A successful renal transplantation in Behçet's syndrome

Renal involvement is not frequent in Behçet's syndrome (BS) and consists of occasional reports of patients having glomerulonephritis, IgA nephropathy and renal amyloidosis. We present the successful outcome of a renal transplantation in a patient who had end stage renal failure secondary to glomerulonephritis. To our knowledge, this is the first patient with BS to receive an organ transplantation.

The detailed history of this patient at the time of the diagnosis of glomerulonephritis was the subject of a case report in 1991. In brief, she was 21 years old when she developed recurrent oral and genital ulcers, bilateral uveitis, erythema nodosum, folliculitis, and intermittent arthritus of the knees. Two years later, she was referred to our centre for further evaluation of eye symptoms. She had no active mucocutaneous lesions at that time, the pathergy reaction was positive and she had LLA and FVL. It was decided to prescribe only local drops for her mild eye involvement. Three months later she experienced two ocular episodes resulting in a sharp decline of visual acuity and azathioprine 2.5 mg/kg/day was prescribed. Two weeks later she was admitted to the hospital because of microscopic haematuria. She was ANA negative, the anti-DNA and serum complement levels were normal. Her glomerular filtration rate was 67 ml/min. An open renal biopsy showed diffuse proliferative glomerulonephritis and weak focal segmental positivity of IgA and IgM. She was treated with three boluses of 1 g methylprednisone and was discharged prescribed azathioprine 150 mg/day, aspirin 300 mg/day and prednisone 30 mg/day. She was well except for occasional mucocutaneous symptoms and a mild decrease in haemoglobin at the end of the next four years. However her renal function deteriorated progressively despite uninterrupted treatment with azathioprine and changing doses of prednisone and she was put on regular haemodialysis twice a week. In the 14th month of haemodialysis, she received a kidney from her mother. The graft function started immediately and she was prescribed maintenance immunosuppression with azathioprine, cyclosporin A and methylprednisolone. An acute interstitial type rejection on the 11th day of transplantation was treated successfully with pulsed corticosteroids. Now 40 months after transplantation, she has normal renal function and is free of any symptoms of BS except for occasional oral ulcers.

We had some hesitation in performing a renal transplantation in our patient initially because of the lack of any previous experience and particularly because of our concern for the heightened inflammatory response of BS patients to simple penetrating trauma that is best characterised by the pathergy reaction. This reaction, however, is not only limited to the skin and development of aneurysms after vascular punctures and episodes of synovitis after arthrocenteses have been observed. Furthermore, postoperative complications leading to a poor outcome such as occlusions of grafts/anastomoses after the surgical treatment of aneurysms or perivalvular leakage and suture breakdown after aortic valve replacement have been reported in BS patients. As these complications are probably related to the pathergy phenomenon reaction, you would also reasonably expect problems after an organ transplantation, an operation with arterial and venous anastomoses. On the other hand, we had previously shown that despite the increased inflammation, wound healing after full thickness skin punch biopsies is not changed in BS. We have not experienced any of the feared complications after the transplantation procedure in this instance. One reason for this favourable outcome might be that our patient was female. It is known that BS runs a milder disease course in women compared with men. Additionally, the rather intensive immunosuppressive/anti-inflammatory post-transplant drug use might also have contributed to the diminished disease activity of our patient as well as to the prevention of a reaction at the site of transplantation. Whatever it might be related to, the outcome in our patient suggests that BS patients can undergo renal transplantation with a satisfactory outcome.

SUYEYLA APAYDIN
EGEBER TOBE
UGER UKLU
Division of Nephrology, Department of Internal Medicine

VEDAT HAMURYUDAN
HASAN YAZICI
Division of Rheumatology, Department of Internal Medicine

MUZAFFER SARIYAR
Department of Surgery, Çerrahpaşa Medical Faculty, University of Istanbul, Istanbul, Turkey

Correspondence to: Dr V Hamuryudan, Veyisipasa sokak 100, Yil Sitesi, I Blok D16 Uskudar, 81190 Istanbul, Turkey.

10 Nakamura K, Kasanuki H, Nakamura T, Nakamura K, Nakamura T, et al. Anti-vascular basement membrane antibodies was positive in seven (24.1 %) patients. The age range of the patients was 20–63 years (mean (SEM) 40 (5)) and the mean (SEM) disease duration was 8.9 (2.3) years.

Lymphocyte phenotypes in systemic sclerosis

Although the pathophysiology of systemic sclerosis (SSc) is not fully clarified, there are considerable data implicating abnormalities of microvascular changes, fibroblast activation and immune system abnormalities. Immune system activation is a major feature as a stimulus in both fibrotic and vascular damage. To investigate the immune system abnormalities in the pathogenesis of SSc we evaluated lymphocyte phenotypes in patients with SSc and healthy subjects by flow cytometry (Epics Profile II) for total T (CD3), T helper (CD4), T suppressor (CD8), B lymphocyte cell surface marker (CD19), activator marker (CD25) and natural (NK) cell surface marker NKH-1 (CD56).

We studied 29 patients (27 women, two men) 16 limited, 12 diffuse and one overlap who fulfilled preliminary criteria for classification of SSc. Anti-nuclear antibody was positive in 25 (86.2%) and anti-Scl70 antibodies was positive in seven (24.1 %) patients. The age range of the patients was 20–63 years (mean (SEM) 40 (5)) and the mean (SEM) disease duration was 8.9 (2.3) years.

Table 1 summarises lymphocyte phenotypes in patients with SSc and healthy controls.

We found a higher expression of T cell activation marker CD25+ and NK cell main surface marker CD56+ in lymphocyte phenotypes there was not any difference in disease subsets and CD25+ and CD56+ were not correlated with the disease duration.

Immune system abnormalities have been suspected in the development of SSc because of the presence of autoantibodies, changed cytokine production and evidence of overlap with other autoimmune diseases. It was suggested that immune system changes play the major part in the development of vascular and fibrosis. Previous reports on T lymphocyte subpopulations in SSc are partially conflicting. Melendro et al demonstrated that there was no significant difference in the levels of CD3+, CD4+ and CD8+ in 22 SSc patients and control group but in rheumatoid arthritis (RA) CD3+ and CD8+, in Sjögren’s syndrome CD3+, CD4+ and CD8+ levels were significantly decreased compared with those of controls and they suggested that the abnormalities in immune regulatory T cell circuits leading to autoimmunity are different in each connective tissue disease.

Table 1 Lymphocyte phenotypes in patients with SSc and healthy controls

<table>
<thead>
<tr>
<th>Serum Anti-NCAM</th>
<th>Systemic Sclerosis (n=29)</th>
<th>Control (n=12)</th>
<th>t Test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 (%)</td>
<td>71 (9)</td>
<td>69 (9)</td>
<td>0.660</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>44 (9)</td>
<td>45 (9)</td>
<td>0.110</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>31 (9)</td>
<td>25 (6)</td>
<td>1.914</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>1.56 (0.6)</td>
<td>1.84 (0.6)</td>
<td>1.339</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD19 (%)</td>
<td>12 (3)</td>
<td>15 (3)</td>
<td>0.445</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD25 (%)</td>
<td>18 (9)</td>
<td>7.1 (3)</td>
<td>4.150</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD56 (%)</td>
<td>22 (9)</td>
<td>14 (5)</td>
<td>2.691</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

*Unpaired Student’s t test. Data shown as mean (SD).
Whitehead et al2 and Barrett et al3 by using the indirect immunofluorescence method, reported that CD8+ suppressor/cytotoxic T cells are decreased in SSc group, our findings differ from those of Whitehead and Barrett; we and Degiannis et al4 have used the more sensitive flow cytometry method and could not find any differences between T lymphocyte subgroups of SSc patients whereas in the pathogenesis of SSc the role of CD4+ and CD8+ T lymphocytes is still obscure.

Presence of autoantibodies and hypergammaglobulinemia support the role of humoral immunity but B lymphocytes were rarely found in the skin biopsy specimens.5 CD19+ is a cell surface marker of B lymphocytes and we could not observe any difference in the levels of CD19+ thus we can say that B lymphocytes might play only a minor part in the pathogenesis of SSc. CD25+ is one of the subunits of high affinity interleukin-2 receptor. CD19+ is a cell surface marker of B lymphocytes easily identified morphologically by immunocytochemical studies of pericardial fluid.6 NK cells are the main cellular immunity but B lymphocytes were decreased in SSc group, our findings may shed light on the pathogenesis of SSc. NK cell percentage can be used in the follow up the disease activity are needed.

The absolute number of lymphocytes was 5280/mm3 of an orange fluid was aspirated. Examination of PF showed white blood cell count of 3700/mm3 (polymorphonuclear cells = 96%). Further studies would be required to confirm the presence of autoantibodies and hypergam- maglobulinaemia support the role of humoral immunity but B lymphocytes were rarely found in the skin biopsy specimens.5 CD19+ is a cell surface marker of B lymphocytes and we could not observe any difference in the levels of CD19+ thus we can say that B lymphocytes might play only a minor part in the pathogenesis of SSc.

CD25+ is one of the subunits of high affinity interleukin-2 receptor. CD19+ is a cell surface marker of B lymphocytes easily identified morphologically by immunocytochemical studies of pericardial fluid.6 NK cells are the main cellular immunity but B lymphocytes were decreased in SSc group, our findings may shed light on the pathogenesis of SSc. NK cell percentage can be used in the follow up the disease activity are needed.

Table 1. Frequency of lymphocyte populations and cytokine concentrations in peripheral blood and pericardial fluid

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Peripheral Blood</th>
<th>Pericardial Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte population (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3+ T cells</td>
<td>57.8</td>
<td>50.0</td>
</tr>
<tr>
<td>CD4+ T cells</td>
<td>17.6</td>
<td>25.0</td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td>34.3</td>
<td>25.0</td>
</tr>
<tr>
<td>B cells</td>
<td>7.8</td>
<td>8.3</td>
</tr>
<tr>
<td>NK cells</td>
<td>34.3</td>
<td>41.7</td>
</tr>
<tr>
<td>Cytokine concentration* (pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL1β</td>
<td>&lt;6.0</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>IL6</td>
<td>&lt;6.0</td>
<td>&lt;6.0</td>
</tr>
<tr>
<td>IL10</td>
<td>16.9</td>
<td>4714.0</td>
</tr>
<tr>
<td>TNFα</td>
<td>&lt;5.0</td>
<td>1930.9</td>
</tr>
<tr>
<td>IFNγ</td>
<td>3.8</td>
<td>15.4</td>
</tr>
</tbody>
</table>

*Manufacturer (Genzyme, Boston, MA) detection limits: 3 pg/ml for IL1β, INFγ and TNFα; 4 pg/ml for IL6; 2 pg/ml for IL10; 18 pg/ml for IL4; and 5 pg/ml for IL10.

Before starting immunosuppressive treatment, PF and PB were obtained simultaneously for immunological analysis. Mononuclear cells from both sources were isolated by gradient centrifugation and the frequency of lymphocyte populations was determined by flow cytometry. The cytokine concentrations from plasma and PF were determined by ELISA. Table 1 shows the results. Among lymphocytes, the percentage of CD4+ T cells and NK cells was higher in PF, whereas the frequency of CD8+ T cells was higher in PB. IL6 concentration was much higher in PF than plasma. Also, IL1β and IL10 concentrations were higher in PF. IL2 was detected in plasma but not in PF. The considerable increase in pericardial IL6 concentrations in our case, IL6 is usually expressed or increased in the affected organ or system rather than pericardial involvement or SLE exacerbations.

The decreased pericardial lymphocyte count and fluid characteristics observed here are in agreement with other studies.7 The higher frequency of CD4+ T cells and NK cells in PF could be associated with the observed cytokine concentration pattern. For example, CD4+ memory T cells from SLE patients highly secrete IL10 compared with normal controls.8 In summary, different patterns of lymphocyte populations and cytokines were found in both sources, with type 2 cytokines predominating in PF and type 1 in PB. Further studies would be required to confirm the results presented here. In addition, immunocytocchemical studies of pericardial
tissue are necessary as the composition of lymphocyte and cytokine profiles may differ between pericardial fluid and tissue.

LUIS M VILÁ
JOSÉ R RIVERA DEL RÍO
Department of Internal Medicine, Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico

ZILKA RIOS
ELIZABETH RIVERA
Department of Microbiology and Immunology, Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico

Correspondence to:
Dr L M Vila, Department of Internal Medicine, Division of Rheumatology, Universidad Central del Caribe School of Medicine, Call Box 60327, Bayamón, Puerto Rico 00960–6032, USA.

Letters, Matters arising

721


Table 1 Lymphocyte populations in AU patients and controls

<table>
<thead>
<tr>
<th>AU patients (n=146)</th>
<th>Controls (n=31)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes (no/mm³)</td>
<td>2425.60 (964.44)</td>
<td>2567.74 (820.72)</td>
</tr>
<tr>
<td>CD3 (no/mm³)</td>
<td>1734.20 (726.67)</td>
<td>1835.64 (856.68)</td>
</tr>
<tr>
<td>CD4 (no/mm³)</td>
<td>1023.91 (489.16)</td>
<td>712.71 (42.88)</td>
</tr>
<tr>
<td>CD8 (no/mm³)</td>
<td>42.56 (9.50)</td>
<td>47.00 (6.13)</td>
</tr>
<tr>
<td>CD19 (no/mm³)</td>
<td>702.21 (359.67)</td>
<td>675.90 (243.54)</td>
</tr>
<tr>
<td>CD4CD45R- (no/mm³)</td>
<td>10.23 (5.63)</td>
<td>13.64 (5.99)</td>
</tr>
<tr>
<td>CD4CD45R+ (no/mm³)</td>
<td>657.70 (301.36)</td>
<td>675.70 (301.36)</td>
</tr>
<tr>
<td>CD4CD45R- (%)</td>
<td>16.70 (9.99)</td>
<td>25.20 (7.76)</td>
</tr>
<tr>
<td>CD4CD45R+ (%)</td>
<td>10.81 (5.65)</td>
<td>13.64 (5.09)</td>
</tr>
<tr>
<td>CD19 (%)</td>
<td>29.25 (8.81)</td>
<td>26.72 (6.81)</td>
</tr>
<tr>
<td>CD4CD45R+ (%)</td>
<td>27.00 (7.84)</td>
<td>20.77 (6.40)</td>
</tr>
<tr>
<td>NK (no/mm³)</td>
<td>300.45 (179.63)</td>
<td>323.80 (182.53)</td>
</tr>
<tr>
<td>CD4CD45R– (%)</td>
<td>13.30 (7.76)</td>
<td>12.81 (5.86)</td>
</tr>
</tbody>
</table>

AU = anterior uveitis, NK = natural killer cells, NS = not significant. Data shown as mean (SEM).

Figure 1 Absolute values of CD4CD45R+ cells. Patients with IAU had absolute values lower than the control group, and percentages lower than those of SA patients (p<0.001). IAU = idiopathic anterior uveitis; AU = anterior uveitis; SA = spondyloarthritis.

Figure 2 Percentages of CD4CD45R– cells. Patients with IAU had higher percentages than the healthy subjects and SA patients (p<0.001). Abbreviations as in figure 1.
MATTERS ARISING

RS3PE: six years later

We read with interest the paper by Cantini et al and would like to comment on it.1

In 1992 we performed a retrospective multicentre study of 275 RS3PE patients. We concluded that personal history of polymyalgia rheumatica (two patients), presence of erosions (one patient) and evolution to haematological diseases (two patients concomitantly developed a T lymphoma and one a myelodysplastic syndrome) suggested that RS3PE syndrome might not be a distinct clinical entity. At that moment 12 patients were asymptomatic and 12 required treatment. This was reported elsewhere.2

Now, six years later, we have reviewed the original cohort of patients with the RS3PE syndrome. A questionnaire was sent to the participating rheumatologists. The survey focused on articular symptoms, treatment and evolution. The current cohort was composed of 22 patients (16 male; 6 female; mean age:77.9; range 64–91). Four patients died (the three with haematological diseases, one stroke) and one was not located. Thirteen patients were asymptomatic and without treatment, in contrast nine required treatment, namely corticosteroids (6), gold salts (1), cloroquine (1) and NSAID (1). Interestingly, two of the patients were identified by their rheumatologist as having a seronegative rheumatoid arthritis, another patient had a chronic disease with separate corticosteroid responsive episodes of bilateral hand oedema and polyosymalgic syndromes at different times. Last but not least one patient developed Raynaud’s phenomena, both hands had sclerodactyly. A nailfold capillary microscopy showed a decreased number of capillary loops, which were widened, suggesting systemic sclerosis.

Our results suggests that RS3PE syndrome has a good prognosis, more than half of the patients are asymptomatic and without treatment six years later. However, there is a subset of patients that have other diseases. Although pure RS3PE syndrome does exist the evolution should be carefully monitored.

MONICA GUMÀ
ENRIQUE CASADO
XAVIER TENA
ALEX OLIVE
Rheumatology Section, Hospital Universitari Germans Trias i Pujol, C/ de Canyet s/n, Badalona 08016, Spain

We appreciate the comment by Olivé et al on our article on RS3PE. They reviewed 27 previously described RS3PE patients after a follow-up of six years.

As we suggested in a previous report, they confirm that RS3PE syndrome should be considered a heterogeneous condition associated with different inflammatory rheumatic diseases and also with neoplastic disorders.

In our study none of the 23 patients with RS3PE syndrome developed complications supporting the diagnosis for another disease. The different study design and selection of patients may in part explain the subset of patients with other diseases and with a worse prognosis observed by Olivé et al.

We designed a prospective follow up study excluding patients satisfying the criteria for the diagnosis of polymyalgia rheumatica, rheumatoid arthritis and seronegative spondyloarthropathies. Moreover, patients with a clinical history of cancer were excluded from the study. In their original report these authors performed a retrospective study including all patients with remitting distal extremity swelling with pitting oedema. They recruited also patients not evaluated for spondyloarthropathies, which may be associated with distal extremity swelling with pitting oedema.

However, in their retrospective evaluation Oliva et al found that 13 of 22 (59%) patients were asymptomatic and drug free over a six year follow up period, confirming that RS3PE not associated with other conditions and with a good prognosis does exist.

The problem is how to label this clinical picture. As discussed in our article,1 the similarities of demographic, clinical and MRI findings between patients with “pure” RS3PE syndrome and those with polymyalgia rheumatica and the concurrence of the two syndromes suggest that these conditions may be part of the clinical spectrum of the same disease. In the series of Olivé et al the patient with a clinical course characterised by alternating relapses of HL-A27 associated oedema or polyosymalgic symptoms further supports our hypothesis. Even those RS3PE patients successfully diagnosed as having seronegative rheumatoid arthritis (elderly onset rheumatoid arthritis) do not conflict with our conclusions. Healey described patients who developed episodes of polymyalgia rheumatica and seronegative rheumatoid arthritis at different times during follow up.3

Similar clinical characteristics have been recently described in a population based cohort of patients with giant cell arteritis followed up over a 42 year period. Four of the six patients who fulfilled the criteria for the diagnosis of rheumatoid arthritis during the follow up experienced multiple separate episodes of symmetrical arthritides, proximal symptoms of polymyalgia rheumatica and distal extremity swelling with pitting oedema.4

Authors’ reply

FRANCISCO SAMANIEGO
Service of Ophthalmology
FRANCISCO RIVERA-CIVICO
Service of Clinical Chemistry and Immunology,
"Virgen de las Nieves" University Hospital,
Granada, Spain

We are indebted to Ms E Velasco for assistance in the preparation of the manuscript.


7 Tamir A, Haim T, Nahir M, Takeuchi T, Daley J, Cívico F, Martín-Armada M, et al. Uveitis and polymyalgic symptoms at different times during follow up experienced multiple separate episodes of symmetrical arthritides, proximal symptoms of polymyalgia rheumatica and distal extremity swelling with pitting oedema.4

2nd Divisione di Medicina, Ospedale di Prato, Italy

CARLO SALVARANI
Servizio di Reumatologia, Azienda Ospedaliera,
Aiaspedic 6 Maria Nova, Reggio Emilia, Italy

IGNAZIO OLIVIERI
Servizio di Reumatologia, Ospedale S Carlo,
Potenza, Italy


2 Linsen A, Jakobsen A, Dandries J, Christiansen BJ, Baarsma GS, Tjoa ST, et al. Possible anklyosing spondylitis in acute anter-

3 Becknagle AB, Davies J, Gibson JM, Rosenhall AH. Acute anterior uveitis, anklyos-

4 Rothova A, van Veenendaal WG, Linsen A, Gla-

5 Rosenbaum JT. Characterization of uveitis asso-

6 Molder P, Vinge O, Olsen E. HL-A27, sacro-
ilitis and peripheral arthropathy in acute ante-


We thank the following rheumatologists for the con-
tribution to the study: Jordi del Blanco, Miquel Pons, Isabel Rotés, Raimon Sanmartí, Eduard Kantarerezicwicz, Miquel Sala, Ivonne Breyseya, Rosa Rosello, Javier Arasa, Marta Larrosa, Genonima Pons, Isabel Rotés, Raimon Sanmartí, Eduardo We designed a prospective follow up study including patients satisfying the criteria for the diagnosis of polymyalgia rheumatica, rheumatoid arthritis and seronegative spondyloarthropathies. Moreover, patients with a clinical history of cancer were excluded from the study. In their original report these authors performed a retrospective study including all patients with remitting distal extremity swelling with pitting oedema. They recruited also patients not evaluated for spondylarthropathies, which may be associated with distal extremity swelling with pitting oedema.4

However, in their retrospective evaluation Oliva et al found that 13 of 22 (59%) patients were asymptomatic and drug free over a six year follow up period, confirming that RS3PE not associated with other conditions and with a good prognosis does exist.

The problem is how to label this clinical picture. As discussed in our article1, the similarities of demographic, clinical and MRI findings between patients with “pure” RS3PE syndrome and those with polymyalgia rheumatica and the concurrence of the two syndromes suggest that these conditions may be part of the clinical spectrum of the same disease. In the series of Olivé et al the patient with a clinical course characterised by alternating relapses of HL-A27 associated oedema or polyosymalgic symptoms further supports our hypothesis. Even those RS3PE patients successfully diagnosed as having seronegative rheumatoid arthritis (elderly onset rheumatoid arthritis) do not conflict with our conclusions. Healey described patients who developed episodes of polymyalgia rheumatica and seronegative rheumatoid arthritis at different times during follow up.4

Similar clinical characteristics have been recently described in a population based cohort of patients with giant cell arteritis followed up over a 42 year period. Four of the six patients who fulfilled the criteria for the diagnosis of rheumatoid arthritis during the follow up experienced multiple separate episodes of symmetrical arthritides, proximal symptoms of polymyalgia rheumatica and distal extremity swelling with pitting oedema.4

FABRIZIO CANTINI
2nd Divisione di Medicina, Ospedale di Prato, Italy

CARLO SALVARANI
Servizio di Reumatologia, Azienda Ospedaliera,
Aiaspedic 6 Maria Nova, Reggio Emilia, Italy

IGNAZIO OLIVIERI
Servizio di Reumatologia, Ospedale S Carlo,
Potenza, Italy
Cryystals in arthritis: new age nonsense or novel therapeutic target?

Apatite crystals are present in up to 70% of fluids from degenerated joints. Their presence correlates strongly with radiographic evidence of cartilage degeneration and is associated with larger joint effusions when compared with joints without crystals. Whether the presence of apatite crystals is a cause of cartilage damage or an effect of cartilage damage is unclear. Several lines of evidence suggest that apatite crystals cause joint destruction. For example, apatite crystals induce both mitogen-activated protein kinase (MAPK) and protein kinase C (PKC). Furthermore, such activation is specific as the crystals do not activate protein tyrosine kinases (PTK) or phosphati-
dylinositol 3-kinases (PI3K). If the crystals were present simply as a consequence of joint destruction, we would expect them to be present in other arthopathies characterised by cartilage dissolution and synovial lining proliferation such as rheumatoid arthritis (RA). However, apatite crystals are rarely found in RA joint fluids. Thus, current data support the theory of a causative role of apatite crystals.

On the other hand, the clinical significance of apatite crystals in joint destruction continues to be questioned. Dieppe and Swan doubt that apatite crystals are of patho-
egenic importance, but they fail to refute the evidence to even the vast body of literature that supports the biological activity of apatite crystals. To add to the confusion, they place apatite in a list of pathogenic crystals in the same way that monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) can be policed by light microscopy. Furthermore, the presence of apatite crystals does not change the management of either osteoarthritis (OA) or any other arthropathy in patients at present. However, Swan concludes therefore that apatite crystals are irrelevant to clinical practice. Historically, the role of cytokines in the pathogenesis of OA was also considered to be speculative. As with apatite crystals, levels of cytokines such as interleukin 1 (IL1) or tumour necrosis factor a (TNFf) are not routinely measured in joint fluid from patients with arthritis. After considerable further investigation, however, the roles of IL1 and TNF in mediating joint degeneration in OA are now considered important. As a consequence of such recognition, Pelletier and coworkers have prevented the development of OA in an experimental model by transfer of the IL1 receptor antagonist gene. We have shown that apatite crystals induce MMP-1 in human OA (HOA) fibroblasts with a potency equivalent to that of IL1 and TNFf in vitro. Furthermore, apatite crystals, IL1 and TNFf act in synergy to increase MMP-1 production by HOA fibroblasts. Efforts continue to discover methods to inhibit the pathogenic effects of IL1 and TNFf. Why not inhibit the effects of apatite crystals?

Currently, there is no drug available to retard the progression of OA. A greater understanding of the pathogenesis of OA is essential to the development of rational treat-
ment thus allowing us to target important pathogenic mediators. While it might be tempting to write apatite crystals off as new age nonsense, a considerable body of evi-
dence suggests that, like cytokines, they could serve as a novel therapeutic target as well as a prognostic marker. Without further study, only those with crystal balls can tell.
tion, at 3.4 per 1000 per year at age 51 and 9.0 per 1000 per year at age 61 are presumably higher than those in long lived Malmöhus County, Sweden.

Of interest, in our own larger study with meticulously computed “expected” values in four different populations we also had an “expected” death rate of about 10% to 15% over 10 years. But, these were not inception cohorts and their age at start of follow up was 60.4, 62.6, 59.8, and 69.1 years. Thus, they were much older cohorts. Given the expected doubling of mortality rates each eight years (Gompertz’s law), expected deaths should have been two to three times more in our cohorts than in a cohort beginning at age 51.

Finally, recent studies have not suggested that “rheumatoid” deaths in themselves are the cause of the increased mortality in RA. The observed “excess” deaths are spread around in multiple disease categories, with accelerated atherosclerosis numerically the largest problem and only a slight relative increase in systemic RA complications, gastrointestinal haemorrhage, and infections.

JAMES F FRIES
DANIEL A BLOCH
Stanford University, School of Medicine, Palo Alto, California, USA

Authors’ reply
We were pleased to notice the interest in our paper shown by Drs Fries and Bloch. In reply to their comments we do not consider the death rate of 10% in the cohort as an excessive one compared with the age and sex matched general population. It is not possible to calculate more precise figures of expected deaths knowing the mean age of the cohort only. To clarify this and make comparison possible we enclose a table of the age distribution in our cohort in five year intervals giving the number of observed and expected deaths for each age interval separately.

Women do live longer in Malmöhus County, Sweden than in the US. Female mortality rates in Malmöhus County were 3.76 per 1000 at age 51 and 7.32 per 1000 at age 61 in 1985. In 1996 the corresponding figures were 2.03 per 1000 at age 51 and 3.39 per 1000 at age 61.

We agree that the main cause of death in RA patients very seldom is the rheumatoid disease in itself. This was true also for our study where no certain connection between RA and death was found in any of the cases.

ELISABET LINDQVIST
KERSTIN EBERHARDT
Department of Rheumatology, Lund University Hospital, Sweden

Table 1

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>Expected mortality</th>
<th>Observed mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-24</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25-29</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30-34</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35-39</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40-44</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>45-49</td>
<td>27</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>50-54</td>
<td>34</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>55-59</td>
<td>24</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>60-64</td>
<td>19</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>65-69</td>
<td>16</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>70-74</td>
<td>11</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>75-79</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>All</td>
<td>183</td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>