TUMOR NECROSIS FACTOR
IN
ACUTE RHEUMATIC FEVER

Thesis
submitted for partial fulfillment of
Master Degree in Pediatrics

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1994

بسم الله الرحمن الرحيم

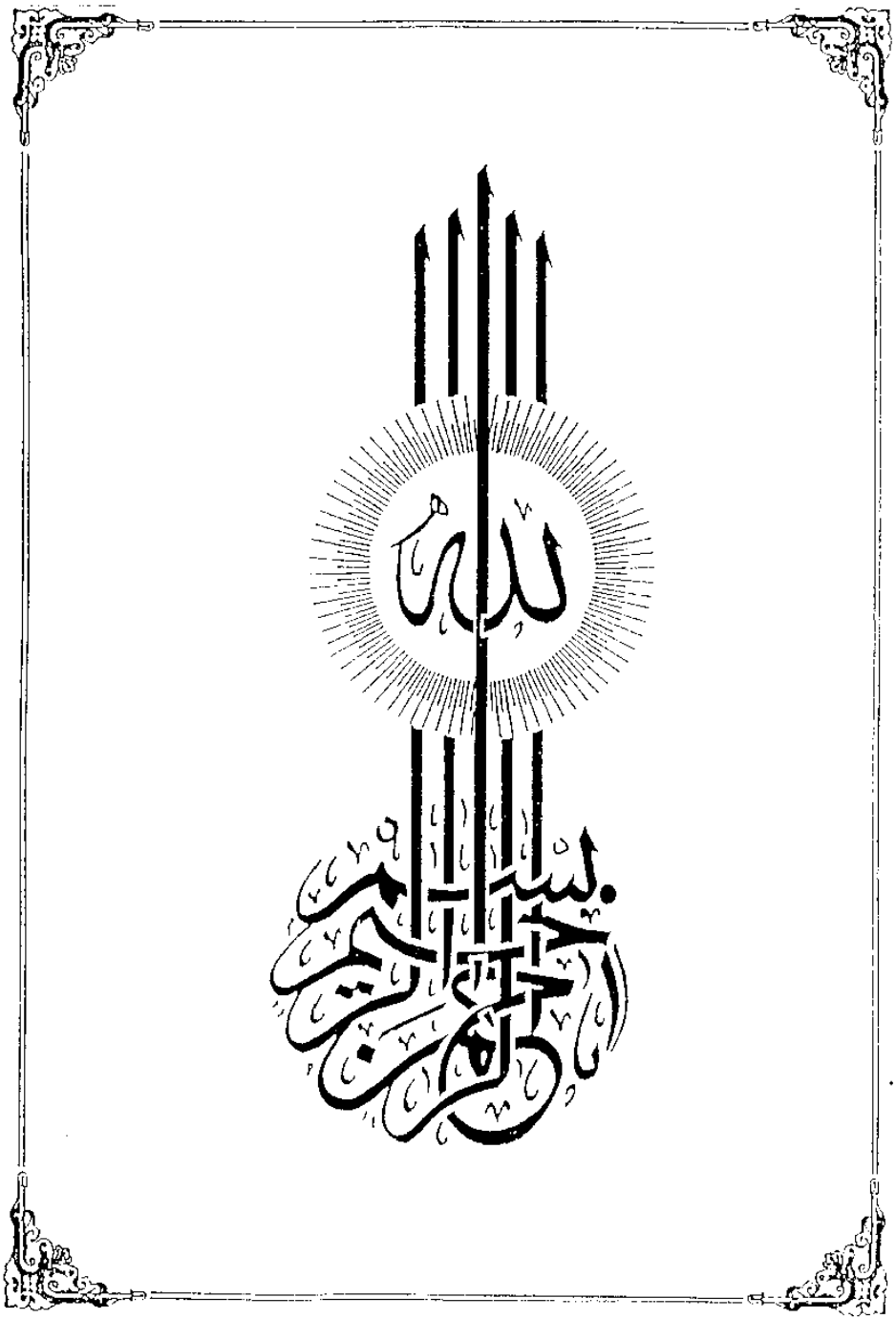
اقرأ باسم ربك الذي خلق

خلق الإنسان من علق

اقرأ وربك الأكرم الذي علم بالقلم

علم الإنسان ما لم يعلم

العلق ١-٥



TO
MY LOVELY SON
KAMAL EL-DIN

ACKNOWLEDGEMENT

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LIST OF ABBREVIATIONS

- Anti-nDNA : Anti-native deoxyribonuclear antibody.
- ATPase : Adenosine triphosphatase.
- BCG : Bacillus Calmette Guerin.
- CRP : C-reactive protein.
- DNA : Deoxyribonucleic acid.
- ELISA : Enzyme linked immunosorbent assay.
- ESR : Erythrocyte sedimentation rate.
- IFN-gamma : Interferon-gamma.
- Ig : Immunoglobulin.
- IL-1 : Interleukin-1.
- KD : Kilo dalton.
- LPS : Lipopolysaccharide.
- rhTNF-alpha : Recombinant human TNF-alpha.
- rTNF-alpha : Recombinant TNF-alpha.
- TNF-alpha : Tumor necrosis factor alpha.

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INTRODUCTION

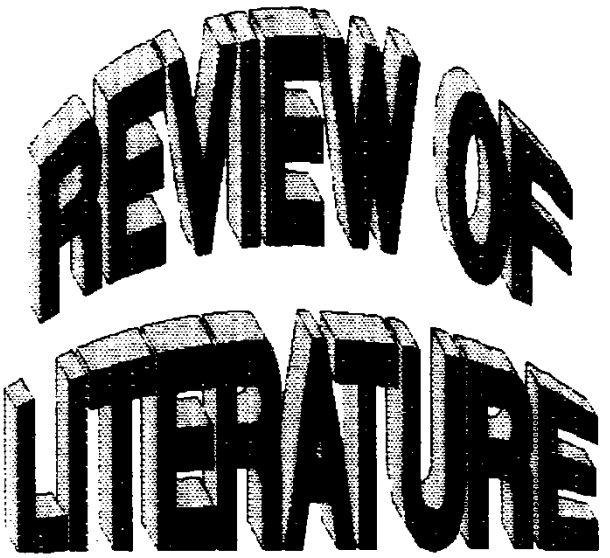
Rheumatic fever is frequently classified as a connective tissue disease because its anatomical hallmark is damage to collagen fibrils and to the ground substance of connective tissues (especially in the heart). Its difference from other rheumatic diseases is that it is specifically a delayed non suppurative sequelae of pharyngeal infection with group A streptococci (Stallerman, 1992).

Human tumor necrosis factor-alpha (TNF-alpha) also named cachectin is a 157 a.a unglycosylated polypeptide cytokine mainly produced by activated macrophage (monocytes). Among the biological activities of TNF-alpha we can mention the metabolic activities, antitumoral growth regulatory activities, immunomodulatory and proinflammatory activities. In fact, TNF activates macrophages/neutrophils and eosinophils as well as endothelial cells. It regulates the production of antibodies by B cells and stimulates cytotoxic cells. It induces the production of several other inflammatory mediators such as IL-1, IL-6, colony stimulating factor and collagenase. TNF-alpha often in combination with other cytokines has also been involved in several autoimmune diseases (Miller, 1989).

because of importance of soluble mediators of the immune response in various rheumatic diseases we speculated whether abnormalities in production of these mediators would be found in sera from patients with rheumatic fever.

AIM OF THE WORK:

To study the level of TNF in different types of rheumatic patients whether rheumatic heart disease, rheumatic chorea or rheumatic arthritis in correlation to disease activity before and after treatment.



RHEUMATIC FEVER

Introduction:

Rheumatic fever is frequently classified as a connective tissue disease because its anatomical hallmark is damage to collagen fibrils and to the ground substance of connective tissue (especially in the heart). Of major clinical importance is the presence of potentially lethal myocarditis during the acute attack or, more commonly, the fibrosis of the heart valves, which leads to the crippling hemodynamics of chronic rheumatic heart disease. Its difference from other rheumatic diseases is that it is specifically a delayed non suppurative sequel of pharyngeal infection with group A streptococci (Stallerman, 1992).

The Infecting organism:

The group Aβ-hemolytic streptococcus is a unicellular bacterium composed of a core of cytoplasm enclosed in a thin cytoplasmic membrane which in turn is surrounded by a rigid cell wall of three layers: an inner mucopeptide layer, a middle layer of group specific carbohydrate, and an outer protein layer, the chief component of which is M protein the major antigen implicated in pathogenesis.

External to the cell wall is a large capsule of hyaluronate which imports a mucoid appearance to the bacterial colonies on culture plates, this property is also associated with virulence.

Fimbriae, made up of M protein and lipoteichoic acid, project from the outer surface of the bacterial cell giving it a "hairy" appearance on E/M, these fimbriae unable it to adhere to host epithelial cells (Haffejee, 1992).

The ability of the group A streptococcus to cause infection is attributed primarily to the surface located M protein, an alpha-helical coiled-coil fibrillar molecule that confers to the organism the ability to resist phagocytic attack (Vincent et al., 1989).

The attachment of the bacteria to the pharyngeal wall occurs between an M protein-lipoteichoic acid complex on the streptococcal surface and fibronectin on the pharyngeal cell membrane.

Adherence may be considered a necessary pre-requisite to virulence. Antigenic difference in M protein allow for immunological subclassification of group.