syndrome who were taking colchicine.¹⁰ They claimed that oligospermia ($<20 \times 10^6/\text{ml}$) 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 two 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 testes has been seldom reported. In an animal model, testicular amyloidosis was induced in hamsters by infecting the animals with *Leishmania donovani*.¹¹ Testicular biopsies disclosed total azoospermia in the final week of the pathological process. This study and other sporadic cases¹² 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 and azoospermia in patients with Behcet's disease¹⁰ 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.

ELDAD BEN-CHETRIT
Department of Medicine

REBECCA BACKENROTH
Nephrology and Hypertension Service

RONIT HAIMOV-KOCHMAN
Department of Gynaecology

GALINA PIZOV
Department of Pathology
Hadassah University Hospital, Jerusalem, Israel

Correspondence to: Dr E Ben-Chetrit, Department of Medicine, Hadassah University Hospital, Jerusalem, Israel, POB: 12000.

1 Eliakim M, Levy M, Ehrenfeld M. *Recurrent polyserositis (familial Mediterranean Fever)*. Amsterdam: Elsevier/North Holland Biomedical Press, 1981.

2 Goldfinger S E. Colchicine for familial Mediterranean fever. [Letter]. *N Engl J Med* 1972;287:1302.

3 Ben-Chetrit E, Levy M. Colchicine treatment in familial Mediterranean fever (FMF): reappraisal after 15 years. *Semin Arthritis Rheum* 1991;20:241-6.

4 Liang J C. Response of murine spermatocytes to the metaphase arresting effect of several mitotic arrestors. *Experientia* 1985;41:1586-8.

5 Handel M A. Effects of colchicine on spermatogenesis in the mouse. *J Embryol Exp Morphol* 1979;51:73-5.

6 Merlin H E. Azoospermia caused by colchicine. A case report. *Fertil Steril* 1972;23:180-1.

7 Levy M, Yaffe C. Testicular function in patients with familial Mediterranean fever on long term colchicine treatment. *Fertil Steril* 1978;29:667-8.

8 Bremner W J, Paulson C A. Colchicine and testicular function in men. *N Engl J Med* 1976;294:1384-5.

9 Ehrenfeld M, Levy M, Margalioth E J. The effect of long term colchicine therapy on male fertility in patients with familial Mediterranean fever. *Andrologia* 1986;18:420-6.

10 Sarica K, Suzer O, Gurler A, Bataci S, Ozdiler E, Dincel C. Urological involvement of behcet patients and the effect of colchicine on fertility. *Eur Urol* 1995;27:39-42.

11 Gonzalez J L, Gallego E, Castano M, Rueda A. Testicular amyloidosis in hamsters experimentally infected with *Leishmania donovani*. *Br J Exp Pathol* 1983;64:518-23.

12 Handelsman D J, Yue D K, Turtle J R. Hypogonadism and massive testicular infiltration due to amyloidosis. *J Urol* 1983;129:610-11.

Colony stimulating factor-1 in synovial fluids from osteoarthritic and injured knees

Subchondral bone density as a possible pathogenetic factor contributing to articular cartilage degeneration in osteoarthritis (OA) has been receiving increasing attention.¹ The Kellgren-Lawrence system for grading joint OA emphasised subchondral bone sclerosis and osteophyte formation more than joint space narrowing, a view, however, that has recently been questioned.² The importance of subchondral bone density in contributing to cartilage degeneration has been emphasised for years in the work of Radin and colleagues.³ 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.^{4,5} However, little is known about the basis for sub-

chondral bone density in OA, or its consequences.

Colony stimulating factor-1 (CSF-1) is the primary regulator of mononuclear phagocyte production and has important effects on bone.^{6,7} Among other cell types, CSF-1 is secreted by osteoblasts, and is required for the differentiation of osteoclast progenitors to osteoclasts.⁸ Our interest in CSF-1 in relation to bone density in OA arose from studies on a mouse model of osteopetrosis (*op/op*)⁸ where an inactivating mutation in the gene encoding CSF-1 impairs osteoclast development; the bone formed cannot be resorbed. We considered that increased bone density in the joint in OA is most probably caused by low CSF-1 concentrations in the subchondral bone; however, it is also possible that low concentrations of synovial fluid CSF-1 could contribute to the increased bone density. We used a radioimmunoassay to measure CSF-1 concentrations in synovial fluid and plasma from subjects with severe knee OA, and compared the results with similar studies on a "control" group with acute traumatic or athletic injury to the knee.

Table 1 summarises aspects of the clinical condition of patients in group A with the diagnosis of OA of the knee,⁹ and those patients in group B who sustained injuries of the knee and underwent arthroscopy. Circulating CSF-1 was measured in plasma and synovial fluid by a modified¹⁰ radioimmunoassay (RIA) that specifically detects biologically active CSF-1 in the range of 0.02-3.60 ng/tube. Synovial fluid samples were incubated with one tenth volume of bovine testicular hyaluronidase (Sigma) (1500 units per ml in RIA buffer) for 10 minutes at 37°C before RIA. Normal rabbit serum (20 µl) was added to 20-100 µl samples of the hyaluronidase treated synovial fluid to control for protein concentration in the RIA before assay. Differences between the groups with regard to standardised CSF-1 concentrations in blood and synovial fluid, as

Table 1 Characteristics of patients in this study

Patient	Age	Sex	Diagnosis
Group A			
Severe OA			
1	73	F	Bilateral knee OA, THR 7/94; TKR
2	80	F	Bilateral knee OA
3	63	M	Bilateral knee OA
4	71	F	Bilateral TKR
5	86	F	Bilateral TKR
6	75	F	Bilateral left TKR 1/91; TKR
7	82	F	Bilateral left TKR 1/91; TKR
8	69	M	Bilateral left TKR 1/91; TKR
9	82	F	Bilateral TKR
Group B			
Traumatic knee injury			
1	46	M	Patella subluxation
2	18	M	Meniscal tear
3	30	M	Osteochondral defect
4	45	F	Patello-femoral irregularity
5	43	M	Meniscal tear
6	16	M	Avulsion fracture tibial plateau
7	35	F	Meniscal tear
8	25	F	Meniscal tear

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

Table 2 Descriptive statistics for patients studied

Characteristic	Severe OA		Traumatic injury		p Value*
	No	Mean (SD)	No	Mean (SD)	
Age (y)	9	76.1 (7.8)	8	32.5 (11.8)	<0.001
Plasma CSF-1 (ng/ml)	8	3.12 (1.30)	8	2.96 (0.68)	>0.20
Synovial fluid CSF-1 (ng/ml)	9	3.03 (0.91)	7	2.60 (1.39)	>0.20

*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 eight 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 is only about 10 minutes,¹² and most of the CSF-1 target cells are not in the joint,⁷ it seemed unlikely that a significant difference in the circulating CSF-1 concentration (rather than a difference in 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 (table 2). In this 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,¹³ eight,¹⁴ and 13¹⁵ 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. Our 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 increased bone density of the joint in OA.

This work was supported in part by NIH grants CA 32551 (to ERS) and AG 14442 (to DH).

DAVID HAMERMAN
Department of Medicine

KATHERINE FREEMAN
Department of Epidemiology and Social
Medicine

E RICHARD STANLEY
Department of Developmental and Molecular
Biology, Albert Einstein College of Medicine,
Montefiore Medical Center, 111 East 210th
Street, Bronx, NY, USA

Correspondence to: Professor Hamerman.

- Dequeker J, Mokassa L, Aerssens J. Bone density and osteoarthritis. *J Rheumatol* 1995; (suppl 43) 22:98-100.
- Spector TD, Cooper C. Radiographic assessment of osteoarthritis in population studies: Whither Kellgren and Lawrence? *Osteoarthritis Cartilage* 1993;1:203-6.
- Radin EL, Burr DB, Caterson B, Fyhrie D, Brown TD, Boyd RD. Mechanical determinants of osteoarthritis. *Semin Arthritis Rheum* 1991; (suppl 2) 21:12-21.

- Carlson CS, Loeser RF, Purser CB, Gardin JF, Jerome CP. Osteoarthritis in cynomolgus macaques III: Effects of age, gender, and subchondral bone thickness on the severity of disease. *J Bone Miner Res* 1996;11:1209-17.
- Brandt KD, Myers SL, Burr D, Albrecht M. Osteoarthritic changes in canine articular cartilage, subchondral bone, and synovium fifty-four months after transection of the anterior cruciate ligament. *Arthritis Rheum* 1991; 34:1560-70.
- Pollard JW, Stanley ER. Pleiotropic roles for CSF-1 in development defined by the mouse mutation osteopetrotic (op). *Adv Develop Biochem* 1996;4:153-93.
- Cecchini MG, Dominguez MG, Mocci S, Wetterwald A, Felix R, Fleisch H, et al. Role of colony stimulating factor-1 in the establishment and regulation of tissue macrophages during postnatal development of the mouse. *Development* 1994;120:1357-72.
- Hamerman D, Stanley ER. Implications of increased bone density in osteoarthritis. *J Bone Miner Res* 1996;11:1205-8.
- Altman RD. Classification of disease: osteoarthritis. *Semin Arthritis Rheum* 1991; 20(suppl 2):40-7.
- Janowska-Wieczorek A, Belch AR, Jacobs A, Bowen D, Padua RA, Paietta E, et al. Increased circulating colony-stimulating factor-1 in patients with preleukemia, leukemia, and lymphoid malignancies. *Blood* 1991;77:1796-803.
- Hamerman D. Clinical implications of osteoarthritis and ageing. *Ann Rheum Dis* 1995;54: 82-5.
- Bartocci A, Mastrogiannis DS, Migliorati G, Stockert RJ, Wolkoff AW, Stanley ER. Macrophages specifically regulate the concentration of their own growth factor in the circulation. *Proc Natl Acad Sci* 1987;84:6179-83.
- Williamson DJ, Begley CG, Vadas MA, Metcalf D. The detection and initial characterization of colony-stimulating factors in synovial fluid. *Clin Exp Immunol* 1988;72:67-73.
- Bell AL, Magill MK, McKane WR, Kirk F, Irvine AE. Measurement of colony-stimulating factors in synovial fluid: potential clinical value. *Rheumatol Int* 1995;14:177-82.
- Smith JB, Bocchieri MH, Smith JB, Jr, Sherbin-Allen L, Abruzzo JL. Colony stimulating factor occurs in both inflammatory and noninflammatory synovial fluids. *Rheumatol Int* 1990;10: 131-4.

Neurogenic diabetes insipidus in patients with systemic lupus erythematosus

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).¹ The coexistence of primary NDI and systemic lupus erythematosus (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).²

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 photosensitive malar erythema, oral ulcers, Raynaud's phenomenon, vasculitic lesions on fingertips, Sjögren's syndrome, and polyarthritis during one year. Blood count, complement, protein electrophoresis, rheumatoid factor, syphilis serological test, and renal function were normal. Antinuclear antibodies (ANA) were positive (1/160). Anticardiolipin antibodies (ACA) were negative. Lupus anticoagulant test (LA) only showed once a prolonged Russell test at the limit of significance (34.8 s). The patient had polyuria-polydipsia for an undetermined time. NDI was detected by using the thirst test (fig 1). Remaining pituitary functions integrity was demon-

strated by basal and dynamic hormonal quantifications (table 1). Antihypophysitis antibodies (monkey hypophysis substrate, Sanofi Pasteur, Marnes-La-Coquette) were negative. Sellar and parasellar areas (computed tomography and magnetic imaging) were normal. The polyuria-polydipsia syndrome was successfully controlled with substitutive hormonal treatment (ADH).

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, thrombopenia, and ANA positive test (1/1280). Glucocorticoids were administered and fever disappeared. Three years later he suffered a new DVT on his right leg and, one year later, a pulmonary thromboembolism. Raised ACA (45 GPL, 20 MPL) were detected and coagulation and LA confirming tests were normal. He also suffered a psychotic episode requiring hospitalisation in 1991. Four years later, endocrinological tests were performed because of recent development of polyuria and impotency. The thirst test showed the diabetes insipidus typical pattern (fig 1). Testosterone, LH, FSH, and GH basal concentrations were below normal values. The GH response to insulin induced hypoglycaemia and the gonadotrophine response to TRH and LHRH were low. The hormonal study excluded hypothalamus-hypophysis-adrenal axis and hypothalamus-hypophysis-thyroid axis alterations (table 1). Antihypophysitis antibodies were negative. Computed tomography and magnetic resonance imaging of sellar and parasellar areas were normal. The patient did well with antidiuretic and substitutive hormonal treatment (ADH and testosterone).

The frequency of NDI in our patients with SLE (0.57%), though relatively low, cannot be explained only at random as the estimated NDI frequency in the general population is 0.0013%. The theoretic probability to observe two cases in a random population of 350 cases would be 0.00108% (Poisson distribution), which is much less than the observed frequency in the patient series ($p < 0.0000001$). No mention was found that related NDI with SLE patients in the data base MEDLINE (1992-1997) and in specialised publications related to SLE.^{3,4} Some isolated NDI cases associated with vasculitis have been reported (Wegener's granulomatosis⁵ or temporal arteritis⁶), so it is possible that the patients underlying lesion described in this paper could be because of a vascular impairment of the

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