LETTERS TO THE EDITOR

Imaging in Transient Regional Osteoporosis

Sir—The demonstration of unilateral reduction in hip bone mineral density (BMD) by dual X-ray absorptiometry (DXA) in pregnancy-associated transient regional osteoporosis (TRO) and its delayed resolution have been reported in this journal [1]. We report a non-pregnant patient with unilateral TRO, imaged by bone scintigraphy and magnetic resonance (MR) scanning, in whom DXA showed generalized reduction in BMD, but failed to identify the affected hip.

A 28-yr-old woman presented with a 3 week history of steadily increasing pain in the right groin of spontaneous onset, made worse by weight bearing and associated with striking incapacity. She reported no menstrual abnormalities, had never been treated with corticosteroids, had a normal diet and had no family history of osteoporosis. Although she denied excessive alcohol intake, previous investigations for abdominal pain, attributed to irritable bowel syndrome, had revealed mild abnormalities of liver function.

She was apyrexial and systemically well. Mild capsulitis of the right hip was apparent with a full range of passive movement. Resisted hip flexion was painful and there was local tenderness over the right groin and upper thigh. Serum γ-glutamyl transferase (92 IU/l, normal < 50) and mean corpuscular volume (103 fl, normal < 98) were elevated. The erythrocyte sedimentation rate was 26 mm/h. Thyroid function tests, full blood count and serum creatinine, electrolytes, calcium, phosphate, alkaline phosphatase, C-reactive protein, liver transaminases and protein electrophoresis were normal.

Initial conventional radiography was normal, but 3 weeks later repeat X-rays demonstrated subtle osteopenia in the intertrochanteric region of the right femur corresponding with a solitary area of uniformly increased uptake on bone scintigraphy (Fig. 1). MR images were consistent with TRO, showing loss of signal in the diaphyseal region of the right femur on T1-weighted images and a matching increase in signal in the corresponding T2-weighted sequence (Fig. 2A and B). The location of the lesion away from subchondral bone, its high T2-weighted signal intensity, its homogeneity and its lack of sharp demarcation made osteonecrosis (ON) unlikely [2]. Contrast medium-enhanced and fat-suppression MR scans were not performed. Further investigation, including radio-labelled white cell scanning and computed tomography of the abdomen and thorax, failed to show any evidence of infection or neoplasia. A diagnosis of TRO was made. Protected weight bearing was advised and analgesia prescribed. Symptoms resolved over 5 months, at the end of which time repeat plain X-ray and MR scan of the right hip were normal.

Fig. 1.—Anterior view of a 99m technetium methylene diphosphonate (MDP) bone scan showing focal uptake in the proximal right femur.

Fig. 2.—Coronal MR images through the hips showing reduction in signal intensity (arrowed) in the proximal right femur in a T1-weighted (TR/TE 640/23) sequence (A) and increased signal intensity (arrowed) in the corresponding T2-weighted (TR/TE 4000/95) view (B) consistent with TRO.
DXA scanning (Hologic QDR1000), performed 7 weeks after the onset of symptoms, showed reduced BMD in the symptomatic right femoral neck (0.647 g/cm², $T = -2.48$, $Z = -2.04$), but even lower BMD in the asymptomatic left side (0.568 g/cm², $T = -3.27$, $Z = -2.82$). Intertrochanteric BMD was also markedly reduced (right, $Z = -1.37$; left, $Z = -1.56$). Repeat densitometry 7 months later, by which time both symptoms and MR changes had resolved, showed a 4% fall in BMD in the right hip and no change in the left. Osteopenia ($Z = -1.78$) was demonstrated in the lumbar spine (L1–L4).

This case illustrates both the importance of MR imaging in the diagnosis of TRO and the problems of interpreting isolated bone densitometry readings. Although not pathognomonic, MR appearances in TRO have a high degree of specificity. ON is an important differential diagnosis in suspected TRO and, in established lesions, MR scanning readily distinguishes the two conditions. This is occasionally not the case in early lesions, however [2, 3]. The diagnosis of TRO in this patient is supported by her subsequent clinical course. In contrast, in the presence of background osteoporosis, DXA scanning proved unhelpful in the initial assessment of the focal lesion in this patient. Follow-up bone densitometry at 7 months showing a further reduction in BMD in the affected hip is in line with the delay in remineralization previously reported during recovery from TRO after pregnancy [1].

Bone densitometry was valuable in demonstrating widespread reduction in BMD, the cause and significance of which are uncertain in this patient (although excessive alcohol intake may have been an aetiological factor). Generalized undermineralization of bone may predispose, in some individuals, to the acute reversible demineralization of intact trabeculae and accompanying marrow oedema that characterize TRO. If so, its detection and correction, as well as being valuable in the prevention of future fracture, would also be expected to reduce the likelihood of recurrence of TRO in other sites. For this reason, we believe that bone densitometry should form part of the assessment of patients with TRO.

R. J. Stevens,† M. L. Hall,* R. A. Hughes†
Heberden Unit, Amersham Hospital, Amersham, Bucks HP7 0JD, *Department of Nuclear Medicine and †Department of Rheumatology, St Peter’s Hospital, Guildford Road, Chertsey KT16 0PZ
Accepted 28 November 1996
†Correspondence to: R. J. Stevens.


On Surgical Microarteriolysis for Treatment of Raynaud’s Phenomenon in Scleroderma

Sir—Controversy still exists about the appropriate surgical treatment of severe Raynaud’s phenomenon. Two clinical cases have raised questions that we would like to discuss.

Mitchell [1] pointed out that the sympathetic fibres of the digital arteries have ramifications between the adventitia and the media. Therefore, Flatt [2] and Wilgis [3, 4] suggested adventicectomies of a short segment of the proper digital arteries in order to perform interruption of the sympathetic pathways. They present good results, but no patient had scleroderma.

In scleroderma, Jones [5, 6] described sympathectomy of the superficial palmar arch, common and proper digital arteries, while O’Brien et al. [7] proposed a more extended approach. He included the ulnar artery and the proper digital arteries up to the distal interphalangeal joint. In both techniques, when the ulnar artery or superficial palmar arch are occluded, a vein graft is interposed. O’Brien reported the largest series in which 13 patients suffering from scleroderma were reviewed.

Two patients with severe Raynaud’s phenomenon associated with severe scleroderma were treated in our department. The first patient was a 55-yr-old man presenting with refractory pain and trophic lesions of the second finger. His left hand was more severely involved than the right one. The arteriogram showed a patent superficial palmar arch and occlusion of the ulnar artery.

Under general anaesthesia and optic magnification, a bypass of the ulnar artery was performed in conjunction with an extended arteriolysis of the proximal ulnar artery, the superficial palmar arch, common and proper digital arteries following the technique described by O’Brien. The total operating time was 9 h. In the post-operative period, the patient was markedly improved. Pain decreased, allowing marked reduction of analgesic drug intake and progressive healing of trophic lesions. The physiotherapy, begun on the fifth post-operative day, progressively improved the mobility of the fingers and the patient was discharged on the eleventh post-operative day. Unfortunately, 1 month after the surgery, the patient was readmitted with abrupt recurrence of severe pain and lividity of the hand due to thrombosis of the bypass. During his hospitalization, the patient died unexpectedly from a mesenteric infarction.

The second patient was a 71-yr-old woman also suffering from severe pain and trophic lesions of both hands. The arteriograms showed that the left radial artery presented arteriosclerotic stenosis, whereas the left ulnar artery was involved both by sclerotic and vasospastic lesions. Microsurgical adventicectomy of the ulnar artery, the palmar arch and the first segment of the common digital arteries was performed with two minimal incisions. The total operating time was only
1.5 h. Post-operatively, immediate pain relief was associated with good colouration of the digits, allowing the analgesic drugs to be decreased. She was discharged on the fifth post-operative day without any complications. Ten days after surgery, healing of the surgical incisions was uneventful and mobility of all the digits was complete without the need for physiotherapy. A few months later, the benefit had disappeared and trophic ulcers developed at two fingertips, requiring phalangeal amputation in one.

Regarding these two cases, we open several points for discussion. First, is the bypass really indicated? Distal resistance despite adventicectomy can still be expected to be higher than normal. Therefore, thrombosis of the bypass appears to be predictable, but the literature does not give follow-up on bypass patency. Second, what is the utility of the distal adventicectomy? Adventicectomy of proper digital arteries necessitates ligations of most collateral branches to be achieved completely. Its overall advantage on finger vascularization remains questionable. Finally, do we really need such an extended approach? Extensive surgery imposes large scars, a long operating time and long rehabilitation. Although immediate results are encouraging, they seem limited in time with relapse within a few months post-operatively. Based on only two clinical cases, the aim of this letter is to share some of our concerns that arose after the first case, which led us to a less extensive approach in the second case. If performed on the permeable major vessels of the hand, we suggest performing adventicectomy of only a short arterial segment. Distal sympathectomy should then increase blood flow to the fingers, as proven by the literature, without the risk of nerve regrowth.

D. VAN DEN BROECK, B. C. COESENS, A. PERETZ*
Department of Plastic Surgery and *Department of Rheumatology, Brugmann Hospital, Brussels, Belgium
Accepted 11 November 1996
Correspondence to: D. Van Den Broeck, Brugmann Hospital, Free University of Brussels, Department of Plastic Surgery, 4, Place Van Gehuchten, 1020 Brussels, Belgium.

Erythema Nodosum Associated with Sjögren’s Syndrome

Sir—A variety of cutaneous manifestations are occasionally associated with Sjögren’s syndrome (SiJS) including hypergamma globulinemia, purpura, urticarial vasculitis, autoimmune anhidrosis, and recently described annular erythema [1–5]. We have studied the clinical and histological features of four cases of erythema nodosum (EN) associated with SiJS.

Case 1 was a 65-yr-old female who visited our department complaining of painful, erythematous plaques of the lower legs in the prior 2 weeks. She had a past history of surgery for thyroid adenoma 20 yr ago. Laboratory examination showed positive antinuclear antibody (×80, speckled), anti-SS-A antibody (×4), CRP, ASO, ASK, serum rheumatoid factor, complements, IgG levels and anti-SS-B antibody were negative or within normal ranges. She complained of sicca condition. Both gum test (5 ml/10 min) and Shirmer test (1; 5 mm, r; 4 mm) were positive. Histological examination revealed dense infiltration of lymphocytes throughout the dermis to s.c. tissue. Fibrinoid degeneration of the vascular wall in the dermis was shown. Numerous giant cells and nuclear dust were also present. Cutaneous lesions improved with a non-steroidal anti-inflammatory drug (NSAID) (mefenamic acid) within 4 weeks.

Case 2 was a 27-yr-old female who was admitted to our hospital complaining of fever up, arthralgias, and painful erythematous plaques scattered on her forearms and lower legs. She complained of sicca condition, Raynaud’s phenomenon and morning stiffness. Physical examination revealed livedo reticularis of her legs, and erythematous plaques were scattered on her forearms and lower legs. Laboratory examination showed antinuclear antibody (×320, speckled), anti-SS-A antibody (×1), decreased complement levels and elevated level of amylase. ASO and ASK were within normal ranges. Both gum test (3 ml/10 min) and Shirmer test (1; 2 mm, r; 6 mm) were positive. Lip biopsy revealed dense lymphocyte infiltration around the dilated ducts (grade 3). Keratoconjunctivitis sicca was not noted. Histological examination revealed s.c. tissue inflammation composed of lymphocytes, neutrophils and histiocytes with mild perivascular infiltrates in the dermis. EN lesions gradually improved with a NSAID (indomethacin) within 4 weeks.

Case 3 was a 43-yr-old female who was followed under a diagnosis of SiJS. She was complaining of morning stiffness, peripheral arthralgia, and multiple alopecia areata, besides oral dryness. Laboratory examinations revealed positive antinuclear antibody (×160, speckled), anti-SS-A antibody (×4), decreased levels of serum complements, increased levels of amylose and γ-globulin. ASO and ASK were within normal ranges. Gum test (5 ml/10 min) and Shirmer test (1; 8 mm, r; 8 mm) were positive. Labial lip biopsy revealed a positive grade 3. She developed a painful, erythematous lesion on her right lower
leg without prior upper respiratory tract infection. Histological features showed lymphocytic infiltration of the s.c. tissue. Dilated vessels and nuclear dust were noted in the lobules. EN improved by resting and with a NSAID (loxpofen sodium) within 2 weeks.

Case 4 was a 77-yr-old female who visited our department complaining of painful erythematous plaques of her lower legs. She had past histories of contact dermatitis due to paraphenylenediamine, urticaria and herpes zoster. Physical examination revealed several erythematous plaques of her lower limbs. Laboratory examination showed increased erythrocyte sedimentation rate (82 mm/h), positive CRP, positive antinuclear antibody (× 160, speckled), increased serum IgG, elevated γ-globulin and decreased complement levels. ASO and ASK were within normal ranges. Anti-SS-A and anti-SS-B antibodies were negative. Although keratoconjunctivitis sicca was not present, Shirmer test (1; 6 mm, r; 7 mm) and gum test (4 ml/10 min) were positive. The lesions improved with a NSAID (indomethacin) within 6 weeks.

EN is an inflammatory reactive vascular dermatosis rather than a true vasculitis [6]. It develops in association with tuberculosis, streptococcal infection, drugs, sarcoidosis or Behçet’s disease [7, 8]. In this report, we ruled out other underlying disorders by examining chest X-ray, purified protein derivative (PPD) test, serum titres of ASO and ASK, angiotensin converting enzyme and lysozyme, and diagnosed our four cases of EN to be associated with SjS.

Our data showed the marked predilection for EN for women. EN occurred bilaterally in three cases. Its onset was sudden and followed by throat pain in one case. In three cases, the onset of EN preceded the diagnosis of SjS. Systemic manifestations were present in two cases. Recurrence was noted in one case. Biopsy specimens from three patients showed septal and lobular panniculitis with varying density of inflammatory cells in the dermis, which is summarized in Table I. It is of note that definite vasculitis was not detected; however, vascular changes (fibrinoid, thick-walled or dilated changes) and nuclear dust were present in the dermis and s.c. tissue in two cases, which may indicate that EN represents vasculitis-like changes in cases with SjS. Direct immunofluorescence did not detect any dermal vessel deposits. The lesions improved with NSAIDs within 2–6 weeks without systemic prednisolone in all cases. For the lymphocyte recruitment to the lesional skin, interaction of vascular endothelial cells and lymphocytes through cell adhesion molecules plays an important role. Cell adhesion molecules on vascular endothelial cells, such as intercellular adhesion molecule-1 (ICAM-1) or vascular cell adhesion molecule-1 (VCAM-1), are upregulated in lacrimal gland or salivary gland in SjS [9, 10]. We speculate that adhesion molecules might also play a role in the induction of EN in SjS. EN may represent one of the cutaneous manifestations of SjS and we suppose that EN or EN-like lesions may show vascular changes in cases associated with SjS. In conclusion, we propose that the investigation of SjS must be needed in case EN occurs without apparent inducing agents.

T. YAMAMOTO, A. YOKOYAMA, Y. YAMAMOTO, A. MAMADA
Department of Dermatology, Tsuchiura Kyodo General Hospital, Ibaraki, Japan
Accepted 28 November 1996

Correspondence to: T. Yamamoto, Department of Dermatology, Tokyo Medical and Dental University, School of Medicine, 1-5-45, Bunkyо-ku, Yushima, Tokyo 113, Japan.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Results of the histological features of three biopsied specimens of EN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal changes</td>
<td>Case 1</td>
</tr>
<tr>
<td>Perivascular lymphocytic infiltrate</td>
<td>+</td>
</tr>
<tr>
<td>Giant cell</td>
<td>+</td>
</tr>
<tr>
<td>Vascular change</td>
<td>+</td>
</tr>
<tr>
<td>Nuclear dust</td>
<td>–</td>
</tr>
<tr>
<td>Collagen atrophy</td>
<td>–</td>
</tr>
<tr>
<td>Septal changes</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte infiltrate</td>
<td>+</td>
</tr>
<tr>
<td>Neutrophil infiltrate</td>
<td>+</td>
</tr>
<tr>
<td>Histocyte infiltrate</td>
<td>+</td>
</tr>
<tr>
<td>Fat degeneration/necrosis</td>
<td>+</td>
</tr>
<tr>
<td>Giant cell</td>
<td>+</td>
</tr>
<tr>
<td>Vascular change</td>
<td>+</td>
</tr>
<tr>
<td>Nuclear dust</td>
<td>–</td>
</tr>
</tbody>
</table>

The Value of Temporal Artery Biopsy in Suspected Cranial Arteritis

Sir—The management of patients with suspected giant cell arteritis (GCA), who have a negative temporal artery biopsy, is often complicated by diagnostic uncertainty and concerns about treatment-related adverse events, particularly because previous large retrospective surveys indicate that none of the typical symptoms of cranial arteritis, except perhaps jaw claudication, are predictive of a positive biopsy result [1]. It is reported, in a study where the mean length of biopsies was 5.6 cm, that 91% of those with a negative biopsy do not require corticosteroids when followed for a median of 70 months [2]. However, since biopsy specimens in routine British practice rarely exceed 1 cm [3], and since the remaining 9% of patients cannot be reliably identified by any other means, therapeutic uncertainty remains and, in practice, a higher proportion of negative biopsies are likely to be false negatives. One possible solution is to perform a second biopsy, although in our experience this is done rarely. It is possible that qualitative differences in symptoms, rather than the presence or absence of symptoms, allow clinicians to stratify patients and minimize the risks of treating, or not treating, patients with suspected GCA who have a negative biopsy. Thus, it might be argued that the biopsy result is superfluous to decision making.

In a prospective study of 28 patients referred to the rheumatology service in Edinburgh, over a 2 yr period, we classified patients into four categories consisting of those with a high probability of GCA (five patients), moderate probability (seven patients), low probability (11 patients) and very low probability (five patients). Patients were classified before arranging temporal artery biopsy and classification was based on the perception of the examining doctor and not on any pre-determined combination of presenting features. No other aspect of the patient’s management, including the need for biopsy and, particularly, any aspect of biopsy taking or analysis, was altered in any way. Patients’ records were reviewed after a mean of 13.5 months (range 2–24) and, where necessary, details were sought from general practitioners. There was no significant difference in age, ESR or the presence of scalp tenderness, jaw pain or claudication, polymyalgia, visual disturbance or weight loss between the four groups, or when those with moderate and high probability of GCA were compared with those judged to have a low or very low probability. All patients with a high and moderately high probability of GCA, except for one who declined biopsy, had a temporal artery biopsy and 6/11 (55%) biopsies showed unequivocal evidence of arteritis. This compares with biopsies in nine patients of those with a low or a very low probability $(P < 0.05$ by $\chi^2$ analysis), none of which were positive. The maximum recorded length of biopsy in this study was 0.8 cm.

Patients believed to have a high or moderate probability of GCA were treated with conventional doses of steroids regardless of biopsy result. Patients received a calculated average daily dose of oral prednisolone of 35 and 31 mg, respectively, during the first 3 months. At review, none of those patients who had a negative biopsy, and who were treated as having GCA, had an alternative diagnosis, whereas of those judged to have a low probability of GCA who were not treated with steroids, 55% (5/9) had alternative diagnoses, including pneumonia in two patients, monoclonal gammopathy, tuberculous meningitis and hypothyroidism.

Our prospective observations indicate that where clinicians judge the probability of GCA to be high or moderate on the basis of a clinical impression, a temporal artery biopsy result does not alter management. This is consistent with Allsop and Gallagher’s view [4]. We also believe that where there is doubt, a second biopsy, of adequate length, is merited and should be performed more commonly [5]. A negative biopsy, even one of inadequate length, where physicians believe that GCA is unlikely, seems to have great value in reassuring physicians (and presumably patients) and this cannot be underestimated.

P. Jobanputra, R. Richmond, E. McRorie
Rheumatic Diseases Unit, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU
Accepted 29 November 1996


The Value of Arthrography in Steroid Injection of the Shoulder Joint

Sir—Intra-articular injection is a widely used method of treating acute non-infective arthritis [1]. However, several studies have shown no symptomatic improvement in patients who underwent blind joint injections [2].

We reviewed retrospectively 23 patients (13 male and 10 female, aged between 24 and 75 yr) with shoulder pain, which was considered on clinical grounds to be due to joint inflammation, who underwent intra-articular injection of corticosteroid in the shoulder joint under fluoroscopic control. Ten patients had a clinical diagnosis of rheumatoid arthritis, six patients had rotator cuff tendinitis, four patients had osteoarthritis and three patients had seronegative arthropathy. All the patients had had previous therapy, including analgesia, physiotherapy and, in a few cases,
blind intra-articular corticosteroid injections, without improvement of their symptoms.

Our technique was to place, under fluoroscopic guidance, a 20G spinal needle into the glenohumeral joint, the position of which was confirmed by injecting non-ionic water-soluble contrast medium (Ultravist 300, Schering Healthcare). A formal arthrogram was then performed, following the injection of 15–20 ml of contrast medium, and 80 mg of depot methylprednisolone were injected into the joint.

The radiological appearances of the 26 arthrograms (three patients had both shoulders injected) are shown in Table I. When reviewed 6–8 weeks later, 23 (88%) shoulders in 20 patients were improved both symptomatically and on clinical examination. A total of 10 (38%) patients were completely symptom free, while 10 (38%) patients described their improvement as moderate and three (12%) as slight. The remaining three (12%) were no better following the injection. Of the 20 patients who improved, six (23%) have had no further symptoms and 14 (65%) were symptom free for between 3 and 23 months with a mean improvement of 11 months.

Of the patients who did not improve, one had an extensive rotator cuff tear on arthrography and responded well to surgery. The second patient had chronic synovitis and a partial tear of the supraspinatus tendon confirmed on subsequent MRI, and he also responded well to surgery. The third patient had osteoarthritis of the acromioclavicular joint and a normal shoulder arthrogram.

There are several methods of injecting the shoulder blindly, although the accuracy is generally poor [3]. When fluoroscopic guidance is used, the injection becomes more reliable as the needle is confirmed to be intra-articular at the time. This ensures that the steroid is injected into the joint and reduces the incidence of side-effects, e.g. local tissue atrophy. An arthrogram performed at the same time is invaluable in planning the future management of the patient. In cases of adhesive capsulitis, it is possible to distend the joint capsule by injecting a larger volume of fluid once the diagnosis is confirmed.

The success rate of injections in our limited study was high. We are planning to undertake a prospective randomized controlled study comparing blind vs screened intra-articular corticosteroid injections.

G. J. M. Goh, K. E. Over,* A. Daroszewska,* G. H. Whitehouse, R. C. Bucknall*  

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal arthrogram</td>
<td>7</td>
</tr>
<tr>
<td>Synovitis</td>
<td>11</td>
</tr>
<tr>
<td>Adhesive capsulitis</td>
<td>5</td>
</tr>
<tr>
<td>Rotator cuff tear</td>
<td>3</td>
</tr>
</tbody>
</table>

Antiperinuclear Factor in Early Synovitis

Sir—We read with interest the paper by Cordonnier et al. [1] on the value of antiperinuclear factor (APF) in comparison with rheumatoid factor (RF) in the diagnosis of rheumatoid arthritis. We are also interested in autoantibodies in early arthritis, and we would like to present our results and to show their relationship with particular class II MHC antigens.

We studied 125 patients with early arthritis (<6 months duration) from early synovitis clinics in Bath and Madrid. At presentation, patients were assessed clinically and serum levels of IgM RF and APF were determined. In 56 (44.8%) patients, the final diagnosis was rheumatoid arthritis (RA). At presentation, 43 (34.4%) and 40 (32%) patients were RF and APF positive, respectively. In the RA patients, 36 (64.2%) and 31 (55.3%) were RF and APF positive. The sensitivity of these markers was 64.2 and 55.3%, and the specificity 89.8 and 86.9%, respectively, showing that APF is as good as RF in the diagnosis of RA. In the 20 RA patients who were RF negative, APF was positive in five (25%). APF and RF were strongly associated as the former was present in the 75% of patients positive for RF.

We have also investigated the relationship between these autoantibodies and the presence of specific class II MHC alleles. Of the total 125 patients, 70 (56%) expressed either DRB1*04 (DR4) or DRB1*01 (DR1). This compared with 36/56 (64%) of the RA group (difference not significant). Analysis of HLA-DQ alleles in the 125 patients showed that 38 (30.4%) expressed DQB1*0301 (DQ7) and 38 (30.4%) expressed DQB1*0302 (DQ8). In the RA subjects, 21 (37.5%) were positive for DQ7 and 18 (32.1%) for DQ8 (difference not significant). However, comparison of all patient data with serum autoantibody levels indicated a clear difference in class II MHC association. The presence of APF was strongly associated with expression of DQ8 ($P < 0.001$, $\chi^2$ analysis), but not with DQ7 or any other DQ allele.

(P = NS), and less strongly with DR4/1 (P < 0.002).
Twenty-one (52.5%) of the 40 APF-positive patients
expressed DQ8, while only 10 (25%) of these patients
were positive for DQ7. Seropositivity for RF
was, not surprisingly, correlated with expression
of DR4/1 (31/43 patients, P < 0.01), but was
markedly less associated with DQ8 (19/43 patients,
P < 0.02).

The presence of APF in established RA has been
confirmed by us [2] and other authors [3–5], with incidence
values ranging from 49 to 86% of patients. Cordonnier
et al. [1] reported that the sensitivity and specificity of
APF for the diagnosis of RA were 36.7 and 90%,
respectively. Equivalent values in our study were 55.3%
sensitivity) and 86.9% specificity). Although the
specificity figures are similar, their finding of a lower
sensitivity is perhaps surprising, given that their
inclusion criteria selected patients with oligo- or
polyarticular involvement. In our early synovitis clinic,
all patients with arthritis of < 6 months duration were
included regardless of clinical involvement. The most
likely explanation for our improved sensitivity of APF
detection in RA lies in differences of detail in the
technique used [2]. Following an extensive comparison
of assays with different dilutions and positivity criteria
[6], we chose 1/5 as the optimal dilution of sera rather
than 1/40, and 5% positive cells as the positivity
criterion instead of 10%. We agree with Cordonnier
et al. that a 1/40 serum dilution gains specificity but loses
sensitivity.

Our data confirm previous reports [1, 7] that APF is
present in the very early stages of rheumatoid disease
and has a diagnostic value similar to RF. In fact,
both autoantibodies are strongly associated, as shown
in our study and by other authors [4, 8]. This is
particularly important in RF-negative patients who can
represent up to 35% of cases [2]. It has been suggested
that APF can be a prognostic marker [8, 9] in early
disease, and in a preliminary report we have shown that
the presence of APF is associated with persistence of
arthritis [10].

In our study, seropositivity for APF was strongly
associated with expression of DQ8*0302 (DQ8), but
no other DQ allele. In contrast, the presence of RF was
less strongly correlated with DR4/1, and even more
weakly with DQ8. Numerous studies have analysed the
association of DR4 with RF seropositivity with
conflicting results [11]. APF has been associated with
DR4 in seronegative RA [12], but this has not been
confirmed by other authors [4]. In Greek RA patients,
antikeratin antibodies, which are closely related to
APF [13], have been associated with DR1 [14]. Our
identification of a strong association between APF
positivity and expression of DQ8 may reflect a similar
class II MHC association to those seen with
anti-centromere [15] and anti-topoisomerase-I [16]
autoantibodies in systemic sclerosis.

Supported by grants Acciones Integradas HB94-046
and 917 (AB, NDH), FIS 95/474 and 96/1183 (AB,
SM), the Harris Trust (NDH, PJM) and ARC core
support (PJM).

S. Muñoz, A. Balsa, N. D. Hall,‡ R. Alvarez-Doforno,*
J. L. Vicario,‡ J. Barnes‡ and P. J. Maddison‡
Rheumatology and *Immunology Units, Hospital
Universitario La Paz, ‡Centro de Transfusión de la
Comunidad de Madrid, Madrid, Spain and ‡Bath
Institute for Rheumatic Diseases and School of
Pharmacy and Pharmacology, University of Bath, Bath
Accepted 27 November 1996
Correspondence to: N. D. Hall, School of Pharmacy and
Pharmacology, University of Bath, Bath BA2 7AY.

value of anti-RA33 antibody, antikeratin antibody,
antiperinuclear factor and antinuclear antibody in early
rheumatoid arthritis: comparison with rheumatoid
2. Muñoz-Fernandez S, Alvarez-Doforno R, Cuesta M,
Balsa A, Fontán G, Gijón J. Antiperinuclear factor: a
useful test for the diagnosis of rheumatoid arthritis.
3. Sondag-Tschroots IRJM, Aaij C, Smit JW, Feltkamp
TEW. The antiperinuclear factor. 1. The diagnostic
significance of the antiperinuclear factor for rheumatoid
P, Jouquan J. The antiperinuclear factor. I. Clinical and
serologic associations. Clin Exp Rheumatol 1990;8:
259–64.
5. Hoet RMA, Boerbooms AMTh, Arends M, Ruiter DJ,
Van Venrooij WJ. Antiperinuclear factor, a marker
autoantibody for rheumatoid arthritis: colocalization of
the perinuclear factor and profilaggrin. Ann Rheum
Fontán G, Gijón J. Factor antiperinuclear: criterio de
positividad y dilución óptima de los sueros problema.
H, Aho K. Prospect for an additional laboratory
criterion for rheumatoid arthritis. Scand J Rheumatol
8. Westgeest AAA, Boerbooms AMTh, Jongmans M,
Vandenbroucke JP, Vierwinden G, van de Putte LBA.
Antiperinuclear factor: indicator of more severe disease
in seronegative rheumatoid arthritis. J Rheumatol
M. Antikeratin antibody and antiperinuclear factor as
markers for subclinical rheumatoid disease process.
10. Balsa A, Barnes J, Muñoz-Fernández S,
Alvarez-Doforno R, Hall ND, Maddison PJ.
Antiperinuclear factor: a prognostic marker in early
11. Grant JT, Husby G. Seronegative rheumatoid arthritis
and HLA DR4: Proposal for criteria. J Rheumatol
1987;14:1979–82.
12. Boerbooms AMTh, Westgeest AAA, Reekers P,
Van de Putte LBA. Immunogenetic heterogeneity of
seronegative rheumatoid arthritis and the antiperinuclear
13. Sebbag M, Simon M, Vincent C et al. The
antiperinuclear factor and the so-called antikeratin
antibodies are the same rheumatoid arthritis-specific
Severe Hypercalcaemia Syndrome with Daily Low-Dose Vitamin D Supplementation

Sir—At present, the prevention of osteoporosis is a major topic in medicine. For prophylactic treatment, daily use of 400 IU vitamin D is generally considered a safe measure [1, 2]. We report an elderly patient who developed a severe hypercalcaemia syndrome during daily use of low-dose vitamin D, i.e. 400 IU cholecalciferol.

An 85-yr-old woman was referred to the rheumatology outpatient clinic because of a mild rheumatoid factor-positive oligoarthritis which had already been treated with 10 mg prednisone a day by her GP during a period of 4 yr. Because of low back pain due to compression fractures of the second and fifth lumbar vertebrae, and transient ischaemic attacks, the GP had also prescribed the daily use of 38 mg acetosal, 100 mg/400 µg diclofenac/misoprostol, 1000 mg acetas/minophen and 400 IU cholecalciferol (Devaron®) since 2 months. The patient then started to complain of severe thirst, fatigue and malaise; she had to be admitted because of severe dehydration. Laboratory analysis: calcium 3.31 mm (normal range 2.10–2.55 mm), paraproteinaemia was excluded; further data are presented in Table I. On admission, cholecalciferol was discontinued and rehydration started. Because her clinical condition improved too slowly, pamidronate was given: 30 mg i.v., followed by 2 dd 150 mg orally during 3 weeks. Within 1 week, plasma calcium normalized and remained normal (see Table I). Further analysis did not reveal hyperparathyroidism, malignancy or an alternative causative explanation for the hypercalcaemia.

To our knowledge, this is the first publication reporting that low-dose vitamin D supplementation in the elderly evoked a severe hypercalcaemia syndrome. The blood vitamin D level normalized within 2 months after cessation of supplementation. Only a few reports on the actual level of 1,25(OH)2 vitamin D in cases with vitamin D intoxication have been reported [3]. Toxic effects including hypercalcaemia have been reported during daily supplementation with 2000–5000 IU a day (50 µg) [1] and at higher, more pharmacological dosing regimens [4]. In the elderly, it is generally advised that the daily vitamin D intake should be at least 200 IU (5 µg), for reasons of altered vitamin D metabolism and limited exposure to UV irradiation. The patient described, however, proved that supplementation with low-dose vitamin D can be the cause of a severe hypercalcaemia syndrome.

T. L. TH, A. JANSEN, M. JANSEN, A. J. L. DE JONG
Department of Rheumatology, Rijnstate Hospital, Wagnerlaan 55, 6815 AD Arnhem, The Netherlands
Accepted 26 November 1996

TABLE I
Time course of biochemical parameters with normal values in parentheses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment</th>
<th>0 (admission)</th>
<th>2</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>(2.10–2.55 mm)</td>
<td>2.47</td>
<td>3.31</td>
<td>2.34</td>
<td>2.35</td>
</tr>
<tr>
<td>Phosphate</td>
<td>(0.87–1.45 mm)</td>
<td>1.43</td>
<td>1.62</td>
<td>1.29</td>
<td>1.18</td>
</tr>
<tr>
<td>Creatinine</td>
<td>(50–80 µm)</td>
<td>–</td>
<td>166</td>
<td>105</td>
<td>109</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>(0.1–15 mm)</td>
<td>–</td>
<td>&lt;2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>25(OH)D3</td>
<td>(19–126 nm)</td>
<td>–</td>
<td>62</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>1,25(OH)2D3</td>
<td>(40–140 pm)</td>
<td>–</td>
<td>257</td>
<td>78</td>
<td>81</td>
</tr>
</tbody>
</table>