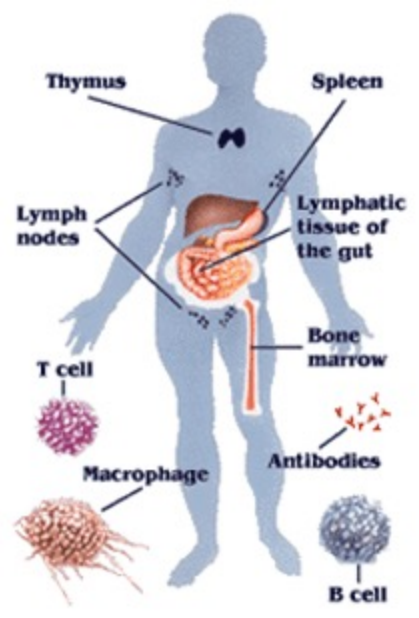
GENETIC CONTROL OF IMMUNE RESPONSE



The Immune System

Immunity: "Free from burden". Ability of an organism to recognize and defend itself against *specific* pathogens or antigens.

Immune Response: Third line of defense. Involves production of antibodies and generation of specialized lymphocytes against specific antigens.

Antigen: Molecules from a pathogen or foreign organism that provoke a specific immune response.

Innate or Genetic Immunity: Immunity an organism is born with.

- Genetically determined.
- May be due to lack of receptors or other molecules required for infection.
  - Immunity of mice to poliovirus.

Acquired Immunity: Immunity that an organism *develops* during lifetime.

- Not genetically determined.
- May be acquired naturally or artificially.
  - Development of immunity to measles in response to infection or vaccination.

Immunity

Innate immunity

Components

- Macrophages
- Granulocytes
- Natural killer cells
- Complement
- Other chemicals: HCL, lysozyme

Characteristics

* Action is immediate
* Response is non-specific
* Response is not enhanced on repeated exposure to pathogen

Adaptive immunity

Humoral | **Cell-mediated**

Components

- antigen presenting cells
- T-cells
- B-cells
- Antibodies
- Complement

Characteristics

* Action requires days to develop
* Response is specific
* Response is enhanced on repeated exposure to pathogen

Overview of the innate immune system

- It is the first line of defense
- It is active at the time of infection
- It consists of:
  - a- protective cellular (WBCs and derivatives)
  - b- chemical components

The response of the innate immune system

It is divided into two stages:

1- non-inflammatory reaction (body's static defenses)
skin, gastric pH, lysozyme in tears, saliva, mucous

2- local inflammation promotes migration of phagocytes and plasma protein into infected tissues
The phagocytes respond to surface structures present in large groups of microorganisms (peptidogcan, mannose)

Acute Inflammation Resulting From Infection

Inflammation is a nonspecific response of living tissue to localize and eliminate the injurious agent

The injury may be:

physical, chemical or biological

The Inflammatory Response

Specialized cells and serum proteins move from plasma to interstitial spaces to provide an immediate defense

The inflammatory cells include:

- Phagocytes which destroy the invading organisms by phagcytosis followed by intracellular digestion
- Natural killer cells which limit infection by releasing compounds toxic to organisms

Types of Acquired Immunity

I. Naturally Acquired Immunity: Obtained in the course of daily life.

A. Naturally Acquired Active Immunity:

- *Antigens* or pathogens enter body naturally.
- Body generates an immune response to antigens.
- Immunity may be lifelong (chickenpox or mumps) or temporary (influenza or intestinal infections).

B. Naturally Acquired Passive Immunity:

- *Antibodies* pass from mother to fetus via placenta or breast feeding (colostrum).
- No immune response to antigens.
- Immunity is usually short-lived (weeks to months).
- Protection until child's immune system develops.

Artificially Acquired Immunity: Obtained by receiving a vaccine or immune serum.

1. Artificially Acquired Active Immunity:

- *Antigens* are introduced in vaccines (immunization).
- Body generates an immune response to antigens.
- Immunity can be lifelong (oral polio vaccine) or temporary (tetanus toxoid).

2. Artificially Acquired Passive Immunity:

- Preformed *antibodies* (antiserum) are introduced into body by injection.
  - Snake antivenom injection from horses or rabbits.
- Immunity is short lived (half life three weeks).
- Host immune system does not respond to antigens.

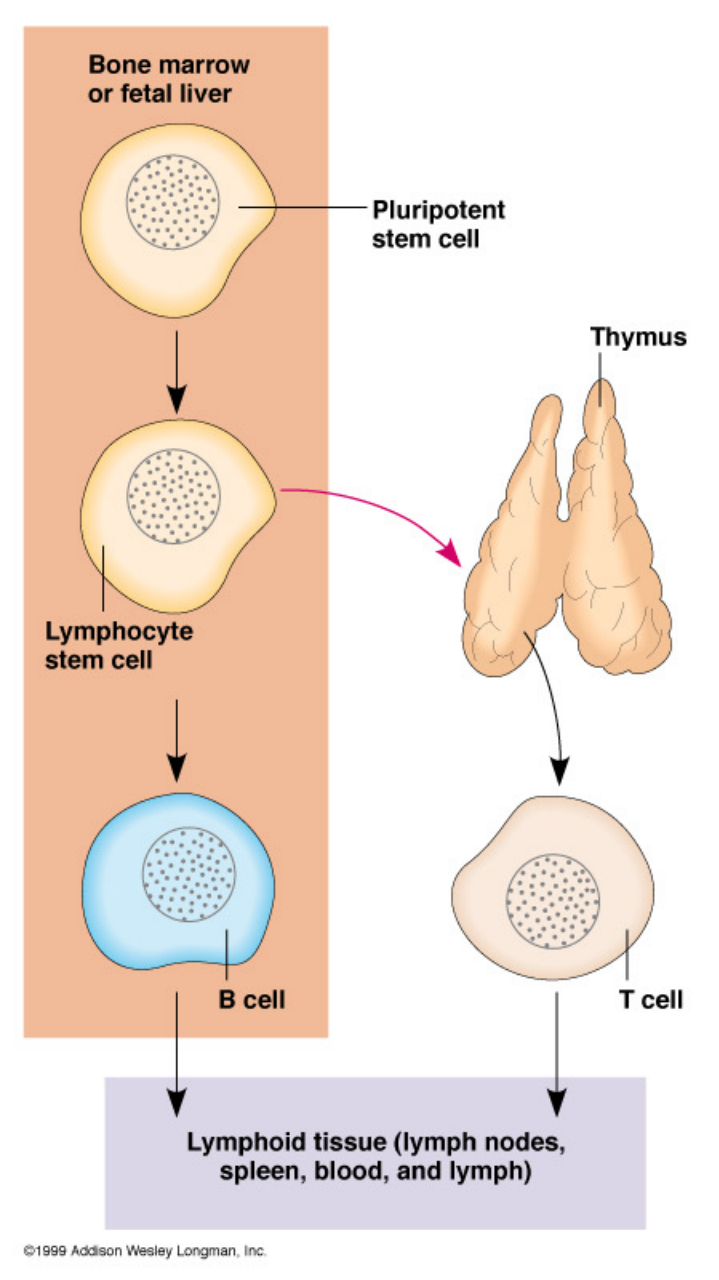
I. Humoral (Antibody-Mediated) Immunity

- Involves production of antibodies against foreign antigens.
- Antibodies are produced by a subset of lymphocytes called B cells.
- B cells that are stimulated will actively secrete antibodies and are called *plasma cells*.
- Antibodies are found in extracellular fluids (blood plasma, lymph, mucus, etc.) and the surface of B cells.
- Defense against bacteria, bacterial toxins, and viruses that circulate freely in body fluids, *before* they enter cells.
- Also cause certain reactions against transplanted tissue.

II. Cell Mediated Immunity

- Involves specialized set of lymphocytes called T cells that recognize foreign antigens on the surface of cells, organisms, or tissues:
  - Helper T cells
  - Cytotoxic T cells
- T cells regulate proliferation and activity of other cells of the immune system: B cells, macrophages, neutrophils, etc.
- Defense against:
  - Bacteria and viruses that are inside host cells and are inaccessible to antibodies.
  - Fungi, protozoa, and helminths
  - Cancer cells
  - Transplanted tissue

Antibodies are Produced by B Lymphocytes



Cells of the Immune System

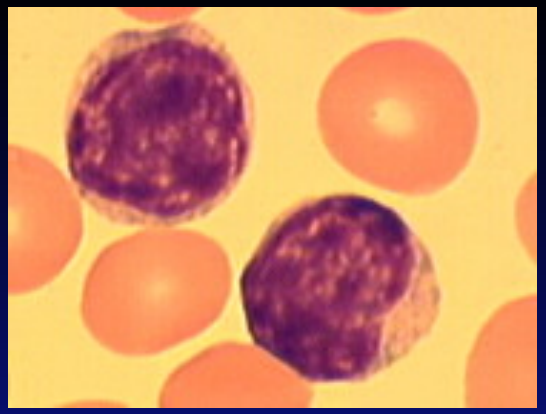
White Blood Cells

- Phagocytes - Neutrophils
  - Macrophages
- Lymphocytes

Phagocytes

- Produced throughout life by the bone marrow.
- Scavengers – remove dead cells and microorganisms.

Lymphocytes

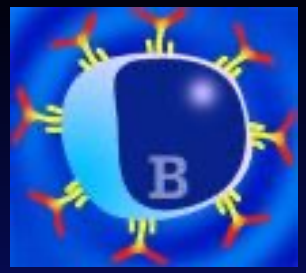


- Produce antibodies
- B-cells mature in bone marrow then concentrate in lymph nodes and spleen
- T-cells mature in thymus
- B and T cells mature then circulate in the blood and lymph
- Circulation ensures they come into contact with pathogens and each other

B -Lymphocytes

- There are about 10 million different B-lymphocytes, each of which make a different antibody.
- The huge variety is caused by genes coding for abs changing slightly during development.
- There are a small group of clones of each type of B-lymphocyte

B -Lymphocytes



- At the clone stage antibodies do not leave the B-cells.
- The abs are embedded in the plasma membrane of the cell and are

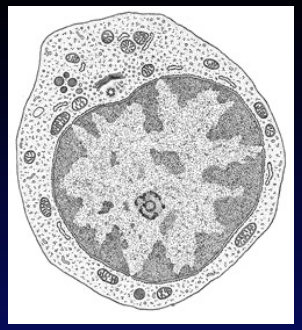
  called antibody receptors.
- When the receptors in the membrane recognise and antigen on the surface of the pathogen the B-cell divides rapidly.
- The antigens are presented to the B-cells by macrophages

B -Lymphocytes

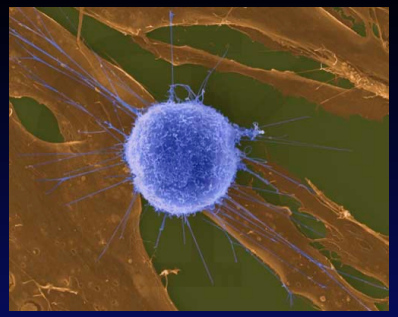
- Some activated B cells → MEMORY CELLS.
- Memory cells divide rapidly as soon as the antigen is reintroduced.
- There are many more memory cells than there were clone cells.
- When the pathogen/infection infects again it is destroyed before any symptoms show.

B -Lymphocytes

- Some activated B cells → PLASMA CELLS
  these produce lots of antibodies, < 1000/sec
- The antibodies travel to the blood, lymph, lining of gut and lungs.
- The number of plasma cells goes down after a few weeks
- Antibodies stay in the blood longer but eventually their numbers go down too.

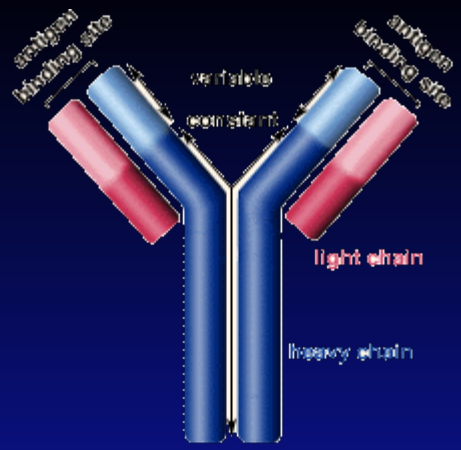


T-Lymphocytes



- Mature T-cells have T cell receptors which have a very similar structure to antibodies and are specific to 1 antigen.
- They are activated when the receptor comes into contact with the Ag with another host cell (e.g. on a macrophage membrane or an invaded body cell)
- After activation the cell divides to form:
- T-helper cells – secrete CYTOKINES
  - → help B cells divide
  - → stimulate macrophages
- Cytotoxic T cells (killer T cells)
  - → Kill body cells displaying antigen
- Memory T cells
  - → remain in body

Antibodies



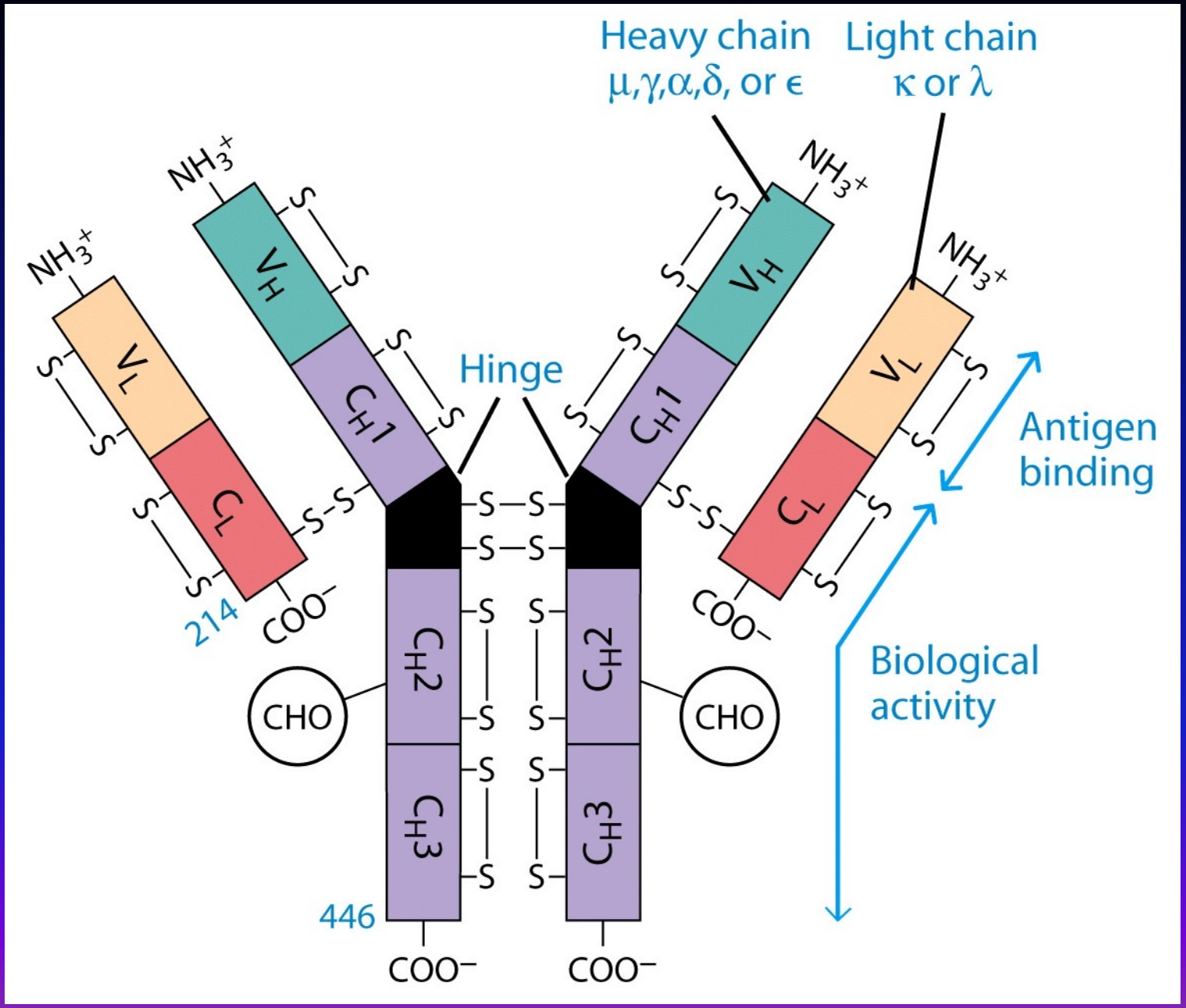
- Also known as immunoglobulins
- Globular glycoproteins
- The heavy and light chains are polypeptides
- The chains are held together by disulphide bridges
- Each ab has 2 identical ag binding sites – variable regions.
- The order of amino acids in the variable region determines the shape of the binding site

How Ab Works

- Some act as labels to identify antigens for phagocytes
- Some work as antitoxins i.e. they block toxins for e.g. those causing diphtheria and tetanus
- Some attach to bacterial flagella making them less active and easier for phagocytes to engulf
- Some cause agglutination (clumping together) of bacteria making them less likely to spread

Antibody Structure

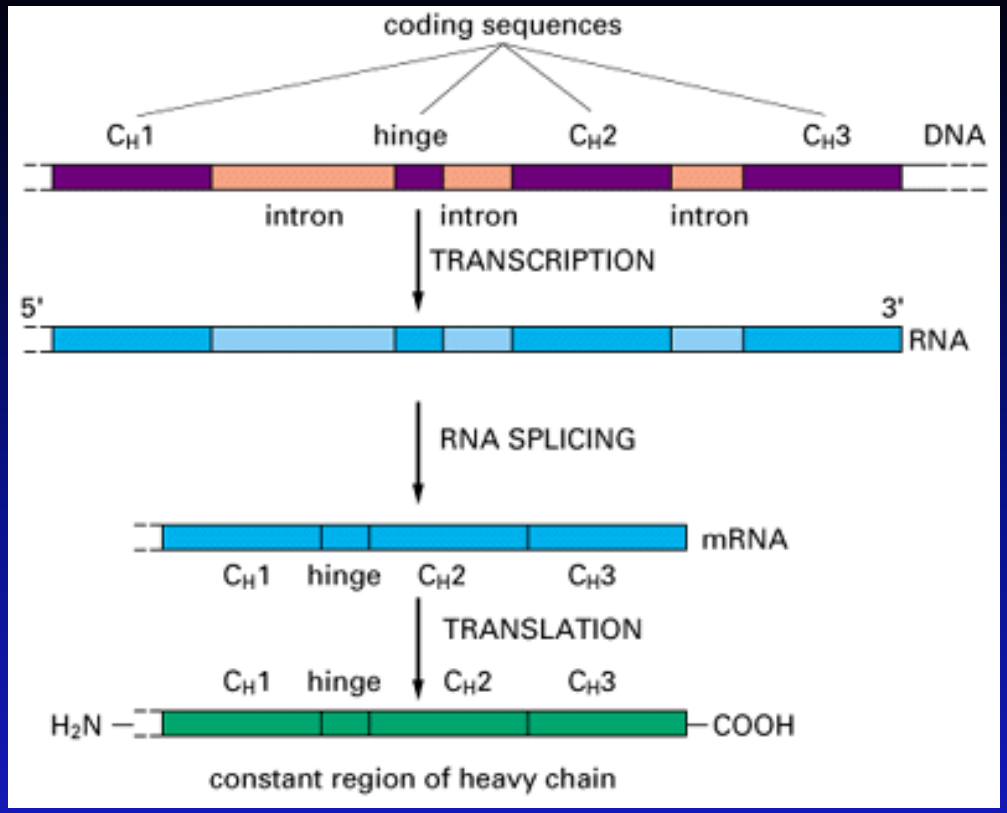
- Monomer: A flexible Y-shaped molecule with four protein chains:
  - 2 identical *light* chains
  - 2 identical *heavy* chains
- Variable Regions: Two sections at the end of Y's arms. Contain the antigen binding sites (Fab). Identical on the same antibody, but vary from one antibody to another.
- Constant Regions: Stem of monomer and lower parts of Y arms.
- Fc region: Stem of monomer only. Important because they can bind to complement or cells.


Heavy chain
μ,γ,α,δ, or ϵ
Light chain
κ or λ
NH3+
VH
CH1
VL
CL
Hinge
CH2
CH3
CHO
COO−
214
446
Antigen binding
Biological activity

Immunoglobulin Classes

I. IgG

- Structure: Monomer
- Percentage serum antibodies: 80%
- Location: Blood, lymph, intestine
- Half-life in serum: 23 days
- Complement Fixation: Yes
- Placental Transfer: Yes
- Known Functions: Enhances phagocytosis, neutralizes toxins and viruses, protects fetus and newborn.



The organization of the DNA sequences that encode the constant region of an Ig heavy chain . The coding sequences (exons) for each domain and for the hinge region are separated by noncoding sequences (introns). The intron sequences are removed by splicing the primary RNA transcripts to form mRNA. The presence of introns in the DNA is thought to have facilitated accidental duplications of DNA segments that gave rise to the antibody genes during evolution

Immunoglobulin Classes

II. IgM

- Structure: Pentamer
- Percentage serum antibodies: 5-10%
- Location: Blood, lymph, B cell surface (monomer)
- Half-life in serum: 5 days
- Complement Fixation: Yes
- Placental Transfer: No
- Known Functions: First antibodies produced during an infection. Effective against microbes and agglutinating antigens.

Immunoglobulin Classes

III. IgA

- Structure: Dimer
- Percentage serum antibodies: 10-15%
- Location: Secretions (tears, saliva, intestine, milk), blood and lymph.
- Half-life in serum: 6 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: Localized protection of *mucosal* surfaces. Provides immunity to infant digestive tract

Immunoglobulin Classes

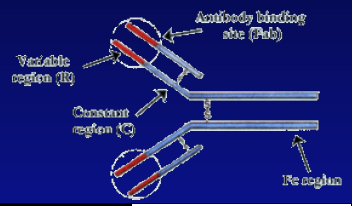
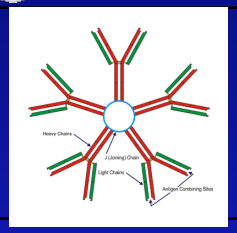
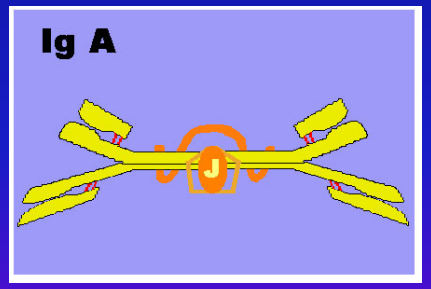
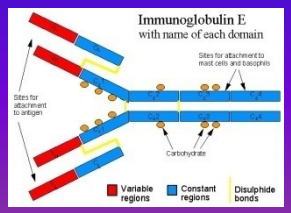
IV. IgD

- Structure: Monomer
- Percentage serum antibodies: 0.2%
- Location: B-cell surface, blood, and lymph
- Half-life in serum: 3 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: In serum function is unknown. On B cell surface, initiate immune response.

Immunoglobulin Classes

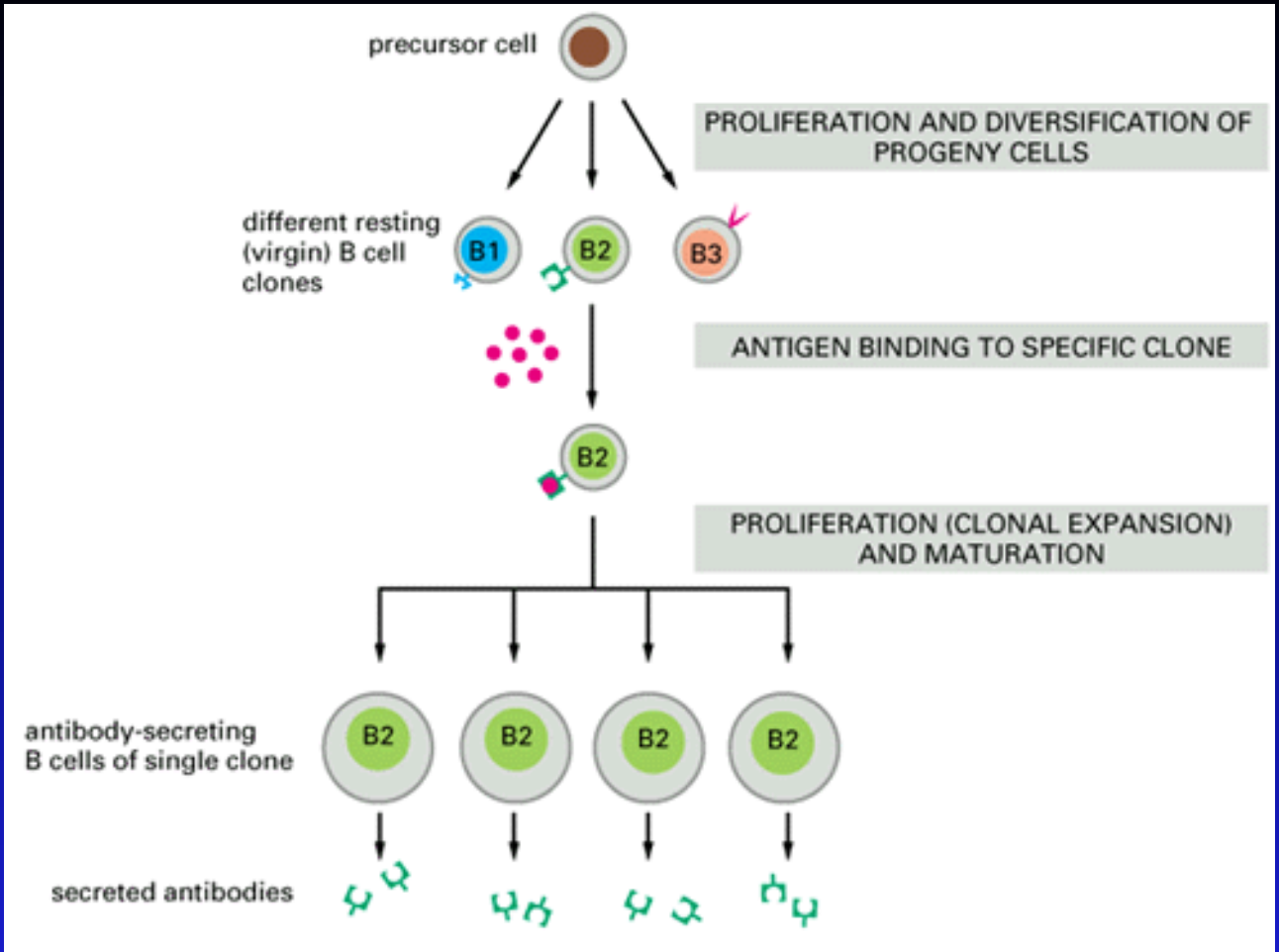
V. IgE

- Structure: Monomer
- Percentage serum antibodies: 0.002%
- Location: Bound to mast cells and basophils throughout body. Blood.
- Half-life in serum: 2 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: Allergic reactions. Possibly lysis of worms.

Type	Number of ag binding sites	Site of action	Functions
IgG 	2	•Blood •Tissue fluid •CAN CROSS PLACENTA	•Increase macrophage activity •Antitoxins •Agglutination
IgM 	10	•Blood •Tissue fluid	Agglutination
IgA 	2 or 4	•Secretions (saliva, tears, small intestine, vaginal, prostate, nasal, breast milk)	•Stop bacteria adhering to host cells •Prevents bacteria forming colonies on mucous membranes
IgE 	2	Tissues	•Activate mast cells → HISTAMINE •Worm response

Antigens

- Most are proteins or large polysaccharides from a foreign organism.
  - Microbes: Capsules, cell walls, toxins, viral capsids, flagella, etc.
  - Nonmicrobes: Pollen, egg white , red blood cell surface molecules, serum proteins, and surface molecules from transplanted tissue.
- Lipids and nucleic acids are only antigenic when combined with proteins or polysaccharides.
- Molecular weight of 10,000 or higher.
  - Hapten: Small foreign molecule that is not antigenic. Must be coupled to a carrier molecule to be antigenic. Once antibodies are formed they will recognize hapten.



The clonal selection theory . An antigen activates only those lymphocyte clones that are already committed to respond to it. A cell committed to respond to a particular antigen displays cell-surface receptors that specifically recognize the antigen, and all cells within a clone display the same receptor. The immune system is thought to consist of millions of different lymphocyte clones, hundreds of which may be activated by a particular antigen. Although only B cells are shown, T cells operate in a similar way.

T Cell Receptors and Subclasses

The two major classes of T cells have very different functions.

Cytotoxic T cells kill cells harboring harmful microbes, while helper T cells help activate the responses of other white blood cells, mainly by secreting a variety of local mediators, collectively called *lymphokines, interleukins, or cytokines .*

Cytotoxic T cells provide protection against pathogenic microorganisms, such as viruses and some intracellular bacteria, that multiply in the host cytoplasm, where they are sheltered from attack by antibodies.

Helper T cells, by contrast, are crucial for stimulating responses to extracellular microorganisms and their toxic products.

There are two types of helper T cells: *TH 1 cells, which activate* macrophages to destroy microorganisms that they have ingested, and *TH 2 cells, which stimulate* B cells to proliferate and secrete antibodies.

Both **cytotoxic T cells** and **helper T cells** recognize antigen in the form of peptide fragments that are generated by the degradation of foreign protein antigens inside the target cell, and both, therefore, depend on the presence in the target cell of special proteins that bind these fragments, carry them to the cell surface, and present them there to the T cells.

These special proteins are called ***MHC*** *molecules because they are encoded by a complex of genes called* ***the major histocompatibility complex (MHC) .***

There are two structurally and functionally distinct classes of MHC molecules: ***class I MHC molecules****, which present foreign peptides to cytotoxic cells, and* ***class II MHC molecules****, which present foreign peptides to helper cells.*

MHC I are expressed on the great majority of cells and recognized by CD8+ T cells MHC II are expressed on B cells, macrophages, dendritic cells and recognized by CD4+ T cells