LECT.9
HUMORAL IMMUNE RESPONSE

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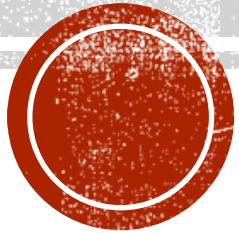


LEARNING OBJECTIVES

Humoral immune response
Primary humoral immune response
Secondary humoral immune response

adaptive immunity: the components of the immune system that adapt themselves to each new disease encountered and are able to generate pathogen-specific immunity

Humoral immunity is also called antibody-mediated immunity. With assistance from helper T cells, B cells will differentiate into plasma B cells that can produce antibodies against a specific antigen.

- ❑ The humoral immune system deals with antigens from pathogens that are freely circulating, or outside the infected cells.
- ❑ Antibodies produced by the B cells will bind to antigens, neutralizing them, or causing lysis (dissolution or destruction of cells by a lysin) or phagocytosi

Cellular immunity occurs inside infected cells and is mediated by T lymphocytes.

- ❑ The pathogen's antigens are expressed on the cell surface or on an antigen-presenting cell.
- ❑ Helper T cells release cytokines that help activated T cells bind to the infected cells' MHC-antigen complex and differentiate the T cell into a cytotoxic T cell. The infected cell then undergoes lysis

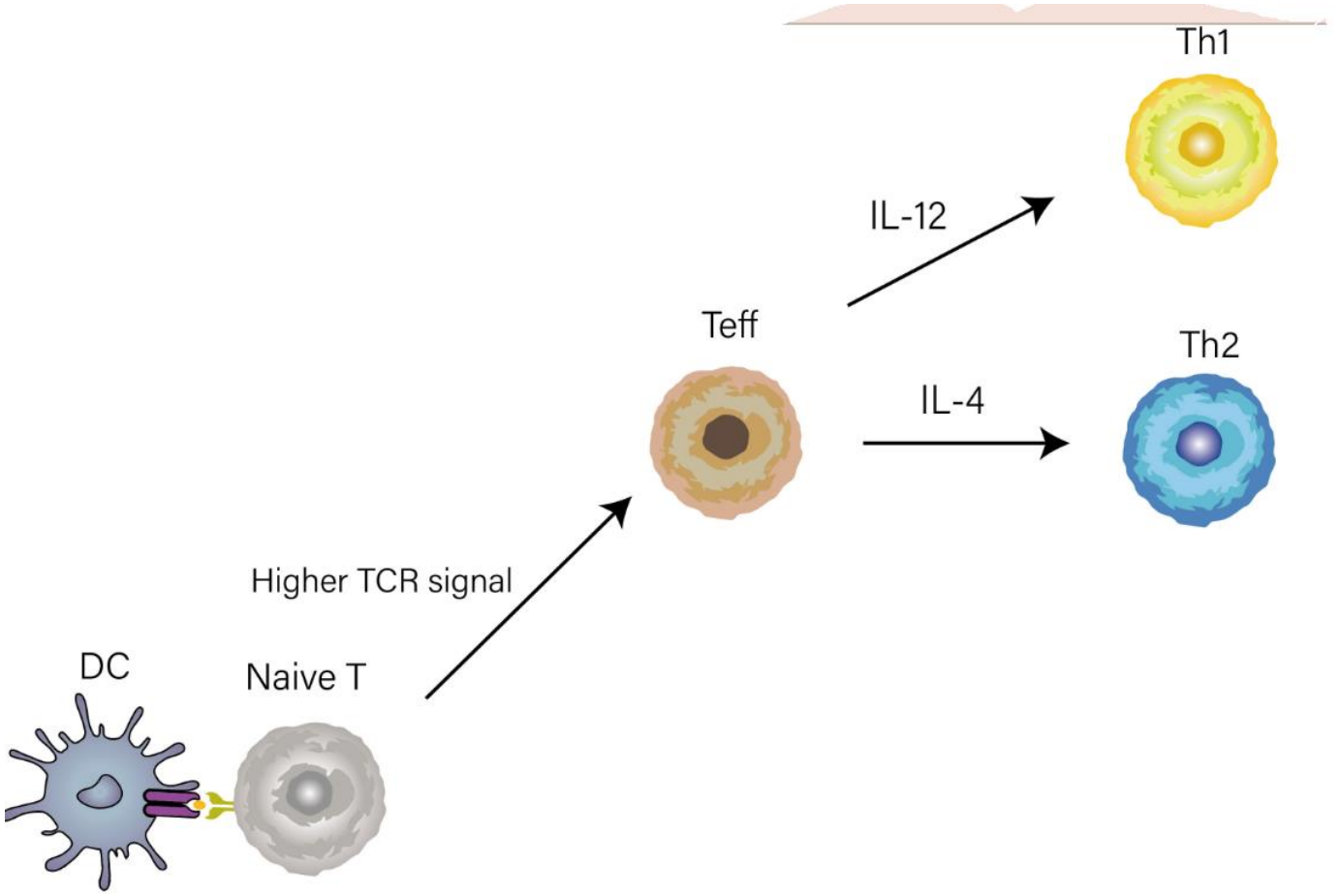
- The factors that determine whether a proliferating CD4 T cell will differentiate into a TH1 or a TH2 cell are not fully understood.

- The cytokines elicited by infectious agents (principally IFN-, IL-12, and IL-4), the co-stimulators used to drive the response, and the nature of the peptide:MHC ligand all have an effect.
- IL-4, in conjunction with antigenic and costimulatory signals, causes naïve T cells to differentiate into Th2 effector cells, whereas IL-12 drives naïve T cells to differentiate into Th1 cells

- TH1 cells leads to cell mediated immunity, whereas the production of predominantly TH2 cells provides humoral immunity.

- Th2 cells play an important role in providing protection against certain extracellular pathogens, such as bacteria and a variety of parasites, and are also involved in asthmatic reactions.

- Effector Th2 cells, produce a different profile of cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, and so on) that together instruct B cells to proliferate and differentiate into antibody-secreting plasma cells


Th1
IL-12
Teff
Th2
IL-4
Higher TCR signal
DC
Naive T

Primary humoral immune response

In a primary immune response, naive B cells are stimulated by antigen, become activated, and differentiate into antibody-secreting cells that produce antibodies specific for the eliciting antigen.

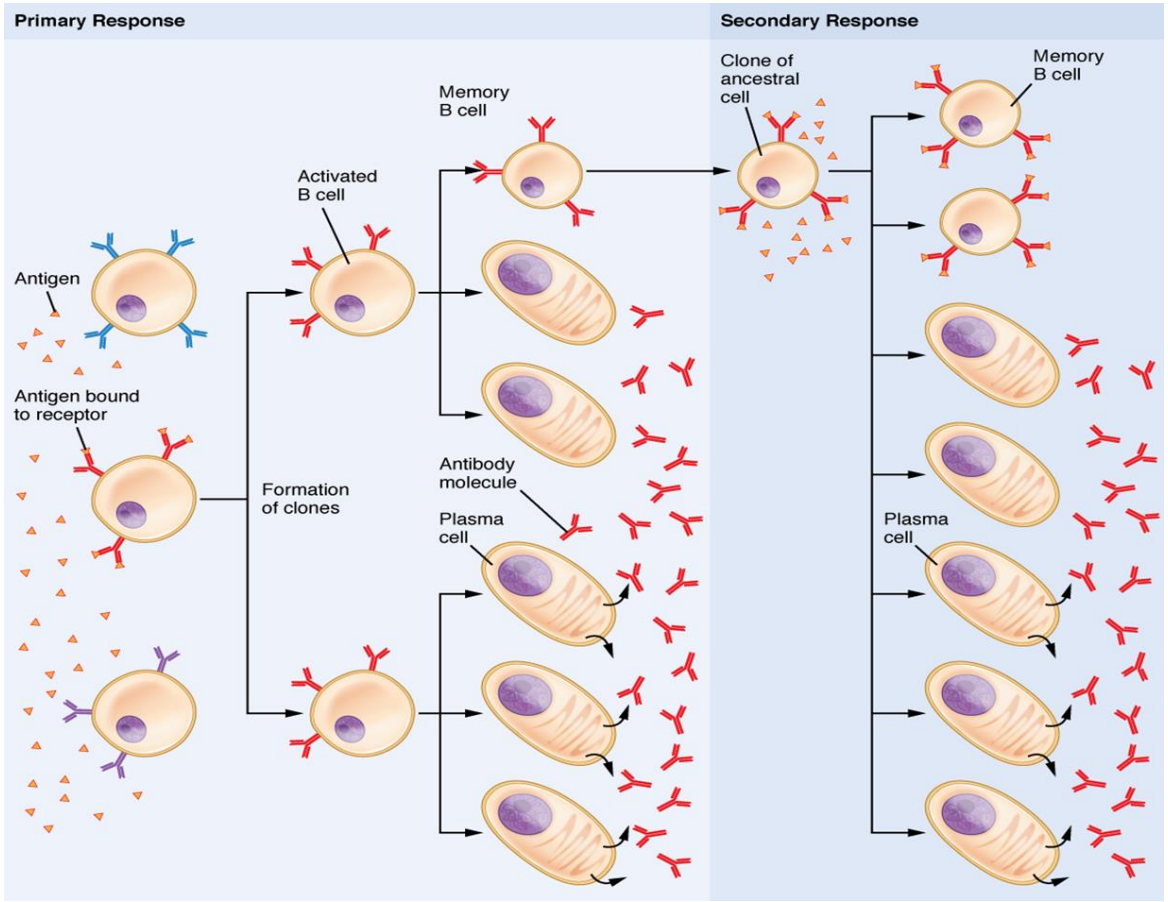
Some of the antibody-secreting plasma cells migrate to and survive in the bone marrow, where they continue to produce antibodies for long periods. Long-lived memory B cells are also generated during the primary response.

Secondary humoral immune responses.

A secondary immune response is elicited when the same antigen stimulates these memory B cells, leading to more rapid proliferation and differentiation and production of greater quantities of specific antibody than are produced in the primary response. These features are typical of T cell–dependent antibody responses to protein antigens.

Clonal Selection of B Cells

Clonal selection and expansion work much the same way in B cells as in T cells. Only B cells with appropriate antigen specificity are selected for and expanded. And then , the plasma cells secrete antibodies with antigenic specificity identical to those that were on the surfaces of the selected B cells and both plasma cells and memory B cells are generated simultaneously.



Immunogen

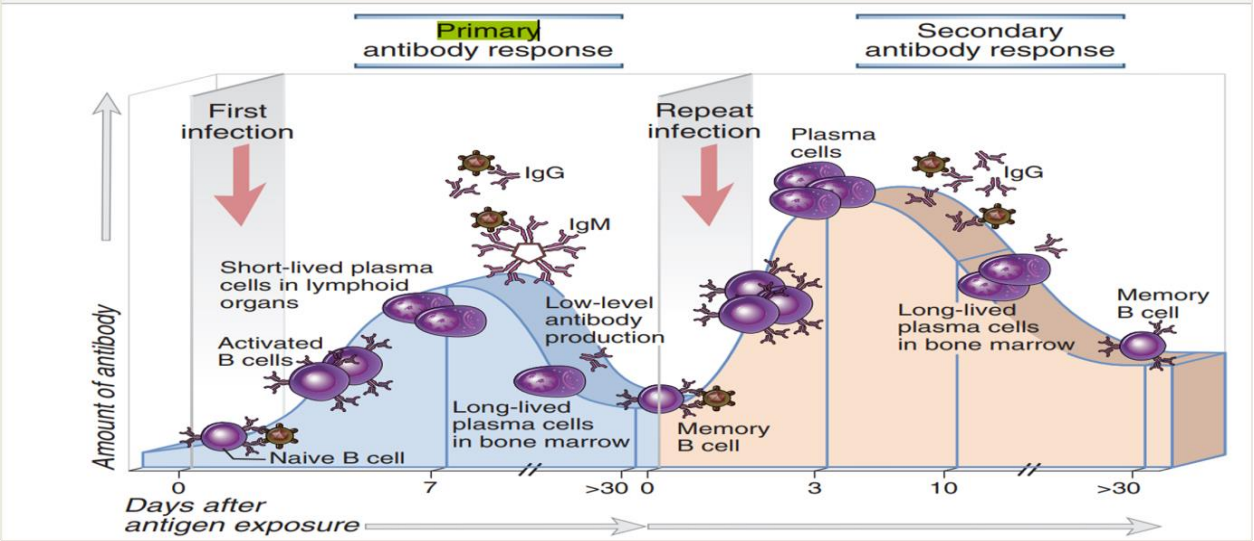
What is an immunogen? An immunogen is a specific type of antigen that is able to elicit an immune response. Antibody development is dependent on a humoral immune response mediated by immune cells recognizing a molecule as being foreign. overall size of antigens that are under 20 kDa (~200 amino acids) will not be immunogenic.

the concentration of the antigen if The the antigen is lower in the immunogenicity, the more concentrated the inoculation volume needs to be.

IgG and IgM antibodies

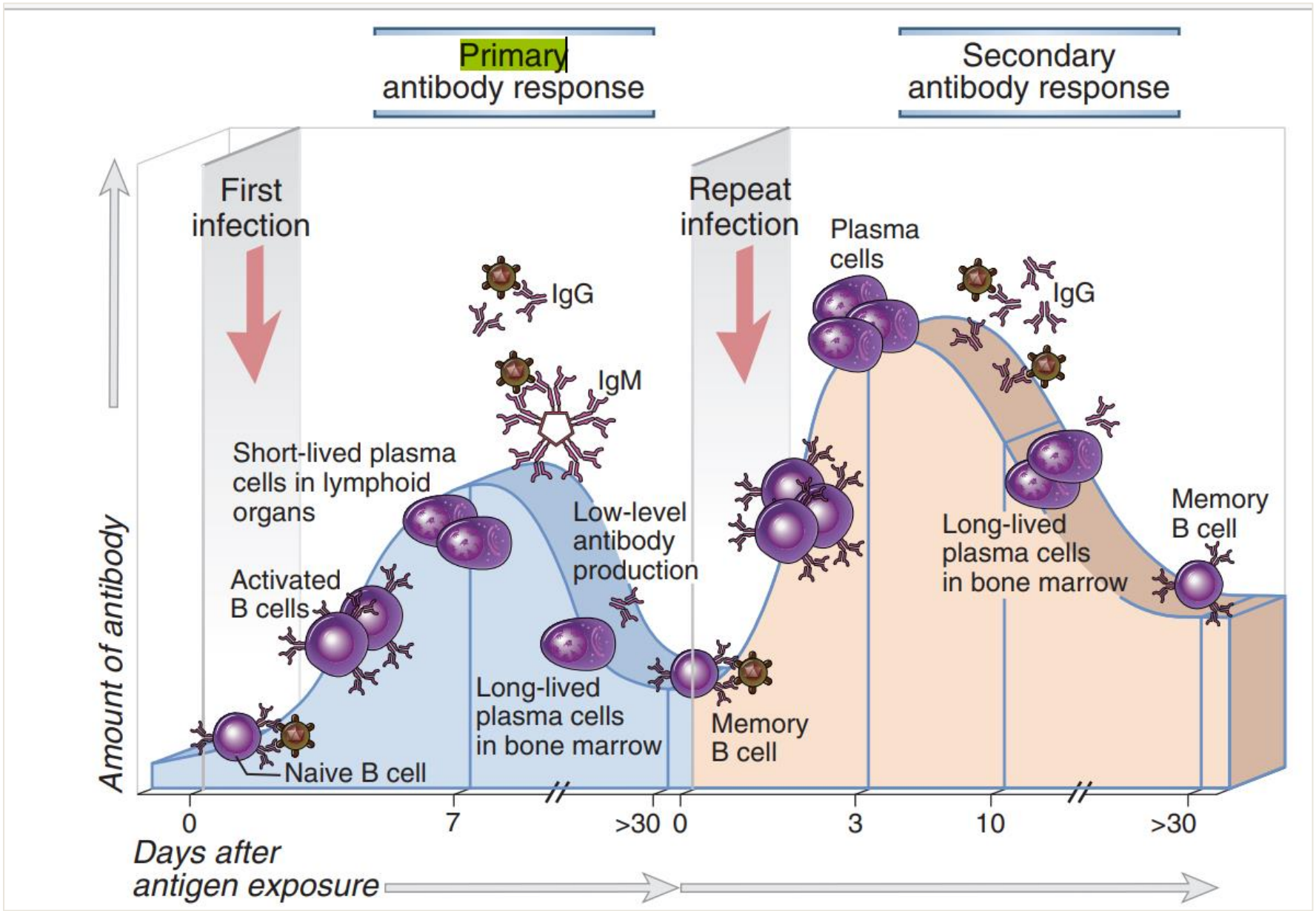
- The primary immune response is characterized by the appearance of neutralizing antibodies of the IgM class between days 4 and 7, several days before detection of IgG antibodies.

- Titers of IgM neutralizing antibodies were 16- to 256-fold higher than IgG antibodies during the first 4–6 weeks after immunization and IgM antibodies were found to persist for at least 18 months (the longest time examined).
- Primary responses result from the activation of previously unstimulated naive B cells, whereas secondary responses are due to the stimulation of expanded clones of memory B cells.
- Therefore, the secondary response develops more rapidly than does the primary response, and larger amounts of antibodies are produced in the secondary response.
- Heavy chain isotype switching and affinity maturation also increase with repeated exposure to protein antigens.



Primary and secondary humoral immune responses

Feature	Primary response	Secondary response
Peak response	Smaller	Larger
Antibody isotype	Usually IgM > IgG	Relative increase in IgG and, under certain situations, in IgA or IgE
Antibody affinity	Lower average affinity, more variable	Higher average affinity (affinity maturation)
Induced by	All immunogens	Only protein antigens


Primary antibody response
Secondary antibody response
First infection
Repeat infection
Plasma cells
IgG
IgG
IgM
Short-lived plasma cells in lymphoid organs
Low-level antibody production
Activated B cells
Long-lived plasma cells in bone marrow
Memory B cell
Long-lived plasma cells in bone marrow
Memory B cell
Naive B cell
Amount of antibody
0
7
>30
0
3
10
>30
Days after antigen exposure

Why IgM > IgG In Primary Response

- Monomeric IgM (mIgM) is always the first Ig produced by naïve B cells that encounter antigen:

Early in a primary response, plasma cell progeny of an activated B cell secrete pentameric IgM (sIgM) absolutely. Because all other antibody isotypes (except IgD) are generated by isotype switching that originates only late in a primary response or not until the secondary response, it is sIgM antibodies that are expressed first in any primary immune response, and those that are synthesized first in a newborn mammal.

- In an adult human, sIgM antibodies normally comprise only about 5–10% of normal total serum Igs. The detection of increased sIgM levels in an adult indicates exposure to either a novel antigen or a Ti antigen(T-Independent Antibody) that can activate a B cell to secrete sIgM but does not induce isotype switching.

- Because of its pentameric nature, the IgM antibody displays 10 Fab sites that can theoretically bind to a pathogen. In practice, however, steric hindrance(الاعاقة الفراغية)usually prevents the IgM molecule from binding to more than **five antigenic epitopes at once.** Nevertheless, this number is sufficient for the IgM antibody to bind with high avidity to a large antigen or pathogen displaying multiple copies of the same antigenic determinant.
- IgM is thus able to reduce the infectivity of the pathogen and increase its clearance much more efficiently (using fewer molecules) than a monomeric Ig molecule can. In addition, because the individual binding sites of an IgM molecule are of relatively low affinity, they exhibit correspondingly higher levels of cross-reactivity to related epitopes. This property allows the host to "cast a broad net," maximizing the number of antigens recognized by each IgM-secreting B cell clone.

IgM activate the complement system

- The first antibodies to be produced in a humoral immune response are always IgM, because IgM can be expressed without isotype switching . These early IgM antibodies are produced before B cells have undergone somatic hypermutation and therefore tend to be of low affinity.

- IgM molecules, however, form pentamers whose 10 antigen-binding sites can bind simultaneously to multivalent antigens such as bacterial capsular polysaccharides. This compensates for the relatively low affinity of the IgM monomers by multipoint binding that confers high overall avidity. As a result of the large size of the pentamers, IgM is mainly found in the blood and, to a lesser extent, the lymph. The pentameric structure of IgM makes it especially effective in activating the complement system.

- Infection of the bloodstream has serious consequences unless it is controlled quickly, and the rapid production of IgM and its efficient activation of the complement system are important in controlling such infections.
- Some IgM is also produced in secondary and subsequent responses, and after somatic hypermutation, although other isotypes dominate the later phases of the antibody response.

What is affinity?

Affinity is the strength of a single bond or interaction. When it comes to the antibody-antigen relationship, the binding affinity is the strength of the interaction between the antigen's epitope and the antibody's paratope at a singular binding site.

When an antigen is encountered for the first time, the affinity of the antibodies produced is low. Once the body is familiar with the antigen

The non-covalent interactions that participate in the affinity of a binding site include:

- ❑ Hydrogen bonds
- ❑ Electrostatic bonds
- ❑ Van der Waals forces
- ❑ Hydrophobic forces

What is avidity?

Antibodies and antigens are multivalent, meaning they possess more than one binding site. The measure of the total binding strength of an antibody at every binding site is termed avidity. Avidity is also known as the functional affinity.

Avidity is determined by three factors.

- ❑ The binding affinity: The strength of the relationship at a singular binding site.
- ❑ The valency: The total number of binding sites involved.
- ❑ The structural arrangement: The structure of the antigen and antibody involved.

Antibody affinity is defined as strength of the binding interaction between antigen and antibody. It depends on the closeness of the stereochemical fit between antibody sites and antigen determinants, the size of the area of contact between them, and the distribution of charged and hydrophobic groups.

The activation of memory B cells

The activation of memory B cells by antigen occurs in much the same way as in the primary response but is more efficient for several reasons.

- **Firstly, because of their expanded battery of adhesion molecules, memory B cells in the periphery can home to the primary follicles of a lymph node more rapidly than naïve B cells can migrate from the bone marrow.**
- **Secondly, due to affinity maturation, the BCR of a memory B cell has an increased affinity for antigen so that the cell is stimulated more easily and efficiently.**
- **Thirdly, memory B cells are both present in increased numbers and can act as APCs for memory Th cells, removing the requirement of having to wait for a DC to activate a naïve Th cell.**

- **Fourthly, antigen presentation by a memory B cell is associated with faster upregulation of the costimulatory molecules needed for complete activation of Th cells.**

- **Fifthly, the progeny of activated memory B cells differentiate into second generation plasma cells that produce antibodies that are already of greater affinity and differentiated isotype.**