



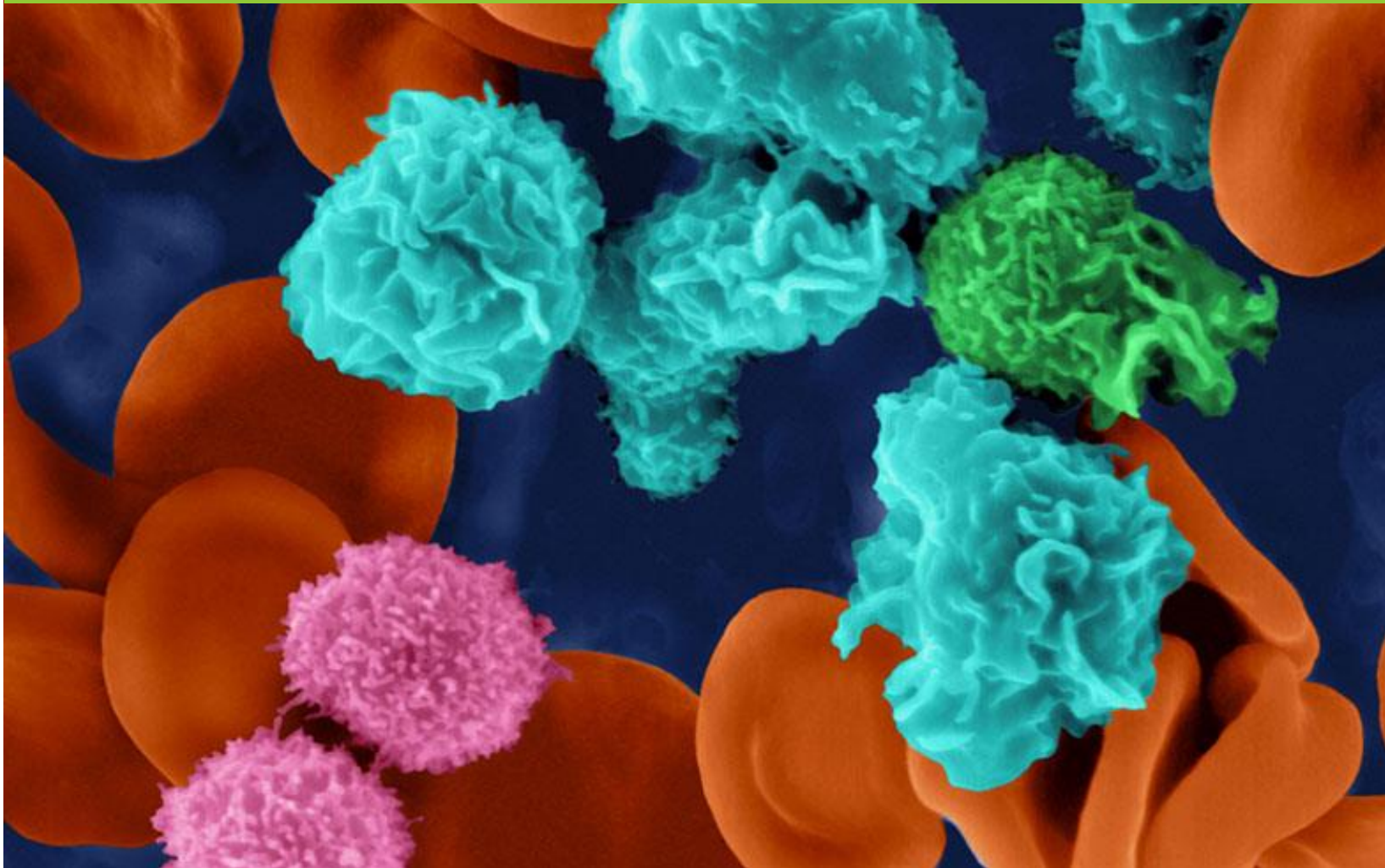
Immune system – physiology, semeiology of the immune disorders. Lymphadenopathy. Immunodeficiencies.

Department of Pediatrics

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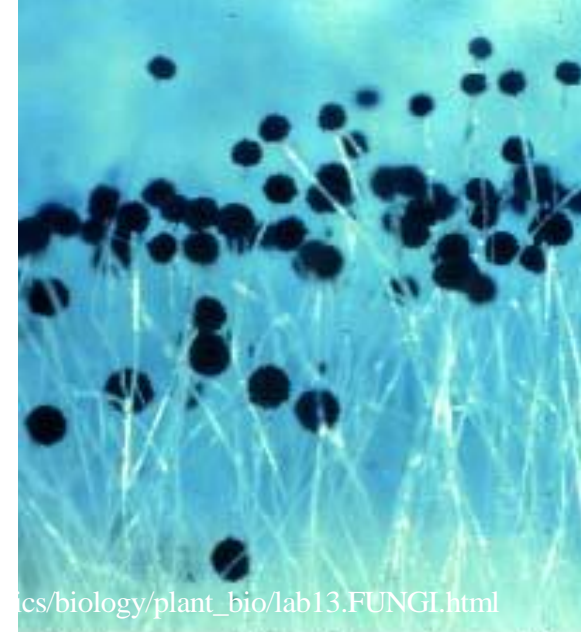
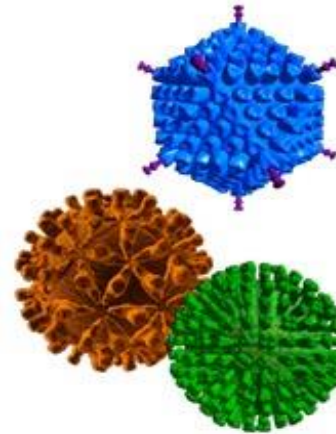
Associate Professor

Body Defenses



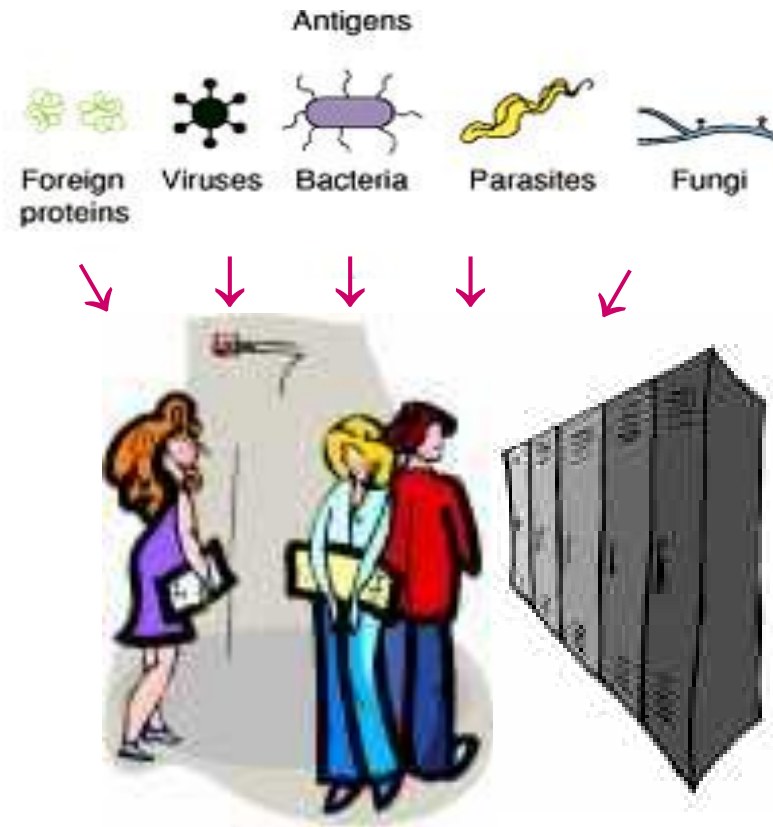
The Invaders...

- **Bacteria**
- **Viruses**
- **Parasites**
fungi
worms



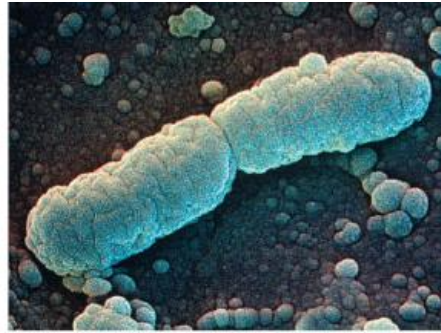
AN IMMUNE RESPONSE

Foreign invaders - viruses, bacteria, allergens, toxins and parasites - constantly bombard our body.



The response to this assault is a carefully orchestrated and controlled interaction between immune cells with the ultimate goal to eliminate the invaders in both pathogen-specific and non-specific mechanisms.

Defense Against Disease



Nonspecific External Barriers
skin, mucous membranes



If these barriers are penetrated,
the body responds with



Innate Immune Response
phagocytic and natural killer cells,
inflammation, fever



If the innate immune response is insufficient,
the body responds with



Adaptive Immune Response
cell-mediated immunity, humoral immunity

The “Ideal” Immune System

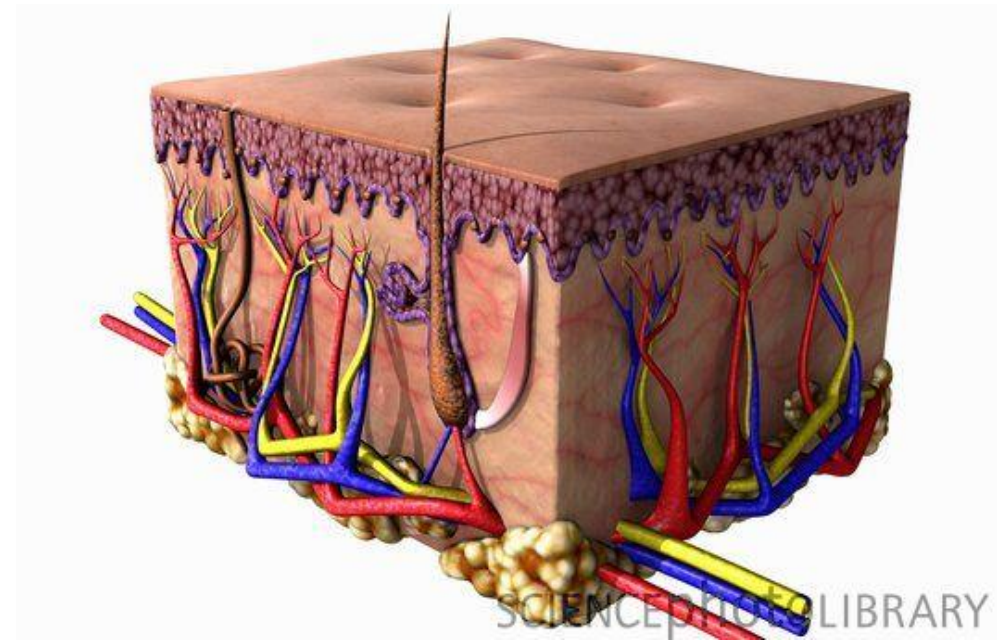
- Recognize all foreign organisms.
 - Bacteria, viruses, parasites (fungi, worms)
- Efficiently and rapidly destroy invaders.
- Prevent a second infection with the same microbe (have a memory).
- Never cause damage to self.

First line of defense

- Non-specific defenses are designed to prevent infections by viruses and bacteria. These include:
 - Intact skin
 - Mucus and Cilia
 - Phagocytes

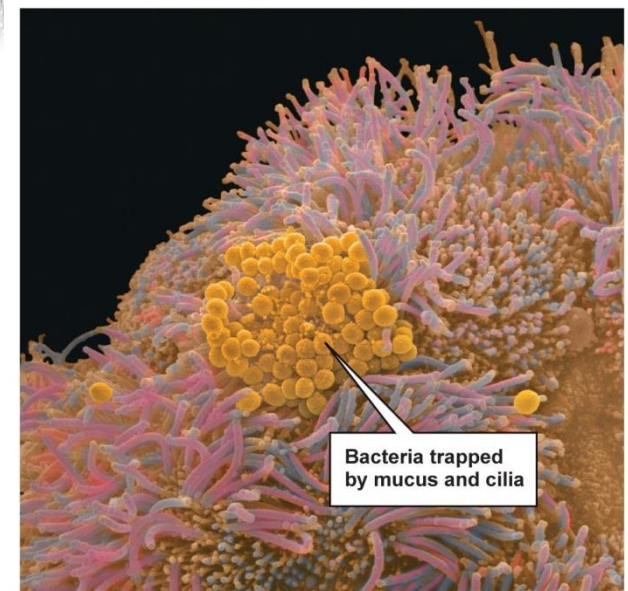
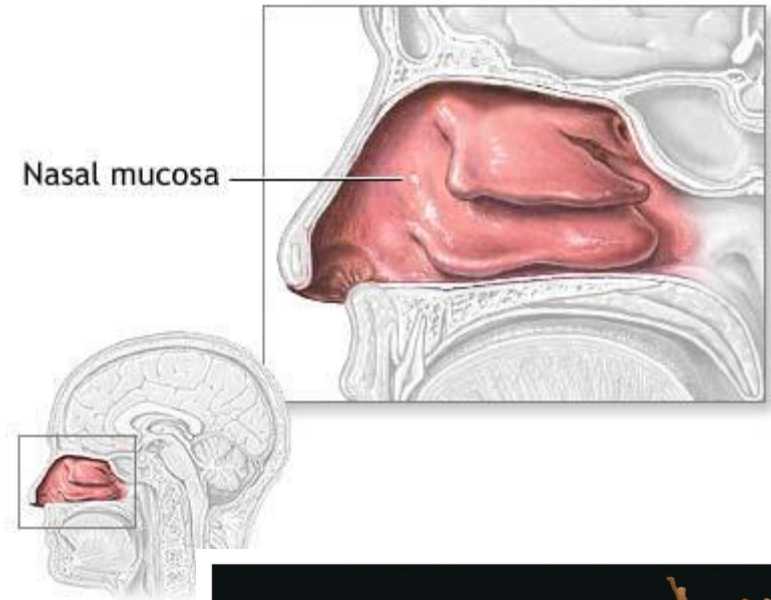
Role of skin

- Dead skin cells are constantly sloughed off, making it hard for invading bacteria to colonize.
- Sweat and oils contain anti-microbial chemicals, including some antibiotics.



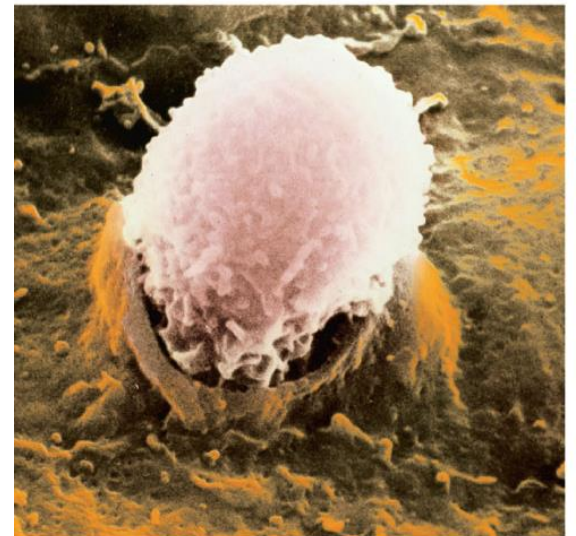
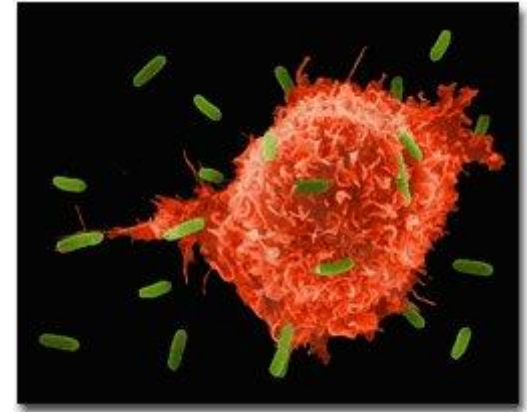
Role of mucus and cilia

- Mucus contains lysozymes, enzymes that destroy bacterial cell walls.
- The normal flow of mucus washes bacteria and viruses off of mucus membranes.
- Cilia in the respiratory tract move mucus out of the lungs to keep bacteria and viruses out.



Role of phagocytes

- Phagocytes are several types of white blood cells (including macrophages and neutrophils) that seek and destroy invaders. Some also destroy damaged body cells.
- Phagocytes are attracted by an inflammatory response of damaged cells.



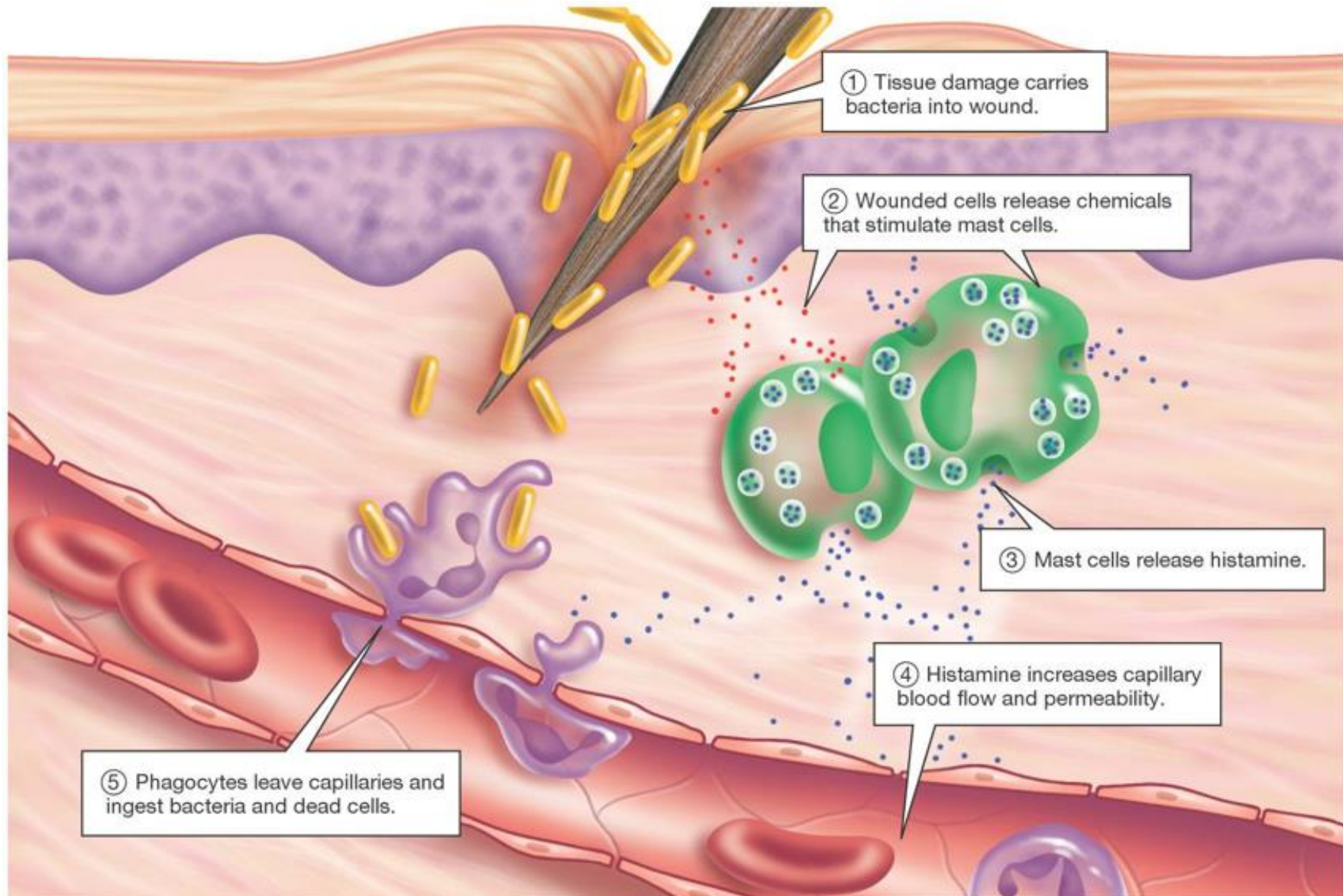
Role of inflammation

- Inflammation is signaled by mast cells, which release histamine.
- Histamine causes fluids to collect around an injury to dilute toxins. This causes swelling.
- The temperature of the tissues may rise, which can kill temperature-sensitive microbes.

Role of fever

- Fever is a defense mechanism that can destroy many types of microbes.
- Fever also helps fight viral infections by increasing interferon production.

Ouch!



Specific defenses

- Specific defenses are those that give us immunity to certain diseases.
- In specific defenses, the immune system forms a chemical “memory” of the invading microbe. If the microbe is encountered again, the body reacts so quickly that few or no symptoms are felt.

Major players

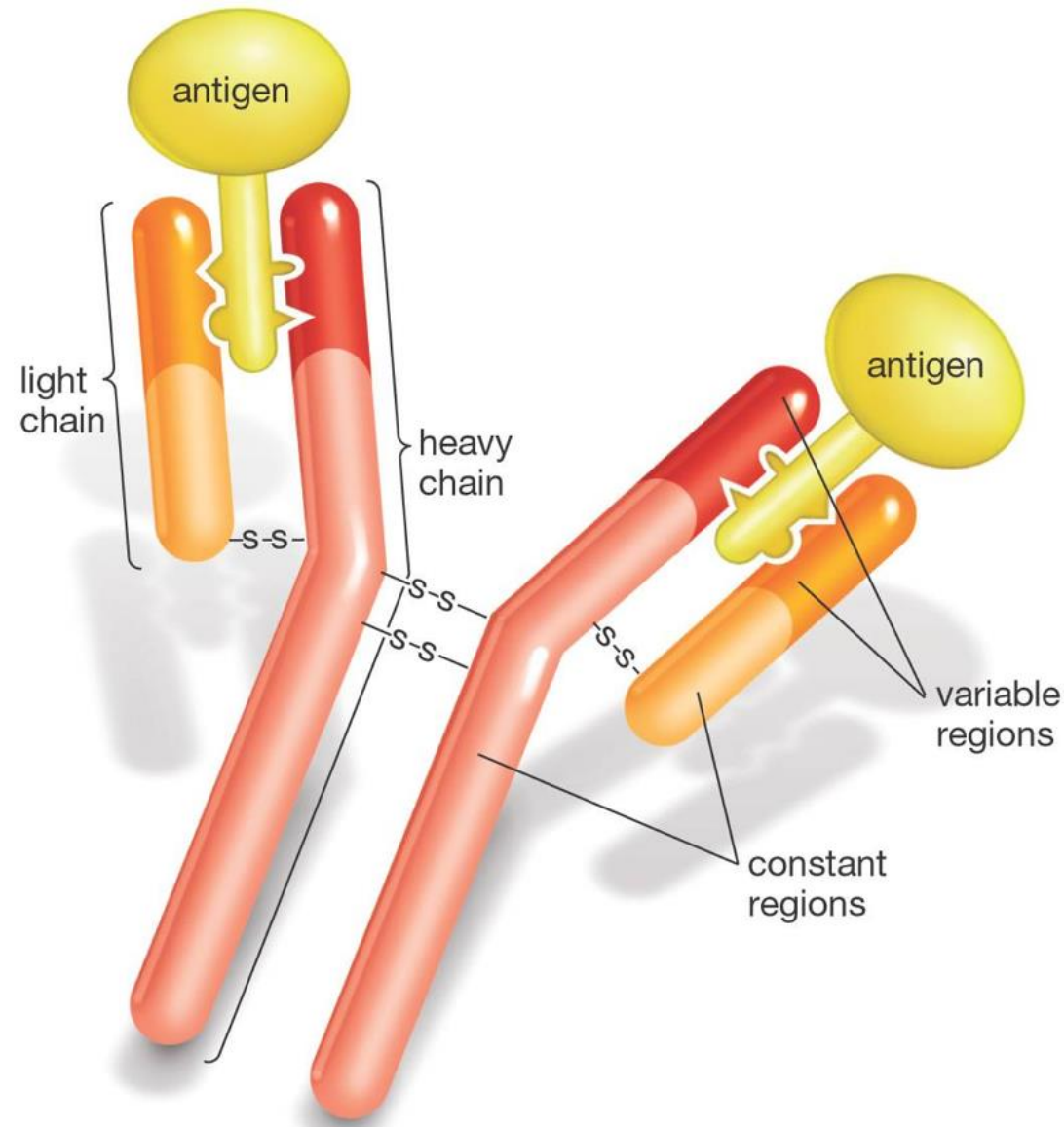
- The major players in the immune system include:
 - Macrophage
 - T cells (helper, cytotoxic, memory)
 - B cells (plasma, memory)
 - Antibodies

Some vocabulary:

- Antibody: a protein produced by the human immune system to tag and destroy invasive microbes.
- Antigen: any protein that our immune system uses to recognize “self” vs. “not self.”

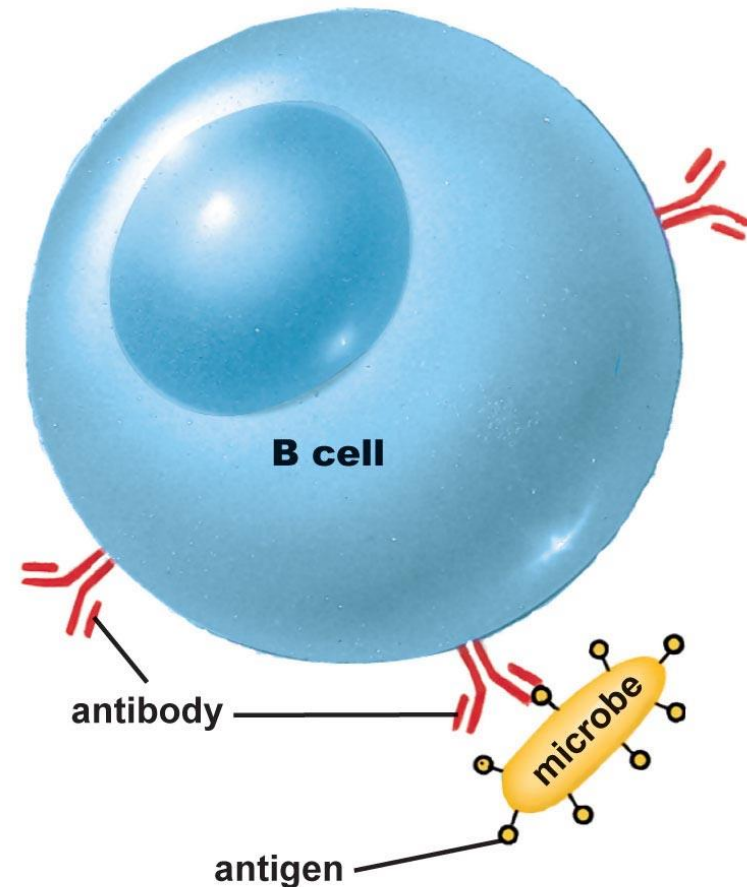
Antibodies

- Antibodies are assembled out of protein chains.
- There are many different chains that the immune system assembles in different ways to make different antibodies.



Antibodies as Receptors

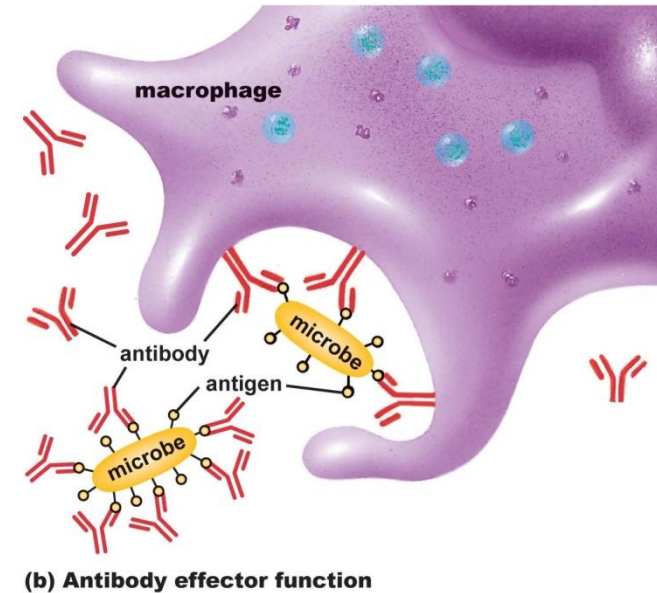
- Antibodies can attach to B cells, and serve to recognize foreign antigens.



(a) Antibody receptor function

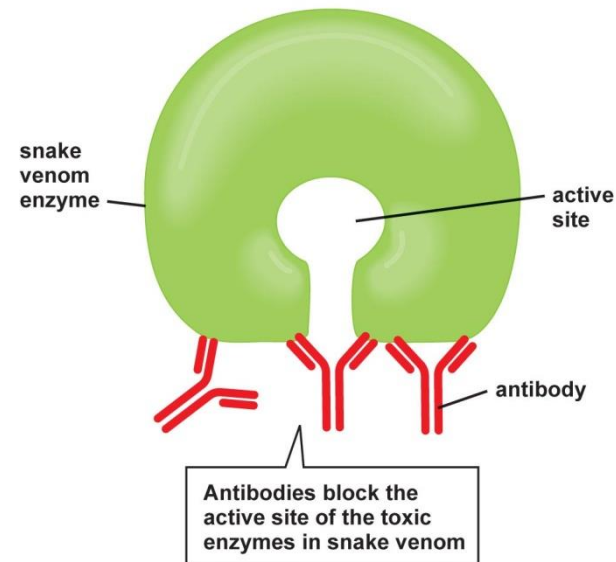
Antigens as Effectors

- Free antibodies can bind to antigens, which “tags” the antigen for the immune system to attack and destroy.



(b) Antibody effector function

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Antigen recognition

- Cells of the immune system are “trained” to recognize “self” proteins vs. “not self” proteins.
- If an antigen (“not self”) protein is encountered by a macrophage, it will bring the protein to a helper T-cell for identification.
- If the helper T-cell recognizes the protein as “not self,” it will launch an immune response.

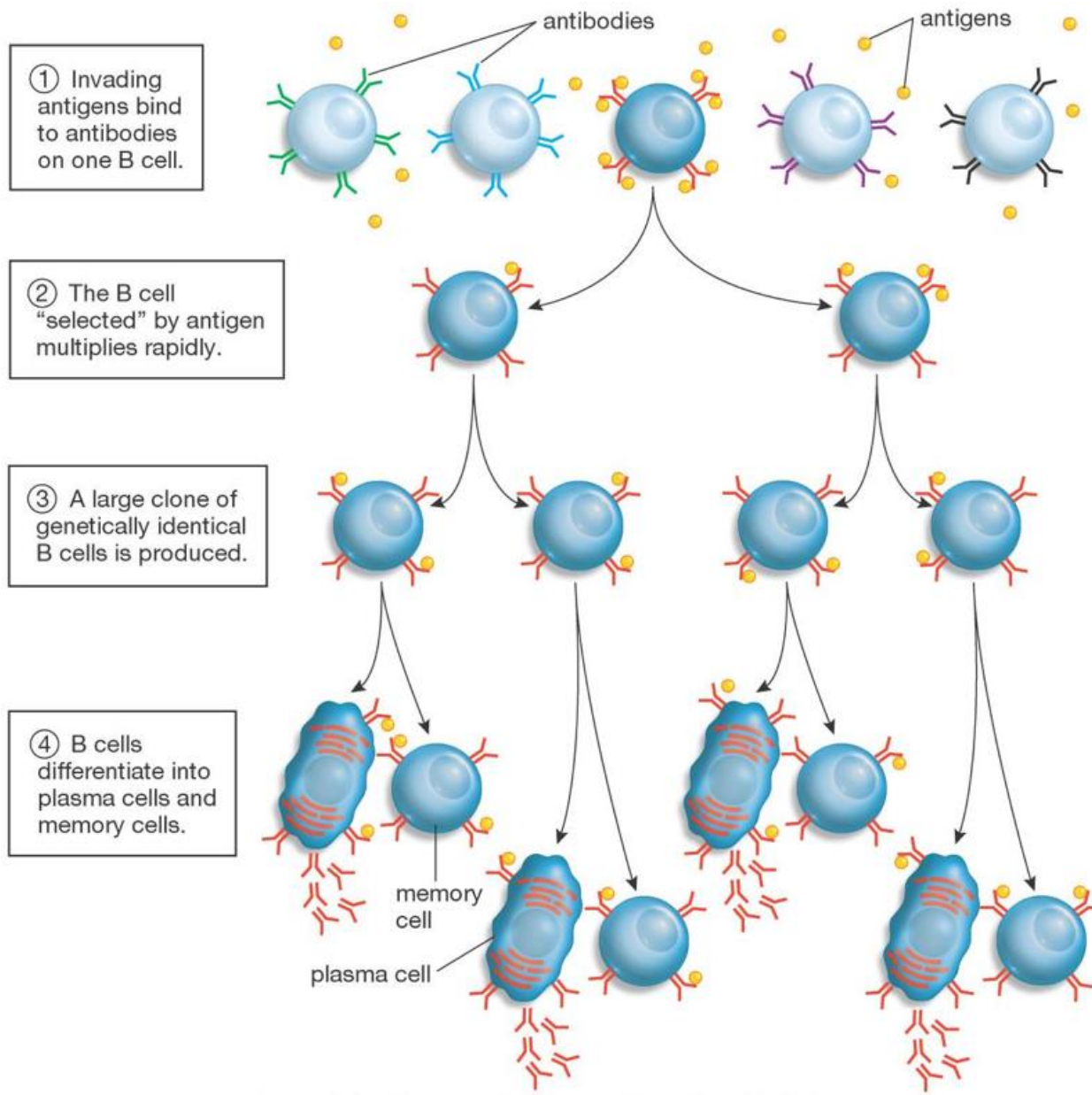
Helper T cells

- Helper T-cells have receptors for recognizing antigens. If they are presented with an antigen, they release cytokines to stimulate B-cell division.
- The helper T-cell is the key cell to signal an immune response.
- If helper T-cells are disabled (ex. In AIDS) the immune system will not respond.

B cells

- B-cells in general produce antibodies. Those with antibodies that bind with the invader's antigen are stimulated to reproduce rapidly.
- B-cells differentiate into either plasma cells or memory B-cells. Plasma cells rapidly produce antibodies. Memory cells retain the “memory” of the invader and remain ready to divide rapidly if an invasion occurs again.

Clonal Selection



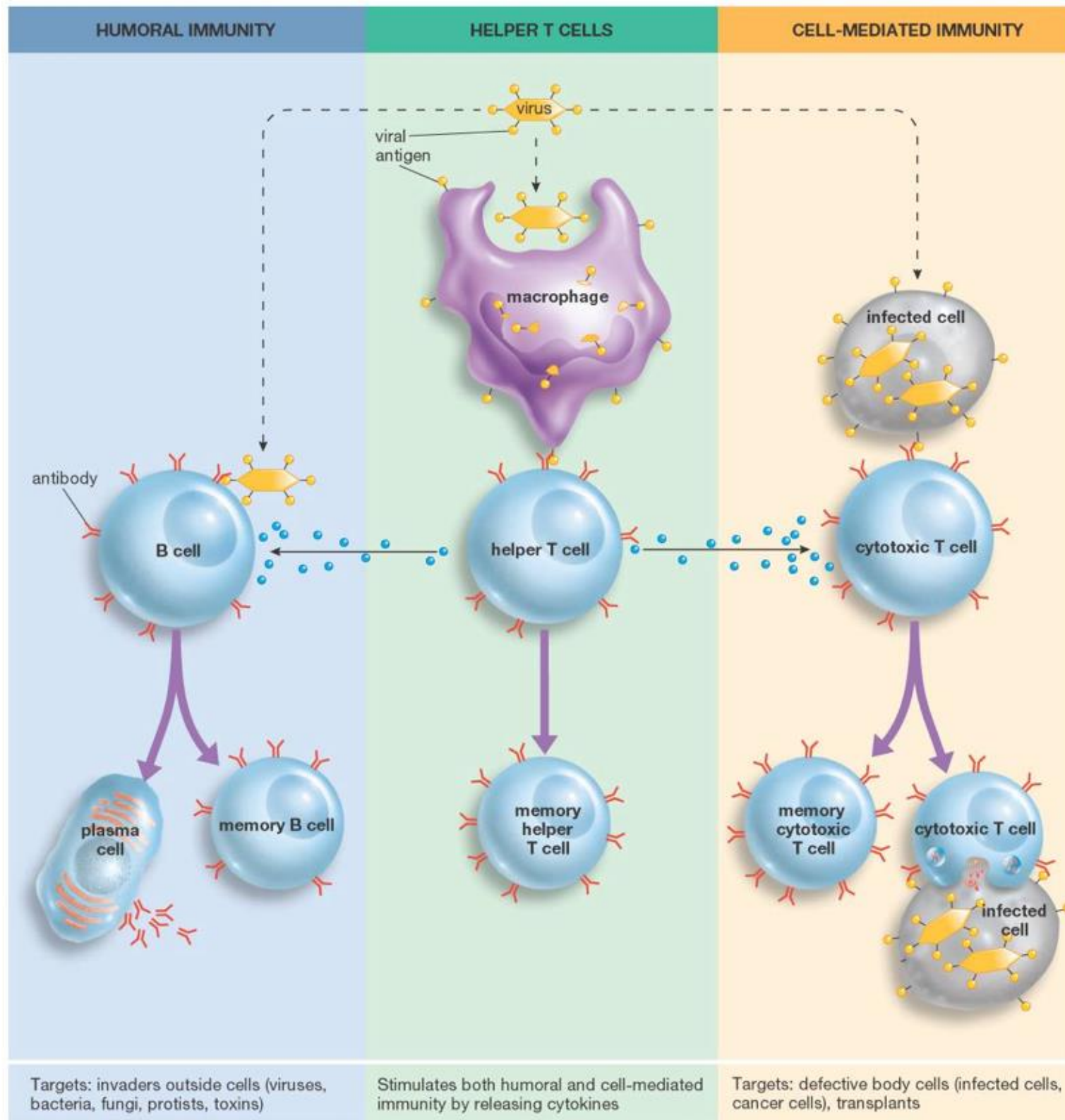
Role of antibodies

- Antibodies released into the blood stream will bind to the antigens that they are specific for.
- Antibodies may disable some microbes, or cause them to stick together (agglutinate). They “tag” microbes so that the microbes are quickly recognized by various white blood cells.

- **Antibodies are divided up into classes**
 - **IgA**: Mucosal surfaces - if low, predisposes to respiratory and GI infections as well as autoimmunity
 - **IgM**: Rapid response bloodstream antibody made at the beginning of an infection
 - **IgG**: Slower but longer lasting bloodstream antibody
 - **IgE**: Allergy

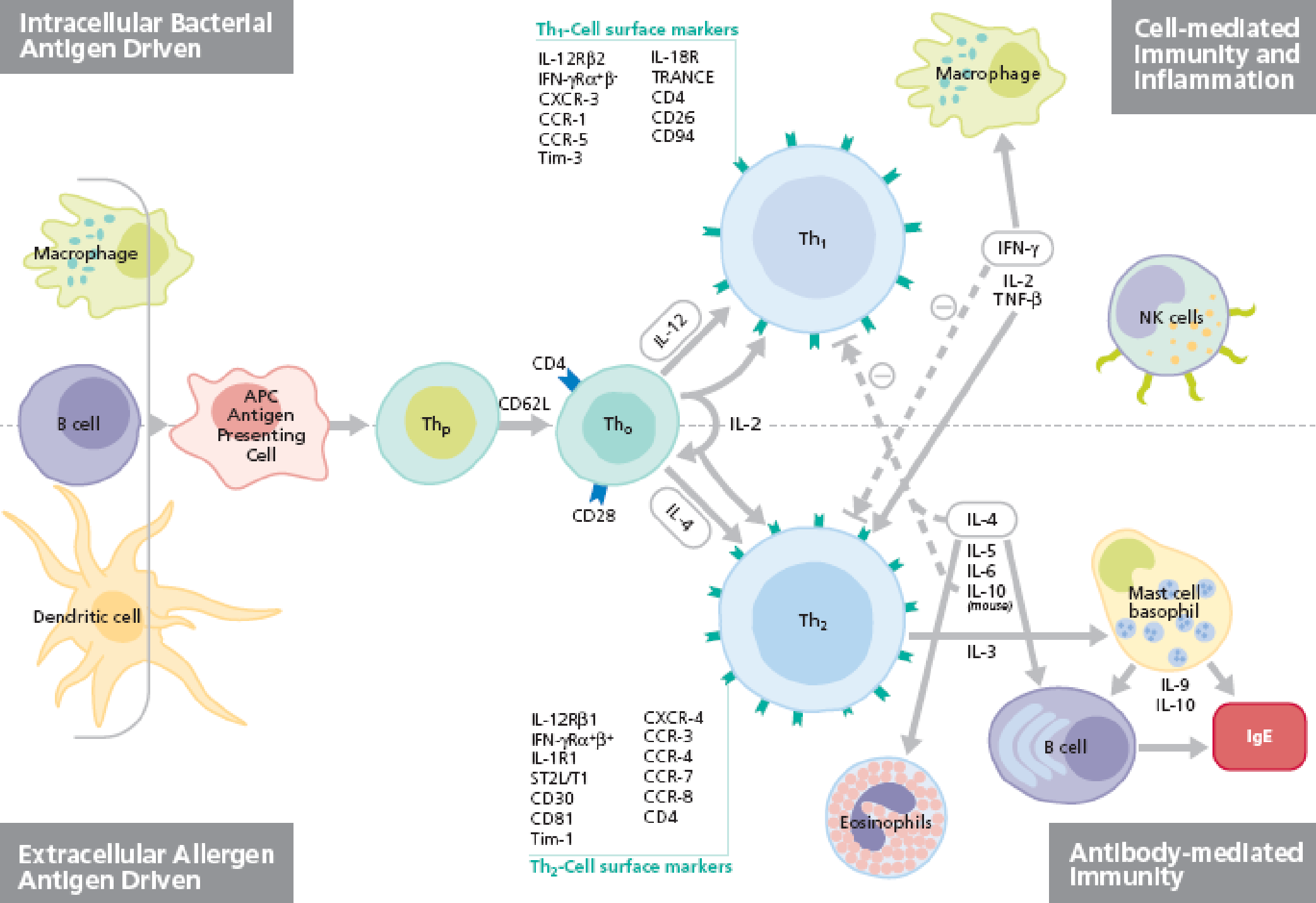
“Killer” T cells

- While B-cells divide and differentiate, so do T-cells.
- Some T-cells become cytotoxic, or “killer” T-cells. These T-cells seek out and destroy any antigens in the system, and destroy microbes “tagged” by antibodies.
- Some cytotoxic T-cells can recognize and destroy cancer cells.



Intracellular Bacterial Antigen Driven

Cell-mediated Immunity and Inflammation

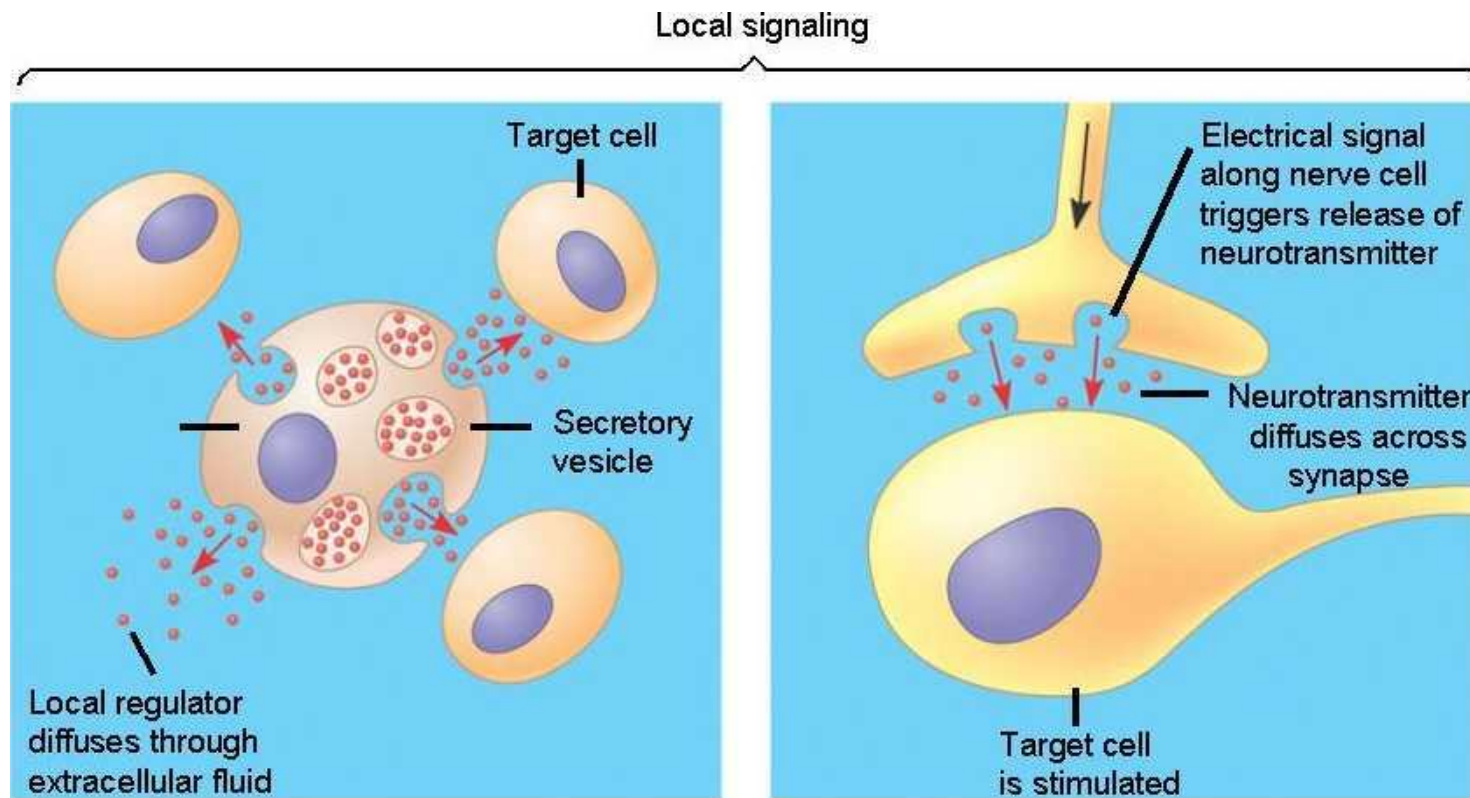


Calling a halt

- When the invader is destroyed, the helper T-cell calls a halt to the immune response.
- Memory T-cells are formed, which can quickly divide and produce cytotoxic T-cells to quickly fight off the invader if it is encountered again in the future.

Cytokines – the Language of the Immune System

Chemical messages that are the main communication system between cells of the immune system and other systems – especially the nervous system



(a) Paracrine signaling. A secreting cell acts on nearby target cells by discharging molecules of a local regulator (a growth factor, for example) into the extracellular fluid.

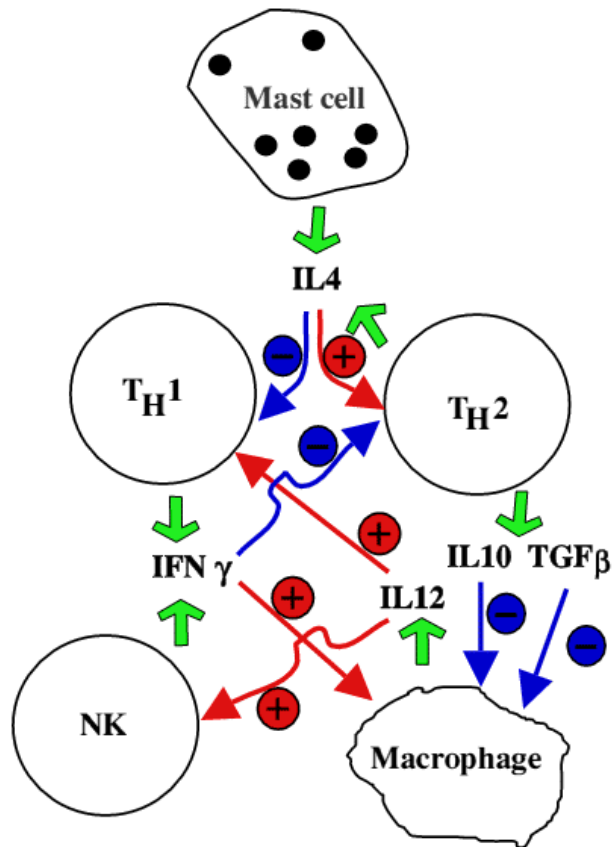
(b) Synaptic signaling. A nerve cell releases neurotransmitter molecules into a synapse, stimulating the target cell.

Cytokines – the Language of the Immune System



Can be divided several ways:

- **Th1** (adaptive/memory, cell mediated): IL-2, IFN- γ
- **Th2** (adaptive/memory, antibodies): IL-4, IL-5, IL-13, IL-10, TGF- β
- **Innate**: TNF- α , IL-1, IL-6, IL-12
- **Pro-inflammatory**: TNF- α , IL-1, IL-6
- **Anti-inflammatory**: TGF- β , IL-10
- **Regulatory**: IL-10, IL-12, TGF- β



Coordinated “Attack” with Feedback Loops using Cytokines

'Regulatory' T
cells

'Pathogenic' T
cells

BALANCE !!!

DEVELOPMENT OF THE IMMUNE SYSTEM

- Early in life, the immune system is not mature enough to fight off pathogens and must depend on antibodies from the mother.
- The body's ability to defend against antigens varies throughout the lifespan.
- Infants respond well to protein antigens but not as well to glycoproteins and polysaccharides.
- After 24 months of age, a child can defend well against glycoproteins and polysaccharides.

Unique Features of the Neonatal Immune System

- Hematological changes in the first few months of life
 - naïve/ memory
 - T vs. B cells
 - T cell subsets
 - B cell development and maternal Ab
- Development of normal flora at mucosal sites
 - Implications for mucosal immune responses?
 - Influence of nutrition, including breast-feeding
- Immune system is immature -
 - Immune system is developing: differences in quality and quantity

Newborns

- Neonates are physiologically immunodeficient, meaning both their innate and adaptive immunological responses are greatly suppressed.
- Once born, a child's immune system responds favorably to protein antigens and less so to glycoproteins and polysaccharides.
- In fact, many of the infections acquired by neonates are caused by low-virulence organisms like staphylococcus and pseudomonas.

Newborns

- In neonates, opsonic activity and the ability to activate the complement cascade is very limited. For example, the mean level of C3 in a newborn is approximately 65% of that found in the adult.
- Phagocytic activity is also greatly impaired in newborns. This is due to lower opsonic activity, as well as diminished upregulation of integrin and selectin receptors, which limit the ability of neutrophils to interact with adhesion molecules in the endothelium.
- It's also limited by slow monocytes with reduced ATP production.

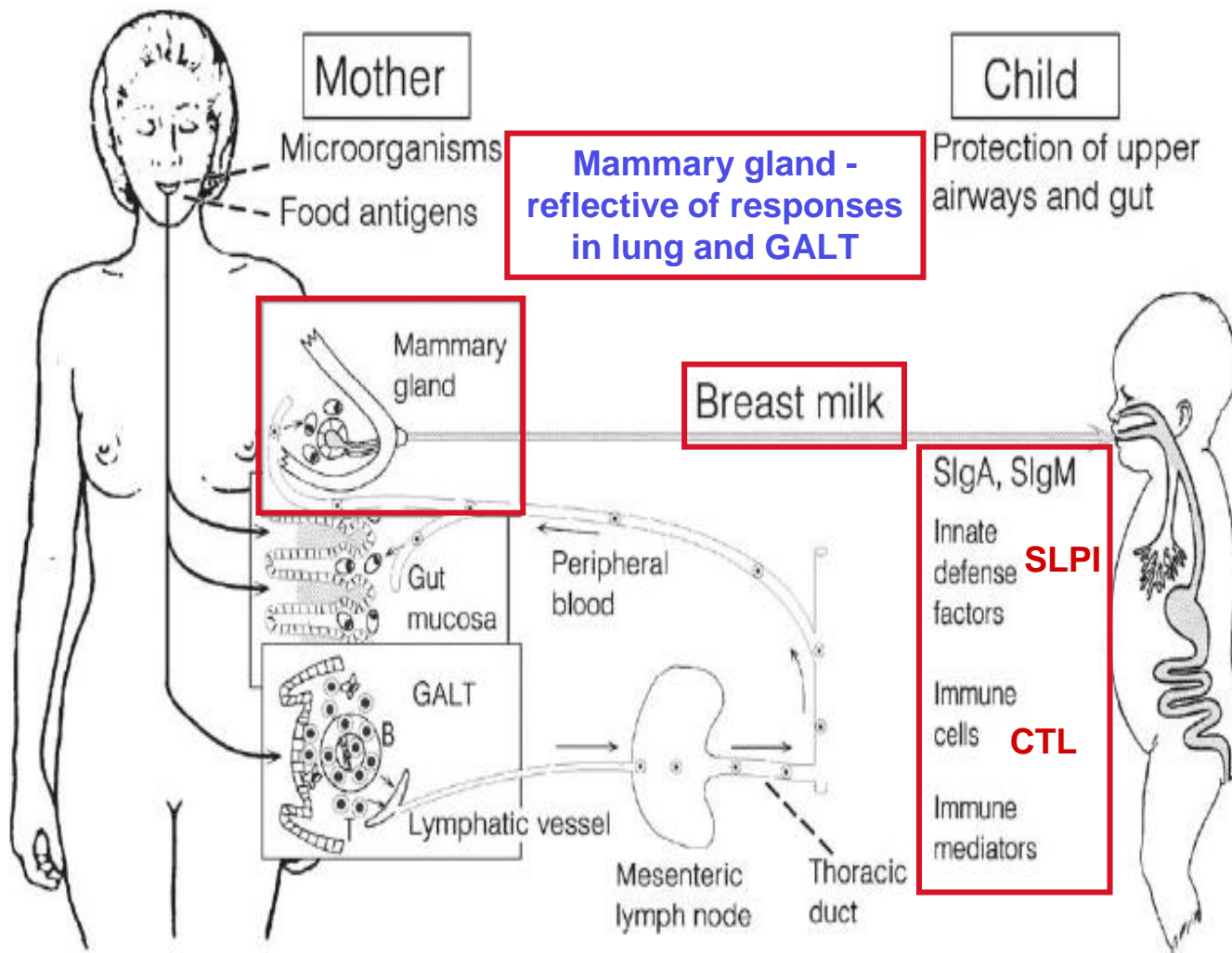
Newborns

- Although the number of total lymphocytes in newborns is significantly higher than in adults, the cellular and humoral immunity is impaired.
- Antigen-presenting cells in newborns have a reduced capability to activate T cells, proliferate poorly, and produce very small amounts of cytokines like IL-2, IL-4, IL-5, IL-12, and IFN-g.
- This limits the capacity of these cells to activate the humoral response and the phagocytic activity of macrophages.
- B cells develop early in gestation but are not fully active.

The Role of Maternal Factors

- At birth, most of the immunoglobulin present is maternal IgG. Because IgM, IgD, IgE and IgA don't cross the placenta, they are almost undetectable at birth, although some IgA is provided in breast milk.
- These passively acquired antibodies can protect the newborn for up to 18 months, but their response is usually short-lived and of low affinity.
- In addition, a child is exposed to the antibody for a particular antigen before being exposed to the antigen itself, the body will produce a dampened response.
- Passively acquired maternal antibodies can suppress the antibody response to active immunization.

The Mammary Gland – Part of the Mucosal Immune System



- PP and tonsils are developed at birth, but GC lack for a few weeks

- mucosal immunity is passively acquired from the mother via breast milk

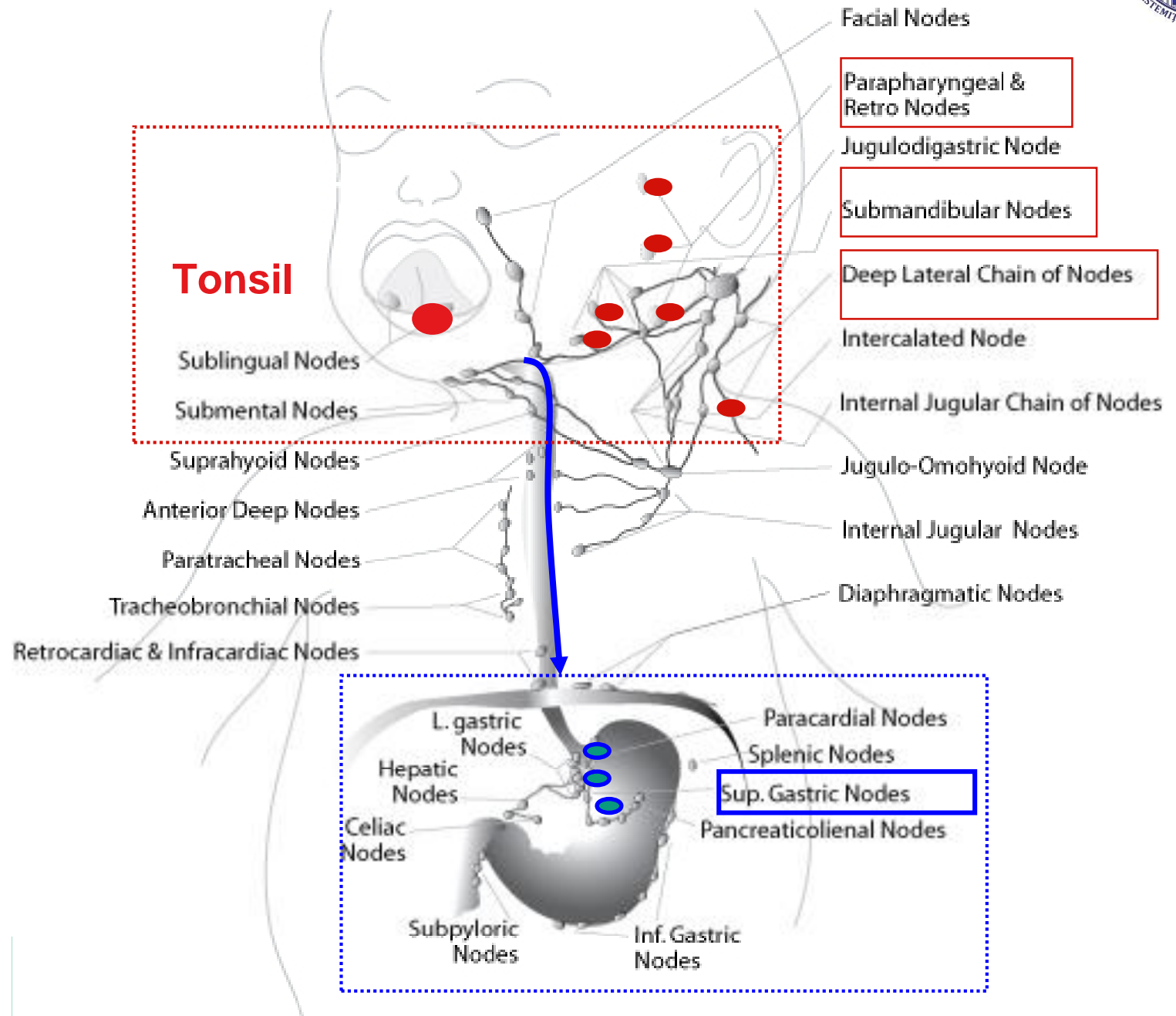
- breast-feeding is estimated to prevent up to 3 million death/ year in newborns

Breast-milk transmission

Virus entry:

oral mucosa
tonsil
intestine

LYMPHATIC DRAINAGE



The response of T-cells to vaccination

- Similarly, the response of T-cells to vaccination differs in children compared to adults, and vaccines that induce Th1 responses in adults do not readily elicit these same responses in neonates.
- By 6 to 9 months after birth, a child's immune system begins to respond more strongly to glycoproteins.
- Not until 12 to 24 months of age is there a marked improvement in the body's response to polysaccharides.

Immunity During Adolescence

- During adolescence the human body undergoes physical, physiological, and immunological changes, triggered and mediated by various hormones.
- Depending on the sex, testosterone or 17- β -oestradiol act on males and females respectively, starting at around age 12 for boys and 10 for girls.

Immunity During Adolescence

- There is evidence that these steroids act directly not only on the primary and secondary sexual characteristics, but also affect the development and regulation of the immune system.
- Pubescent and post-pubescent females and males are at increased risk for autoimmune disorders.
- There is some evidence that cell surface receptors on B cells and macrophages may detect sex hormones in the system.

Lymphadenopathy

Lymphadenopathy - DIAGNOSIS

- **Is the mass a lymph node?**

Nonlymphoid masses occur frequently in the neck and less often in other areas:

cervical rib,

thyroglossal cyst,

branchial cleft cyst or infected sinus,

cystic hygroma,

goiter,

sternomastoid muscle tumor,

thyroiditis, thyroid abscess,

neurofibroma

Lymphadenopathy - DIAGNOSIS

- **Is the node enlarged?**

Lymph nodes are not usually palpable in the newborn.

With antigenic exposure, lymphoid tissue increases in volume.

They are not considered enlarged until their diameter exceeds 1 cm for cervical and axillary nodes and 1.5 cm for inguinal nodes.

Other lymph nodes usually are not palpable or visualized with plain radiographs.

Lymphadenopathy - DIAGNOSIS

- **What are the characteristics of the node?**

Acutely infected nodes are usually tender.

There may also be erythema and warmth of the overlying skin.

Fluctuance suggests abscess formation.

Tuberculous nodes may be matted.

With chronic infection, many of these signs are not present.

Tumor-bearing nodes are usually firm and nontender and may be matted or fixed to the skin or underlying structures.

Lymphadenopathy - DIAGNOSIS

- **Is the lymphadenopathy localized or generalized?**

Generalized adenopathy (enlargement of >2 noncontiguous node regions) is caused by systemic disease and is often accompanied by abnormal physical findings in other systems.

Regional adenopathy is most frequently the result of infection in the involved node and/or its drainage area.

Lymphadenopathy - DIAGNOSIS

- When caused by infectious agents other than bacteria, adenopathy may be characterized by atypical anatomic areas, a prolonged course, a draining sinus, lack of prior pyogenic infection, and unusual clues in the history (cat scratches, tuberculosis exposure, venereal disease).
- A firm, fixed node should always raise the question of malignancy, regardless of the presence or absence of systemic symptoms or other abnormal physical findings.

Differential Diagnosis of Systemic Generalized Lymphadenopathy



INFANT	CHILD	ADOLESCENT
COMMON CAUSES		
Syphilis	Viral infection	Viral infection
Toxoplasmosis	EBV	EBV
CMV	CMV	CMV
HIV	HIV	HIV
Toxoplasmosis	Toxoplasmosis	Syphilis
RARE CAUSES		
Chagas disease (congenital)	Serum sickness	Serum sickness
Leukemia	SLE, JIA	SLE, JIA
Tuberculosis	Leukemia/lymphoma	Leukemia/lymphoma
Reticuloendotheliosis	Tuberculosis	Tuberculosis

Differential Diagnosis of Systemic Generalized Lymphadenopathy



INFANT	CHILD	ADOLESCENT
RARE CAUSES		
Lymphoproliferative disease	Measles	Measles
Metabolic storage disease	Sarcoidosis	Sarcoidosis
Histiocytic disorders	Fungal infection	Fungal infection
	Plague	Plague
	Langerhans cell histiocytosis	Langerhans cell histiocytosis
	Chronic granulomatous disease	Chronic granulomatous disease
	Sinus histiocytosis	Sinus histiocytosis
	Drug reaction	Drug reaction

Sites of Local Lymphadenopathy and Associated Diseases

CERVICAL

- Oropharyngeal infection (viral or group A streptococcal, staphylococcal)
- Scalp infection/infestation (head lice)
- Mycobacterial lymphadenitis (tuberculosis and nontuberculous mycobacteria)
- Viral infection (EBV, CMV, HHV-6)
- Cat-scratch disease
- Toxoplasmosis

Sites of Local Lymphadenopathy and Associated Diseases

CERVICAL

- Kawasaki disease
- Thyroid disease
- Kikuchi disease
- Sinus histiocytosis (Rosai-Dorfman disease)
- Autoimmune lymphoproliferative disease
- Periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy
- (PFAPA) syndrome

Sites of Local Lymphadenopathy and Associated Diseases

ANTERIOR AURICULAR

- Conjunctivitis
- Other eye infection
- Oculoglandular tularemia
- Facial cellulitis
- Otitis media
- Viral infection (especially rubella, parvovirus)

Sites of Local Lymphadenopathy and Associated Diseases

SUPRACLAVICULAR

- Malignancy or infection in the mediastinum (right)
- Metastatic malignancy from the abdomen (left)
- Lymphoma
- Tuberculosis

Sites of Local Lymphadenopathy and Associated Diseases

EPITROCHLEAR

- Hand infection, arm infection (unilateral)
- Lymphoma (bilateral)
- Sarcoid
- Syphilis

Sites of Local Lymphadenopathy and Associated Diseases

INGUINAL

- Urinary tract infection
- Venereal disease (especially syphilis or lymphogranuloma venereum)
- Other perineal infections
- Lower extremity suppurative infection
- Plague

Sites of Local Lymphadenopathy and Associated Diseases

HILAR (not palpable, found on chest radiograph or CT)

- Tuberculosis (bilateral)
- Histoplasmosis (bilateral)
- Blastomycosis (bilateral)
- Coccidioidomycosis (bilateral)
- Leukemia/lymphoma (bilateral)
- Hodgkin disease (bilateral)
- Metastatic malignancy (unilateral)
- Sarcoidosis (bilateral)
- Castleman disease

Sites of Local Lymphadenopathy and Associated Diseases

AXILLARY

- Cat-scratch disease
- Arm or chest wall infection
- Malignancy of chest wall
- Leukemia/lymphoma
- Brucellosis

Sites of Local Lymphadenopathy and Associated Diseases

ABDOMINAL

- Malignancies
- Mesenteric adenitis (measles, tuberculosis, *Yersinia*, group A streptococcus)

Lymphadenopathy

- Evaluation and treatment of lymphadenopathy is guided by the probable etiologic factor, as determined from the history and physical examination.
- Many patients with cervical adenopathy have a history compatible with viral infection and need no intervention.
- If bacterial infection is suspected, antibiotic treatment covering at least streptococci and staphylococci is indicated.
- Those who do not respond to oral antibiotics, as demonstrated by persistent swelling and fever, require IV antistaphylococcal antibiotics.

Lymphadenopathy

- If there is no response in 1-2 days, or if there are signs of airway obstruction or significant toxicity, ultrasound, CT, or MRI of the neck should be obtained.
- If pus is present, it may be aspirated, with CT or ultrasound guidance, or if it is extensive, may require incision and drainage.
- Gram stain and culture of the pus should be obtained.
- The sizes of involved nodes should be documented before treatment.

Lymphadenopathy

- Failure to decrease in size within 10-14 days also suggests the need for further evaluation.
- This may include a complete blood cell count with differential; Epstein-Barr virus, cytomegalovirus, *Toxoplasma*, and cat-scratch disease titers; antistreptolysin O or anti-DNAse serologic tests; tuberculin skin test; and chest radiograph.

Lymphadenopathy

- Biopsy should be considered if there is persistent or unexplained fever, weight loss, night sweats, supraclavicular location, mediastinal mass, hard nodes, or fixation of the nodes to surrounding tissues.
- Biopsy may also be indicated if there is an increase in size over baseline in 2 wk, no decrease in size in 4-6 wk, no regression to “normal” in 8-12 wk, or if new signs and symptoms develop.

Lymphadenopathy

- Differentiating benign disorders from a malignancy may initially be difficult.
- Hard, nontender, nonerythematous nodes involving multiple regions (including mediastinum and abdomen), hepatic or splenic enlargement, fever, night sweats, and weight loss suggest malignancy or a granulomatous process.
- Persistence of symptoms and lymphadenopathy greater than 2 wk and certain locations (supraclavicular, mediastinal, abdomen) also suggest malignancy.

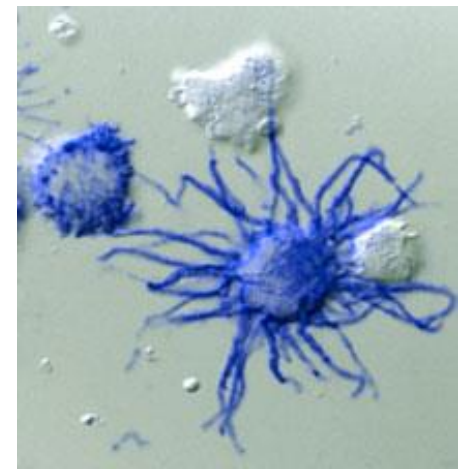
Lymphadenopathy

- Cytopenias and elevated blood lactate dehydrogenase are associated with malignancy and certain inflammatory disorders.
- CT imaging is helpful in identifying other affected nodes and organs; CT or ultrasonographic guided biopsy is helpful in determining the etiology.
- Fine needle aspiration or excisional biopsy may be needed for superficial nodes to determine a diagnosis.

Immunologic Disorders

Things that can go wrong...

- Immune **deficiency/dysfunction**: defective or ineffective response.
- **Hypersensitivity**: Over-reaction to innocuous foreign material, out of proportion to potential damage - Allergy.
- **Autoimmunity**: Inappropriate reaction towards self, loss of self-recognition.
- **Inflammation**: Too vigorous attack against invaders with “bystander” damage to normal tissue.



Deficiency



Th1 and/or Th2

Autoimmunity



Th1 and/or Th2

Allergy



Th2

Inflammation



**Innate and/or
Th1 Th2**

IMMUNE DISEASES

Immunosuppressive response

- Increased rates of infectious diseases and neoplasia

Immunostimulatory response

- Hypersensitivity reactions

Immune diseases and children



Examples:

- Asthma, rhinitis, eczema, urticaria, anaphylaxis
- Autoimmune diseases : diabetes 1, rheumatoid arthritis, systemic lupus
- Allergic alveolitis
- Contact dermatitis (T lymphocytes-mediated)
- Hemolytic disease of the newborn
- Glomerular basement membrane damage

Primary Immunodeficiencies are

- Caused by a defect in the immunesystem
- Much more common than one would think (1/1 000 to 1/2000)
- Not always easy to recognize:
 - Many different symptoms
 - Many different diagnoses

But important not to miss the possible diagnosis!

Quality of life

Organ damage (scar tissue, bronchiectases)

Best way to recognize an PID

- From the clinical point of view

→ Any patient with

- Too many infections
- Infections that don't heal properly
- Weird infectious agents (opportunistic infections)
- Weird localization (deep abscess)
- Non infectious problems (cfr next slide)
- Family history

PID should be in the differential diagnosis!

Non-infectious problems

- Failure to thrive
- Eczema
- Teeth problems
- Gastro intestinal problems (food allergies, diarrhea)
- Autoimmunity
- Lymphoproliferation
- Increased risk of malignancy

Take into account

- Age of the patient
- Gender
- Type of infection (viral, bacterial, fungi)
- Other symptoms
- Familial history

→ Estimate the possibility

Patterns

- B cell problem
 - No B cells, No antibodies, weak antibodies
 - “Always ill”, autoimmunity
- T cell problems
 - No T cells, bad function of T cells
 - Viral infections, sometimes early onset.
- Innate immunity
 - No neutrophils, bad function of neutrophils, complement disorders
 - Severe invasive bacterial infections

Case example

B cell problems

- A 5 years old girl that is often ill
 - Always coughing, running nose, ear infections.
 - Had 4 pneumonia's so far (1/year)
 - Often uses antibiotics, sometimes with good results
 - Intensive treatment by pneumologists (inhalers, physiotherapy) because of viral induced wheezing. Suboptimal effect.
 - Not growing very well

Typical picture of an antibody deficiency

- “always ill”
- Poor response to standard of care
- Failure to thrive
- 5 years is too old for this.

Initial work-up

- Full blood count
→ Lack of neutrophils or lymphocytes?
- Immunoglobulines (IgG, A, M and maybe IgG2 and IgG3).
- Anti Pneumococcal antibodies

- The younger the child, the more difficult to pick those children out that are abnormal.
- On the other hand: costs are low for these tests.
- Wait and see?

Antibody deficiencies

- Most common known PID is *common variable immunodeficiency*
- Onset all ages, diagnosis only > 5 years
- Usually many infections at younger age, better between 7 -17, worse in adulthood
- Non infectious complications

B cell deficiency

- Transient hypogammaglobulinemia
 - No way to make the difference
- Agammaglobulinemia
 - No B cells, no antibodies
- Selective anti Pneumococcal antibody deficiency
 - Difficult to prove since introduction conjugated vaccine

Diagnosis

- Immunoglobulin levels
 - Take care of lower normal values when a patient is ill all the time
- Response to vaccination
- B cell repertoire

Treatment

- Immunoglobulin substitution therapy
 - Temporarily
 - Lifelong
- Supportive therapy
 - Multidisciplinary (ENT, pneumologist)
- Screening

Case example

T cell deficiency

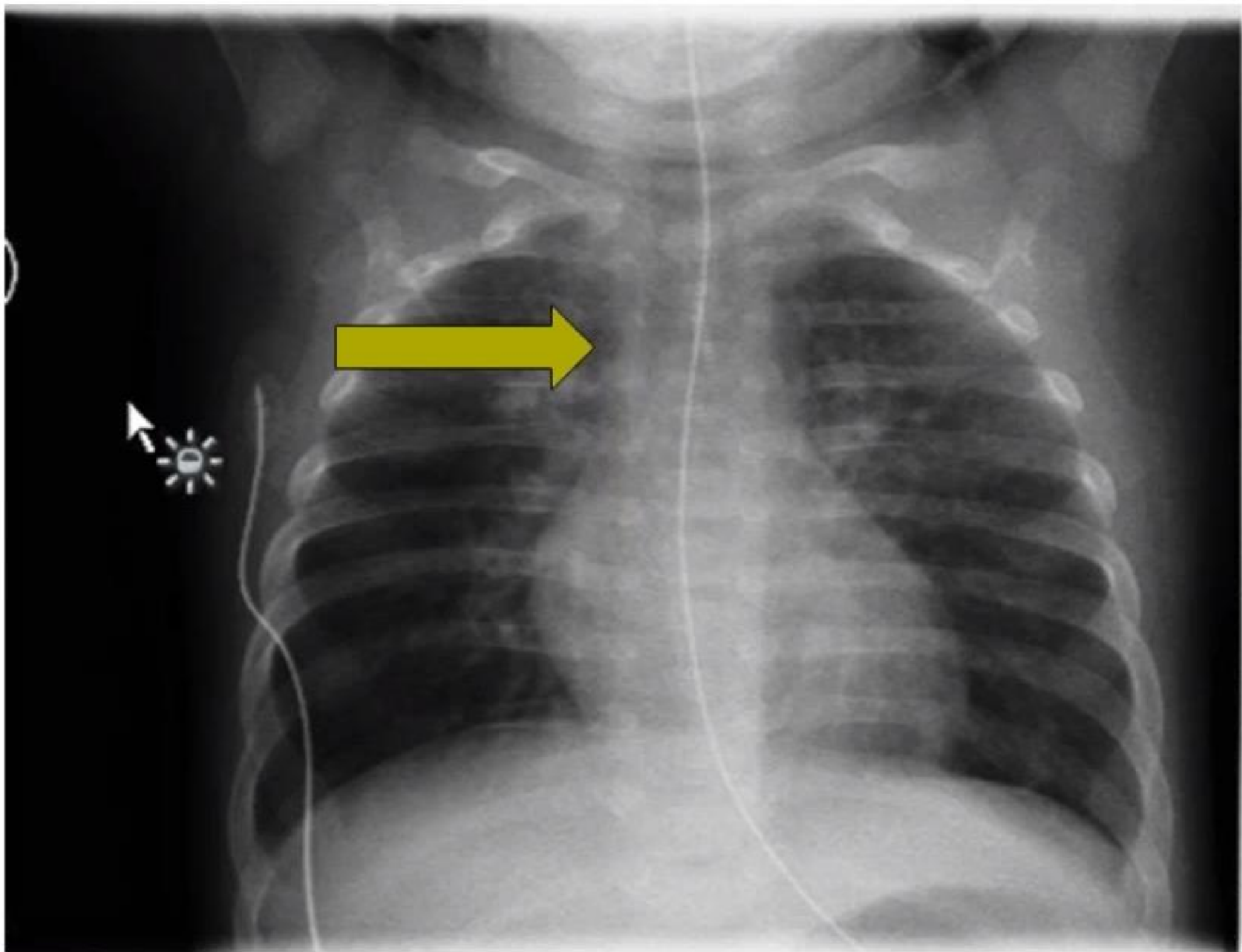
- 3 months old baby
- Severe failure to thrive
- Admitted in PICU with severe respiratory distress
- CMV is cultured from a respiratory sample
- Hepatitis

Hematologie					
Plaatjes	Bloed	158 - 470	$\times 10^3/\text{mm}^3$	(7)	205
Rode bloedcellen	Bloed	3.9 - 5.2	$\times 10^6/\text{mm}^3$	1.7	2.8
Hemoglobine	Bloed	9.8 - 13.8	g/dL	5.2	8.8
Hematocriet	Bloed	29.4 - 42.0	%	5.2	25.4
MCV	Bloed	68.0 - 90.0	fL	1.1	89.2
MCH	Bloed	23.0 - 31.0	pg	1.2	31.0
MCHC	Bloed	32.0 - 35.0	g/dL	4.2	34.7
Reticulocyten	Bloed	0.6 - 2.0	%		
Reticulocyten (absoluut)	Bloed	30.0 - 100.0	$\times 10^3/\text{mm}^3$		
Immature reticulocytenfractie	Bloed	0.1 - 0.2			
Witte bloedcellen	Bloed	3.5 - 17.3	$\times 10^3/\text{mm}^3$	3.0	2.9
Formule					
Neutrofiel	Bloed	12.0 - 60.0	%		88.0
Basofiel	Bloed	0.0 - 2.0	%		0.0
Eosinofiel	Bloed	0.0 - 6.0	%		0.0
Lymfocyt	Bloed	28.0 - 76.0	%		9.0
Monocyt	Bloed	1.0 - 13.0	%		2.0
Andere	Bloed	0	%		1.0
Myelocyt	Bloed		%		1.0
Metamyelocyt	Bloed		%		
Atypische lymfocyt	Bloed		%		
Erytroblast	Bloed		$/10^9 \text{ wbc}$		1.0
Neutrofiel (absoluut)	Bloed	1.7 - 8.7	$\times 10^3/\text{mm}^3$		2.552
Basofiel (absoluut)	Bloed	0.0 - 0.1	$\times 10^3/\text{mm}^3$		0.000
Eosinofiel (absoluut)	Bloed	0.0 - 0.4	$\times 10^3/\text{mm}^3$		0.000
Lymfocyt (absoluut)	Bloed	2.7 - 8.7	$\times 10^3/\text{mm}^3$		0.261
Monocyt (absoluut)	Bloed	0.3 - 1.8	$\times 10^3/\text{mm}^3$		0.052
Myelocyt (absoluut)	Bloed		$\times 10^3/\text{mm}^3$		0.029
Metamyelocyt (absoluut)	Bloed		$\times 10^3/\text{mm}^3$		
Atypische lymfocyt (absoluut)	Bloed		$\times 10^3/\text{mm}^3$		
Erytroblast (absoluut)	Bloed		$\times 10^3/\text{mm}^3$		0.029
Bloedfilm	Bloed				! * (8)

Case example

- Young child
- Severe viral infection
- Lymphopenia
- No Thymus on X-ray

- Severe combined immunodeficiency?
- Immunological emergency
 - Referral to academic center



T cell deficiency

- Wide range of the clinical spectrum
 - Very early onset (SCID) vs later onset (CID)
 - Many different genetic diagnoses
 - Viral infections, bacterial as well
- Treatment stemcell transplantation

Case example

Innate immunodeficiencies

- 1 months old baby boy
- Admitted for fever
- Work up was done and he was put under antibiotics
 - Umbilical cord still present and infected

Severe congenital neutropenia

- Absence of neutrophils in peripheral blood
→ absolute numbers
- Severe infections, omphalitis
- Life threatening
- Treatment GCSF
- DD with chronic benign neutropenia:
→ no infections

Take home message

- Children that are *always ill* or have strange infections might have an underlying immunodeficiency
- These children often have an antibody disorder and measuring antibodies is cheap and easy
- However, if antibodies are normal and the patient doesn't improve: think of referring

10 Warning Signs of an Immune Deficiency

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- | | | | |
|---|---|---|----|
| 1 | Eight or more new ear infections within 1 year. | Recurrent, deep skin or organ abscesses. | 6 |
| 2 | Two or more serious sinus infections within 1 year. | Persistent thrush in mouth or elsewhere on skin, after age 1. | 7 |
| 3 | Two or more months on antibiotics with little effect. | Need for intravenous antibiotics to clear infections. | 8 |
| 4 | Two or more pneumonias within 1 year. | Two or more deep-seated infections. | 9 |
| 5 | Failure of an infant to gain weight or grow normally. | A family history of Primary Immunodeficiency. | 10 |

Recurrent Infections if IgG, IgM, or IgA are low