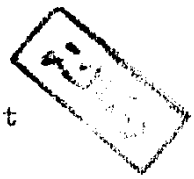
COMPLEMENT STUDIES IN SCHISTOSOMIASIS

THESIS

Submitted in Partial Fulfilment
Of Master Degree
(Tropical Medicine)



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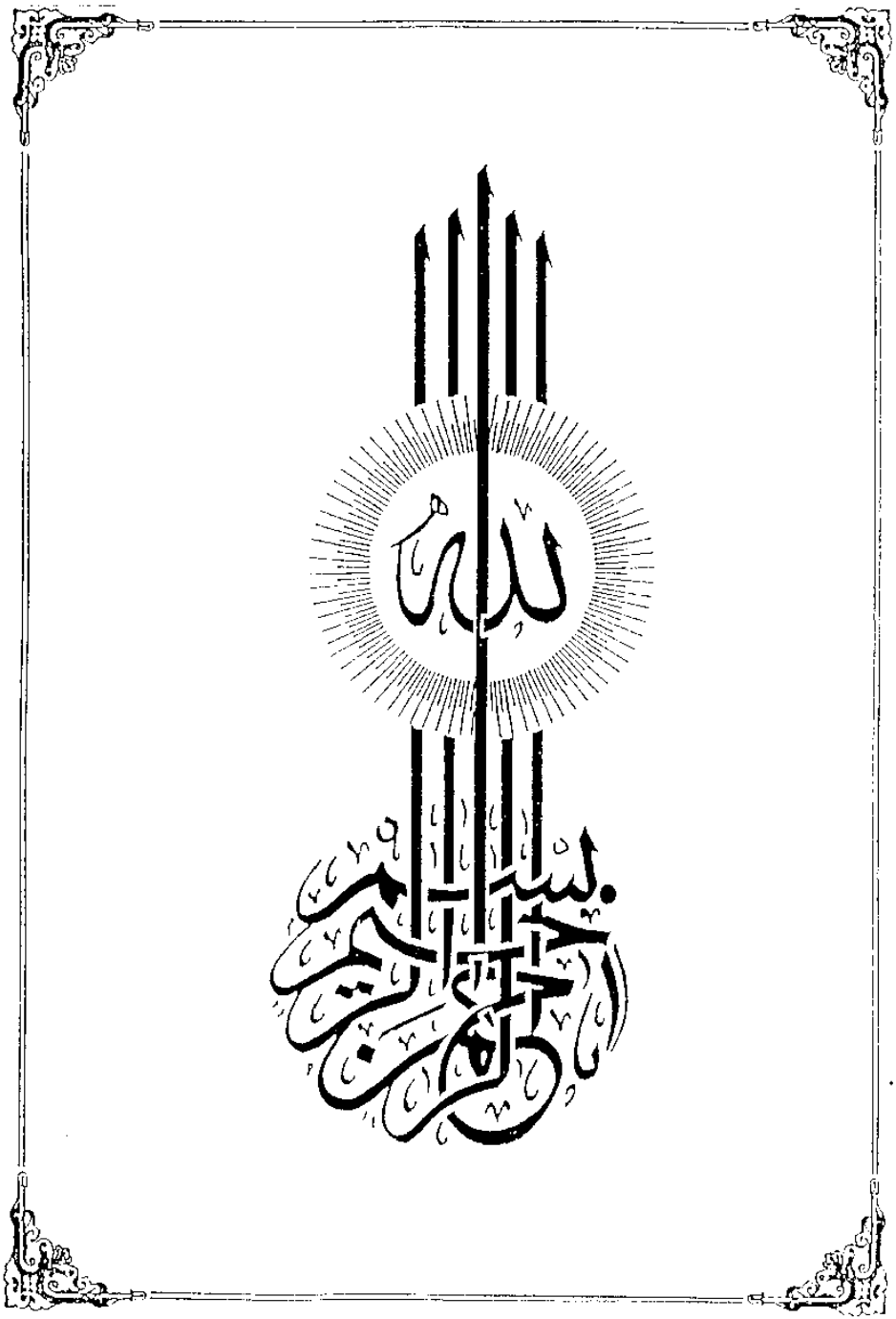
TO MY PARENTS



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C O N T E N T S

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INTRODUCTION

AND

AIM OF THE WORK

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Schistosomiasis is one of the most prevalent disease in Egypt. In the last few years it has been considered to be one of the immune complex diseases (Sela, 1979).

Several circulating antigens in the blood and also in the urine were found to be the consequence of parasitic infection by schistosomes (Capron, 1978). These antigens stimulate the formation of antibodies with which they form antigen-antibody complexes.

The aim of the work is to study the level of complement component, C_3 in schistosomal patients sera as indirect method detecting the presence of circulating antigen-antibody complexes. Also, to correlate intensity of infection of schistosomiasis with the level of C_3.

Other immune complex diseases such as viral hepatitis were excluded. The correlation between the level of C_3 and those carrying HBsAg in their sera was also studied.

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REVIEW OF LITERATURE

THE COMPLEMENT SYSTEM

1- Nature of the Complement :

Complement is the collective term for a complex system of sequentially interacting serum proteins which determines the biological consequences of antigen-antibody interactions and also participates, independent of antibody, in both physiogenic and pathogenic host responses. Included in the system are components of the classic and alternative activation path way and proteins which control the multiple biological activities arising from activation of specific components. Complement components are present in the extra cellular fluid (Roitt, 1982).

2- Historical Background :

In 1898 Bordet observed that heat stable antibody could not lyse cholera vibrio without participation of a heat-labile serum cofactor which was called "Alexin". However, paul Ehrlich, named it complement because it completes the antibody's immune response after it reacts with the antigen. (Barber, 1977).

Over the next thirty years, four separate components were recognized in haemolytically active serum. Dialysis against distilled water separated an euglobulin component C_1, which reacted with erythrocyte

coated antibody, EA, from a subsequently reacting pseudo-globulin component C_2, C_3 was recognized next, when cobra venom and certain gram negative bacteria and yeast were found to eliminate haemolytic activity without destroying C_1 or C_2. Finally, C_4 was identified by its inactivation when serum was treated with ammonia (Alper and Rosen 1976, Polly and Bearh, 1976). Since then, there has been exponential growth and information regarding the composition and biological functions of the complement system (Muller-Eberhard, 1975).

3- Nomenclature :

The complement components have been assigned a number in the order of their discovery and are preceeded by the letter C, C_1 has three subcomponents C_1q, C_1r and C_1S (Nelson et al., 1966). C_1t has recently been described as a further subunit of C_1 and its function and significance are not yet clarified (Assimeh & Painter 1975).

Fragments of components resulting from cleavage by other components acting as enzymes are assigned small letters (a, b, c & d), with the exception of C_2 fragments. When a component is active (i.e. become an active enzyme) a bar is placed above it, e.g. $\bar{C}_1$ (Nelson et al., 1966).

Components of alternative pathway have been assigned lettres; B, C and P (Properdin), these components has active forms denoted as $\overline{Bb}$, $\overline{D}$ and $\overline{P}$. C_3 is a component of both the classical and alternative pathways (Nelson et al., 1966). C proteins represent approximately 10% of the globulin fraction in normal human serum C_3 concentration was found to range from 86 to 184 mg/ 100 ml in healthy adults (Peter, 1978). Its molecular weight is 1800 daltons and has an electrophoretic mobility of B_2 globulins.

CLASSICAL PATHWAY OF COMPLEMENT ACTIVATION

The classical pathway is mainly activated by immunoglobulin factors which are either antigen antibody complexes or aggregated immunoglobulins, IgG or IgM, (Kholer, 1978 and McConnell et al., 1981). The classical pathway may also be activated non-immunologically by a number of substances e.g. DNA, some trypsin like enzymes such as plasmin and C-reactive proteins and also staphylococcal protein A. Activation occurs by direct binding of C_1 to these substances or by direct proteolytic attack on the C_1 molecule (McConnell etal., 1981).

The components of the classical pathway can be grouped into three functional units, the recognition unit, the activation unit and the membrane attack unit (Muller and Eberhard, 1975).

* The Recognition unit (C_1) :

It reacts with the antigen-antibody complexes or other activators and initiates the complement cascade. C_{1q} is the molecular bridge linking one IgM or two IgG to C_{1r} and C_{1s} subunits (Reid and Porter, 1976) through the Fc regions (Dorrington and Painter, 1974).

On binding a conformational change occur in C_{1q} which converts C_{1r} to an active internal enzyme which in turn activates C_{1s} to C_1 estrase (Sakai and Strand, 1973).

* Activation unit C_4, C_2 and C_3 :

The activation unite proceeds in two steps and involves the formation of two enzymes, C_3 convertase (McConnell et al., 1981), and C_5 convertase (Muller-Eberhard, 1975 and Cooper 1978). C_{1S} cleaves C_4 into C_{4a} and C_{4b} (Schreiber and Muller-Eberhard, 1974). C_{4a} is released into a fluid phase while C_{4b} binds to the call membrane recept ore at a site distinct from antibody binding site. Only 10% of C_{4b} become bound, the remainder passes in the fluid phase as C_{4bi} (inactive) (Kohler, 1978). The presence of C_{4b} and C_{4bi} enhances the cleavage of C_2 by C_{1S} into C_{2a} and C_{2b} (Gigli and Austin, 1969 and McConnell et al., 1981). C_{2b} fragment is released to the fluid phase. In presence of Mg^{++} about 5% of C_{2a} fuses with C_4 to form bimolecular complex, C_{4b}, 2a which is C_3 convertase, it fragments C_3 into C_{3a} and C_{ab} (Muller-Eberhard, 1975). Only 10% of C_3 combines with membrane site thus C_5 convertase (C_{4b},2a, 3b)is formed (Kohler, 1978).

* Membrane attack unit C_{5b}, 6, 7, 8, 9 :

Attack of C_5 by C_5 convertase (C_{4b}, 2a, 3b), initiates the formation of the stable C_{5b-9} complex C_5 convertase cleaves C_5 into small fragment C_{5a} and large fragment C_{5b} which has binding site to the cell membrane along side with $C_{4,2,3}$ complex (Cooper and Muller 1970; Kohler, 1978). C_{5b} acquires ability to bind C_6 and C_7 to form a trimolecular complex $C_{5b,6,7}$ (Lachmann and Thompson 1970, Arroyave, 1973). That complex combines with a single C_8 molecule and six of C_9 molecules (Kolb and Muller-Eberhard, 1975).

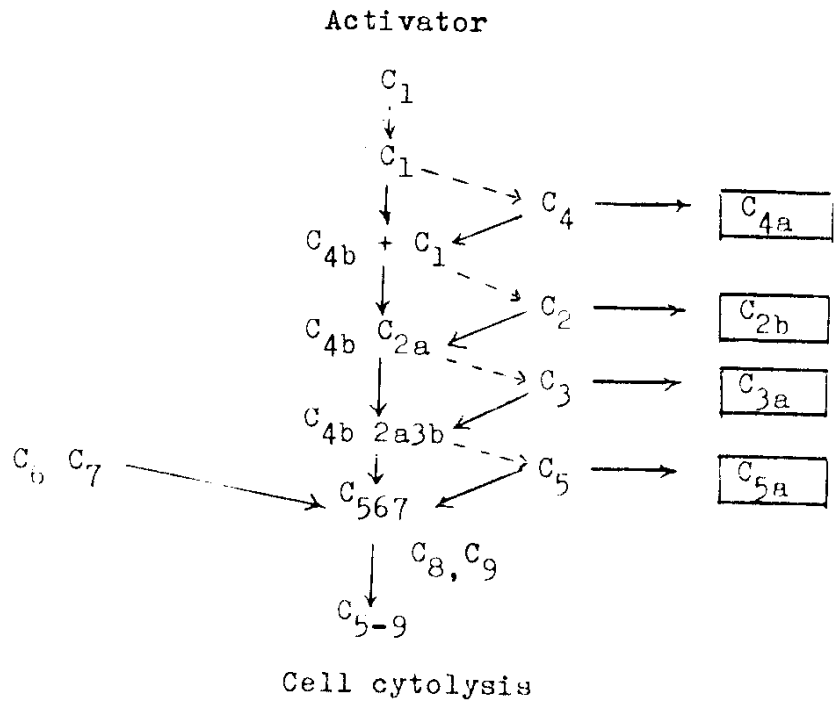

DIAGRAM OF THE CLASSICAL PATHWAY OF COMPLEMENT ACTIVATION(COOPER,1978)