have shown variable results which suggests that a significant relationship is unlikely. Using similar techniques, several workers have found the frequency of the class II antigen HLA-DR4 in polymyalgia rheumatica and giant cell arteritis to be about twice that in normal controls [12-14]. In some reports of patients with giant cell arteritis, HLA-DR4 has been increased only in those with polymyalgia rheumatica [14]. In the study by Sakkas et al. [15] published in this issue, 44 patients with polymyalgia rheumatica were included. Only two had giant cell arteritis. Standard techniques were used for restriction fragment length polymorphism analysis to determine class II antigens, the switch region of immunoglobulin mu heavy chain gene (Sμ), and T-cell antigen receptor (TCR) α, β, λ chain genes in order to identify possible genetic markers associated with this disease. As in previous studies, an increased frequency of HLA-DR4 specificity was found which was highly statistically significant. The other analyses were negative. In addition, the number of DR4 homozygous patients was greater than expected by chance. These results confirm earlier studies with the additional result of showing the increased frequency of homozygous DR4 genotypes. The findings clearly strengthen the concept that HLA-DR4 is an important susceptibility factor for polymyalgia rheumatica.

It has become apparent from mixed lymphocyte culture testing that HLA-DR4 can be divided into five subtypes, namely, Dw10, Dw13, Dw14 and Dw15 [16]. In order to investigate the similarities or differences from other diseases associated with HLA-DR4, especially rheumatoid arthritis, testing of these subtypes is indicated. Although this will not be the final answer on the potential influence of immunogenetic factors in the development of polymyalgia rheumatica, it may provide further insight as to whether the HLA-DR4 molecule is aberrant, or point investigation in some other direction such as further search for changes in the T-cell receptor, also genetically controlled, and screened by Sakkas and co-workers.

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ANTI-RNP ANTIBODIES AND THEIR CLINICAL SIGNIFICANCE

Since 1972, antibodies to RNP (anti-RNP) have achieved a notable clinical importance through their association with mixed connective tissue disease (MCTD) [1]. However, anti-RNP can also be detected in patients with systemic lupus erythematosus (SLE) and have been occasionally reported in a broad range of autoimmune diseases [2]. In the original description, MCTD patients lacked renal involvement, responded to corticosteroids, and were reported to have a good prognosis [1]. Since then, many confirmatory reports have been published, but other studies have failed to find any clinical correlation with anti-RNP or have focused on the occurrence of severe systemic features with a poor clinical outcome in anti-RNP positive patients [3–5]. In this issue, Pirinen [6] reports a very high frequency of severe erosive arthritis after a 10-year follow-up in patients with anti-RNP.

Controversies on the clinical significance of these antibodies can be ascribed to three main points. The first one is that anti-RNP detected by immunodiffusion or counterimmunoelectrophoresis appear heterogeneous as for their fine specificities. Anti-RNP recognize a ribonucleoprotein particle that plays a central role in pre-messenger RNA splicing [7]. This particle is com-

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posed of a small nuclear RNA designated U1, and three or more distinct U1-RNA-binding proteins. In immunodiffusion and haemagglutination assays, the reaction of U1-RNP with its antibody requires the whole particle, i.e. both RNA and proteins, and is abolished by pretreating the antigen with either RNAase or trypsin. However, immunoblot studies have shown that the immunoreactive sites are located on the protein moiety and that anti-RNP sera can react with different proteins. Sera from patients with MCTD react predominantly with a 68 kDa protein, whereas many anti-RNP sera from SLE patients do not [8]. The development of specific immunoassays for detecting antibodies to the 68 kDa protein will probably contribute to a better definition of MCTD [9].

The second point is that other autoantibodies present, together with anti-RNP, may have clinical relevance. Most investigators agree that the autoantibody profile is strikingly restricted to anti-RNP in MCTD, while multiple ANA specificities including anti-Sm, anti-Ro and antibodies to other non-histone nuclear antigens can be present along with anti-RNP in SLE patients [10]. However, in recent years it has become apparent that antinuclear antibodies other than anti-RNP can be detected in MCTD sera [11], e.g. those antibodies to heterogeneous nuclear RNP core proteins that have been detected also in SLE and rheumatoid arthritis [12]. In SLE patients, anti-RNP are often associated with antibodies to Sm, a nuclear antigenic complex related to RNP [8]. Anti-Sm is considered specific for SLE but the titre may rise and wane during the course of the disease. Low-titre anti-Sm was found by immunoblot assay in several anti-RNP sera proved to be negative for anti-Sm when tested by counterimmunoelectrophoresis [13]. The occurrence of both anti-RNP and anti-Ro in a single patient is not a rare event though these antibodies do usually identify distinctive serological subsets [14]. On the other hand, antibodies to double stranded DNA occur rarely in anti-RNP positive (anti-Sm negative) patients and this may explain a negative association with renal disease [1]. Pulmonary hypertension and thrombocytopenia have been reported to be associated with anti-RNP [3–5] and with antiphospholipid antibodies as well [15]. A recent study has shown a very high frequency of antiphospholipid antibodies in children with connective tissue disease [16]. This might partially explain why thrombocytopenia and pulmonary hypertension seem to occur more frequently in children with MCTD than in adult patients [5].

The third point is that the diagnostic and prognostic importance of anti-RNP in different studies is largely dependent on the criteria of patient selection and the duration of follow-up. When all patients with clinical suspicion of connective tissue disease were analysed, the presence of anti-RNP was mainly associated with Raynaud's phenomenon and overlap features. Accordingly, the presence of clinical myositis with SLE is almost exclusively restricted to those patients with anti-RNP [17]. However, when overlap syndromes were analysed in both adults [4] and children [18], no definite clinical difference could be found between anti-RNP positive and anti-RNP negative patients. These findings do not support the view that anti-RNP can identify a definite clinical picture within the spectrum of the overlap syndromes, no matter whether or not MCTD constitutes a distinct entity. Furthermore, long-term follow-up studies have shown that anti-RNP can appear in previously negative patients and can disappear in some patients who once had them [4]. Thus, it could be fallacious to classify a patient as anti-RNP positive or anti-RNP negative on the basis of a single evaluation.

We hope that prospective studies with periodic careful serological and clinical evaluation will determine the actual value of detecting anti-RNP in a patient with connective tissue disease. At present, however, it is quite disappointing for a clinician to see that these antibodies have achieved more information about the molecular biology of pre-messenger RNA [7] than any advance of clinical classification or prognosis of connective tissue diseases.

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