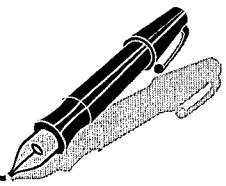
Correspondence



INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

***Contact.* The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M6J 3G7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

Patterns of Drug Use in Rheumatoid Arthritis

To the Editor:

We read with interest the publication of Paulus, *et al*[1] saying that there was no effect of low dose prednisolone treatment on radiographic progression in patients with rheumatoid arthritis (RA) when compared with non-steroidal antiinflammatory drug (NSAID) treatment without prednisolone. This conclusion is in contrast to the observations of other groups, cited in that article, and especially to the study of Kirwan[2] and also to a randomized prospective study, preliminary data of which are so far only published in abstract and extended abstract form[3-5]. In our view there are 2 major methodological problems in the study of Paulus[1], which may explain the divergent results. First, the prednisolone and the non-prednisolone group are not comparable: in spite of prednisolone treatment for at least 6 months these patients had significantly more swollen joints at baseline ($p < 0.001$), higher C-reactive protein levels ($p < 0.001$), and a higher rheumatoid factor titer, all indicating a worse prognosis. If we assume a continuing effect of prednisolone on disease activity, the differences between groups would have been even greater without prednisolone treatment. In addition, the study was not randomized to compare NSAID with and without prednisone. Only 824 of 1433 patients included in the study had radiography.

The second important aspect is that the effect of prednisolone on clinical and laboratory data as well as radiographic progression may be temporary: in the study by Kirwan[2] prednisolone treatment was initiated at baseline: after 3 months of treatment there was no difference between the prednisolone and the non-prednisolone group [both treated with disease modifying antirheumatic drugs (DMARD)] regarding clinical and laboratory data (while a difference may be assumed during the early phase of treatment). In our own study, DMARD treatment with methotrexate or parenteral gold was initiated in 192 patients with early RA (symptoms for < 1 year) and in addition 5 mg prednisolone/day or placebo were added in a randomized double blind fashion over 2 years: in this study there was also no significant difference at baseline and at 6 months between the prednisolone or placebo treated patients regarding clinical or laboratory variables of disease activity (in between data were not recorded). However, the radiographic progression rate was 5 times higher in the non-prednisolone group than in the prednisolone group during the first 6 months. This difference became smaller during the second 6 months, with decreasing progression in the non-prednisolone group (beginning DMARD effect); it was nearly abolished during the second year of treatment[3-5]. These findings may indicate that the effect of prednisolone treatment is most prominent during the first 6 months and can hardly be captured in patients already treated with prednisolone for 6 months or longer.

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To the Editor:

What is the most difficult of all? It is what appears most simple: To see with your eyes what lies in front of you. — Goethe

Berard, *et al* illustrate with somber clarity the legacy of nonsteroidal antirheumatic drug (NSAID) therapy in rheumatoid arthritis over the last century[1]. Only 68% of 10,262 patients with RA filled one prescription over one year of study. NSAID were used in 57%, corticosteroids in 23%, and disease modifying antirheumatic drugs (DMARD) in 13%[1]. Yet these patients had access and choice of medications. We can add 35 to 40 million uninsured to this group.

In the managed care sector the numbers are worse. One study by Noe, *et al*[2] examined therapy of RA in 5354 patients. Of these, 87% received monotherapy with NSAID, 8% received monotherapy with prednisone, and only 3% a DMARD. The other patients with RA cared for in the fee-for-service and tertiary care sectors are an insignificant minority; all in all, a national tragedy.

Nonetheless, an NSAID study by Paulus, *et al* claims little delay in radiologic progression in cases of RA taking etodolac and prednisone[3]. Hardly surprising, prednisone is 43% less potent than triamcinolone and less effective combined with a joint medication. In contrast, of the first 100 patients with RA taking low dose triamcinolone-gold that presented in 1991 we showed 75% delay in radiologic progression in a subset intervened within one year of onset[4]. (Conventional therapy allows 75% radiologic progression in the first 2 years of illness.) To understand what lies behind the endless support for NSAID therapy in RA one must examine closely: (1) how the true gravity of the illness is perceived, and (2) the meaning of the word "monotherapy" in the tertiary care sector.

In clinical and pathophysiologic terms, RA lies firmly in the middle of lymphoproliferative disorders. Like most of these, it is a chronic, genetically predisposed, systemic, incurable disease. Unlike these, it targets the joints, but only as a part of a generalized multiorgan process. Its onset and exacerbations appear to be a reactive response to diverse antigenic stimuli

like new-onset infection or stress-replication of endogenous viruses, bacteria or/and major mycoses, some of which are easy suspects (herpesviruses, cytomegalovirus, Epstein-Barr virus, hepatitis B, C, *Chlamydia,* and gram negative flora). Spontaneous remissions are rare and exacerbations frequent; the illness demands chronic suppression.

In spite of this evidence in favor of clinical malignancy, conventional therapy proponents remain focused on the response of the joints to therapy instead of remission induction of the disease. Most clinical trials in RA make little reference to remission, they report response to the American College of Rheumatology 20% or 50% improvement criteria. Since these measure joint inflammation mostly, they are meaningless for an incurable illness with this morbidity and mortality.

Monotherapy is defined in *Dorland's*[5] as "treatment of a condition by means of a single drug." But monotherapy is consistently misused in most rheumatology clinical trials. The use of any DMARD with a glucocorticoid is not monotherapy, it is combination therapy. Yet for decades most drug trials in RA have reported tests of an NSAID or a DMARD as monotherapy when these were enhanced by an adjunct glucocorticoid. In light of this, it is a giant leap of faith for physicians to embrace the steroid-sparing idea.

We need to go beyond treatment of the joints in RA. Any therapy that yields major improvement in clinical joint disease without an index of remission of at least 50% in early cases is meaningless to the longterm outcome of RA. In this context, we can very well accept the risk-benefit ratio of low dose glucocorticoid enhancement in combination therapy, as with any other DMARD. Glucocorticoids are essential modifiers in most remission induction protocols for lymphoproliferative disorders; they are neither a silent partner nor a joint medication. The only way to improve RA significantly is to blanket all active patients using a step-up approach with remission-inducing, glucocorticoid enhanced combination therapy.

To this day, trials of methotrexate, NSAID, and biologics, alone or combined with prednisone, do not show significant remission, because glucocorticoid enhancement does not work as well if we miss the therapeutic window of remission. We have lost millions of patients with RA since 1991. What will it take for Academic Rheumatology to get serious?

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Dr. Paulus, *et al* reply

To the Editor:

We appreciate the thoughtful comments of Drs. Rau, Wassenberg and Zeidler and of Dr. Roger on our article[1]. They illustrate the difficulty of generalizing from one published report to another, or to unreported clinical practice. This difficulty is particularly great when attempting to compare studies done with quite different study designs. The pharmaceutical management of the patients in the studies cited by Rau differs from that of our patients in that all of Rau's[2] patients started methotrexate or gold simultaneous with the initiation of prednisolone 5 mg daily or placebo, and almost all of Kirwan's[3] patients added permitted ad libitum disease modifying antirheumatic drugs (DMARD) during the double blind randomized trial of placebo or prednisolone 7.5 mg daily. Because our patients were not allowed any DMARD for 6 months before and during the trial, they had to withdraw from the nonsteroidal antiinflammatory drug (NSAID) trial before a DMARD could be begun. In addition, clinical judgment played no part in the assignment to prednisolone or placebo in these randomized clinical trials[2,3], whereas in our study prednisone had been initiated months or years before study entry in 23% of the patients based on the clinical judgment of their physicians and without consideration of their possible later inclusion in the NSAID trial. In this respect our patients resemble those being managed with NSAID in clinical practice, where some patients are also prescribed concomitant cortocosteroid therapy. Since low dose prednisolone appeared to arrest the progression of joint damage in Kirwan's patients, we hypothesized that it also would have arrested progression in our patients who were taking prednisone. Although one can only speculate about what the progression rate of our prednisone treated patients would have been if they had not taken prednisone, it is quite clear that structural damage of their joints progressed during an average of 23 months of careful observation during prednisone therapy. This agrees with longterm clinical experience, where a history of prolonged corticosteroid treatment is not unusual in patients who are undergoing total joint replacement surgery.

The studies by Kirwan[3] and Rau[2], and also by Boers, *et al*[4] (combination of methotrexate, sulfasalazine, and prednisolone vs sulfasalazine) in patients with early rheumatoid arthritis (RA) collectively could be interpreted to indicate that the *combination* of *de novo* prednisolone and a DMARD is additive or synergistic, and accelerates or enhances the anticipated DMARD induced retardation of radiographic damage, while our study suggests that the continuation of low dose prednisone alone largely lacks this beneficial effect. The cause of a postulated initial DMARD/corticosteroid synergy is not obvious, but, if real, it may help to justify the common clinical practice of adding low dose corticosteroid as temporary "bridge" therapy when a DMARD is started.

van Everdingen, *et al*[5] reported that 41 patients treated with prednisone 10 mg daily had less radiographic progression than 40 placebo patients during a 2 year study with only NSAID background therapy for the first 6 months; after 6 months sulfasalazine was added by 35% of patients. Higher doses of prednisolone were started and then tapered during the first 6 months of the study by Boers, *et al*[4], and in the classic early trials sponsored by the Empire Rheumatism Council and the Nuffield Foundation, which compared prednisolone 20 mg daily with aspirin, but tapered to an average dose of 10 mg after 2 years[6,7].

The suggestion by Rau, *et al* that the radiographic benefit of low dose corticosteroids may wane with time is consistent with the clinical observation that patients with RA often note marked initial improvement of symptoms when 5 mg of prednisone is started, but lose this benefit after 6 months or so when the dose must be increased in order to regain the initial benefit. It is well known that an adrenal-pituitary feedback mechanism reduces endogenous corticosteroid production and is slowly responsive in the recovery phase after corticosteroid treatment is withdrawn following prolonged administration, but it is not known how long it takes this control mechanism to shut down endogenous steroid production when initial corticoid is introduced in a low (physiologic) dose. It is conceivable that starting such a low dose has an initial pharmacologic effect when added to persisting endogenous cortocosteroid production, but with time, feedback inhibition gradually shuts down endogenous production and the administered low dose becomes merely a physiologic replacement for the normal production, leading to a gradual increase in symptoms and loss of radiographic benefit.

Either or both of these lines of reasoning — (1) corticosteroid enhancement of DMARD benefit; (2) initial benefit from *de novo* low dose steroids, waning with time — could rationalize the discordant findings in the various studies, and could be consistent with Roger's suggestion that low dose glucocorticoid enhancement of DMARD therapy "does not work if we miss the therapeutic window of remission." Both lines of reasoning suggest that

in RA the duration of low dose corticosteroids should be limited, as the benefit wanes but the risks do not.

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Drs. Berard, *et al* reply:

To the Editor:

We agree with Dr. Roger that prescribing data often reveal a rather shocking picture of current practice. The data we presented in our article show that patients diagnosed with rheumatoid arthritis, not necessarily seen by a rheumatologist, are often treated with NSAID alone. While this treatment may suffice for some patients, a portion who might not necessarily have RA, it is almost surely not the optimal treatment for most patients with RA. As well, other data suggest that management of common comorbid conditions in RA, osteoporosis, and cardiovascular disease leaves something to be desired.

While data from randomized controlled clinical trials must form the evidence basis for optimal treatment, pharmacoepidemiologic data such as ours provide insights into the "state-of-prescribing." These data should inform quality improvement efforts mounted locally by health systems and globally by professional systems and public health organizations.

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New Thoughts on Old Bones

To the Editor:

I echo the sentiments of Dr. Eric Gershwin[1] but several require clarification. While DNA analysis brings exciting new opportunities to the understanding of disease origins, it is critical not to forget the contributions of paleoepidemiology[2].

The second clarification is actually intrinsic to the scientific approach to paleopathology. When Alan Walker and Mike Zimmerman[3] reported with Richard Leakey observations on KNM 1808 (a 1.6 million-year-old *Homo erectus* skeleton), they attributed the long bone periosteal reaction to hypervitaminosis A. However, there was no entheseal reaction, a requirement for diagnosis of hypervitaminosis A[4–7]. Absence of entheseal reaction (ossification at sites of tendon or ligament insertion in KNM-ER 1808) made that diagnosis untenable[2,4–7]. Walker and Zimmerman subsequently indicated (personal communication) that they did not have comparative cases (of individuals clinically documented as afflicted with hypervitaminosis A) at the time. When presented with the subsequent analysis[8], they both indicated that they no longer subscribed to their original diagnosis.

As the thick periosteal reaction in KNM-1808 was indistinguishable from that seen in yaws[9], that alternative diagnosis[8] appears substantiated. In sum, application of data based criteria[2,9,10] for identification of treponemal disease allowed clarification.

The future of scientific paleopathology is data based paleoepidemiology, predicated upon clinically documented cases and population analysis. The field has transcended hypothetical concepts of disease (authoritative pronouncements) to depend upon data. DNA analysis will contribute to that data base, as it further evidences the accuracy of data based skeletal analysis in paleopathology. However, the DNA data cannot be evaluated in isolation. As many human remains are being returned to Native populations, it is critical that archiving not simply be DNA based — even when Native populations will still allow destructive analysis. The skeletons must also be examined in a substantiated, data based manner — to assure that other pathology related data are not lost. After all, many disorders (e.g., spondyloarthropathy and rheumatoid arthritis) do not have a pathognomonic DNA marker. DNA will contribute to our understanding, but what a loss if it is the only information retained/available.

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Dr. Gershwin replies:

To the Editor

Paleobiology, paleoepidemiology, paleopathology, paleodemography — however we might hybridize disciplines, we are keenly interested in where we came from and in the evolution of the route. In 1982, a long bone analysis was performed on a woman who died nearly 1.6 million years ago; the data suggested that she suffered from vitamin A toxicity[1]. Dr. Rothschild is correct in pointing out flaws in this interpretation. However, the jury remains out on this specific conclusion, although the data continue to support the intriguing hypothesis that she succumbed following consumption of either a lion or leopard liver. Either way, emerging technologies have become considerably more precise and include DNA analysis, which has recently confirmed, using mitochondrial DNA, the origin of humans in Africa[2]. Even more important, it has led to the use of mitochondrial genome variation to define the origin of modern humans[3]. Similarly, the use of carbon 14 for dating specimen age has led, over the past decade, to the skeletal analysis of stable isotopes of carbon, oxygen, and strontium from bones and subsequently to the concept of stable isotope variation. Essentially, to use carbon as an example, this permits dissection of the origin of specific carbon isotopes found in skeletal remains based on the variation of different carbon isotopes in plants versus animals; i.e., the ratio of carbon 12 and carbon 13 are different in plants than found in carbon dioxide[4]. The use of stable isotope variation technology permits a focused analysis of collagen and defining whether humans (as an example) consumed marine versus terrestrial based diets. It can also be used to study the migration of populations. We do not yet have a pathognomonic marker for rheumatoid arthritis or ankylosing spondylitis, but the identification of polymorphisms may well lead in that direction. Indeed, the use of the WAVE, a high throughput analysis of polymerase chain reaction products, allows the study of single base pair changes in a considerably more time effective fashion[5]. Finally, we note that there is interest in the fecal material of ancestral humans as it allows definition of evolutionary changes in bacterial flora[6,7]. Our gut flora are now considerably more inflammatory and pro-oxidant as the result of changing diet and possible use of antibiotics. In fact, study of fecal material from ancient remains may lead to the development of newer antimicrobials. One should conclude by reemphasizing how important it will be to develop molecular libraries of antiquities but, at the same time, maintaining the dignity of the past.

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HLA-B27 Associated Spondyloarthropathy and Severe Ascending Aortitis

To the Editor:

I read with interest the report of Stamp, et al regarding a 27-year-old woman with HLA-B27 associated spondyloarthropathy (SpA) who developed early aortitis[1]. The authors seem to have missed our report on aortic insufficiency detected in a 10-year-old boy 32 months after onset of HLA-B27 associated post-diarrhea Reiter's syndrome[2]. The pathologic changes were also reported at the time of an aortic valve replacement at age 14 years[3].

Both cases presented a dilated ascending aorta and the main abnormality consisted of destruction of the arterial media. Interestingly, giant cells were part of the inflammatory arterial infiltrate in our patient. Aortitis leading to aortic incompetence in SpA has been reported in elderly patients with a long history of disease. In the other extreme, this complication has also been described in a handful of young and even juvenile patients as part of the early course of the SpA.

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Osvaldo Hubscher, MD.

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Dr. O'Donnell replies

To the Editor:

We thank Dr. Hubscher for highlighting his case report[1,2]. As discussed in our case report[3], our patient has continued with a persistently elevated C-reactive protein. Subsequent to the publication of her case she developed claudicant symptoms in the right arm, and a stenotic lesion in the right subclavian artery was treated by angioplasty with symptomatic improvement. Apart from high dose steroids no other therapy to date has been associated with a fall in her inflammatory markers, which clinically we regard as a reflection of ongoing arteritis. In addition to oral chlorambucil she has been given a 3 month trial of mycophenolate mofetil. Like cyclophosphamide both these agents have not been associated with any convincing evidence of either suppression of her inflammatory markers or clinical improvement. At the time of writing she continues prednisone 10 mg per day, continuing to feel systemically unwell with persisting elevation of inflammatory serology.

We would be very interested to know of others' experience of the treatment of HLA-B27 associated aortitis and arteritis, in particular what was the progress of Dr. Hubscher's patient?

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Development of Systemic Lupus Erythematosus Following Autologous Bone Marrow Transplant for Acute Lymphocytic Leukemia

To the Editor:

There have been numerous reports of patients with systemic lupus erythematosus (SLE) who later developed hematologic malignancies[1,2], but we report only the third case of a patient with acute lymphocytic leukemia (ALL) who developed SLE.

Our patient is a now 8.5-year-old Hispanic male who presented at age 4 with a 2 week history of fever and pallor. An initial complete blood count revealed a white blood cell count of 621,000 with an absolute neutrophil count of 0, hemoglobin 10.5 g/dl, platelets 20,000. He was diagnosed with high risk ALL, and while undergoing maintenance therapy a bone marrow aspirate showed relapse, so he underwent autologous bone marrow transplant (BMT). He did well post transplant, showing good engraftment, with only mild persistent thrombocytopenia of 50,000–120,000 platelets. Three and a half years after transplant he began to complain of intermittent hip and knee pain with swelling and stiffness in the morning. One month later he also developed a malar rash, fever, weight loss, and worse thrombocytopenia (platelets 30,000–60,000).

Bone marrow aspirates revealed no evidence of relapse of ALL or other malignancy, with decreased megakaryocytes and otherwise normal lineage. Laboratory studies revealed an erythrocyte sedimentation rate 80 mm/h (reference values 0–10 mm/h), antinuclear antibodies > 1:640 (< 1:40) in a homogenous pattern, anti-dsDNA 1:1280, antiphospholipid antibodies negative, anti-RNP antibodies positive, anti-Sm antibodies positive, C3 33.7 (92–161 mg/dl), C4 < 10 (13.0–52.0 mg/dl). No complement deficiency was detected. IgG was high normal, IgM and IgA were normal, lymphocyte mitogen stimulation was normal 6 months post-BMT, and lymphocyte subsets were not obtained. SLE was diagnosed; of note, his maternal aunt also has SLE.

His major manifestations were fever, weight loss, arthritis, anemia, thrombocytopenia, rash, and nephritis diagnosed by urinalysis. Renal biopsy was not performed. Treatment was begun with corticosteroids and intravenous (IV) monthly pulse cyclophosphamide was added to his regimen for treatment of nephritis. All his symptoms resolved and his platelet count normalized (platelets 200–300,000) for the first time since transplant. Platelet antibody was not tested. He has subsequently become quiescent taking 3-monthly IV cyclophosphamide and low dose corticosteroids.

Both myeloproliferative and lymphoproliferative malignancies have been described following the diagnosis and treatment of SLE[2,3], but there is no clear evidence that malignancy predisposes to development of SLE. In 1965 brief mention was made of a patient who developed SLE 5 years after mercaptopurine had induced complete remission from ALL and the author postulated common immunologic hyperactivity[4]. Lately Kitahara, et al reported a 13-year-old girl who developed lupus nephritis and Hashimoto thyroiditis 12 years after diagnosis of juvenile myelomonocytic leukemia[5]. This patient had no other immune dysfunction recorded, no family history of SLE, and her SLE symptoms resolved with corticosteroids.

Autoimmunity after allogenic BMT is recognized, and autoimmune cytopenias have been reported after allogenic or autologous BMT[6,7]. Clinical SLE has not been reported after allogenic BMT, but SLE antibodies have been detected in patients[6,7] and murine models[8]. However, this is the first patient with a clinical syndrome of autoimmunity after autologous BMT.

The major question surrounding this case is whether the development of SLE was induced or accelerated by the BMT or treatment for leukemia, or whether it is a separate event in a patient with a family history of SLE. Immunologic dysfunction after BMT could favor a causal relationship. Autoimmune disorders have recently been accepted as stem cell disorders, a theory complementing the previous 2 case reports. In support of a possible relationship between SLE and BMT and treatment for leukemia is the relative rarity of onset of SLE in his age group. In addition, the persistent mild thrombocytopenia after BMT that completely resolved with treatment for SLE argues that he had an immune mediated thrombocytopenia rather than inadequate engraftment. Normal, increased, and decreased numbers of megakaryocytes have been noted with thrombocytopenia in connective tissue diseases[9]. Arguing against a causal relationship is the 3.5 year delay in onset of SLE after BMT, but the actual onset of his SLE is not really known, since his thrombocytopenia may have been the first sign.

Autoimmune disease after autologous BMT in animal models can be induced with cyclosporine[10]. The hypothesized mechanism is that cyclosporine interferes with thymic selection post-BMT, leading to emergence of autoreactive T cells. It is possible that autologous BMT, in a patient who may have a genetic predisposition to development of an autoimmune disease, may lead to immune imbalance favoring autoimmune disease. This may be operational in the case described here, with a prodrome of thrombocytopenia and ultimate expression of SLE.

To our knowledge this is the third reported case of SLE occurring in a patient with a hematologic malignancy, and the first case following autologous BMT. The scenario of autoimmunity after allogenic BMT is known, but although animal models have shown transference of SLE autoantibody production, ours is the first patient with a clinical autoimmune syndrome after autologous BMT. There is no known relationship between BMT and SLE, so the question remains: Is this a coincidental observation or a newly discovered causal relationship?

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Morning Stiffness: How Common Is It and Does It Correlate with Physician and Patient Global Assessment of Disease Activity?

To the Editor:

Morning stiffness is used in clinical trials of rheumatoid arthritis (RA) to help determine disease activity and response to treatment[1-4], and to differentiate "inflammatory" from "noninflammatory" arthritic conditions[5]. It is also one of the American Rheumatism Association 1987 revised criteria for the diagnosis of RA[6].

Several studies evaluated morning stiffness in RA, ankylosing spondylitis, and osteoarthritis (OA) and compared what it signifies to patients and physicians[7-9]. We found no studies evaluating the correlation of morning stiffness with physician and patient global assessment of disease activity.

To address this, we administered a questionnaire assessing the presence and duration of morning stiffness to consecutive patients presenting to our rheumatology outpatient clinic for routine care over a one month period. Both patients and physicians assessed disease activity at the clinic visit on a visual analog scale (graded 0 to 10, 0 = no symptoms, 10 = very severe symptoms). Physicians were not aware of the patients' evaluations of their disease activity.

Correlation between physician global assessment (MDGA), patient global assessment (PTGA), and duration of morning stiffness was determined using Spearman's rank correlation. One-way analysis of variance was done with age as the independent variable and time of morning stiffness and physician and patient assessment of disease activity as the factors.

One hundred thirty patients were seen in a one month period. Six patients with missing data were excluded from the analysis, with 124 remaining for evaluation (92 women, 32 men, mean age 55.7 ± 17.1 yrs). Table 1 shows the distribution of diagnosis, number of patients reporting morning stiffness, and the duration of morning stiffness among patients with OA, RA, and systemic lupus erythematosus (SLE).

For all patients, age was weakly associated with duration of morning stiffness ($r = 0.3$, $p = 0.001$). For RA alone, age was strongly inversely correlated with morning stiffness ($r = -0.5$, $p = 0.006$), and younger patients with RA assessed their disease as worse compared to other patients with other diagnoses ($r = -0.4$, $p = 0.02$). No such association was seen in patients with OA, who had a narrower age range and were older on average [mean age (range) for OA 58 (40–85) yrs, for RA 48 (26–79) yrs]. There was no association of age with the MDGA. There was no association between sex and morning stiffness ($p = 0.7$).

Because of low numbers of other disorders, only patients with diagnosis of OA, RA, or SLE were analyzed further. Between patients with OA, RA, and SLE, no difference was found in the prevalence of reported morning stiffness (Table 1). Duration of morning stiffness did not differ when OA-RA, RA-SLE, and OA-SLE were compared (OA vs RA $p = 0.8$; RA vs SLE $p = 0.8$; OA vs SLE $p = 0.6$).

Reported duration of morning stiffness did not correlate with either MDGA or PTGA in patients with either RA or SLE. No correlation was noted between MDGA and PTGA in patients with RA or SLE (Table 2).

Among patients with OA, a correlation between duration of morning stiffness and PTGA and a weak correlation between PTGA and MDGA was seen. No significant correlation was noted between duration of morning stiffness and MDGA among OA patients, however.

In this cohort of patients, duration of morning stiffness did not differ among patients with OA and RA, traditionally taught as examples of noninflammatory and inflammatory disease, respectively, and did not correlate with either PTGA or MDGA, except in the case of PTGA for OA. There was no difference among the 3 diagnoses (OA, RA, SLE) with regard to duration of MS, or association of MS with PTGA or MDGA. Lack of correlation between SLE and RA patients in regard to PTGA and MDGA could be due to different frames of reference for disease activity for physicians and patients, lack of understanding the term disease activity, or the small numbers of patients in each group. Another interesting finding was that younger patients with RA assessed their disease as more severe than their physicians did. This may be because morning stiffness may be more important, and more noticeable, in younger people, interfering with their activities of daily living.

Hazes, *et al*[7] reported that presence and duration of morning stiffness was a poor discriminator between RA and noninflammatory joint disease. Their patients with active RA reported higher severity scores, but there was no difference in recalled duration. They recommended that a scale based on the severity of morning stiffness would be more helpful than using the duration of morning stiffness. Our study showed no association between duration of morning stiffness or severity of disease as assessed by the patient or physician.

Table 2. Correlation of morning stiffness (MS) with physician global assessment of disease activity (MDGA), patient global assessment of disease activity (PTGA), and correlation between MDGA and PTGA.

	MS vs MDGA		MS vs PTGA		MDGA vs PTGA	
	r	p	r	p	r	p
OA	0.34	0.049	0.61	< 0.001	0.53	0.001
RA	0.06	0.7	0.25	0.2	0.28	0.1
SLE	0.37	0.09	0.2	0.3	0.2	0.4

Table 1. Number of patients and prevalence and duration of morning stiffness (MS).

Diagnosis	Total Patients	MS (+)	%	< 15 min	16–30 min	31–60 min	> 60 min
OA*	34	24	71	10	8	2	4
RA*	31	22	71	9	5	3	5
SLE*	23	14	61	2	3	4	5
PM	12	7	58				
RRC	11	6	55				
DM	9	7	78				
PMR	2	1	50				
Gout	2	0	0				
Total	124	81	65				

*Only patients with OA, RA, or SLE were analyzed because of low number of patients.
PM: polymyositis, RRC: regional rheumatic conditions, DM: dermatomyositis, PMR: polymyalgia rheumatica.

This raises the question of the clinical significance and specificity of morning stiffness. Our study was a cross sectional look at morning stiffness in a rheumatology clinic population. Longitudinal assessment of morning stiffness could be helpful in individual patients, but morning stiffness did not seem to differentiate between inflammatory and noninflammatory rheumatologic disorders. At the same time, our number of patients might have been too small to show a significant difference. Another possible explanation, addressed by several authors[9,10], may be the difference between what physicians and patients mean by morning stiffness; however, Hazel, *et al*[7] found no gain in attempting to obtain, by interview, a better qualitative description of morning stiffness.

We believe a larger, prospective trial is necessary to determine the role of morning stiffness in the diagnosis and everyday management of patients with rheumatic diseases.

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Femoral Head Necrosis and Hyperhomocysteinemia

To the Editor:

Clinical situations associated with the development of osteonecrosis include traumatic disruption of the blood supply (fractures), hemoglobinopathies (sickle cell disease), hypercorticism, Gaucher's disease, dysbaric disorders, irradiation, pregnancy, pancreatitis, alcoholism, collagen vascular diseases (systemic lupus erythematosus and antiphospholipid syndrome) and HIV infection[1]. Heritable thrombophilic disorders have only anecdotally been related to osteonecrosis, but epidemiologic evidence is lacking. Recently, in children with Legg-Calve-Perthes disease, thrombophilia, including hyperhomocysteinemia (HH), was not found to play an etiological role[2]. There is a high proportion of patients with osteonecrosis in whom none of the above conditions are implicated. "Idiopathic" femoral head necrosis mostly occurs in men aged 40 to 70 who are obese. We describe a case of bilateral femoral head necrosis that could be related to HH.

A 59-year-old woman was admitted to the hospital for pain of the left hip of 3 months' duration. Bilateral femoral head necrosis was diagnosed. She smoked about 5 cigarettes a day and drank a glass a wine twice a day. Postmenopausal hormone replacement therapy had been prescribed for 4 years. She had no vascular risk factor other than tobacco use, mild hypertriglyceridemia, and moderate obesity (71 kg for 170 cm). A history of early venous phlebitis was noted in her mother, a maternal aunt, and a cousin. Laboratory findings showed elevated mean corpuscular volume (102/fl). Plasma folic acid depletion (6 nmol/l) and HH (29 µmol/l; normal value < 14 µmol/l) were diagnosed. She was found to be homozygotic for the C677T mutation of the MTHFR gene. No other thrombotic risk factor could be found despite extensive evaluation. Folate supplementation (5 mg per day) was started. Three months later, plasma homocysteine concentration had returned to normal values (10.4 µmol/l).

There is epidemiologic evidence that moderately elevated plasma homocysteine concentration is an independent risk factor for atherosclerosis and atherothrombosis[3]. Mild HH occurs in about 5 to 7% of the general population and generally remains asymptomatic until the fourth decade of life. The rare homozygous forms of cystathionine beta-synthase, methionine synthase, and N^5,N^{10}-methylene tetrahydrofolate reductase (MTHFR) deficiencies lead to severe early fatal HH. Heterozygotes (1 in 250 births) have mild HH. Persons with the thermolabile variant of MTHFR caused by homozygote point mutation (C677T) in the coding region for the binding site of the enzyme have an exaggerated hyperhomocysteinemic response to folic acid depletion. Five to 15 percent of the general population could be homozygotic for this mutation. Even without known genetic abnormality, deficiencies in the vitamin cofactors (B6, B9, B12) of the enzymes are observed in two-thirds of mild HH. Other causes of mild HH include renal failure and hypothyroidism. HH is a risk factor for vascular disease, mostly arterial macroangiopathy, including coronary and cerebrovascular disease but also, as recently reported, retinovascular venous and arterial disease[4]. Treatment of HH is easy, especially when folic acid is added in patients with the thermolabile variant of MTHFR, and could decrease the risk of premature occlusive disease. To our knowledge, HH has never been reported in association with osteonecrosis. Our case report suggests HH could be a risk factor to osteonecrosis, but this possibility remains to be established by appropriate epidemiologic studies.

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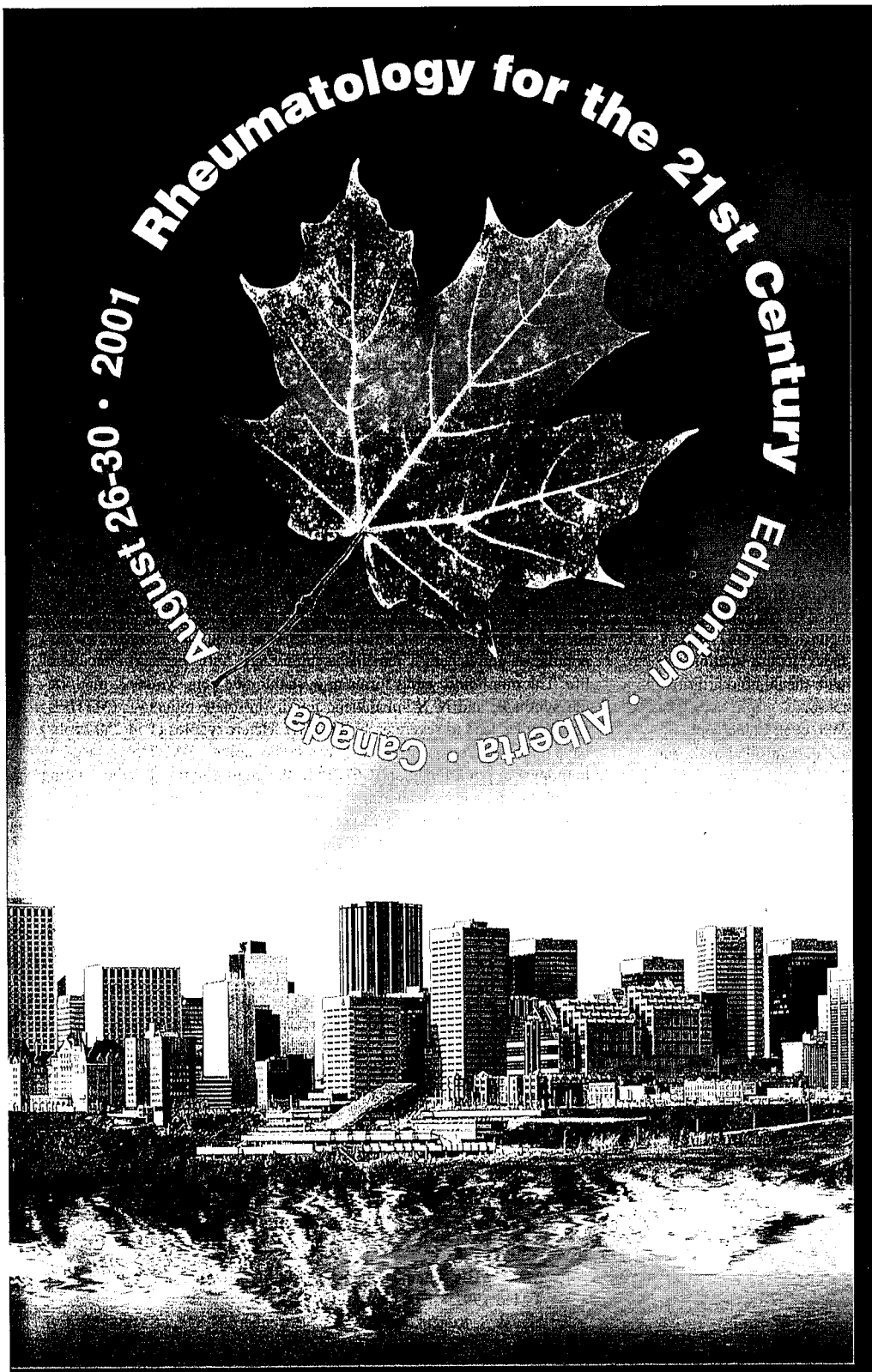

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