

## **LECTURE: 05**

### **Title: ACQUIRED "ADAPTIVE" IMMUNITY & CLONAL SELECTION THEORY**

#### **LEARNING OBJECTIVES:**

The student should be able to:

- Recognize that, acquired or adaptive immunity is a specific immunity.
- Explain the mechanism of development of the specific immunity.
- Enumerate the components of the specific immunity such as
  - A. Primary immune response.
  - B. Secondary immune response
- Explain the different phases that are included in the primary and secondary immune responses such as:
  - A. The induction phase.
  - B. Exponential phase.
  - C. Steady phase.
  - D. Decline phase.
- Compare between the phases of the primary and secondary immune responses.
- Determine the type of the immunoglobulins involved in each phase.
- Determine which immunoglobulin is induced first and, that last longer.
- Enumerate the characteristics of the specific immunity such as:
  - A. The ability to distinguish self from non-self.
  - B. Specificity.
  - C. Immunological memory.
- Explain naturally and artificially acquired immunity (passive, and active).
- Explain the two interrelated and independent mechanisms of the specific immune response such as :
  - A. Humoral immunity.
  - B. Cell-mediated (cellular) immunity.
- Recognize that, the specific immunity is not always protective, for example; sometimes it causes allergies (hay fever), or it may be directed against one of the body's own constituents, resulting in autoimmunity (thyroiditis).

#### **LECTURE REFERENCE:**

1. TEXTBOOK: ROITT, BROSTOFF, MALE  
IMMUNOLOGY. 6<sup>th</sup> edition. Chapter 2. pp. 15-31
2. TEXTBOOK: ABUL K. ABBAS. ANDREW H. LICHTMAN. CELLULAR AND MOLECULAR  
IMMUNOLOGY. 5<sup>TH</sup> EDITION. Chapter 1. pg 3-12.

# ACQUIRED (SPECIFIC) IMMUNITY

## INTRODUCTION

Adaptive immunity is created after an interaction of lymphocytes with particular foreign substances which are recognized **specifically** by those lymphocytes. This recognition process triggers proliferation and maturation of the lymphocytes which in the case of **B lymphocyte** results in the **secretion of antibodies** and the “**memorizing**” of that particular agent in a process called the **primary immune response**. **On the second contact** with the same agent the **magnitude** of the response is increased as a result of the **more rapid** and more **abundant** production of specific antibodies: a process called **secondary immune response**.

The adaptive immune response is a more highly developed system than the innate immune system. It includes not only humoral immunity but also cellular immunity, the production of specific-lymphocytes. As its name implies, acquired immunity is a consequence of an encounter with a foreign substance. The first encounter with a foreign substance that has penetrated the body triggers a chain of events that induces an immune response with specificity against the foreign substance. Although an individual is genetically endowed with the capacity to mount an immune response against a certain substance, acquired immunity is usually exhibited only after an initial encounter with the substance. Thus acquired immunity develops only after exposure to, or **immunization** with, a given substance. Development of the adaptive immunity requires specific **immune responses**.

## IMMUNE RESPONSE

When an individual exposed to non-self substance either by injection or infection, a complex series of events are created:

- a. An **antigen-presenting cell** (usually a macrophage) processes the antigen and presents it to the **lymphoid cells** of the immune system.
  - (1) For a **successful immune response** to occur, the **processed antigen** (specifically, its **epitope**) must be **presented to lymphocytes** in association with a glycoprotein encoded by genes of the major histocompatibility complex (MHC).
  - (2) This requirement for effective cell interaction is called **MHC restriction**.

- b. The lymphoid cells recognize that particular epitope and acquire the ability to react with it.
- c. The result of these consequences of events is the **activation of antigen-specific B and T cells**, causing them to proliferate and mature.

The consequences of the initial interaction between lymphocytes and their homologous epitopes are far-reaching.

- d. A subsequent exposure to antigen will induce some **B lymphocytes** (memory B cells) to proliferate and differentiate into **antibody-secreting plasma cells**.
  - (1) These **active plasma cells** secrete their specific antibody in large amounts when they contact antigen a second time, a phenomenon known as **anamnesis**.
  - (2) The **secreted antibodies** react specifically with the antigen that originally induced the B cell to proliferate. The potential exists to produce an extremely large (> 100,000) variety of different, specifically reactive, antibodies.
- e. Some **T lymphocytes** (memory T cells) are induced to differentiate and proliferate to form mature progeny that will be triggered to release biologically active metabolites when they contact antigen a second time.

The immune response is under highly complex genetic control. Most of the genes that code for chain segments of the immunoglobulin molecule or the T cell receptor are polycistronic (present in the cell in many forms). The process of **DNA re-arrangement and deletion**, followed by RNA splicing, selects alleles that code for a particular **immunologic specificity**.

## CELLULAR ACQUIRED IMMUNITY E

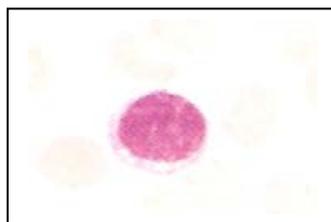
The cells participate in the immune response arise from pluripotent stem cells through two main lines of differentiation. All acquire instructions from the T-lymphocyte called T-helper cells. These cells are:

- the lymphoid lineage produces lymphocytes
- the myeloid lineage produces phagocytes (monocytes, macrophages, and neutrophils) and other cells.
- the accessory cells which include:
  - A. Antigen presenting cells (APCs) present antigen to T cells.
  - B. Mast cells which is structurally and functionally similar to basophils
  - C. Endothelial cells, which can recognize certain lymphocytes by expressing some surface molecules, and through this way, these cells can control the distribution of the lymphocytes.
  - D. Platelets which is one of the major components of the clotting system and inflammation.

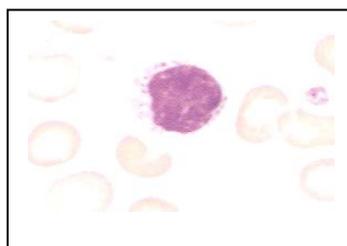
## LYMPHOCYTES

Lymphocytes are produced in the central lymphoid or primary lymphoid organs (Thymus and adult bone marrow), some of these cells migrate to the secondary lymphoid organs, such as tonsil, lymph nodes, spleen, and mucosa-associated lymphoid tissues. The lymphocytes represent about 20% of the circulating human leukocytes. The lymphoid memory cells are of long-lived cells, they can circulate for several years or even the lifetime of the individual. The morphology of the lymphocytes is heterogeneous. They have different sizes range from 6-10 micro-meters. The differences also can be recognized in the nuclear to cytoplasmic ratio (N: C ratio), the presence or absence of the azurophilic granules, and the nuclear shape.

Two types of lymphocytes can be seen in the conventional blood smear stained with Giemsa stain. One population is relatively small with high N:C ratio, and a granular lymphocytes. The other population shows a low N:C ratio, with intracytoplasmic azurophilic granules, these are called (LGL) large granular lymphocytes (**Figure 1-1, 2,3, and 4**).



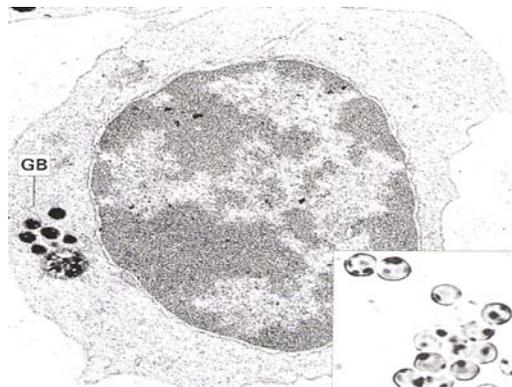
**Figure 1-1 Morphological heterogeneity of lymphocytes.** The small lymphocyte has no granules, around nucleus nada high N:C ration.



**Figure 1-2 Morphological heterogeneity of lymphocytes.** The large granular lymphocytes has a lower N:C ration, indented nucleus and azurophilic granules in the cytoplasm.

## Resting blood T lymphocytes

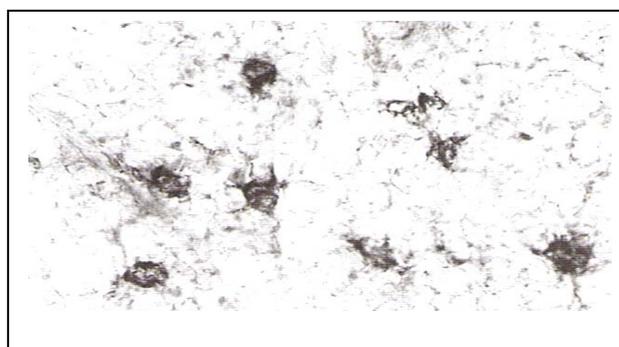
These cells can be either LGL or small lymphocytes. The majority (>90%) of T helper cells and proportion (>65%) of cytotoxic T (Tc) cells are of the small type (non-granular with a high N:C ratio). They also contain in their cytoplasm a structure called **Gall body** (a cluster of primary lysosomes associated with a lipid droplet). The rest of these cells of LGL morphology with primary lysosomes dispersed in the cytoplasm and a well developed Golgi apparatus. The gamma/delta or TCR-1<sup>+</sup> lymphocytes population is another subset of T cells with LGL morphology.



**Figure 1-3 Ultrastructure of non-granular T cell.** This electron micrograph shows the **Gall body (GB)** that is characteristic of the majority of resting T cells. It consists of primary lysosomes and a lipid droplet. This structure is also seen as a single "spot" after staining for non-specific esterases in light microscopy.



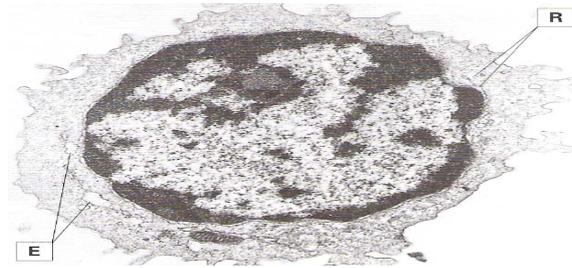
**Figure 1-4 Ultrastructure of T cells with granular morphology.** These cells characteristically have electron dense peroxide .negative granules (primary lysosomes, pl), scattered throughout the cytoplasm, with some close to the Golgi apparatus (GA). There are many mitochondria (M) present.



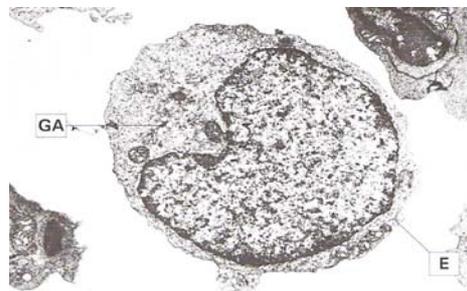
**Figure 1-5 dendritic morphology of  $\gamma\delta$  T cells in the tonsil.** This T-cell population is predominantly localized into intermolecular T cell-dependent zones. Note the dendritic morphology of the cells. Anti- $\gamma\delta$  T cell mAb and immunoperoxidase.

## Resting blood B lymphocytes

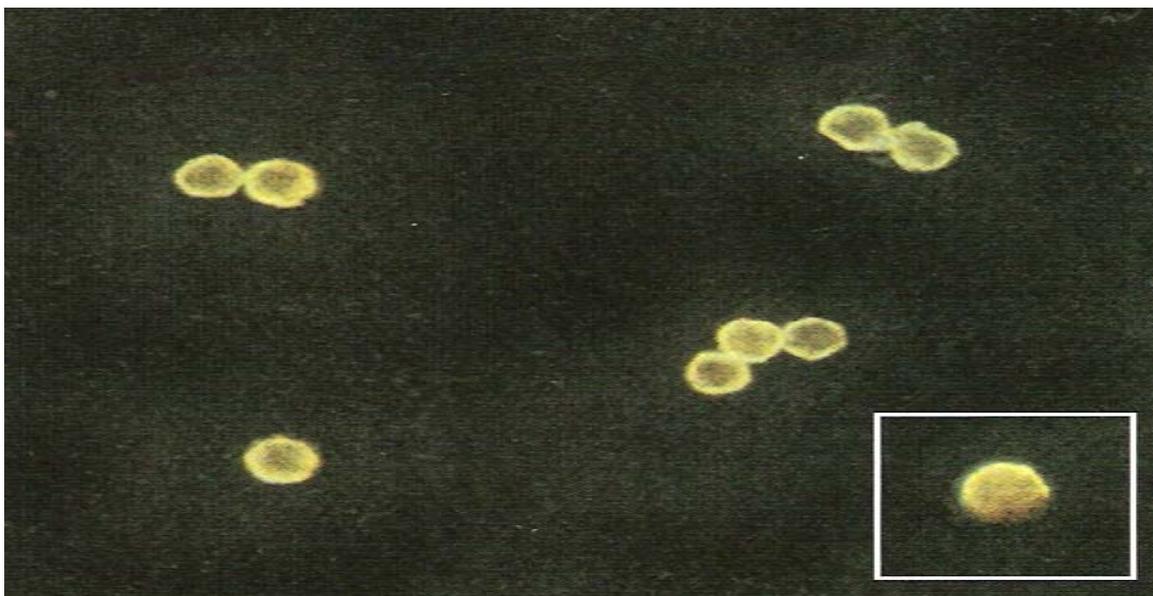
These cells do not show Gall body or LGL morphology, and contain scattered single ribosomes in their cytoplasm, when activated, the rough endoplasmic reticulum are recognized. B cell stained for antibody (Figure 1-6, 7, 8).



**Figure 1-6 Ultrastructure of resting B cells.** These cells have no Gall body or granules. Scattered ribosomes (R) and isolated strands of rough endoplasmic reticulum (E) are seen in the cytoplasm. Development of Golgi-lysosomal system in the B cell occurs on activation.



**Figure 1-7 Ultrastructure of B cell blasts.** The main feature of activated B cells is the development of the machinery for immunoglobulin synthesis. This includes rough endoplasmic reticulum (E), free polyribosome and the Golgi apparatus (GA), which is involved in glycosylation of the immunoglobulins.



**Figure 1-8 B cells stained for surface immunoglobulin.** B cells stained with fluorescent anti-IgM in the cold show a surface ring-like pattern under UV light. A polar redistribution (capping) is seen when the cells are incubated at 37° C in the presence of the antibody (inset).

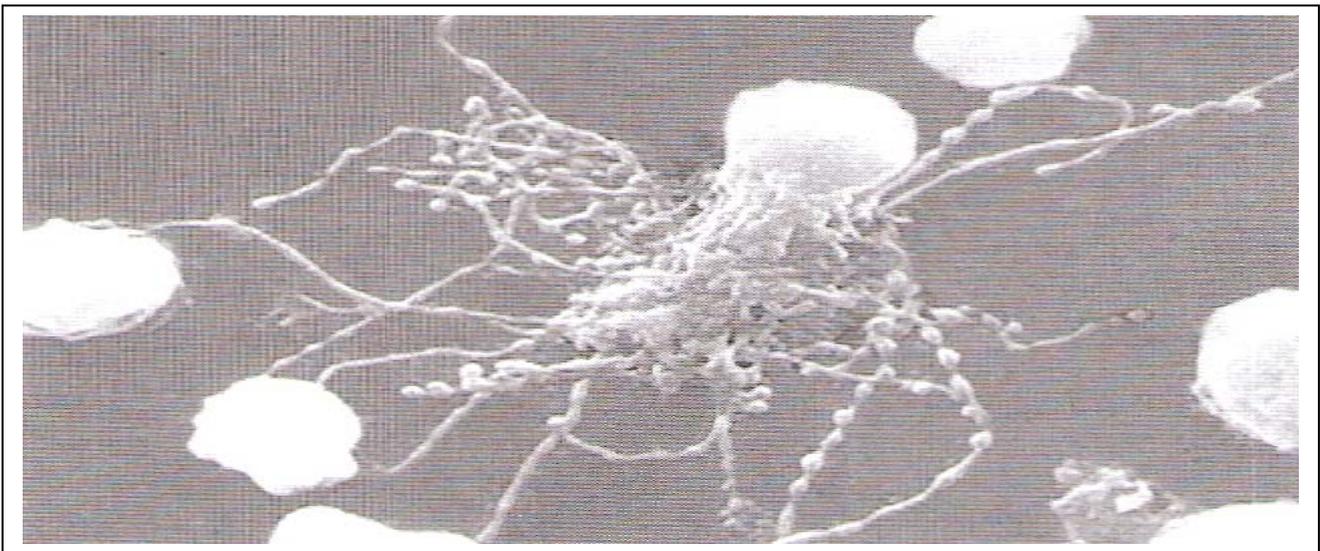
## MONONUCLEAR PHAGOCYTES

The phagocytic tissue macrophages, together with endothelial cells, were previously termed as “the reticuloendothelial system (RES). These cells perform two main functions:

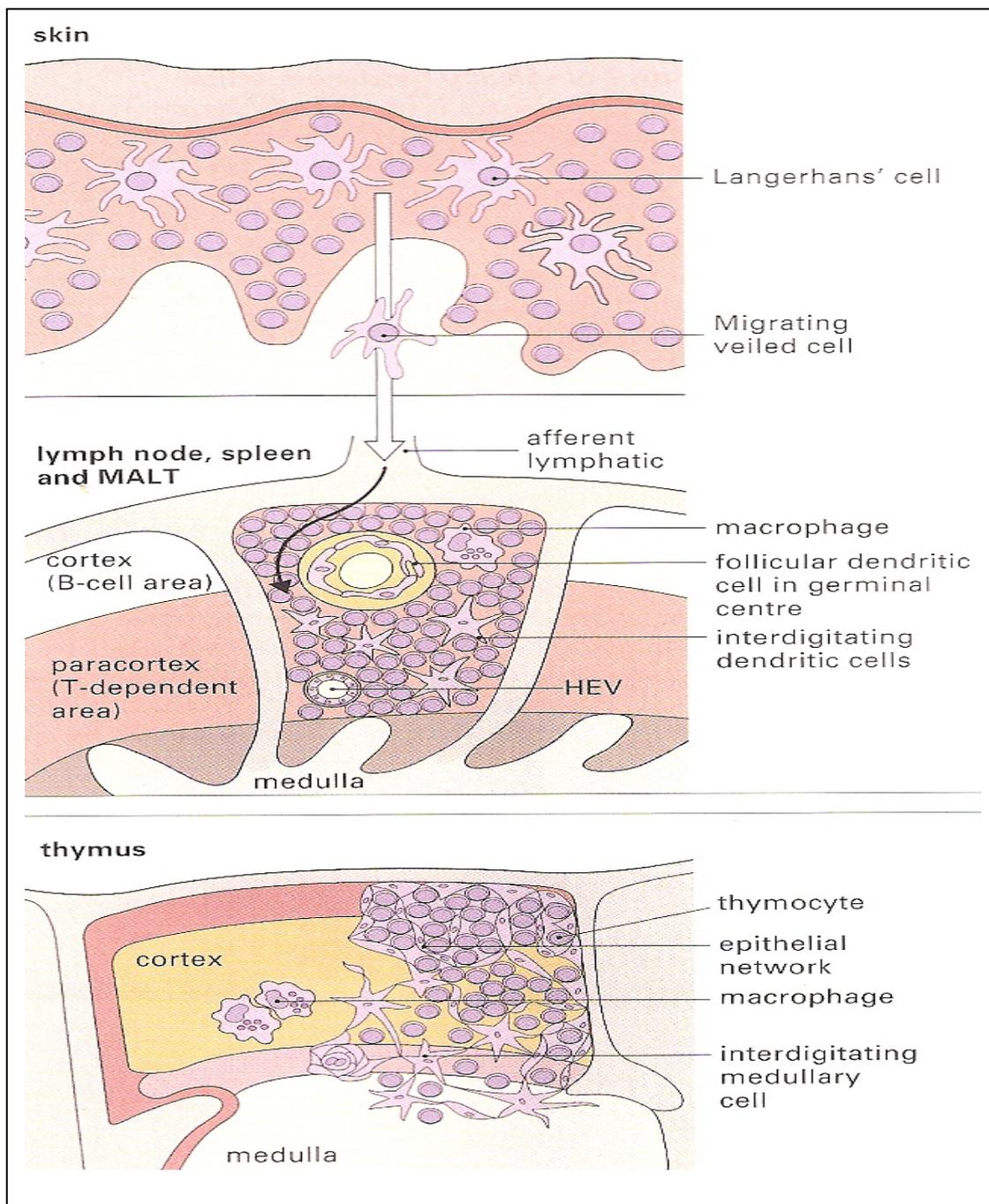
- Professional phagocytic macrophages, which remove particulate antigens.
- Antigen-presenting cells (APCs), which bind, process, and present antigen to **T cells**.

### ANTIGEN- PRESENTING CELLS (APCs)

These cells are rich in class II MHC molecules, which are important for presenting antigen to TH cells. APCs are a heterogeneous population of leukocytes. Cells other than leukocytes such as endothelial or epithelial cells can be classified as APCs. These cells can presents antigens to T cells when they stimulated with cytokines. APCs are found mainly in lymph nodes e.g., Follicular dendretic cells (**Figure 1-9**), and in skin e.g., Langerhans’ cells (**Figure 1-10**), thymus, and spleen.



**Figure 1-9 Follicular dendritic cells (FDC).** An isolated follicular dendritic cell from the lymph node, the FDC is of intermediate maturity with smooth filiform dendrites typical of young FDCs, and beaded dendrites which participate in the formation of incosomes of mature FDCs. The adjacent small white cells are lymphocytes.



**Figure 1-10 Langerhan's cells.** Bone marrow derived antigen presenting cells (APCs) are found especially in lymphoid tissue, in the skin and in mucosa. APCs in the form of Langerhan's cells are found in the epidermis and are characterized by special granules (the tennis racquet-shaped Birbeck granules). These cells, rich in MHC class II, carry processed antigens and migrate via the afferent lymphatics (where they appear as "veiled" cells) into the paracortex of the draining lymph nodes. Here they make contact with T cells. These "interdigitating cells", localized in the T-cell dependent cells areas of the lymph node, present antigen to T helper cells. Exposure of antigen to B cells occurs on the follicular dendritic cells (FDCs) in the germinal centers of B cell follicles. Some macrophages located in the outer cortex and marginal sinus may also act as APCs. In the thymus, APCs occur as interdigitating cells in the medulla.

## The characteristic properties of the adaptive immunity

1. The ability to **distinguish** self from **non-self**.
2. The **induction phase** which is the time required for lymphocytes to proliferate and mature into antibody-secrete lymphokines and cytotoxins.
3. Specificity developed when the immune system selects antibodies and lymphocytes for responding to their antigens.
4. An **immunologic memory** that allows sensitized lymphocytes to remember their recognized antigen and respond to them later producing elements of both cellular and humoral immunity.

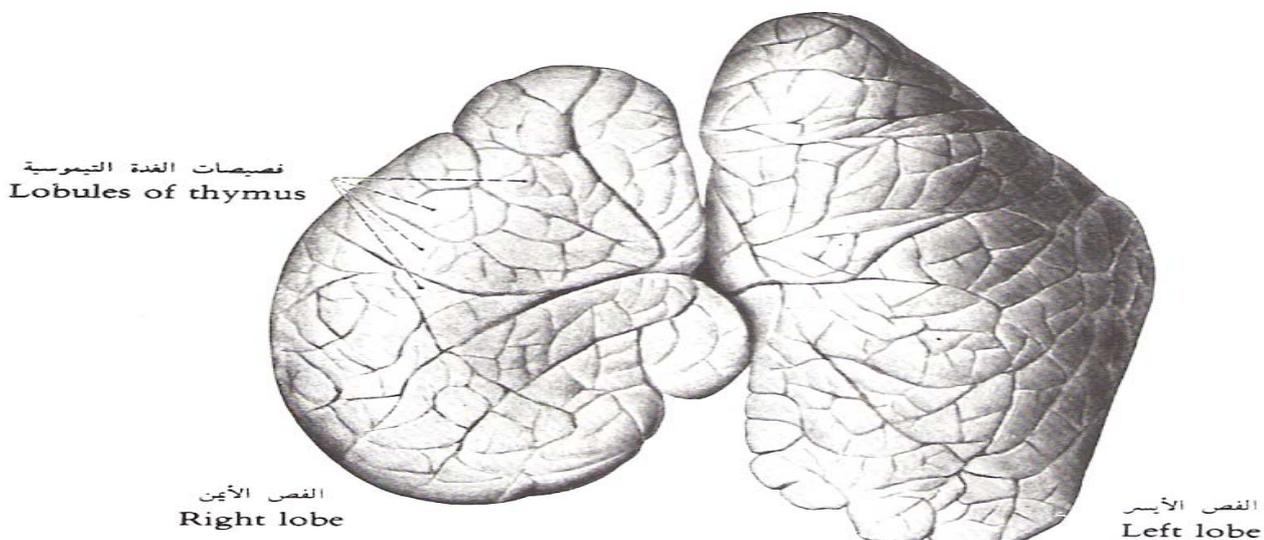
## Lymphatic Organs

The **lymphatic organs** are those organs in which maturation, differentiation, and proliferation of lymphocytes take place. **Lymphocytes** are derived from the pluripotential **haematopoietic bone marrow stem cells**, which give rise to all blood cells. The **erythroid** and **myeloid** cells, which differentiate into erythrocytes and granulocytes, are derived from these stem cell progenitors. Lymphoid progenitor cells differentiate into lymphocytes.

The lymphoid organs are generally divided into two categories: the **primary or central, lymphoid organs** are those in which the maturation of T and B lymphocytes into antigen recognizing lymphocytes takes place. The **secondary lymphoid organs** are those organs in which antigen driven proliferation and differentiation take place.

## Primary lymphoid organs

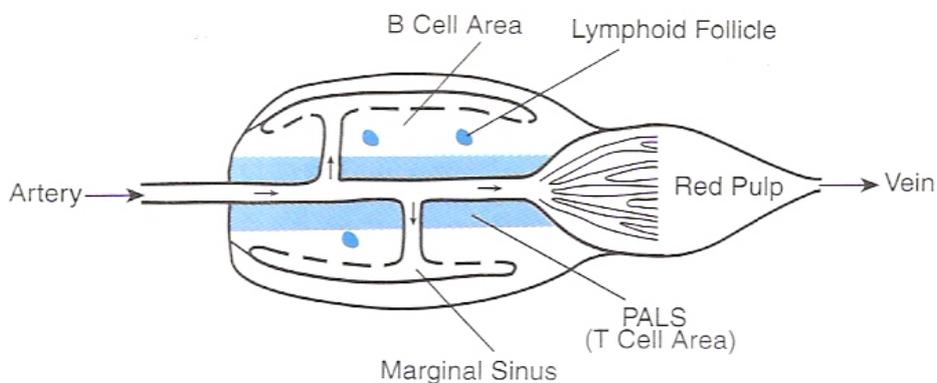
There are two major primary lymphoid organs, one in which the T cells develop and the other in which the B cells develop. The **Bone marrow** and the **Thymus gland** is illustrated in (Figure 1-11). The thymus gland is a bilobed structure, derived from the endoderm of the third and fourth pharyngeal pouches. It reaches its maximum size around birth, after which it begins to decrease in size and undergoes atrophy with aging.



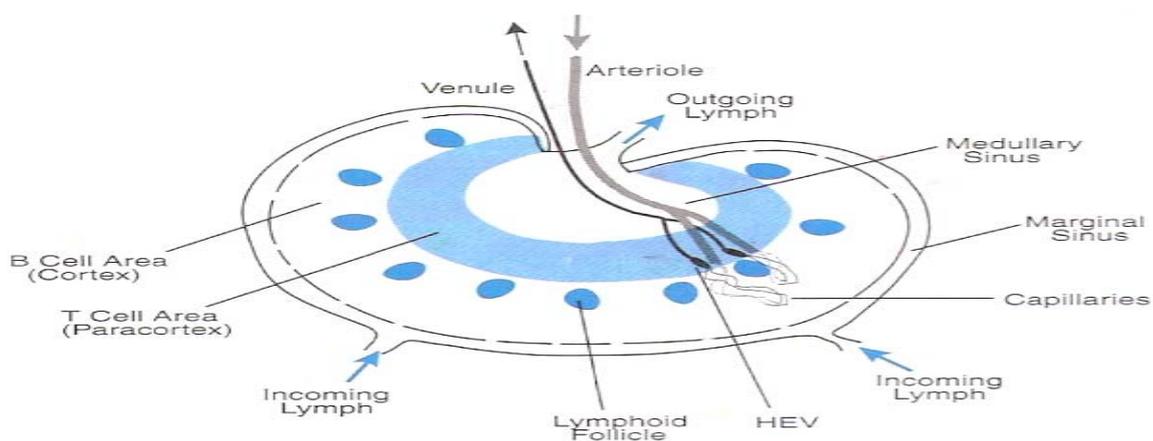
**Figure 1-11.** A diagrammatic representation of right and left lobes of the thymus gland.

## Secondary lymphoid organs

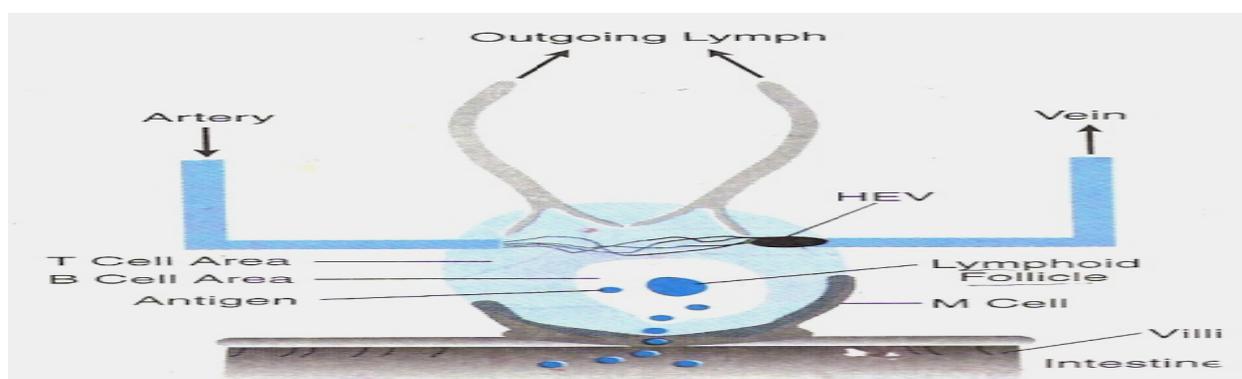
These represent the locations where the pathogenic recognition occurs, these organs are; the spleen (Figure 1-2), lymph node (Figure 1-12, 13, and 14), and the Peyer's patches (Figure 1-4) which is considered as a mucosal associated Tissues (MALT).



**Figure 1-12 Spleen is an example of secondary lymphoid organs**



**Figure 1-13 Lymph node is an example of the secondary lymphoid organs**



**Figure 1-14 Peyer's patches is an example of the MALT (Mucosal Associated Lymphoid Tissues)**

## Humoral (non-cellular) immunity

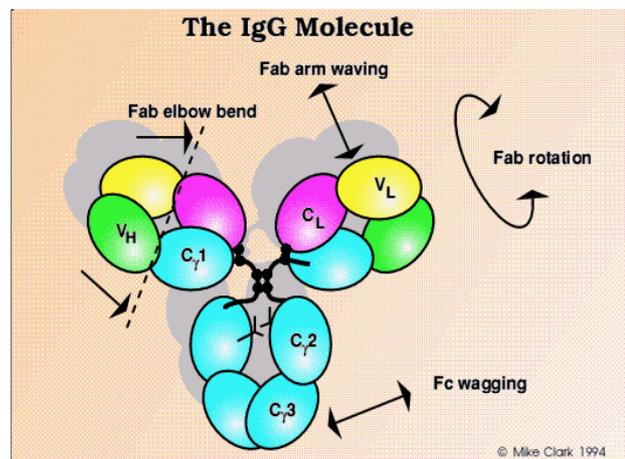
Primarily involves bursa- or bone marrow-derived **(B) lymphocytes, or B cells**.

(1) The B cell expresses specific immunoglobulin on its surface.

(2) When this surface immunoglobulin **interacts (meet)** with its matching (homologous) **antigen**, the B cell is **triggered** to “**proliferate**” and “**differentiate**” into **plasma cell [antibody producing cell (APC)]** which excrete vast quantities of **immunoglobulins (Figure 1-15)**.

(a) These produced immunoglobulins are **specific** for the same antigen (non-self) that originally triggered the **B lymphocyte**.

(b) Immunoglobulins, as proteins in the plasma fraction of the blood, comprise the **humoral (soluble)** components of the **specific** immune system.



**Figure 15-** An example of acquired humoral immunity is the IgG antibody.

## PHASES OF HUMORAL IMMUNE RESPONSE

### A. The primary and secondary immune responses

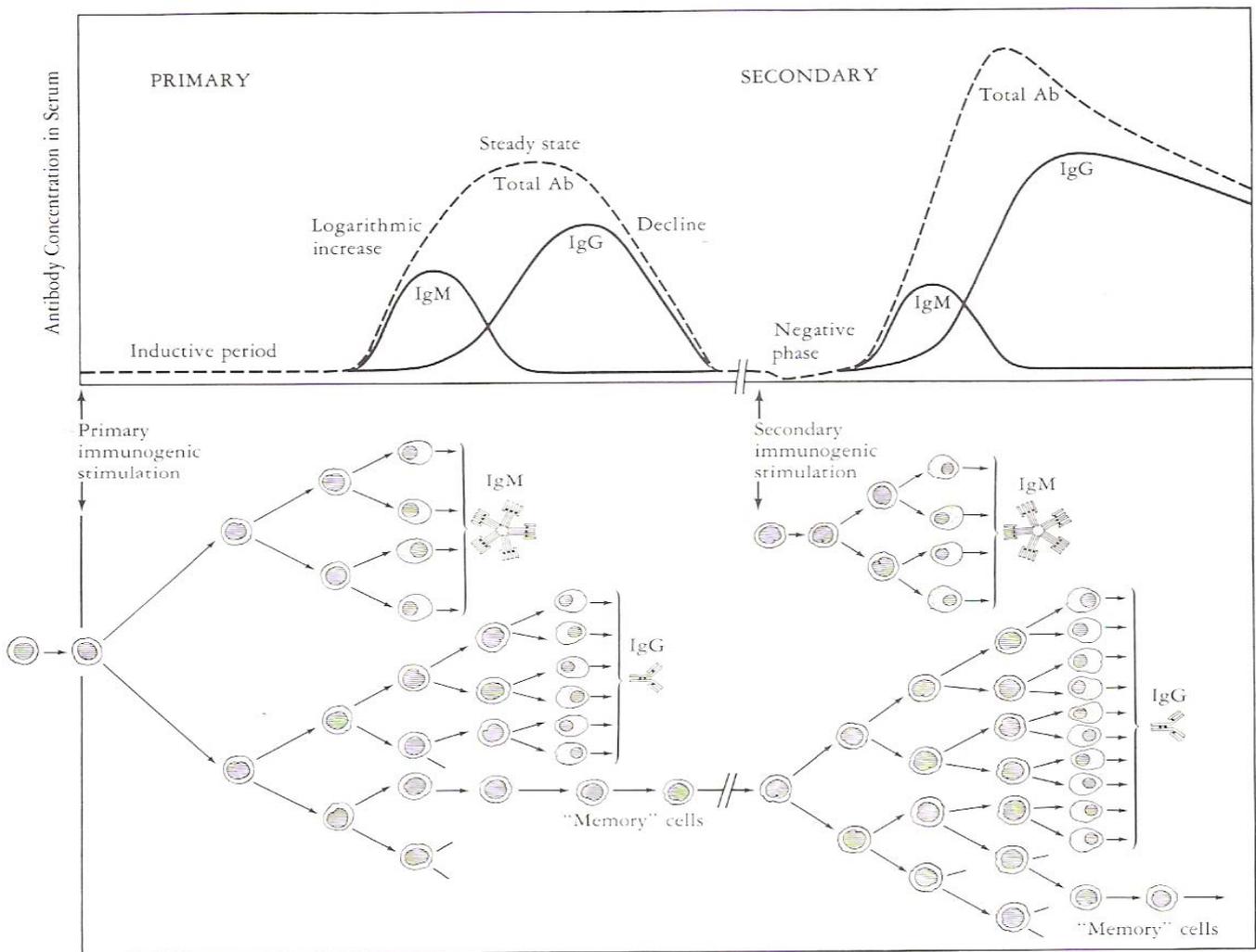
#### 1. Characteristics

- The **primary immune response** occurs following the **first exposure to antigen** and produces a relatively **small amount of antibody**.
- If a sufficient length of time elapses after the primary antigenic stimulation, the antibody level will decrease markedly.
- However, subsequent exposure to even a small amount of antigen will evoke an **anamnestic response** (also called **booster response, memory response, or secondary immune response**).

- The anamnestic response consists of a **rapid proliferation of plasma cells**, with the concomitant production of **large amounts of specific antibody**.
- The anamnestic response occurs because a large population of **memory B and T cells** are recruited into the humoral immune response.

(a) These memory cells are produced during the initial exposure to the antigen.

(b) The memory cells are precursors of the Th cells and plasma cells, and represent another product of the collaboration between T cells and B cells (**Figure 1-16**).



**Figure 1-16.** Schematic representation exhibiting human cellular events in the primary and secondary (anamnestic) antibody responses.

## 2. Immunoglobulin class switching

### a. The IgM-IgG switch

- (1) In the **primary immune response**, the immunoglobulin produced is mainly **IgM**. **Subsequent exposures** to antigen will cause the response to **shift to IgG** production.
- (2) This change occurs within individual plasma cells; it is not the result of recruitment of new IgG-producing cell to replace effete IgM-producing plasma cells.
- (3) The individual plasma cell splices out the  $\mu$  constant region gene complex and replaces it with a  $\gamma 3$ ,  $\gamma 1$ , or another constant region gene.
- (4) The entire light (L) chain gene complex and the variable, diversity, and joining segments of the heavy (H) chain remain intact. Thus, the antigenic specificity of the plasma cell and its immunoglobulins is not changed.

**b. Class switching to IgA, IgD, or IgE** takes place by similar splicing processes.

## B. Ontogeny of the immune response

1. **IgG** is the major fetal antibody, and it is **acquired from the mother** through the placenta.
  - a. Transplacental passage of IgG occurs almost exclusively during the last 4 to 6 weeks of gestation.
  - b. Serum antibody levels in the newborn are directly related to gestational age.
    - (1) Term newborns have adult levels of IgG.
    - (2) Infants of less than 32 week's gestational age have extremely low levels of immunoglobulins and have heightened susceptibility to infections of all types.
2. **IgM** synthesis begins prior to birth and IgM is the major antibody **produced by a fetus**. If IgM levels are elevated at birth, the infant may have an infection.
3. The **secretory IgA** in maternal **colostrum** provides local immunity for the infant's upper respiratory and intestinal tracts.
4. During the **null period**, several months after birth, the maternal IgG is being rapidly degraded and the infant has not yet begun to synthesize large quantities of IgG. This is the most dangerous time for an infant.
5. The development of **full immunocompetence** takes several years in human and occurs in an ordered sequence that in many ways parallels the phylogenetic development of immune responses. Adult levels of antibodies are not reached until the teenage years.

### Natural or artificial immunological processes can cause the specific immunity

Specific immunity may be acquired by natural or artificial processes (**Table 1-1**). **Naturally acquired immunity** includes the immunity that develops during convalescence from an infection (**actively acquired**) and the placental passage of antibody from mother to fetus (**passive acquired**).

**Artificially acquired immunity** includes vaccination (**actively acquired**) and administration of antitoxin [injection of gamma globulin (IgG immunoglobulin)] for the induction of an immune state (**passively acquired**).

Types of Resistance	Examples
<b>Specific</b>	
Naturally acquired	Placental transfer of antibody (passive) Recovery from disease (active)
Artificially acquired	Administration of antitoxin (passive) Vaccination (active)

**Table 1-1** Specific (acquired) resistance mechanisms.

## Clonal Selection Theory

The theory proposed that:

1. Antibodies and lymphocytes of myriad specificities exist before there is any contact with the foreign antigen.
2. The lymphocytes participating in the immune response have **antigen-specific** receptors on their surface membranes. In the case of B lymphocytes, the receptors are molecules bearing the same specificity as the antibody which the cell will subsequently produce and secrete.
3. Each lymphocyte carries on its surface receptor molecules of only a single specificity.

These three postulates describe the existence of a large **repertoire** of possible specificities formed by cellular multiplication and differentiation before there is any contact with the foreign substance to which the response is to be made.

The introduction of the foreign then selects from among all the available specificities those that are adapted to respond (e.g., those with specificity for the antigen enabling binding to occur (**Figure 1-17**).

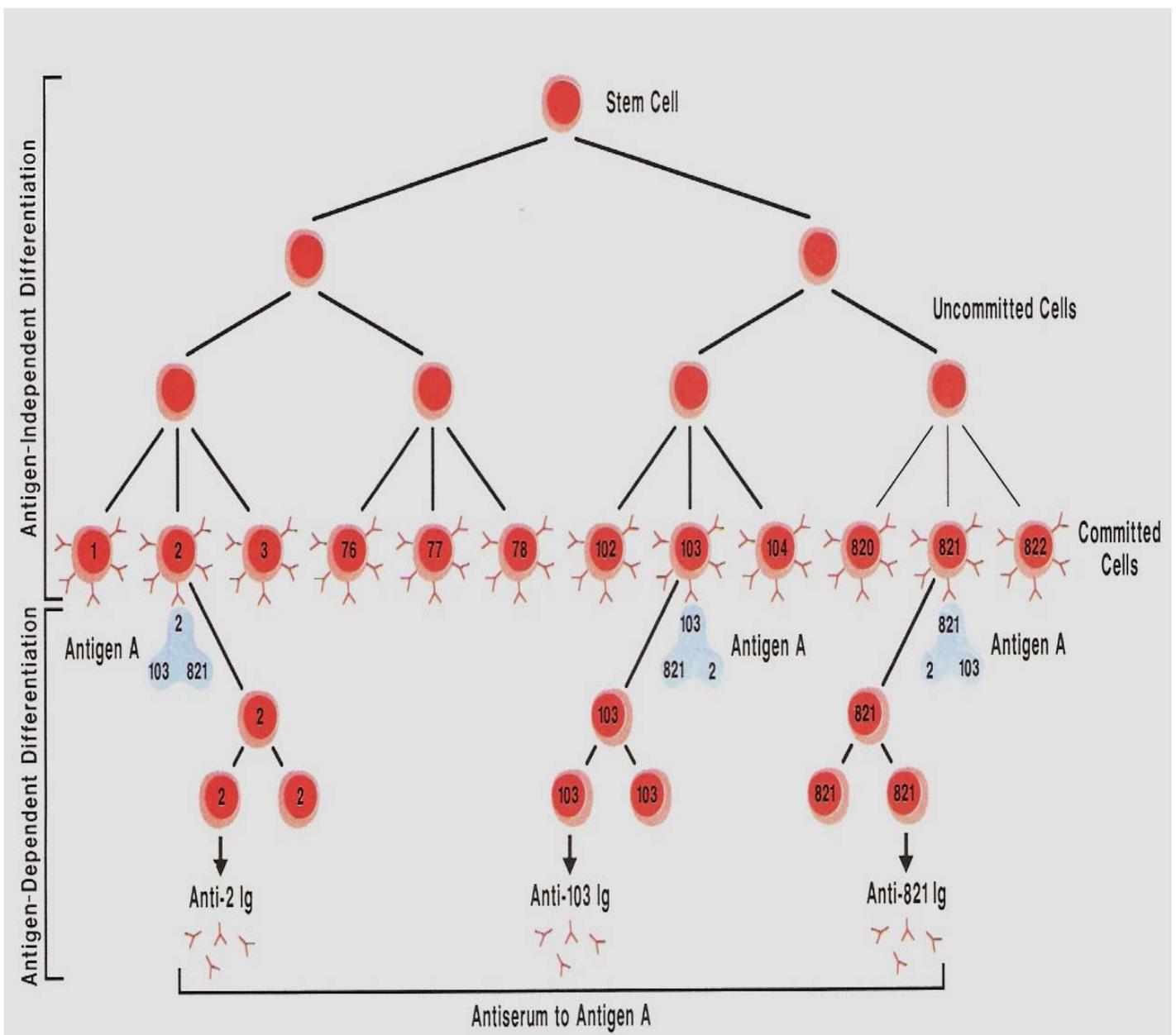
The remaining postulates of the clonal selection theory account for this process of selection by the antigen from among all the available cells in the repertoire.

4. Immunocompetent lymphocytes, combining with the foreign antigen by virtue of their surface receptors, are stimulated under appropriate conditions to proliferate and differentiate into clones of cells making antibody (immunoglobulins or Ig) of that particular specificity. It should be noted that if several distinct regions of an antigen can be recognized, several different clones of cells will be stimulated to produce antibody, the sum total of which would represent an antiserum specific for that antigen but made up of antibodies of differing specificity(**Figure 1-2**).

A final postulate was added to account for the ability to **recognize "self"** antigens without making a response:

5. Circulating "self" antigens that reach the developing lymphoid system prior to some undesignated maturational step will serve to shut off those cells that recognize it specifically and no subsequent immune response will be induced.

The above example of clonal selection pertains to antigen specific B lymphocytes which synthesize antibodies. The same mechanism operates in the selection of antigen specific T lymphocytes which do not make antibodies but which play a major role in antigen specific immune response. This formulation of immune response had a truly revolutionary effect on the field and changed forever our way of looking at and studying immunology.



**Figure 1-17** Representation of the clonal selection theory

**Acquired immunity is not always protective, but some times offensive**

**Examples:**

1. Hypersensitivity reactions.
2. Autoimmunity reactions.
3. Immunodeficiency diseases.
4. Transplantation rejections.

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