Arthritis model are now available to people to work. Between navel gazing self-help systems and anxiety, gramme significantly decrease pain, fatigue, importantly of all, self-management programs, and relaxation techniques. Probably most important of symptoms, improved communication in which patients with fibromyalgia think and behave in an attempt to decrease the impact of their disorder, I have merely pointed out that in an interested rheumatologist can employ communication and motivational skills, which in many cases will serve the same purpose as formal psychological management.

Ms Lloyd makes much of the “Challenging Arthritis” self-management program run by Arthritis Care. Fibromyalgia, of course, is not a form of arthritis but a form of non-articular rheumatism. I have little doubt that an appropriately run education program can help people with fibromyalgia cope more effectively with their symptoms. However, self-help groups often work to a different agenda than treating clinicians. They function as a lobby to increase recognition and acceptance of a particular disorder, and sometimes such a campaign has financial rewards through litigation and compensation. Not only the objectives but also the objectivity of such a group can be called into question. However, I am delighted to learn from Ms Lloyd that the “Challenging Arthritis” program is so good and so effective.

Finally, to accuse a paper published in 1992 of being “ancient research” is not only insulting to the authors but also inaccurate. As the authors note, high quality research has a longer shelf life. The e-ectiveness of similar programs in the USA is well recorded. Experience in the United Kingdom shows similar results, including better understanding of symptoms, improved communication with medical staff, and increased use of exercise and relaxation techniques. Probably most importantly of all, self-management programs significantly decrease pain, fatigue, and anxiety.

So it is extremely important to differentiate between navel-gazing self-help systems and courses such as ours, which encourage people to take control for themselves—and which work.

Similar courses run on the Challenging Arthritis model are now available to people with other chronic conditions.

Given Dr Reilly’s desire to disabuse patients of the notion that their fibromyalgia is his problem alone, shouldn’t his effective courses encourage people to take control for themselves be a welcome adjunct to his treatment, even if it is run by a patient self-management group?

ROBINA LLOYD Arthritis Care, 18 Stephenson Way, London NW1 2HD, UK

Author’s reply

I am surprised that Ms Lloyd has chosen to be rather negative about an editorial that was designed to combine optimism with realism. Although one might be optimistic that every patient with fibromyalgia, and similar functional pain syndromes, might have access to professional psychological advice and management, reality dictates that this is not the case, at least not within the health service as it operates in the United Kingdom. As cognitive-behavioral therapy sets out to influence the manner in which patients with fibromyalgia think and behave in an attempt to decrease the impact of their disorder, I have merely pointed out that an interested rheumatologist can employ communication and motivational skills, which in many cases will serve the same purpose as formal psychological management.

Ms Lloyd makes much of the “Challenging Arthritis” self-management program run by Arthritis Care. Fibromyalgia, of course, is not a form of arthritis but a form of non-articular rheumatism. I have little doubt that an appropriately run education program can help people with fibromyalgia cope more effectively with their symptoms. However, self-help groups often work to a different agenda than treating clinicians. They function as a lobby to increase recognition and acceptance of a particular disorder, and sometimes such a campaign has financial rewards through litigation and compensation. Not only the objectives but also the objectivity of such a group can be called into question. However, I am delighted to learn from Ms Lloyd that the “Challenging Arthritis” program is so good and so effective.

Finally, to accuse a paper published in 1992 of being “ancient research” is not only insulting to the authors but also inaccurate. High quality research has a longer shelf life. So it is extremely important to differentiate between navel-gazing self-help systems and courses such as ours, which encourage people to take control for themselves—and which work.

Similar courses run on the Challenging Arthritis model are now available to people with other chronic conditions.

Given Dr Reilly’s desire to disabuse patients of the notion that their fibromyalgia is his problem alone, shouldn’t his effective courses encourage people to take control for themselves be a welcome adjunct to his treatment, even if it is run by a patient self-management group?

ROBINA LLOYD Arthritis Care, 18 Stephenson Way, London NW1 2HD, UK

Author’s reply

I am surprised that Ms Lloyd has chosen to be rather negative about an editorial that was designed to combine optimism with realism. Although one might be optimistic that every patient with fibromyalgia, and similar functional pain syndromes, might have access to professional psychological advice and management, reality dictates that this is not the case, at least not within the health service as it operates in the United Kingdom. As cognitive-behavioral therapy sets out to influence the manner in which patients with fibromyalgia think and behave in an attempt to decrease the impact of their disorder, I have merely pointed out that an interested rheumatologist can employ communication and motivational skills, which in many cases will serve the same purpose as formal psychological management.

Ms Lloyd makes much of the “Challenging Arthritis” self-management program run by Arthritis Care. Fibromyalgia, of course, is not a form of arthritis but a form of non-articular rheumatism. I have little doubt that an appropriately run education program can help people with fibromyalgia cope more effectively with their symptoms. However, self-help groups often work to a different agenda than treating clinicians. They function as a lobby to increase recognition and acceptance of a particular disorder, and sometimes such a campaign has financial rewards through litigation and compensation. Not only the objectives but also the objectivity of such a group can be called into question. However, I am delighted to learn from Ms Lloyd that the “Challenging Arthritis” program is so good and so effective.

Finally, to accuse a paper published in 1992 of being “ancient research” is not only insulting to the authors but also inaccurate. High quality research has a longer shelf life. So it is extremely important to differentiate between navel-gazing self-help systems and courses such as ours, which encourage people to take control for themselves—and which work.

Similar courses run on the Challenging Arthritis model are now available to people with other chronic conditions.

Given Dr Reilly’s desire to disabuse patients of the notion that their fibromyalgia is his problem alone, shouldn’t his effective courses encourage people to take control for themselves be a welcome adjunct to his treatment, even if it is run by a patient self-management group?
Table 1  Evolution of cryoglobulinaemia, rheumatoid factor, and complement levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Cryoglobulinaemia (µg/ml)</th>
<th>Type</th>
<th>Rheumatoid factor (Rose-Waaler test)</th>
<th>C4 (g/l)</th>
<th>CH50 (%) ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 1994</td>
<td>29</td>
<td>Oligoclonal IgM</td>
<td>0</td>
<td>&lt;0.06</td>
<td></td>
</tr>
<tr>
<td>June 1996</td>
<td>25</td>
<td>Oligoclonal IgM</td>
<td>1 / 128</td>
<td>&lt;0.06</td>
<td>25</td>
</tr>
<tr>
<td>August 1996</td>
<td>17</td>
<td>Oligoclonal IgM</td>
<td>ND</td>
<td>&lt;0.06</td>
<td>&lt;20</td>
</tr>
<tr>
<td>December 1996</td>
<td>188</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>&lt;0.07</td>
<td>&lt;20</td>
</tr>
<tr>
<td>March 1997</td>
<td>4</td>
<td></td>
<td>1 / 128</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>October 1998</td>
<td>63</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>November 1998</td>
<td>110†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>December 1998</td>
<td>166†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>January 1999</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>February 1999</td>
<td>1031†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.08</td>
<td>60</td>
</tr>
<tr>
<td>March 1999</td>
<td>1000†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.09</td>
<td>30</td>
</tr>
<tr>
<td>April 1999</td>
<td>273† (after plasmapheresis)</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>May 1999</td>
<td>848†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

*Normal <15 µg/ml.
†Determination performed using the method described above since November 1998.
‡Normal range 60–120%.

...
Computed digital absorptiometry of the hand: screening method of bone loss in postmenopausal women with RA

Dual energy $x$ ray absorptiometry (DXA) is the most commonly used method of measuring bone mineral density (BMD). It has been shown to be a good predictor of the future risk of fracture. Unfortunately, the generalised use of DXA is limited as it is expensive and time consuming, is not portable, and is available only in centres.

Computed digital absorptiometry (CDA) of the hand is a new bone densitometry technique, designed to assess the BMD of the middle phalanx of the third finger using a direct, automated measurement of $x$ ray attenuation. This technique is similar to radiographic absorptiometry but provides immediate results; in current radiographic absorptiometry, radiographs are sent to an of site processing centre and the results are received a few days later. CDA is cheap and quick. Its precision and accuracy seem acceptable, but its ability to discriminate between patients with osteoporosis and normal subjects, to predict risk of future fracture, and to monitor the response to therapeutic intervention has not been established.

Rheumatoid arthritis (RA) is a risk factor for osteoporosis. The available data suggest that there is an increased risk of hip fracture in patients with RA, especially when they are treated with glucocorticoids. DXA is the preferred technique for assessing the presence of bone loss in these patients. However, the prevalence of RA in the general population is high, and it is, therefore, necessary to use DXA to investigate only those patients at high risk of osteoporosis. Criteria to decide who should be evaluated are not currently available. Recently, in this journal, Lems and Dijkmans presented a proposal from rheumatologists in Amsterdam based on clinical risk factors.

We have undertaken a study to evaluate whether CDA might be a useful screening technique for identifying patients with RA who should be examined by DXA. Over a period of three months, we evaluated women with RA, evaluated in the rheumatology outpatient clinic, who fulfilled the inclusion criteria, and who should be examined by DXA to investigate bone mineral density in these patients.

For the study, we considered 12 women with RA. Five patients fulfilled the inclusion criteria and consent was obtained from 4 of these. In these patients BMD was assessed by DXA and CDA on the same day. One further patient was not included in the study as she had a severe ulnar deviation that did not allow CDA to be used.

For DXA, BMD (g/cm²) of the lumbar spine and upper femur was assessed using a dual energy $x$ ray system (Hologic QDR 1000, Hologic Inc, Waltham, Mass); we considered the mean of the 2 scans for each site and the value of the femoral neck. For CDA, BMD (g/cm²) of the middle phalanx of the third finger of the non-dominant hand was assessed using a dual energy $x$ ray system (AccuDEXA, Schick Technologies, Long Island, NY). The $x$ ray attenuation data were automatically processed and represented as a grey scale image. To assess the in vivo short term precision, 10 serial measurements (with interim repositioning) were performed in seven healthy volunteers.

### Table 1 Clinical characteristics of the patients with RA and BMD values obtained (n=39). Values are expressed as mean (SD)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>61.2 (8.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of postmenopausal period (y)</td>
<td>13.3 (7.5)</td>
</tr>
<tr>
<td>Duration of rheumatoid arthritis (y)</td>
<td>9.7 (6.4)</td>
</tr>
<tr>
<td>Rheumatoid factor positive (n)</td>
<td>32</td>
</tr>
<tr>
<td>Erosive RA (n)</td>
<td>16</td>
</tr>
<tr>
<td>Treatment with low dose glucocorticoids (n)</td>
<td>32</td>
</tr>
<tr>
<td>BMD at the lumbar spine (g/cm²)</td>
<td>0.840 (0.150)</td>
</tr>
<tr>
<td>BMD at the femoral neck (g/cm²)</td>
<td>0.560 (0.110)</td>
</tr>
<tr>
<td>BMD at the middle phalanx of the third finger (g/cm²)</td>
<td>0.390 (0.090)</td>
</tr>
</tbody>
</table>

* BMD = bone mineral density.
Rubella infection in adult onset Still’s disease

The aetiology of adult onset Still’s disease remains unknown although some authors have tried to relate it to a viral infection.1 We describe here a case of typical adult onset Still’s disease with a seroconversion in the rubella IgG antibody titre to emphasise that it is probably more than a coincidental event. A 26 year old woman was admitted because of fever with chills, a pruritic rash, myalgia, sore throat and headache. At the time of physical examination the temperature was 40°C and the pulse rate 104 beat/min. The rash consisted of small pruritic macules over back, periorbicular, legs and arms. The pustules were hemorrhagic. Some small cervical lymphadenopathies were detected. The leucocyte count was 42.3 × 109 cells/l (93.2% neutrophils) and the haemoglobin concentration was 79 g/l. Liver enzymes were slightly increased, alanine aminotransferase (AST) 0.80 µkat/l and alanine aminotransferase (ALT) 0.73 µkat/l, but increased to AST 11.77 µkat/l and ALT 7.68 µkat/l after acetylsalicylic acid administration. Lactate dehydrogenase was 17.33 µkat/l. The serum albumin concentration was 26 g/l and the erythrocyte sedimentation rate 60 mm 1st h. The serum ferritin was more than 1500 µg/l (normal value: 20–250 µg/l). Roentgenogram of chest and urine analysis were normal as well as blood and urine cultures. Abdominal computed tomography showed hepatosplenomegaly. An electromyographic study was normal. Tests for antinuclear antibodies and rheumatoid factor were negative. Serum concentrations of immunoglobulins and complement were normal. Serological tests for hepatitis A, B or C, cytomegalovirus, parvovirus B19, human immunodeficiency virus 1 and 2, Epstein-Barr virus, Mycoplasma, Treponema pallidum, Borrelia burgdorferi, Toxoplasma, Salmonella, Brucella, Legioneila, Coxsiella burnetti, Chlamydia and Rickettsia were negative. The initial rubella IgG antibody titre was 140 000 IU/l. During admission the patient looked acutely ill. Temperature rose to 40°C every evening with chills. The patient developed swelling and tenderness of proximal interphalangeal joints, elbows, wrists and knees. Roentgenograms of joints were normal. Because of cough a new chest roentgenogram was made. It showed a right basal lobe alveolar infiltrate that resolved spontaneously in 72 hours.

At this point, our patient fulfilled the criteria of Yamaguchi for adult onset Still’s disease.1 Initially, she was treated with acetylsalicylic acid 4 g/day by mouth, which had to be stopped because of an increase in liver enzymes, so prednisone 1 mg/kg/day orally was given with no improvement. Two weeks later, adrenocorticoid hormone methotrexate was added to diminish arthritis. The dose achieved was 7.5 mg by mouth weekly. The patient was discharged feeling well after staying in hospital for 54 days. At this moment rubella IgG antibody titre rose to 600 000 IU/l.

Our patient fulfilled Yamaguchi’s criteria for adult onset Still’s disease so this diagnosis was well established.1,5 There was also strong evidence for acute rubella infection because the IgG antibody titre increased more than fourfold the initial one. It has been shown that children with primary rubella infection developing Still’s disease increase both rubella IgG and IgM antibody titres.1 In our case we think that rubella was more probably attributable to a re-infection than to a primary infection because the patient had been correctly vaccinated in childhood and this is also supported by the increase in IgM antibody titre without increase in IgG concentration. The seroconversion is not explained by a non-specific polyclonal stimulation after a generalised inflammatory disease because there was no increase in other measured antibody titres.

Although aetiology of adult onset Still’s disease is unknown, some authors have tried to demonstrate that infective agents, especially viruses, can be the trigger of the illness in susceptible patients.1 Acyclovir, cytoherivirus 7, mumps, cytomegalovirus, influenza A, influenza B, parvovirus B19, hepatitis B or C and rubella1,5,8 have been associated. The relation between rubella virus and adult onset Still’s disease has been reported in some series and case reports1,8,15 since the initial description by Bywaters in 1971.16 Wouters et al performed exhaustive virological studies in patients with adult onset Still’s disease in an early phase of the illness and found evidence of viral infection in three cases, two of them corresponding to rubella.17 The rubella virus genome has also been detected in peripheral blood cell population from patients with adult onset Still’s disease.18

In summary, we think that the increased rubella IgG antibody titre in our patient should not be considered an anecdotal event and probably rubella virus has been the trigger of the illness. Our case, together with previously published reports,18,19 supports the hypothesis about the role of viruses in the aetopathogenesis of adult onset Still’s disease.

FRANCISCO JAVIER ESCUDERO VÍCTOR LENICOMO Mª PATRICIA ROMÁN \nSERVICIO DE RHEUMATOLOGÍA, HOSPITAL GENERALE ARTURO AGUSTÍ SELLAS VICTÓRIA ALBA \nVENTURA, BARCELONA, SPAIN

AGUSTÍ SELLAS \nService of Rheumatology, Hospital General Universitario Vall d’Hebron, Barcelona, Spain

Correspondence to: Escudero, C; Amapolas, 37 2nd floor 10896 L’Hospital de Llobregat, Spain


Raised plasma adrenomedullin in patients with systemic sclerosis complicated by pulmonary hypertension

Adrenomedullin is a hypotensive peptide newly found in human phaeochromocytoma tissue.1 The peptide comprises 52 amino acids with an intramolecular disulphide bond. The mRNA of adrenomedullin has been detected in normal adrenal medulla, heart, kidney, and lung. Adrenomedullin is produced in endothelial cells, vascular smooth muscle cells and vascular endothelial cells. Adrenomedullin receptors are expressed in both vascular smooth muscle cells and vascular endothelial cells. Adrenomedullin has a vasoexcessorant effect, antagonising the vaso- pastic effect of endothelin-1 and seems to be implicated in the physiological and pathological control of circulation. Through multiple biological effects in the circulatory system, adrenomedullin appears to reduce plasma volume and blood pressure and is also implicated in the cardiovascular system.1 Furthermore, adrenomedullin regulates not only vascular tonus but also vascular function through the autocrine/paracrine system, stimulating cAMP formation via the cAMP-dependent manner,1 and exerting an anti-inflammatory effect by inhibiting the production of a chemotaxicant from alveolar macrophages.1

Systemic sclerosis (SSc) is a chronic disease of unknown cause characterised by vascular changes and fibrosis of the skin and the visceral organs. Major complications of SSc are renal, myocardioid, and pulmonary. Pulmonary hypertension (PH) is a common cause of death in patients with SSc.1 In the plasma of patients with PH the endothelin-1 level is raised.1 In addition, it was recently reported that the adrenomedullin level is raised also in the plasma of patients with Raynaud’s disease2 or rheumatoid arthritis.3 Therefore, we measured the concentrations of adrenomedullin and endothelin-1 in the plasma from patients with SSc, with or without PH, to elucidate the role of adrenomedullin in the pathogenesis of PH.

We obtained plasma from three women with SSc with PH (aged 43–72), 10 patients with SSc without PH (nine women, one man, aged 22–60), and one female patient with primary PH. The diagnosis of SSc was based on accepted criteria.1 We diagnosed PH in
patients with SSc whose right ventricular systolic pressure was higher than 25 mm Hg measured by echocardiogram. In the three patients with SSc with PH we confirmed PH by catheterisation. The pressures of the pulmonary artery of these three patients were 45, 51, and 54 mm Hg, respectively. All patients with SSc had diffuse-type SSC without interstitial pneumonia, which was diagnosed as interstitial fibrosis by computed tomography. The three patients with PH were taking the following drugs: triclopidine hydrochloride (patient 1), nifedipine and triclopidine hydrochloride (patient 2), and nifedipine hydrochloride and methylprednisolone (patient 3).

For the comparison group we selected patients with diffuse-type SSC without PH, as all of three patients with SSc with PH had diffuse-type SSC. Six normal volunteers (three women and three men, age 29–40) were also studied. Concentrations of adrenomedullin were measured by radioimmunassay. Statistical significance was analysed by the Mann-Whitney U test.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011). The concentrations of adrenomedullin or endothelin-1 in patients with SSc with PH were raised compared with those in patients with SSc without PH (p = 0.020) (fig 1A). The concentrations of adrenomedullin in the plasma increased enough to antagonise the effects of endothelin-1 in patients with PH. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats.7 Thus our results also suggest the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.

We recently obtained similar results when measuring the levels of the mature form of adrenomedullin and total adrenomedullin in a different group of patients with SSc with (patients 4, 5, and 6) or without PH, by immunoradiometric assay. The three patients with SSc with PH were women aged 43–54, and two patients with SSc without PH were women aged 47 and 55. The duration of disease was two to seven years. The pulmonary artery pressures of patients 4, 5, and 6 were 24.9, 58.1, and 27.5, respectively, whereas those of the two patients with SSc without PH were 16.4 and 14.7 pg/ml. These results, however, did not reach statistical significance as the number of patients was small.

Patients 4, 5, and 6 were taking the following drugs: nifedipine, tocopherol acetate, and beraprost sodium (patient 4); nifedipine and triclopidine hydrochloride (patient 5); and nifedipine (patient 6). Levels of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011).

Our results suggest that the amount of adrenomedullin is insufficient to either the spasm of pulmonary vessels or the proliferation of endothelial cells of the vessels, though the levels of adrenomedullin in plasma increased enough to antagonise the effects of endothelin-1 in patients with SSc. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats.7 Thus our results also suggest the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.

Concentrations of adrenomedullin in the plasma of patients 4, 5, and 6 were 24.9, 58.1, and 27.5, respectively, whereas those of the two patients with SSc without PH were 16.4 and 14.7 pg/ml. These results, however, did not reach statistical significance as the number of patients was small.

For the comparison group we selected patients with diffuse-type SSC without PH, as all of three patients with SSc with PH had diffuse-type SSC. Six normal volunteers (three women and three men, age 29–40) were also studied. Concentrations of adrenomedullin were measured by radioimmunassay. Statistical significance was analysed by the Mann-Whitney U test.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011). The concentrations of adrenomedullin or endothelin-1 in patients with SSc with PH were raised compared with those in patients with SSc without PH (data not shown). The levels of endothelin-1 in patients with SSc with PH were raised compared with those in patients with SSc without PH (p = 0.041) (fig 1B). We did not measure levels of endothelin-1 in normal volunteers (fig 1B).

We recently obtained similar results when measuring the levels of the mature form of adrenomedullin and total adrenomedullin in a different group of patients with SSc with (patients 4, 5, and 6) or without PH, by immunoradiometric assay. The three patients with SSc with PH were women aged 43–54, and two patients with SSc without PH were women aged 47 and 55. The duration of disease was two to seven years. The pulmonary artery pressures of patients 4, 5, and 6 were 24.9, 58.1, and 27.5, respectively, whereas those of the two patients with SSc without PH were 16.4 and 14.7 pg/ml. These results, however, did not reach statistical significance as the number of patients was small.

Patients 4, 5, and 6 were taking the following drugs: nifedipine, tocopherol acetate, and beraprost sodium (patient 4); nifedipine and triclopidine hydrochloride (patient 5); and nifedipine (patient 6). Levels of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011).

Our results suggest that the amount of adrenomedullin is insufficient to either the spasm of pulmonary vessels or the proliferation of endothelial cells of the vessels, though the levels of adrenomedullin in plasma increased enough to antagonise the effects of endothelin-1 in patients with SSc. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats.7 Thus our results also suggest the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011).

Our results suggest that the amount of adrenomedullin is insufficient to either the spasm of pulmonary vessels or the proliferation of endothelial cells of the vessels, though the levels of adrenomedullin in plasma increased enough to antagonise the effects of endothelin-1 in patients with SSc. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats.7 Thus our results also suggest the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.

Concentrations of adrenomedullin in the plasma of patients 4, 5, and 6 were 24.9, 58.1, and 27.5, respectively, whereas those of the two patients with SSc without PH were 16.4 and 14.7 pg/ml. These results, however, did not reach statistical significance as the number of patients was small.

For the comparison group we selected patients with diffuse-type SSC without PH, as all of three patients with SSc with PH had diffuse-type SSC. Six normal volunteers (three women and three men, age 29–40) were also studied. Concentrations of adrenomedullin were measured by radioimmunassay. Statistical significance was analysed by the Mann-Whitney U test.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011). The concentrations of adrenomedullin or endothelin-1 in patients with SSc with PH were raised compared with those in patients with SSc without PH (p = 0.020) (fig 1A). The concentrations of adrenomedullin in the plasma increased enough to antagonise the effects of endothelin-1 in patients with SSc. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats.7 Thus our results also suggest the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.

Concentrations of adrenomedullin in the plasma of patients 4, 5, and 6 were 24.9, 58.1, and 27.5, respectively, whereas those of the two patients with SSc without PH were 16.4 and 14.7 pg/ml. These results, however, did not reach statistical significance as the number of patients was small.

For the comparison group we selected patients with diffuse-type SSC without PH, as all of three patients with SSc with PH had diffuse-type SSC. Six normal volunteers (three women and three men, age 29–40) were also studied. Concentrations of adrenomedullin were measured by radioimmunassay. Statistical significance was analysed by the Mann-Whitney U test.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011). The concentrations of adrenomedullin or endothelin-1 in patients with SSc with PH were raised compared with those in patients with SSc without PH (p = 0.020) (fig 1A). The concentrations of adrenomedullin in the plasma increased enough to antagonise the effects of endothelin-1 in patients with SSc. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats.7 Thus our results also suggest the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.
tive anti-throid microsomal antibodies. Antibodies to the extractable nuclear antigens (ENA) were negative. Liver biopsy showed features compatible with chronic active hepa-
titis. SLE with an associated hepatitis was diagnosed and she was prescribed pred-
nisilone 15 mg daily, which was gradually reduced over two years as her liver function and platelet count stabilised. Over the next four years, she developed recurrent deep vein thrombosis in her left popliteal, left femoral and hepatic veins. She had three spontaneous abortions, all early in the second trimester. Subsequent investigations showed a positive lupus anticoagulant (LAC) and IgG anti-
cardiolipin antibody (ACA). She was treated with warfarin. She was pregnant in 1980: she developed severe migranous headache, fever and polyarthralgia and was diagnosed as having a flare of her underlying lupus and secondary APLS.

She was given corticosteroids with satisfac-
tory response and she was later maintained with azathioprine while the oral prednisolone dose was gradually brought down to 10 mg daily. She was also given dipiridamole, an anti-platelet agent, and atenolol for hyperten-
sion that was diagnosed during subsequent follow ups but there was no other evidence of renal involvement. Calcium supplements and vitamin D were started for prophylaxis against osteoporosis. She had another flare of her SLE in October 1988 when she presented with polyarthralgia and significant thrombo-
cytopения. Her warfarin was stopped in view of the potential increase risk in bleeding ten-
dency. Her prednisolone was increased to 40 mg daily to no avail. Splenectomy was performed, after which her platelet count sta-
 bilised. She had an unsuccessful pregnancy with intrauterine death in the same year. Her disease was better controlled with pred-
nisolone (9–10 mg/day) and azathioprine until April 1998 when she complained of constant and severe back pain, which was aggravated by movement. A plain radiograph showed no obvious abnormality but magnetic resonance imaging of the thoracolumbar spine showed features suggestive of bone infar-
tection of the L2 vertebral body. Bone scan did not pick up any other site of involvement by AVN. Figure 1 shows the plain radiogra-
ph of the lumbosacral spine. Figure 2 shows the T2 weighted magnetic reso-
nance sagittal image of the thoracolumbar spine with increase in signal over the L2 ver-
tebral body. She was referred to the orthopaed-
dic surgery unit for a L1 to L3 vertebral ar-
sction of the L2 vertebral body. Bone scan
Figure 1 Plain radiograph of the lumbosacral spine (AP view of the patient.
Figure 2 T2 weighted magnetic resonance scan sagittal image of the lumbosacral spine of the patient.

In summary, this patient suffering from SLE with secondary APLS who had been managed with low dose corticosteroids for more than 20 years was complicated by the development of AVN at an atypical site. Some indications and suggestions of bone necrosis and features compatible with AVN. Her back pain was much improved after the operation. She has all along been normotensive and she has no hyperlipidaemia.

In summary, this patient suffering from SLE with secondary APLS who had been managed with low dose corticosteroids for more than 20 years was complicated by the development of AVN at an atypical site. This case highlights two interesting points. The first is the atypical presentation of the AVN involving an isolated L2 vertebral body. Vertebral body involvement by APLS is seldom reported. Egan et al reported on a patient with catastrophic APLS who pre-
sented with onset of AVN involving multiple sites including T8, L4 and L5 verte-
brales bodies in 1994. Bone marrow necrosis without bony destruction has also been reported to be associated with APLS, usually in the context of catastrophic APLS and picked up by bone scan as multiple hot spots. The lunate bone is another unusual site of involvement by AVN. Kienbock's disease (AVN of lunate bone) was reported in a patient with primary APLS and two others with antiphospholipid (APL) antibodies but without other clinical features that satisfied the diagnosis of APLS.

Secondly, the pathogenesis of AVN is com-
plex. AVN is a known complication of various systemic conditions including sickle cell disease, prolonged corticosteroid treatment, alcohol abuse and Gaucher's disease. When occurring in the hip, it is commonly seen in elderly patients after fracture neck of femur, as a result of disturbance to its blood supply. Previous studies in patients with SLE have suggested high dose and prolonged use of corticosteroids causes AVN. Active disease and the presence of APL antibodies may also have important roles in the development of AVN in these patients. It is interesting that our patient had features of secondary APLS with previous venous thrombosis and recur-
rent fetal abortion. Additionally, she had a relapsing and remitting disease that required the prolonged use of corticosteroids for disease control. Whether the presence of APL antibodies, active disease, or the prolonged use of corticosteroids is important remains uncertain. In view of this, we have recently performed a case-
control study to evaluate the role of each of these individual potential risk factors.
Comparison of patients with and without adverse reactions. V alues are shown as mean (SD).

Table 1 Pretreatment value, decrease, decrease ratio, and threshold value of immunoglobulin levels and lymphocyte count in patients used to differentiate between patients with and without adverse reactions. Values are shown as mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>With adverse reaction</th>
<th>Without adverse reaction</th>
<th>p Value‡</th>
<th>Threshold value</th>
<th>p Value¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>20.87 (7.34)(15)</td>
<td>20.12 (5.50)(83)</td>
<td>NS</td>
<td>4.62</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−6.23 (5.53)(15)</td>
<td>−1.47 (3.73)(81)</td>
<td>***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Post−pre)/pre</td>
<td>−0.30 (0.13)(15)</td>
<td>−0.06 (0.10)(81)</td>
<td>NS</td>
<td>0.171</td>
<td>***</td>
</tr>
<tr>
<td>IgA†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>4.50 (2.17)(15)</td>
<td>4.13 (1.61)(93)</td>
<td>NS</td>
<td>0.83</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−1.15 (0.87)(15)</td>
<td>−0.21 (0.65)(81)</td>
<td>***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Post−pre)/pre</td>
<td>−0.31 (0.14)(15)</td>
<td>−0.03 (0.18)(81)</td>
<td>***</td>
<td>0.189</td>
<td>***</td>
</tr>
<tr>
<td>IgM†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.03 (0.86)(15)</td>
<td>2.04 (0.84)(93)</td>
<td>NS</td>
<td>0.26</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−0.35 (0.17)(15)</td>
<td>−0.07 (0.17)(81)</td>
<td>***</td>
<td>0.257</td>
<td>***</td>
</tr>
<tr>
<td>γ Globulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>15.64 (7.00)(13)</td>
<td>15.54 (4.69)(74)</td>
<td>NS</td>
<td>2.38</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−5.07 (3.61)(12)</td>
<td>−1.30 (3.22)(67)</td>
<td>NS</td>
<td>2.243</td>
<td>***</td>
</tr>
<tr>
<td>(Post−pre)/pre</td>
<td>−0.30 (0.15)(12)</td>
<td>−0.08 (0.18)(67)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1.82 (0.80)(15)</td>
<td>1.38 (0.61)(81)</td>
<td>*</td>
<td>0.18</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (10⁶/l)</td>
<td>−0.6 (0.55)(14)</td>
<td>−0.01 (0.58)(80)</td>
<td>***</td>
<td>0.267</td>
<td>***</td>
</tr>
<tr>
<td>(Post−pre)/pre</td>
<td>−0.35 (0.31)(14)</td>
<td>0.12 (0.71)(80)</td>
<td>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS = p<0.05;*p<0.005;****p<0.0001.
†Comparison of patients with and without adverse reactions.
‡To differentiate between patients with and without adverse reactions.

CRP from 63 (36) to 32 (55) mg/l, whereas all 22 non-responders who had no adverse events showed a decrease in CRP from 46 (39) to 41 (34) mg/l. A significant relation was found between a good response to treatment and the appearance of adverse reactions. The patients with adverse reactions had a higher creatinine level, and more frequent use of steroid at high dose (7.9 (7.8) vs 2.8 (3.5) mg/day prednisolone). The patients with the higher creatinine level were older.

The albumin level increased more in responders. The rheumatoid factor titre decreased in responders and in patients without adverse reactions. The eosinophil count did not correlate either with response or adverse reactions.

After treatment the levels of IgG, IgA, and IgM, γ fractions, and lymphocyte count in the 15 patients who had adverse reactions were significantly reduced compared with the values before treatment. The reductions and reduction ratios compared with pretreatment values were significantly greater in patients with adverse reactions than in those without. Table 1 gives the results obtained and the threshold values that could differentiate between patients with and without adverse reactions.

Table 1 Pretreatment value, decrease, decrease ratio, and threshold value of immunoglobulin levels and lymphocyte count in patients used to differentiate between patients with and without adverse reactions. Values are shown as mean (SD)

The reduction in interleukin 6 level was reported to parallel an improvement during methotrexate treatment. The reduction in lymphocyte numbers is controversial. Immunomodulation might relate mainly to adverse reactions, whereas the effect might appear owing to anti-inflammatory mechanisms. It can only be speculated whether consumption or leakage of immunoglobulin plays a part in the previously supposed mechanism of acute hypersensitivity or cytotoxicity, or in an independent epi-phenomenon. There is the encouraging possibility that monitoring the immunoglobulin level and the lymphocyte count might disclose life threatening reactions and enable the doctor to know when to reduce the dosage or to stop the drug entirely.

The authors thank Dr Victoria Elegant and Ms Keiko Miyahara for their help.

SHIGEKO INOKUMA
HAJIME KONO
HISANORI NAKAYAMA
JUNIKO YAMAZAKI
Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Dr Shigeko Inokuma, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo, 113-8677, Japan

Email: inokuma-k@komagome-hospital.bunkyo.tokyo.jp