MATTERS ARISING

How should we manage fibromyalgia?

We read with interest your leader, "How should we manage fibromyalgia?"¹ We were puzzled by Paul Reilly's statement that a comprehensive pain management programme...has the best chances of success, although even rheumatologists can practise amateur cognitive behavioural therapy in the clinic". Is Dr Reilly really suggesting that a rheumatologist's amateur efforts offer the best outcome for people with fibromyalgia?

Dr Reilly offers no evidence to support this statement. He does, however, find evidence to raise questions as to the value of patient self help groups. Dr Reilly cites a 1992 paper that reports an association between membership of such a group and worse prognosis in chronic fatigue syndrome.² As the authors emphasised the caution with which the results should be interpreted, it is surprising that Dr Reilly has used this evidence to inform his clinical practice.

Firstly, this is ancient research. Things have moved on. Although we would agree that some so called self help groups can end up as a circular review of symptoms, self management courses, which we at Arthritis Care espouse, are a very different matter.

Challenging Arthritis is a self management programme—and that title was chosen very deliberately. It is run by people with arthritis for people with arthritis. It gives people the skills to take control of their lives and their arthritis. It is practical and positive, and it works. The effectiveness of similar programmes in the USA is well recorded.³

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 programmes significantly decrease pain, fatigue, and anxiety.⁴

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 effective courses which 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?

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- 1 Reilly PA. How should we manage fibromyalgia? *Ann Rheum Dis* 1999;58:325-6.
- 2 Sharpe M, Hawton K, Seagroatt V, Pasvol G. Follow up of patients presenting with fatigue to an infectious diseases clinic. *BMJ* 1992;305:147-52.
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4 Barlow JH, Turner AP, Wright CC. Sharing, caring and learning to take control: self management training for people with arthritis. *Psychological Health* 1998;3:387-93.

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 behavioural 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 programme 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 programme 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" programme 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 than eight years.

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LETTERS

A "missed" cryoglobulin: the importance of in vitro calcium concentration

Cryoglobulins are immunoglobulins which precipitate at reduced temperature and that redissolve by warming the serum sample to 37 °C. Mixed cryoglobulinaemia may manifest clinically as skin, articular, renal, and peripheral nerve complications.¹ To ensure optimal detection, blood samples must be obtained and preserved at 37 °C. We report on a patient whose clinical presentation was suggestive of cryoglobulinaemia. Because cryoglobulins had been either undetectable or found at very low levels for several years despite repeated careful blood sample exami-

nations with conventional assays, we initially thought he had Henoch-Schönlein purpura. The recent use of a modified assay finally led us to diagnose mixed cryoglobulinaemia. Included below is a description of the method used for cryoglobulin detection, emphasising the importance of in vitro calcium concentration.

Case report

A 52 year old man with multiple lipoma had a 20 year history of polyarthralgias affecting elbows, wrists, hands, knees, and feet, a 10 year history of Raynaud's disease affecting the hands and feet, and a seven year history of palpable purpura. His sister had coeliac disease. In June 1996 he developed attacks of abdominal pain concomitantly with arthralgias and palpable purpura of both legs. Serum creatinine was 95 µmol/l. Gamma-globulins were low (4.2 g/l) on serum protein electrophoresis. Serum concentrations of immunoglobulins were 4.49 g/l for IgG (normal range 6.42-11.92), 1.84 g/l for IgM (normal range 0.52-1.47), and 2.51 g/l for IgA (normal range 1.05-3.36). Tests for rheumatoid factors, including the Rose-Waaler test (Sanofi Pasteur, Marnes La Coquette, France), were positive (table 1), but other serum autoantibodies remained negative, including antinuclear, anti-DNA, and antineutrophil cytoplasmic antibodies. Complement concentrations were notably down, both for C4 <0.06 g/l (normal range 0.10-0.40; Behring Dade, Deerfield, USA) and for CH₅₀ (home method) 25% of the normal range (60-120%). C3c and C3PA were also decreased at respectively 0.34 g/l (normal range 0.60-1.10) and <0.04 g/l (normal range 0.10-0.40). A complete set of serum markers was negative for hepatitis B and C viruses. Cryoglobulin measurements were initially negative or inconclusive (table 1). Proteinuria was negative. Radiographs of the affected joints were normal. A computed tomographic scan of the abdomen showed a thickened aspect of the duodenal and jejunal loop wall. Skin biopsy was not performed. Prednisone treatment (30 mg/day) was started but, owing to poor response, plasmapheresis was carried out in March 1997; azathioprine (150 mg/day) and colchicine (2 mg/day) were then added and, finally, a marked clinical improvement was obtained. A new flare up occurred in August 1998, including 3 g daily proteinuria of recent onset. The urinary sediment contained 20 red cells per high power field. Renal biopsy showed endocapillary proliferative glomerulonephritis with glomerular crescents and capillary loop fibrinous thrombi (no glomerulus on the sample for immunofluorescence study). The patient temporarily improved with plasmapheresis and methylprednisolone pulses followed by high dose oral prednisone (60 mg/day). From September 1998 to January 1999, proteinuria increased to 5.4 g daily, and a high serum cryoglobulin concentration was then first detected with the assay described below (table 1). Azathioprine was replaced by monthly intravenous cyclophosphamide (1 g per infusion), associated with subsequent plasmapheresis in January and April 1999. Despite this treatment the patient's symptoms persisted and renal complications worsened, with a raised proteinuria at 6.28 g/day and a serum creatinine at 192 µmol/l in July 1999. A new evaluation was made. A bone marrow biopsy was normal. The skin biopsy showed leukocytoclastic vasculitis with slight

Table 1 Evolution of cryoglobulinaemia, rheumatoid factor, and complement levels

Date	Cryoglobulinaemia ($\mu\text{g/ml}$)*	Type	Rheumatoid factor (Rose-Waaler test)	C4 (g/l) CH ₅₀ (%)‡
January 1994	29	Oligoclonal IgM	0	<0.06 40
June 1996	25	Oligoclonal IgM	1 / 128	<0.06 25
August 1996	17	Oligoclonal IgM	ND	<0.06 <20
December 1996	188	III, polyclonal IgG, IgA, and IgM	ND	<0.07 <20
March 1997	4		1 / 128	0.10 50
October 1998	63	III, polyclonal IgG, IgA, and IgM	ND	ND
November 1998	1105†	II, IgMκ + polyclonal IgG, IgA, and IgM	ND	ND
December 1998	1663†	II, IgMκ + polyclonal IgG, IgA, and IgM	ND	ND
January 1999	1660†	II, IgMκ + polyclonal IgG, IgA, and IgM	ND	ND
February 1999	1031†	II, IgMκ + polyclonal IgG, IgA, and IgM	1/128	0.08 60
March 1999	1000†	II, IgMκ + polyclonal IgG, IgA, and IgM	1/128	ND
April 1999	273† (after plasmapheresis)	II, IgMκ + polyclonal IgG, IgA, and IgM	1/128	0.09 30
May 1999	848†	II, IgMκ + polyclonal IgG, IgA, and IgM	ND	ND

*Normal <15 $\mu\text{g/ml}$.

†Determination performed using the method described above since November 1998.

‡Normal range 60–120%.

Figure 1 Western blot of cryoglobulin. Pattern obtained with anti IgG, IgA, IgM, κ and λ chain labelled with alkaline phosphatase on cryoglobulins transferred onto nitrocellulose sheets: oligoclonal (top) and polyclonal pattern (middle) for cryoglobulin washed with conventional assay, type II pattern IgMκ (arrow) and polyclonal IgG, IgA, and IgM for cryoglobulin washed with current assay (bottom).

deposits of IgM, IgA, and C3 on immunofluorescence study. Renal biopsy showed an endocapillary and extracapillary glomerulonephritis with glomerular crescents in a mean of 30% of glomeruli, and IgG, IgM, and C3 deposits on immunofluorescence study. Prednisone was continued and cyclophosphamide was given orally (150 mg/day). The patient's condition is stabilised at the present time.

A modified assay was developed to detect a possible cryoglobulin. Briefly, a serum sample was obtained and centrifuged at 37 °C, then stored at 4 °C for eight days. The precipitate was separated by centrifugation, then washed each day for three consecutive days with either cold phosphate buffered saline (PBS; conventional assay) or distilled water to enhance the protein solubility (current assay). Indeed, we noted that some of the precipitate was lost in the PBS. Then, each precipitate was dissolved in a low volume of PBS for measurement of protein (Hartree assay adapted for cryoglobulins) and typed by Western blot (fig 1).² Precipitates obtained by both methods were analysed with two dimen-

sional polyacrylamide gel electrophoresis.^{3,4} In addition, some cryoprecipitate samples were passed at 37 °C over protein G-Sepharose columns. Proteins were then eluted using HCl-glycine, pH 2, and analysed with two dimensional polyacrylamide gel electrophoresis.³ The influence of calcium concentration on cryoglobulin solubility was investigated as follows. Solubility of the cryoglobulin obtained with distilled water was tested by adding Hanks's solution containing either Ca²⁺ (1.26 mM) and Mg²⁺ (0.80 mM), Ca²⁺ (1.26 mM) without Mg²⁺, or Mg²⁺ (0.80 mM) without Ca²⁺. The dissolved proteins were measured as described above. About 50% of the precipitate became soluble when Ca²⁺ was present in the milieu, contrasting with 5% solubility only when Ca²⁺ was absent.

Our observation indicates that cryoglobulinaemia must remain highly suspected despite apparently negative laboratory results when clinical and biological data—namely, low C4 associated with positive rheumatoid factors—are consistent with, or even more suggestive of this diagnosis. Indeed, monoclonal or

polyclonal rheumatoid factors are nearly always part of mixed cryoglobulins, where they bind to immune complexes—principally antigen complexed IgG—that subsequently precipitate.^{5–8} Nevertheless, when using conventional assay, cryoglobulin remained negative or weakly positive in our patient. Interestingly, a monoclonal IgMκ was sometimes found on immunofixation analysis. In November 1998 the occurrence of a glomerulonephritis consistent with cryoglobulin related kidney complications prompted us to perform further tests for cryoglobulins, including the method described above. Then, a high titre type II cryoglobulin (>1000 $\mu\text{g/ml}$) was isolated, and subsequently shown to consist of monoclonal IgMκ and polyclonal IgG, the former being thought to support the previously detected rheumatoid factor activity. Two dimensional polyacrylamide gel electrophoresis confirmed the presence of polyclonal IgG and monoclonal IgM in the cryoprecipitate, and allowed identification of an additional monoclonal IgA. Finally, electrophoretic studies of the proteins eluted from protein G columns showed the presence of polyclonal IgG, with only traces of the monoclonal IgMκ, indicating that the complex dissociated at 37 °C.

This cryoglobulin has unusual properties because it became soluble in PBS, while it precipitated in serum, distilled water, or calcium buffers. Usually, cryoprecipitation is a two step process.^{5–10} Firstly, rheumatoid factors bind to immune complexes at reduced temperature because of a cold enhanced affinity. Secondly, the large immune complexes precipitate. This requires favourable physicochemical conditions, including suitable pH and ionic strength of the solvent. Usually, the precipitate is stable in saline. Our data suggest that calcium concentration may be crucial for cryoglobulin precipitation, as in the case reported by Qi *et al.*¹⁰ This property might account for some of the discrepancies observed between the conventional and the current assay. It might also explain the severity of the symptoms *in vivo*. Further investigation is needed to approach the other determinant factors of precipitation. Hypocryoglobulins display a quite different property in the way they are isolated from hypotonic serum, though they lead to the same clinical syndrome.¹¹

To conclude, patients with clinical and biological manifestations suggestive of cryoglobulins constitute a pitfall for clinicians and biologists when standard laboratory investigations remain negative for cryoglobulinaemia. Unusual in vitro properties of cryoglobulins, including dependence upon calcium concentration, should be looked for in such circumstances.

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

Age (y)	61.2 (8.3)
Duration of postmenopausal period (y)	13.3 (7.5)
Duration of rheumatoid arthritis (y)	9.7 (6.4)
Rheumatoid factor positive (n)	30
Erosive RA (n)	16
Treatment with low dose glucocorticoids (n)	32
BMD* at the lumbar spine (g/cm ²)	0.840 (0.150)
BMD at the femoral neck (g/cm ²)	0.660 (0.110)
BMD at the middle phalanx of the third finger (g/cm ²)	0.390 (0.090)

*BMD = bone mineral density.

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.¹ Unfortunately, the generalised use of DXA is limited as it is expensive and time consuming, is not portable, and is available only in specialised clinics.

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.² This technique is similar to radiographic absorptiometry but provides immediate results; in current radiographic absorptiometry, radiographs are sent to an off site processing centre and the results are received a few days later. CDA is cheap and quick. Its precision and accuracy seem to be 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.³ The available data suggest that there is an increased risk of hip fracture in patients with RA, especially when they are treated with glucocorticoids.⁴ 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 currently not available. Recently, in this journal,⁵ 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 the patients with RA who should be examined by DXA. Over a period of three months all postmenopausal women with RA, evaluated in the rheumatology outpatient clinic, who fulfilled the inclusion criteria were asked to participate. The inclusion criteria were (a) duration of RA longer than one year, (b) duration of postmenopausal period longer than one year, and (c) no current treatment with bone thinning agents.

Forty five patients fulfilled the inclusion criteria and consent was obtained from 40 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 value of the L2-4 vertebrae 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. The in vivo precision of AccuDEXA, expressed as a coefficient of variation, was 1.16% (0.74 to 1.56). Data were cross referenced with the T score. According to WHO criteria,¹ osteoporosis is defined as a T score below -2.5.

A Spearman correlation test and linear regression analysis were used to test the relation between the variables; p<0.05 was considered significant. A 2x2 table was used to evaluate the positive and negative predictive value of CDA for the diagnosis of osteoporosis established by DXA.

Table 1 lists the clinical characteristics of the patients and the mean BMD values obtained.

BMD at the lumbar spine and at the non-dominant hand correlated significantly (r = 0.51, p<0.01). Similarly, BMD at the femoral neck and at the non-dominant hand were significantly correlated (r = 0.51, p<0.01).

DXA showed that 13 patients had osteoporosis and CDA that 16 patients had the disease in at least one of the evaluated zones. The positive predictive value of CDA for the diagnosis of osteoporosis was 56%. The negative predictive value for the diagnosis of osteoporosis was 83%.

The correlations found between BMD at the non-dominant hand and BMD at the lumbar spine and femoral neck were moderate. A negative predictive value was considered acceptable. Our results suggest that CDA could be a screening method used to decide which patients with RA should be investigated for osteoporosis. Further investigations are needed to confirm our findings.

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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.¹⁻¹⁰ We describe here a case of typical adult onset Still's disease with a seroconversion in the rubella 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 pharynx was erythematous. Some small cervical lymphadenopathies were detected. The leucocyte count was 42.3×10^9 cells/l (93.2% neutrophils) and the haemoglobin concentration was 79 g/l. Liver enzymes were slightly increased, aspartate aminotransferase (AST) 0.80 μ kat/l and alanine aminotransferase (ALT) 0.73 μ kat/l, but increased to AST 11.77 μ kat/l and ALT 7.68 μ kat/l after acetylsalicylic acid administration. Lactate dehydrogenase was 17.33 μ kat/l. The serum albumin concentration was 26 g/l and the erythrocyte sedimentation rate 60 mm 1st h. The serum ferritin was higher than 1500 μ g/l (normal value: 20–250 μ g/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, Legionella, Coxiella burnetii, Chlamydia and Rickettsia conorii 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.¹¹ 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 after admission 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 34 days. At this moment rubella IgG antibody titre rose to 660 000 IU/l.

Our patient fulfilled Yamaguchi's criteria for adult onset Still's disease so this diagnosis was well established.^{11,12} 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.¹³ In

our case we think that rubella was more probably attributable to a reinfection than to a primary infection because the patient had been correctly vaccinated in childhood and this is also supported by the increase in IgG antibody titre without increase in IgM concentrations.¹⁴ Moreover this 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. In this way, echovirus 7,¹ mumps,² cytomegalovirus,^{3,5} parainfluenza,³ Epstein-Barr virus,^{3,5} influenza A,⁴ parvovirus B19,⁶ hepatitis B or C^{7,8} and rubella^{1,3,9,10} have been associated.

The relation between rubella virus and adult onset Still's disease has been reported in some series and case reports^{1,3,9,10} since the initial description by Bywaters in 1971.¹⁵ Wouters *et al* performed exhaustive virological studies in five 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.¹ The rubella virus genome has also been detected in peripheral blood cell population from patients with adult onset Still's disease.¹⁶

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,¹⁻¹⁰ supports the hypothesis about the role of viruses in the aetiopathogenesis of adult onset Still's disease.

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

Adrenomedullin is a hypotensive peptide newly found in human pheochromocytoma 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 fibroblasts.² Adrenomedullin receptors are expressed in both vascular smooth muscle cells and vascular endothelial cells. Adrenomedullin has a vasorelaxant effect, antagonising the vasoconstrictive 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, thereby protecting the cardiovascular system.³ Furthermore, adrenomedullin regulates not only vascular tone but also vascular function through the autocrine/paracrine system, stimulating cAMP formation in a dose dependent manner,³ and exerting an anti-inflammatory effect by inhibiting the production of a chemo-attractant from alveolar macrophages.⁴

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, myocardial, and pulmonary. Pulmonary hypertension (PH) is a common cause of death in patients with SSc. In the plasma of patients with PH the endothelin-1 level is raised.⁵ In addition, it was recently reported that the adrenomedullin level is raised also in the plasma of patients with Raynaud's disease⁶ or rheumatoid arthritis.⁷ 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 in SSc.

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.⁸ 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 nicardipine 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 radioimmunoassay. Statistical significance was analysed with the Mann-Whitney U test.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in those with SSc without PH ($p = 0.011$) or than in normal volunteers ($p = 0.020$) (fig 1A). The concentrations of adrenomedullin or endothelin-1 in the plasma from a patient with primary PH were similar to those from 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 ($p = 0.41$) (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 46, 59, and 60 mmHg, respectively. The levels 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.

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 inhibit 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.⁹ 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.

Figure 1 Concentrations of (A) adrenomedullin and (B) endothelin-1 in plasma. Short horizontal lines = 10th and 90th centiles; long horizontal lines = 25th, 50th, and 75th centiles; the circles denote the value outside 10th and 90th centiles in patients with SSc with and without (–) pulmonary hypertension (PH), and normal volunteers. ND = not done.

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Avascular necrosis of a single vertebral body, an atypical site of disease in a patient with SLE and secondary APLS

Antiphospholipid syndrome (APLS) is characterised by recurrent arterial or venous thrombosis. Deep veins, such as the femoral and popliteal veins are by far the commonest sites of thrombosis. The arterial and venous systems of the mesenteries, liver, kidneys and the adrenal glands are also involved.¹ We report here a 39 year old woman with systemic lupus erythematosus (SLE) and secondary APLS who presented with subacute onset of back pain and was found to have avascular necrosis (AVN) of a single vertebral body at L2, an atypical presentation of this complication.

In 1976, a 17 year old white woman complained of gastrointestinal upset and frequent joint pain in her hands and knees a few months after she started taking oral contraceptives. She was found to have Coombs' positive haemolytic anaemia, leucopenia, thrombocytopenia and deranged liver function. Serologically, she had positive antinuclear antibody (ANA, 1/1280 on rat liver cells), anti-double stranded (ds) DNA antibodies (1/320 on *Criethidia lucidiae*) and posi-

tive anti-thyroid microsomal antibodies. Antibodies to the extractable nuclear antigens (ENA) were negative. Liver biopsy showed features compatible with chronic active hepatitis. SLE with an associated hepatitis was diagnosed and she was prescribed prednisolone 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. 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 satisfactory 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 dipyridamole, an anti-platelet agent, and atenolol for hypertension 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 thrombocytopenia. Her warfarin was stopped in view of the potential increase risk in bleeding tendency. Her prednisolone was increased to 40 mg daily to no avail. Splenectomy was performed, after which her platelet count stabilised. She had an unsuccessful pregnancy with intrauterine death in the same year. Her disease was better controlled with prednisolone (5–10 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 infarction of the L2 vertebral body. Bone scan did not pick up any other site of involvement by AVN. Figure 1 shows the plain radiographic image of the lumbosacral spine. Figure 2 shows the T2 weighted magnetic resonance sagittal image of the thoracolumbar spine with increase in signal over the L2 vertebral body. She was referred to the orthopaedic surgery unit for a L1 to L3 vertebral fusion. Histological examination of the involved site showed 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 maintained with low dose corticosteroid 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 presented with acute onset of AVN involving multiple sites including T8, L4 and L5 vertebral 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

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.

spots.³⁻⁵ 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) antibodies⁶ but without other clinical features that satisfied the diagnosis of APLS.

Secondly, the pathogenesis of AVN is complex. 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.⁷ Active disease and the presence of APL antibodies may also have important roles in the development of AVN in these patients.⁸ It is interesting that our patient had features of secondary APLS with previous venous thrombosis and recurrent 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, or all three, led to AVN of her L2 vertebral body is unclear. In view of this, we have recently performed a case-control study to evaluate the role of each of these individual potential risk factors.

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Immunoglobulin and lymphocyte decrease concurrent with adverse reactions induced by methotrexate for RA

The limiting factor in low dose pulse methotrexate treatment for rheumatoid arthritis (RA) has been its toxicity.^{1,2} We recently treated a female patient with RA, in whom pneumonitis and granulocytopenia developed during methotrexate treatment; her white blood cell count was $1.10 \times 10^9/l$ and Pao_2 was 37 mm Hg. Before treatment, at the time of development of adverse reactions, and after recovery after methotrexate was withdrawn, her IgG levels were 17.99, 10.15, 16.75 g/l; IgA 5.14, 3.69, 4.33 g/l; IgM 1.73, 1.06, 1.36 g/l; and lymphocyte count 1.96, 0.42, $1.56 \times 10^9/l$, respectively. We then investigated whether immunoglobulin levels and lymphocyte count decrease when adverse reactions to methotrexate treatment develop.

One hundred consecutive patients with RA (80 women and 20 men, mean (SD) age 57.5 (9.2) years) receiving between 2.5 and 15 mg of methotrexate weekly in Tokyo Metropolitan Komagome Hospital were followed up from 1991 to 1998. When the patients did not respond and had no adverse reactions, the dose was increased by 1.25 to 2.5 mg/week. Response to treatment, assessed by the patient's impression of improvement, a decrease in swelling and pain of more than two joints, a decrease of >20 mg/l in the C reactive protein (CRP) level, adverse reactions, lymphocyte and eosinophil counts, serum concentrations of immunoglobulins, γ fraction, rheumatoid factor, and albumin were studied.

Sixteen adverse reactions occurred in 15 patients; the reaction affected the liver (six patients), the lung (three), the skin (three), the bone marrow (three), and the oral mucosa (one). They recovered after methotrexate was discontinued or reduced, without steroid treatment. Thirteen of these 15 patients showed a mean (SD) decrease in

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)

	With adverse reaction (n)	Without adverse reaction (n)	p Value‡	Threshold value	p Value¶
IgG†					
Pre	20.87 (7.34)(15)	20.12 (5.50)(83)	NS		
Post-pre (g/l)	-6.23 (3.53)(15)	-1.47 (3.73)(81)	****	4.62	***
(Post-pre)/pre	-0.30 (0.13)(15)	-0.06 (0.16)(81)	****	0.171	***
IgA†					
Pre	4.50 (2.17)(15)	4.13 (1.61)(83)	NS		
Post-pre (g/l)	-1.35 (0.87)(15)	-0.21 (0.65)(81)	****	0.83	***
(Post-pre)/pre	-0.31 (0.14)(15)	-0.03 (0.18)(81)	****	0.189	***
IgM†					
Pre	2.03 (0.86)(15)	2.04 (0.84)(83)	NS		
Post-pre (g/l)	-0.77 (0.60)(15)	-0.15 (0.44)(81)	****	0.26	***
(Post-pre)/pre	-0.35 (0.17)(15)	-0.07 (0.17)(81)	****	0.257	***
γ Globulin					
Pre	15.64 (7.00)(13)	15.54 (4.69)(74)	NS		
Post-pre (g/l)	-5.07 (3.61)(12)	-1.30 (3.22)(67)	****	2.38	***
(Post-pre)/pre	-0.30 (0.15)(12)	-0.08 (0.18)(67)	****	0.243	***
Lymphocyte					
Pre	1.82 (0.80)(15)	1.38 (0.61)(81)	*		
Post-pre (10 ⁹ /l)	-0.6 (0.55)(14)	-0.01 (0.58)(80)	****	0.18	***
(Post-pre)/pre	-0.35 (0.31)(14)	0.12 (0.71)(80)	*	0.267	***

NS = p < 0.05; *p < 0.05; ***p < 0.005; ****p < 0.0001.

†Normal range for IgG is 8.71–20.7 g/l, IgA 0.12–5.80 g/l, and IgM 0.53–2.98 g/l.

‡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) v 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. When the patients were grouped according to therapeutic response, significant reductions were seen only in the levels of immunoglobulins and γ fractions, but no reduction was seen in lymphocyte counts, in 78 responders. The greater decreases in responders than in non-responders were seen

only in IgG and IgA levels. The reductions and reduction ratios of immunoglobulins were greater in patients with adverse reactions, grouped according to toxicity (30–35%, table 1), than in those with therapeutic response grouped according to efficacy (13–14%, data not shown).

Our study shows that when a patient's immunoglobulin levels and lymphocyte count decrease globally by as much as 25% or more from the pretreatment level, this decrease is suggestive of toxicity. Conversely, in patients without adverse reactions, the decreases were less than 20%. The clinical improvement contributed only partially to the reductions; steroid treatment was not likely to have been the cause either, as they had been given for a long time without a significant change in the dose.

Recently, we reported that the immunoglobulin level decreases with adverse reactions, during a disease modifying antirheumatic drug, bucillamine, treatment.^{3–5} A reduction in interleukin 6 level was reported to parallel an improvement during methotrexate treatment.^{6–7} The reduction in lymphocyte numbers is controversial.^{8–9} Immunomodulation might relate mainly to adverse reactions, whereas the effect might appear owing to anti-inflammatory mechanisms.¹⁰

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.

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