P. G. Sem III, CC-10, Unit III 'A' (Pg-1)

Subunit 3.4 (18/08/20)

Topic: Complement System, Activation, Function & Deficiencies (Part II)

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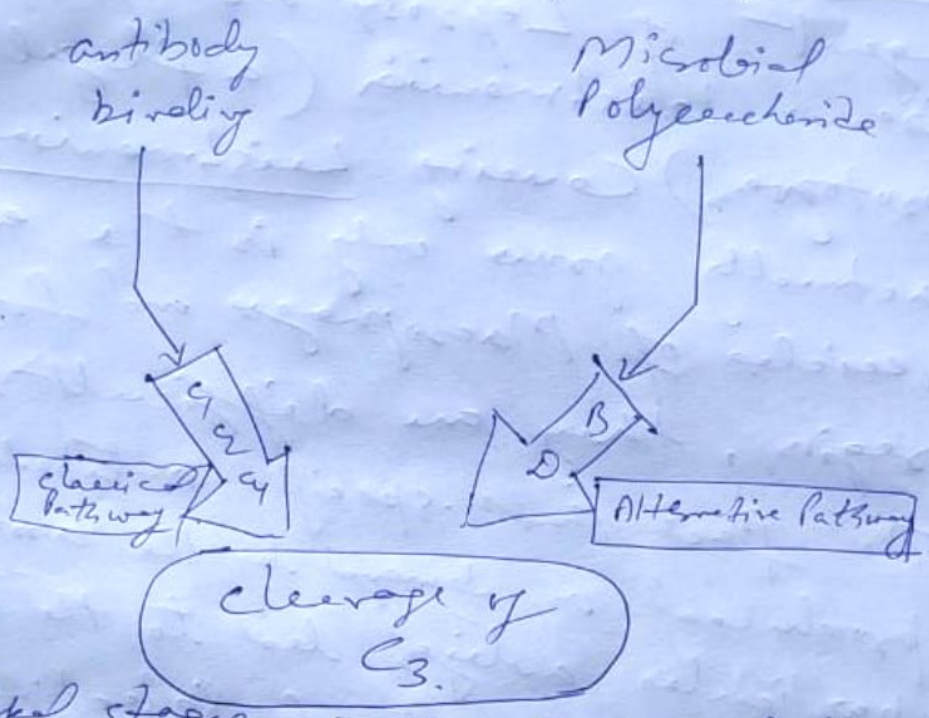
Contd. from Part I –

The activation of C_3 by cleavage is the central reaction in the complement activation sequence, and it is here that the classical and alternative pathway converge. In both pathway, C_3 is cleaved by an enzyme complex called C_3 convertase. A different C_3 convertase is produced by each pathway formed by spontaneous assembly of two of the complement components activated earlier in the cascade. Both types of C_3 convertase cleave C_3 into two fragments. The larger of (C_3b) binds covalently to the target cell membrane and binds C_5. Once bound the C_5 protein is cleaved by the C_3 convertase to initiate the spontaneous assembly of the late components (C_5 through C_9) that forms the membrane attack complex. Since each activate-

enzyme cleaves many molecules of the next proteenzyme in the chain, the activation of the early components consists of an amplifying proteolytic cascade; each molecule activated at the beginning of the sequence lead to the production of many membrane attack complexes. The classical pathway usually activated by IgG or IgM antibodies bound to the antigen on the surface of a micro-organism or the target cell. The binding of antigen by these antibodies enable their constant regions to bind its turn to the first component in the classical pathway, C_1 which is the large complex composed of three sub-components C_1Q; C_1R, and C_1S. The molecule of C_1Q protein is large sized (400,000 daltons) and made up of six identical subunits; each composed of three different polypeptide chains. The carboxyl terminal (-COO) halves of each of the polypeptide chains in a subunit are folded in a globular structure, the NH terminal halves; here a collagen amino acid sequence wound together to form a

collagen like triple stranded helix. The six subunits are linked together by di-sulphide bonds between their triple helical stems; forming a structure that resembles a leaves of Tulips.



The Principal stages in Complement Activation by classical & alternative Pathway.

Such as Activation occurs at the surface of an invading bacterium (After Alberts et. al. 1989)

The binding of a globular head of C1Q to an IgG or IgM antibody bound to antigen activate C1Q to start the early proteolytic cascade of the classical pathway. Activation of the C1Q activate C1R to become proteolytic and C1R in turn, cleaves and activate C1S. Activated C1S then cleaves C4 into two fragments. C4a and C4b smaller designated as small and C4b immediately binds cove-

-lently to the membrane and binds C_2
Once bound C_2 is also cleared by C_4S.
There are some microbes, which are ingested but not killed by macrophages. e.g. mycobacterium leprae, the causative agent of Leprosy and parasite of Genus Leishmania (a flagellated protozoa) causing Leishmaniasis, actually grow only in the endocytic vesicles of Macrophages and for this reason, they are difficult to kill.

The fact that specific antibodies are produced on demand by the arrival of particular antigen led to the development of the Clonal Selection Principle. This theory specifies the idea that an enormously wide range of B lymphocytes, each potentially capable of producing a specific kind of antibody, is present in the body before birth. When an antigen get in to the body after birth, it selects a lymphocyte of appropriate type, adheres to its surface and causes it to proliferate into a clone of cells, all of which proceed to produce appropriate antibodies. This is further added by the complement system, which speed up the rate of proliferation.