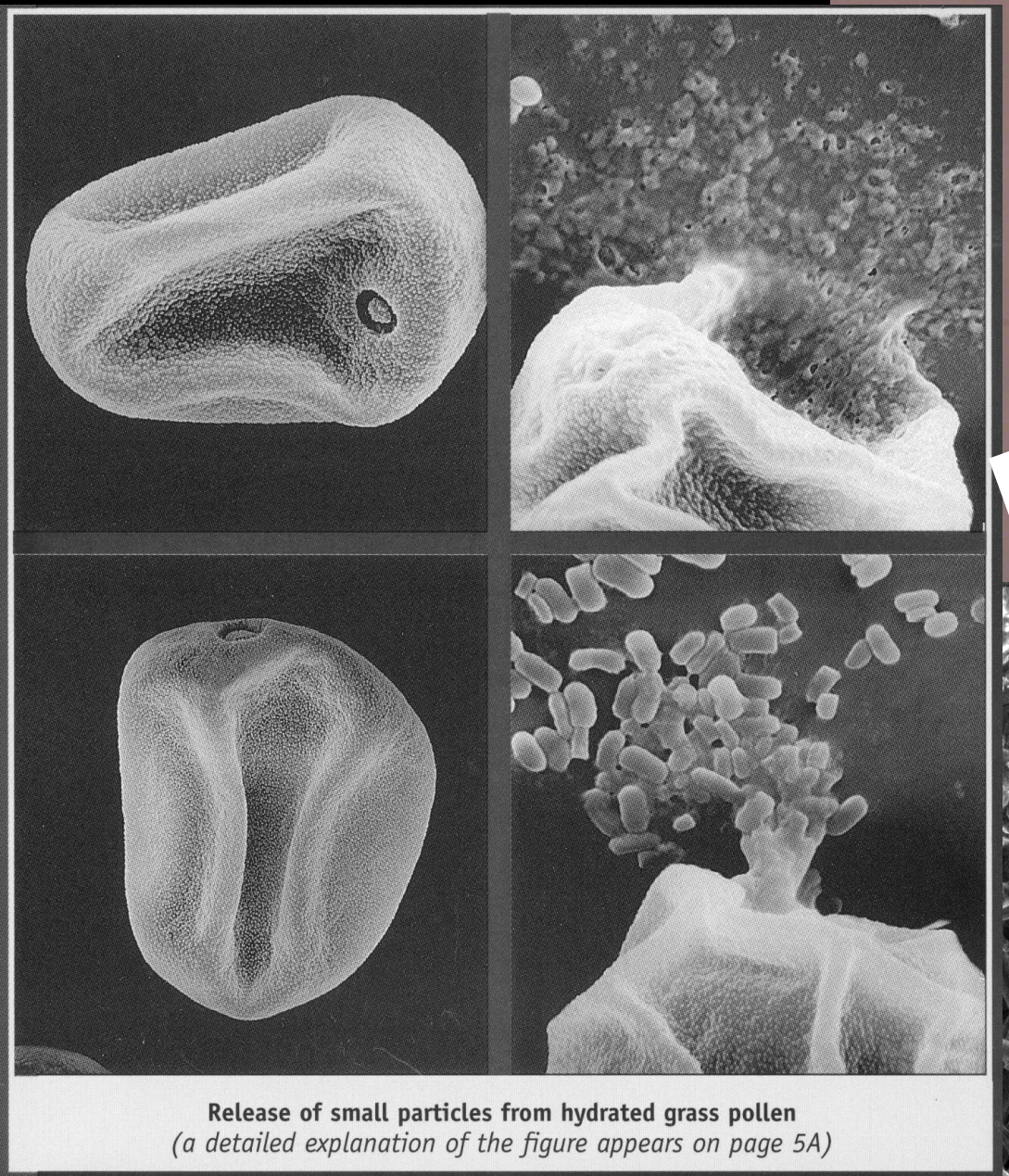


Lebanon
Sodaville
Waterloo
Sweet Home
Brownsville
Halsey
Yachats
Monroe
Harrisburg
Junction City
Coburg
Veneta
Eugene
126
Springfield
Florence
Dunes City
Creswell
Lowell

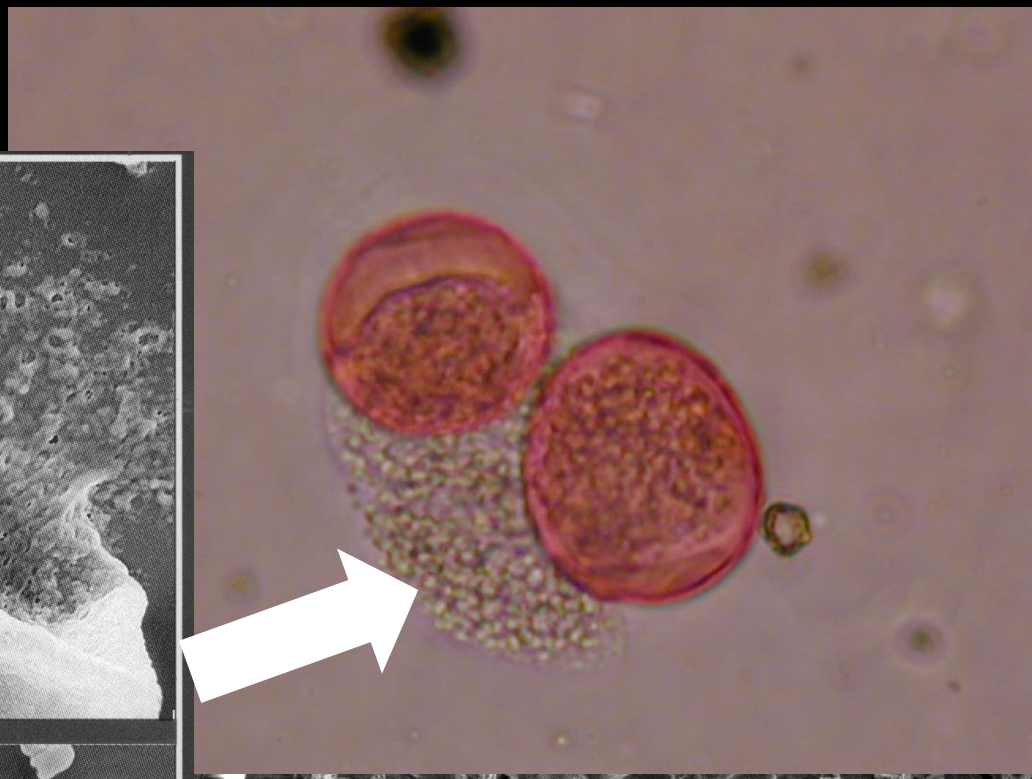

Acute Asthma Due to Grass Pollen in Oregon
2006
Pollen grains/ m3
Asthma admissions
Date
Coburg Pollen Counts (gr/m3
Eugene Pollen Counts (gr/m3)
Asthma Admissions

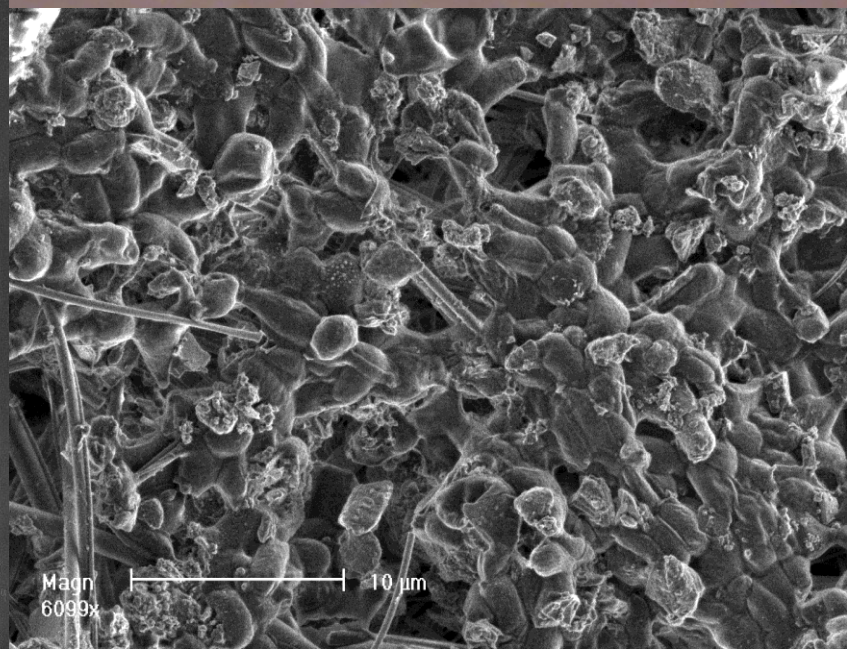

Grass Allergic Asthma Patients with Asthma Symptoms to Grass Pollen Peaks
Eugene, OR 2006
n: 37 Patients
600
500
400
300
200
100
0
6
5
4
3
2
1
0
4/14/2006
4/21/2006
4/28/2006
5/5/2006
5/12/2006
5/19/2006
5/26/2006
6/2/2006
6/9/2006
6/16/2006
6/23/2006
6/30/2006
Pollen Count
Total Daily Asthma Symptom Score

Pollen Particles



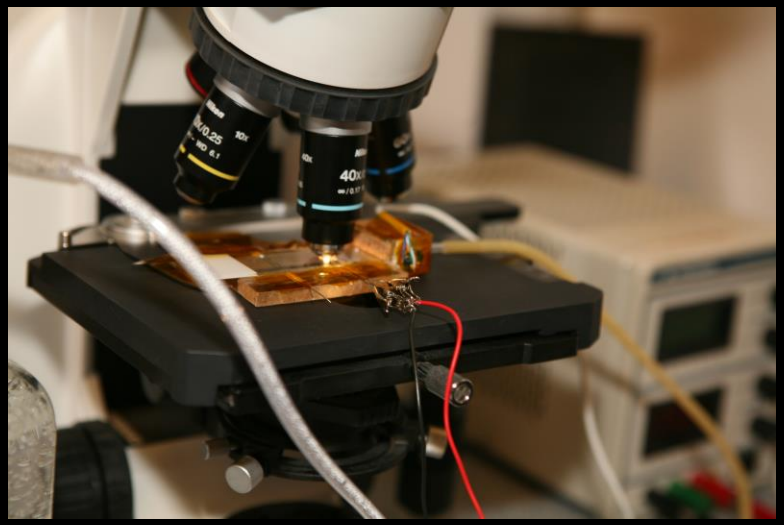
Release of small particles from hydrated grass pollen
(a detailed explanation of the figure appears on page 5A)

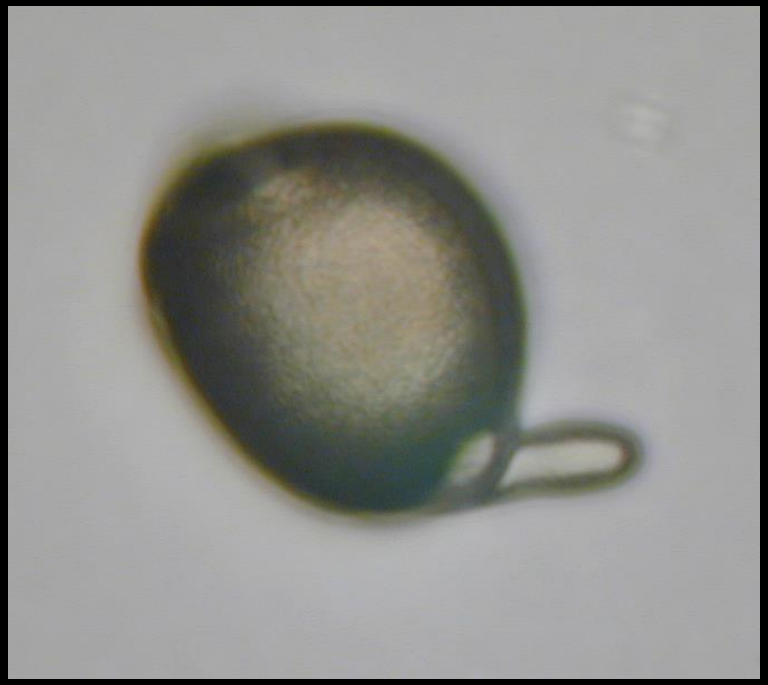




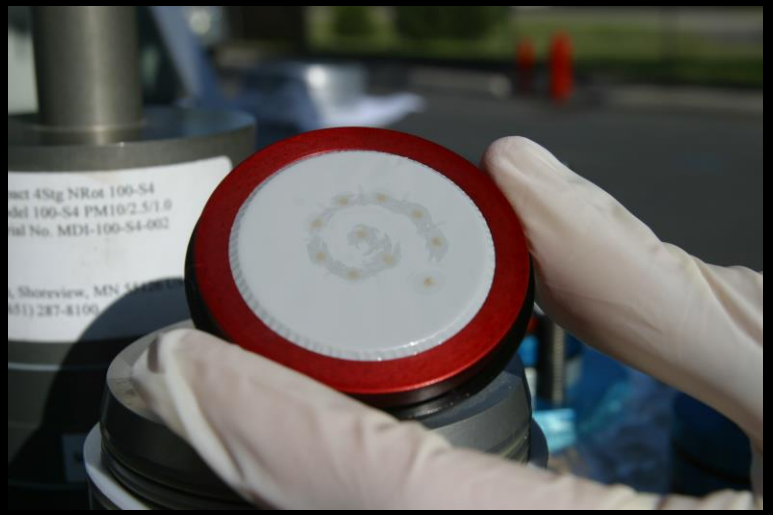

EUDORA HULL SPALDING
LABORATORY OF ENGINEERING
ENVIRONMENTAL
ENGINEERING
SCIENCE

At the Coburg Fire Station






MDI-100-S4-002-S1
MDI-100-S4-002-S2



Questions?