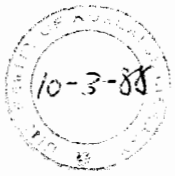

LOW MOLECULAR WEIGHT IgM IN HEALTH AND DISEASE

by

Peter John ROBERTS-THOMSON, M.B.,B.S.(Adelaide); D.Phil. (Oxford)

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ABSTRACT

This thesis examines the presence and role of low molecular weight (LMW) IgM in health and disease. LMW IgM is the naturally occurring monomeric subunit of pentameric IgM and has been previously observed in the blood from patients suffering from a variety of disorders but rarely in health.

In Chapter one there is a general description of the known physicochemical properties, function and role of both pentameric IgM and LMW IgM. Possible theories for the presence of LMW IgM in human disease are briefly discussed.

In Chapter two a description is given of three sensitive methods to detect and quantitate LMW IgM. One of these, viz immunoblotting, appears both sensitive and specific for LMW IgM and has revealed for the first time additional oligomers of IgM in sera containing LMW IgM.

In Chapter three sera from healthy controls and cord blood were examined for the presence of LMW IgM. This moiety was not found in sera from healthy subjects but was observed in low levels in a minority of cord sera.

Chapter four details a study of LMW IgM in sera and synovial fluid from patients with a variety of rheumatic disorders. In rheumatoid arthritis, 80% of the patients were found to have circulating LMW IgM and its levels correlated significantly with absolute IgM levels (measured nephelometrically) and with levels of rheumatoid factor and

circulating immune complexes. Separated column fractions containing LMW IgM were observed to contain IgM rheumatoid factor activity.

In Chapter five peripheral blood mononuclear cells taken from patients with active rheumatoid arthritis were found to secrete considerable quantities of LMW IgM in vitro. This did not occur with cells obtained from healthy controls. A significant correlation was found between the percentage of circulating LMW IgM and with the percentage of LMW IgM secreted in vitro. No evidence was obtained to suggest that LMW IgM occurred as a consequence of proteolytic breakdown of pentameric IgM.

In Chapters six, seven, eight and nine LMW IgM was observed in a varying proportion of patients suffering from infective endocarditis, mixed cryoglobulinaemia, selective IgA deficiency and in malignant B cell lymphoproliferative disorders but not in benign macroglobulinaemia. In 3 patients with mixed cryoglobulinaemia the LMW IgM was monoclonal and of the same light chain type (kappa) as the monoclonal pentameric IgM rheumatoid factor suggesting a common clonal origin.

In Chapter ten there is a brief discussion concerning the most likely explanations for the occurrence of LMW IgM in human disease and its possible role in the pathogenesis of these disorders. It is concluded that it is highly likely that LMW IgM has a pathogenic role in human disease. Further studies concerning this long neglected immunoglobulin are indicated as there is a distinct possibility that therapeutically reverting the disorded monomeric IgM humoral response

to a normal pentameric IgM response may result in resolution or amelioration of the disease.

Finally, the findings described in this thesis and from other observations are best accounted by postulating a defect in the assembly of the monomeric IgM subunits during pentameric IgM synthesis and secretion. Possible defects are discussed together with avenues of exploring such defects in future studies.