بسم الله الرحمن الرحيم

Physiology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

MID | Lecture 6

Allergy and Immunity (Pt.1)

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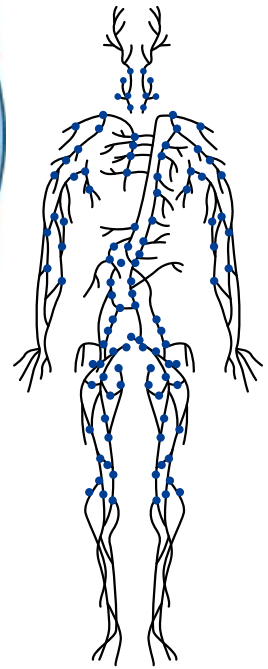
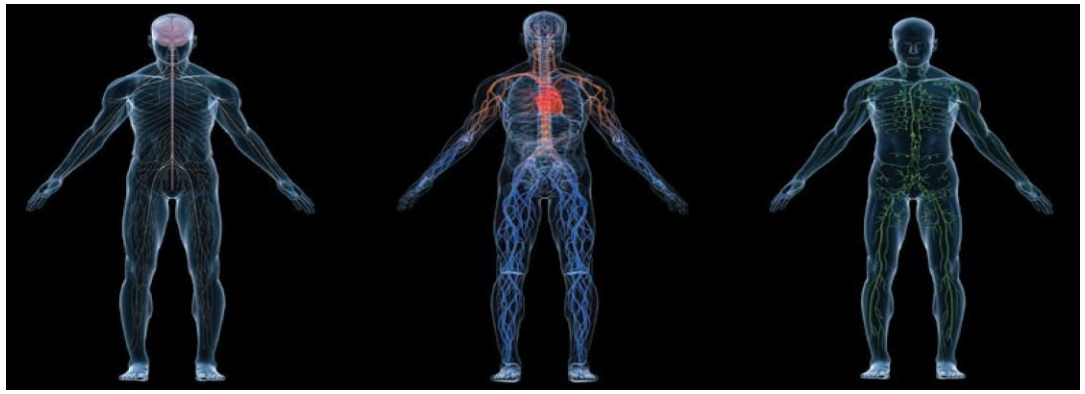


UNIT VI

Chapter 35:



Resistance of the Body to Infection:

II. Immunity and Allergy; Innate Immunity

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Immunity

- **Innate** (general immunity) **- inborn ability to resist damaging organisms and toxins** non specifically, our bodies have several ways as innate immunity: **skin, gastric acids** like HCL which destroys any microorganism **, tissue neutrophils and macrophages, complement system** Although it has some specific aspects, like sometimes it requires binding of antibodies to antigens to activate it but it still non specific **, microbicidal and lytic chemicals** for example digestive chemical found in lysosomes **in blood and blood cells**

- **Acquired** (adaptive) **= specific** 2 types : 1)Humoral B cells 2) cellular T cells

Humoral ⟶ **circulating antibodies** Our immune system produces specific antibodies against the pathogen or microorganism to destroy or neutralize there toxins

cellular ⟶ **activated cells** our system activates certain cells that directly destroy and attack the pathogen

Acquired Immunity

- **Antibodies** secreted from B cells **or activated cells** T cells **that specifically target and destroy invading organisms and toxins**

- **Powerful: can neutralize 100,000 x lethal dose of some toxins**

It means if the body doesn't have acquired immunity a very simple dose of toxins will be lethal.. Our acquired immunity give us a powerful protection against toxins

- **Two types of acquired immunity:**
  - **Humoral (B cell)**
  - **Cell-mediated (T cell)**

Antigen : antibody generator

- A substance that can elicit an immune response to generate antibodies against these antigens when they are **foreign**.
- Recall: we have two types of Antigens, self and foreign.

- Unique to each invading organism

- Usually proteins or large polysaccharides expressed on plasma membrane of pathogens or normal cells

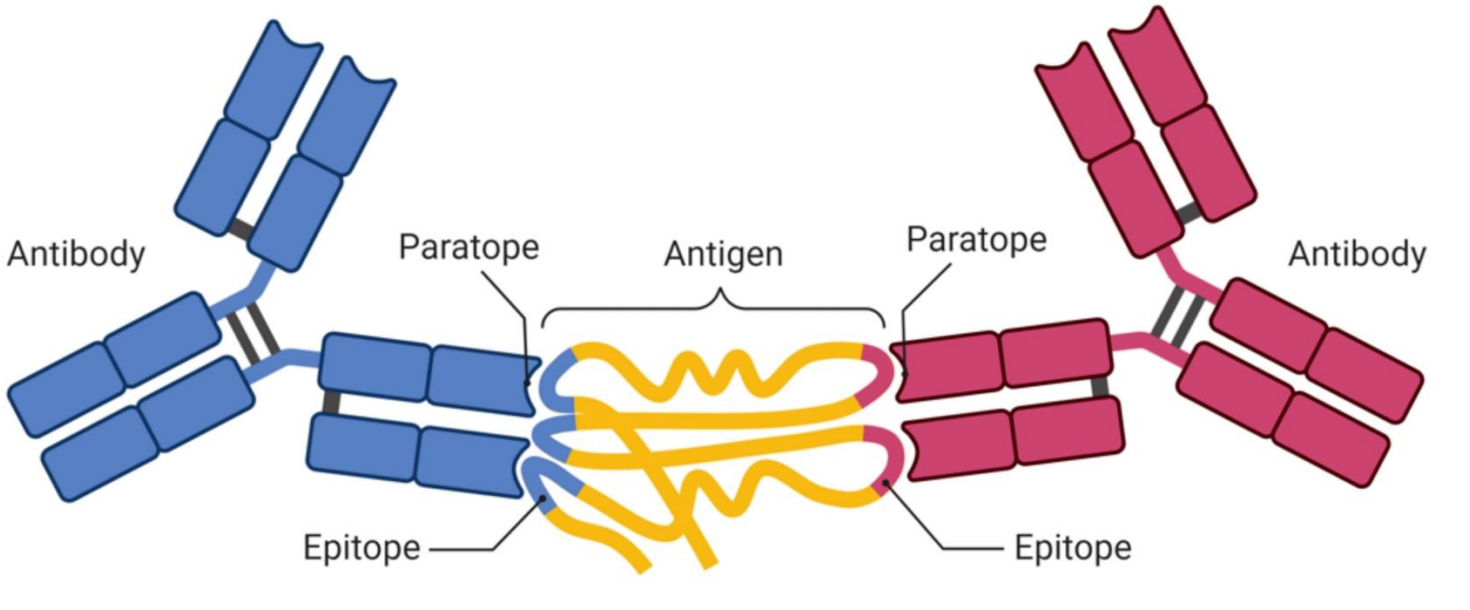
- Most are large (MW > 8,000) and have recurring molecular groups on their surfaces (specific sequences for the certain molecular groups act as a barcode for these type of microorganisms.)

- The antigens bind specifically to certain receptors on immune cells to activate an immune response

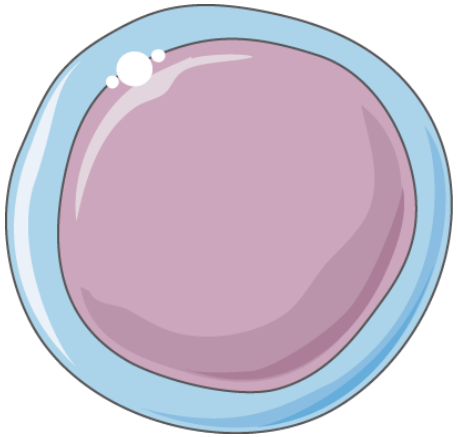
- The molecular structures that are specifically recognized in acquired immunity are called “epitopes”

Extra image

The epitope is a specific sequence on the antigen that will be recognized and identified by the immune system.



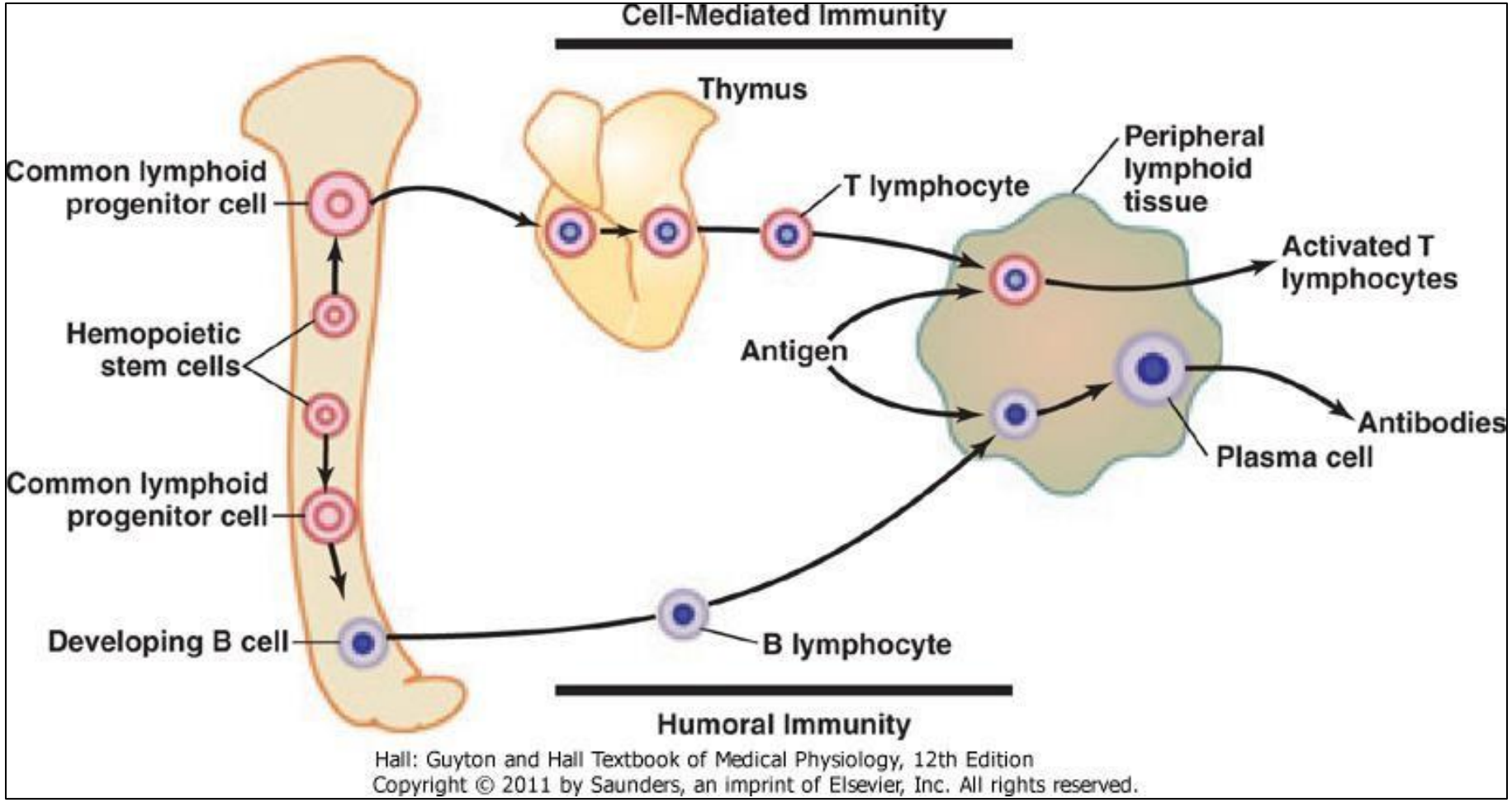
Lymphocytes



- **Mediate acquired immunity** main player in it
- **Develop in lymphoid tissues** (they start in the liver in the mid fetal life Then bone marrow and complete their development and lodge in the lymphoid tissues such as :**tonsils / adenoids, Peyer's patches (GI), lymph nodes, spleen, thymus, marrow**
- **Are strategically positioned** so they can sense and recognize the pathogens since they enter the body

See the next slides

Two types of lymphocytes



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The development and processing of B and T lymphocytes

- They start production from bone marrow just before the birth and after it.

- Recall : Hematopoietic stem cells will give rise to lymphoid progenitor cells and these cells will give B and T lymphocytes.

- There are two types of lymphoid progenitor cells :

1- Progenitor cells that committed to produce T cells
2- progenitor cells that committed to produce B cells

- ✓ T lymphocytes will leave the bone marrow through circulation in to the thymus to complete processing, before that they can't start there function and activate against pathogens that may face during its life .

- ✓ In thymus they increase in there numbers make thousands of clones in it , each clone will recognize specific antigen and become activated if that antigen is released in the blood.

- How the body can produce thousands of offsprings T lymphocytes?
  We don't have a gene for each offspring(every single T cell), but we have hundreds segments (V,D and J) of genes that will recombine in different ways in offsprings giving us thousands of clones that will recognise different antigens.

-Some of these T lymphocytes can recognize self antigens so they will start attacking host cells , so in **thymus** apoptosis will happen to all cell clones that are reactive against our own tissues(another important process in the **thymus** which is called **Development of tolerance/preprocessing** against host cells (immune cells will not develop reactivity against our own cells) , the T lymphocyte may be mixed with our self antigens , any reactive T cell will go apoptosis . The only T cells that will release in to the blood or go to lymph nodes are the ones that will recognize foreign antigens

-When T cell bind to its foreign antigen , it will activate , proliferate and expand and start attacking the pathogen.

- when preprocessing occurs ? Weeks before birth till months after birth

- **Now let's go to B lymphocytes**

  The same as T lymphocytes in bone marrow or in the liver if in mid fetal life , they will be processed to develop activity against millions of antigens , producing **millions** of offsprings the same way as T lymphocytes .

  B lymphocytes will be released to the blood (small numbers in blood , the majority in lymph nodes) and go to lymph nodes or lymph tissues

  Once B lymphocyte recognize or interface the antigen that it is raised against, it will be activated , proliferate and secrete a lot of antibodies

Maturation of T cells in the Thymus

- **Rapid expansion**
  - Increase in numbers and production high number of clones , that will recognize thousands of antigens.
- **Each clone is specific for a single antigen**
- **Self-reactive clones are deleted (up to 90%)**
  - Destroyed or apoptosis
- **Migrate to peripheral lymphoid organs**
- **Much of the above occurs just before and shortly after birth**

questions from the doctor

- If the thymus is removed before birth what will happened? What would you expect happen to acquired immunity?

Acquired immunity rely on the function of T helper cells to a very high extent and even on B cells, So if all these processes didn't happen, T cells will not be functional ,this will affect the whole acquired immunity.

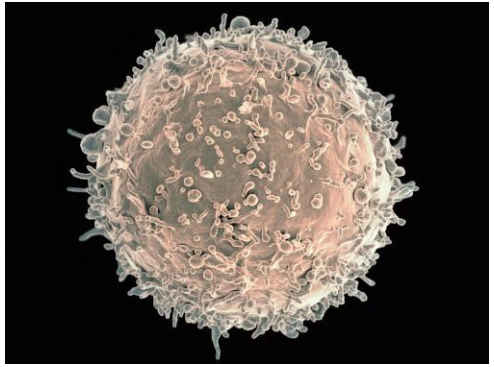
- if a child who lacks acquired immunity(he has no thymus) and doctors want transplant an organ for him , will he have rejection?

No , as rejection is a function of T cells.

- if the thymus is removed after 6 months or a year of age what will happened to the acquired immunity?

There will be a lot of T lymphocytes that were processed before, although the immunity will be diminished but we will not loose the whole acquired immunity.

B cell Development



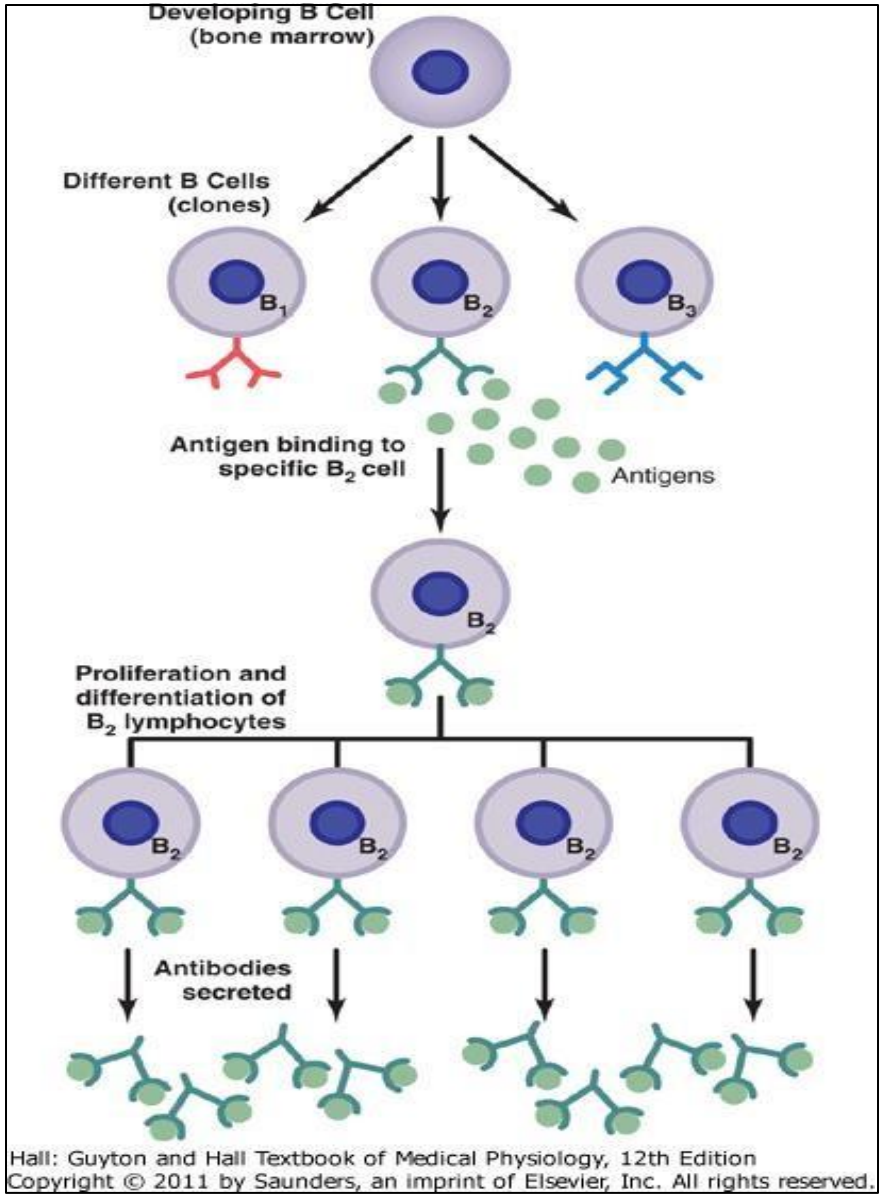
- **Initial growth and differentiation in the liver (fetal) and bone marrow (after birth)**
- **Migrate to the peripheral lymphoid organs**
- **Each clone is specific for a single antigen**
  - There will be limitless antibody specificity, they are nightly specific and millions of antigens can be recognized, each clone is specific to one Ag.
- **Clonal development provides almost limitless antibody specificity**
- **After being activated by specific antigens, the secreted antibodies destroy or neutralize molecules or organisms bearing their cognate antigen**

B cell proliferation in response to antigen

- This figure shows how different clones of B lymphocytes are produced during the processing, when one of these clones binds to its respective antigen, it will get activated then proliferate to increase in number and secrete a high amount of antibodies in order to fight microorganisms.

- This process usually occurs in lymph nodes (or lymphoid tissues in general) where B cells recognize pathogens and get activated.

- They are all a clone of the same lymphocyte that is reactive to an antigen .



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Immunologic Specificity

- **Each B or T cell clone is specific for a single epitope of a single antigen**
- **The genes for B cell receptors (immuno-globulins) and T cell receptors have hundreds of "gene segments" that are used in varying combinations**
- **Permutations (arrangements) of these cassettes allow specificity for millions of distinct epitopes**

- Each B or T cell has specific receptors for each single epitope of various antigens.
- The variability of receptors are created from the rearrangement of hundreds of gene **segments** not from a whole gene , allowing millions of unique specificities and ability to recognize different antigens.

Lymphocyte Activation

Macrophages in lymphoid organs…

- ingest antigen and present antigenic peptides to "helper" T cells
- Secrete IL-1, other cytokines that promote lymphocyte growth and differentiation

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

Both B and T cells require antigenic stimulation to proliferate

Lymphocyte activation

- Note that B lymphocytes require the function of T helper cells.
- T helper cells get activated once T lymphocytes are activated by certain antigens. T helper cells then release lymphokines that are important for the function of both B and T cells.
- T cells in torder to become activated need **antigen presenting cells (APCs)**(as T lymphocytes can't recognize antigens alone without help) such as macrophages,B lymphocytes, or dendritic cells that destroy microorganisms and digest their antigens to expose them into the surface using **major histocompatibility (MHC) proteins** so that T cells are able to recognize the pathogen's antigens.

Antibody Production

➢ A function of B lymphocytes

- **B cells bind intact antigen**

Naïve B cells interact with an antigen for the first time, but are able to recognize them by the huge amount of receptors on their surface.

- **T cells bind presented antigenic peptides**
- **B cells proliferate (with T cell help), developing lymphoblasts and plasmablasts**

Some of B lymphocytes when get activated will be kept as latent memory cells until the next exposure of the same antigen in the future, and the activation process will be faster.

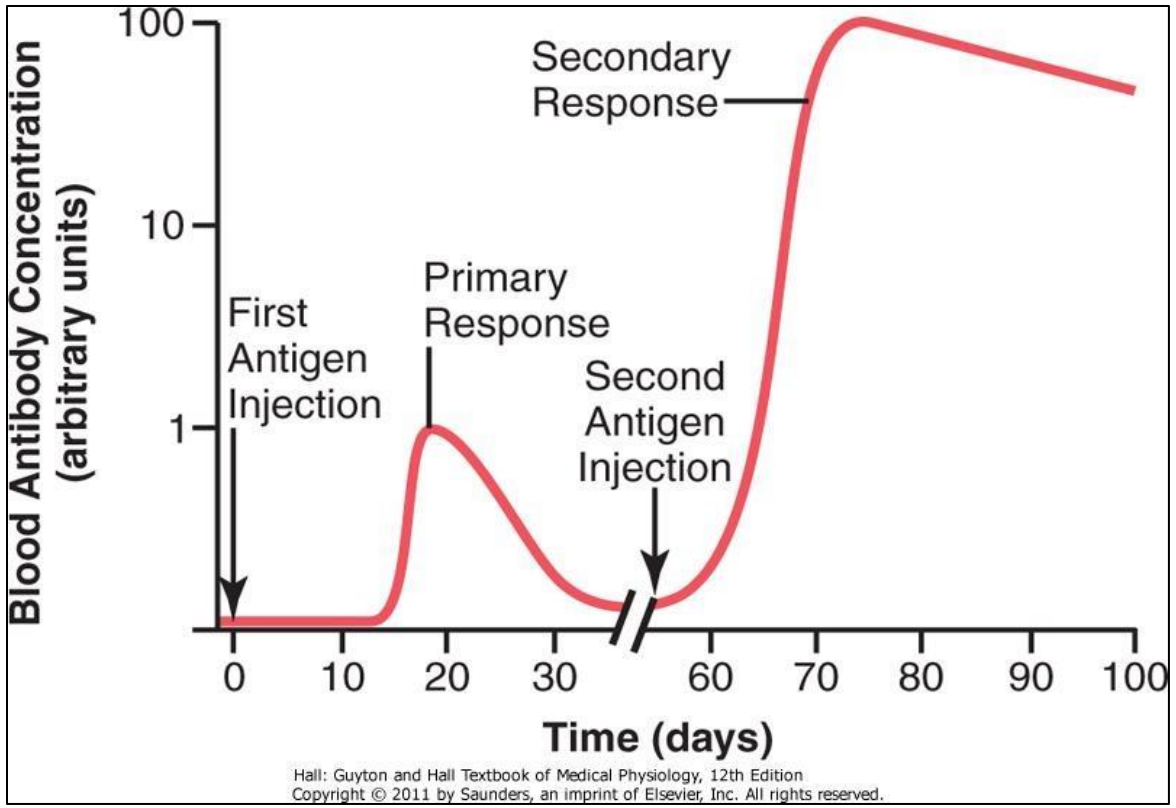
- **Up to 500 antigen-specific progeny in 4 days by each activated lymphoblast, each producing as many as 2,000 Ig molecules/sec**

Antigenic stimulation differs between primary or secondary responses. يعني كفاءة الاستجابة بالمرة الثانية الي بننصاب فيها مش نفس المرة الأولى

- **Can persist for many weeks (short lived), if antigenic stimulation persists**

Some are long lived and continue the production of antibodies for years and for the rest of a person's life.

Memory B cells and secondary responses



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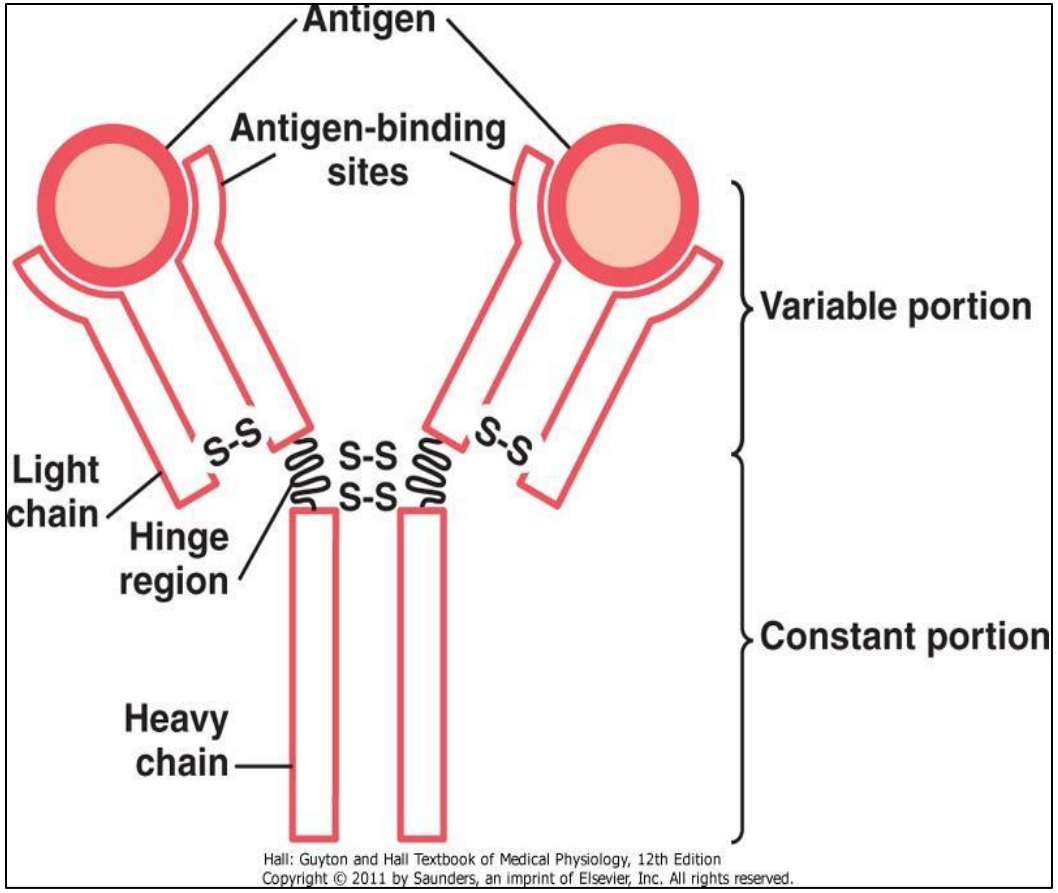
- After the first Ag injection, the increased of antibody titer will be delayed from ten days to two weeks and the potency will be low and won't last for longer than 20 days.
- After the second exposure the titer will robust (a hundred times more than the first response) with a very fast increase that will remain high for much longer and more potent
- This concept is used in immunization where we give newborns vaccines at different time intervals to strengthen their immunity against pathogens .

Structure of Immunoglobulins

- The simplest form of immunoglobulin has two light chains and two heavy chains with two binding sites.
- Each binding site is composed of one light and one heavy chain.
- The antigen binding site is the **variable part**, because of the high variabilities of chemical composition of segments to recognize different antigens.
- The **constant part** is important for different characteristics, such as diffusibility in tissues, attachment to tissues, and activation of the compliment system.

✓ A **Bivalent Ig** has two binding sites



Antibody Specificity

- **Each antibody has a steric configuration specific to its antigen (in the variable part)**

- **Multiple prosthetic groups of each antigen interact with complementary structures of the antibody, through…**
  - **hydrophobic bonding**
  - **hydrogen bonding**
  - **ionic interactions**
  - **van der Waals forces**

The more bonds that we have, the more specific and tighter binding which affects the quality of activation of antibodies.

- **Antibodies are at least bivalent**

✓ Certain antibodies could have up to ten binding sites depending on the number of light and heavy chains. For example, IgM has 10 binding sites (5 pairs of light and heavy chains).

Antibody classes (isotypes)

- IgM (earliest produced and primary response, five pairs of heavy chains and light chains)
- IgG (75% of all immunoglobulins)
- IgA
- IgD
- IgE (critically involved in allergic reactions)

  - Immunoglobulins make up about 20% of all plasma proteins

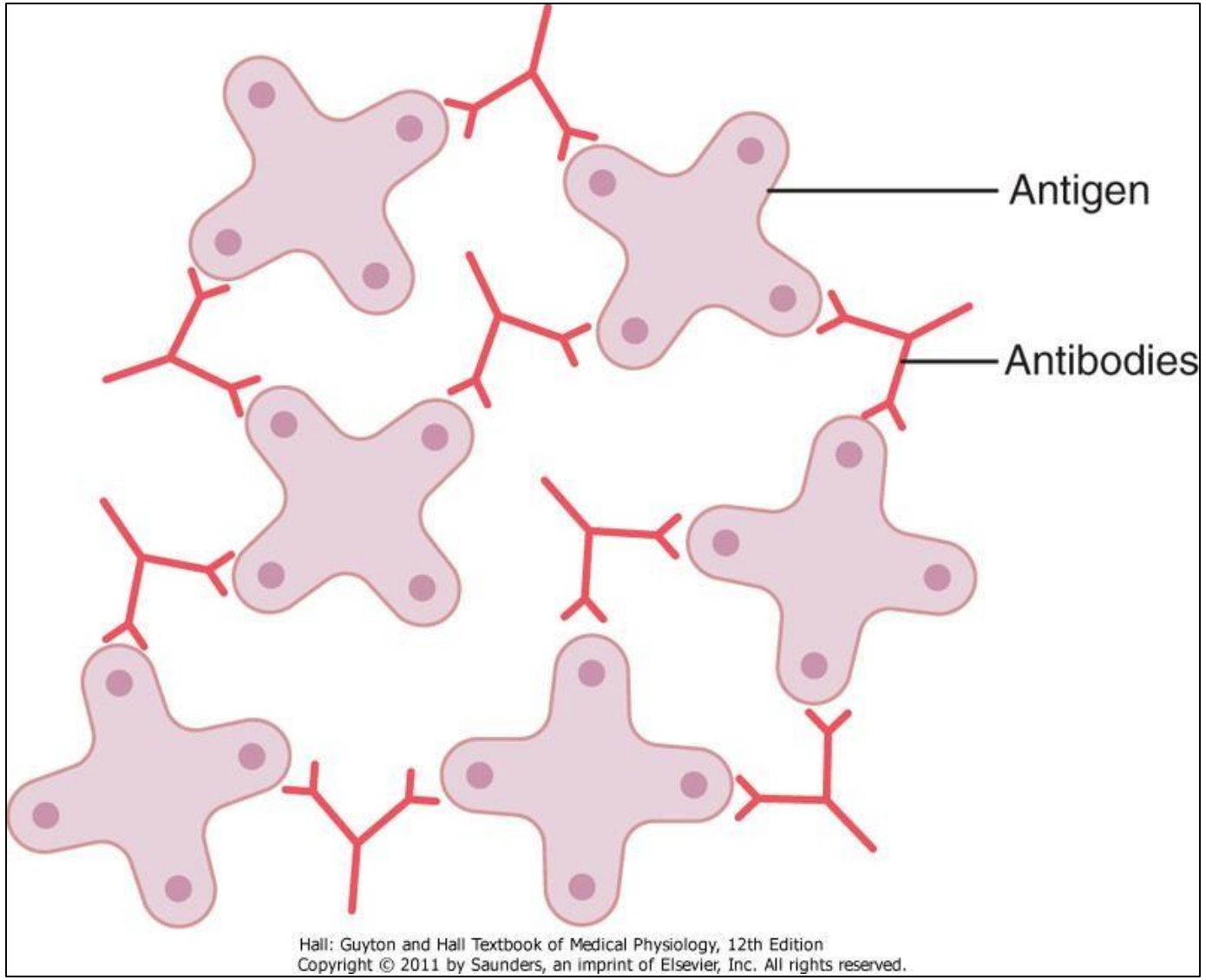
Antibodies: mechanisms of action

- Agglutination
- Precipitation
- Neutralization
- Lysis
- Complement activation

Antibodies mechanisms of action

1. **Agglutination** reaction involves binding of the antigen by several antibodies and each antibody can bind to several antigens in order to make a clump of toxins and microorganisms to isolate them from other body tissue.
2. **Precipitation** happens when an antigen is soluble and when it clumps it becomes insoluble which will also help isolate it.
3. **Neutralization** is covering up the active site on the pathogen to prevent its harmful effects.
4. **Lysis** is when the antibodies poke holes into the pathogen that will result in swelling of the pathogen and lysis.
5. The binding between the antigen and the antibody (the constant portion) will result in activation of certain members of the **compliment system,** then a cascade of activation of pro-enzymes present in the blood of different functions.

Agglutination



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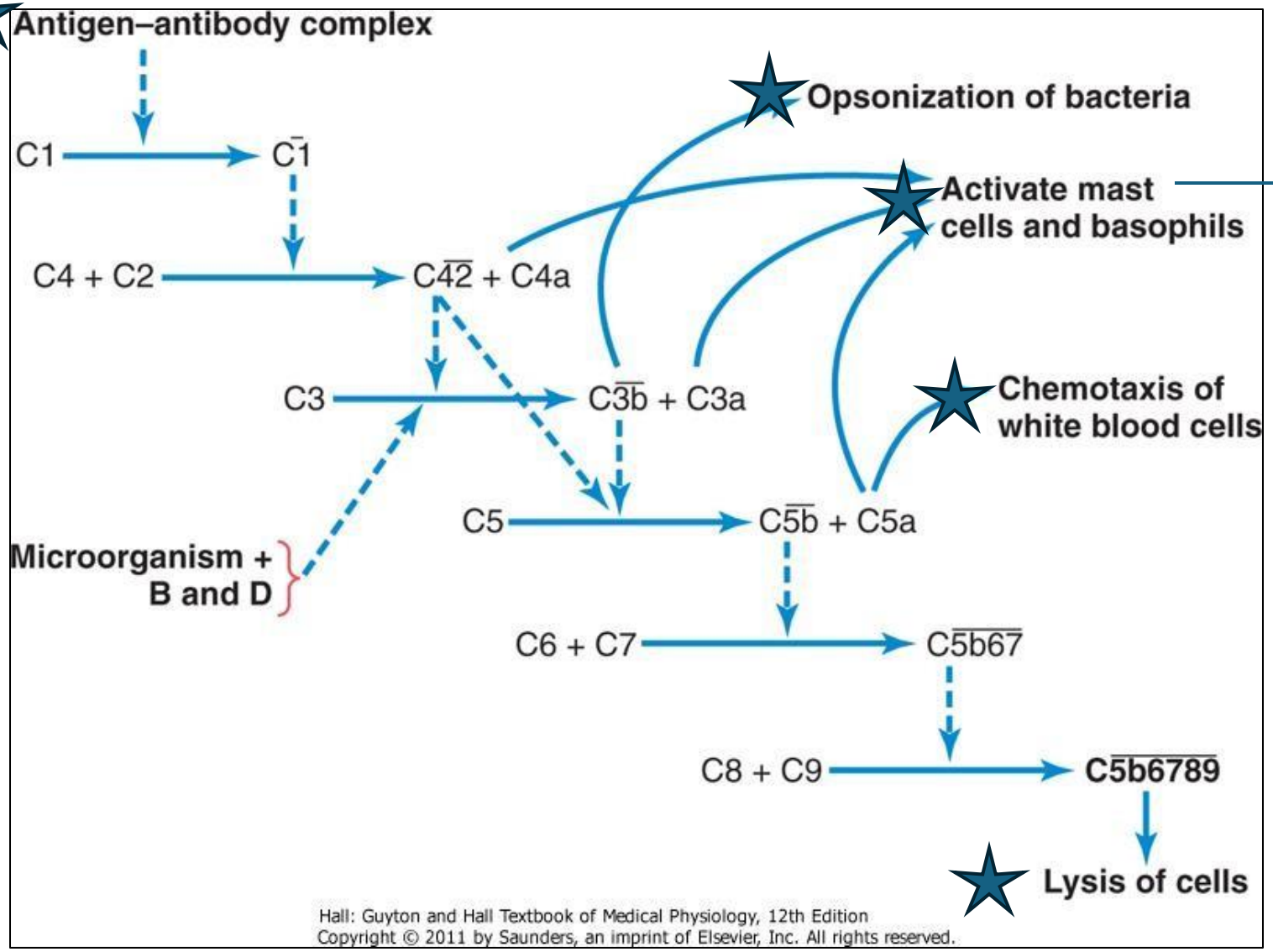
The Complement System



Release of histamine, bradykinin and serotonin aggravating the inflammation

Look thoroughly at this figure, you shlould recognize the functions of each.

C3a, C4a, and C5a activate mast cells and basophils,

T cell activation

- Binds to cognate antigen presented by antigen-presenting cell
- Rapid expansion of T helper (CD4) cells
- T helper cells produce cytokines

Cytokines regulate the functions of the whole immune system such as cytotoxic T cells, B lymphocytes, and macrophages.

- Drives expansion of both T helper (CD4) and cytotoxic (CD8) T
- cells
- Both types of cells also generate clonal memory T cells

Physiology Quiz

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	22 12	5 binding sites G0%	10 binding sites The doctor wrote this wrong she said in section 1 that 90% of self reactive clones are removed Quiz link fixed
V1 → V2			