SEX HORMONES STATUS IN WOMEN SUFFERING FROM SYSTEMIC LUPUS ERYTHEMATOSUS

THESIS

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Master Degree in **Physical Medicine**

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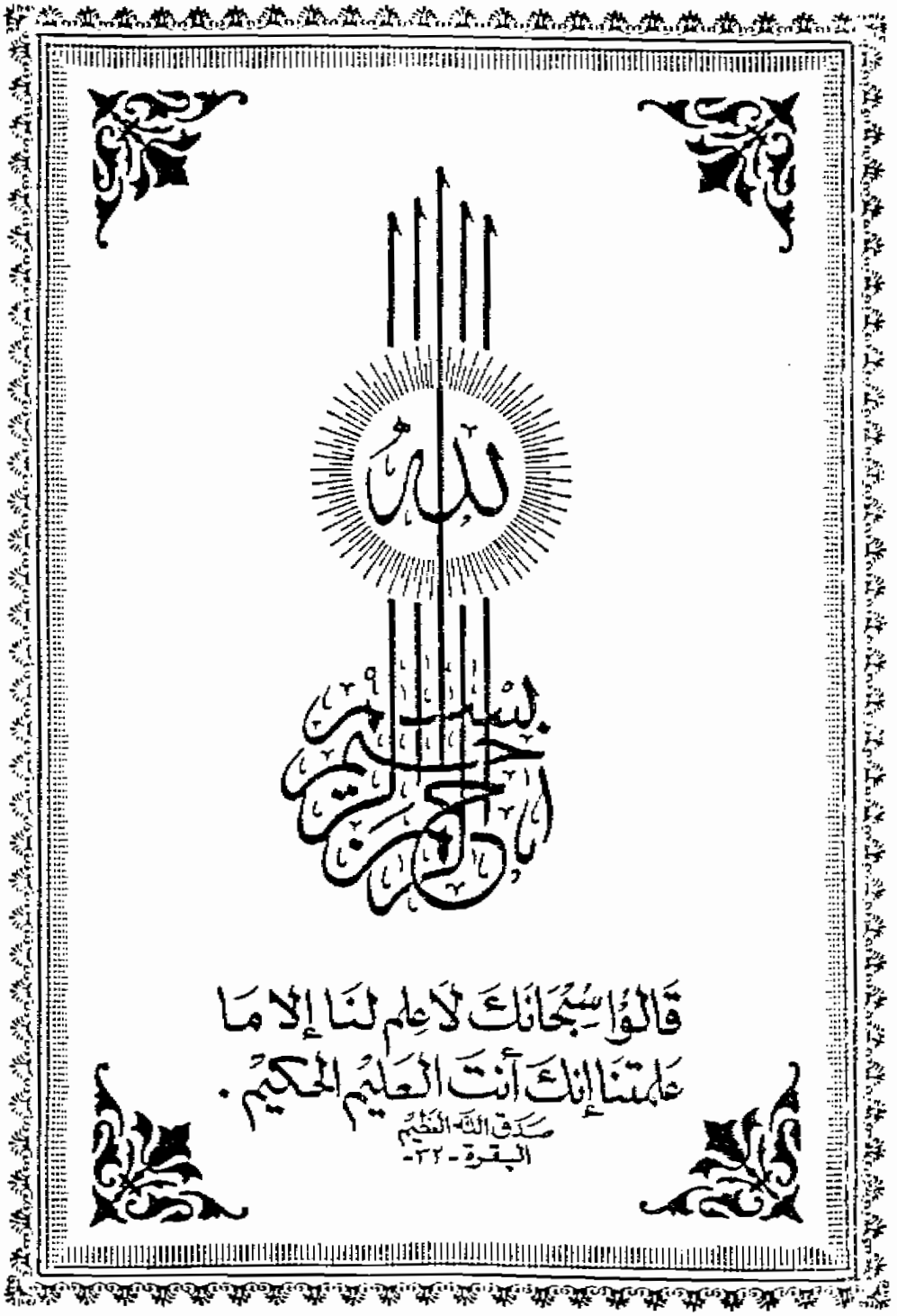

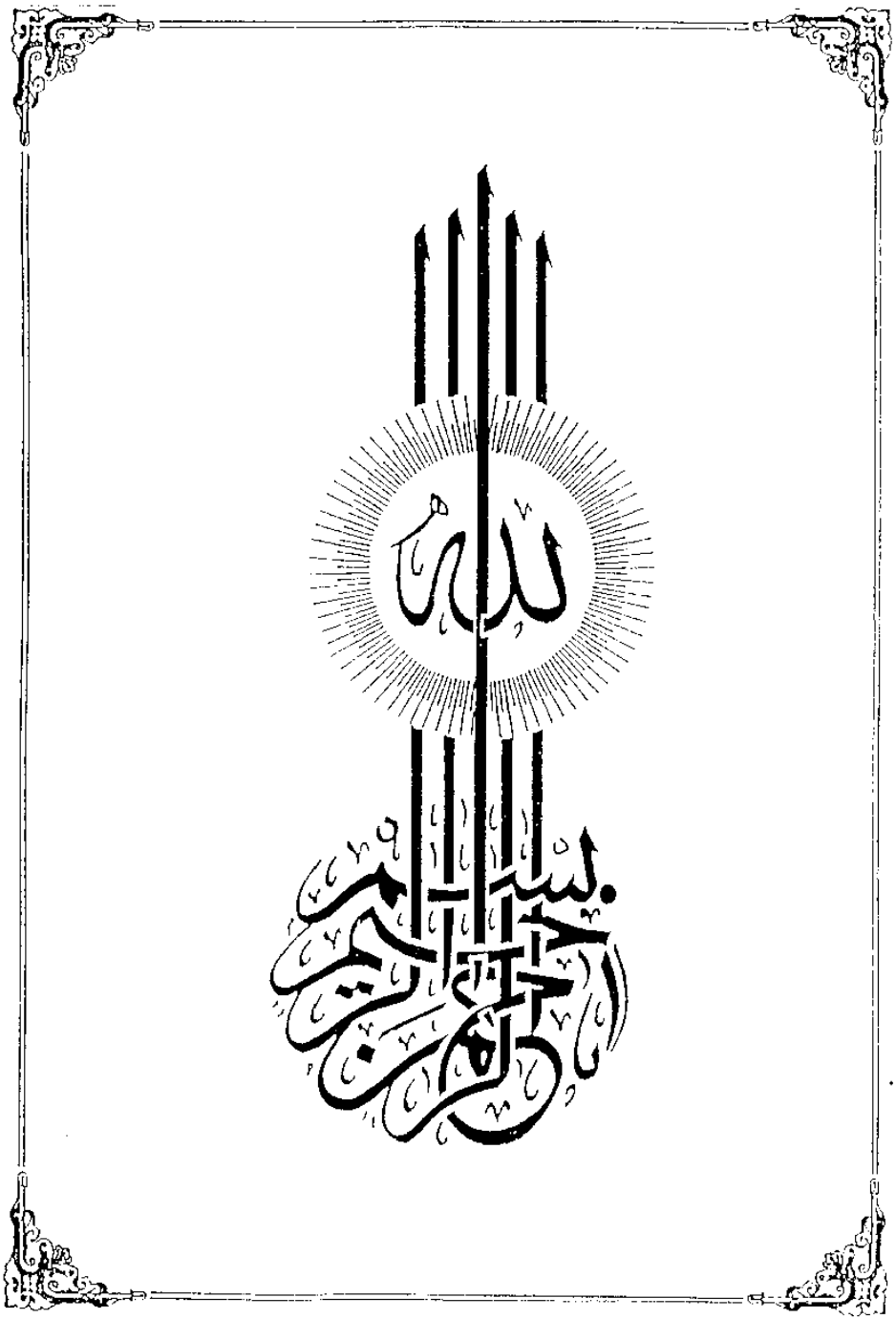

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INTRODUCTION

Systemic lupus erythematosus SLE, the prototype autoimmune rheumatic disease *(Asherson & Lahita, 1991)* is characterized by protean clinical manifestations and occurance of a variety of autoantibodies *(Borg et al., 1990).* Depite intensive efforts, no aetiology has yet been found for SLE.

A variety of factors have been proposed to be aetiologic for SLE including viral, genetic environmental and hormonal influences.

There is a marked female predominance with many series reporting a 9:1 female to male ratio *(Schumacher et al., 1988).* The marked gender influence on the occurrence of SLE indicates that hormonal factors may be important in the aeitology of this illness *(Ward & Studensk, 1990),*

Reviews on the role of sex hormones in the immune system informs us that the inter-relation between the immune system and reproductive system is extremely complex. Oestrogen has dualistic effect on the immune system *(Holmdahle et al., 1986).* It exaggerates lupus disease and enhances autoantibodies productions in SLE *(Holmdahle et al., 1989).*

How sex hormones modulate the immune response is unclear there may be a relation with steroid receptors:
Sex steroid receptors have been found on the thymus and oestrogen receptors are localized specifically to OKT8+ (suppressor / cytotoxic) subset of T-cell *(Cohen et al., 1983).*

Menstruation may be associated with adverse symptomatology in 60% of lupus patients *(Asherson & Lahita 1991).*

During pregnancy, and especially in the puerperium "flares" of the disease may also occur *(Asherson & Lahita, 1991).*

The use of conjugated symmetric oestrogen for birth control may be assoiated with such "flares" and it has been suggested that oral contraceptive pills may be associated with development of such complications as chorea and thromboembolism in the subset of SLE with antiphospholipid antibodies *(Asherson et al., 1986).*

Studies of androgen metabolism revealed that testosterone level in female SLE patients with active disease have been reported to be low, wheras females with inactive SLE had normal levels *(Junger et al., 1982b).*

These data suggested that there is a fundamental problem with sex steroid metabolism in patients with SLE *(Lahita, 1985).*

Aim of the work

The aim of the work is to conduct a clinical study on SLE Egyptian female patients and measure their serum levels of oestrogen, progesteron and testosteron to assess their role in the aetiology and pathogenesis of SLE.

REVIEW OF LITERATURE

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a chronic inflammatory disease appears to result from an immunoregulatory disturbance brought about by the interplay of genetic, viral, environmental and hormonal factors *(Segovia, 1988).*

1) Genetic susceptibility

SLE occurs in relatives of patients with the disease with a frequencey between 0.4 and 5% , represnting a several hundred-fold increase over the incidence in the general population *(Lehman et al., 1979).* Immunologic abnorma-lities are also found more often in family members of SLE patients than in control subjects *(Winchester & Nunez, 1982).* Block and his colleagues in (1976) have found that more than 50% of seventeen monozygotic twin pairs appeared to be concordant for the disease and 71% concordant for the presence of antinuclear antibodies and disease expression between identical twins. On other hand the frequency of SLE in dizygotic twins is considerably lower *(Arnett & Sculman, 1978).* Also antinuclear antibodies have been found more frequently in relatives of SLE patients (3-44)% than in the general population (0-14)% *(Cleland et al., 1978).*

Patients with discoid lupus were reported to have an increased frequency of HLA-B7, whereas HLA-B8 predominated in patients with systemic disease and/or severe renal disease. Interestingly, 3 of the 4 HLA-B8 positive patients presenting with only discoid lesions progressed to develop systemic lupus *(Mikkelsen et al., 1981).*

Recent investigation have demonstrated a high association of HLA-DR2 with lupus nephritis, especially, in a non white population. On the other hand HLA DR3 positive SLE patients, are not preisposed to nephrites *(Jacob et al., 1990).*

Furthermore, genes controlling the production of several complements, are located within HLA region.

Deficiency of early complements, particularly C2 and C4, are frequently assoiated with SLE and discoid lupus *(Green et al., 1986).* In a study conducted by Kemp et al. in (1987) 50% of all caucasian SLE patients have been found to have a deletion of C4A from one or both chromosomes, making deletion of C4A gene a very common genetic marker for disease susceptibility.

Many theoretical mechanisms are proposed to explain how disease susceptibility might be related to human lymphocyte

antigens (HLA) encoded antigens:

A) The binding hypothesis suggests that the HLA coded surface antigens can act as a receptor site for attachment of pathogenic agents, such as viruses.

B) The lindked-gene hypothesis asserts that the HLA gene is not itself involved in the pathogenesis of disease but is closely linked to another specific disease gene and inherited by linkage disequilbrium.

C) The molecular mimicry theory states that certain antigens, such as those coded for by viruses, may mimic certain HLA antigenic properties, thereby allowing for cross tolerance and inablity to eliminate the pathogen.

D) Aberrant expression of class II major histocompa-tibility complex (MHC) molecules on the surface of cells that do not normally express it.

Recently, Jones et al. in (1991) have studied the prevalence of raised levels of anti-cardiolipin antibodies in a group of Malaysian population with SLE and found a low prevalence of rasied levels of anticardiolipin antibodies in conjunction with a rare occurrence of thrombosis. The data obtained from their study contrast with the findings in European patients with SLE and lend support to the influence of local factors, which may be genetic or environmental, on the

clinical manifestation of this disease.

2) Chronic virus infection

Enthusiasm for a viral aetiology for SLE followed from the electromicroscopical observation of tubuloreticular inclusion in SLE tissues that bear a superficial resemblance to the tubuloreticular structures and internal nucleoprotein core of paramyxovirus, of which measeles is an example. However, other studies have shown that, these structures are a non specific manifestation of cell injury induced by the action of increased levels of alpha-interferon in SLE patients *(Woods & Zvailfer, 1989).*

Evidence of C-type viral complex was found in biopsies of clinically involved skin in 16 patiens; biopsy tissues of uninvolved skin were normal *(Mikkelsen et al., 1981).*

Serologic studies of serum antiviral antibodies in SLE patients reveal although elevated levels are often found, they are diercted at a number of apparently unrelated. Viruses, including measles, rubella, parainfluenza, mumps and epstein barr virus. This suggests that the antibodies may be the result of non specific B-lymphocyte activition and not due to antigenic exposure. *(Mikkelsen et al., 1981).*