INCIDENCE AND COMPONENTS OF CRYOGLOBULINS IN SLE PATIENTS WITH AND WITHOUT RAYNAUD'S PHENOMENON

THESIS

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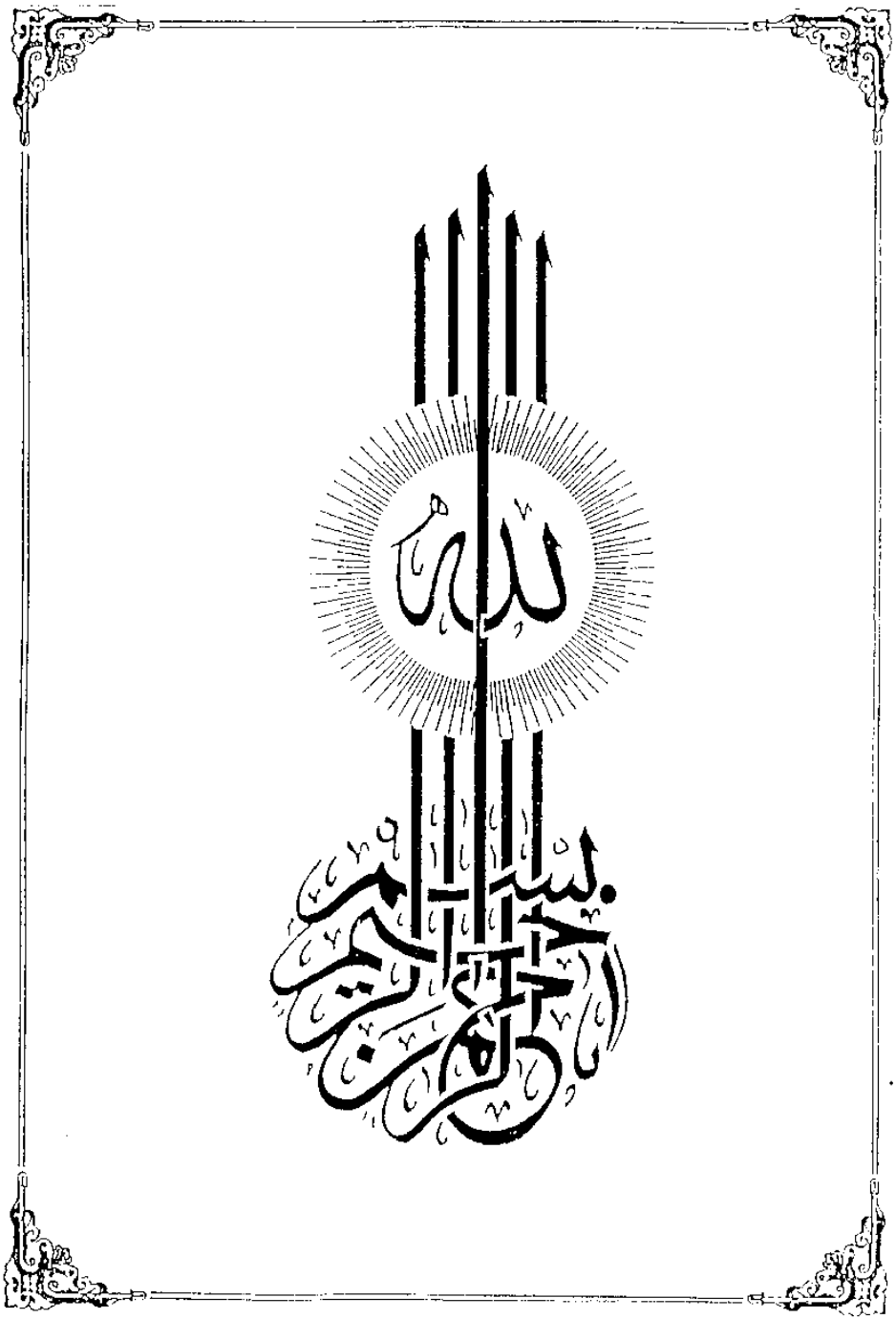

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ANA	Antinuclear antibody
BUN	Blood urea nitrogen
C3	Complement 3
CBC	Complete blood count
CH_{50}	Hemolytic complement
CNS	Central nervous system
DNA	Deoxyribonucleic acid
ENA	Extractable nuclear antigen
ESR	Erythrocyte sedimentation rate
FTA	Fluorescent treponemal antibody
I-Cs	Immune complexes
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgM	Immunoglobulin M
MHA-TP	Microhemagglutination assay for *Treponema pallidum.*
NSAIDs	Non-steroidal anti-inflammatory drugs
PEG	Polyethylene glycol

PGE	Prostaglandin E
PGI	Prostaglandin I
RA	Rheumatoid Arthritis
RES	Reticuloendothelial system
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
RPM	Revolution per minute
SLE	Systemic Lupus Erythematosus
TPI	*Treponema pallidum* immobilization
VDRL	Venereal disease research laboratory
WHO	World Health Organization.

INTRODUCTION AND AIM OF THE WORK

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Cryoglobulins or cold precipitable immunoglobulins were first observed in the setting of reticuloendothelial malignancy by **Wintrobe and Buell (1933).** Fourteen years later, they were described in the absence of malignancy in a patient whose clinical features suggested an immunologically mediated disease **(Lerner and Watson, 1947).** Then,they were found regularly in the sera of patients with diseases of known infectious etiology associated with autoimmune features such as subacute bacterial endocarditis **(Lerner and Watson, 1947)**, infectious mononucleosis **(Kaplan, 1968)** cytomegalovirus syndromes **(Wager et al.,1968)**, poststreptococcal glomerulonephritis **(McIntosh,1970)**, tropical splenomegaly syndrome resulting from chronic malarial exposure **(Barnett et al.,1970)**, and leprosy **(Galli et al.,1986).** In addition, they have been described in rheumatic disorders of unknown etiology such as SLE **(Hanauer and Christian,1967).**

Initially, studies of these proteins had focused largely on the physico-chemical nature of cryoprecipitation and the immunochemical properties that determine their unique solubility characteristics **(Grey and Kohler, 1973).** Subsequently, the emphasis of investigations concerning these proteins had changed. Now, they are being considered as circulating immune complexes because they contain appropriate antigens, antibodies, or other immunoreactants, that may be related to the pathogenesis of the diseases they accompany **(Barnett et al.,1970).** In fact, immune complexes play a major role in the pathogenesis of a variety of

diseases such as SLE **(Mannik, 1982)**.

The aim of this work is to study the incidence, the type and the components of cryoglobulins in SLE patients with and without Raynaud's phenomenon, as well as, their correlation with the clinical picture and the severity of the disease.

REVIEW OF LITERATURE

SYSTEMIC LUPUS ERYTHEMATOSUS

INTRODUCTION

Systemic lupus erythematosus is a common disease of chronic nature. It is an autoimmune disease, or one in which the immune system in all of its complexity turns against self and attacks the body's own tissues. The cause of the illness is unknown, but genetic, hormonal or environmental factors may have an effect on immunoregulation **(Lahita, 1987)**. It is multisystemic, that is to say,it affects every or any organ system of the body. The clinical manifestations are variable and depend largely on which organ system or systems are affected **(Ballou et al.,1982)**. The disease can be mild to severe, and no successful targeted therapy presently exists **(Decker, 1982)**.

SLE affects people of all races and ages. It is more common in blacks than in whites. The female : male ratio is 8:1. It affects 1 in 700 females between the ages of 15 and 64 years **(Roberts and Hughes, 1989)**.

HISTORY

Lupus is a term attributed to the thirteenth century's physician Rogerius. It is the latin word for "Wolf". It was used to describe the erosive facial lesions that were reminiscent of a wolf's bite **(Blotzer, 1983)**. IN **1845 Von Hebra,** a Viennese physician, used butterfly to describe the familiar malar rash of the disease. The name of the disease was latinized in his book in 1856. In **1851** the Frenchman **Cazenave,** was the first one to apply

the term "Lupus erythemateaux" **(Lahita, 1987).** But it was not until **Moretz Kaposi** recognized the visceral involvement in **1872** that physicians began to appreciate the disseminated forms of the disease which then came to be known as acute disseminated lupus erythematosus **(Blotzer, 1983).**

In **1875** fever, adenopathy, and arthritis were recognized as occasional features. **William Osler (1904),** described two women who developed renal failure within ten months of the appearance of a facial erythema. He did not give them a diagnosis at that time. At the same time in Vienna, **Jadassoohn** was describing similar syndromes in some patients. Both **Jadassoohn** and **Osler** had, therefore, established SLE as a separate disease entity by the turn of the century **(Benedek and Rodnan, 1983).** However, considerable confusion still remained well into this century since SLE was commonly thought by many to be a variant of tuberculosis. Even typical cases of SLE were reported under a variety of names **(Reifenstein, 1939).**

In the **1920s** and **1930s,** SLE was identified as a distinct clinical entity, which was largely the result of the work of pathologists who had described the morbid anatomic changes that were acceptable as characteristic of SLE **(Lahita, 1987).** In **1936, Friedberg et al.,** made a postmortem diagnosis of SLE in which there were no cutaneous lesions, recognizing for the first time that the disease could occur without skin manifestations **(Benedek and Rodnan, 1983).**

In 1941, Klemperer et al., implicated collagen in the disease after noting the ubiquity of fibrinoid degeneration and

staining alterations in ground substance of the connective tissues. This gave birth to the label "collagen disease" and perpetuated its use even in the present day **(Lahita, 1987)**. In **1948, Hargraves et al.,** described the "LE cell" in the bone marrow of SLE patients. This test was later adapted to peripheral blood. This single discovery revolutionized our ideas of SLE and LE cell was thought to be pathognomonic until it was associated with RA and other illnesses **(Benedek and Rodnan, 1983)**. **Dubois (1953)** and **Harvey et al. (1954),** attempted to certify the chronicity of SLE and the diagnostic importance of the LE cell test.

In **1957,** an American physician, **George Friou,** applied the indirect Fluorescent technique of Coons to the study of auto-antibodies. At about the same time, **Deicher et al. (1959),** described antibodies to DNA. In **1966, Tan and Kunkel** described anti-Sm.antibody. Being unknown at that time, this antibody is highly specific for SLE, although it is present in only 30% of patients **(Nakamura and Tan, 1978)**.

Since the original description of the disease and the subsequent serologic dissection of its laboratory presentation, the diagnosis of SLE has become more common **(Lahita, 1987)**.

CLINICAL FEATURES

Patients with SLE may present with single or multiple organ involvement. At initial evaluation, the most common complaints are fatigue, fever, and weight loss. Also, some of its manifestations may be incorrectly diagnosed as acute self-limited processes. Therefore, SlE may remain undiagnosed early in its

course **(Roberts and Hughes, 1989).**

Arthritis or arthralgias are present sometimes in up to 95% of SLE patients, making the joints the most frequently involved organ in SLE **(Rothfield, 1985).** The arthritis associated with SLE is classically nondeforming, nonerosive, and symmetrical **(Russel et al., 1974).** Multiple joints are usually involved, most frequently the proximal interphalangeal joints, knees, wrists, and metacarpophalangeal joints **(Labowitz and Schumacher, 1971).** Deforming arthritis may occasionally occur, leading to typical joint abnormalities, such as swan-neck deformity, but radiographs of the involved joints generally reveal no erosions or pannus **(Weissman et al., 1978).** Muscle inflammation may also occur, resulting in proximal muscle weakness, as seen in polymyositis **(Steinberg, 1988).**

Skin involvement occurs in approximately 70-80% of SLE patients **(Estes and Christian, 1971).** The classic cutaneous manifestation of SLE is an erythematous "butterfly" malar rash. Subacute cutaneous lupus is characterized by symmetrical and superficial lesions, usually occurring on the upper body. Like the malar rash, these lesions may be photosensitive **(Gilliam and Sontheimer, 1982).** Discoid lupus is sometimes an early manifestation of SLE, and these erythematous plaques also occur most commonly on the upper body **(O'loughlin et al.,1978).** Alopecia may be present in up to 50% of SLE patients **(Steinberg, 1988).** In some patients, ulcers of mucous membranes, especially over the palate and nasal septum, occur during Flares of systemic disease. They heal slowly, and often persist after most other symptoms have markedly

improved **(Urman et al.,1978)**. Oral ulcers are one of the criteria in the diagnosis of SLE **(Tan et al.,1982)**. Involvement of the oral cavity was reported to be 17.6% in Harvey's series **(Harvey et al.,1954)** and 9.1% in Dubois series **(Dubois and Tuffanelli, 1964)**.

Cardiac involvement in SLE is found in 30-50% or more of all patients **(Chang, 1982)**. Pericarditis is the most common manifestation of cardiovascular lupus and occurs in approximately 25% of patients. The electrocardiogram shows typical T wave abnormalities in about three-fourths of these patients **(Collins et al.,1978)**. Pericardial tamponade and constrictive pericarditis are rare complications **(Jacobsen and Reza, 1978)**. Myocarditis is seen in 5-10% of SLE patients, and may be manifested by tachycardia, ventricular enlargement, or conduction abnormalities **(Borenstein et al.,1978)**. Systolic murmurs are heard in 30-70% of SLE patients, but it is difficult to determine whether they are due to classical Libman-Sacks endocarditis or to fever, anemia, or hypoxemia that may be associated with SLE. Libman-Sacks verrucous endocarditis is usually asymptomatic but severe valvular disease is possible, although rare **(Pritzker et al.,1980 and Roberts and Hughes,1989)**.

Inflammation of terminal arterioles causing vasculitis in the extremities occurs more commonly than vasculitic changes in large vessels. An urticaria-vasculitis syndrome manifested by angioedema, Laryngeal obstruction, and attacks of abdominal pain may also occur **(Roberts and Hughes, 1989)**. Raynaud's phenomenon is present in about 20 to 30 percent of SLE patients **(Miller et al.,1983)**. It occurs early in SLE, and in 1 to 5% of patients, it