

## LETTERS TO THE EDITOR

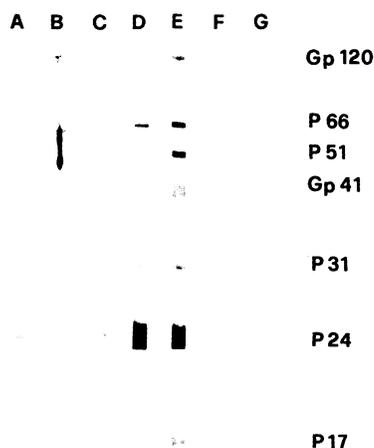
### Antibodies to retroviral proteins in Sjögren's syndrome

Sir: Recently, increased frequency of antibodies to retroviral proteins has been found in serum samples from patients with primary Sjögren's syndrome. Talal *et al* reported the presence of antibodies to p24 gag protein of HIV-1 in serum samples of 14 of 47 patients (30%) with primary Sjögren's syndrome.<sup>1</sup> Moreover, they found that two samples also reacted with p17 protein. Coll *et al* similarly reported high prevalence (33%) of antibodies to p24 in 21 patients with primary Sjögren's syndrome.<sup>2</sup> In addition, they found in the seven positive samples reactivity with other HIV-1 proteins—namely, with p68 (four samples), with p55 (six), and with p18 (two). No other studies have hitherto confirmed these interesting results.

The aim of our study was to verify these findings in northern Italian patients with primary Sjögren's syndrome. We evaluated 48 outpatients with primary Sjögren's syndrome followed up at two institutions (Clinical Immunology, Brescia and Clinical Rheumatology, Ferrara). All the patients were female (mean age 53.4 years, range 21-80). None was in a risk group for AIDS. Diagnosis of Sjögren's syndrome was made according to established criteria.<sup>3</sup> No patient fulfilled American Rheumatism Association criteria for diagnosis of associated classical connective tissue disease.

Antinuclear antibodies were detected by indirect immunofluorescence using HEp-2 cells as a substrate.

Antibodies to extractable nuclear antigens were detected by counterimmunoelectrophoresis according to Bernstein *et al*<sup>4</sup> using both rabbit thymus acetone powder and human spleen extract.



Strips A, B, and C=patients with Sjögren's syndrome; strips D and E=patients positive for antibody to HIV; strips F and G=negative controls.

Western blot assay for HIV-1 was performed as follows. Detergent lysates of HIV were fractionated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis. Proteins were electrophoretically transferred to nitrocellulose sheets according to the method of Towbin *et al*.<sup>5</sup> Strips were then incubated overnight in individual test tubes together with 2.5 ml of blocking medium. Immunoglobulins bound to HIV proteins were visualised by goat antihuman IgG conjugated with biotin, avidin conjugated horseradish peroxidase, and an enzyme substrate (4-chloro-1-naphthol).

Western blot assay for HTLV-1 was performed by a commercially available kit (Cambridge Biotech Corporation, 365 Plantation Street, Worcester, MA 01605, USA).

Forty patients (83%) had antinuclear antibodies at indirect immunofluorescence examination. Thirty four (71%) had antibodies to Ro (six patients) or to Ro and La antigens (28 patients). In the Western blot assay serum samples from three patients showed strong reactivity with p24 gag protein of HIV-1 (figure). No additional reactivity with other HIV-1 proteins was detected. Immunoblot analysis of the three samples positive against HTLV-1 proteins showed no reactivity.

The three patients were women, aged respectively 62, 68, and 80 years, and were all negative for antibodies to Ro and La antigens. Our study has shown the presence of antibodies to p24 in three of 48 patients (6%) with a prevalence much lower than in previous studies<sup>1,2</sup> but still much higher than in normal adult subjects from the same geographical area (<0.5% in 12 000 subjects). Of particular interest is our finding that the three patients with antibodies to the p24 protein were all negative for antibodies to Ro and La antigens, with a prevalence of anti-p24 positivity of 21% (three out of 14 patients) in this subset of Sjögren's syndrome. This finding is in agreement with the results of the study of Talal *et al*,<sup>1</sup> whose patients with anti-p24 reactivity had in common a paucity of antibodies to Ro and La. No data are available as to the patients studied by Coll *et al*.<sup>2</sup> The lower prevalence of anti-p24 in our patients than in those studied by Talal *et al*<sup>1</sup> might thus be explained on the basis of the different proportion, respectively 29% and 55%, of patients lacking antibodies to Ro and La in the two case series.

The presence of isolated reactivity with the p24 protein is not consistent with infection with classic HIV-1. It may reflect a cross reaction against a different retrovirus. In this context a recent report by Brookes *et al*<sup>6</sup> may be of interest which showed that antibodies to retroviral gag cross react with endogenous retroviral sequences, such as HRES-1. In agreement with the results of Talal *et al*<sup>1</sup> we found no reactivity with HTLV-1 proteins.

In conclusion, our data, while confirming previous reports<sup>1,2</sup> of increased frequency of anti-p24 gag protein reactivity in patients with primary Sjögren's syndrome, point to a restriction of this finding to the subset of patients lacking antibodies to Ro and La.

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### Insufficiency fractures of the sacrum

Insufficiency fractures, as defined by Pentecost *et al*,<sup>1</sup> occur when the elastic strength of bone is not sufficient to withstand normal physiological stresses. Most commonly, reduction of bone strength is due to osteoporosis, but can be secondary to a variety of metabolic bone diseases. Frequently recognised sites of fracture include the thoracic and lumbar vertebral bodies, femoral neck, distal forearm bones and, less commonly, the pubic rami. Insufficiency fracture of the osteoporotic sacrum was first described in 1982 by Lourie,<sup>2</sup> and although further cases have been reported,<sup>3-9</sup> they are thought to be uncommon. They occur primarily in elderly women, either spontaneously or after minimal trauma, and present with low back pain with or without radiation to the leg.

We report a retrospective analysis of a series of 12 consecutive sacral insufficiency fractures diagnosed at Royal Newcastle Hospital over a four year period. The table outlines individual patient details.

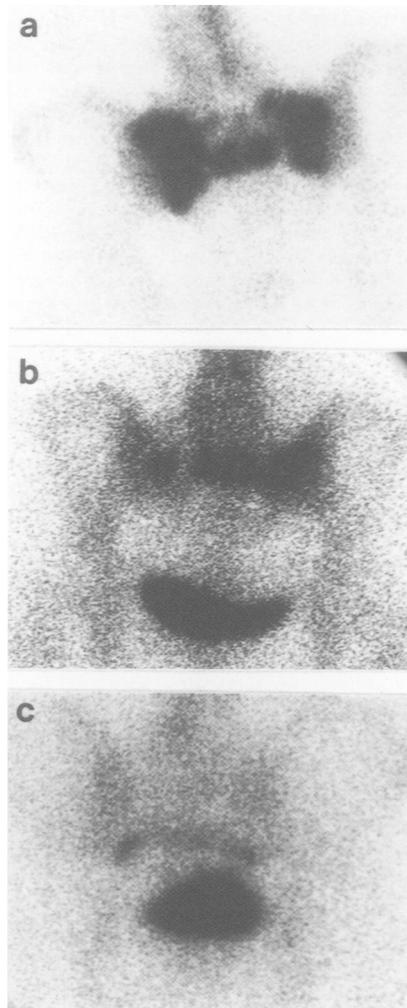
In keeping with other series most of our cases occurred in elderly women, though this series includes two elderly men and three women under the age of 65. In all cases, however, there was evident osteoporosis. Characteristically, sacral fracture occurred following a fall onto the buttocks. This results in forward movement of the sacrum relative to a stationary ilium, and vertical buckling of the osteoporotic ala. In other cases trauma was minimal or not recalled. Recent hip replacement had been performed in three cases. This has been reported as an independent risk for sacral fracture.<sup>9</sup>

## Clinical details of 12 cases of sacral insufficiency fracture

Patient No	Age/Sex	Preceding trauma	Risk factors	Pain severity*	Site of pain†	Associated fractures	x Ray	Bone scan uptake	CT scan	Recovery time (weeks)
1	92/M	Fall onto buttocks	Dementia	III	A	Nil	Osteopenia	Classical 'H'	Not done	8
2	69/F	N.K.		N.K.	N.K.	Pubic ramus	N.K.	Classical 'H'	Not done	N.K.
3	85/F	Fall onto buttocks	Vertigo	II	A,B,C	Pubic ramus Lumbar vertebrae	Osteopenia	Classical 'H'	Bilateral alae fracture	4
4	79/M	Nil	Steroid dependent pulmonary disease	0	N.A.	Ribs Thoracic vertebrae	Osteopenia Vertebral compression fracture	Curvilinear	Not done	N.A.
5	52/F	Nil	Steroid dependent RA	II	A	Rib	Osteopenia	Asymmetric 'H'	Bilateral alae fracture	4
6	76/F	Fall from own height	Cerebrovascular disease	II	A,B	Pubic ramus	Osteopenia Pubic ramus fracture	Asymmetric 'H'	Not done	3
7	76/F	Nil	Steroid dependent respiratory disease	II	A,B,C	Pubic ramus	Pubic ramus fracture	Classical 'H'	Bilateral alae, with horizontal component	8
8	88/F	Fall onto buttocks	Dementia Recent hip replacement	III	A	Pubic ramus Rib	N.K.	Classical 'H'	Not done	4
9	84/F	Fall from own height	Dementia	III	A	Pubic ramus Rib Lumbar vertebrae	N.K.	Asymmetric 'H'	Bilateral alae fracture	4
10	53/F	Fall onto buttocks	Alcohol abuse	I	A	Fibula	N.K.	Curvilinear	Not done	6
11	61/F	Nil	Steroid dependent RA Recent hip replacement	II	A,B,C	Acetabular	Osteopenia	Classical 'H'	Bilateral alae and horizontal component	3
12	70/F	Fall (3 steps)	Steroid dependent RA Recent hip replacement	III	A,B	Pubic ramus Neck of femur	Osteopenia Fractures pubic ramus, femur	Classical 'H'	Bilateral alae fracture	3

\*Pain severity: 0=asymptomatic; I=mild to moderate, admission to hospital not required; II=moderate to severe, elective admission to hospital; III=severe unable to ambulate, urgent admission to hospital.

†Pain localisation: A=low back/buttock; B=groin; C=radiation to leg.  
N.K.=Not known; N.A.=not applicable.



(a) The classical 'H' shape distribution denoting bilateral sacral alae fractures with horizontal sacral component; (b) horizontal sacral component and asymmetrical alae involvement; (c) linear or curvilinear uptake denoting fracture within the body of the sacrum.

The description of pain varied. In four cases the severity of pain required immediate admission to hospital, and a further five cases required elective admission to hospital for pain control. One was managed as an outpatient and in one instance the sacral fracture was asymptomatic, detected by bone scan performed for investigation of anterior chest wall pain. The site of pain consistently included the low back and buttock, and was aggravated by weight bearing. Five patients experienced groin pain and three reported pain radiating to the leg; however, all these patients had associated pelvic fractures. Pelvic fractures were reported in eight cases, seven affecting the pubic rami, and one the acetabulum. Extra pelvic fracture was detected on bone scan in seven cases.

Even in retrospect conventional x ray examination failed to detect sacral insufficiency fractures, and the diagnosis was made by technetium-99m bone scan. Three different patterns of isotope were reported (figure). The classical 'H' shaped pattern reflecting bilateral vertical sacral alae fracture uptake, with a horizontal splitting of the body of the sacral vertebrae, was found in seven scans. Uptake within the sacral body, but with asymmetry between the sacral alae, in three, and linear or curvilinear uptake within the sacrum indicative of fracture within the body of the sacrum only<sup>7</sup> was found in two scans. Computed tomography scanning of the sacrum was performed in six cases, and in all confirmed the presence of fracture.

Clinical outcome was uniformly good. Treatment consisted of a period of bed rest until pain had settled, followed by a graduated weight bearing programme.

As a distinct entity the insufficiency fracture of the sacrum has only recently been individualised. This series serves to emphasise the frequency of the condition and

that it does cause significant morbidity. Furthermore, although in this series cases were drawn from multiple disciplines, six of the 12 patients presented to the rheumatology unit, highlighting the need for rheumatologists to be aware of the condition. On plain x ray films, sacral fractures are notoriously difficult to detect, particularly in association with osteopenia. The diagnosis hinges on clinical suspicion and the correct interpretation of technetium-99m bone scanning. The diagnosis can be confirmed by computed tomography, but in the typical setting this is not mandatory.

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## Absence of antiphospholipid antibodies in Behçet's disease

Sir: Anticardiolipin antibodies (aCLA) and lupus anticoagulant (LA), both antiphospholipid antibodies (aPLA), are associated with multiple arterial or venous thrombosis, recurrent fetal losses, and thrombocytopenia.<sup>1,2</sup> They have been investigated in Behçet's disease (BD) with conflicting results. The purpose of our work was to extend the previous search for aCLA, LA, and antibodies detected by the Venereal Disease Research Laboratory (VDRL) test in BD, to aPLA directed against several anionic and zwitterionic phospholipids.

Nineteen patients (six women, 13 men), fulfilling the international criteria for diagnosis of BD<sup>3</sup> were studied. Their mean age was 34 years. Among them, eight had had venous thrombosis, one arterial thrombosis, and two both. Neurological disease, uveitis, or retinal

vasculitis were each present in six patients. Seven patients were HLA-B5 positive. Fourteen patients were treated with daily colchicine—as the sole treatment in nine, associated with corticosteroids in five. Corticosteroids were used in five other patients, associated with immunosuppressive agents in three.

For all patients IgG and IgM antibodies directed against cardiolipin alone, or a mixture of five anionic phospholipids (cardiolipin/phosphatidic acid/phosphatidylglycerol/phosphatidylinositol/phosphatidylserine), or phosphatidylethanolamine—a zwitterionic phospholipid—were investigated using a slightly modified enzyme linked immunosorbent assay (ELISA)<sup>4</sup> according to Harris's recommendations.<sup>2</sup> For each phospholipid normal optical values were defined as the mean optical density of a panel of 40 adult blood donor serum samples, after subtraction of optical density obtained for each serum on wells containing no phospholipids. The threshold for positivity was defined as a value higher than the mean+three standard deviations. Ten plasma samples were screened for the presence of LA with a dilute activated partial thromboplastin time and a kaolin clotting time. Lupus anticoagulant was subsequently confirmed by failure to correct the anticoagulant activity in a mixture of test and normal plasmas. A VDRL test was performed in nine patients.

Using ELISA, aPLA could not be demonstrated even with extensive investigations, including measurement of antibodies directed against phosphatidylethanolamine (recently described in systemic lupus erythematosus with thrombosis<sup>5</sup>), aCLA, and aPLA directed against five anionic phospholipids. Similarly, LA was not found and the VDRL test was negative. Therefore, no correlation was found between clinical manifestations and aPLA.

In a few studies aCLA have been found to be positive in BD. In 1984, using a radioimmunoassay, Hull *et al*<sup>6</sup> detected 13 patients positive for aCLA out of 70 (19%) with BD: seven were IgG, three IgM, and three IgG+IgM. A higher incidence of aCLA (35%) was later reported in 20 patients with BD,<sup>6</sup> but in this study the ELISA method and the threshold for positivity were not described. Bergman *et al*<sup>7</sup> detected aCLA in 13 out of 26 (50%) patients with BD, and only the IgM isotype was significantly found in BD. Interestingly, in all these studies no correlation could be found between the presence of aPLA and either biological or clinical features, except for retinal vascular disease in the first study.<sup>5</sup> Our results, however, are in agreement with other studies about aPLA in BD. In 1985 Efthimiou *et al*<sup>8</sup> did not confirm the study of Hull *et al*.<sup>5</sup> They found only two positive IgM aCLA in 25 (8%) patients with BD, but the same results were observed in controls. Another study of aCLA in 37 patients with BD was performed in 1986,<sup>9</sup> and no positive results were found. Similarly, the search for LA was negative in 69 patients with BD.<sup>10</sup>

The reason for the disparity between these studies remains unclear. It cannot be explained by clinical or ethnic differences in the groups with BD studied. Unlike Pereira *et al*,<sup>6</sup> we do not think that the use of immunosuppressive treatment can explain the absence of aPLA as only three of our 19 patients were taking such agents. This discrepancy might rather result from different technical approaches in the measurement of

aPLA as false positive results can be found in an ELISA when non-specific binding on ELISA plates devoid of phospholipids has not been subtracted or when the threshold for positivity is too low.<sup>2</sup>

We conclude that aPLA, including antiphosphatidylethanolamine antibodies, are generally absent in BD, and therefore cannot explain the thrombotic manifestations of this disease.

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## MATTERS ARISING

### Still too early for the gold rush

Sir: In their recent editorial Taha and Sturrock suggest that in arthritic patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) concomitant gold treatment might be useful in protecting the stomach from the development of mucosal injury.<sup>1</sup> As a gastroenterologist I find this hypothesis fascinating as adequate protection of the gastric mucosa against the noxious effects of long term NSAID intake is still an open issue. In fact H<sub>2</sub> blockers effectively prevent NSAID induced duodenal ulcers but are