Comparative study of seropositive versus seronegative rheumatoid arthritis

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By

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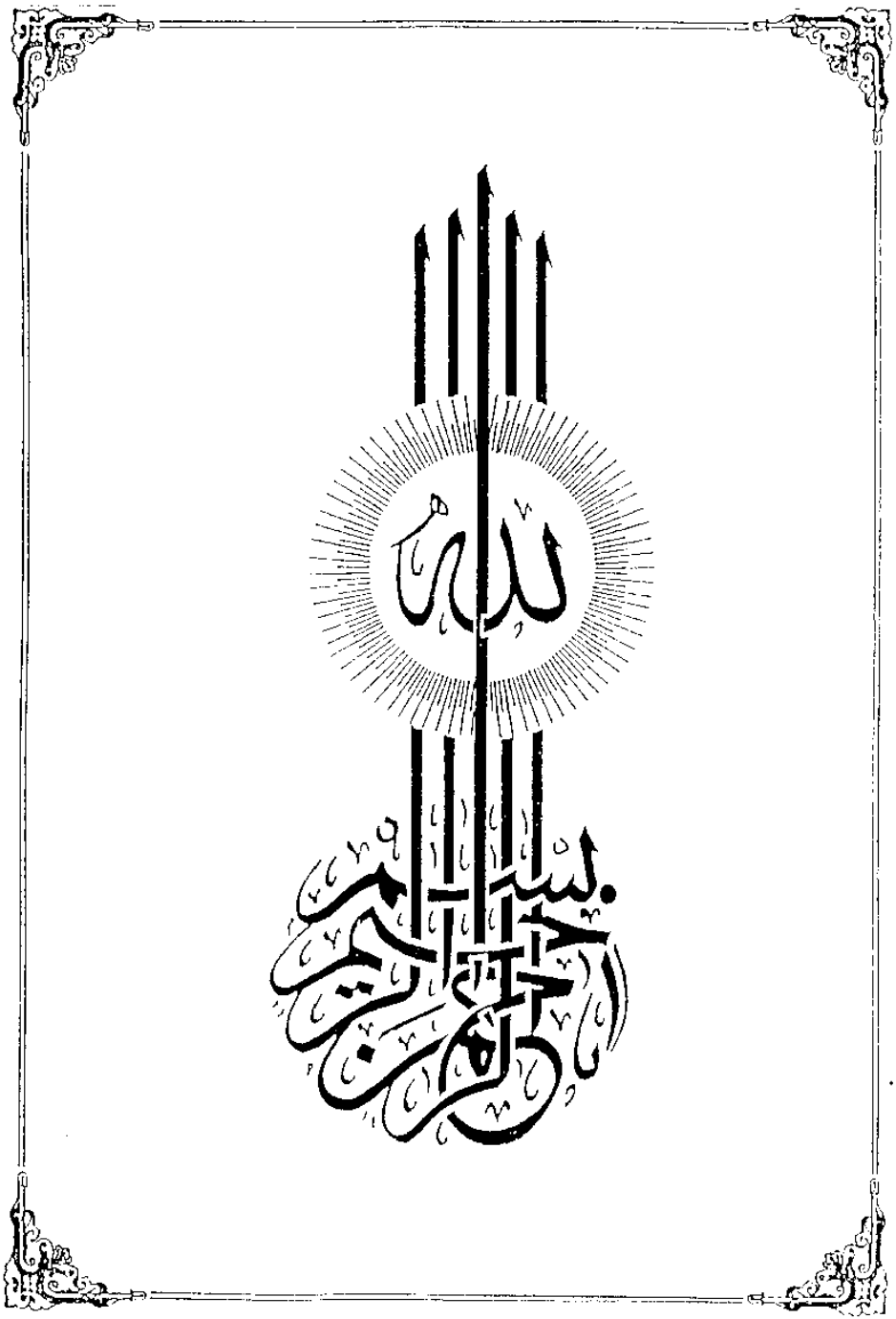

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"Rheumatoid factors" are immunoglobulins mostly IgM but also sometimes IgG or IgA (Stage and Mannik, 1973). It is believed to be an antibody to autologous IgG. It also reacts with heat-denatured human IgG (aggregated) and with rabbit antibody IgG in the latex fixation (LFT) and sensitized sheep cell agglutination tests. These are characteristic serological features of approximately 80% of patients with classical definite and probable rheumatoid arthritis as defined by the "American Rheumatism Association". (Mongan, et al., 1969). In the remaining 20% when complexes between Rheumatoid factor and IgG form in vivo "Rheumatoid factor" activity may be hidden, (Hanson and Winblad, 1978), so that sera yield negative results by classical tests. These patients present a similar clinical picture to positive group with two exceptions:- Subcutaneous rheumatoid nodules are rarely present and the disease tends to run a more benign course.

Moreover the juvenile onset rheumatoid arthritis is usually accompanied with seronegative disease. This has led to the concept that seronegative rheumatoid arthritis may be a somewhat different disease entity from the

seropositive group of patients. Many studies were done to either proove or disproove this concept. The finding that the distribution of LFT titres in patients with rheumatoid arthritis had a bimodal pattern emphasizes the possibility that LFT - positive and LFT - negative patients may represent distinct rather than merging populations. The number of patients who were LFT - negative was too large in proportion to the number who were LFT - positive for them to be considered simply as one tail on the apparently bell - shaped curve of distribution of the LFT - positive group (Mongan, et al., 1969).

It must be emphasized that the bimodality found in the study of Mongan, et al., (1969), is serologic only. What is suggested by it is that the bulk of patients called seronegative are in fact seronegative and not simply a group of seropositive patients with a low LFT. A qualitative rather than a quantitative difference in serologic state is thus implied. It is in this sense alone that the present data may suggest distinct rather than merging populations.

Nevertheless, the other laboratory differences which exist between the LFT - positive and LFT - negative groups

may signal the operation of different pathogenetic pathways in them.

Both for diagnosis and prognosis, tests able to detect and qualify hidden "Rheumatoid factors" would be of clinical value and might help to elucidate the biological significance of such complexes.

In this review stress will be done on what is common between the two groups and the points of difference between them. Evaluation of the different techniques used to detect rheumatoid factors will be discussed.

IMMUNOLOGICAL CHANGES
IN
RHEUMATOID ARTHRITIS.

RHEUMATOID FACTORS

The interaction of rheumatoid sera with gamma globulins has been known for many years. This reaction has been found to be mediated by a macroglobulin commonly called the "Rheumatoid factor" (RF) (Franklin et al., 1957a).

The Rheumatoid factors are now defined as antibodies specific to antigenic determinants on the Fc fragments of human immunoglobulin G (Natvig et al., 1971).

As detected in routine serological tests, "Rheumatoid factor is IgM antibody, (Franklin et al., 1957b).

Immunoglobulin M Rheumatoid factor is characteristic serological feature of approximately 80% of patients. This factor apart from its diagnostic value, has been known to correlate with: nodules, worse over-all prognosis, severe bone destruction in rheumatoid joints, multisystem involvement and vasculitis (Morgan, et al., 1969). In the remaining 20% the sheep red cells agglutination test is persistantly negative and therefore lacking IgM Rheumatoid factor. These seronegative patients were found to contain

Rheumatoid factor of the IgG or IgA class (Stage and Mannik, 1973), this was first called intermediate complexes (Kunkel, et al., 1961; Schrohenloher, 1966) and later recognized as self - associating IgG anti γ globulin molecules (Pope et al., 1974; 1975). These patients present a similar clinical picture to positive group with two exceptions: Subcutaneous nodules are rarely present, and the disease tends to run a more benign course (Mongan et al., 1969).

In general, patients who are seropositive remain so and seronegative patients continue to be seronegative regardless of subsequent clinical events. There are few exceptions, for example, for a given serological system, subjects with borderline or low positive titers may fluctuate between negative and the low order of positivity, and patients experiencing complete remission in some studies, have changed from positive to negative (Max Samter, 1978).

In 5% of healthy persons older than 60 years, rheumatoid factor may be detected in a significant titer. (Torrigiani and Roitt, 1967).

Also it should be emphasized that Rheumatoid factors are not specific for rheumatoid arthritis. A significant

percentage of patients with other connective tissue syndromes and a variety of illnesses such as pulmonary TB , sarcoidosis, leprosy, syphilis, liver disease, leishmaniasis and bacterial endocarditis give positive agglutination test (Kunkel, et al., 1958; Peltier and Christian, 1959; Singer et al., 1962).

Patients with juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, arthritis associated with ulcerative colitis, regional enteritis, agammaglobulinaemia are sometimes classified as variants of rheumatoid arthritis as they are in general seronegative. An exception to this is the fact that the majority of patients with juvenile rheumatoid arthritis were judged seropositive on the basis of an inhibition test. This procedure is difficult to perform and interpret and remains, after several years of study, a research tool, (Parker, 1980).

IMMUNOGLOBULINS LEVELS IN "RHEUMATOID ARTHRITIS"

Mongan, et al in 1969, stated that latex flocculation test (LFT) positive patients with rheumatoid arthritis had statistically significant elevations of all three classes of immunoglobulins (IgG, IgA, IgM) above the normal values. Meanwhile the LFT - negative patients had significant elevations of IgG and IgM only. The euglobulin levels were highest in the LFT - positive patients in whom the mean was considerably above the range established for normal in this laboratory. In the LFT - negative patients with rheumatoid arthritis the means of the euglobulin levels were at the upper limit of the normal range.

The IgG to IgA relationship that is present in normal populations, (Lightman, et al., 1967), was well preserved in the LFT - positive group, but less clearly present in the LFT - negative group. In the LFT - negative group an abnormal IgG : IgM relationship was exhibited, (Mongan et al., 1969).

In the LFT - positive group, the euglobulin level was significantly related to LFT, as might be expected

because of the lesser solubility of RF complexes (Lamont-Havers, 1955). For unknown reasons, however, the euglobulin level also correlated with IgA. There were positive correlations in the LFT - positive group of euglobulin with IgG and IgM, but these did not reach statistically significant levels. A positive correlation was also found between LFT titer and the IgM level and a weak negative correlation between LFT and C'H 50. There was no significant correlation between LFT and IgG or IgA levels. In the LFT - negative group the strongest correlations for the euglobulins were with the hematocrit (negatively) and IgM (positively), but because of the paucity of observations neither of these correlations was statistically significant, (Mongan, et al., 1969).