TUMOR NECROSIS FACTOR-ALPHA IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

Thesis
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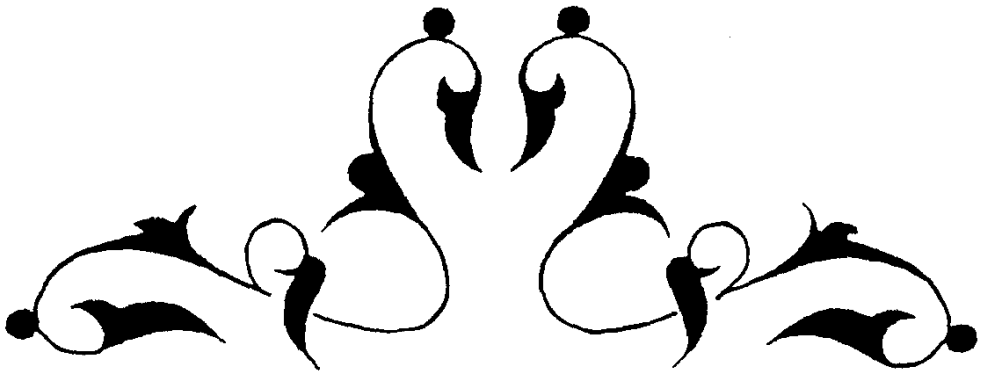

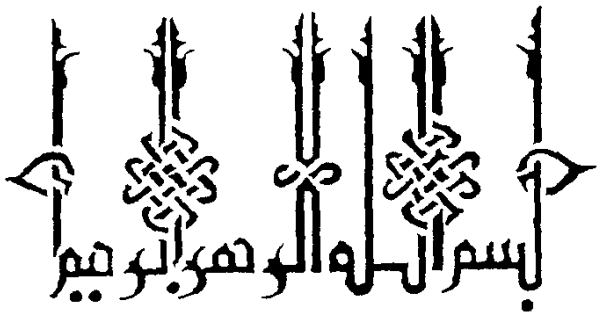

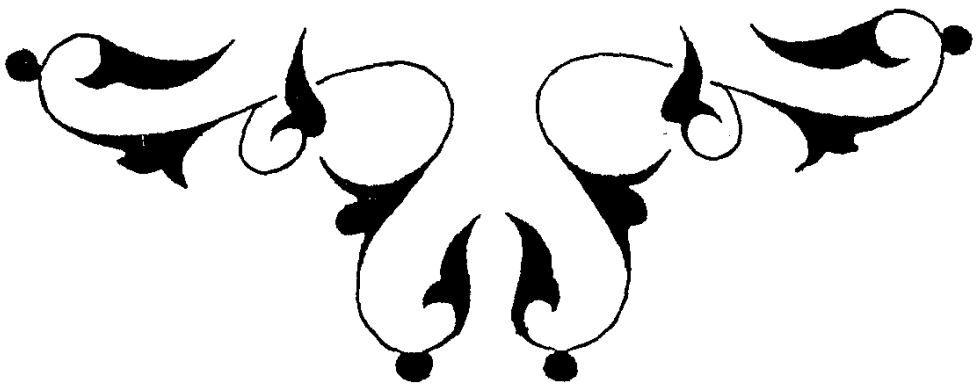

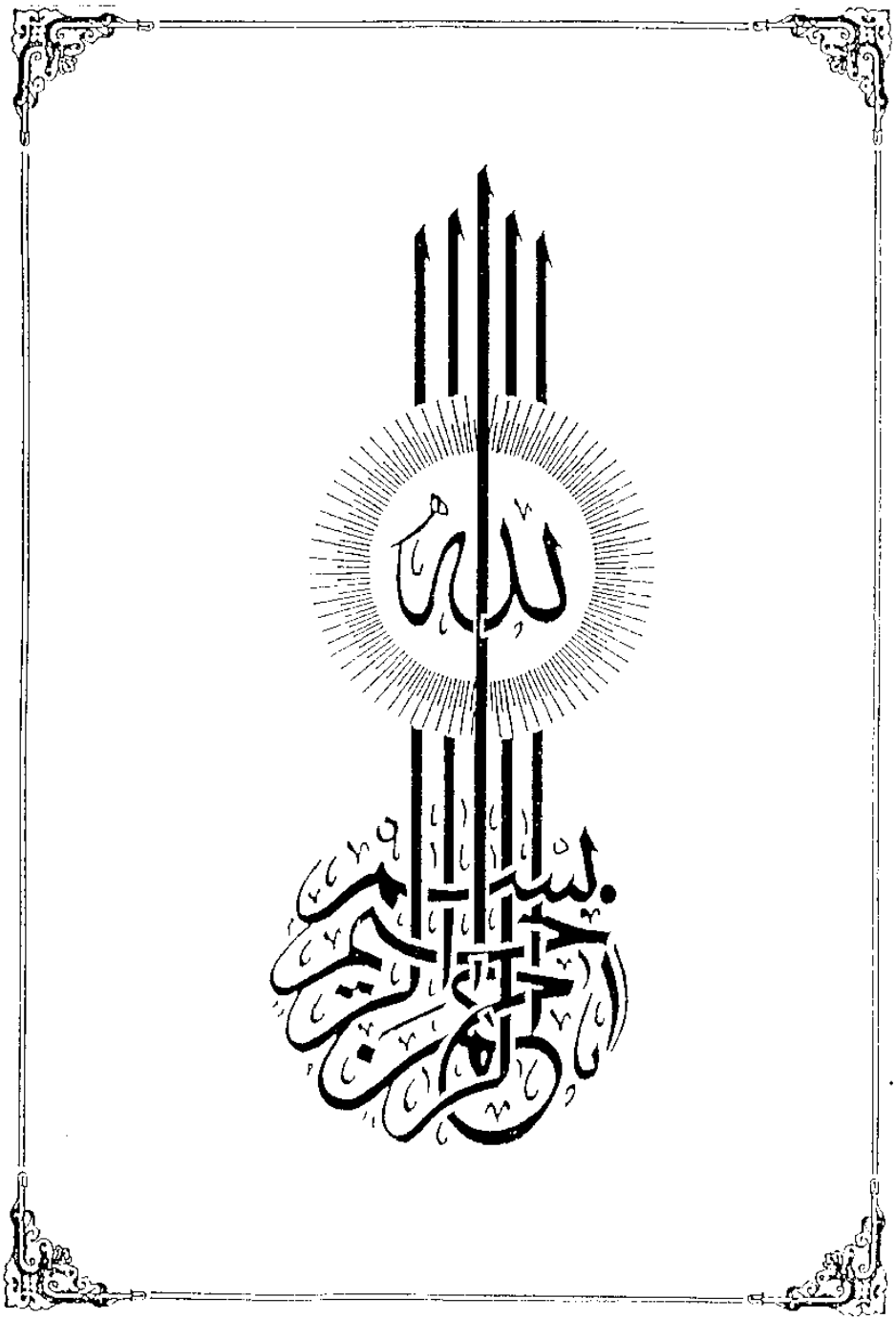

TO MY SON

" SHADY "

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LIST OF ABBREVIATIONS

- Ab:	Antibody.
- ADCC:	Antibody-dependent cell-mediated cytotoxicity.
- Ag:	Antigen.
- ANA:	Antinuclear antibody.
- Anti-dsDNA:	Anti-double stranded DNA.
- Anti-nDNA:	Anti-native deoxyribonuclear antibody.
- ARA:	American Rheumatism Association.
- ATPase:	Adenosine triphosphatase.
- BCG:	Bacillus Calmette-Guerin.
- BSA:	Bovine serum albumin.
- CBC:	Complete blood count.
- CNS:	Central nervous system.
- cpm:	Count per minute.
- CRP:	C-reactive protein.
- CSF:	Cerebrospinal fluid.
- DNA:	Deoxyribonucleic acid.
- DTH:	Delayed-type hypersensitivity.
- EBV:	Epstein-Barr virus.
- EDTA:	Ethylene diamine tetra-acetate.
- ELISA:	Enzyme-linked immunosorbent assay.
- EMEM:	Eagle's minimal essential media.
- ESR:	Erythrocyte sedimentation rate.
- FCS:	Fetal calf serum.
- GM-CSF:	Granulocyte-macrophage colony stimulating factor.
- GVHD:	Graft-versus-host disease.
- IFN:	Interferon.
- Ig:	Immunoglobulin.
- IL:	Interleukin.
- KD:	Kilo dalton.
- LPS:	Lipopolysaccharide.

- MCP: Metacarpophalangeal.
- MHC: Major Histocompatibility Complex.
- Mr: Relative molecular mass.
- MTP: Metatarsophalangeal.
- NK: Natural killer cells.
- OPD: Orthophenylene diamine.
- PAF: Platelet activating factor.
- PBS: Phosphate buffered saline.
- PG: Proteoglycan.
- PGE_2: Prostaglandin E_2.
- PIP: Proximal interphalangeal.
- PV: Plasma viscosity.
- RA: Rheumatoid arthritis.
- RANA: Rheumatoid arthritis nuclear antigen.
- RAP: Rheumatoid arthritis precipitin.
- RBCs: Red blood cells.
- RF: Rheumatoid factor.
- rh-TNF: Recombinant human tumor necrosis factor.
- RIA: Radioimmunoassay.
- RNP: Ribonucleoprotein.
- rTNF-alpha: Recombinant tumor necrosis factor-alpha.
- SAA: Serum amyloid-A.
- SLE: Systemic lupus erythematosus.
- TLC: Total leucocytic count.
- TNF-alpha: Tumor necrosis factor-alpha.
- UV: Ultra-violet.

CONTENTS

INTRODUCTION

INTRODUCTION

Tumor necrosis factor-alpha (TNF-alpha) is a hormone-like intercellular signal peptide produced mainly by activated monocytes/macrophages (Beutler and Cerami, 1987). Besides a possible role in host defense against tumor cell growth (Matthews, 1983) and parasitic infection (Scuderi et al., 1986), TNF-alpha appears to have a more general role as an effector molecule in various inflammatory processes (Maury and Teppo, 1989).

The gene coding for human TNF has been cloned and mapped to the short arm of chromosome 6, and is in close linkage with genes of the major histocompatibility complex (MHC) (Spies et al., 1986).

Since some haplotypes of the MHC are associated with certain diseases, including rheumatic disorders, the possibility of abnormal TNF gene expression as a factor in various disease mechanisms has been proposed (Maury and Teppo, 1989).

Studies with recombinant TNF have shown that it enhances procoagulant activity in endothelial cells (Bauer et al., 1989), stimulates neutrophils (Berger et al., 1988), increases the surface expression of class I MHC antigens (Collins et al., 1986), stimulates osteoclastic bone resorption (Bertolini et al., 1986) and regulates hepatic acute phase gene expression (Perlumtter et al., 1986). TNF

also stimulates the production of granulocyte-macrophage colony stimulating factor (Munker et al., 1986), platelet activating factor (Camussi et al., 1987) and interleukin-1 (Nawroth et al., 1986). It inhibits lipoprotein lipase activity (Price et al., 1986) and induces shock (Cannon et al., 1990), fever (Dinarello et al., 1986), cachexia (Brenner et al., 1990), anaemia and inflammation (Tracey et al., 1988).

TNF was suggested to be a mediator of the lethal effects of endotoxin (Tracey et al., 1987) and to be involved in the pathogenesis of graft-versus-host disease (Piguet et al., 1987), cerebral malaria (Grau et al., 1987), Kawakami disease (Maury et al., 1989) and murine autoimmune lupus nephritis (Jacob and McDevitt, 1988).

The cause of increased TNF concentration in the serum of some rheumatic patients is not known. Observations that TNF stimulates collagenase and prostaglandin E_2 production by synovial cells and fibroblasts (Dayer et al., 1985) and causes osteoclastic bone resorption (Bertolini et al., 1986) are interesting in this connection (Teppo and Maury, 1987).

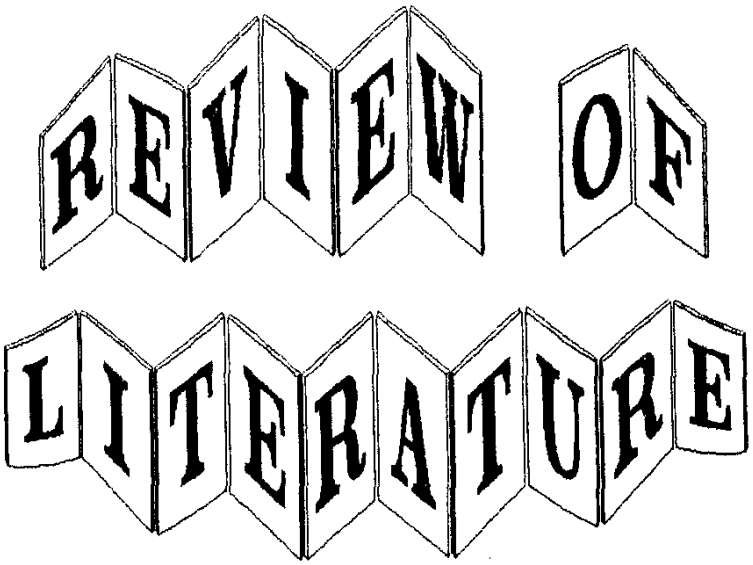
AIM OF THE WORK

1- Is to gain insight into the association between circulating TNF-alpha and the acute phase response in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

2- Is to evaluate the possible role of TNF-alpha in the pathogenesis of SLE and RA.

3- Comparison between concentrations of TNF-alpha and CRP (an acute phase protein known to be produced by the liver).

4- Correlation between TNF-alpha concentration and the severity or the activity of SLE and RA.



TUMOR NECROSIS FACTOR-ALPHA

Introduction:

Invasive diseases, whether infectious or neoplastic were known to frequently precipitate metabolic derangements that threatens the integrity of the host. Abnormalities of host glucose, protein and lipid metabolism are well documented in acute and chronic disease states (Beutler and Cerami, 1987) and represent systemic consequences of defective cellular homeostasis. Gross imbalances of host physiology, manifested as wasting of the body (cachexia) or shock, might themselves lead to death.

It was once widely believed that invasive agents were themselves responsible for these metabolic derangements. In recent years, however, there has been a growing awareness that both acute and chronic metabolic derangements seem to be mediated largely by the immune system through endogenous mediators (Beutler and Cerami, 1986). These mediators (or cytokines) include interleukin-1 (IL-1) (Buchan et al., 1988), lymphotoxin (Aggarwal et al., 1984), gamma-interferon (Nathan et al., 1984) and the substance known as either cachectin or tumor necrosis factor (Beutler et al., 1985a).

The role of bacterial endotoxin in the pathogenesis of septic shock is due to a host factor (or factors) elicited by endotoxin probably from cells of hemopoietic origin (Michalek et al., 1980).