Orderly arrayed deposit of urate crystals in gout suggest epitaxial formation

The mechanisms responsible for the initial deposit of monosodium urate (MSU) crystals in gouty joints remain obscure. We report on nine small fragments of tissue that showed an arranged deposit MSU crystals, which were obtained along with synovial fluid (SF) from asymptomatic gouty joints. Three of the fragments had chondrocytic islands, indicating their cartilaginous nature; MSU crystals were found in their depth, all oriented in the same direction and in two of them, a parallel fibrillar appearance of its matrix was apparent following the MSU crystals in the same direction as the fibres (fig 1A). Bundles of undulating parallel fibres—probably of cartilage collagen—detached from two of these fragments. The remaining fragments were composed by similar bundles of undulating parallel fibres without a cellular component, and may constitute remnants of fibrillating cartilage. In four of these fragments, individual crystals were deposited densely packed in transverse rows, following the undulations of the fibres, and always positioned alongside them (fig 1B). Finally, in two additional fragments fewer crystals were seen, always laying parallel: the fibres and following their undulations (fig 1C).

All the SF samples in which the fragments were found contained abundant typical MSU crystals: strongly birefringent needle shaped, showing negative elongation when observed with compensated polarised light, and similar to those found on the tissue fragments. We have an interest in gout, and run a gout clinic where we screen for asymptomatic gout; thus, the association is likely to be real.

The MSU crystals were deposited alongside the fibres and following their undulations, and their orientation indicated that the same mechanism may be leading to crystallisation. Thus, the MSU crystals may originate from the synovial fluid (under the microscope, crystals lying on the tissue and those MSU crystals freely floating in the synovial fluid had similar characteristics).

Fig. 1. (A): Cartilage fragments; a chondrocyte in an island is seen. MSU crystals are placed in parallel, following the direction of the fibrillary matrix. Many of the crystals show dark against the bright birefringent matrix (under the microscope, crystals lying on the tissue and those MSU crystals freely floating in the synovial fluid had similar characteristics).

(B): Fragment constituted by fibres with densely packed crystals deposited adjacentely, the rows of crystals following the ups and downs of the undulations of the fibres are seen. (Under the microscope, crystals lying on the tissue and those MSU crystals freely floating in the synovial fluid had similar characteristics). Polarisated light and first order red compensator original magnification × 1000. (C): One of the bundles of fibres containing only a few MSU crystals, which loosely follow the ups and downs of its undulations. Uncompensated polarised light original magnification × 1000.

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Serum IgD as a discriminator between the two periodic febrile syndromes hyper-immunoglobulinaemia D syndrome and Behçet’s disease

The hyper-immunoglobulinaemia D (IgD) syndrome (HIDS) is a recently described periodic disease, manifested by febrile episodes, lasting several days and accompanied by abdominal pain, symmetrical oligoarthritides, cervical lymphadenopathy, skin lesions, and constantly increased serum IgD concentrations (>100 units/ml). HIDS shares its episodic febrile nature and many painful manifestations with several other clinical conditions, including familial Mediterranean fever, familial Hibernian fever, and Behçet’s disease (BD). Indeed, in a leading textbook of rheumatology, these entities were recently grouped in one chapter, entitled Intermittent and Periodic Articular Syndromes. Manifestations, distinguishing between these periodic
syndromes, are therefore of considerable interest and thoroughly investigated.

Normal or low concentrations of serum IgD exclude HIDS. However, as about 10-15% of familial Mediterranean fever and familial Hibernian fever patients have increased concentrations of IgD (published data),4,5 increased IgD concentrations cannot safely differentiate between HIDS and familial Mediterranean fever or familial Hibernian fever in a patient presenting with periodic arthritic syndrome. As for BD, comparative IgD studies with HIDS are lacking and the status of IgD as a discriminator between the diseases is not known.

We have studied IgD concentrations in 30 serum samples of patients with BD, in whom the diagnosis agreed with the International Study Group Criteria for the diagnosis of BD.7 Serum IgD concentrations were determined using a sensitive enzyme linked immunosor bent assay (ELISA). In contrast, rabbit anti-human IgD anti-serum was used to coat a multitrile plate, followed by the sequential addition of the examined serum samples or standards, monoclonal mouse anti-human IgD, rabbit anti-mouse peroxidase conjugated, and substrate. Serum samples of five healthy people and five HIDS patients served as controls.

The mean (SD) IgD serum concentrations in patients with BD and healthy controls were comparable (62.1 (36.6) compared with 60.2 (35.2) units/ml, respectively. Only one patient with BD had raised serum IgD concentrations (240 units/ml). In contrast the IgD concentrations in all HIDS serum samples were high (188.7 (144.7) units/ml, p < 0.001 by Student’s t test, compared with either healthy controls or BD patients). Our study is consistent with a previous study in BD patients.8 This assay, rabbit anti-human IgD anti-serum was used to coat a multitrile plate, followed by the sequential addition of the examined serum samples or standards, monoclonal mouse anti-human IgD, rabbit anti-mouse peroxidase conjugated, and substrate. Serum samples of five healthy people and five HIDS patients served as controls.

A case of Churg-Strauss vasculitis after hepatitis B vaccination

Vaccination against hepatitis B with recombinant vaccine is highly effective in producing immunity in immunocompetent patients. It has few side effects, usually consisting of early local reactions to the thimerosal or aluminium components of the vaccine. Vasculitis have been reported after BCG inoculation and vaccination against flu, measles, and hepatitis B. For the latter, some cases have been described after inoculation of both plasma derived and recombinant vaccine: cryoglobulinaemia, pulmonary and cutaneous vasculitis, erythema nodosum, Takayasu’s arteritis, and polyarteritis nodosa.1,2 We describe a case of Churg-Strauss vasculitis (CSV) developing after vaccination against hepatitis B with recombinant vaccine.

The patient’s personal and family histories were negative for autoimmune and allergic diseases; in particular, neither atopy nor eczema were reported. The patient’s available previous full blood counts with differential counts were normal. At the age of 20, from November 1989 to May 1990, using the recommended dosing and time schedule, she had been vaccinated with HBV (recombinant vaccine Engerix B, Smith Kline Beecham). On the same occasion, four other members of her family had been vaccinated, presumably with the same “batch” of vaccine and no adverse events were observed. In contrast, one month after the last dose the patient developed a chronic rhinitis followed, after about one year, by a severe and corticopenodasthenic and asthma and by the appearance, in 1993, of nasal polyposis, treated surgically. One year later she developed fever, fatigue, weight loss, and digital paresthesia. Physical examination showed petechial purpur in the nail bed of her fingers and on her feet. Laboratory investigations revealed a haemoglobin of 11 g/dl, WBC of 24 500/mm³ with absolute eosinophilia (48%), erythrocyte sedimentation rate 50 mm 1st hour. Circulating immunocomplexes and rheumatoid factor were present; anti-HbsAg antibodies were 250 IU; ANA, ANCA, anti-HCV antibodies, cryoglobulins, skin tests for inha lent allergens were negative. Chest radiography was normal. Pulmonary function tests revealed an obstructive pattern. The patient also developed pericarditis and azotemia, with microscopic haematuria and hylene cylinduria. A skin biopsy specimen taken from the left leg showed perivascular polymorphonuclear and eosinophilic infiltrate, with eosinophilic karyorrhexis, consistent with leukocytoelastic vasculitis. According to the American College of Rheumatology 1990 criteria a diagnosis of CSV was made and the patient was referred to our hospital. Treatment with deflazacort 75 mg daily for six months, then slowly tapered, included a rapid regression of symptoms and the complete normalisation of urine analysis. At lower doses asthma recurred, but it was successfully controlled by inhaled theophylline and fluticasone propionate and nedocromil sodium. An episode of anterior uveitis in 1996 was responsive to topical corticosteroids. The patient is now well with low doses of oral corticosteroids and inhalers.

Even if other cases of vasculitis have been described in consequence of HBV vaccination, to our knowledge this is the first report of CSV. Obviously, in our opinion the time elapsed between the beginning of the vaccination and the first symptoms was too long to clearly confirm such a possible association. Indeed, in our patient only a few weeks elapsed between the vaccination and the appearance of such respiratory symptoms, thus supporting the triggering role of vaccination. Moreover, CSV shares many symptoms with polyarteritis nodosa, another well known possible sequela of HBV infection or vaccination.

Finally, a question could be raised about the possible role of the specific “batch” of vaccines in inducing adverse reactions. Again, the time elapsed from vaccination is too long for a definite answer. However, the simultaneous vaccination of other members of the same family, presumably with the same “batch” without any adverse reaction, seems to exclude such a possibility.

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Hypopituitarism in a woman with a severe primary antiphospholipid syndrome

The antiphospholipid syndrome (APS) is an acquired thrombotic disorder characterised by recurrent venous or arterial thromboses or recurrent miscarriages, or both, associated with the presence of antibodies directed against negatively charged phospholipids—the is, lupus anticoagulant (LA), or anticardiolipin antibodies (aCL), or phospholipid binding proteins, or all three. It mainly occurs within systemic lupus erythematosus or as a primary disorder. Nearly all organs or tissues may be involved by thrombosis, but to date endocrine manifestations of the APS are mainly restricted to acute or chronic adrenal insufficiency resulting from adrenal haemorrhagic infarction. We describe the case of a patient with primary APS who developed hypopituitarism assumed to result from hypothalamic dysfunction.

A 48 year old woman was referred in 1996 for asthma and a weight gain of 8 kg during the last six months. Her past medical history included two normal pregnancies in 1966 and 1970 and the chance discovery of LA in 1976, which remained present on subsequent determinations. She had experienced four fetal losses after 14–22 weeks of gestation between 1977 and 1980 and multiple thrombotic events affecting deep veins of both legs, left eye, right iliac, and coronary arteries. At that time, she had no classic vascular risk factors besides heavy smoking. Arterial angiograms showed arterial thrombosis in the absence of overt atheroma. Since the occurrence of myocardial infarction in 1984, she had been treated with long term oral anticoagulation; however deep vein thromboses recurred in two occasions despite low intensity fluidine therapy (international normalised ratio (INR) <3). Thereafter, the INR was maintained over 3. Menopause occurred in 1987 at the age of 40. She complained at this time of hot flushes.

On admission, she was afebrile. Physical examination was unremarkable except for reduced arterial pulses on right leg. Blood pressure was 120/80 mm Hg and pulse 65. She was taking fludione, isosorbide dinitrate, diltiazem and fenofibrate started three years earlier for moderate type II dyslipidaemia. She had a blood haemoglobin of 12.3 g/dl and a platelet count of 200 × 10⁹. Erythrocyte sedimentation rate, white blood count, differential, haptoglobin, C reactive protein, alanine transaminase, aspartate transaminase, alkaline phosphatase, albumin, globulins, and urine analysis were normal. Total serum cholesterol and triglycerides concentrations were 5.33 and 3.46 mmol/l, respectively. The presence of LA was confirmed, associated with high titre IgG aCL on ELISA. The following tests were normal or negative: antithrombin III, protein C, protein S, activated protein C resistance, antinuclear, anti-dsDNA and anti-ENA antibodies, and complement levels.

Endocrinological examination (table 1) showed hypopituitarism without posterior pituitary dysfunction. Dynamic studies suggested a hypothalamic origin for these deficits. On brain magnetic resonance imaging (MRI), the sellar and juxta-sellar region were normal but there was a small sized lesion of the left thalamus that appeared on low signal intensity on T1 weighted sequences and on high signal intensity on T2 weighted sequences (fig 1). This lesion did not enhance after intravenous gadolinium administration. Replacement therapy with hydrocortisone and thyroxine resulted in the progressive disappearance of asthenia and overweight.

This patient undoubtedly had primary APS attested by history of multiple and severe thrombotic events associated with longstanding clearcut LA and aCL, in the absence of clinical and biological features of systemic lupus erythematosus. She had menopause at 40 and subsequently developed features of hypopituitarism. This diagnosis was confirmed by hormonal evaluation showing low basal plasma levels of free T4, TSH, ACTH, LH, FSH, and GH with low 24 hour cortisol excretion. A clear cut and protracted response of TSH on TRH test, and an increase in FSH and LH with Gn-RH stimulation were suggestive of a suprasellar origin. The usual causes of acquired hypopituitarism, such as tumours or systemic granulomatous disorders, were ruled out but the precise mechanism leading to hypopituitarism could not be established. The sole abnormality found on MRI examination was a small sized image in the left thalamus, probably of ischaemic origin, whose relation with hypopituitarism is far from clear. Indeed, APS complicated by bilateral paramedian thalamic infarction was reported in a 16 year old girl who had normal thyroid function tests. The rare endocrinological complications of APS are usually unusual. They mainly consist in acute rather than chronic adrenal insufficiency secondary to bilateral haemorrhagic infarction. Focal necrosis of the pituitary gland has been found at postmortem examination in a young woman who developed a fatal catastrophic APS at 30 weeks gestation. Hormonal evaluation and MRI findings were not consistent with this mechanism to explain hypopituitarism in our case.

On a practical basis, two conclusions can be drawn from our case report. Firstly, besides adrenal haemorrhage, hypopituitarism should be considered as a possible cause of hypoadrenalism in the antiphospholipid syndrome. Secondly, LA and aCL should be searched for in the evaluation of patients with hypopituitarism, especially when a history of thrombosis is present.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Normal range</th>
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</thead>
<tbody>
<tr>
<td>TSH (mIU/l)</td>
<td>0.04</td>
<td>0.35–5.50</td>
</tr>
<tr>
<td>Free T4 (pmol/l)</td>
<td>5.0</td>
<td>8.5–18.5</td>
</tr>
<tr>
<td>Cortisol in the 24 hour urine (nmol/24 h)</td>
<td>≤28</td>
<td>80–280</td>
</tr>
<tr>
<td>ACTH (pmol/l)</td>
<td>2.9</td>
<td>2.2–13.2</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>22.8</td>
<td>34.4–95.8</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>15.6</td>
<td>39.7–103.5</td>
</tr>
<tr>
<td>Prolactin (mIU/l)</td>
<td>63</td>
<td>39–428</td>
</tr>
<tr>
<td>GH (mIU/l)</td>
<td>&lt;0.1</td>
<td>&lt;11.5</td>
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<tr>
<td>Plasma FSH and LH after an intravenous injection of GnRH</td>
<td>maximal FSH 38.1 IU/l at 60 min</td>
<td></td>
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<tr>
<td>Plasma TSH and prolactin (PRL) after an intravenous injection of TRH</td>
<td>maximal TSH 17.54 mIU/l at 30 min persistent at 11.21 mIU/l at 60 min</td>
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</tr>
<tr>
<td></td>
<td>maximal LH 47.5 IU/l at 60 min</td>
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</tr>
<tr>
<td></td>
<td>maximal PRL 671 mIU/l at 30 min</td>
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Long term follow up of small airways obstruction in patients with rheumatoid arthritis

Rheumatoid arthritis (RA) affects the respiratory system in a number of ways, including interstitial lung disease, nodules, pleural effusion, bronchiectasis, bronchiolitis obliterans, and interstitial lung disease, nodules, pleural effusion. RA patients with isolated small airways obstruction. At follow up a further two non-smokers (with previous normal respiratory function) had developed a reduction in FEF$_{25–75}$ <65%, resulting in a total of six non-smoking patients (30%) having isolated small airways obstruction. The mean value (SD) of FEF$_{25–75}$ in these six patients was significantly reduced from baseline after eight years, 63.6 (19.4) compared with 48.0 (12.9); p<0.01 (paired t test). None of the patients with small airways obstruction had symptoms or clinical signs of pulmonary disease and all had normal chest radiographs. There was no significant difference in the FEF$_{25–75}$ after eight years in non-smoking patients with >65% predicted at baseline, 91 (26.9) compared with 92 (21.4); p>0.7. At initial evaluation only one non-smoking patient had a significant reduction in TLCO (35% predicted). This patient had clinical and radiographic evidence of pulmonary fibrosis and at follow up had a further reduction in TLCO (20% predicted).

Interestingly, there was no significant difference in the mean TLCO between baseline and follow up in the non-smoking patients, 90 (21.3) compared with 85 (25.8); p>0.12, in keeping with the findings of Linstow. Table 1 shows the clinical features and pulmonary function of those patients having small airways obstruction at follow up. There was no significant difference in mean age at study (60 ± 60 years), sex, mean age at disease onset (39 ± 38 years), mean disease duration (19 ± 18 years), titre of rheumatoid factor or the presence of extracellular features (nodules, vasculitis or sicca symptoms) between non-smoking patients with isolated airways obstruction and those with normal respiratory function and there was no increase in episodes of recurrent bronchitis. There was no difference in the number or type of disease modifying agents, or use of NSIADs, between patients with airways obstruction and those without.

Pulmonary function, α, antitrypsin deficiency, and drug treatment have been proposed as possible predisposing factors for small airways obstruction in RA, however the exact mechanism is not well known. Mucosal oedema secondary to pre-existing airways inflammation in RA leading to bronchial narrowing and airways obstruction has been proposed as a mechanism. This study confirmed the existence of a subgroup of non-smoking patients with RA who have isolated small airways obstruction. The abnormalities seem to be progressive and the number of patients with airways obstruction may increase over time.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Disease duration (years)</th>
<th>RF score</th>
<th>EAF*</th>
<th>FEV1</th>
<th>FVC</th>
<th>FEV1/FVC</th>
<th>TLCO</th>
<th>FEF$_{25–75}$ (1996)**</th>
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<tbody>
<tr>
<td>55</td>
<td>F</td>
<td>38</td>
<td>1280</td>
<td>No</td>
<td>92</td>
<td>99</td>
<td>93</td>
<td>85</td>
<td>95 (63)</td>
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<tr>
<td>73</td>
<td>F</td>
<td>23</td>
<td>2560</td>
<td>No</td>
<td>85</td>
<td>90</td>
<td>94</td>
<td>65</td>
<td>76 (62)</td>
</tr>
<tr>
<td>65</td>
<td>F</td>
<td>18</td>
<td>40</td>
<td>82</td>
<td>94</td>
<td>87</td>
<td>79</td>
<td>60</td>
<td>47</td>
</tr>
<tr>
<td>63</td>
<td>M</td>
<td>36</td>
<td>640</td>
<td>No</td>
<td>70</td>
<td>90</td>
<td>76</td>
<td>83</td>
<td>39 (37)</td>
</tr>
<tr>
<td>56</td>
<td>M</td>
<td>10</td>
<td>2560</td>
<td>No</td>
<td>71</td>
<td>94</td>
<td>75</td>
<td>80</td>
<td>54 (31)</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>10</td>
<td>640</td>
<td>No</td>
<td>79</td>
<td>88</td>
<td>89</td>
<td>98</td>
<td>58 (48)</td>
</tr>
</tbody>
</table>

Pulmonary function tests given as % predicted. Small airways obstruction defined as FEF$_{25–75}$ <65% predicted. *EAF, extra-articular features. **p<0.01.

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Cyclosporin in the treatment of Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) is a eosinophilic granulomatous vasculitic condition associated with asthma or allergic rhinitis, or both. Established management of severe disease includes high dose corticosteroids and intravenous cyclophosphamide therapy. We present a patient with CSS who was resistant to treatment with pulse intravenous cyclophosphamide but responded to cyclosporin therapy. A 31 year old white woman was admitted to hospital with a 10 day history of pain and numbness in the left foot, an arthreathmic rash on her chest and lower legs, generalised myalgia, polyarthralgia, and fever. She had a eight year history of asthma that had deteriorated over the previous 12 months. Examination revealed a vasculitic rash on the chest and lower legs and a peripheral sensory neuropathy affecting the left foot. She was found to have an increased erythrocyte sedimentation rate of 58 mm 1st h, C reactive protein 48 mg/l (normal up to 10 mg/l), cosinophilia 10,70 x 10^7/l and echocardiography revealed a small pericardial effusion. The diagnosis of CSS was made and she was started on prednisolone with partial symptomatic improvement and lowering of the eosinophil count. The prednisolone was slowly reduced but on reaching 15 mg/0 mg
alternate days the neuropathy worsened, the rash returned, and the eosinophil count rose. Azathioprine was added but despite 200 mg daily, giving a neutrophil count of 3.74 × 10⁹/l, the fever, rash and eosinophilia recurred each time the prednisolone dose was reduced below 15 mg/0.025 g alternate days. After more than 12 months from initial diagnosis she was referred to our unit for further treatment.

On initial presentation to our unit, she was grossly cushingoid (weight 80 kg) and still complained of numbness in her foot, fatigue, and myalgia. She was started on weekly cyclophosphamide infusions (1 g), the first three infusions with methylprednisolone. Despite weekly cyclophosphamide infusions the neutrophil count remained above 3.5 × 10⁹/l so we were able to increase the cyclophosphamide dose to 1.25 g weekly and then 1.5 g weekly, which brought the pre-treatment neutrophil count down to 1.9 × 10⁹/l. However, all attempts to reduce the prednisolone dose to 5 mg daily precipitated a flare of disease with recurrent rash, fatigue, and neuropathy. After 12 months on pulse cyclophosphamide (total dose 44.75 g) she was still requiring oral prednisolone to control the rash, fatigue, neuropathy, and eosinophilia and her asthma had again deteriorated. The cyclophosphamide was therefore stopped and she was immediately given cyclosporin (Neoral, Sandoz) 150 mg 12 hourly (3.5 mg/kg per day) giving trough blood values of 117 ng/ml. At the time of writing, she has been receiving this treatment for five months, has been asymptomatic from CSS and her asthma since starting the cyclosporin and managed to reduce and stop oral prednisolone without recurrence of symptoms for the first time in 2.5 years. The only side effects experienced were the “burning” sensation in her hands and feet and intermittent mild nausea.

To our knowledge, this is the first report of severe CSS being treated with cyclosporin. Despite 44.75 g cyclophosphamide in 12 months our patient’s disease flared each time the oral prednisolone dose was reduced. Clearly, in this patient corticosteroids and pulse cyclophosphamide therapy failed to control the disease although these remain the drugs of choice in severe CSS. Plasma exchange and interferon γ have been used separately in resistant cases of CSS but the role of these treatments is still being evaluated. There are a few reports of cyclosporin used in Wegener’s granulomatosis with response in doses 5–10 mg/kg per day. Promising results have recently been seen with cyclosporin in the treatment of corticosteroid resistant asthma although larger controlled studies are still awaited. Troublesome residual asthma in CSS may necessitate continuing oral prednisolone even when the vasculitic disease has abated. Cyclosporin therefore, may be a useful treatment in cases of resistant CSS controlling both the vasculitic process and the residual asthma.

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Letters, Matters arising

Azoospermia in familial Mediterranean fever patients: the role of colchicine and amyloidosis

Familial Mediterranean fever (FMF) is a hereditary disease characterised by recurrent episodes of fever, peritonitis, pleuritis, arthritis or erysipelas-like skin lesions. The disease affects mainly Jews, Armenians, Arabs, and Turks. Typically, the episodes last two to three days and resolve spontaneously. One of the main complications of FMF is the development of secondary amyloidosis (AA type). The kidneys are the main target organ involved, leading to chronic renal failure. Colchicine has been the preferred treatment for FMF since 1972. It is effective in suppressing the episodes in more than 90% of the patients and prevents both the development of amyloidosis and the additional deterioration of renal functions in those with early amyloidosis. Colchicine exerts its main effect at the cellular level by its interaction with tubulin at the microtubules, inhibiting motility and exostosis of intracellular granules. Furthermore, it has also a powerful antimitotic effect by causing metaphase arrest and is capable of arresting meiosis. Therefore, in cases of infertility in patients treated with colchicine, it has been speculated that this medication cause azoospermia.

In this report we describe three patients with FMF and infertility who had been taking colchicine for about one to three years before the documentation of azoospermia. All the patients had FMF for at least four years. Two of the patients (A and B) had nephrotic syndrome at the time of diagnosis and amyloid was demonstrated by kidney and rectal biopsies. The third patient (C) had no clinical signs of amyloidosis. None of the patients experienced any scrotal attack or epididymoorchitis. All of the patients had normal serum profile of sex hormones and a normal karyotype. However, in patient A, testicular biopsy disclosed marked atrophy with Sertoli cells only. The blood vessels were thickened and their staining by Congo red revealed abundant amyloid (fig 1). In patient B, the biopsy revealed maturation arrest of the spermatocytes with amyloidosis of the walls of the blood vessels (fig 2). In the third patient testicular biopsy showed a pure maturation arrest. Congo red staining failed to show amyloidosis.

Since the introduction of long term preventive colchicine therapy for patients with FMF, concerns have been raised about the development of adverse effects of the drug, including infertility. Initial findings suggested that male fertility was not affected by colchicine. A study by Bremner and Paulsen failed to show any evidence for side effects in six healthy male volunteers with normal liver and kidney function, who received commonly used doses of colchicine during four to six months. However, later observations disclosed that, as many as 20% of male FMF patients receiving long term colchicine therapy may develop fertility problems associated with either azoospermia or impairment of sperm penetration. In a recent study, Sarnia et al evaluated 62 male patients with Behcet’s disease.
syndrome who were taking colchicine. They claimed that oligospermia (≤20 × 10⁹/ml) was present in 23 patients (37.1%) and azoospermia in two patients. Our experience in treating more than 150 (male) FMF patients, is much more favourable. We have found only patients with oligospermia and none of whom had amyloidosis.

Usually, FMF associated amyloidosis of the AA type involves the kidneys, liver, spleen, heart, and intestines. Involvement of the testicles has been rarely reported. In an animal model, testicular amyloidosis was induced in hamsters by infecting the animals with Leishmania donovani. Testicular biopsies disclosed total azoospermia in the final week of the pathological process. This study and other sporadic cases show that amyloidosis by itself can cause oligo or azoospermia.

In FMF patients, it is tempting to ascribe the complication of azoospermia to colchicine therapy. However, testicular biopsies in two of our cases demonstrated amyloidosis of the testes. Furthermore, one of the patients had taken little colchicine before the diagnosis of infertility. Therefore, it is conceivable that the pathological process of amyloidosis may also be responsible for azoospermia in these patients.

The relatively high frequency of oligospermia or azoospermia in patients with Behcet’s disease compared with patients with FMF or gout is puzzling. The common presence of epididymitis or vasculitis, or both, of the testes in Behcet’s disease may have an important role in predisposing the patients to this complication while they are taking colchicine. In FMF, recurrent orchitis or epididymitis are relatively rare. However, amyloidosis of the testicular blood vessels in these patients may have a role parallel to the vasculitis in Behcet’s disease in predisposing to azoospermia while on colchicine therapy.

Based upon these findings we propose that the possibility of testicular amyloidosis should be included in the differential diagnosis of oligo or azoospermia in FMF patients.

### Colony stimulating factor-1 in synovial fluids and injured knees

Subchondral bone density as a possible pathogenetic factor contributing to articular cartilage degeneration in osteoarthritis (OA) has been receiving increasing attention. The Kellgren-Lawrence system for grading joint OA emphasised subchondral bone sclerosis and osteocyte formation more than joint space narrowing, a view, however, that has recently been questioned. The importance of subchondral bone density in contributing to cartilage degeneration has been emphasised for years in the work of Radin and colleagues. Observations that dense subchondral bone may indeed precede cartilage degeneration and thereby be an initiating factor, or that bone density may be involved in the progression of OA, have been advanced by studies on animal models. However, little is known about the basis for subchondral bone density in OA, or its consequences.

### Table 1 Characteristics of patients in this study

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Severe OA</td>
<td></td>
<td></td>
<td>Bilateral knee OA, THR 7/94; TKR</td>
</tr>
<tr>
<td>1</td>
<td>73</td>
<td>F</td>
<td>Bilateral knee OA</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>F</td>
<td>Bilateral knee OA</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>Bilateral TKR</td>
</tr>
<tr>
<td>4</td>
<td>86</td>
<td>F</td>
<td>Bilateral TKR</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>F</td>
<td>Bilateral left TKR 1/91; TKR</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>M</td>
<td>Bilateral left TKR 1/91; TKR</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>Bilateral left TKR 1/91; TKR</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>F</td>
<td>Bilateral TKR</td>
</tr>
</tbody>
</table>

**Group B**

<table>
<thead>
<tr>
<th>Traumatic knee injury</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>M</td>
<td>Patella subluxation</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>M</td>
<td>Meniscal tear</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>M</td>
<td>Osteochondral defect</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>F</td>
<td>Patello-femoral irregularity</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>M</td>
<td>Meniscal tear</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>M</td>
<td>Avulsion fracture tibial plateau</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>F</td>
<td>Meniscal tear</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>F</td>
<td>Meniscal tear</td>
</tr>
</tbody>
</table>

OA = osteoarthritis; THR = total hip replacement; TKR = total knee replacement during course of this study.

### Table 2 Descriptive statistics for patients studied

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe OA</th>
<th>Traumatic injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>76.1 (1.8)</td>
<td>32.5 (1.1)</td>
</tr>
<tr>
<td>Plasma CSF-1 (ng/ml)</td>
<td>3.12 (1.30)</td>
<td>2.96 (0.68)</td>
</tr>
<tr>
<td>Synovial fluid CSF-1 (ng/ml)</td>
<td>3.03 (0.91)</td>
<td>2.60 (1.39)</td>
</tr>
</tbody>
</table>

*p Value based on standardised scores.
well as age, were tested for significance using t tests for independent samples. All tests of significance were two tailed with an α level of 0.05. No power analysis was performed.

In this study there were nine patients in group A with knee complaints extending over many years and radiographically severe OA. Subsequently, five of these patients had a total knee replacement of the joint that was aspirated during the course of the study. None of the patients with knee injury in group B had complaints of more than six months’ duration and none had radiographic evidence of OA. Table 2 shows that age was significantly different (p<0.001) between the two groups, as would be anticipated based on the late life clinical manifestations of OA.11

The studies reported here seem to be the first to use a RIA specific for CSF-1, and to compare plasma and synovial fluid samples simultaneously. As the half life of circulating CSF-1 concentration (rather than local concentration) would be observed in OA. This opinion is supported by the lack of significant difference in the plasma CSF-1 concentrations of patients with severe OA and the control group (fig 2). In a pilot study, the number of subjects with OA was small, although earlier studies on synovial fluids in OA patients were also done on only two, eight,12 and 13 subjects, respectively. No statistically significant differences in the synovial fluid CSF-1 concentrations were found between the two groups in this study (table 2). Thus, these results indicate that patients with severe OA do not have a decreased synovial fluid CSF-1 concentration.

It is possible to conceive of OA initially as a “limited form of osteopetrosis” restricted to the subchondral plate, with ensuing cartilage degeneration.13 The findings that the concentrations of CSF-1 in synovial fluids of subjects with severe OA were not appreciably lower than those from subjects with acute knee injury indicates that OA may not be related to low synovial fluid CSF-1 concentrations. These studies, however, do not eliminate the possibility that the reduced synthesis or recruitment of CSF-1 at the local subchondral site is important for the increase in bone density of the joint in OA.

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Neurogenic diabetes insipidus in patients with systemic lupus erythematous

Neurogenic diabetes insipidus (NDI) approximately affects one of 25 000 people. The idiopathic type represents about 30% of all NDI cases (one of 75 000). The coexistence of primary NDI and systemic lupus erythematous (SLE) is an exceptional fact that has not been previously described. We report two cases belonging to a series of 350 SLE patients (ARA criteria,1988).4

CASE 1
A 48 year old woman who had suffered from pulmonary tuberculosis in 1976. Ten years later she was examined because of a suspected myopericarditis. She also had a pulmonary tuberculosis in 1976. Ten years later she was examined because of a suspected myopericarditis. She also had a

CASE 2
A 69 year old man who had suffered deep venous thrombosis (DVT) on his left leg in 1983, and another episode a year later. Four years later, he was admitted to hospital because of a longlasting fever. He presented with polyarthritis, leucopenia, thrombo-

Figure 1 Thirst test. Osmolality (urine) = administration of DDAVP.

3 Patient 1
2 Patient 2

Time (min)

Urine osmolality (mOsm/kg)

0 60 120 180 240

300

250

200

150

100

50

0

0
Neuralgic amyotrophy and polyarthritis caused by parvovirus B19 infection

Infection with human parvovirus B19 causes a wide range of clinical manifestations, which may vary according to the immune status of the patient. They include erythema infectiosum (fifth disease), symmetrical polyarthritis, vasculitis, transient aplastic crisis in patients with low red cell production, and chronic infection in immunocompromised patients. We report a patient treated with immunosuppressive drugs in whom bilateral brachial plexitis and polyarthritis were associated with parvovirus B19 acute infection.

A 33 year old woman presented with severe pain in the arms. She had a two year history of severe Crohn's disease and was treated with prednisone (10 mg/day). The patient developed fever (38°C), then a maculopapular rash, which resolved within 24 hours and a lancinating pain in both arms that persisted. Physical examination disclosed bilateral polyarthritis involving the fingers and a characteristic of the host.

We conclude that a diagnosis of parvovirus B19 infection should be considered in patients presenting with brachial plexus neuralgic amyotrophy, particularly those who are young women with a history of arthralgia and rash. In addition, the association of a neuralgic amyotrophy with a symmetrical polyarthritis, which appears not to have been reported previously, might be linked to the specific characteristics of the host.
Stressful life events and rheumatoid arthritis

Stressful life events have long been supposed to act as a precipitating factor for rheumatoid arthritis (RA). In 1860 Fuller expressed the opinion that ‘...when the rheumatic poison is present in the system, any disturbing circumstance, even of temporary duration, such as overfatigue, anxiety, grief or anger, by rendering the system more susceptible of its influence, may prove the accidental or exciting cause of the disease...’. In modern terms, the rheumatic poison may reflect the underlying immunological process preceding RA. Jackson et al. highlighted the stressful life events to support his contention that low androgen values are a contributory cause of RA.

We have studied serum testosterone values in healthy subjects who later developed RA. The preliminary results were not in line with the hypothesis that low values of testosterone play an aetiological part in RA. We would like to propose another pathway by which stressful life events could precipitate RA. As recently reviewed, there is evidence for cigarette smoking as a risk factor for RA.

It has been observed that depressed mood significantly predicts lung cancer but not any other form of cancer. A possible explanation is that depressive persons tend to smoke more often and to inhale the smoke more intensively than others and, thus, to have an increased risk of lung cancer. This model can probably be generalised from depression to other psychological disorders and from lung cancer to other smoking related diseases.

Thus, the experience of stress may exert its influence on RA through smoking.

Author’s reply

Dr Aho does not respond to the point I was trying to make in my letter. I was drawing attention to what may be a rare phenomenon but which nevertheless exists—that is, a stressful life event causing a remission (not an exacerbation) in rheumatoid arthritis (RA). The word “stressful” needs careful qualification. Of the two cases I cited, one was an 86 year old lady (my aunt) who was at the scene of, if not subject to, a strike of lightning. This was a terrifying experience for her. The other case was of a lady whose husband and son died in close succession. Such experiences are unusual in their formality and suddenness, and contrast with the more routine misfortunes that comprise the adverse circumstances more frequently recorded in psychological life events questionnaires. The point is important because one may suspect that the immediate physiological response to such acute shocks is quite different to the physiological response to more minor adverse events. The latter are associated with depression; and depression is associated with low steroid hormone values in both sexes, and, ex hypothesis, to exacerbation of RA.

However, acute shocks of the sort described may be expected to have different effects on the androgen status of men and women. In men, pituitary regulation lowers gonadal testosterone secretion: whereas in women, adrenal androgens would be expected to be raised in response to acute shocks.

Thus, if I am correct, adverse life events will cause amelioration of RA if, and only if (a) the events are sudden and severe, and (b) the patient is female.

If either of these is not fulfilled, then I would expect adverse life events to be associated with exacerbation of RA. The point is testable and should be tested.

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Ankylosing spondylitis: evidence for a non-HLA-B*27 protective effect

The question whether or not there is evidence for a non-HLA-B*27 protective effect is still open to debate.1"1 The likelihood of finding cases of ankylosing spondylitis (AS) depends on assumptions on the risk for RA-B27 positive persons to develop the disease. Prevalence figures as low as 1.3% and 1.4% have been reported for population based studies in Zottemeer (the Netherlands) and Busselton (Australia). Those figures are based on populations where most people underwent pelvic radiography.1"1 Estimates based on completion of questionnaires and random sampling provide higher figures. For example, in northern Norway AS may develop in 6.7% of HLA-B27 positive people.2 Studies that have reported that as many as 20% of HLA-B27 positive subjects develop AS are indeed striking, because as much as 6% of HLA-B27 negative controls were found to have radiographic sacroiliitis. This raises the possibility of systematic over reading of the films because of low specificity of the observers. Later, the same group reported a much lower risk (1.9%) studying HLA-B27 positive relatives of healthy blood donors.3 Recently, the prevalence of all spondyloarthropathies, including AS, was studied among HLA-B27 positive and negative blood donors in Berlin.4 AS occurred in 6.4% of HLA-B27 positive persons; of the nineteen patients there were seven men and twelve women. The latter is compatible with the usually reported sex ratio (male: female) of about 3:1. Therefore, although there are clearly proponents and opponents for each extreme, it is fair to say that the true risk for HLA-B27 positive people in the general population lies somewhere between 1% and 7%, but that there might be regional or geographical variations in risk. Probably, non-HLA-B27 genetic and environmental factors might modify the risk of developing AS for those who possess HLA-B27.

Correspondence to: Professor van der Linden.


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Authors’ reply

As mentioned in the letter by van der Linden and van der Heijde, Jurgen Braun’s excellent recent paper describing a survey of blood donors by questionnaire, clinical, and magnetic resonance imaging examinations revealed a prevalence of ankylosing
spondylitis in B27 positive blood donors (6.4%)\(^1\) very similar to that reported by Gran et al (6.7%).\(^2\) It is probable that some of the differences in reported prevalence of ankylosing spondylitis by the various studies are because of methodological differences. Nonetheless, the rarity of spondyloarthritides in West African natives seems to be real and not explained either by the frequency of B27, or the B27 subtypes present. While cases of ankylosing spondylitis have been reported in B*2703 positive persons,\(^3,4\) no case has yet been reported from the Gambia despite a B27 prevalence in some ethnic groups as high as 7.8%.\(^5\) Why not?

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Orderly arrayed deposit of urate crystals in gout suggest epitaxial formation

ELISEO PASCUAL and SALVADOR ORDÓÑEZ

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