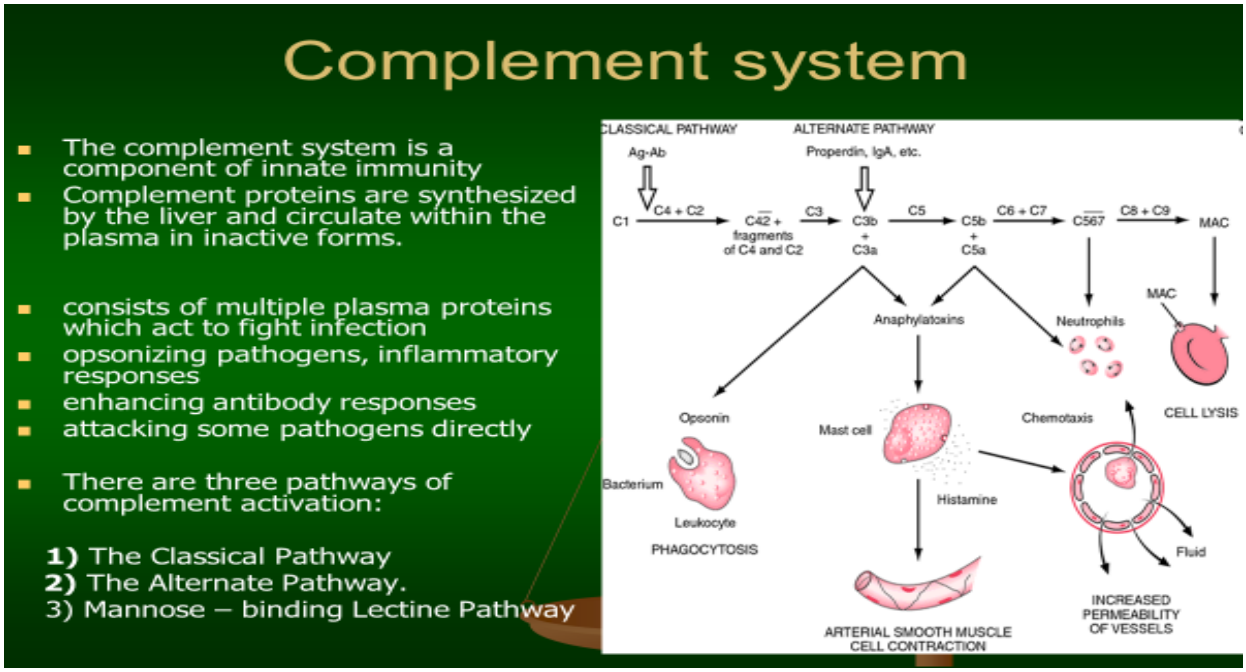
SLIDE 1



The **complement system**, also known as **complement cascade:**

- is a part of the immune system that enhances (complements) the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism,

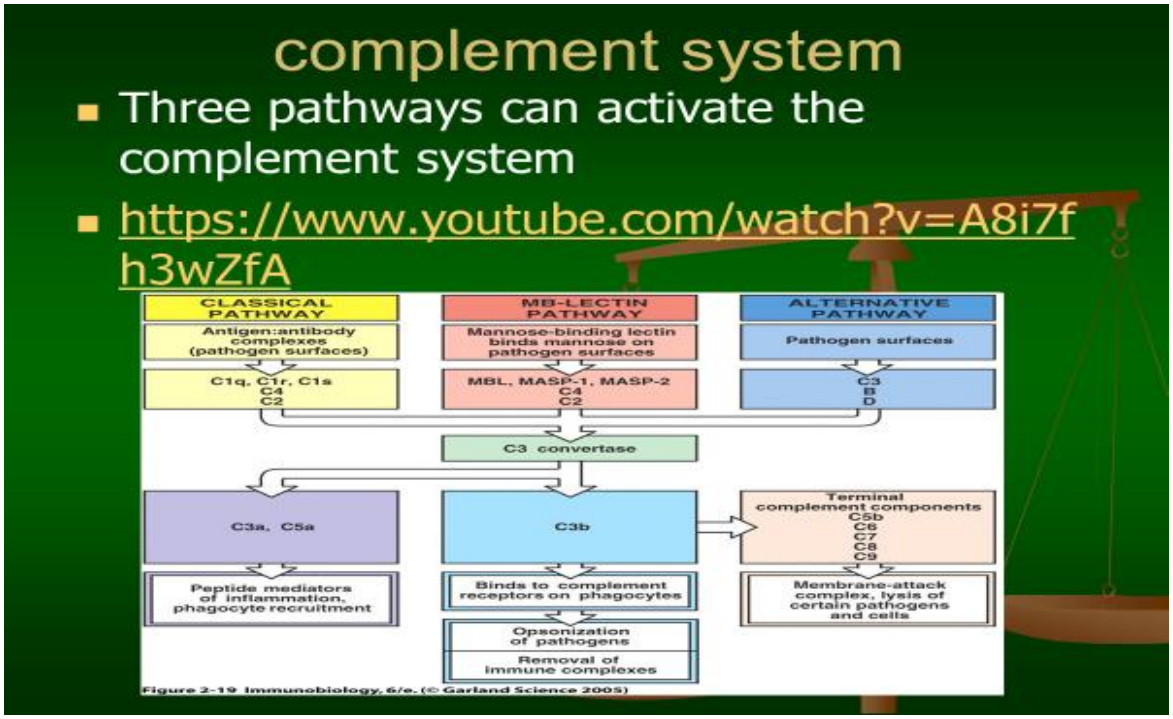
- promote inflammation,

- attack the pathogen's cell membrane.

It is part of the innate immune system. (The complement system can, however, be recruited and brought into action by antibodies generated by the adaptive immune system).

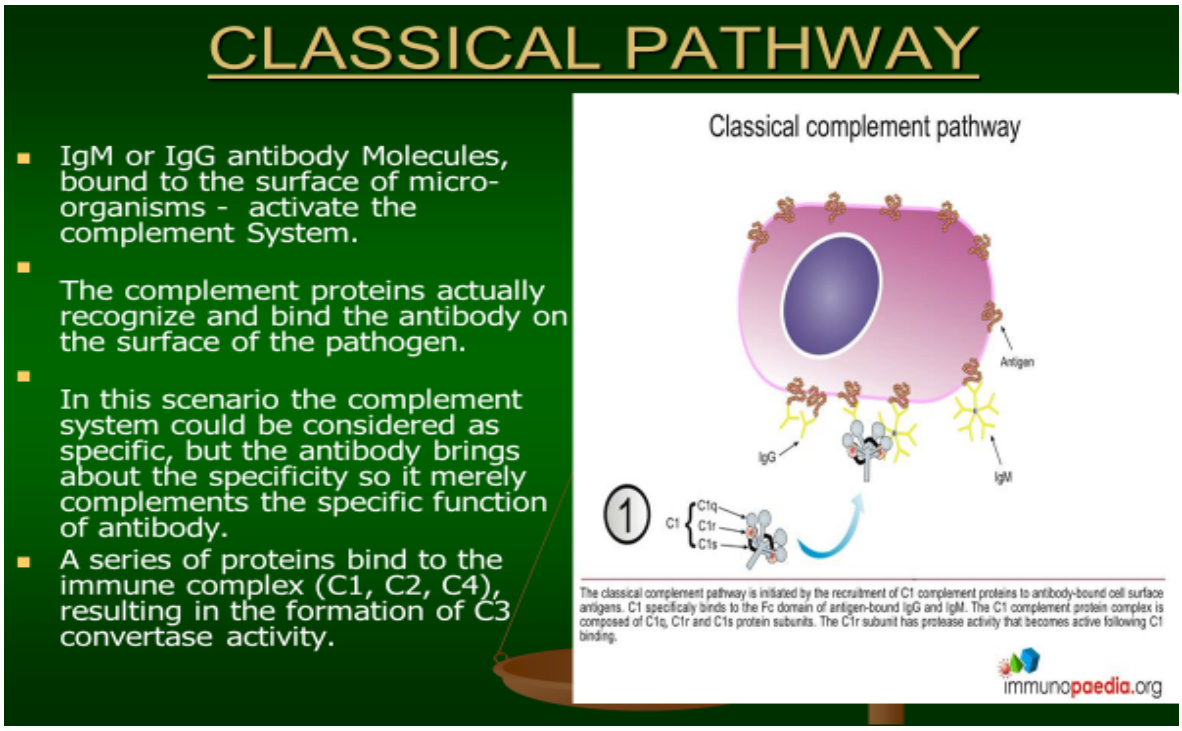
Complement comprises over 20 different serum proteins that are produced by a variety of cells including, hepatocytes, macrophages and gut epithelial cells. Some complement proteins bind to immunoglobulins or to membrane components of cells. Others are proenzymes that, when activated, cleave one or more other complement proteins. Upon cleavage some of the complement proteins yield fragments that activate cells, increase vascular permeability or opsonize bacteria.

SLIDE 2 Activation of complement. See also: https://www.youtube.com/watch?v=2jjyiXq8toc



Complement activation can be divided into three pathways: the classical pathway, the lectin pathway, the alternative pathway. Both classical and alternative pathways lead to the activation of C5 convertase and result in the production of C5b which is essential for the activation of the membrane attack pathway.

SLIDE 3



C1 activation

C1, a multi-subunit protein containing three different proteins (C1q, C1r and C1s), **binds to the Fc region of IgG and IgM antibody molecules that have interacted with antigen.** C1 binding does

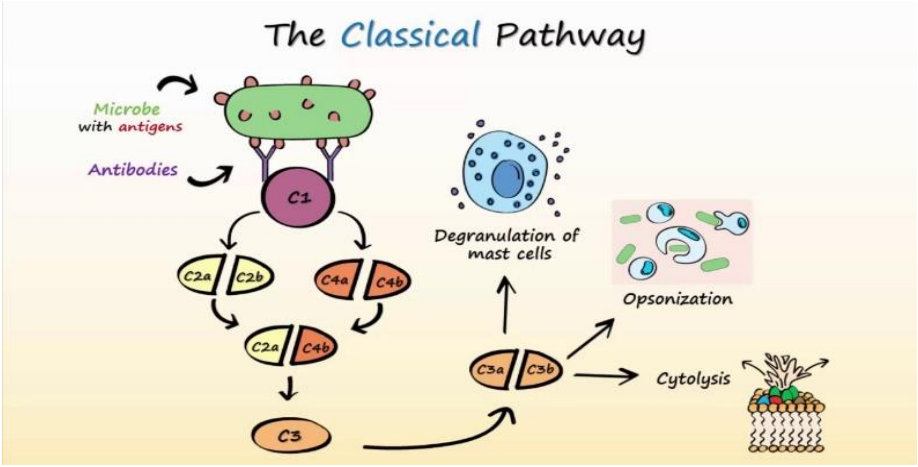
not occur to antibodies that have not complexed with antigen and binding requires calcium and magnesium ions.

C4 and C2 activation (generation of C3 convertase)

The C4b fragment binds to the membrane and the C4a fragment is released into the microenvironment. Activated "C1qrs" also cleaves C2 into C2a and C2b. C2a binds to the membrane in association with C4b, and C2b is released into the microenvironment. **The resulting C4bC2a complex is a C3 convertase, which cleaves C3 into C3a and C3b.**

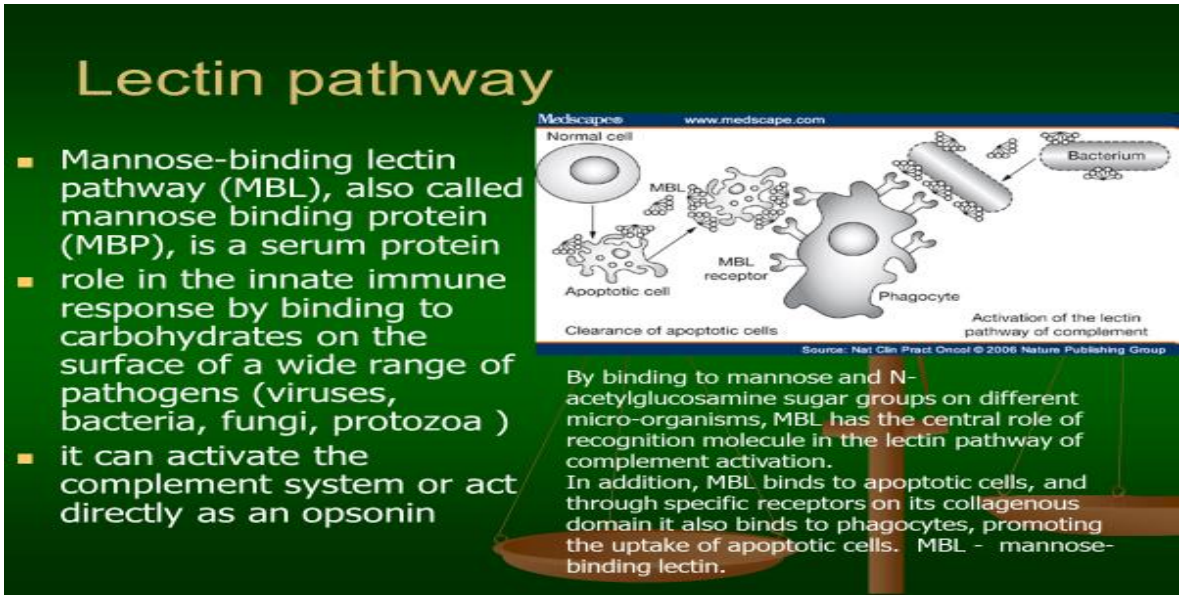
C3 activation (generation of C5 convertase)

C3b binds to the membrane in association with C4b and C2a, and C3a is released into the microenvironment. The resulting C4bC2aC3b is a C5 convertase. **The generation of C5 convertase is the end of the classical pathway.**



https://www.youtube.com/watch?v=2jjyiXq8toc

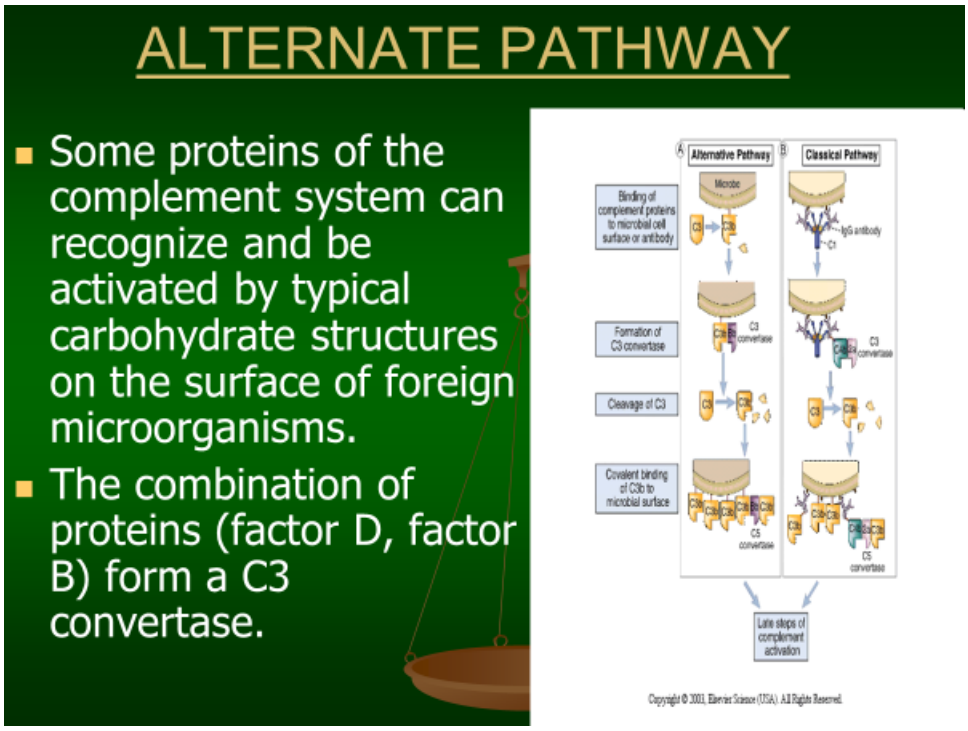
SLIDE 4



The lectin pathway is very similar to the classical pathway. **It is initiated by the binding of mannose-binding lectin (MBL) to bacterial surfaces with mannose-containing polysaccharides (mannans).** Binding of MBL to a pathogen results in the association of two serine proteases, MASP-1 and MASP-2 (MBL-associated serine proteases). MASP-1 and MASP-2 are similar to C1r and C1s, respectively and MBL is similar to C1q.

C4bC2a complex is a C3 convertase, which cleaves C3 into C3a and C3b. C3b binds to the membrane in association with C4b and C2a and C3a is released into the microenvironment. The resulting C4bC2aC3b is a C5 convertase. **The generation of C5 convertase is the end of the lectin pathway.**

SLIDE 5

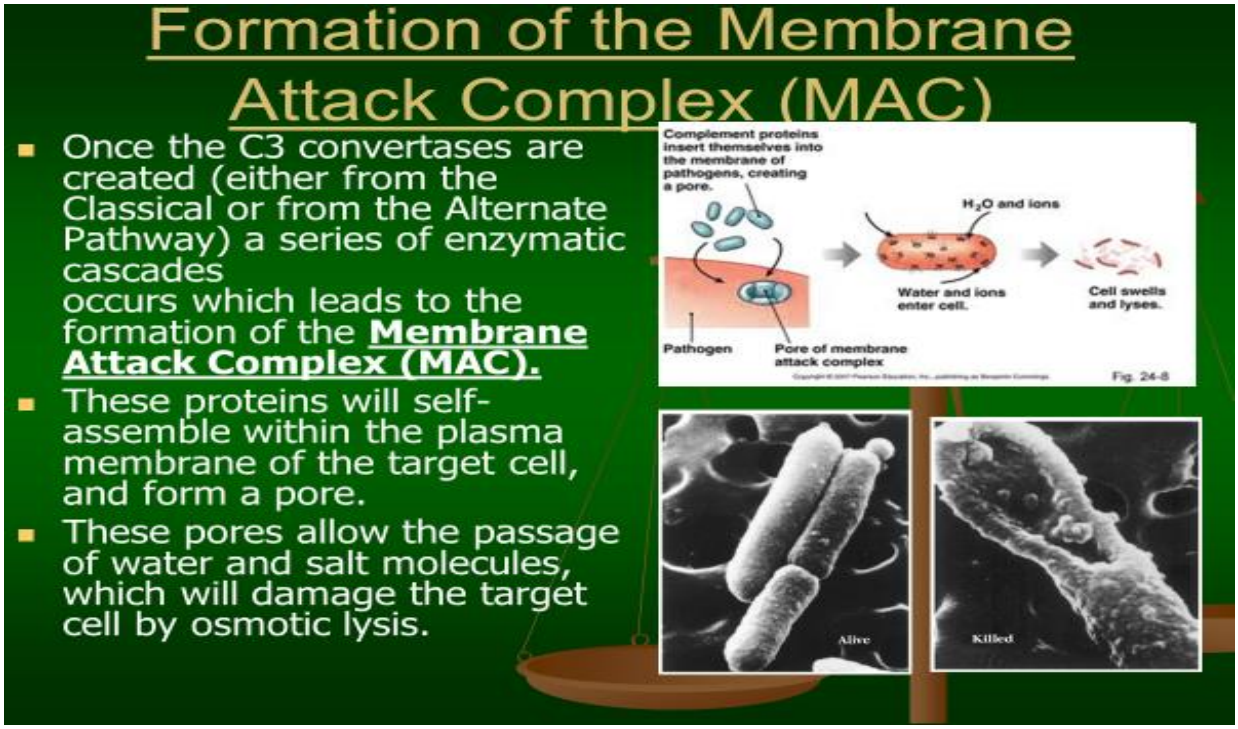


The alternative pathway begins with the activation of C3 and requires Factors B and D and Mg^{++} cation, all present in normal serum. **In serum there is low level spontaneous hydrolysis of C3** to produce C3i. Factor B binds to C3i and becomes susceptible to Factor D, which cleaves Factor B into Bb. The C3iBb complex acts as a C3 convertase and cleaves C3 into C3a and C3b. Once C3b is formed, Factor B will bind to it and becomes susceptible to cleavage by Factor D. The resulting C3bBb complex is a C3 convertase that will continue to generate more C3b, thus amplifying C3b production. If this process continues unchecked, the result would be the consumption of all C3 in the serum. Thus, the spontaneous production of C3b is tightly controlled.

Remember that the alternative pathway provides a means of non-specific resistance against infection without the participation of antibodies and hence provides a first line of defense against a number of infectious agents.

Many gram negative and some gram positive bacteria, certain viruses, parasites, heterologous red cells, aggregated immunoglobulins (particularly, IgA) and some other proteins (e.g. proteases, clotting pathway products) can activate the alternative pathway.

SLIDE 6



C5 convertase from the classical (C4b2a3b), lectin (C4b2a3b) or alternative (C3bBb3b) pathway cleaves C5 into C5a and C5b. C5a remains in the fluid phase and the C5b rapidly associates with C6 and C7 and inserts into the membrane. Subsequently C8 binds, followed by several molecules of C9. The C9 molecules form a pore in the membrane through which the cellular contents leak and lysis occurs. Lysis is not an enzymatic process; it is thought to be due to physical damage to the membrane. **The complex consisting of C5bC6C7C8C9 is referred to as the membrane attack complex (MAC).**

C5a generated in the lytic pathway has several potent biological activities. It is the most potent anaphylotoxin. In addition, it is a chemotactic factor for neutrophils and stimulates the respiratory burst in them and it stimulates inflammatory cytokine production by macrophages.

COMPLEMENT SUMMARY

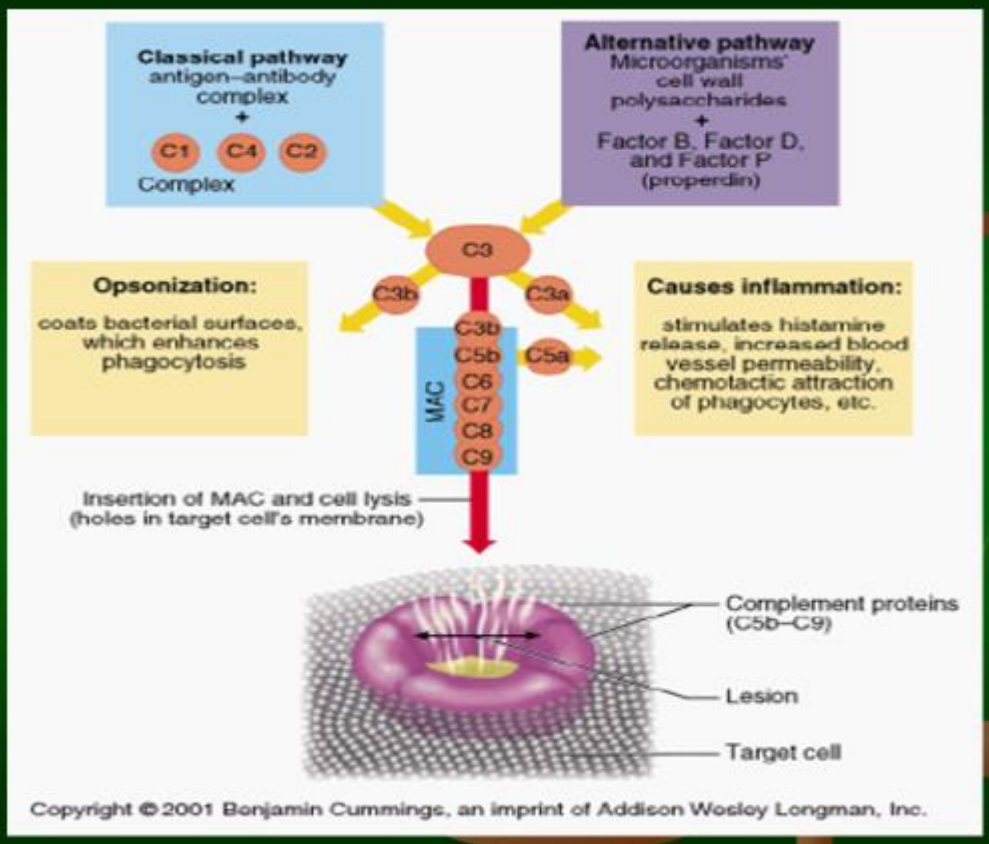
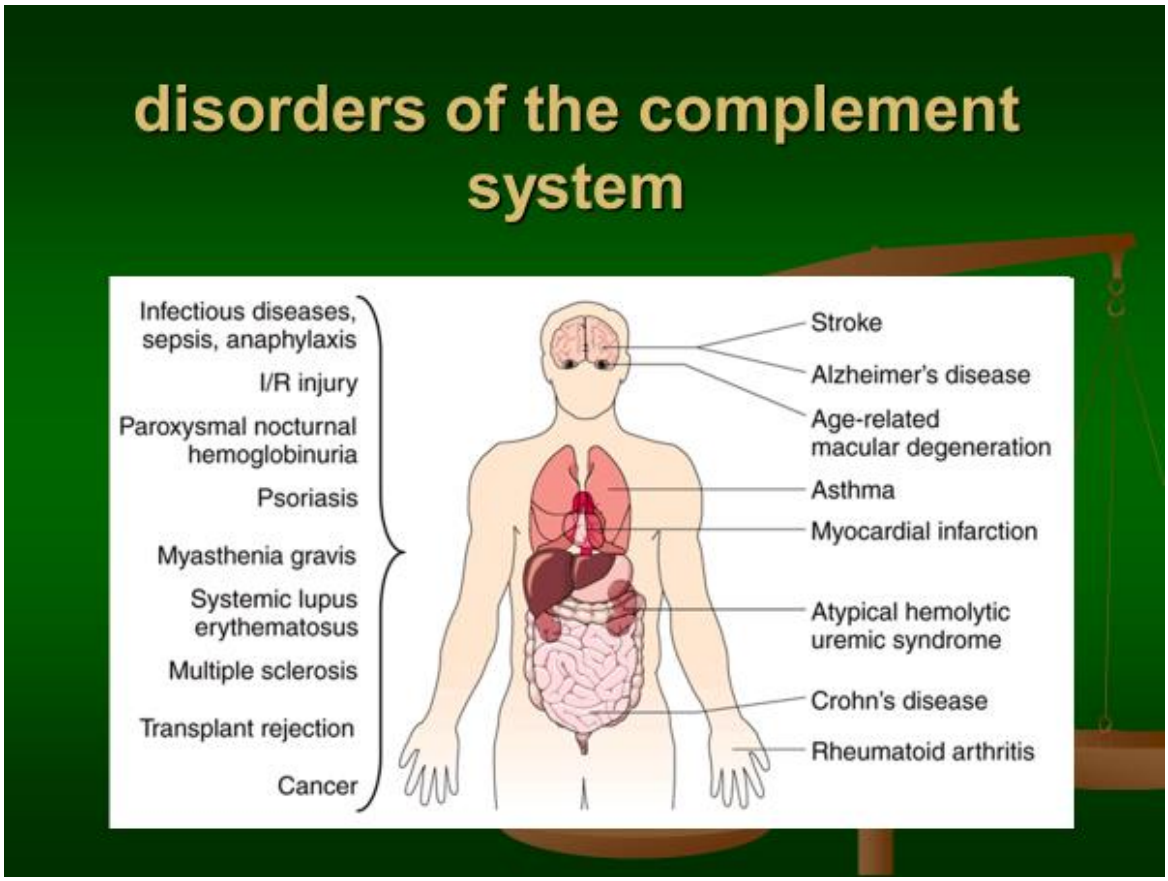


TABLE 13-7 SUMMARY OF BIOLOGICAL EFFECTS MEDIATED BY COMPLEMENT PRODUCTS

Effect	Complement product mediating*
Cell lysis	C5b–9, the membrane-attack complex (MAC)
Inflammatory response	
Degranulation of mast cells and basophils†	C3a, C4a, and C5a (anaphylatoxins)
Degranulation of eosinophils	C3a, C5a
Extravasation and chemotaxis of leukocytes at inflammatory site	C3a, **C5a,** C5b67
Aggregation of platelets	C3a, C5a
Inhibition of monocyte/macrophage migration and induction of their spreading	Bb
Release of neutrophils from bone marrow	C3c
Release of hydrolytic enzymes from neutrophils	C5a
Increased expression of complement receptors type 1 and 3 (CR1 and CR3) on neutrophils	C5a
Opsonization of particulate antigens, increasing their phagocytosis	**C3b,** C4b, iC3b
Viral neutralization	C3b, C5b–9 (MAC)
Solubilization and clearance of immune complexes	C3b

*Boldfaced component is most important in mediating indicated effect.

†Degranulation leads to release of histamine and other mediators that induce contraction of smooth muscle and increased permeability of vessels.



PRACTICAL TEST FOR COMPLEMENT

Excessive complement activation is part of the pathogenesis of a large number of inflammatory diseases. The pathologic effect may be due either to an increased and persistent activation, for example, caused by the presence of immune complexes (such as in systemic lupus erythematosus, SLE, and related disorders).

Complement activation and insufficient regulation play important roles in IR injury, and activation by all three pathways of complement has been implicated in the damage. The result is an multifunctional inflammatory process, involving generation of anaphylatoxins, upregulation of adhesion proteins and tissue factor on endothelial cells, and recruitment and extravasation of PMNs

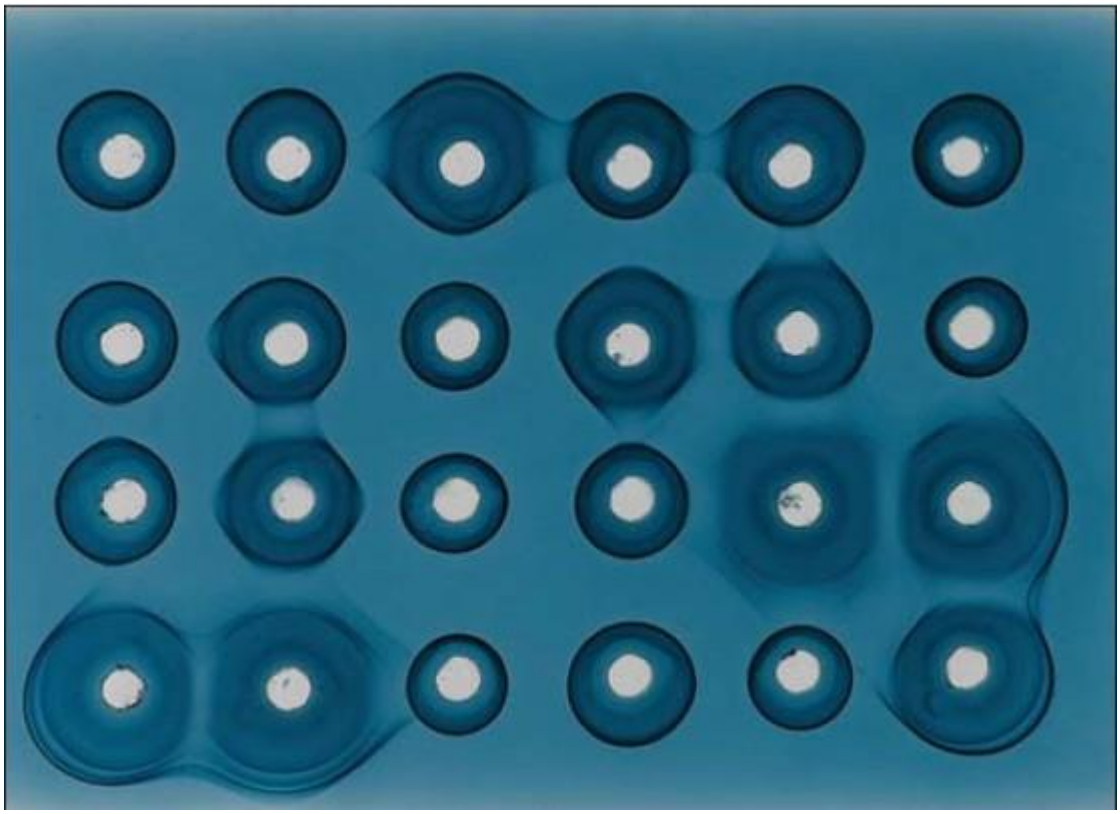
Examples of Indications for Complement Analysis:

- Complement Factor Deficiencies
- Monitoring of Complement Regulatory Drugs
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- SLE and Urticarial Vasculitides
- Membranoproliferative Glomerulonephritis
- Poststreptococcal Glomerulonephritis (PSGN)
- Atypical Hemolytic Uremic Syndrome (aHUS)

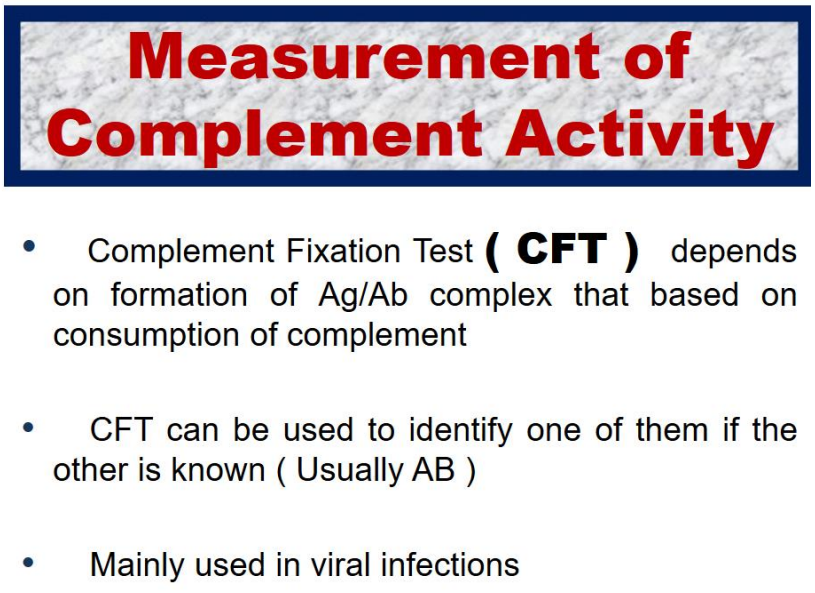
Source: Nilsson B, Ekdahl KN. Complement diagnostics: concepts, indications, and practical guidelines. *Clin Dev Immunol*. 2012;2012:962702. doi:10.1155/2012/962702

Detection of C3 and C4 levels – single radial immunodiffusion

Principle



Single radial immunodiffusion test to estimate C3 levels (Modi S, Rashid M, Malik A, Shahid M. Study of complement activation, C3 and interleukin-6 levels in burn patients and their role as prognostic markers. Indian J Med Microbiol [serial online] 2014 [cited 2020 Mar 24];32:137-42. Available from: http://www.ijmm.org/text.asp?2014/32/2/137/129793)



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