LETTERS TO THE EDITOR

What is meant by 'rheumatoid'?

The term *'rheumatoid arthritis'* is now established worldwide in the nosography of rheumatic diseases. Its origin can be found in the following statement by the London physician Alfred Baring Garrod, who proposed this term as an alternative to *'rheumatic gout'*, which was previously used: 'Although unwilling to add to the number of names, I cannot help expressing a desire that one may be found for the disease under consideration, not implying any necessary relation to gout or rheumatism. Shortly before the first edition of the present work was published, about 1858, I proposed the term *Rheumatoid Arthritis*, by which name I wish to imply an inflammatory affection of the joints, not unlike rheumatism in some of its characters, but differing materially from it in its pathology.'[1] As was clearly stated in a comparative table in Garrod's book, *rheumatism* thus referred to the condition that is now known as rheumatic fever. Therefore, *rheumatoid arthritis* was then introduced as a new nosographical term associating two ideas: first, that of a comparison with another nosological entity established in the XVIIth century when Baillou initiated a series of studies that, together with those of Sydenham and Heberden, led to the modern nosography of rheumatic diseases;[2-4] and second, that of a joint illness.

After more than a century, today the term *rheumatoid arthritis* remains a useful tool, despite some dismemberment as a result of advances in biology, pathology, and medical imaging, and a heterogeneity which had already been noted by Archibald, the son of A B Garrod: 'For this name, which, was introduced by my father, I have naturally a pious respect, but I am fully alive to its shortcomings. It was certainly an advance upon the term "rheumatic gout", which it superseded in the middle of the last century, but this in turn has lost its utility, and might be superseded by a better name if such could meet with general acceptance.'[5] Archibald Garrod also said that one of the questions 'is whether there be any one specific disease to which the name rheumatoid arthritis may be applied, or whether the condition so called is rather a syndrome ....'[5] Nevertheless the persistence of the term illustrates the words of the philosopher John Locke: '...language had yet a farther improvement in the use of general terms, whereby one word was made to mark a multitude of particular existences ....'[6]

In parallel, it is interesting to note that the term *rheumatoid* had already been proposed in 1826 by the physician Louis-André Gosse of Geneva: 'Although far away as I may be from a pedantic neologism, I was forced nevertheless to create new terms to generalise my ideas; the term *Rheumatoid* (*) seemed to me a convenient term to assemble this group of diseases with which I am dealing, of which the commonest example is Rheumatism ....'[7] The asterisked footnote indicated, with Greek characters, 'from rheuma, fluxion and from oidos, similar to.'

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,[2] which today remains in popular use in 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' concerning *rheumatoid* were thus an extension of the above mechanisms to a large panoply of conditions including practically all those which are painful, congestive, or both. This study is obsolete as 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 pathogenic concept. Today, 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 adjective *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.

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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.[1] 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 recovery. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) are used as aids in the management of the disease,[2 3] but their values remain normal in about 50% of patients with clinical relapses of polymyalgia rheumatica and giant cell arteritis who are receiving treatment.[4] Furthermore, diagnosis of relapse is frequently based on the clinician's experience in detecting clinical symptoms. Additional tests 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,[5 6] and while this increase is not specific to these disorders, 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 the variations in IL-6 concentrations, 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*[7]) and three with giant cell arteritis (American College of Rheumatology 1990 criteria[8])) were followed prospectively. 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 assays. When it occurred, and after 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; CRP (normal value (NV) < 10 mg/l), orosomucoid (α_1-acid glycoprotein; NV < 1·2 g/l), and haptoglobin (NV < 4·1 g/l for men, < 2·6 g/l for women) were measured by immunonephelometry; fibrinogen (NV < 5 g/l) was measured by a chronometric method. Plasma samples were stored at −80°C until required for determination of IL-6 concentration by radioimmunoassay (Medgenix).

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 $p < 0{\cdot}05$.

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) mg/day). The mean disease duration was 53·3 months (range 12–170). 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

	Without clinical relapse (n = 11)	*With clinical relapse (n = 9)*
Age (y)	75·1 (8·3)	75·6 (7·6)
Sex ratio (M:F)	1:10	4:5
Diseases	9 PMR 2 GCA	8 PMR 1 GCA
Disease duration (months)	57·8 (51·4)	51·4 (43·7)
Prednisone dose (mg/day)		
Initial	19·7 (8·4)	16·8 (6)
Before reduction	3·9 (1·9)	5 (2·1)
After reduction	1·8 (1·1)	2·1 (1·4)

Values are mean (SD).
PMR = Polymyalgia rheumatica; GCA = giant cell arteritis.

Table 2 Results of laboratory tests in nine patients before prednisone reduction and at clinical relapse

	Before prednisone reduction	*At clinical relapse*	*Wilcoxon test p value*
ESR (mm/1st h)	20 (14)	25 (16)	0·19
CRP (mg/l)	9·8 (2·3)	15·3 (12·7)	0·18
Orosomucoid (g/l)	0·85 (0·21)	0·91 (0·24)	0·24
Haptoglobin (g/l)	1·41 (0·63)	1·64 (0·92)	0·10
Fibrinogen (g/l)	4 (0·8)	4·5 (1·4)	0·29
IL-6 (pg/ml)	4 (12)	14 (23)	0·04

Values are mean (SD).
ESR = Erythrocyte sedimentation rate; CRP = C reactive protein; IL-6 = interleukin-6.

reduction of their prednisone dose (data not shown). In the nine patients with clinical relapse, ESR, CRP, orosomucoid, haptoglobin, and fibrinogen each showed a non-significant increase at clinical relapse compared with the values observed before the reduction of prednisone, while IL-6 values were significantly increased ($p = 0·04$) (table 2). Among the same nine patients, only two had an ESR ≥ 30 mm/1st h, and two had CRP concentrations ≥ 10 mg/l, while four had IL-6 concentrations ≥ 5 pg/ml at clinical relapse. In all patients experiencing clinical relapse, symptoms were controlled after their dose of prednisone was increased again. Among the three patients with giant cell arteritis, two had no relapse and did not have increased concentrations of IL-6. No unexpected increase in IL-6 concentration occurred in patients without relapse: the IL-6 value in this group of patients was 7 (20) pg/ml before reduction of the dose of prednisone, and 5 (10) pg/ml one month afterwards.

These preliminary data have demonstrated an increase in the plasma concentration of IL-6 during clinical relapses of polymyalgia rheumatica and giant cell arteritis, while ESR, CRP, haptoglobin, orosomucoid, and fibrinogen showed minimal variations. Additional studies are required to determine the further potential usefulness of IL-6 in the management of polymyalgia rheumatica and giant cell arteritis.

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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.[1] Androgen concentrations also appear to be regulated by genes encoded within the HLA region, with lower concentrations reported among men who are HLA-B15 positive[2] and women who are HLA-DR4 positive.[3] Other data supporting the hypothesis that androgen concentrations influence the onset of RA are based on the observation that siblings of RA probands are more likely to be female.[4]

Number of sons and daughters among women with RA, according to mothers' HLA-DR4 status

Mothers' HLA-DR status	*Number of daughters*	*Number of sons*
DR4+ (n = 159)	84 (53%)	75 (47%)
DR4– (n = 43)	15 (35%)	28 (65%)

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.[5] 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.

If this hypothesis were true, it would also be 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,[3] though numbers were small (16 daughters and seven 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-DR4 status, the analysis was conducted separately for HLA-DR4 positive and negative women.

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). The odds ratio associated with being HLA-DR4 positive and bearing a daughter was 2·1 (95% confidence interval 1·1 to 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. However, these observations need to be repeated in other populations.

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