

Immunity

- **Immunity**
- Self - and non-self recognition / protection against
 - **foreign macromolecular substances** (proteins, polysaccharides)
 - **pathogens** (bacteria, viruses, fungi, protozoa, nematodes, flatworms)
- **Immune system**
 - **nonspecific immunity** - uptake of pathogens by phagocytic cells, release of defensive proteins
 - **specific immunity** - lymphocytes

Balance between infection and immunity

infection

immunity



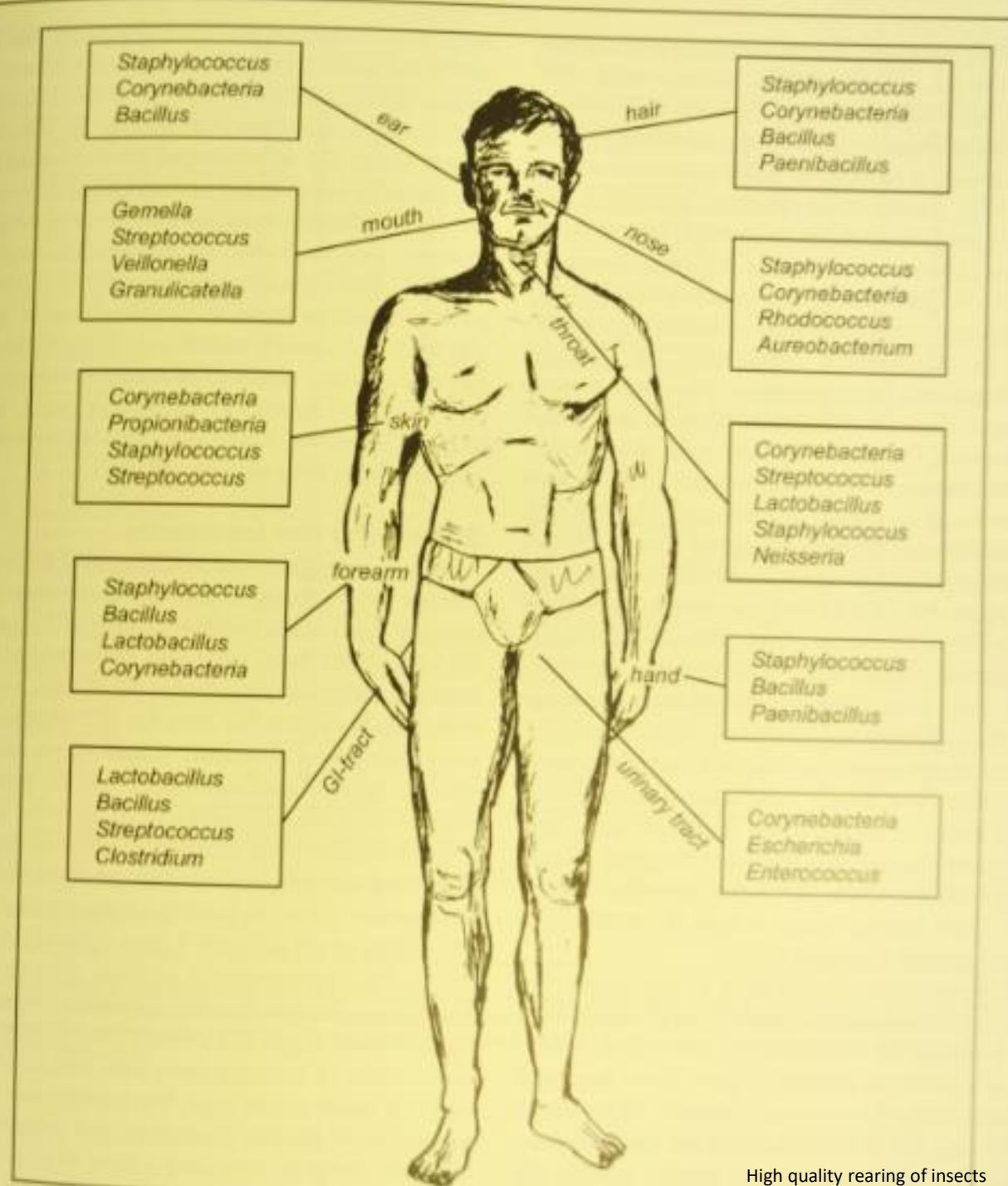
Immunology originated from microbiology

- planet of microorganisms, almost 3 billion years without other organisms, the carbon bound in microorganisms is twice as much as in all other organisms
- microorganisms are ubiquitous as pathogens, symbionts, commensals... inseparable from higher organisms (including the genome)
- 1-10 bacterial cells per 1 human cell, 1-1.5 kg of human weight, about 1000 species, 1 g of soil contains 10^9 bacteria in 7,000 species
- during diseases the number of species of intestinal bacteria is reduced, changing the composition of species can significantly facilitate healing - probiotics (bacteria of lactic fermentation, e.g. lactobacilli, bifidobacteria) + prebiotics (support growth of beneficial bacteria, such as carbohydrate components - inulin), synbiotics - contain pro- and prebiotics
- fecal transplantation of microbiota to patients with intestinal infection
- life without bacteria is complicated - immature immunity
- antibiotic resistance is 30,000 years old - ice samples - resistance genes are common in the environment, there are bacteria resistant to up to 100 antibiotics)

- Even on the surface of the skin of a very clean person live up to tens of grams of various types of bacteria and other microorganisms, after washing their number decreases, but soon reaches its original values.



- **The microbiome that inhabits the skin, respiratory tract, urogenital and gastrointestinal tracts is the primary regulator of health and disease.**
- The ability to defend integrity is called immunity (in plants and microbes often as resistance).



SO YOU THINK YOU ARE ALONE?

YouTube



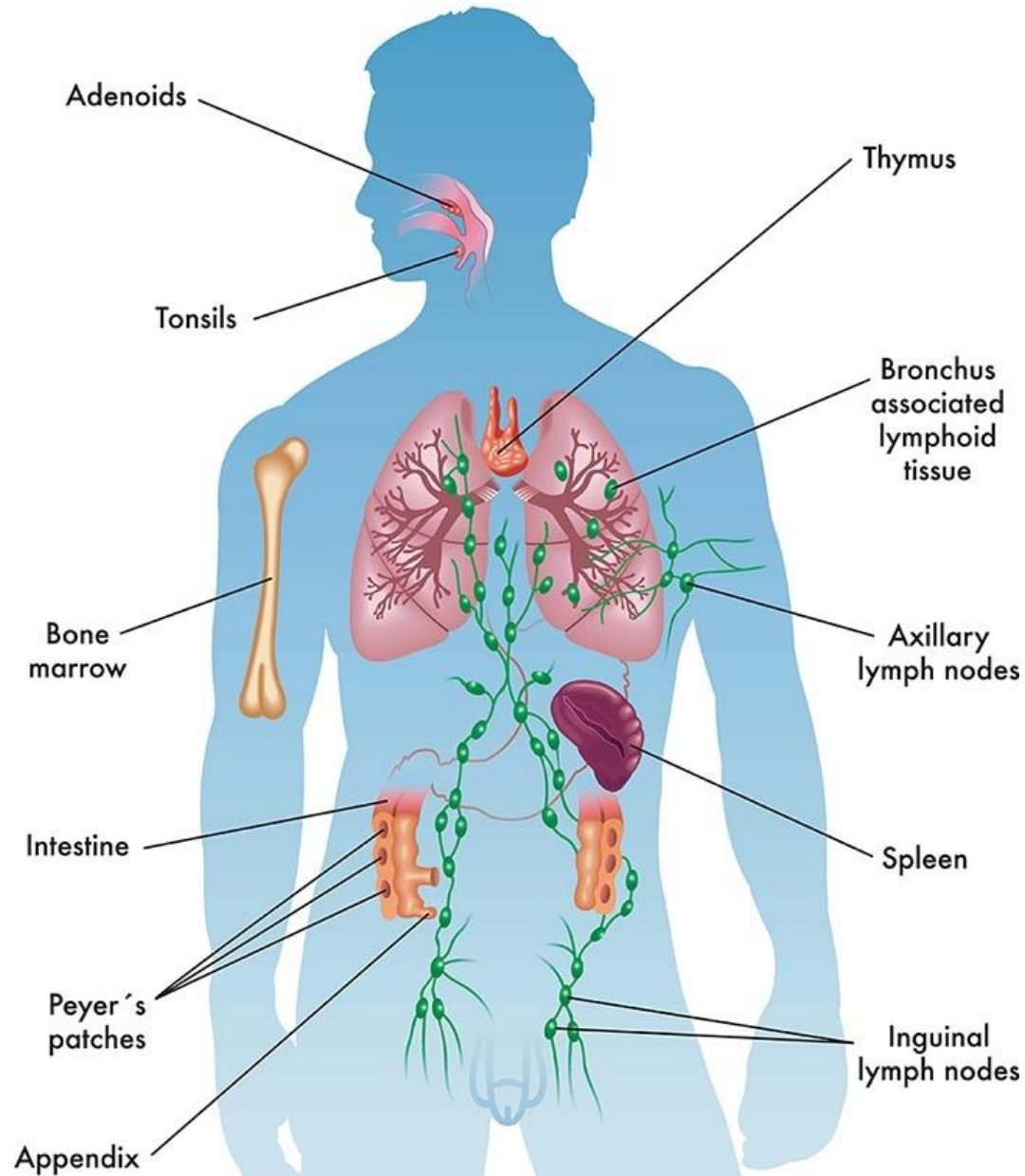
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WE ARE NOT ALONE: How the Human "Planet" Is Colonized and a Gut Microbiome Is Built

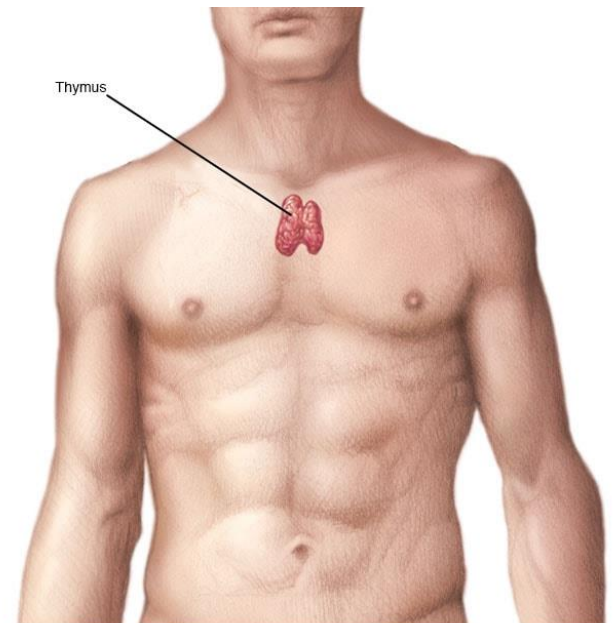
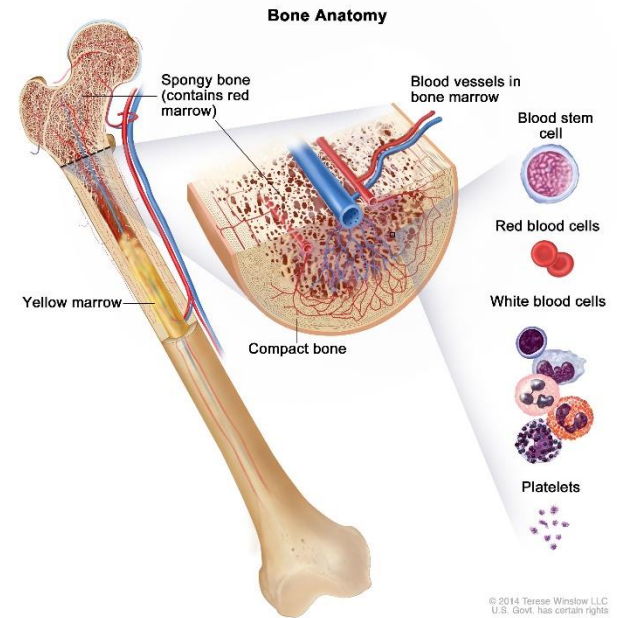
<https://www.youtube.com/watch?v=WEtJYXsYKxc>

Organs of the immune system



Primary lymphoid organs

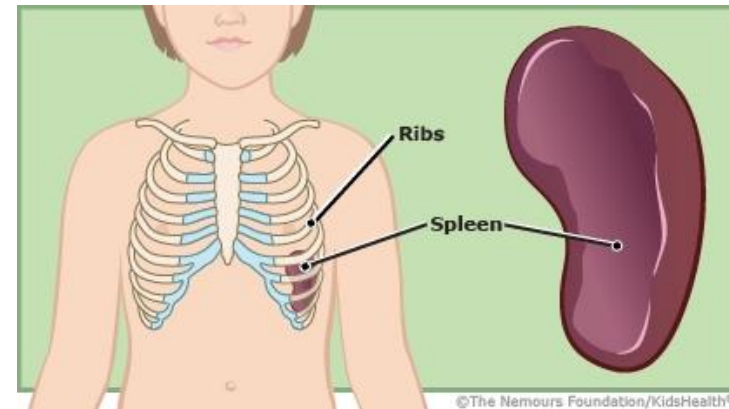
- Bone marrow
 - Stem cells
 - Myeloid precursors
 - Lymphoid precursors
- Thymus
 - Two types of tissues
 - Cortex
 - Marrow area



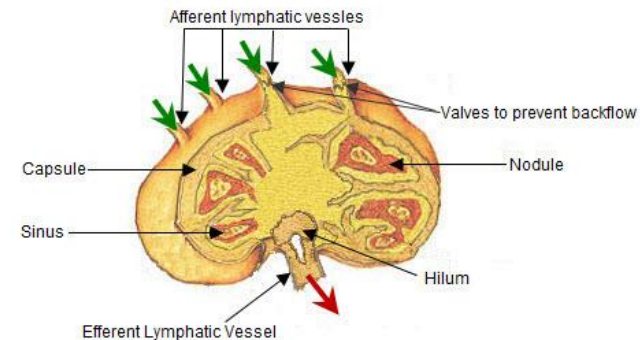
Secondary lymphoid organs

- Spleen
 - It absorbs microbial stimuli from the blood
 - Red pulp (larger) - macrophages
 - White pulp - T and B lymphocytes

- Lymph node
 - Here, IS cells encounter the antigen
 - Development of a specific immune response



Lymph Node Structure



Mucosal immune system

- MALT (**M**ucosa **A**ssociated **L**ymfoid **T**issue)
- GALT (**G**ut **A**ssociated **L**ymfoid **T**issue)
- BALT (**B**ronchus **A**ssociated **L**ymfoid **T**issue)
- this means that the immune cells are in the blood, but also on the skin, mucous membranes, genitourinary tract, etc. (protects huge areas)
- forms the interface between the organism and the external environment

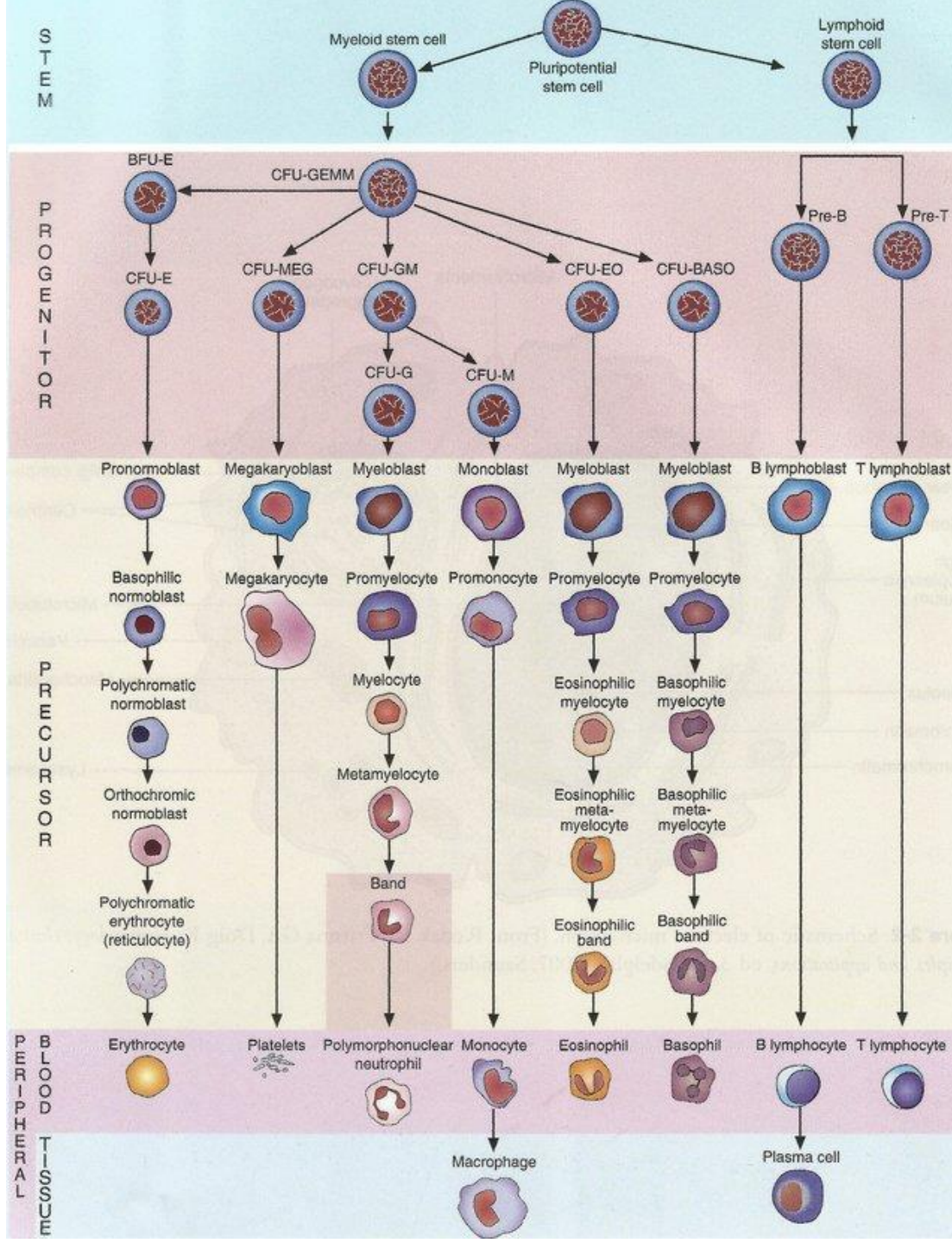


Figure from Carr & Rodak, 2012 (15).

Cells of the immune system

- **Neutrophil granulocytes**

- they live very shortly in the blood, performing functions quickly and breaking down
- primary protection **against extracellular bacteria**
- phagocytosis (intracellular killing), function in primary inflammation
- CD66 positive,

Cluster Designation (sometimes also referred to as *cluster of differentiation*)

Neutrophil



- **Eosinophilic granulocytes**

- defense **against large parasites** (protozoa, tapeworms)
- release of lytic enzymes from the granules
- apply **in allergic reactions**

Eosinophil



- **Basophilic granulocytes**

- in granules heparin and histamine: function **in inflammation (dilation of blood vessels)**
- specific / adaptive immunity

Basophil

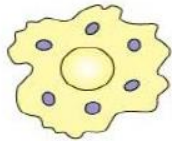


Cells of the immune system

- **Monocytes (mobile) → macrophages (tissue)**

- phagocytosis of pathogens / cancer / apoptotic bodies, tissue regeneration
- **APC:** antigen presentation (specific / adaptive immunity), MHC-II proteins
- CD14 positive, adherence to glass and plastic
- production of cytokines
- defense **against extracellular and intracellular pathogens**

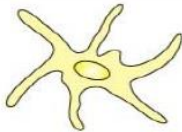
Macrophage



- **Dendritic cells**

- **APC in tissues** - uptake Ag
- node migration, presentation APC and development of immune responses

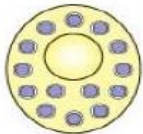
Dendritic cell



- **Mast cells (heparinocytes, mast cells)**

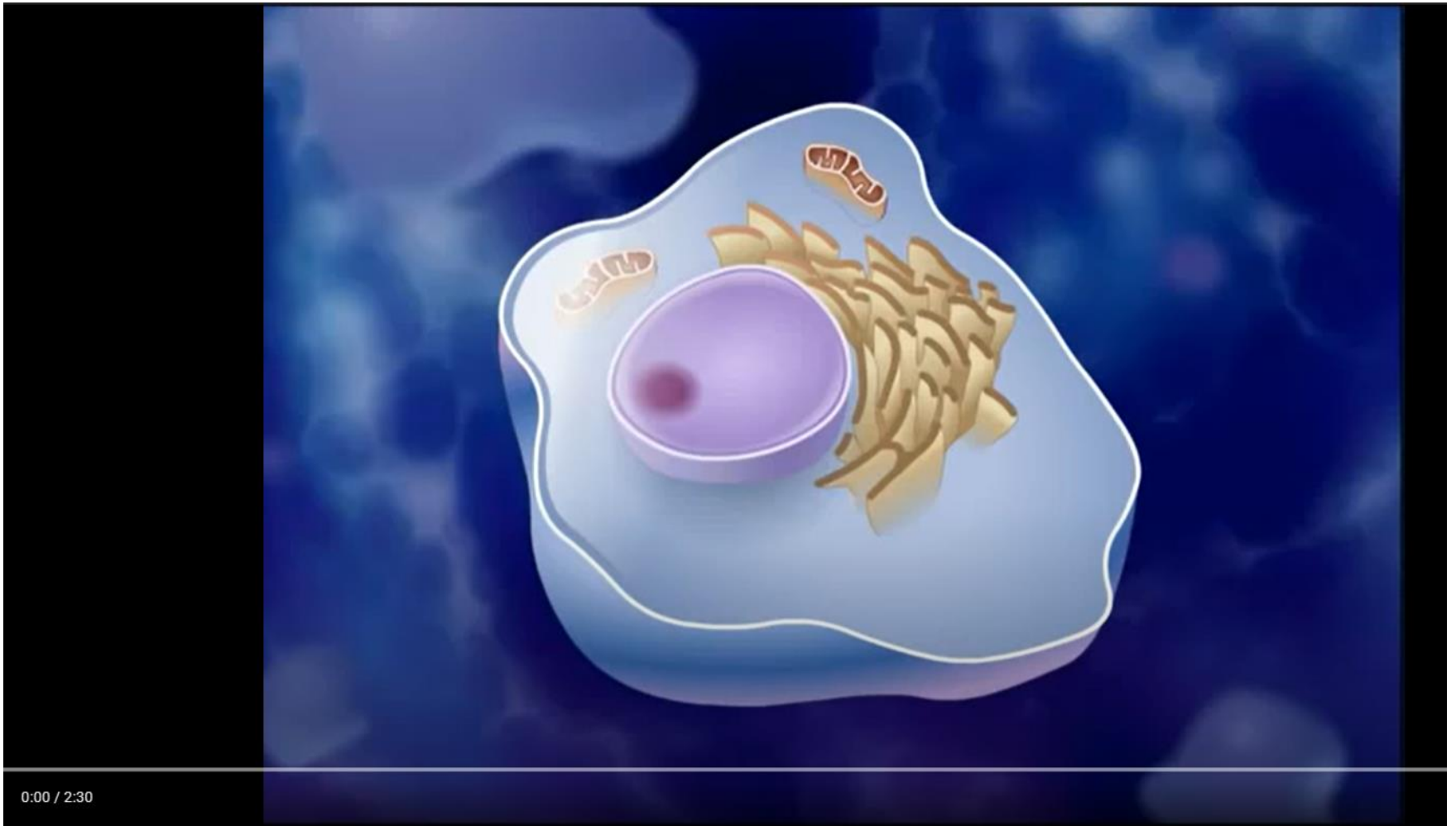
- tissue equivalent basophils

Mast cell



Cells of the immune system - LYMPHOCYTES

- **T-lymphocytes (CD3 +)**
 - management and decision-making in IS
 - Subpopulation - Th (CD4 +) Tc (CD8 +) Treg
- **B-lymphocytes (CD19 +, CD20 +)**
 - antigen reception, processing and **presentation (APC)**
 - able to process soluble Ag (compared to other APCs)
- **NK cells (CD56 +)**
 - they look like T-cells but they don't have T-cell receptor (CD3-)
 - recognition and disposal (such as Tc) low expression / MHC-I sites
(i.e. tumor sites, virus-infected cells)



0:00 / 2:30

The Immune Response HD Animation



The Humoral Response - I

<https://www.youtube.com/watch?v=AucZlvEv29Y>

Immune-relevant molecules

Vertebrates:

- pathogen-host relationship: greater variability means greater resistance (however, an extreme increase in variability is detrimental)
- looking for sexual partners: better coloring means more offspring
- by smell they are able to recognize a suitable combination of genes, related individuals are less attractive

MHC genes (from cartilaginous fish)

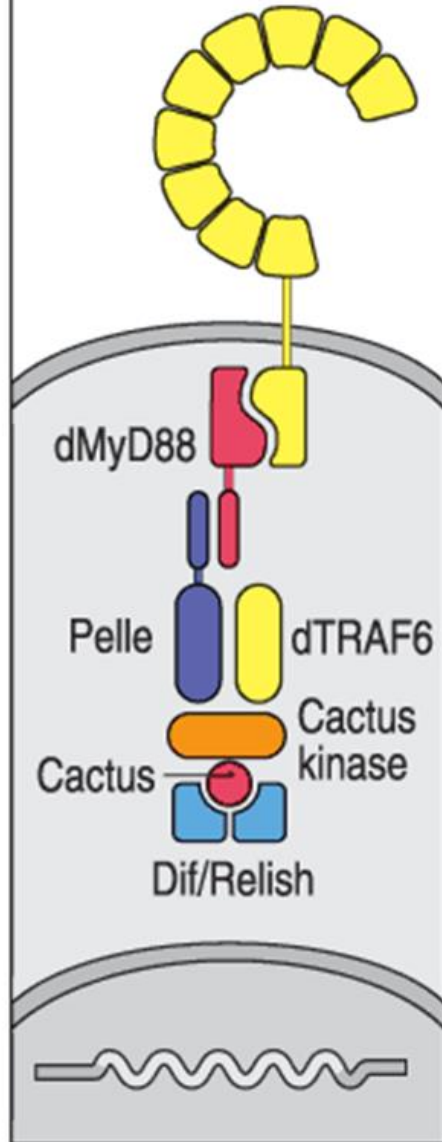
Toll-like receptors (from bony fish)

- study on birds - paternity of young in permanent pairs
- rodent studies

Molecules in IS - differentiation of "own" from "foreign" = MHC

- **The body's cells carry proteins on the surface MHC**
 - Major Histocompatibility Complex (also "HLA"- Human Leukocyte Antigens)
 - ALL the cells of the body carry MHC-I
 - APC the cells carry extra MHC-II (have MHC-I + MHC-II)
- **Function MHC**
 - mark of cell affiliation to the organism
 - processing and exposure Ag
 - MHC-I → CD8+ T-cells
 - MHC-II → CD4+ T-cells
- **Variability in structure of MHC**
 - genetic "relationship" → possibility of organ transplants
- **IS cells**
 - they will learn to recognize their own MHC (T-cells, NK-cells)
 - they can recognize MHC with bound of Ag and respond (T-cells)
 - "foreign" MHC in the body: very strong reaction (transplantation)

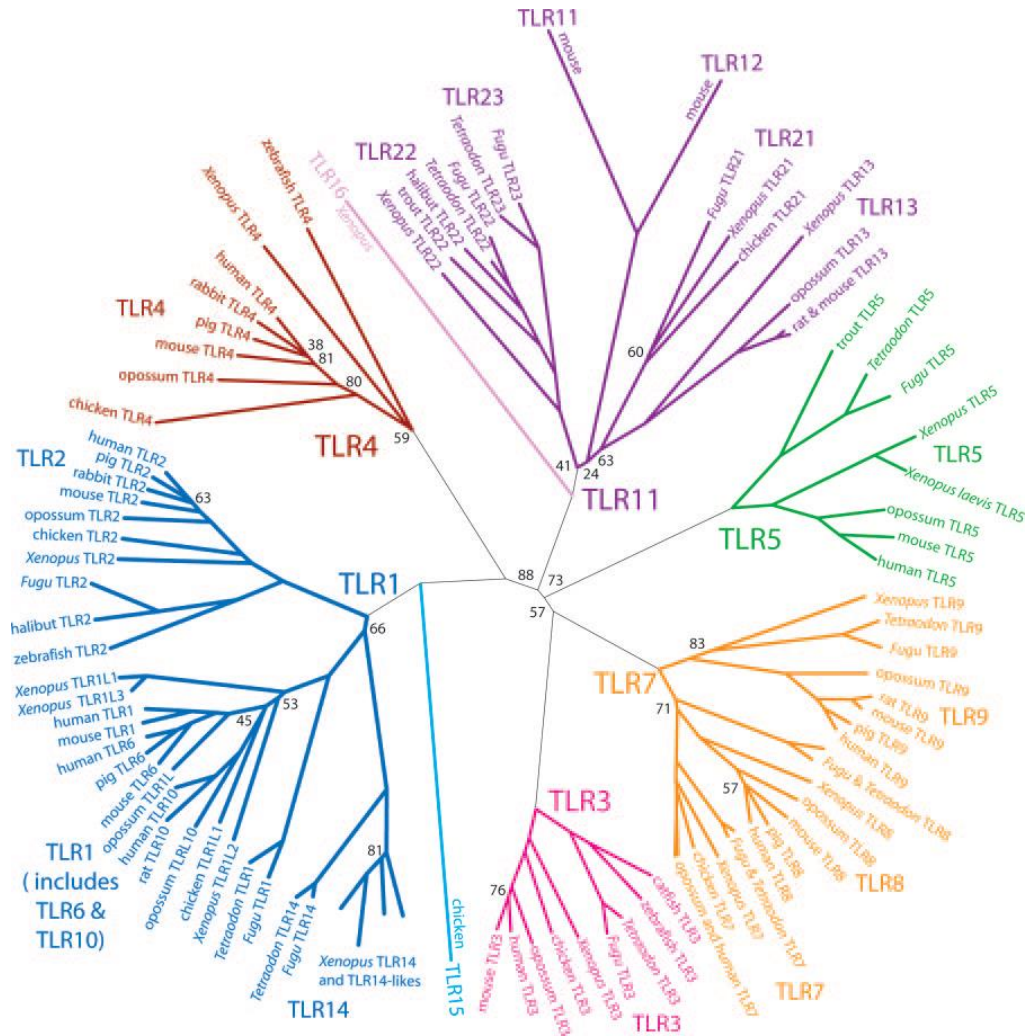
The *Drosophila* Toll signaling pathway



2001 Garland Science

In *Drosophila* dual function - dorso-ventral axis in embryonic development and immunity...

This is crazy, das ist toll !!!



Overview - The main molecules of the immune system

- *Glycoproteins of MHC Classes I and II (= HLA in humans), TLR receptors - see before*
- **Ag-specific receptors** on the surface of T- and B-cells (TCR/BCR)
- **Antibodies** (Ab) / Immunoglobulins (Ig) - B-cells
- **Receptors for Fc fragments of Ig** - different cells
- **Cytokines** - different cells in the body
- **Receptors for cytokines** - different cells in the body
- **Complement** & receptors (different cells in the body)
- **Adhesive** molecules
- **Costimulatory** molecules
- **Interleukins**

Innate / Nonspecific immunity

non-specific immunity:

- evolutionarily older, it occurs in various forms throughout the animal kingdom from invertebrates to mammals

basic characteristics:

- is congenital
 - the organism has it from birth
 - it does not matter whether it has encountered the disease or the pathogen
- is not specific
 - the cells act in the same way against all foreign particles
- has no immunological memory
 - the action against the antigen is always with the same force, even if it is repeated

Non-specific immunity

– skin:

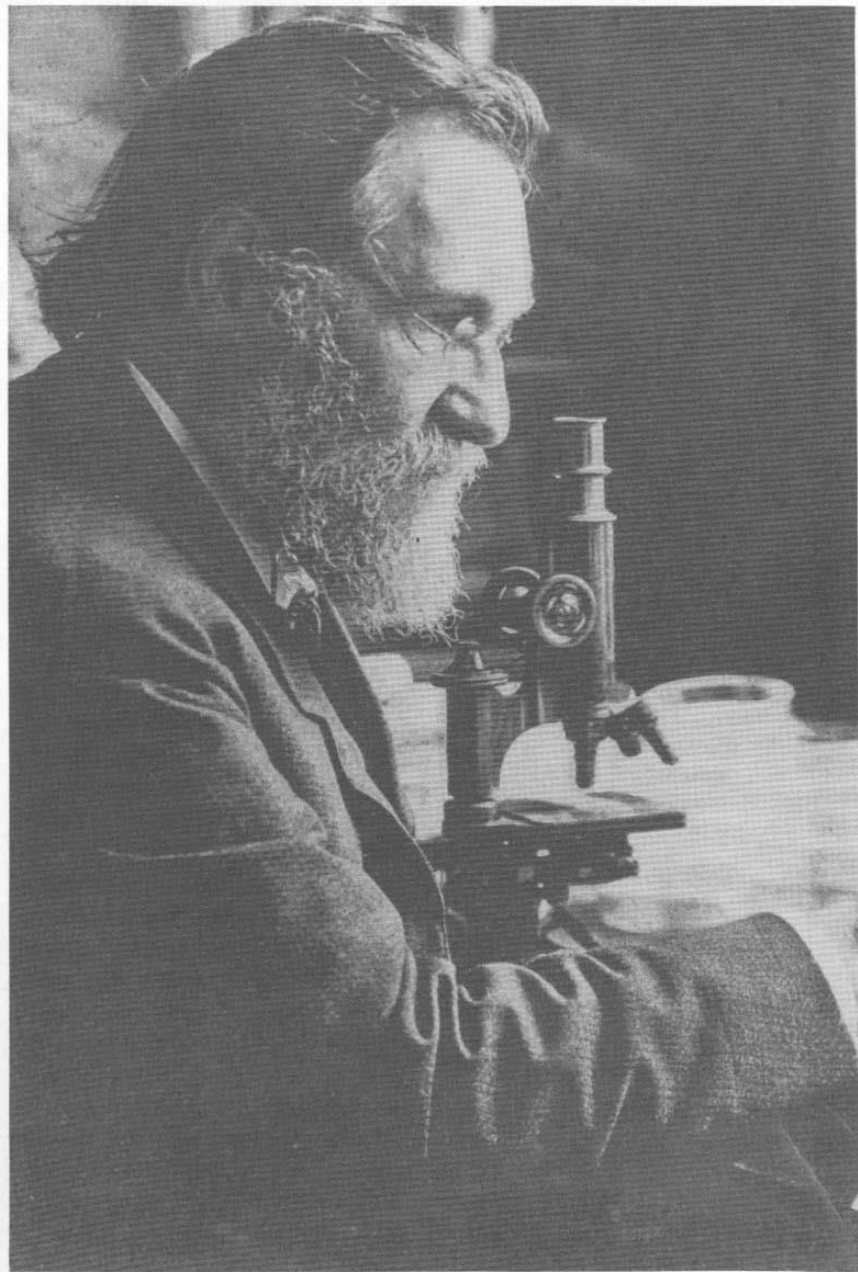
- the boundary layer separating the organism from the external environment creates an unfavorable environment for many microorganisms
- mechanical protection
- sweat - bactericidal (organic acids, urea, salts)

– mucous membrane:

- enzyme lysozyme in saliva and tears
- HCl in the stomach
- acid secretion of the vagina
- mucus on the surface mucus respiratory and digestive tract

– phagocytosis:

- uptake of foreign material by specialized cells
 - monocytes, macrophages, eosinophilic and neutrophilic granulocytes



Elie Metchnikoff (Courtesy National Library of Medicine)

Ilya Mechnikov

term used for the first time
phagocyte

Origin from Greek words
phagein - to eat
cytos - cell

The cellular nature of
immunity

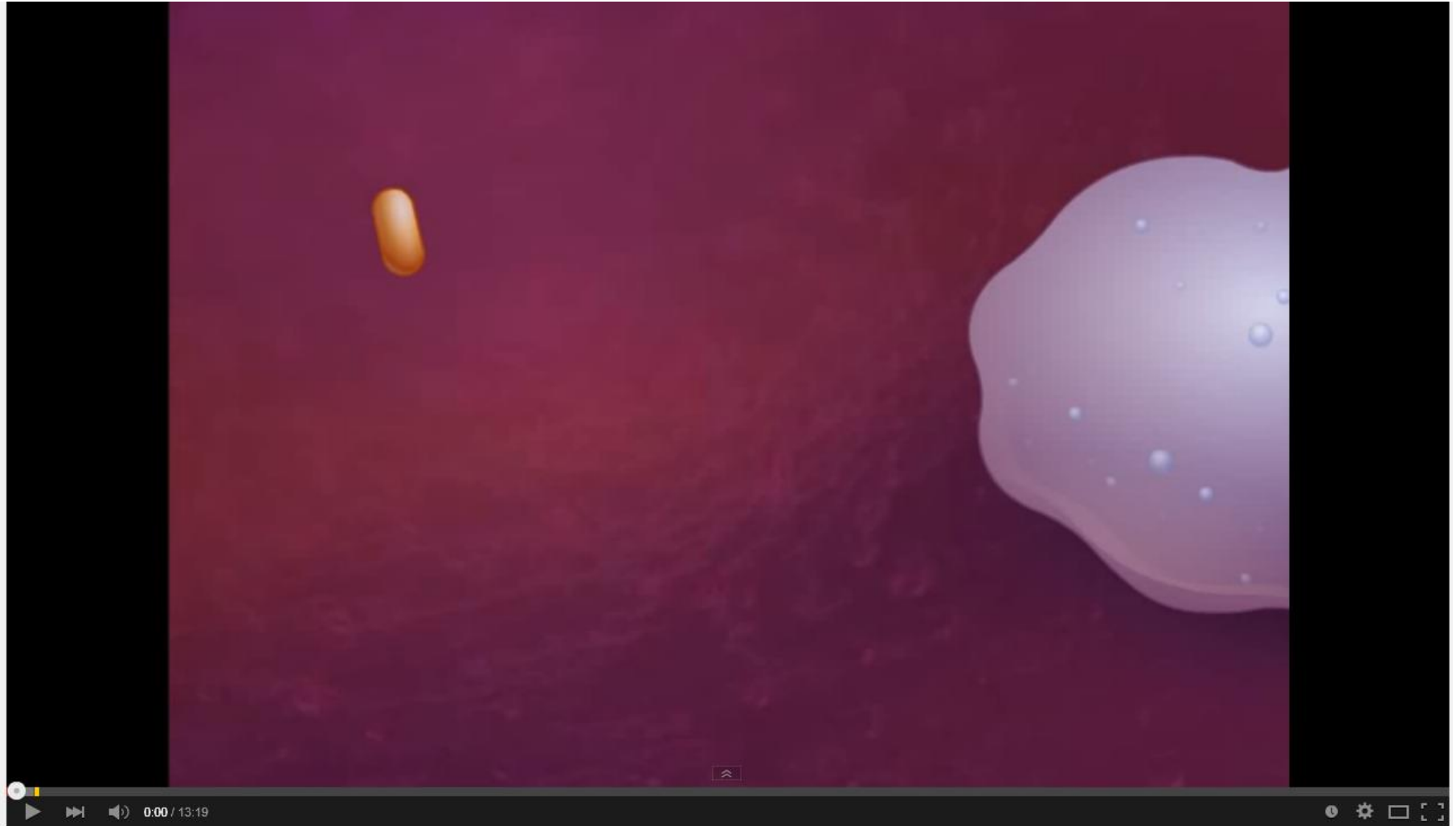


PHAGOCYTES attempt to engulf a rose thorn inserted into the transparent larva of a starfish. In 1882 the Russian zoologist Élie Metchnikoff (*photograph at right*) first noted this example of an innate host defense response. His subsequent studies established the field of cellular immunology.

- process in which specialized cells of the organism, called **phagocytes**, recognize, absorb and process foreign material ($> 1 \mu\text{m}$) after its penetration into the body
- the oldest and most effective mechanism of nonspecific immunity from unicellular to vertebrates
- an integral part of the physiological reactions of the organism
 - it is subject to the control signals of other components of the immune system and other physiological systems
 - phagocytes form mediators acting on other components of the immune system or other physiological systems

Reasons: nutrition, development and formation of tissues, immune reactions, repair of damaged tissues

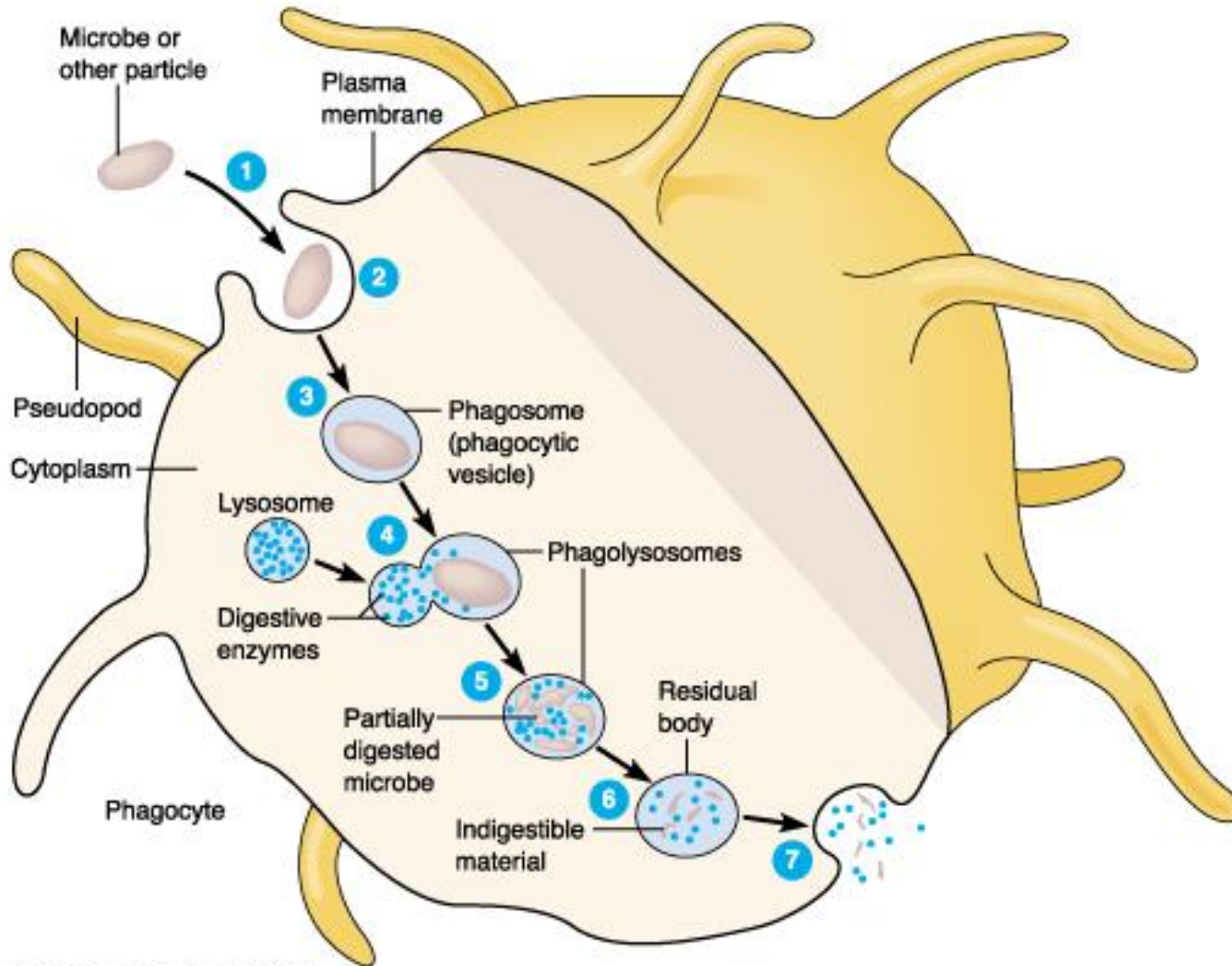
Endosymbiotic theory....



Process of Phagocytosis [HD Animation]

<https://www.youtube.com/watch?v=7VQU28itVVw>

Phagocytosis



- 1** Chemotaxis and adherence of microbe to phagocyte.
- 2** Ingestion of microbe by phagocyte.
- 3** Formation of a phagosome.
- 4** Fusion of the phagosome with a lysosome to form a phagolysosome.
- 5** Digestion of ingested microbe by enzymes.
- 6** Formation of residual body containing indigestible material.
- 7** Discharge of waste materials.

(a) Phases of phagocytosis

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Microbicidal mechanisms

Independent of oxygen

- acidic pH in a phagolysosome
- acid hydrolases, neutral proteinases
- granular cationic proteins (eg phagocytin): damage the cell membranes of bacteria, inhibit their respiration
- lysozyme: cleaves β -1-4-glycosidic binding of bacterial cell wall polysaccharides
- lactoferrin: stops the growth of bacteria, supports the effect of lysozyme

Dependent on oxygen

- myeloperoxidase dependent and independent

A visible example of phagocytosis...

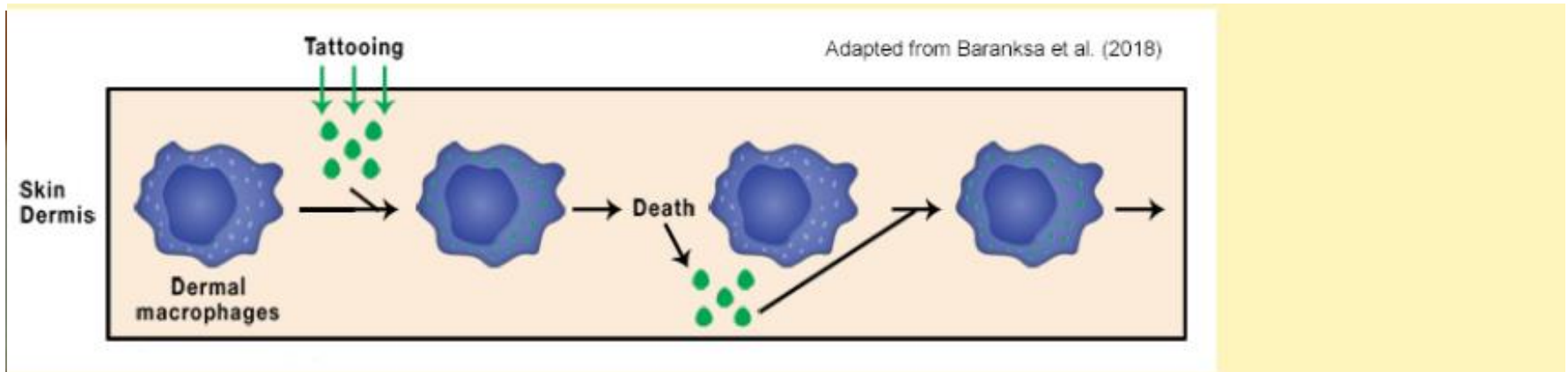


Fig. 1. Release-recapture cycle. Dermal macrophages phagocytose tattoo ink and it is retained in their vacuoles. Upon their death, the ink is released but then recaptured by new incoming macrophages that are derived from bone marrow monocytes.

<https://www.bio-rad-antibodies.com/blog/how-macrophages-make-tattoos-last.html>



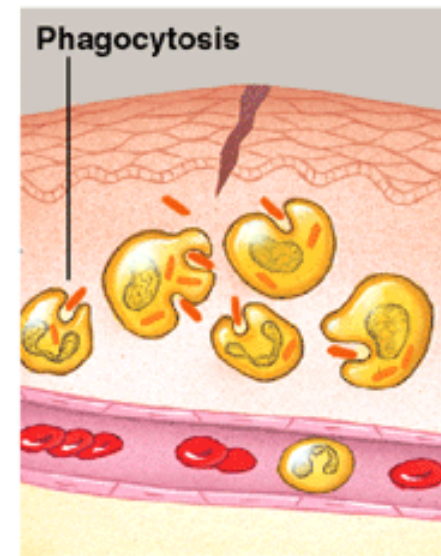
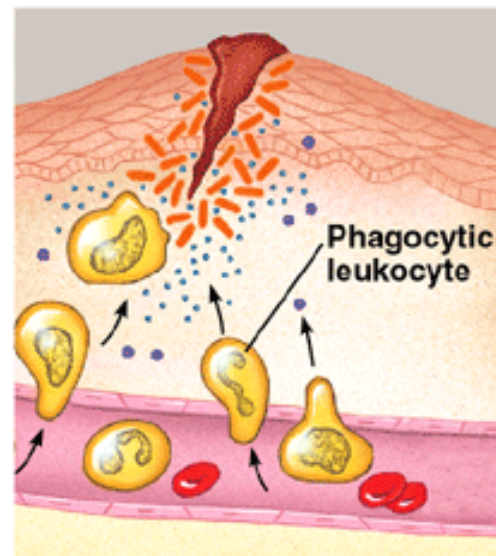
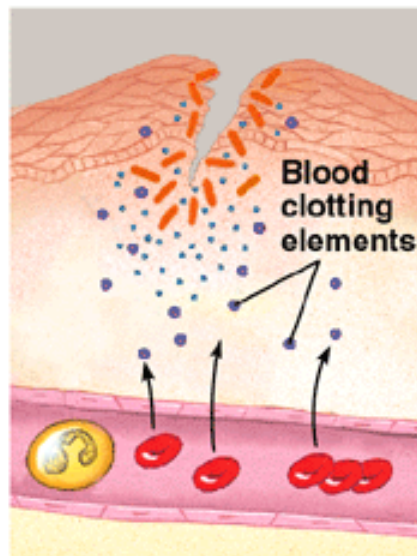
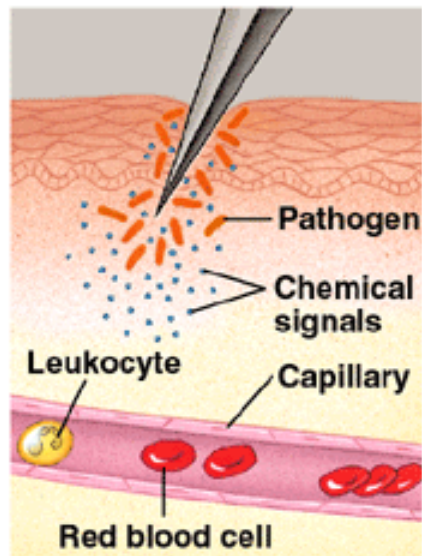
Ink phagocytosis...

Non-specific immunity

- **natural cytotoxicity:**
 - release of perforin - substances causing perforation of the target cell membrane
 - natural killers **NK cells = natural killers**
 - non-specific defense against viruses and tumor cells
 - recognize pathological changes on the cell surface
- non - specific tissue response to irritation or infection **INFLAMMATION**
 - phagocytic cells penetrate the affected area
 - increase in blood sedimentation
 - purulent inflammation - pus - white blood cells
 - ending - ITIS, ITIDA (bronchitis, encephalitis)
 - **pyrogens** (from leukocytes) - fever
 - leukocytes acting on the thermoregulatory center in the hypothalamus + general nausea → increase the effectiveness of the immune system

Inflammation

- increased blood flow and dilation of capillaries allow phagocytes to penetrate the wound site
- macrophages phagocytose pathogens and cleanse damaged tissue cells, pus are dead phagocytes, proteins and fluid from the blood capillaries

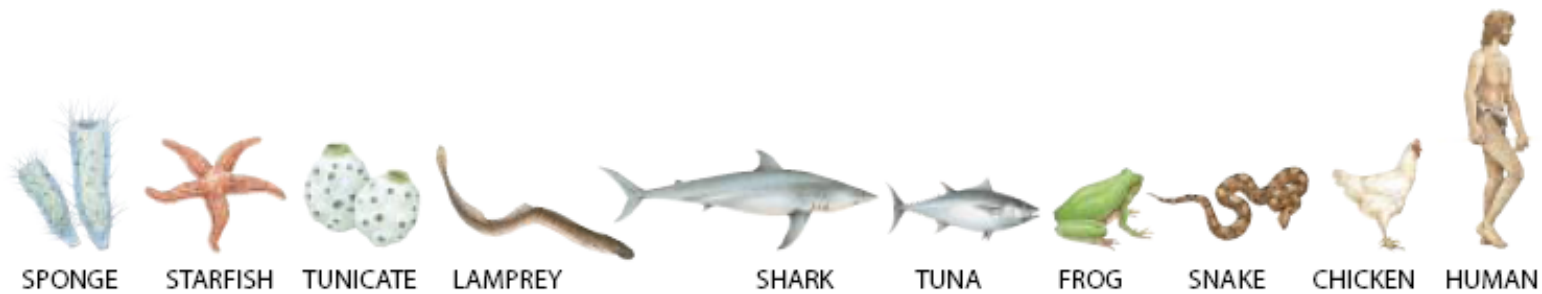


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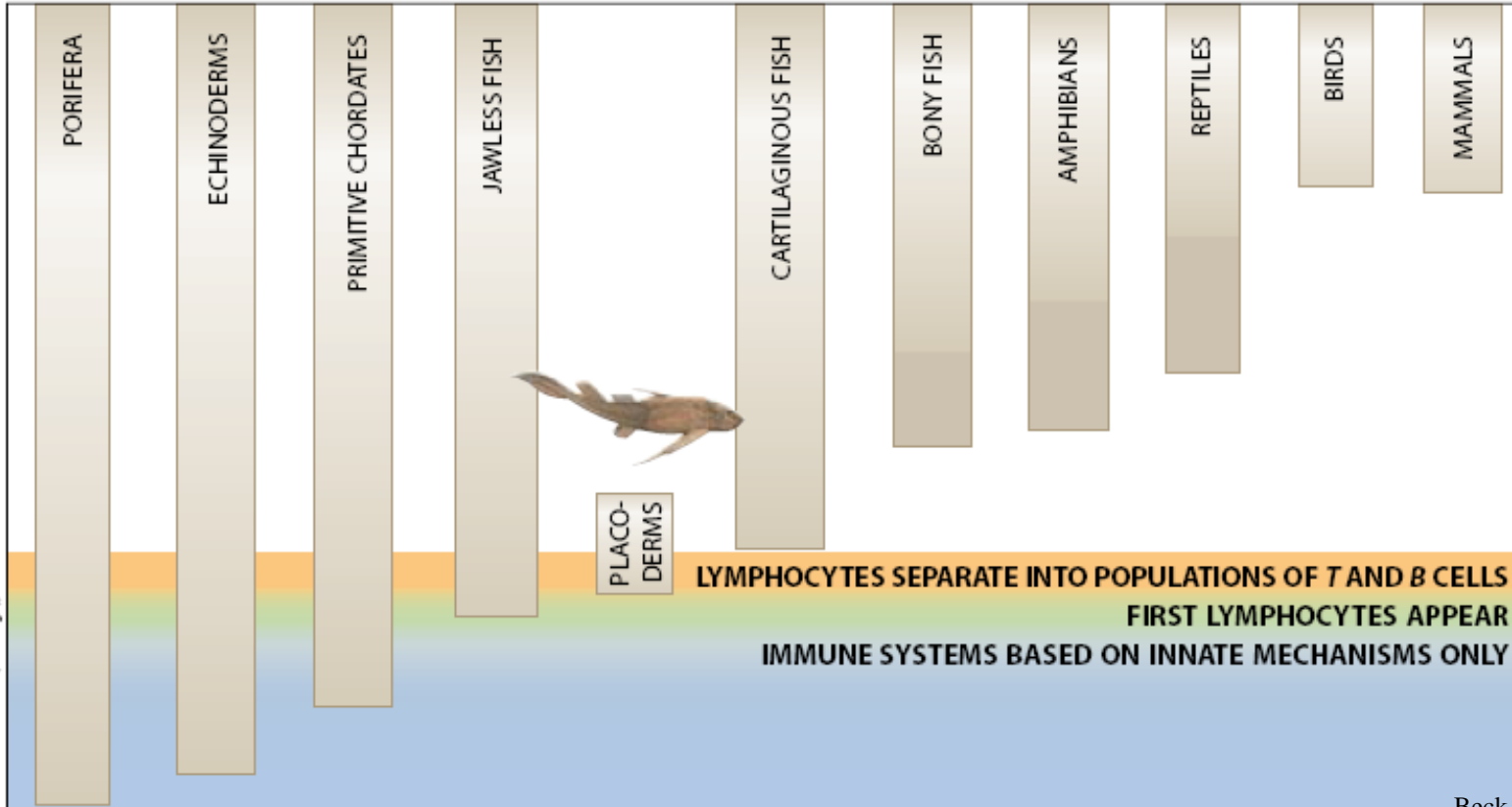
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3

4



SPONGE STARFISH TUNICATE LAMPREY SHARK TUNA FROG SNAKE CHICKEN HUMAN



YEARS BEFORE PRESENT (MILLIONS)

100

200

300

400

500

TOMO NARASHIMA (drawing by LAURIE GRACE)

Beck & Habicht, 1996

Specific / adaptive immunity

specific immunity:

- realized by lymphocytes
- production of antibodies - formed against antigens
 - antibodies = proteins - immunoglobulins

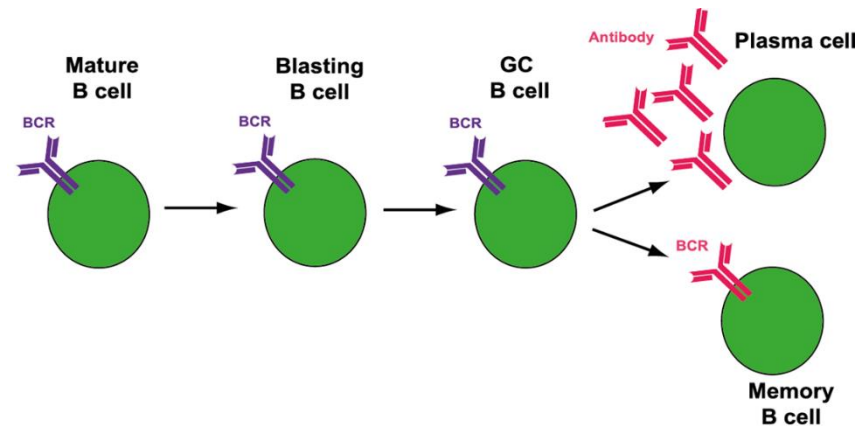
distribution:

- **humoral immunity:**
 - antibodies produced by B – lymphocytes
- **cellular immunity:**
 - T - lymphocytes

Humoral specific immunity

humoral immunity:

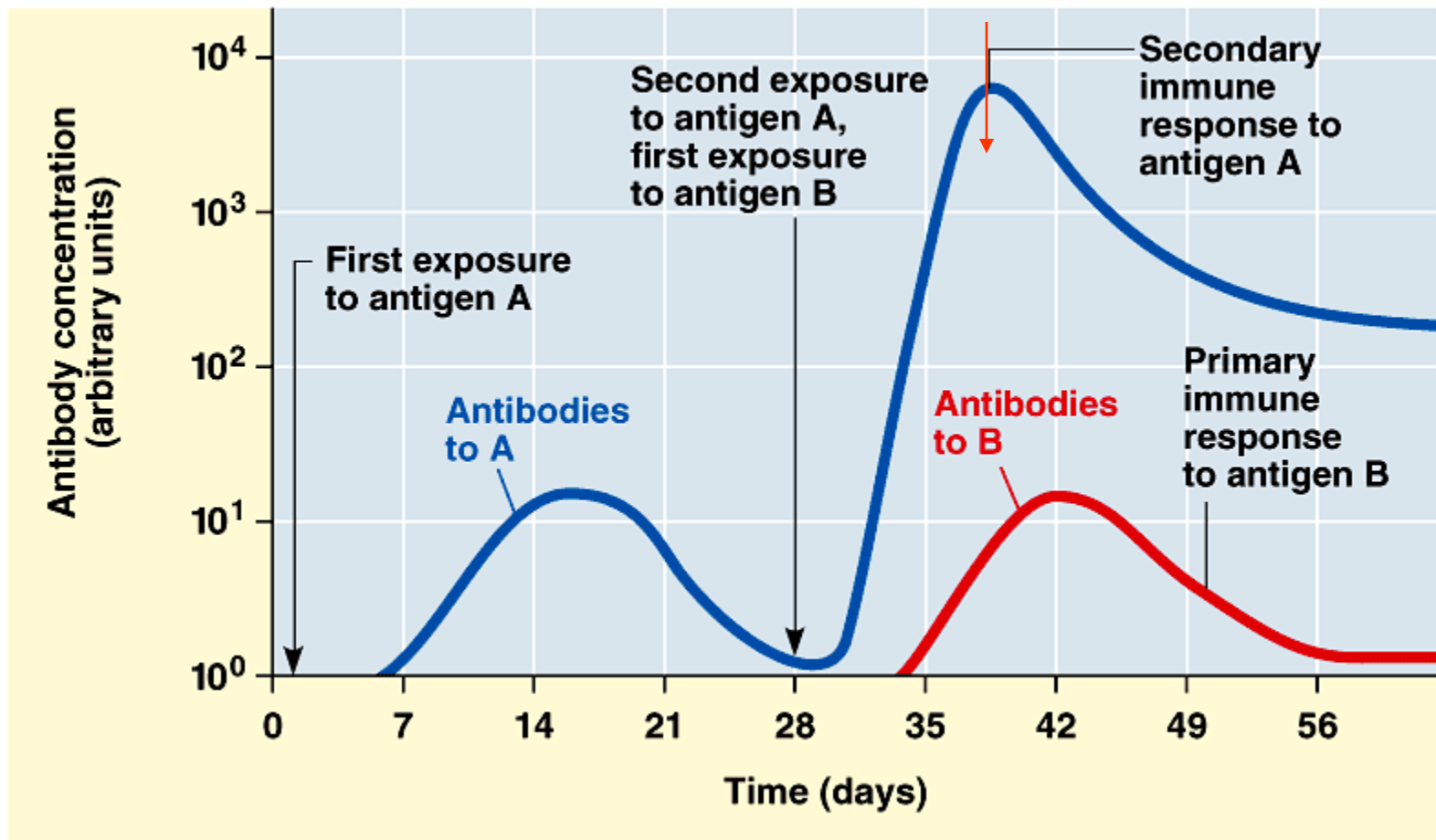
1. B cells recognize the antigen
2. antigens react with protein binding sites (receptors - immunoglobulins) on B cell membranes
3. cells multiply - **proliferation**
 1. **plasma cells** - active stage of B lymphocytes, producers of antibodies against the given antigen (pathogen) → **primary immune response**
 2. **memory cells** - they live for a very long time, they condition a rapid immune reaction (antibodies) when they meet the same antigen again → **secondary immune response**



<https://www.immunology.org/public-information/bitesized-immunology/immune-development/b-cell-activation-and-the-germinal-centre>

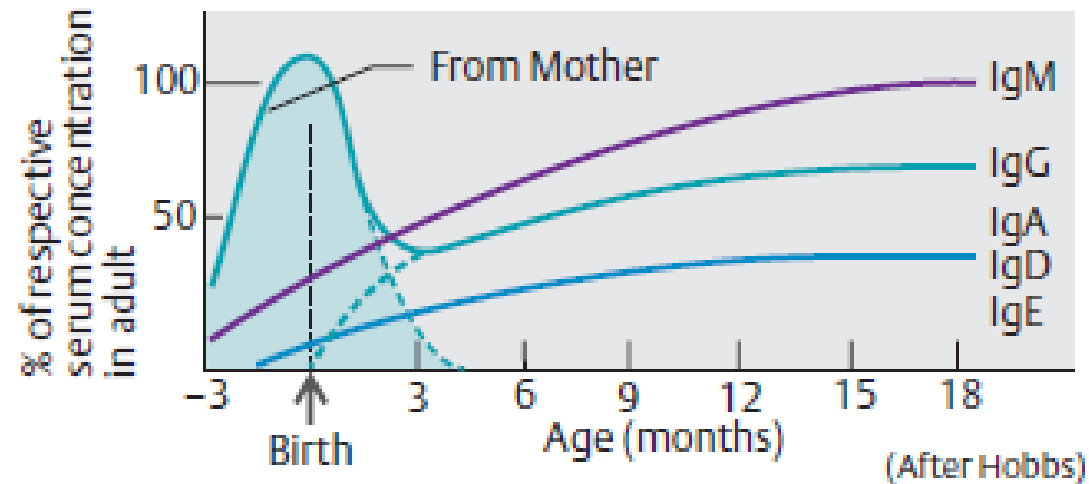
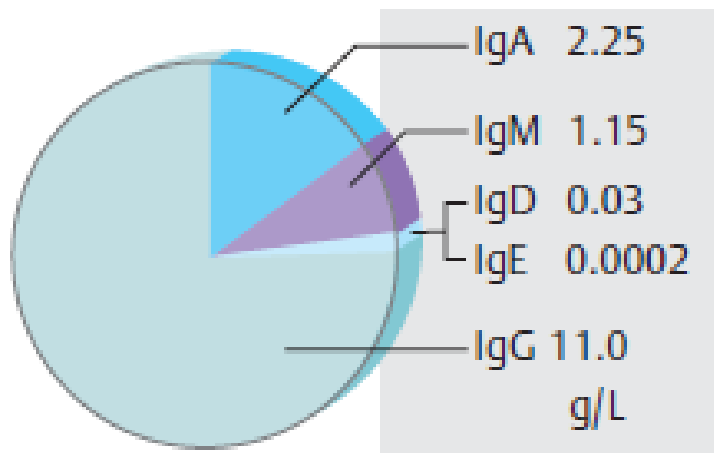
Secondary immune response

- if a person encounters the same antigen later in life, the body's response is faster (2-7 days) and sharper and takes longer



antibodies

D. Concentrations of immunoglobulins in serum



IgG class



IgG

Properties of IgG:

- Molecular weight: 150,000
- H-chain type (MW): gamma (53,000)
- Serum concentration: 10 to 16 mg/mL
- Percent of total immunoglobulin: 75%
- Glycosylation (by weight): 3%
- Distribution: intra- and extravascular
- Function: secondary response
- [Learn more about IgG »](#)

IgM class

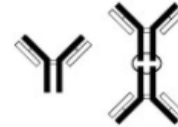


IgM

Properties of IgM:

- Molecular weight: 900,000
- H-chain type (MW): mu (65,000)
- Serum concentration: 0.5 to 2 mg/mL
- Percent of total immunoglobulin: 10%
- Glycosylation (by weight): 12%
- Distribution: mostly intravascular
- Function: primary response
- [Learn more about IgM »](#)

IgA class



IgA

Properties of IgA:

- Molecular weight: 320,000 (secretory)
- H-chain type (MW): alpha (55,000)
- Serum concentration: 1 to 4 mg/mL
- Percent of total immunoglobulin: 15%
- Glycosylation (by weight): 10%
- Distribution: intravascular and secretions
- Function: protect mucus membranes
- [Learn more about IgA »](#)

IgD and IgE class



IgD



IgE

Properties of IgD:

- Molecular weight: 180,000
- H-chain type (MW): delta (70,000)
- Serum concentration: 0 to 0.4 mg/mL
- Percent of total immunoglobulin: 0.2%
- Glycosylation (by weight): 13%
- Distribution: lymphocyte surface
- Function: unknown

Properties of IgE:

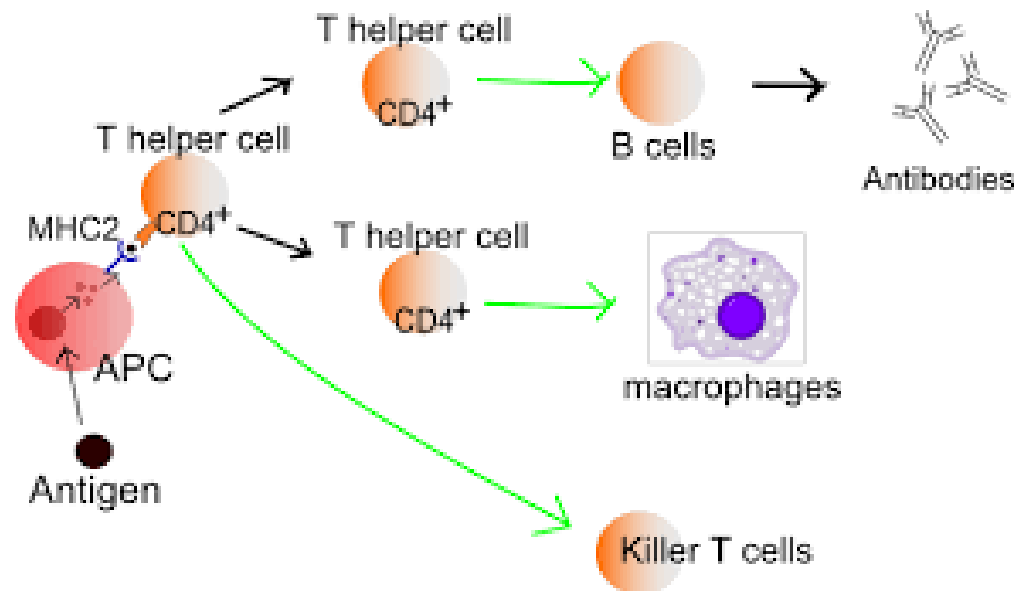
- Molecular weight: 200,000
- H-chain type (MW): epsilon (73,000)
- Serum concentration: 10 to 400 ng/mL
- Percent of total immunoglobulin: 0.002%
- Glycosylation (by weight): 12%
- Distribution: basophils and mast cells in saliva and nasal secretions
- Function: protect against parasites
- [Learn more about IgE »](#)

- The origin of adaptive immunity is accompanied by the RAG-1 and RAG-2 genes (recombination activation genes).
- They encode recombinase enzymes - rearranging gene segments for the antigen binding site on an immunoglobulin molecule, thereby generating diversity.
- Probably transferred horizontally from bacteria.
- They are only in lymphocytes, in no other cells ...

Cellular specific immunity

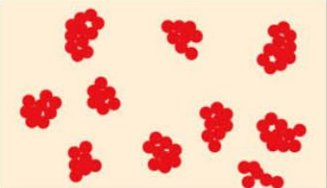
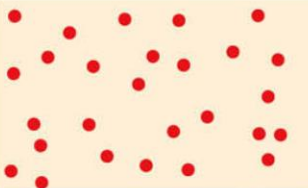
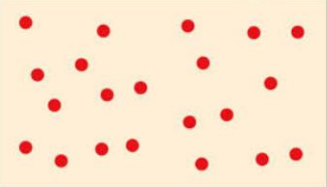
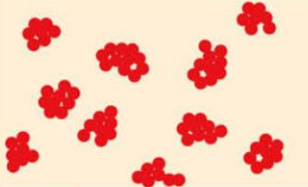

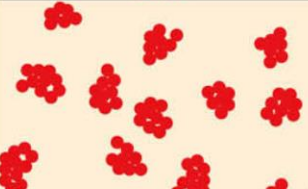
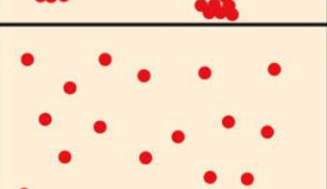
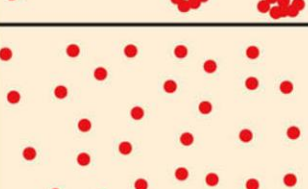
cellular immunity:

- T-lymphocytes, Th, Tc, Treg
- no antibodies are formed
- antigens **presented by other cells** binds to T-cell receptors - followed by direct contact with a foreign cell - destruction of a foreign cell
- part of the cells remains - memory
- they can reduce tumor growth - they cause non-acceptance of transplants organs (immunosuppressive substances)
- regulate the activity of B-lymphocytes



Blood groups

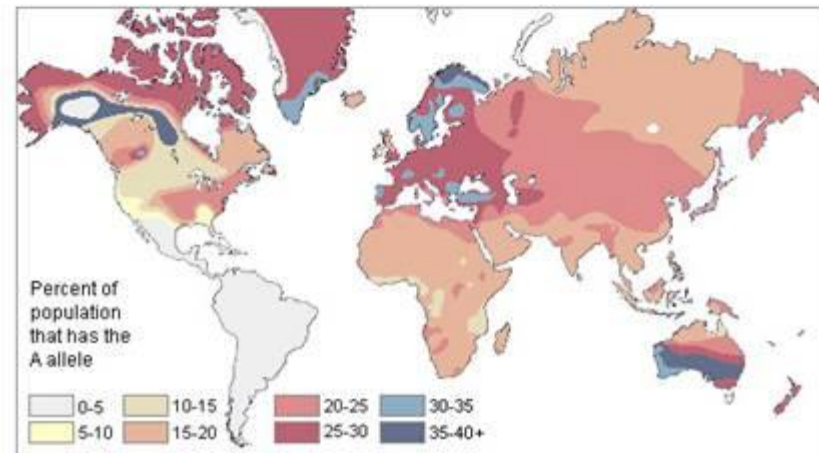
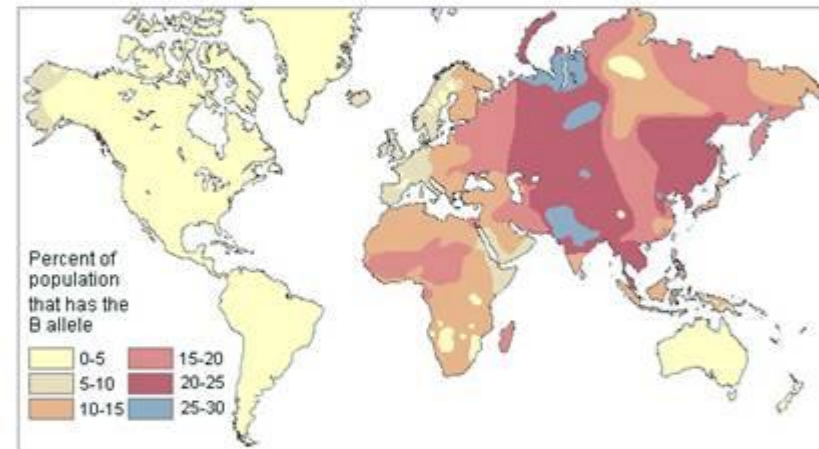
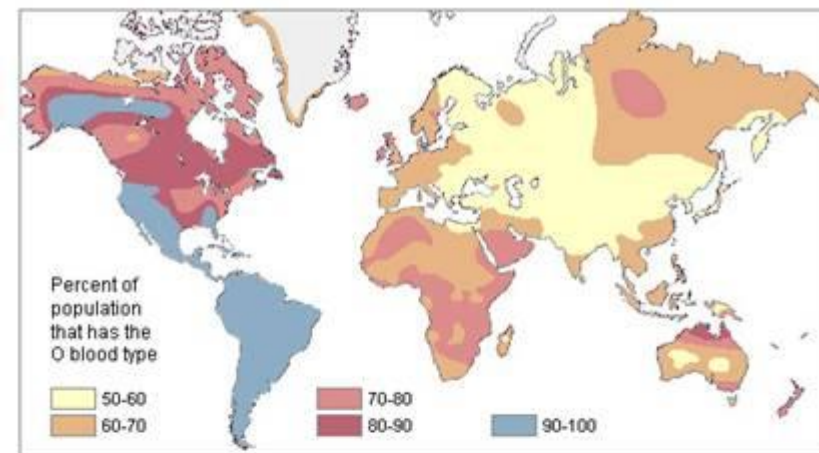
- more systems - best known: ABO, Rh-factor
- ABO
 - structures on the surface of blood cells = agglutinogens
 - A and B, act as antigens
 - plasma antibodies = agglutinins
 - anti-A and anti-B, cause clumping of blood cells - **agglutination**
 - 4 blood groups according to agglutinin
 - A, B, AB, 0

Blood type of cells	Genotype	Antibodies made by body	Reaction to added antibodies	
			Anti-A	Anti-B
A	$I^A I^A$ or $I^A i^O$	Anti-B		
B	$I^B I^B$ or $I^B i^O$	Anti-A		
AB	$I^A I^B$	Neither anti-A nor anti-B		
O	$i^O i^O$	Both anti-A and anti-B		

Blood group / percentage

A	42%
B	12%
AB	8%
O	38%

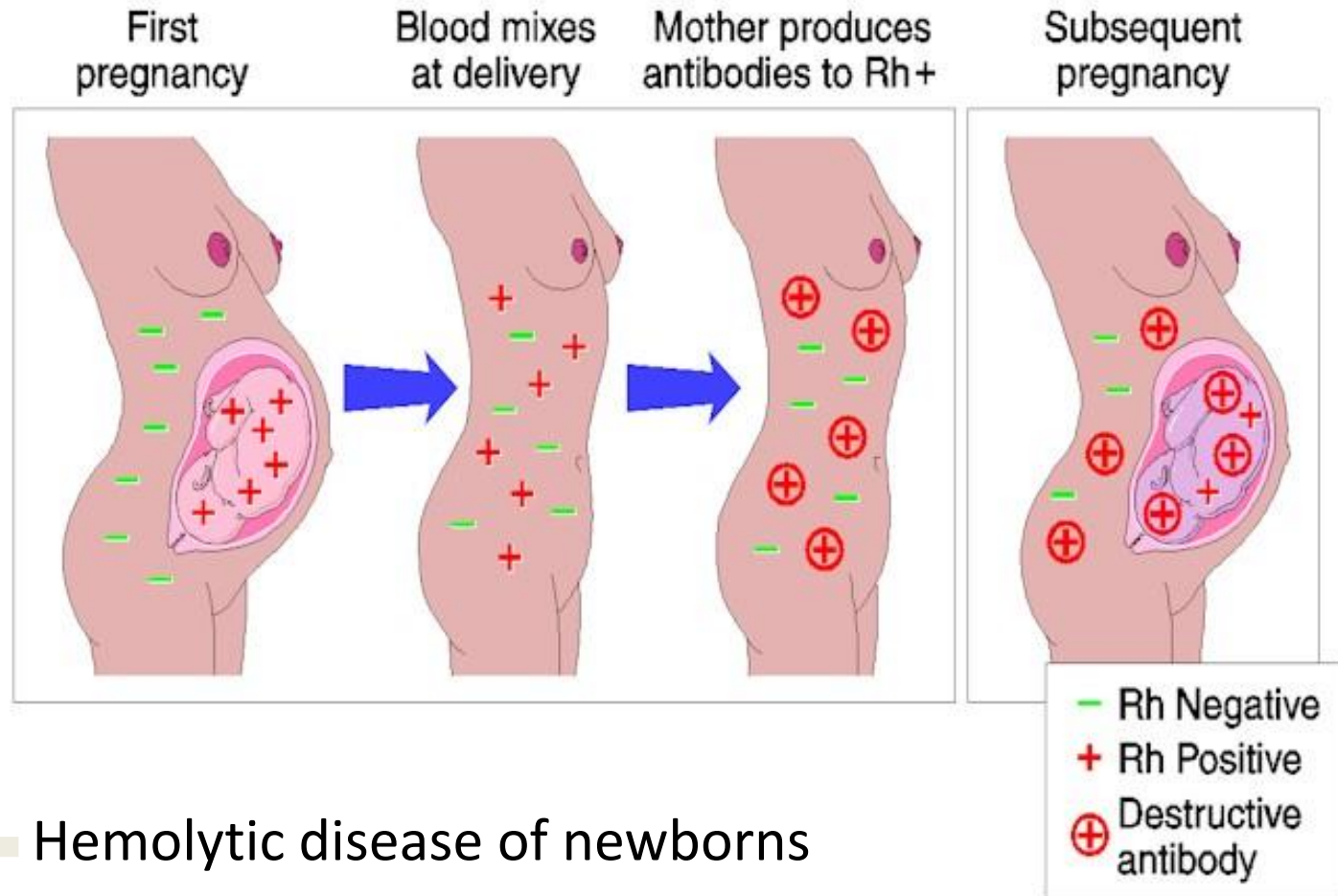
- representation of blood groups
 - different in different parts of the world
 - from west to east decreases A and B increase
 - A have the Eskimos and Lapps
 - Koreans have the most B
 - Indians have at most O (up to 100%)



Rh factor

- another agglutinogen Rh (macaque rhesus)
- anti-D antibodies
- Rh+ a Rh- (about 15% of the population)
- problems during pregnancy
 - Rh- mother a Rh+ child
 - first pregnancy - blood mixing → formation of antibodies in the mother's body → second pregnancy → antibodies damage the fetus, premature births
 - examination of mother and father

Rh factor and pregnancy



- Hemolytic disease of newborns

Diseases, illnesses and disorders

- **allergies, allergic reactions:**
 - caused by hypersensitivity to otherwise generally harmless substances, so-called allergens
 - typical local manifestations: redness, swelling, itchy skin, sneezing, vomiting, diarrhea, urticaria
- **autoimmunity:**
 - failure of the ability to distinguish foreign substances from the body's own substances - the formation of antibodies against its own tissues
 - multiple sclerosis (disruption of myelin sheaths in the CNS), haemolytic anemia (antibodies to erythrocyte antigens)
- **AIDS:**
 - agent retrovirus HIV - attacks T-lymphocytes
- **tumors**
 - in addition to foreign pathogens, the immune system must recognize its own abnormal cells and then eliminate them
 - in the case of tumors, this mechanism fails

Failure of immunity

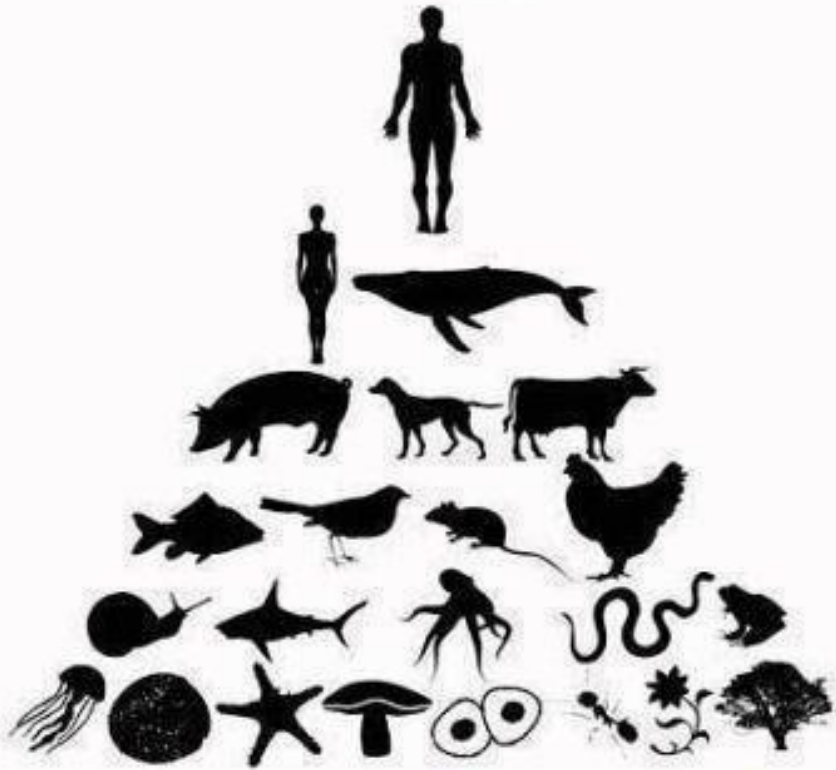
Mechanism of immune evasion	Organism (example)	Mechanism
Resistance to phagocytosis	<i>Pneumococcus</i>	Capsular polysaccharide inhibits phagocytosis
Resistance to reactive oxygen intermediates in phagocytes	Staphylococci	Production of catalase, which breaks down reactive oxygen intermediates
Resistance to complement activation (alternative pathway)	<i>Neisseria meningitides</i>	Sialic acid expression inhibits C3 and C5 convertases
	<i>Streptococcus</i>	M protein blocks C3 binding to organism and C3b binding to complement receptors
Resistance to antimicrobial peptide antibiotics	<i>Pseudomonas</i>	Synthesis of modified LPS that resists action of peptide antibiotics

Immunization

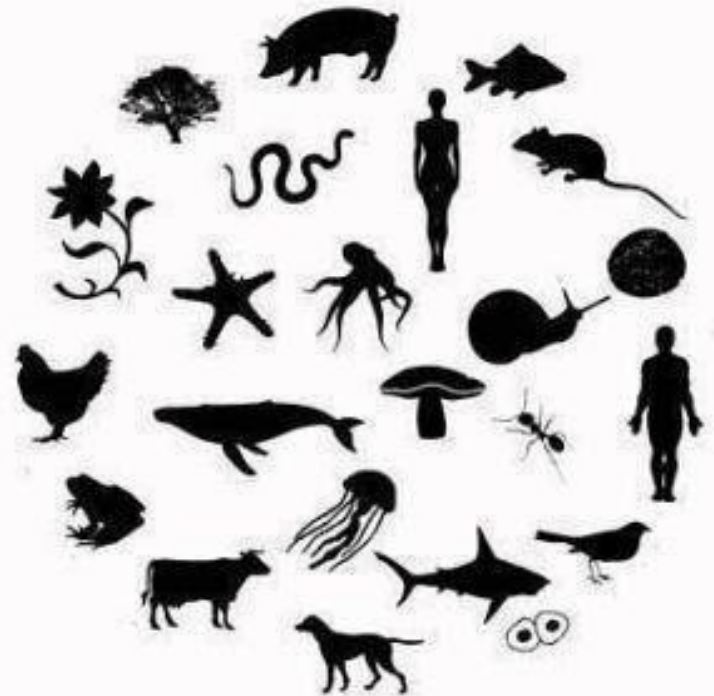
- many variants of immunoglobulins
- **vaccination** → immunization
 - active immunization - insertion of killed or weakened microorganisms
 - passive immunization - insertion of antibodies



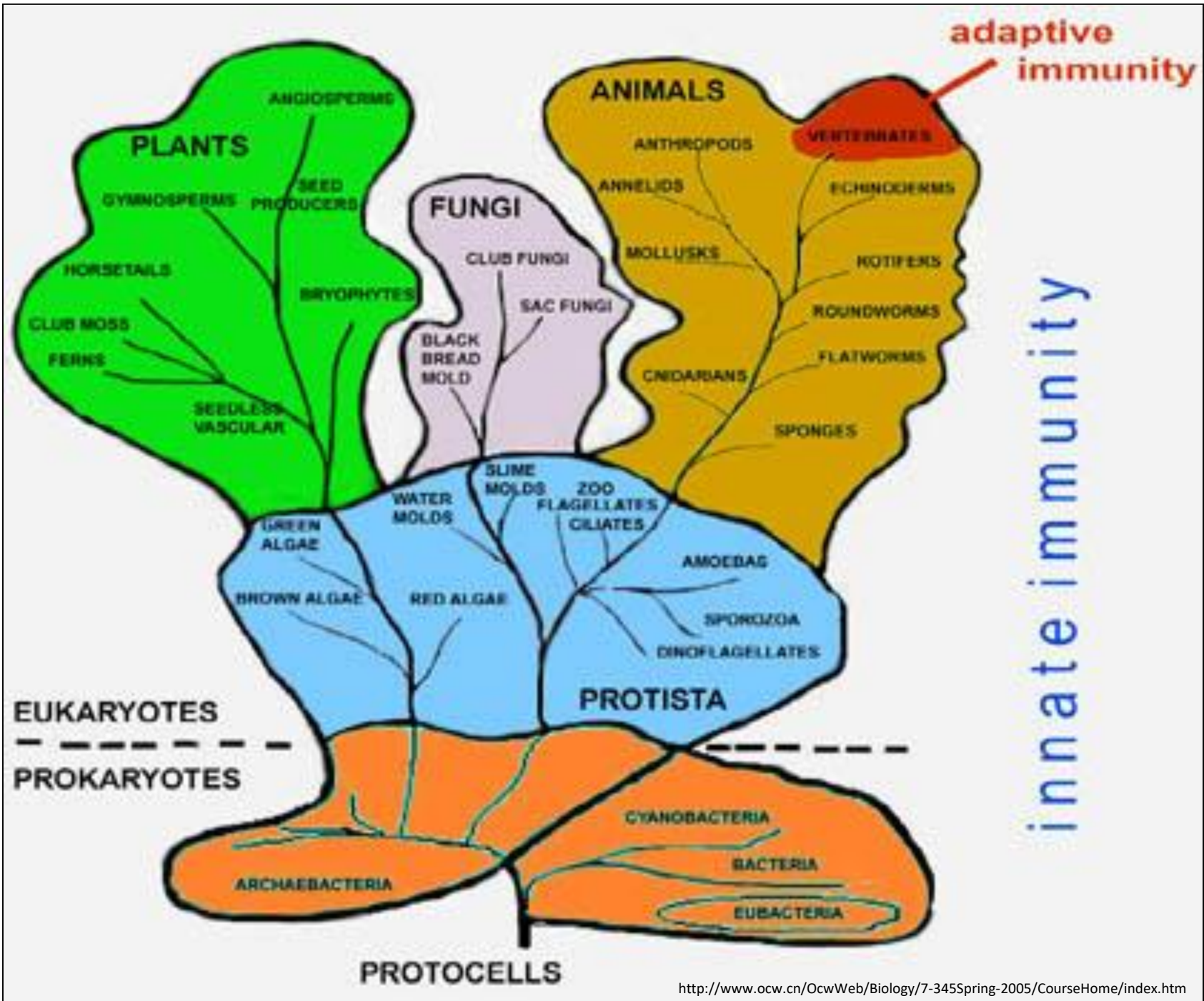
Phylogeny of immunity

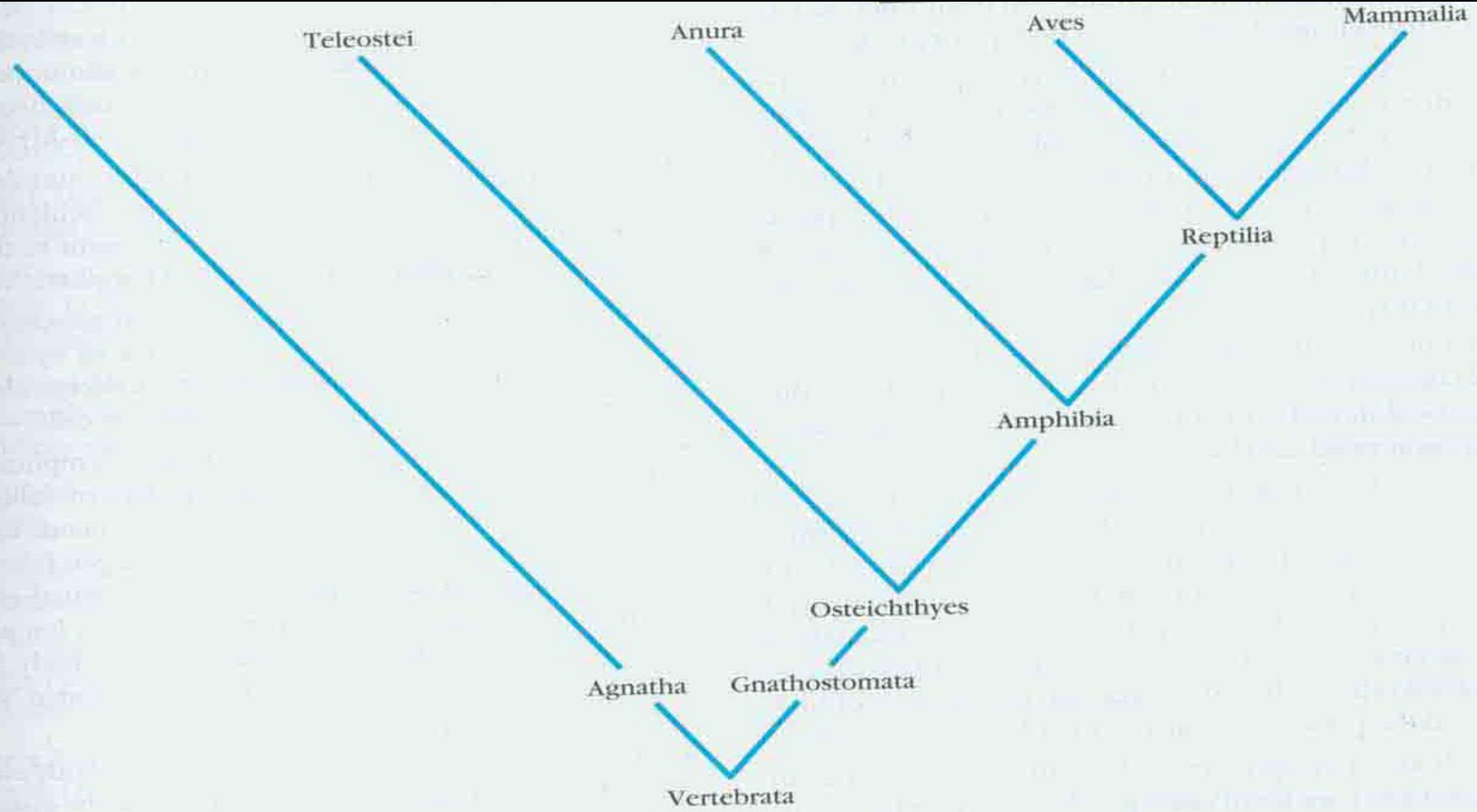
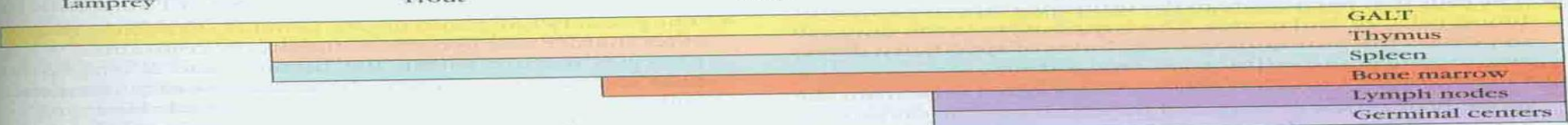
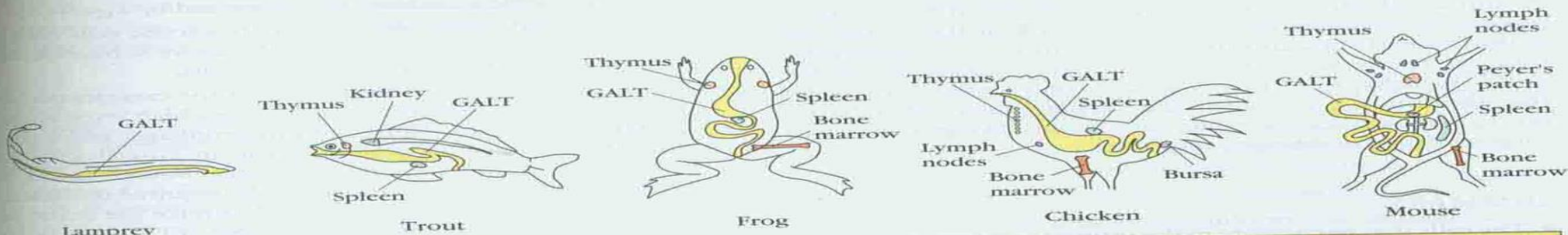


EGO



NATURE





Examples of final exam questions for Immunity:

1. White blood cells - list their main roles in the body and types (without details of immune reactions).
2. Characterize the specific immunity of mammals. What is the specificity based on, which cells, meaning.
3. Characterize the non-specific immunity of mammals. Which cells, meaning.
4. What do you know about the powerful components of innate (non-specific) immunity?
5. Characterize the cooperation between the nonspecific and specific mammalian immunity.
6. Characterize B-lymphocytes and their function in the mammalian immune system.
7. Characterize T-lymphocytes and their function in the mammalian immune system.
8. Characterize antigen presenting cells and their function in the immune system.
9. Compare the immune mechanisms of invertebrates and vertebrates.
10. Describe the principle of the Rh group system and its importance in pregnancy.
11. According to what abilities can the performance of the immune systems of animals be compared?
Characterize the evolution and variation of immunity in major animal taxa.
12. Describe the immune basis of blood groups. What happens in case of incompatibility. How does AB differ from the Rh system immunologically?
13. What do you know about the powerful cells of the immune system? How are they activated and how do they participate in specific immune responses?
14. Describe the relationships between microorganisms and vertebrate immunity. What is the microbiome?
Localization, recognition.
15. How are specific and non-specific immune cells activated?
16. How does the immune system of mammals distinguish foreign structures from their own? How does it "know" which is foreign and which is own?
17. What diseases and disorders of the immune system do you know? What do you know about them?