In fact, unlike A B Garrod, Gosse used rheumatism with the general meaning of algic fluxion not restricted to the joints, a meaning in line with that used by Galen, which today remains in popular use parallel with the nosographical nomenclature. He emphasised the relationship of such congestive changes with cold (particularly a rapid passage from warm to cold) and with the nervous system. His ‘ideas’ of rheumatism were part of an extension of the above mechanisms to a large panoply of conditions including practically all those which are painful, congestive, or pathogenic. This study is obsolete regards today’s nosology, and was obviously expressed in the words of its day, before knowledge of the aetiological data that were revealed by advances in bacteriology. However, it foretold the modern investigations into the diffuse role of non-specific vascular disturbances and of neurotransmitters in neurogenic inflammation.

While each of these meanings of rheumatoid had its own logic, a long term follow through confirms that the term had a useful place in the progress of an already established nosography, though it was abandoned when it served only to extend an already unclear pathogenicity. At a time when modern biology is providing a plethora of basic information in rheumatology, the origin of the term rheumatoid arthritis must not be forgotten. In extensions such as rheumatoid nodules or rheumatoid factor, the adventitious rheumatoid is elliptical, as the changes which are thus named cannot be directly explained by the etymology, but are indirectly related to it through a nosological entity.

RENE LAGIER
Department of Pathology, Genova Medical School, Genova, Switzerland

Correspondence to: Dr Rene Lagier, Departement de Pathologie, C M U, 1 rue Michel Servet, C H 1011 Genova 4, Switzerland


Interleukin-6 in clinical relapses of polymyalgia rheumatica and giant cell arteritis

Polymyalgia rheumatica and giant cell arteritis are related diseases associated with increased concentrations of acute phase reactants. Clinical symptoms and acute phase reactants respond promptly to corticosteroid treatment in most patients, and a decision to withdraw prednisone may be recommended after two years of evolution of the disease. This may represent a critical phase for patients with polymyalgia rheumatica, who are exposed to relapse with threatening symptoms of giant cell arteritis. At present there are no signs or tests that distinguish patients with evolving disease from those in complete or partial remission. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) are used as aids in the management of the disease, but their values remain normal in about 50% of patients with clinical relapses of polymyalgia rheumatica and giant cell arteritis who are receiving treatment.

Furthermore, diagnosis of relapse is frequently based on the clinician’s experience in detecting clinical symptoms and signs. Additionally, this would be of help in enabling more precise monitoring of patients receiving treatment, and might also make possible a reduction in the duration of steroid treatment.

Interleukin-6 (IL-6) mediates the acute phase response by hepatocytes. Its concentration is increased in patients with polymyalgia rheumatica and giant cell arteritis before corticosteroid treatment, and while this increase is not specific to these diseases, IL-6 could be a biological marker of their disease activity. To determine the value of IL-6 as such a marker in clinical relapses of polymyalgia rheumatica and giant cell arteritis, we studied if IL-6 concentration, compared with those of acute phase reactants, during the reduction of prednisone dosage in patients with polymyalgia rheumatica and giant cell arteritis.

Twenty patients (15 women, five men; 17 with polymyalgia rheumatica (criteria of Bird et al) and three with giant cell arteritis (American College of Rheumatology 1990 criteria)) were studied retrospectively. Clinical evaluations were made by a consultant rheumatologist and blood samples were taken before and one month after 50% reduction of the prednisone dose, and at clinical relapse. The latter, defined as the reappearance of typical morning pain and stiffness of the shoulder and pelvic girdles, was identified by a rheumatologist blinded to the results of acute phase reactant and IL-6 assay. When in consecutive samples blood was taken, clinicians took the decision to increase the dose of prednisone to that given before relapse.

ESR was measured by the Westergren method; rheumatoid factor (RF) (titre < 1/160), haptoglobin (HP) (titre < 1/2 g/l), and fibrinogen (Fg) (titre < 4-1 g/l) were measured by a chromometric method. Plasma samples were stored at −80°C until required for determination of IL-6 concentration by radioimmunoassay (Medegenix).

Statistical analyses for unpaired and paired data were performed using the Mann-Whitney test and the Wilcoxon test, respectively. The level of significance was set at p < 0.05.

At entry to the study, all patients were in remission and were receiving a stable dose of prednisone less than 10 mg/day (mean 4.4 (SD 2.4) mg/day). The mean disease duration was 33.3 months (range 12-240). Nine patients had a clinical relapse within one month after their prednisone dose was tapered. No subsequent evaluation was made, so the occurrence of late relapse could not be determined in this study. The clinical characteristics of patients who did or did not experience clinical relapse were not different (table 1), and there was also no difference in concentrations of IL-6 and acute phase reactants between these two groups before...
Table 1  Clinical features of patients with or without clinical relapse

<table>
<thead>
<tr>
<th></th>
<th>Without clinical relapse</th>
<th>With clinical relapse</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n = 11)</td>
<td>(n = 9)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>75-1 (8-3)</td>
<td>75-6 (7-6)</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>1:10</td>
<td>4:3</td>
</tr>
<tr>
<td>Diseases</td>
<td>9 PRM</td>
<td>8 PRM</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>57-8 (51-4)</td>
<td>51-4 (43-7)</td>
</tr>
<tr>
<td>Prednisone dose (mg/day)</td>
<td>Initial</td>
<td>After reduction</td>
</tr>
<tr>
<td></td>
<td>19-7 (8-4)</td>
<td>1-8 (1-1)</td>
</tr>
<tr>
<td>Values are mean (SD).</td>
<td>PMR = Polymyalgia rheumatica; GCA = giant cell arteritis.</td>
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It is feasible that the sex ratio of siblings may be associated with the development of autoimmune disease, as hormone concentrations are believed to affect the sex of offspring. Therefore, parents with low testosterone concentrations may be more likely to have female children, with these children being at an increased risk of developing RA because of their inherited tendency for low testosterone concentrations.

It was also expected that women with RA would themselves be more likely to have daughters instead of sons. Indeed, Deighton et al have previously reported such a finding, although numbers were small (16 daughters and 25 sons). We have therefore investigated this relationship among a larger group of 94 women with RA. These women had provided pregnancy information and undergone HLA-DR typing for the purpose of another study (submitted for publication). The hypothesis was that if women with RA experience reduced concentrations of androgens, they might be expected to have an excess of daughters. Given that androgen concentrations may be partially regulated by HLA-DR status, the analysis was conducted separately for HLA-DR positive and negative populations.

Overall, the 94 women had 202 children: 99 girls and 103 boys. The observed proportion of children that were daughters (0.49) was the same as that expected. When considered separately by HLA-DR status, however, there was an excess of sons among the HLA-DR4 negative mothers, and an excess of daughters among the HLA-DR4 positive mothers (table II). The ratio associated with being HLA-DR4 positive and bearing a daughter was 2:1 (95% confidence interval 1.1-4.2). This therefore does appear to provide tentative evidence of a link between HLA-DR status and the gender of offspring, supporting a role for androgens in the aetiology of RA. These observations need to be repeated in other populations.

Number of sons and daughters among women with RA, according to mothers’ HLA-DR status

<table>
<thead>
<tr>
<th>Mothers’ HLA-DR status</th>
<th>Number of mothers</th>
<th>Number of daughters</th>
<th>Number of sons</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR4+ (n = 159)</td>
<td>84 (55%)</td>
<td>75 (47%)</td>
<td>79 (53%)</td>
</tr>
<tr>
<td>DR4- (n = 35)</td>
<td>15 (35%)</td>
<td>28 (65%)</td>
<td>18 (40%)</td>
</tr>
</tbody>
</table>

Role of androgens in the aetiology of rheumatoid arthritis

It is likely that the gender difference in the occurrence of rheumatoid arthritis (RA) can be explained, at least in part, by the effects of sex hormones, with both increased concentrations of prolactin and decreased concentrations of androgen being implicated. Androgen concentrations also appear to be regulated by genes encoded within the HLA region, with lower concentrations reported among women who are HLA-B15 positive and women who are HLA-DR4 positive. Other data supporting the hypothesis that androgen concentrations influence the onset of RA are based on the observation that siblings of probands are more likely to be female.

Paul Brennen, Alan Silman
ARC Epidemiology Research Unit
University of Manchester Medical School
Manchester M13 9PT, United Kingdom