Complement system

Complement is a defensive system consisting of serum proteins that participate in **lysis of foreign cells , inflammation ,and phagocytosis.**The system can be activated by an immune reaction by: **classical pathway or by direct interaction with a bacterium in the alternative pathway, or by mannose binding proteins.**Complement is non specific ,since the same proteins can be activated in response to any foreign cells. The complement system consist of a group of least 20 different interacting proteins found in normal serum.Proteins of the complement system make up about 5% of the serum proteins in vertebrates.

The major components of the classical pathway are designated by a complex numbering system ranging from C1 through C9 (C stands for complement).The C1 proteins also has three subcomponents , C1q , C1r , C1s .The alternative pathway consist of proteins called factor B and factor D along with the C3 and C5 through C9 proteins active in the classical pathway .

Pathway of action

The proteins of the classical and alternative pathways act in an ordered sequence , or cascade In a series of steps , each protein activates the next one in the series , usually by cleaving (splitting) it. The fragments of the cleaved proteins have new physiological or enzymatic functions . For example , one fragment might caused blood vessel dilation , whereas another fragment serves as apart of the enzyme that cleaves the next protein in the series.C3 plays a central role in the complement system its activation triggers several mechanisms that contribute to microbial distraction

1.Classical pathway (fig.1).

The classical pathway is initiated by the binding of antibodies to antigens . The antigen could consist of bacteria or other foreign cells . Once a pair of antibodies recognizes and attaches to the antigens , the complement protein C1(which actually consist of three subcomponents) binds to two or more adjacent antibodies , thus activating C1 (Fig.2 a).Next , activated C1 in turn activate C2 and C4 . It does this by functioning as a proteolytic (protein – splitting) enzyme and splitting the C2 and C4 proteins . C2 is split into fragments called C2a and C2b , and C4 into fragment called C4a and C4b (Fig . 2b).The C2b and C4b combine to form another proteolytic enzyme , which in turn activate C3 by splitting it into two fragments , C3a and C3b .

2.Alternative pathway (Fig.1).

The alternative pathway does not involve antibodies ; it is initiated by the interaction between certain polysaccharide and the proteins of the pathway .Factors B and D react with C3 to produce low levels of C3b in the serum .The alternative pathway indicated in Fig. 1 does not involve antibodies ; it is initiated when C3b , factor B , factor D combine with certain polysaccharide .Most of these polysaccharide are contained in the cell walls of certain bacteria and fungi , although they also include molecules on the surface of some foreign mammalian red blood cells .The alternative pathway is of particular importance in combating enteric Gram negative bacteria .The outer membrane of the bacteria's cell wall contains a lipopolysaccharide that is an endotoxin (lipid A),a triggering the alternative pathway . This pathway does not involve C1 , C2 or C4 .

Complement system

3. Mannose-binding proteins(The lectin pathway)

The lectin pathway is the most recently discovered mechanism for complement activation. When macrophages ingest bacteria, viruses, and other foreign matter by phagocytosis, they release cytokines that stimulate the liver to produce lectins, proteins that bind to carbohydrates .

Consequence of complement activation

Both the classical and alternative pathways lead to the cleavage of C3 into two fragments , C3a and C3b . These fragments induce three processes that are destructive to microorganisms –cytolysis , inflammation , and opsonization.

1.Cytolysis (Fig.2e).

The main function of the complement system is to destroy foreign cells by damaging their plasma membranes , causing the cellular contents to leak out (Fig . 2 c). C3b initiates a sequence of reactions involving C5 , C6 , C7 ,C8 , and C9 , which are known collectively as the membrane attack complexes (C5-C9) . The activated complements of these proteins , with C9 proteins possibly playing a key role , attack the invading cell's membrane and produce circular lesions , called transmembrane channels (Fig.2d), that lead to loss of ions and eventual cytolysis . The utilization of the complement components in this process is called complement fixation ; it forms the basis of an important clinical laboratory test (Fig.2e).

2. Inflammation

C3a, a cleavage product from C3,and C5a,a cleavage product from C5, contribute to the development of acute inflammation(fig.3a)C3a and C5a bind to mast cells, basophils , and blood platelets to trigger the release of histamine ,which increases blood vessel permeability . C5a also function as a powerful chemotactic factor that attracts phagocytes to the site of complement fixation (Fig.3b).

3. Opsonization

When bond to the surface of a microorganisms , C3b can interact with special receptors on phagocytes to promote phagocytosis (Fig.4).This phenomenon is called opsonization or immune adherence .In the process , C3b function as an opsonin by coating the microorganisms and promoting attachment of the phagocyte to the microbe .

Complement regulation

Once complement is activated , it's distractive capabilities usually cease very quickly in order to minimize distraction of the host cells .This is complished by various regulatory proteins found in the host's blood and on certain cells , such as blood cells . They bring about the breakdown of activated complement and function as inhibitors and destructive enzymes .

Complement deficiency

In addition to it's important in defense , the complement system assumes a role in causing disease as a result of inherited deficiencies . For example , deficiencies of C1, C2 , or C4 cause collagen vascular disorders that result in hypersensitivity (anaphylaxis).Deficiency of C3 , through rare , result in increased susceptibility to bacterial infections ; and C5 through C9 defects result in increased susceptibility to *Neisseria meningitidis* and *N. gonorrhoeae* infections.

Complement system

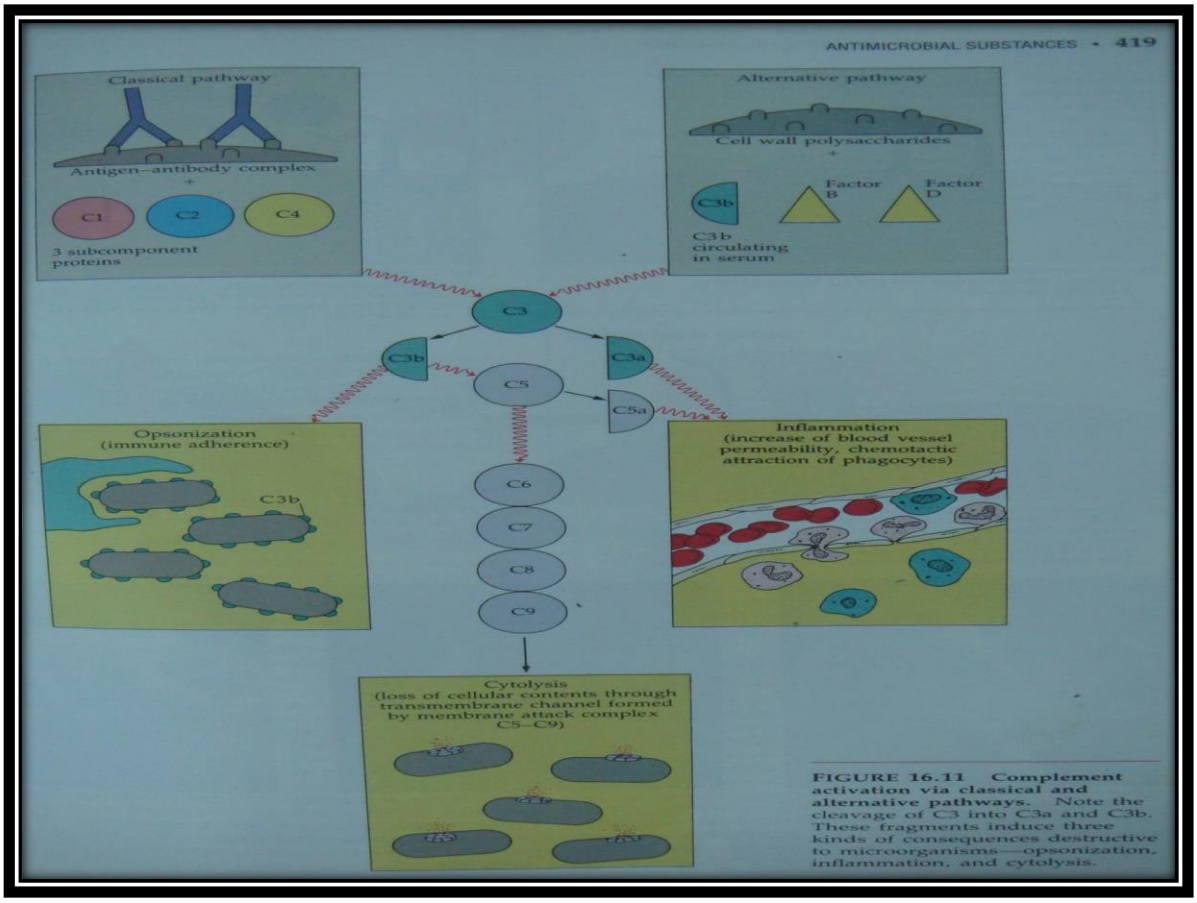


Fig.1 : Complement activation via classical and alternative pathway. Note the cleavage of C3 into C3a and C3b.These fragment include three kinds of consequences destructive to microorganisms-opsonnization,inflammation,and cytolysis.

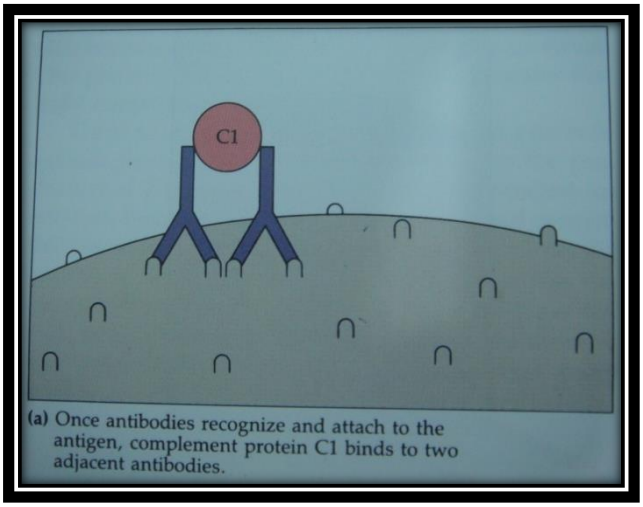


Fig.2a (Tortora *etal*,1992)

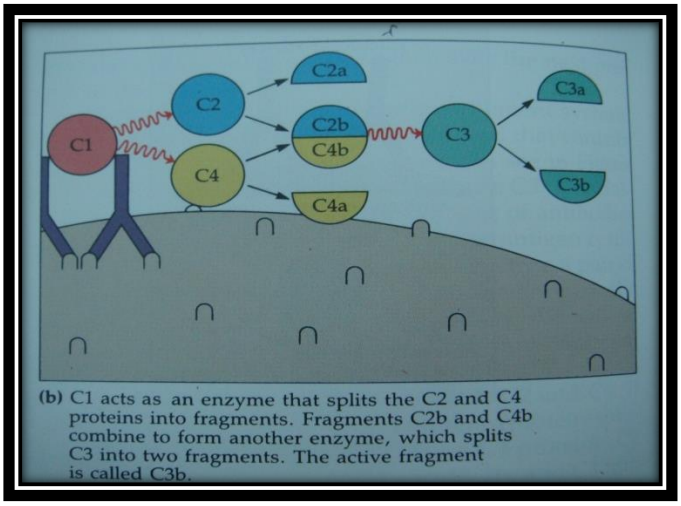
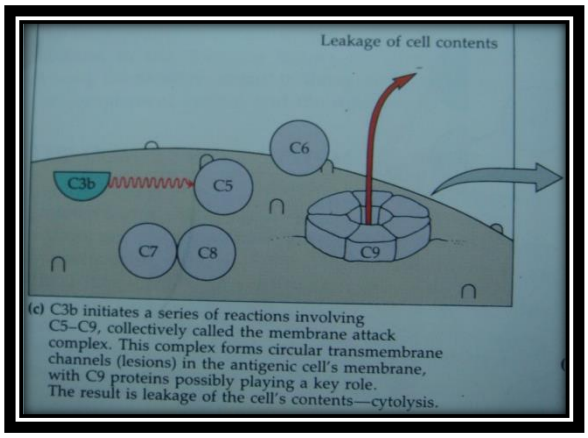


Fig2b (Tortora etal,1992)

Complement system



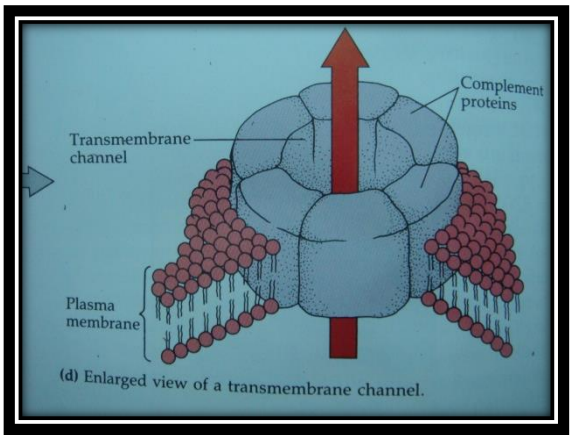


Fig.2c.(T ortora *et al*,1992)

Fig.2d (Tortora *et al*,1992)

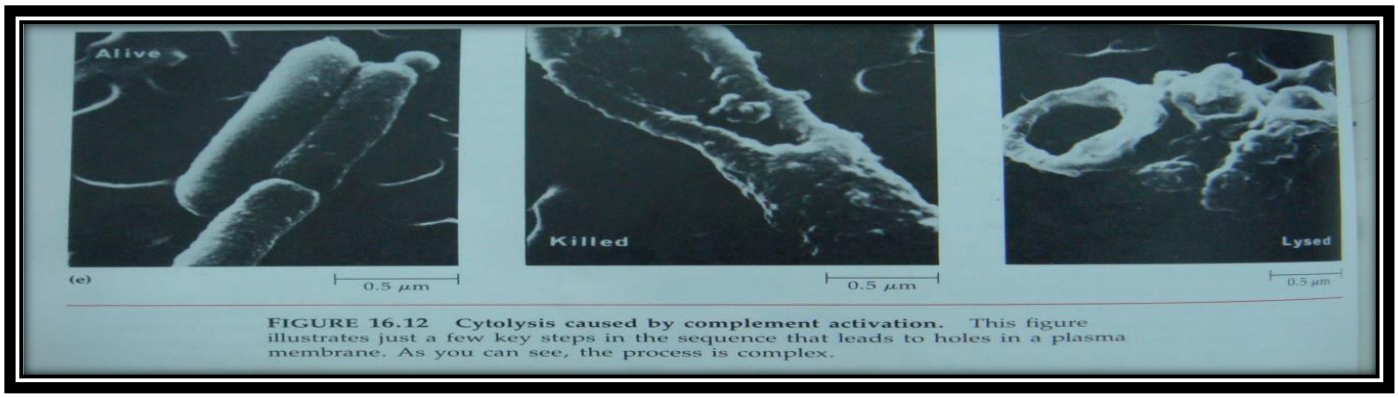
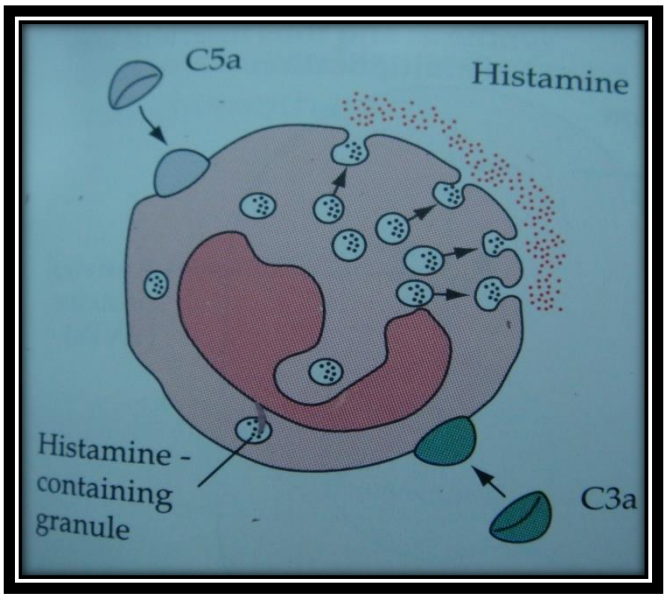


Fig.2e (Tortora *et al*,1992)



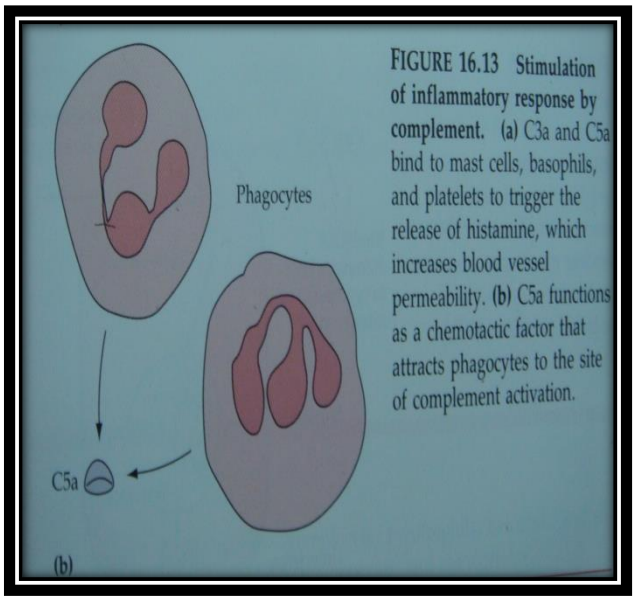


Fig.3a(Tortora *et al*,1992)

Fig.3b(Tortora *et al*,1992)

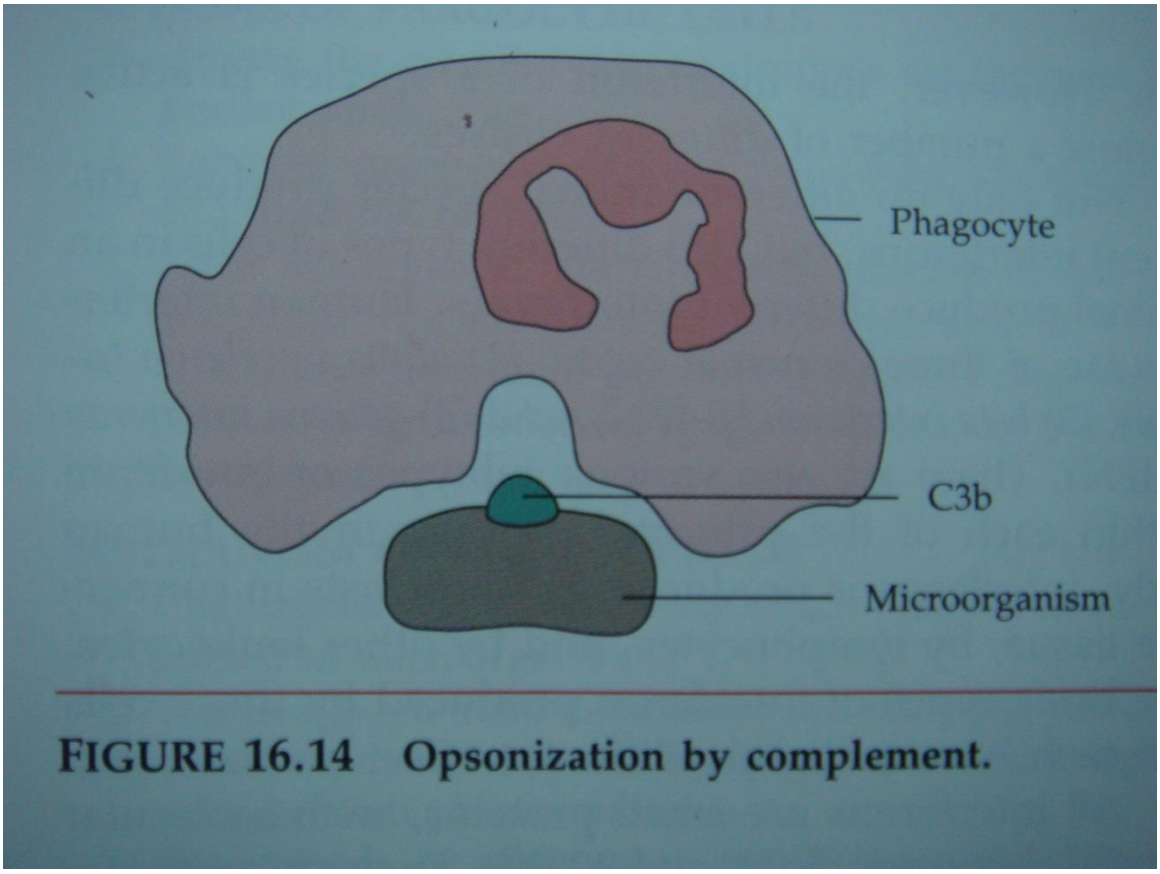


FIGURE 16.14 Opsonization by complement.

Fig.4 (Tortora *et al* ,1992)