ANTICARDIOLIPIN ANTIBODIES IN RHEUMATOID DISEASE

Thesis

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By

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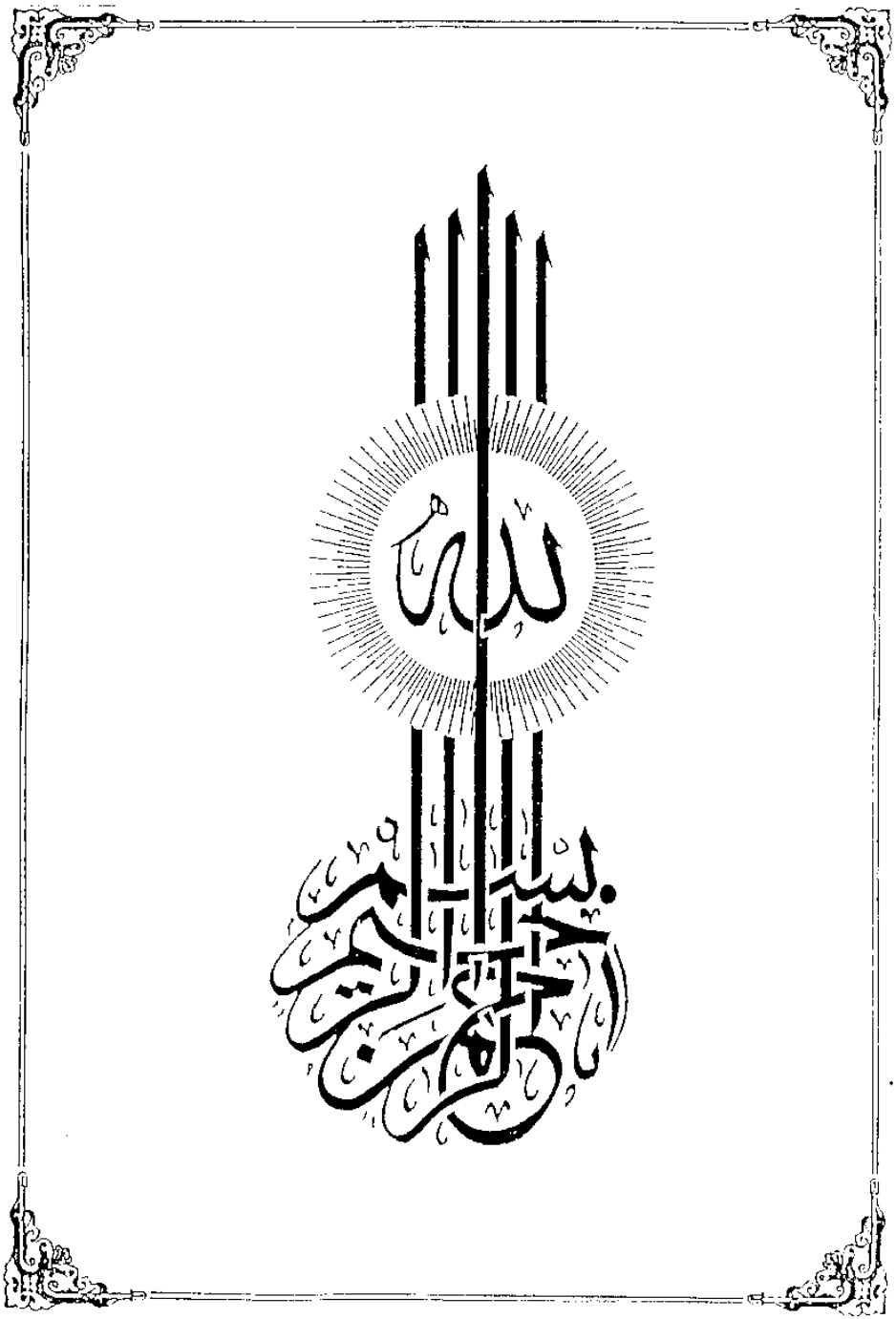

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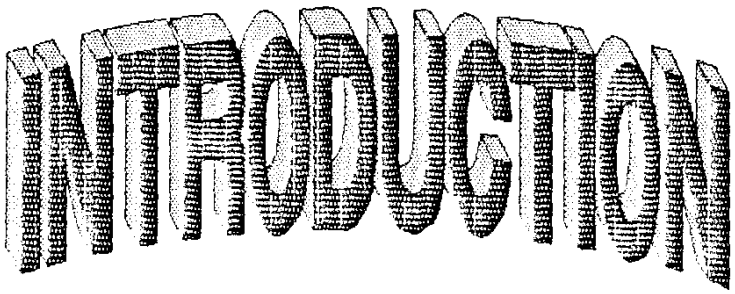


INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic disease in which nonsuppurative inflammation of the diarthrodial joints is frequently combined with a variety of extra-articular manifestations. The course of the disease varies greatly from one patient to another. However, it is characterized by a striking tendency towards spontaneous remissions and exacerbations. In many instances the arthritis is of mild degree and clears completely or remains confined to a few joints, causing little or no impairment of joint function. Commonly however, there is a tendency towards relapse or continued inflammation, leading to destructive joint changes.

The etiology of this disease is still obscure. Several theories were developed to explain its fluctuating nature, but all proved to be unsuccessful. However, there is evidence of an immune response which might play a prominent role in the process of inflammation (*Zvaifler,* 1988).

As a pronounced manifestation vasculitis is the most important extra-articular feature of rheumatoid disease. It has a potential to involve multiple organs such as the skin, peripheral nerves, heart and kidneys which may lead to

visceral infarction.

In 1963, *Sokoloff* pointed out the importance of vasculitis as the basis of all manifestations of rheumatoid arthritis, as the initial pathologic lesion in both synovitis and rheumatoid nodules, it is believed to be an arteriolitis and a venulitis. However, as commonly used, the term rheumatoid arteritis or rheumatoid vasculitis refers to extra-articular clinical manifestations of the disease. These manifestations and their prognosis depend on the type of lesion, as well as the number, size and location of vessels involved (*Bywaters & Scott*, 1963 and *Glass et al.*, 1976).

In 1981, *Scott et al.*, found that necrotizing vasculitis whether recognized clinically as motor neuropathy or visceral infarction or identified histologically in muscle or rectal biopsy, has poor prognosis. *Healey* (1985) observed that vascular lesions, urticaria and palpable purpura tend to subside most quickly, although they may recur. The digital infarcts of obliterative endarteritis are also self-limited, although these necrotic lesions last longer, passing through the stages of pigmentation, sloughing and repair. Even severe finger-tip cyanosis and necrosis may slowly resolve spontaneously over many months.

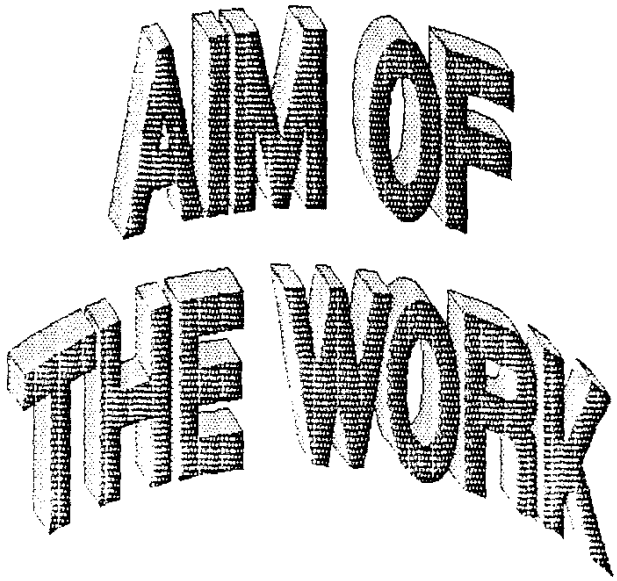
Anticardiolipin antibodies (ACA) are a group of a family of antibodies directed against negatively charged phospholipids (*Harris et al.*, 1983 a). Relatively little is known about anticardiolipin antibodies although these antibodies were first detected several decades ago (*Harris et al.*, 1985c). Few studies were done to detect the presence of these antibodies in different rheumatic diseases and much attention has been focused on the pathogenetic role of these anticardiolipin antibodies in the development of rheumatoid vasculitis.

Anticardiolipin antibodies in rheumatoid arthritis have been investigated in a number of studies. Best estimates of its prevalence are conflicting and the clinical implications of the antibodies in this disease remain controversial (*Keane et al.*, 1987 and *Love & Santoro,* 1990). *Peter et al.* (1991) showed that anticardiolipin antibodies may be involved at least occasionally in the pathogenesis of skin lesions in rheumatoid disease. However, they observed widespread cutaneous necrosis as a rare manifestation of the antiphospholipid syndrome in a patient with rheumatoid disease.

Evaluation of the severity of inflammation in patients

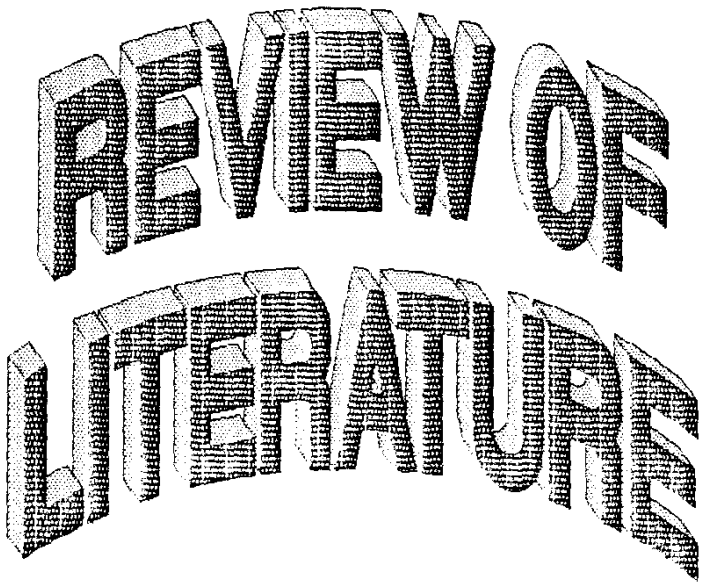
with rheumatoid arthritis is important in the assessment of the disease activity. Many methods have been developed to assess the disease activity in this disease; these include: clinical, laboratory, and radiological indices. *Keane et al.* (1987) found a significant correlation between anticardiolipin antibodies and the overall disease activity in rheumatoid arthritis patients and suggested that the fluctuation in anticardiolipin antibodies appears to parallel the inflammatory response.

Westedt et al. (1987) showed that many patients with rheumatoid disease who appeared to have only joint disease, in fact had sub clinical systemic disease as reflected by a positive skin biopsy which showed sub clinical damage to dermal blood vessels that was insufficient to produce vasculitis. Also, *Heurkens et al.* (1989) found that the frequency of IgG anticardiolipin antibodies was at least four times higher in rheumatoid patients with vasculitis than those without vasculitis. Patients whose rheumatoid vasculitis was in remission tended to have lower titer of ACA than did patients with active disease. So, they pointed out that the presence of anticardiolipin antibodies may be a valuable tool for the diagnosis of vasculitis in patients with rheumatoid disease and also in assessing the disease activity.



AIM OF THE WORK

The aim of this work was to study anticardiolipin antibodies ACA in rheumatoid patients in order to detect their relation to vasculitis and other manifestations of disease activity. This would be important in the early detection of the pre-clinical stages of vasculitis and as a matter of fact may help in predicting those patients susceptible to it even before it sets in.



BIOSYNTHESIS OF CARDIOLIPIN

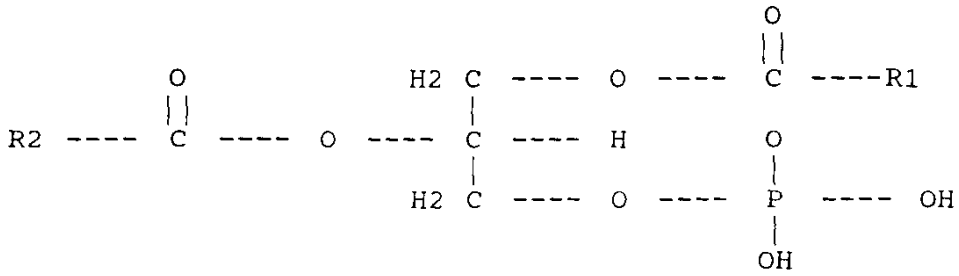
Phospholipids are present in all cells, plant as well as animal tissues specially heart muscle and hence the name. They are the predominating structure of biological membranes, such as plasma membranes and specific membranes that surround the nucleus and mitochondria (*Khalifa,* 1989). They constitute about 7% of the mitochondrial outer membrane lipids and about 26% of the inner membrane lipids (*Guarnieri et al.,* 1971).

Phospholipids play a vital role as constituents of cell membranes, and factors regulating cellular permeability. Cardiolipins play an essential functional and possibly structural role in the cytochrome oxidase complex. They are used in the serologic tests for syphilis, Since cardiolipin is the principle antigen of the venereal disease research laboratory (VDRL) precipitation test (Caterral, 1973). Blood clotting is triggered by phospholipid-containing factors. Also they are unique in that they are the only lipids known to be antigenic (Jones et al., 1991).

The phospholipids include phosphatidic acid, phosphatidyl glycerol (cardiolipin), phosphatidylinositol and phosphatidyl serine which are negatively charged

phospholipids. They also include phosphatidylcholine, phosphatidyl ethanolamine, lysophospholipids, plasmalogens and sphingomyelin.

Phosphatidic acids are the simplest types of phospholipids. They are derived from glycerophosphoric acid by esterification of the two remaining hydroxyl groups, with fatty acids.



Phosphatidic Acid

Cardiolipin is a phospholipid that is composed of two molecules of phosphatidic acid linked together covalently through a molecule of glycerol, thus making it diphosphatidyl glycerol. Each of the phosphates has one dissociable group which accounts for the lipid's acidic properties and ability to bind cations. *Pangborn* (1947) observed that the mixed fatty acids of cardiolipin were composed mainly of unsaturated fatty acids in the form of linoleic acid 72%, oleic acid 11%, linolenic acid 8% and palmitoleic acid 5.2%.