Heberden Society

Clinical Meeting, February 1982

At a clinical meeting held at the Royal Postgraduate Medical School and Hammersmith Hospital, Ducane Road, London W12, on 25–26 February 1982 the Heberden Round was conducted by Dr G. R. V. Hughes and the following papers were presented.

High-dose methylprednisolone (MP) infusions in acute rheumatoid arthritis (RA); a double-blind, placebo-controlled trial. I. A. Williams, E. M. Baylis, M. E. Shipley. Kent and Sussex Hospital, Tunbridge Wells, Kent.

Acute RA is painful and disabling and produces an acute inflammatory process in affected joints. Non-steroid anti-inflammatory therapy often produces incomplete relief of symptoms, and gold or penicillamine may take several months to induce remission. Corticosteroids control symptoms rapidly, but their use is limited by both problems with withdrawal and long-term side effects.

We report the results of a double-blind, placebo-controlled study of 20 patients with acute RA using Ig MP or saline infused in 16 ml over 20 min. No patient had previously received penicillamine or oral steroids. Two were on established gold therapy, despite which their disease flared. All were outpatients.

Subjects were assessed at 0, 2, 4, and 6 weeks using various clinical measurements (Table 1). At 6 weeks those patients deemed treatment failures were given a second infusion containing Ig MP and then assessed for a further 6 weeks.

The results (Table 1) show a significant improvement in all measurements in the MP group sustained for at least 6 weeks. The placebo response was limited and did not last beyond 2 weeks. No significant side effects were encountered, and adrenal suppression was transient. Eleven patients were therapeutic failures, including all 10 controls. Subsequent MP infusion produced a sustained and significant response in this group, who acted as their own controls.

We conclude that MP infusions are a valuable means of achieving rapid symptomatic relief in patients with acute RA and suggest that they warrant further study.

A long-term comparative study of the effects of fenofenac and gold in rheumatoid arthritis. N. L. Cox, W. Goodall. Royal Hants County Hospital, Winchester, Hants.

Recent evidence has suggested that fenofenac has an activity profile which differs from that of other non-steroidal anti-inflammatory agents. In a long-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical measurements in acute RA: the effect of infusion of MP (Ig) or of placebo with subsequent MP infusion at 6 weeks. Mean (±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP (Ig)</td>
<td>(n=10)</td>
</tr>
<tr>
<td>Pre</td>
<td>2/52</td>
</tr>
<tr>
<td>15-4</td>
<td>1-8</td>
</tr>
<tr>
<td>10-0</td>
<td>21*</td>
</tr>
<tr>
<td>24-3</td>
<td>314*</td>
</tr>
<tr>
<td>6-6</td>
<td>634*</td>
</tr>
<tr>
<td>18-1</td>
<td>(18)</td>
</tr>
<tr>
<td>39-7</td>
<td>16-5*</td>
</tr>
<tr>
<td>5-5</td>
<td>(4-8)</td>
</tr>
</tbody>
</table>

*p<0-01; t<0-05 Wilcoxon’s matched-pairs signed-ranks test.

Minutes. *mmHg. **mm. d Visual analogue scale mm.
term open study it produced a significant decrease in ESR, and controlled studies have shown significant decreases in ESR and C-reactive protein (CRP).

This study was set up to investigate this further. Patients with definite or classical seropositive RA were randomly allocated to treatment with gold or fenclofenac in addition to their already stable anti-inflammatory therapy. Assessments were carried out monthly for the first 6 months and then at 9, 12, 18, and 24 months. Clinical measurements were carried out by a 'blind' external observer.

Sixty patients have entered the study and will be followed up for 2 years. So far 46 patients have been followed up for 6 months and 30 patients for 1 year. Clinical measurements show a marked improvement in both groups at 6 months, with results favouring the fenclofenac group in pain score, early morning stiffness (EMS), Ritchie score, and joint count. Laboratory measurements showed a significant decrease in ESR, CRP, IgA in both groups. At 12 months CRP, joint count, and EMS were significantly better in the fenclofenac group.

It is suggested that fenclofenac has genuine disease modifying activity in RA comparable to that of gold. Further reports comparing erosive change in the 2 groups will be presented later.

A placebo-controlled clinical and laboratory comparison of auranofin and Myocrisin in patients with rheumatoid arthritis. D. Lewis, C. McNeil, W. E. Smith, H. A. Capell. Centre for Rheumatic Diseases, University Department of Medicine, Glasgow, and Department of Chemistry, Strathclyde University.

The comparative efficacy and toxicity of auranofin and Myocrisin as second-line therapy for rheumatoid arthritis are not yet established. We have studied 90 patients who were randomly allocated to receive auranofin 3 mg b.d., Myocrisin (sodium aurothiomalate), or placebo (30 in each group). Sixty-three patients (21 in each group) have been followed up for at least 6 months. Three patients on auranofin, 5 on Myocrisin, and 9 on placebo discontinued therapy before 6 months had elapsed.

All patients withdrawn from active therapy had experienced side effects (leucopenia, diarrhoea, and haematuria on auranofin, and rash (3), nitritoid reaction, and proteinuria on Myocrisin). Most of the placebo withdrawals were because of inefficacy.

Initial, 3, and 6 month clinical and laboratory assessments of disease activity were compared in those who remained on therapy. Improvement was seen earlier in the Myocrisin group, but by 6 months significant benefit was observed in ESR and CRP in both active treatment groups. Pain score improved significantly only in patients on Myocrisin, although the trend was favourable on auranofin. Initial superoxide dismutase activity was abnormal in the majority of the patients studied. Clinical and laboratory improvement in the auranofin and Myocrisin treated patients was associated with a favourable trend in these measurements.

There was no significant improvement in any variable in the group on placebo. Auranofin produces a second-line effect when compared with placebo; its performance in relation to myocrisin is more complex.

Ultrasound in tennis elbow. A. Binder, G. Parr, B. Hazleman. Rheumatology Research Unit, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

There have been few controlled studies to assess the efficacy of ultrasound. Tennis elbow has been chosen for study in view of the discrete superficial nature of the lesion. Double-blind control has been achieved by inserting an 'on-off' switch into the oscillator circuit, so that mock insonation ('placebo') could be given.

Forty-eight patients (52 elbows) with tennis elbow were randomly allocated to the placebo group (19 elbows) or ultrasound group (33 elbows) and were reviewed fortnightly but encouraged to continue their initial therapy until 12 treatments (over 4-6 weeks) had been completed. True ultrasound or local injections (hydrocortisone acetate) were offered if symptoms continued. At each visit thermographic and clinical assessments were performed.

Results are shown in Table 2. Only 3 patients from the placebo group were not prepared to continue further ultrasound and received an injection.

Table 2 Response to ultrasound

<table>
<thead>
<tr>
<th>Placebo group</th>
<th>Ultrasound group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number treated</td>
</tr>
<tr>
<td>Initial therapy</td>
<td>19</td>
</tr>
<tr>
<td>Further ultrasound</td>
<td>11</td>
</tr>
<tr>
<td>Steroid injection</td>
<td>6</td>
</tr>
</tbody>
</table>

Seven remained symptomatic (13%). Three withdrew after initial therapy (6%).

We conclude that ultrasound does influence the natural history of this condition. The role of thermography in the assessment of this condition will be discussed.

Microvascular changes produced by prostaglandin E1, M. F. R. Martin, J. E. Tooke, V. Wright. University Department of Rheumatology and Medicine, Leeds General Infirmary, Leeds.
Previous work suggests that PGE<sub>1</sub> infusions increase peripheral blood flow and may be of value in the treatment of severe peripheral ischaemia.

We have studied a group of 8 patients with Raynaud’s phenomenon and systemic sclerosis (SS). All subjects had characteristic nail-fold capillary abnormalities, including reduced capillary numbers, haemorrhages, and bizarre widened forms. The study was designed to investigate whether the observed increase in peripheral blood flow following PGE<sub>1</sub> therapy corresponded to (i) subjective benefit; (ii) objective improvement in digital microvascular circulation.

Vascular measurements were made in a constant temperature room (24°C) before, during, one week, and 6 weeks after a 72-hour PGE<sub>1</sub> infusion (maximum dose 10 ng/kg/min). At each visit nail fold capillary pressures were determined by the Landis micromagnification technique. Digital blood flow was measured using an ECG-triggered mercury strain gauge plethysmograph and finger temperature using adherent thermocouples and radiometry.

Six subjects reported a reduction in ischaemic pain and frequency of vasospastic attacks. Ischaemic ulcers healed in 3. Clinical improvement correlated well with improved capillary pressure gradients and blood flow (Table 3).

Table 3 Results (means n=8)

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>During</th>
<th>1 week</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial limb capillary pressure (cm H&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>31-0</td>
<td><em>44-0</em></td>
<td>40-0</td>
<td>33-1</td>
</tr>
<tr>
<td>Capillary pressure gradient (cm H&lt;sub&gt;2&lt;/sub&gt;O min&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0</td>
<td><em>11-7</em></td>
<td>3-0</td>
<td>4-1</td>
</tr>
<tr>
<td>Rest flow (ml/100 ml tissue/min)</td>
<td>3-6</td>
<td><em>9-0</em></td>
<td>4-3</td>
<td>8-6</td>
</tr>
<tr>
<td>Nail fold skin temperature (°C)</td>
<td>28-8</td>
<td><em>29-8</em></td>
<td>29-3</td>
<td>29-1</td>
</tr>
<tr>
<td>Finger radiometry (°C)</td>
<td>26-9</td>
<td><em>29-2</em></td>
<td><em>28-2</em></td>
<td>27-5</td>
</tr>
</tbody>
</table>

*Statistically significantly different from preinfusion values, p<0.05.

This study provides clinical and experimental evidence of improvement in digital nutritional circulation following PGE<sub>1</sub> infusion in patients with Raynaud’s phenomenon secondary to systemic sclerosis.

Reference

PGE<sub>1</sub>, vasospastic disease, and thermography. M. V. Kyle, G. Parr, R. Salisbury, P. Page Thomas, B. L. Hazleman. Rheumatology Research Unit, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 2QO.

Prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) appears to be of value in treating vasospastic conditions, but improvement thermographically after cold stress test has not been shown.

We treated 8 patients with Raynaud’s phenomenon, 5 of whom had digital ulceration unresponsive to treatment, with PGE<sub>1</sub>, given by central venous infusion for 72 hours at a dosage of 6-10 ng/kg/min. Our cold stress test was done immediately before and after treatment and at weekly intervals for 2 months.

The ulcers in all 5 patients healed within 3 weeks. All but one patient reported a significant reduction in attacks of Raynaud’s phenomenon and pain and felt much warmer. Thermographic assessment showed improvement in 7 of the 8 with a combination of the following features: development of hyperaemia within 15 minutes and rewarming over the final phase of the test (features which occur in normal controls in our experience) and loss of the marked ‘banded’ gradient pattern which has been characteristic of patients with secondary Raynaud’s phenomenon. These effects persisted for 2-6 weeks.

We conclude that PGE<sub>1</sub> is of benefit in treating digital ulceration and severe Raynaud’s phenomenon, and that thermography will demonstrate this improvement.

Indolent Wegener’s granulomatosis. D. G. Macfarlane, J. Bourne, P. A. Dieppe. Department of Medicine, Bristol Royal Infirmary.

Textbook descriptions of Wegener’s granulomatosis (WG) adhere to the original concept of the disease as relentlessly progressive and fatal unless treated. Limited forms have longer survival but are also usually progressive. We report 3 women with signs and/or symptoms of WG for at least 10 years prior to diagnosis.


Multiple nasal biopsies were unhelpful in all 3, but histological confirmation was obtained in 2. All responded rapidly to cyclophosphamide. This suggests the existence of an indolent form of WG which is difficult to diagnose by conventional biopsy techniques but which requires recognition since, as case 2...
illustrated, the indolent form may suddenly become virulent and life-threatening.

Reference
1 Wegener F. Beir Pathol 1939; 102: 36-68.

Cheiroarthropathy without diabetes: a family study.
D. L. Scott,1 J. P. Delamere,1 P. Mackintosh,2 S. Jobson,2 1Rheumatism Research Wing, and 2Regional Blood Transfusion Centre, Birmingham.

Cheiroarthropathy (or limited joint mobility) occurs in 30% of patients with juvenile onset diabetes mellitus. It principally involves the hands and is characterised by contractures at the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints associated with a waxy thickening of the skin. It has been ascribed to poor diabetic control; however, an increased incidence has been found in nondiabetic siblings of diabetics.

We report a family in which the father and 5 of 8 siblings had the typical features of cheiroarthropathy, but none had overt diabetes. Three siblings were markedly affected and 2 to a less extent. All had limited mobility of MCP and PIP joints with some waxy thickening of the overlying skin; none had sclerodactyly, calcinosis, or telangiectasia. Two of the involved siblings showed minimal Raynaud’s phenomena; one had a homogenous IgG antinuclear factor (titre 1:160); there were no other abnormal findings. The clinical features, which had developed over 2–3 years, had been static for 10 years. Tissue typing showed no clear genetic basis for the hand changes, but all the involved siblings were HLA B8 and the 3 severely involved were homozgyous for this antigen.

We suggest that cheiroarthropathy may be an unusual variant of scleroderma which does not progress to systemic involvement. Although it is common in diabetics, it can occur in patients without overt diabetes and may have an independent genetic basis.

Reference

Extravascular (e-v) fibrin in rheumatoid arthritis (RA): persistence and continuous turnover. C. D. Holland,1 J. A. N. Rennie,4 I. F. Hassan,3 M. K. Jasani,3 M. I. V. Jayson.1 1Rheumatic Diseases Centre, University of Manchester, Hope Hospital, Salford M6 8HD; 3Research Centre, Ciba Geigy Pharmaceuticals Division, Horsham, West Sussex RH12 4AB; 4City General Hospital, Aberdeen.

Hyperfibrinogenaemia is a feature of RA and the extensive e-v fibrin deposition seen in synovium and joint fluid in RA reflects the conversion of e-v fibrinogen (Fg) to fibrin. This is matched by increased fibrinolysis, yet fibrin persists in RA and may play a pathogenetic role in the persistence of joint effusions and chronicity of the inflammation. We investigated the extent to which an intravenous dose of 125I-human Fg accumulated e-v in 10 patients with active classical seropositive RA on a standardised anti-inflammatory drug regimen. The extent to which this reflected fibrin formation as opposed to merely e-v extravasation of Fg was determined by measuring the e-v accumulation of a simultaneously intravenously administered tracer dose of 125I-human serum albumin.

Seven patients with osteoarthritis (OA) on the same drug regimen were studied for comparison. The results showed that although the mean e-v accumulation of albumin was similar in the 2 conditions, the e-v accumulation of Fg was significantly greater in RA as compared with OA (p<0.01) (Table 4). The urinary excretion of 125I, but not 125I, was also significantly greater in RA than OA (p<0.01), reflecting increased fibrinolysis (Table 5).

Table 4  Comparison of extravascular accumulation of fibrinogen (mg/kg) and albumin (mg/kg) in 10 RA and 7 OA patients. Accumulation measured by determining the blood clearance of the radioiodinated tracer proteins. Results shown are mean ±SE (*p<0.05,**p<0.01)

<table>
<thead>
<tr>
<th>Time (hours) after injection of tracer</th>
<th>2</th>
<th>10</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrinogen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>47±8**</td>
<td>71±11**</td>
<td>66±15*</td>
</tr>
<tr>
<td>OA</td>
<td>20±2</td>
<td>26±1</td>
<td>29±2</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>393±43</td>
<td>799±80</td>
<td>890±58</td>
</tr>
<tr>
<td>OA</td>
<td>389±50</td>
<td>709±28</td>
<td>947±49</td>
</tr>
</tbody>
</table>

Table 5  Comparison of the cumulative degradation of fibrinogen and albumin in 10 RA and 7 OA patients. Degradation measured by determining the urinary excretion of radioligands tagged to appropriate tracer protein. Results shown are mean ±SE (*p<0.01)

<table>
<thead>
<tr>
<th>Time (hours) after injection of tracer</th>
<th>10</th>
<th>24</th>
<th>30</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrinogen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>18±3</td>
<td>42±5</td>
<td>54±7</td>
<td>80±7*</td>
</tr>
<tr>
<td>OA</td>
<td>14±3</td>
<td>28±5</td>
<td>34±7</td>
<td>44±8</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>95±13</td>
<td>183±24</td>
<td>227±27</td>
<td>354±56</td>
</tr>
<tr>
<td>OA</td>
<td>165±39</td>
<td>292±68</td>
<td>348±82</td>
<td>442±106</td>
</tr>
</tbody>
</table>

This low dose double isotope technique provides a new method of quantifying the extent of e-v Fg accumulation as fibrin and the degree of fibrinolysis. The technique provides a basis for the study of the effect of drugs on modifying fibrin formation or enhancing fibrinolysis in RA.
Campylobacter reactive arthritis—an epidemiological study. C. J. Eastmond, J. A. N. Rennie, T. M. S. Reid. Department of Rheumatology and Regional Laboratory, City Hospital, Aberdeen AB9 8AU.

Reactive arthritis and Reiter's syndrome are recognised sequelae to Campylobacter jejuni enteritis. In 1979 a local community in Grampian Region suffered a single outbreak of campylobacter enteritis from a local dairy. The infected population has been reviewed to determine the frequency of subsequent reactive arthritis.

The local general practitioners' records of the 88 symptomatic infected patients together with those of the 46 asymptomatic contacts were studied. Two male patients reported musculoskeletal complaints within 3 months of their episode of diarrhoea and a positive stool culture for campylobacter. One of these had typical sciatica which resolved with conservative management. The other developed a synovitis of the right elbow one month after his enteric infection, lasting 2 weeks with complete resolution.

This survey suggests a frequency of campylobacter reactive arthritis of one in 88 symptomatic infected persons (1.1%), which is a similar frequency to that observed with other specific enteric infections and non-specific urethritis, suggesting a common pathogenesis.

Detection and measurement of free thiomalate in urine of patients receiving sodium aurothiomalate. S. R. Rudge, A. J. Swannell, D. Perrett, P. L. Drury. Department of Rheumatology, City Hospital, Nottingham, and Dunn Laboratories, St Bartholomew's Hospital, London.

Sodium aurothiomalate (SATM), penicillamine, and levamisole are all sulphhydryl (—SH) compounds. Each is effective in the treatment of rheumatoid arthritis and their courses of action and side effects are very similar. Prediction of the efficacy and toxicity of SATM using serum or urinary gold levels has proved uniformly unsuccessful. Studies in mice have shown free thiomalate in urine following injection of SATM but few data exist for man. An early report suggests that sodium thiomalate (without gold) may be an effective antirheumatic agent.

We have developed a method for the measurement of free thiomalate in human urine using high-performance liquid chromatography and electrochemical detection. Sensitivity is 10 pmol and reproducibility ±1.9% (n=10). Thiomalate was easily detectable in urine within an hour of intramuscular SATM (10 mg). In patients commencing gold therapy 8–20% of the injected dose was excreted as thiomalate within the first 8 hours, peak levels being seen within the first hour.

If, as appears possible, the actions and toxic effects of SATM are related to its SH group, free thiomalate measurements may enable safer and more efficient prescribing of this drug.

Reference

Eosinophilia in rheumatoid patients treated with D-penicillamine. D. H. Smith, D. Scott, G. C. Zaphiropoulos. Department of Rheumatology, Coventry and Warwickshire Hospital, Coventry CV1 4FH; *Rheumatism Research Wing, Medical School, Queen Elizabeth Hospital, Birmingham B15 2TJ.

The occurrence of eosinophilia during gold therapy and its clinical significance is well documented. Its relevance, however, during treatment with penicillamine is not clearly defined.

In a retrospective study of 89 patients with rheumatoid arthritis 47 patients (52.8%) showed an eosinophilia (greater than 0.4 × 109/l) at some time during penicillamine therapy. Of these, 18 had had previous gold therapy during which 4 had eosinophilia. The mean penicillamine dose at the onset of eosinophilia was 336 mg (range 125–750 mg) and the mean duration of this treatment was 5–6 months (range one week–37 months). In 10 patients (11.2%) a rash developed during treatment, but only in 3 cases was there a temporal relationship with eosinophilia, and in all 3 the drug was continued. None of these 3 patients had had gold therapy previously.

We conclude that mild to moderate eosinophilia is not uncommon during treatment with penicillamine and does not appear to presage the onset of cutaneous reactions. Routine eosinophil counts would not therefore seem to be relevant in monitoring the onset of adverse reactions during therapy.

Reference

Characterisation of calcium phosphate crystals relevant to crystal deposition diseases. J. S. Shah, J. E. Harris, P. Heap, P. A. Dieppe. Department of Physics and Medicine, University of Bristol.

Many arthropathies are associated with crystalline deposits, notably hydroxyapatite (HA) and calcium pyrophosphate dihydrate (CPPD). The relationship between tissue damage and crystal deposition remain
obscure, and due to complexities of the growth systems many different phosphate salts can grow from the same reaction solutions. We have attempted to characterise these crystals more carefully, and compare in-vivo with in-vitro grown crystals.

HA crystals were recovered from human periarticular and subcutaneous calcific deposits. Their chemical composition was checked by infrared spectrometry and x-ray energy spectroscopy. Crystal structure and particle size were obtained from x-ray powder diffraction patterns. The results were compared with those for HA grown from aqueous solutions. The Ca:P ratio of the periarticular deposits was variable (range 2.05–2.38) and particle size was larger than that of bone crystals.

CPPD crystals were recovered from articular cartilage and synovium. Their morphology, as shown by electron microscopy, was compared with that of crystals grown from both aqueous solution and gels. In addition to a variety of intermediates, CPPD crystals identical to those found in joints have been grown from the gels.

These results suggest that a variety of intermediary phases exist, and emphasise the chemical and morphological variability of calcium phosphate crystals found in articular and periarticular tissues.

**Examination of crimp morphology in human palmaris longus tendon.** J. S. Shah, L. J. Gathercole, S. W. Nicholls. HH Wills Physics Laboratory, University of Bristol.

It is well known that collagen fibres from tissues which bear tension in vivo show sharp apical undulations called crimps. It has, however, been inferred from the scanning electron microscopy of the enzyme digested human palmaris longus tendon that crimping is absent in the fibres of the above tissue.1

A systematic study was therefore undertaken to check the existence of crimps in human palmaris longus tendons. Polarisation microscopy revealed that light and extinction bands, characteristic of crimps, can be seen in native untreated tissues. Low-angle x-ray diffraction of the tissue was also undertaken. It clearly showed that the diffraction patterns of the fibres at 2 orientations, 90° apart, are different and show that in principle the crimp structure resembles that of a flat zigzag ribbon. Scanning electron microscopy of the native, untreated, tissues was performed. It has been possible to establish a clear correlation between the topological features seen in the scanning electron microscope and the band pattern in polarisation microscope. It will be shown that the surface features, especially outer layers surrounding the fibres, can obscure the underlying crimp structure.

**Reference**


**Increased polymorphonuclear leucocyte (PMN) motility in B27+ ve controls and patients with ankylosing spondylitis (AS).** C. T. Pease, J. N. Fordham, H. L. F. Currey. Bone and Joint Research Unit, The London Hospital Medical College, London E1 2AD.

Among patients with yersinia arthritis those with HLA B27 have more severe disease and more extra-articular features. Leirisalo et al.1 suggest that this may be due to increased PMN motility.

We have investigated PMN motility in 24 disease-free control subjects (12 with and 12 without the B27 antigen) and have compared these data with results obtained from 12 patients with AS. PMN motility was assessed by using both a modified Boyden chamber and an agarose plate method.

Various aspects of cell motility were studied, including the 2 cell leading front, leucotactic index, and counts of absolute numbers of migrating cells. Our results with the Boyden chamber suggest that directed motility of PMN from B27+ve control subjects and B27+ve ankylosing spondylitics was increased compared with the B27–ve control group (p = 0.05 and p = 0.05 respectively).

Analysis of the cell profile revealed a significant difference (p<0.001) between the B27–ve control group and the B27+ve AS. Insufficient numbers of B27–ve AS have so far been available for comparison.

Our results suggest that PMN motility may be related to HLA status.

**Reference**

fluid (SF) PMN from patients with rheumatoid arthritis.

SF-PMN had a higher baseline chemiluminescent activity than PB-PMN and rheumatoid synovial fluid was found to directly stimulate PB-PMN. When washed SF-PMN were re-exposed to rheumatoid synovial fluid, their chemiluminescence was also stimulated and the response was greater than that of PB-PMN (p<0.001). These findings suggested that not only are there factors in rheumatoid synovial fluid which stimulate PMN chemiluminescence but also that PMN which have migrated into the fluid have a greater reactivity than PB-PMN.

To mimic in-vivo events PB-PMN were pre-treated with the synthetic chemotaxin n-formylmethionyl-leucyl-phenylalanine before stimulation with heat aggregated gammaglobulin. Treatment with the chemotaxin resulted in an enhanced subsequent responsiveness of the PMN (p<0.001).


VAS are frequently used in clinical trials of anti-rheumatic drugs. We have previously demonstrated serious variation of reproducibility along the length of a 10 cm vertical VAS. We have now extended our studies to the serial use of both vertical and horizontal VAS (so as to mimic clinical trials) with righthanded subjects.

Thirty normal volunteers each attempted to reproduce the position of a mark on 13 vertical VAS and 13 horizontal VAS on to blank scales. Eight of the volunteers repeated this exercise at weekly intervals for 8 weeks.

The reproducibility of both vertical and horizontal VAS was found to be best near the apices and midpoint, confirming our earlier results. It was worst at the golden sections of the lines. There was a tendency to estimate towards the left of a horizontal VAS.

The standard deviation of serial estimates for each volunteer varied according to the point at which the line was marked. It was lowest for the apices and mid-point and highest around the golden section. There was considerable intra- and intersubject variation.

Even if patients adequately understand their use, reproducibility of VAS is far from satisfactory.

C-reactive protein as an index of response to drug therapy in rheumatoid arthritis. J. S. Dixon, H. A. Bird, N. G. Sitton, V. Wright. Clinical Pharmacology Unit, Royal Bath Hospital, Harrogate, and Rheumatism Research Unit, University of Leeds.

A number of serum proteins have been advocated as potential markers of disease activity in rheumatoid arthritis (RA), but their relative usefulness in the assessment of disease activity and serial improvement has not previously been rigorously elucidated. We have therefore correlated C-reactive protein (CRP), haptoglobin, fibrinogen, ESR, and plasma viscosity (PV) with selected clinical assessments, including articular index (AI), in 105 patients with RA.

Groups of 15 patients were assessed during treatment with slow-acting antirheumatoid drugs; D-penicillamine, alclofenac, hydroxychloroquine, gold, sulphasalazine, and azathioprine. A control group treated with aspirin alone was also included. Patients were assessed clinically (pain score, articular index, and summed change score) and in terms of acute phase reactants at 8 separate clinic visits during a 6-month treatment period.

CRP correlated better with AI than haptoglobin, which in turn correlated better than fibrinogen in all treatment groups. CRP correlated marginally better with AI than PV and certainly better than ESR.

Although there is unlikely to be a single 'best test' to cover all antirheumatoid drugs, assuming AI to be one of the most satisfactory clinical assessments, CRP and PV are likely to provide the maximum complementary information.

Failure of Trien to improve rheumatoid arthritis. H. A. Bird, P. A. Leatham, J. S. Dixon, N. G. Sitton, V. Wright. Clinical Pharmacology Unit, Royal Bath Hospital, Harrogate, and Rheumatism Research Unit, University of Leeds.

The mode of action of D-penicillamine (DPA) in rheumatoid arthritis (RA) remains uncertain. Although analogy with aurothiomalate suggests the -SH group may be important, it may also act by chelating heavy metals such as copper. If the latter is correct, then other metal chelating agents such as Trien, which is used as an alternative to DPA in Wilson's disease, might be expected to improve RA.

We have obtained enough Trien to treat 15 patients with RA for 6 months with a dose of 400 mg t.d.s. This dose was judged to be near the maximum that would be tolerated by patients with a disease in which there was no gross evidence of abnormal copper metabolism.

Patients were seen on 8 occasions, when 8 clinical and 24 biochemical assessments were performed. No
significant improvement was seen in any clinical or biochemical parameter, and for many there was significant deterioration (ESR at 8 and 12 weeks, p = 0.05; CRP at 8 weeks, p = 0.01; PV at 4, 8, 12 weeks, p = 0.05; AI at 12 weeks, p = 0.05). By contrast, comparable groups of patients on DPA or aurothiomalate showed significant improvement in these parameters.

These results suggest that DPA may not work in RA by simple chelation of heavy metals. Whether we observed serial deterioration of ‘untreated’ disease or whether Treni makes the disease worse requires further study.

Methotrexate (MTX) therapy in steroid resistant polymyositis (PM): a clinical and pharmacokinetic study. N. Christophidis, E. C. Huskisson. St Bartholomew’s Hospital, London EC1A 7BE.

In the treatment of steroid-resistant PM with MTX, although the intravenous (IV) route of administration is commonly used, there are no clinical or pharmacokinetic data to suggest that it is preferable to the intramuscular (IM) or oral (O) routes.

Nine patients (7F, 2M) with a mean age of 53.2 (range 44–71 years) and weight 56.3 (range 45–80) kg were studied prospectively during MTX therapy of biopsy-proved PM. MTX was added because of unresponsiveness to steroids in 7 patients or steroid side effects in 2. The dose of MTX ranged 15–50 mg/wk or 0.3–0.9 mg/kg/wk. Five patients, 2 on O, 2 on IM, and 1 on IV MTX showed clear clinical benefit with improved muscle power of at least 1 grade and normalisation of CPK levels after a mean of 6 (range 1–12) weeks of therapy. In the 5 responders the dose of prednisolone could be reduced from a mean of 40 mg/day to 8 mg/day over a period of 11 (range 3–30) months. Four patients experienced mild side effects, including mouth ulcers (2), petechial rash (1), thrombocytopenia (1), and nausea (1). No clinically significant liver toxicity occurred. Measurements of MTX plasma levels after IV, O, and IM administration of 15–25 mg revealed mean peak levels of 4.7 (3.4–5.8) μg/ml, 1.5 (0.5–2.6) μg/ml respectively. The mean areas under the plasma concentration time curves (AUC) 0–6' corrected for dose, were 186, 140, and 173 μg/min/ml respectively, giving bioavailability values of 75% and 93% for the O and IM routes.

We conclude that MTX is often effective in the treatment of steroid resistant PM and that the O and IM routes of administration are useful, convenient alternatives to the IV route.

Arthritis and angioimmunoblastic lymphadenopathy. P. G. Davies, J. N. Fordham. Departments of Rheumatology, Hackney Hospital, London E9, and Prince of Wales Hospital, London N15.

Angioimmunoblastic lymphadenopathy (AILD) is a lymphoproliferative disorder of unknown aetiology and pathogenesis. The typical features are of lymphadenopathy, hepatosplenomegaly, rash, and hypergammaglobulinaemia. Both arthralgia and arthritis have also been described in occasional cases.1

We report 2 contrasting cases of a seronegative polyarthritis associated with AILD. Both cases were nonerosive, with symmetrical involvement of the elbows, wrists, knees, and ankles. In one case the arthritis appeared concurrent with the main systemic manifestations of AILD. Previous case reports suggest that this is the usual time for the arthritis to appear. The second patient presented with polyarthritis alone, which clinically resembled seronegative rheumatoid arthritis. Nonsteroidal anti-inflammatory drugs did not help and azathioprine was commenced with good effect. The onset of AILD with lethargy and lymphadenopathy hepatosplenomegaly did not occur until 18 months after presentation with arthritis.

Reference

Antinuclear antibodies in progressive systemic sclerosis. R. M. Bernstein, L. J. Catoggio, C. M. Black, P. M. Maddison, G. R. V. Hughes. Rheumatology Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London W12, and Royal National Hospital for Rheumatic Diseases, Bath.

We have investigated the clinical relevance of precipitating antibody to SCL-70 antigen and of anticientromere antibody (ACA) in progressive systemic sclerosis. SCL-70 precipitin was detected by immunodiffusion in serum from 16 (21%) of 75 patients with PSS, but in only 1/100 (1%) sera from other connective tissue diseases. Anti-SCL-70 is thus a specific but insensitive marker of PSS; it was associated with increased lung involvement (75% v. 39%, p<0.05).

ACA was detected by immunofluorescence on HEP-2 cells in 16/32 (50%) patients with CREST syndrome and 4/14 (28%) patients with incomplete forms of CREST. This contrasted with 2/29 (7%) patients with diffuse scleroderma, 1/15 (7%) patients with primary Raynaud’s syndrome, and 2/100 (2%)
SLE sera. ACA was associated with less lung involvement (34% v. 54%, p<0.05), longer median disease duration (17 v. 8-5 years), and no recent deaths (0% v. 6%); ACA preceded sclerodactyly in 2 cases. These data support previous evidence that ACA is an early and stable prognostic marker of limited scleroderma and prolonged survival in patients with systemic sclerosis.

**Left ventricular function in patients with ankylosing spondylitis and Reiter's disease.** K. D. Morley, P. A. Ribeiro*, R. A. F. Garnett,† J. F. Goodwin,* G. R. V. Hughes. Rheumatology Unit and *Division of Cardiovascular Disease, Royal Postgraduate Medical School and Hammersmith Hospital; †Queen Elizabeth Military Hospital, Woolwich, London.

Most previous cardiac studies of patients with ankylosing spondylitis have been directed towards abnormalities of the aortic valve and conducting system, though Takkunen et al. 1 reported that 28 of 55 (51%) patients with established ankylosing spondylitis (AS) had clinical evidence of cardiomyopathy of unknown aetiology.

We have assessed the left ventricular (LV) function by computerised M-mode echocardiography in 30 patients with AS and 13 with Reiter's disease all of whom possess HLA B27 but none had aortic valve disease. Compared with 45 age-matched controls, 43% of the patients had abnormal diastolic function manifest by slow ventricular filling and impaired relaxation, and 18% of patients had abnormal systolic function with a dilated left ventricle and cardiomegaly on chest radiograph. There was no significant association between LV dysfunction and duration of disease.

Our results suggest that ankylosing spondylitis and Reiter's disease are associated with abnormal left ventricular function independent of aortic valve disease.

**Reference**


**HLA antigens in patients with rheumatoid arthritis and serum antibodies to native type II collagen.** R. B. Clague, S. Firth, P. J. L. Holt, P. Dyer, * P. Klouda,* R. Harris.* Rheumatism Research Centre, Manchester Royal Infirmary and *Department of Medical Genetics, St Mary's Hospital, Manchester.

Previous studies in caucasoid patients with RA have shown a significant increase in DR4. 1 We have determined the HLA A, B, and DR antigens in 31 patients with definite RA who had elevated serum IgG antibody levels to native type II collagen (<180 μg/l) measured by radioimmunoassay and compared their frequencies with our normal control panel. The results of relevant antigens are shown in Table 6.

**Table 6 HLA antigens in patients with RA and antibodies to native type II collagen**

<table>
<thead>
<tr>
<th>HLA</th>
<th>Patients (31)</th>
<th>Controls (230)</th>
<th>Corr. p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>16 (52)</td>
<td>79 (34)</td>
<td>0·59</td>
</tr>
<tr>
<td>B8</td>
<td>16 (52)</td>
<td>65 (28)</td>
<td>0·16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA</td>
<td>Patients (31)</td>
<td>Controls (105)</td>
<td>Corr. p</td>
</tr>
<tr>
<td>DR2</td>
<td>1 (3)</td>
<td>29 (28)</td>
<td>0·014</td>
</tr>
<tr>
<td>DR3</td>
<td>15 (48)</td>
<td>28 (27)</td>
<td>0·17</td>
</tr>
<tr>
<td>DR4</td>
<td>9 (29)</td>
<td>38 (36)</td>
<td>&gt;1·0</td>
</tr>
<tr>
<td>DR7</td>
<td>13 (42)</td>
<td>19 (18)</td>
<td>0·06</td>
</tr>
</tbody>
</table>


Surprisingly, there was no increase in DR4. There was a significant decrease in DR2. Although DR3 and DR7 were increased, the corrected p values were not significant. However, 25 (81%) of the 31 patients possessed DR3 and/or DR7 compared with 42 (40%) of the 105 controls (χ² = 14·2, p<0·001). These 15 patients possessing DR3 had significantly higher antibody levels (range 561–5,044 μg/l; median 1993 μg/l) than the 16 patients without DR3 (range 301–2748 μg/l; median 1154 μg/l) (U = 58, p<0·02). The A1, B8, DR3 antigens were present (possibly as a haplotype) in 11 patients.

This study suggests that in RA serum antibodies to native type II collagen are associated with two HLA DR antigens, with DR3 being associated with the highest levels. The lack of increase in DR4 in this group of patients with RA suggests that this is a separate subset of this disease.

**Reference**


**Muscle involvement in ankylosing spondylitis.** G. O. Hopkins,* J. McDougall, K. Mills, D. Isenberg, A. Ebringer.† *Departments of Rheumatology, The Middlesex Hospital and University College Hospital, and †Immunology Unit, Queen Elizabeth College.

Muscle stiffness in ankylosing spondylitis (AS) has long been attributed to joint inflammation. This fails to explain the discrepancy between the dramatic relief of symptoms given by exercise in this condition...
as compared with other inflammatory joint diseases. Muscle involvement is postulated and investigated.

Method. Twenty patients (18 male, 2 female) with definite AS were studied. Quadriceps needle biopsy was carried out in all, serum enzymes and muscle strength in 16, and electromyographic (EMG) studies in 9 patients.

Results. Histologically abnormal changes were seen to be present in all specimens to a varying degree. The most commonly observed changes were central migration of nuclei (80% of patients), patchy increased localised area of acid phosphatase activity within many fibres (75%), and on NAD-M-TR (tetrazolium reductase) staining there was a peripheral condensing of reaction product in type 1 fibres (55%). On muscle strength measurement all but 2 were below predicted values in spite of most patients being highly motivated exercise addicts. Surface EMG studies were abnormal in 6 out of 9. No significant alteration in serum enzymes was noted.

This indicates that there are alterations in muscle tissue in AS, but the pathogenetic mechanism producing these changes is at present unknown.

The mode of formation of synovial villi. J. C. W. Edwards. Department of Experimental Pathology, St Bartholomew’s Hospital, London EC1.

Synovial villi are often assumed to form by outgrowth. However, they may form by tissue splitting.1 A study of synovial microstructure was made to assess the evidence for a splitting mechanism.

Synovial samples from 16 patients were examined by dissecting microscopy. Serial sections were made of one osteoarthritic and 2 rheumatoid samples. Sections were projected onto polystyrene sheets at 160 times magnification. The sheets were cut to the tissue outline and stacked to form scale models.

Both under the dissecting microscope and in scale models tissue bridging was seen. Outgrowth alone does not produce bridging, and there was no indication that bridges formed from organised fibrin. The appearance suggested splitting or perforation. Subintimal cavities were found in scale models which carried synovial lining (on H and E sections), continuous with the surface through narrow pores. The cavities followed the collagenous laminations of the tissue. Intermediate appearances between intercellular clefts, subintimal lined cavities, and unlined laminations were seen, including spaces lined on one side only or intermittently lined. Avascular strips of collagen lined with cells were seen. Haemosiderin in the lining was common. It is suggested that traumatic splitting of tissue laminae contributes significantly to the formation of villi.

Reference

A 20-year follow-up of 100 patients with rheumatoid arthritis (RA). J. A. Cosh, J. J. Rasker Royal National Hospital for Rheumatic Diseases, Bath.

A prospective study has been made of 100 patients with definite or classical RA, initially seen within a few months of the onset of arthritis and now followed up for 20 years. Forty-six have died, 9 as a direct result of the disease, 8 with RA as a contributory cause, and 29 of unrelated causes.1

The 54 survivors are 16 men (mean age 67 years) and 38 women (mean age 63 years), whose present functional capacity and ARA category are shown in Table 7. Seven of the 54 were seronegative through-out, and 22 have converted from positive to negative (titre <1:32). The titre of the remaining 25 has fallen from an original mean of about 1:1024 to 1:128. Those patients now seronegative (9 M, 20 F) are better than the rest as regards functional capacity, American Rheumatism Association (ARA) category, joint score, Ritchie index, and plasma viscosity. Men have done better than women.

The long-term pattern of disease over the 20 years was one of chronic persistent activity in 25, a remitting and relapsing course in 12, a sustained remission in 12, and atypical in 5.

Thirty-nine of the 48 tested for HLA DR4 are positive. No correlation has been found between the presence of DR4 and seropositivity, functional capacity, disease pattern, or sex.

Reference
Complement activating rheumatoid factor containing immune complexes in rheumatoid vasculitis. D. G. I. Scott, C. J. Elson, M. Ahern, D. R. Blake, P. A. Bacon. Royal National Hospital for Rheumatic Diseases, Bath, and Department of Immunology, Bristol University.

Serological features of rheumatoid vasculitis (RV) include high titres of rheumatoid factors (RF), high titres of circulating immune complexes (IC), and hypocomplementaemia. It is not clear whether these findings are directly related or whether the hypocomplementaemia results from immune complexes containing different autoantibodies such as ANA. We have developed a radioimmunoassay to detect complement bound to immune complexes by incubating test sera with F(ab)2 fragments of anti-human C3 attached to a solid matrix. To determine whether RF activity was expressed by these bound complexes 125I-labelled heat-aggregated IgG was then added to the assay system.

All sera from 15 patients with active RV contained C3 bound rheumatoid factor compared with only 6 out of 28 sera from patients with other extra-articular lesions or uncomplicated synovitis. This activity was not present in sera from patients with SLE, ankylosing spondylitis, or normal controls. Tests carried out using heat aggregated human IgG gave similar results to those using rabbit IgG. In whole serum the C3 bound RF activity appeared to be in immune complexes, since it was precipitated by 2.5% polyethylene glycol and was also restricted to high molecular weight (>19s) fractions.

These results confirm that rheumatoid factors play an important role in complement activating immune complexes in patients with RV. The normal results in patients with uncomplicated RA and SLE, many of whom had high titres of RF, and some (SLE) also hypocomplementaemia, suggests that serum RFs only rarely activate complement and that complement activation in SLE is not due to RF-containing IC.

Psychological coping styles among juvenile chronic arthritis (JCA) patients and their parents. J. G. Beales, P. J. L. Holt, J. H. Keen, University of Manchester Medical School and Booth Hall Children’s Hospital, Manchester.

A long-term study of 75 JCA patients and their parents has been undertaken to identify factors influencing the child’s ability to cope successfully with the psychological impact of the condition. Patients displayed 4 basic coping styles: (i) seeking alternatives—establishing new interests, ambitions and self-image to compensate for the effects of the disease; (ii) giving up—abandoning interests and ambitions; (iii) regressing—adopting interests, ambitions, and self-image appropriate to a younger child and welcoming parental over-protecting; (iv) denial—refusing to acknowledge the impact of the arthritis.

Only style (i) was compatible with successful long-term adjustment and motivation to comply with therapy. The coping style adopted by the child was usually determined by the parents’ own style of response. Only 21% of children adopted a coping style different from that employed by either parent. In 35% of families child and both parents shared a similar style of coping. In 44% of families the mother and father adopted different coping styles; the child identified with one parent in opposition to the other and serious conflict occurred. Seeking alternatives for the child and overprotecting were most frequent among mothers; giving up interest in the child and denying the significance of the condition were most frequent among fathers.

The study shows the need to provide psychological counselling of patient and both parents in order to motivate the child to adopt the best possible coping style and minimise conflict within the family.


An illness resembling systemic onset juvenile chronic arthritis occurs infrequently in adults. We reviewed 13 patients with this disease to determine the long-term course and immunopathology. The mean follow-up on these patients was 20 years. All but one of the patients had a course characterised by remissions and exacerbations of the systemic features. Carpal fusion was present in 11 of the 13 patients, and distal interphalangeal involvement (resembling Heberden’s nodes) was noted in 5. Fusion of the cervical spine and interphalangeal and tarsal joints also occurred in a smaller number of patients.

The characteristic Still’s skin rash was studied in 3 patients by light microscopy, immunofluorescence (IF), and electron microscopy (EM). Vascular dilatation and dermal oedema were present in all lesions. A perivascular neutrophil infiltrate was found in the superficial dermis, although one patient also showed a lymphohistiocytic infiltrate around the deeper vessels. EM showed an intact endothelium with fragmentation of the basal lamina in some sections. Perivascular mast cell degranulation, neutrophil lysis,
and fibrin deposition were also seen. Immune complexes were not identified by IF or EM.

Although circulating and synovial fluid immune complexes were found in some patients, the pathogenesis of this syndrome requires further evaluation.


As part of a screening programme 55 patients were identified with antibodies to the nuclear antigen SS-B, using counter immunodiffusion. Fifteen of these patients agreed to undergo independent examination, and 11 were diagnosed as having Sjögren's syndrome on clinical and histological evidence, although in only 3 cases had this been suspected by the referring physicians. In a control group of 17 patients with histologically confirmed Sjögren's syndrome 13 patients had rheumatoid arthritis and only 2 had SS-B antibodies.

Analysis of the 15 SS-B positive patients from the original group showed (1) that patients presenting with polyarthritis who are SS-B positive are likely to develop Sjögren's syndrome but unlikely to develop rheumatoid arthritis; and (2) that the detection of SS-B antibody may antedate clinical features of Sjögren's syndrome by months or even years.


Heart block of different degrees may be caused by rheumatoid disease, but is rare. Seventeen cases of complete block are described in the world literature and it is stated that treatment with artificial pacemakers has only rarely been more than temporarily successful. We present data on a further 8 patients with CHB.

Seven of the 8 were females. The mean age of developing CHB was 62 and the mean duration of RA prior to the onset of CHB was 13 years. All patients had received corticosteroids and 7 had received gold or D-penicillamine. All had high titres of rheumatoid factor (>1/512) and 6 subcutaneous nodules. Four had permanent pace-makers; 2 died from heart failure secondary to aortic incompetence and mitral valve disease 35 and 14 months after pacing, and the remaining 2 are alive and well. Of the 4 not paced one had temporary complete heart block for 3 days, one is asymptomatic, and 2 died within 6 months of onset of CHB.

Post-mortem examination was performed on the 2 patients who died despite pacing. In both cases typical granulomas in the region of the AV node were found, with other significant cardiac pathology.

Conclusion. (1) All the patients are elderly and have long-established seropositive erosive disease, treated with steroids. (2) It suggests that once the patient is paced, prognosis is reasonable provided no other cardiac involvement is present.

Reference


Detection of metalloproteinases and collagenase inhibitor in rheumatoid synovial fluid. T. E. Cawston, E. Mercer, M. V. Kyle, A. Binder, M. De Silva, B. L. Hazleman. Rheumatology Research Unit, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QO.

In many connective tissue diseases the loss of collagen from the extracellular matrix causes irreversible damage. Collagenase is a metalloproteinase which specifically cleaves the collagen molecule and is secreted when connective tissues are placed in culture. Two other metalloproteinases which degrade gelatin and proteoglycan are also secreted into culture medium. In addition an inhibitor of all these enzymes has been detected and purified from culture medium, and it has been proposed that the extracellular activities of these enzymes are controlled by the level of this inhibitor.

We have examined inflammatory joint effusions for the presence of these enzymes. Joint fluids were centrifuged, the supernatant treated with hyaluronidase and methylene blue (to destroy $\alpha_2$ macroglobulin activity), and subjected to gel filtration. The column fractions were assayed for each enzyme using $^{14}$C-labelled substrates. Three latent metalloproteinases and collagenase inhibitor were detected after separation.

This is the first report of a human collagenase inhibitor present in synovial fluid which resembles the inhibitor produced by connective tissues in culture.

A relationship between the menstrual cycle and disease activity in rheumatoid arthritis. S. R. Rudge, I. C. Kowanko, P. L. Drury. Department of Rheumatology, City Hospital, Nottingham,
Many women with rheumatoid arthritis (RA) experience worsening symptoms at or about the time of menstruation. Nineteen women (9 with RA and 10 normal subjects) were asked to make daily measurements of nude weight, finger joint size (FJS), and grip strength throughout 2 complete menstrual cycles. In addition rheumatoid subjects were asked to record duration of morning stiffness and a subjective assessment of joint pain. Ovulation was determined by a serum progesterone estimation on day 21 ± 1.

Sine wave analysis of the group data showed a significant 28-day cycle for FJS (p<0.05) with a peak at 27-6 days. Analysis based on individual menstrual cycles showed significant cyclical changes in 10 of 19 subjects for FJS and 15 of 19 for weight (p<0.05). In 12 subjects there was a highly significant correlation (p<0.02) between FJS and body weight. In ovulating controls most of the variation in FJS could be explained by weight change, but this was not so in rheumatoid patients.

Our data suggest that significant variations in disease activity do occur during the menstrual cycle and that these changes are not totally explained by alterations in body weight. Recognition of this pattern may allow useful modification of therapy in such patients and is of particular importance in drug trials employing a cross-over period of less than 4 weeks.


Several reports suggest hyperlipidaemia (HL) is associated with significant and severe arthopathies. We have assessed the nature and significance of musculoskeletal disorders in a large group of patients with HL attending a lipid clinic. During 1974–80 231 patients were enrolled at this clinic: 65 were excluded from the study (5 never seen at clinic, 10 had died, 23 were untraceable, 27 had normal lipids). The incidence of musculoskeletal disorders in the remaining 166 patients was determined by 3 methods in all cases: (a) patient questionnaire; (b) general practitioner inquiry; (c) hospital record review. To ensure the sensitivity of these methods a series of the negatively responding cases were seen and examined; none had identifiable joint disease.

Musculoskeletal symptoms had been present in 95% of the patients at some time since attending the lipid clinic. A diagnosis based on clinical haematological, immunological, radiological, and biochemical findings was made in all cases and these are shown in Table 8. Gout occurred in 8 males with type IV HL, a prevalence of 16%, and all of these had acute attacks. The only other musculoskeletal disorder attributable to an association with HL was a transient polyarthritis in 3 patients which was inflammatory and recurrent but nondeforming. It principally involved the small joints and did not require specific therapy nor lead to disability.

Type IV HL is associated with arthritis, and gout is a major problem. There is little evidence for significant arthritis associated with other forms of HL.


An increased incidence of lymphoproliferative malignancy (LPM) occurs in autoimmune disorders such as SLE and the sicca syndrome. This may result from the persisting immune stimulation in these diseases. But there is only one previous report of an increased incidence of LPM in RA.1 We have further examined this relationship in 2 ways.

Firstly, we report 14 patients with RA and 4 with polymyalgia rheumatica who developed LPM. Details are given in Table 9. Nine of the cases of LPM were from 536 consecutive cases of RA seen at one clinic in 1964–78, giving a minimum incidence of 1.7%. None of the patients had documented sicca syndrome, although one developed a lymphoma of the parotid. None of these patients had
received cytotoxic therapy and the malignancies seemed to be related to disease chronicity rather than its severity or treatment. Secondly, an attempt was made to detect an intermediate stage of restricted clone development in 9 patients with marked hyper-}

### Notes

**Fourth Alessandro Robecchi international prize**

This prize, equivalent to 1.5 million lire, is intended to reward clinical, biological, and experimental researches in rheumatology. It will be confined to medical works published in the course of the last 4 years or accepted for publication, and will be delivered during the X Congress of the European League against Rheumatism at Moscow in June 1983. The work must be written in English, Italian, French, German, or Spanish. Seven copies of the work and summary should be sent before 1 December 1982 to Professor Vittorio Daneo, Direttore del Centro di Reumatologia, Ospedale Maggiore di San Giovanni Battista, Corso Bramante 88, 10126 Torino, Italy.

**Ogryzlo International Fellowship**

The fourth Ogryzlo fellowship will be for training in rheumatology at a Canadian Rheumatic Disease Unit for the 12 months commencing 1 July, 1983. Applications must be submitted to the Arthritis Society, 920 Yonge Street, Ste. 420, Toronto, Ontario, Canada M4W 3J7, by 15 October, 1982. Application forms and regulations may be obtained from the society. Canadian citizens and landed immigrants to Canada are not eligible. The Ogryzlo fellowship carries a stipend of $20 000 US per annum. It is a gift by members of the Canadian Rheumatism Association in memory of their late colleague, Dr Metro A. Ogryzlo.

**South African Rheumatism and Arthritis Association**

The Eighth Biennial Congress of the South African Rheumatism and Arthritis Association will be held in Durban on 20–22 September 1982, preceded by a one-day rheumatology teach-in on 18 September. Details from the Organising Committee, Department of Medicine, Faculty of Medicine, PO Box 17039, Congella 4013, South Africa.

### Table 9 Details of lymphoproliferative malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Rheumatoid arthritis</th>
<th>Polymyalgia rheumatica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Macroglobulinaemias</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Leukaemias</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Duration of disease preceding malignancy: mean and range in years</td>
<td>9.2 (range 1–24)</td>
<td>5.3 (range 3–9)</td>
</tr>
</tbody>
</table>

**Volvo awards**

To encourage research in low-back pain the Volvo Company of Göteborg, Sweden, has sponsored three prizes of $5000 each for 1983. Awards will be made competitively on the basis of scientific merit in the areas of clinical studies, basic science, and engineering. Papers entered for the contest must contain original material not previously submitted for publication. Multiple authorship is acceptable. The manuscripts, in the English language, should be full-length, in a form suitable for submission as an original paper (not a thesis) to a scientific journal. Five copies of each paper in full must reach the address given below not later than 10 December 1982. One of the authors should be prepared to come to Cambridge, England, at the time of the meeting of the International Society for the Study of the Lumbar Spine, 7–10 April 1983, to present the paper and to receive the prize. The board of referees will be chaired by Professor Nachemson and will contain members from the fields of clinical medicine, bioengineering, and biochemistry. Correspondence to Professor Alf Nachemson, Department of Orthopaedic Surgery I, Sahlgren Hospital, S-413 45 Göteborg, Sweden.

Reference