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 M4W 3C7, 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.**

Identification of Radiologic Healing Phenomena in Patients with Rheumatoid Arthritis

To the Editor:

Professor Rau and his colleagues deserve credit for bringing to our attention several cases of rheumatoid arthritis (RA) in which serial radiographic examination has provided evidence that some improvement in erosive bone damage may occur[1]. Although not the first to report healing in RA, Dr. Rau has over the last several years reported several such cases. Unfortunately, reproduction of radiographic film images almost always results in some loss of detail and some of the cases illustrated in the literature in the reports of Rau and others are not convincing. However, enough are convincing, so that the possibility of stabilization and some degree of improvement in bony erosions must be taken into account in all followup studies on RA that include serial radiographic study. The question of terminology and whether the term "healing" should be used is controversial and will be discussed in some detail in a forthcoming supplement to *The Journal* reporting the deliberations of the subcommittee on healing of erosions in RA held at OMERACT 6, Brisbane, Australia, April 2002.

In the article by Rau I would like to call attention to two errors. On page 2609, Rau, *et al* state "Some authors exclude the possibility of a score reduction *expressis verbis* ('once an erosion, always an erosion,' Sharp, personal communication)."[1] On the same page they state ". . . in most clinical trials scoring . . . was done knowing the chronological order . . .". To my knowledge I have never made such a statement. From the earliest time when I began the use of radiographic films to evaluate RA joint damage I have pointed out that it is important that even though we did not have evidence at that time that bone damage could improve, we should keep in mind that effective treatment should lead to repair of bony injury. For that reason, after the original report I have always randomized and blinded sequence of serial films in every study I have organized.

JOHN T. SHARP, MD, Affiliate Professor of Medicine, University of Washington School of Medicine, Seattle, Washington, USA.

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Dr. Rau replies

To the Editor:

We thank Dr. John Sharp for his thoughtful comments to our article[1]. Dr. Sharp is completely right that the reproduction of radiographic films almost always results in loss of detail and therefore is less convincing than the original films. Despite intensive efforts to optimize the reproduction using technical advances in processing images, the result is often disappointing.

On the other hand we have published cases followed over many years showing progressive destruction and — later — increasing repair in the same joint, thereby overcoming problems of reproduction and changing projection (Figures 1, 5, 6, published in 1996[2]). It is not relevant if these changes are called "healing" or "repair." Our study[1] displayed some case reports only for the purposes of illustration. It was a formal study in which 24 cases with and 10 cases without healing were read by 3 observers blinded to sequence. They had to state which of the films was first and which was second and decide if there was healing or not. The agreement regarding both questions was approximately 90%.

The only difference from the study performed by the above mentioned OMERACT subcommittee on healing (perfectly organized by Dr. Sharp) was that the readers had not only digitized images of the one but also the original radiographs of hands, wrists, and feet at 2 time points, making it much easier to find the right sequence of the films. Consequently, the agreement among readers of our study was better than that of the OMERACT trial. Moreover, it might have been also easier to identify healing phenomena.

We have to apologize for offering the impression that Drs. Sharp and Larsen *expressis verbis* said "once an erosion, always an erosion." This statement was cited from a publication by van der Heijde[3]. Drs. Sharp and Larsen were mentioned in a second bracket, which should indicate that they were or still are very skeptical to accept the idea of improvement of radiographic findings or healing. This impression is documented again in Dr. Sharp's present letter. We admire the farsightedness of Dr. Sharp to read serial radiographs blinded to sequence in studies he organized. However, the vast majority of trials we are aware of were read with known sequence.

We also appreciate the great job he did by organizing the above mentioned OMERACT subcommittee study, which has demonstrated again that healing or repair is a reproducible phenomenon. Results like that are most convincing if they are reported by authorities who originally were most skeptical and did not expect that result.

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How Many Angels Could Dance on the Head of a Pin?

To the Editor:

Medieval theologians argued how many angels could dance on the head of a pin. Contemporary rheumatologists seem to be repeating this futility by arguing about fibromyalgia (FM). The exchange of letters[1,2] in the *Journal* in February refers to FM as a disease. It isn't. It is merely a portion of the spectrum of diffuse chronic pain, and its definition and boundaries are so variable that it has lost any claim to consideration as a diagnostic entity. As Werle, *et al*[3] point out, the specificity of antibodies against serotonin and phospholipids is questionable, and I would maintain that neither the clinical features nor the laboratory findings can be used to classify or to ascribe etiology. It is high time we abandoned the misleading diagnosis "FM," which support groups and other interested parties have distorted, recognize that the classification criteria[4] merely assure that series are comparable but have no diagnostic significance, and help the patients abandon victimhood and get on with their lives.

GEORGE E. EHRLICH, MD, Philadelphia, Pennsylvania, USA.

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2. Klein R, Berg PA. Diagnostic relevance of antibodies to serotonin and phospholipids in fibromyalgia syndrome [letter]. Eich W, Werle E, Mueller A. [Reply]. J Rheumatol 2002;29:395.
3. Werle E, Fischer HP, Mueller A, et al. Antibodies against serotonin have no diagnostic relevance in patients with fibromyalgia syndrome. J Rheumatol 2001;28:595-600.
4. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.

Drs. Klein and Berg reply

To the Editor:

We appreciate the sophisticated statement by Dr. Ehrlich concerning the problem of defining fibromyalgia (FM) as a disease. However, the author of this letter has probably not carefully read our reply[1] to the article by Werle, *et al*[2]. From our arguing it is obvious that, first, we never classified FM as a single disease; second, we referred to other authors who defined FM as belonging to the "functional somatic syndromes"[3]; and third, we interpreted our serological data about the occurrence of antibodies to serotonin, gangliosides, and phospholipids in patients with FM as an indicator for its "heterogeneity" and outlined that the presence of these antibodies in different clinical manifestations is a further argument that FM may belong to the spectrum of functional somatic syndromes. There are quite a few reports that indicate that features suggesting an alteration of the sympathic adrenergic and sensory nerve system as well as of immunological functions can be found quite frequently in patients with FM or other functional somatic syndromes[4-6]. The underlying pathogenic mechanisms in FM may, therefore, also relate to a disturbance in the neuroendocrine immune network[6].

Although FM has been primarily defined by generalized pain and psychological alterations, we should not worry too much how closely FM criteria are related to the real clinical condition reflecting the manifold above mentioned psychoneuroimmunological disturbances frequently occurring in this disease. Indeed, we should rather listen carefully with an open mind to these patients, hoping to improve our understanding of this still badly defined and multifaceted syndrome.

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Drs. Werle and Eich reply

To the Editor:

How many angels could dance on the head of a pin? The scholastics, medieval philosophers of the Catholic Church, like Thomas Aquinas could have very reasonably focused on this question, for it does concentrate several of their points of dispute, including whether angels have a corporeal (bodily) or merely spiritual existence. These theologians of the Middle Ages had no idea what sort of thing an angel was. What is knowledge? There was a time when everyone knew what a demon was, or that the world is composed of 4 elements. To answer this ridiculous sounding question about dancing angels on the top of a pin one should have enough information about angels, and we must have more data to answer today's scientific topic — fibromyalgia.

Therefore, in our recent article[1], we reevaluated repeatedly published data on laboratory tests for the diagnosis of FM. In his letter, however, Dr. Ehrlich argues against FM as a disease entity and strongly recommends we abandon this misleading diagnosis. His opinion may be the conclusion from his own experience and from more than 100 articles published in 2001 in peer reviewed journals with "fibromyalgia" as a key word in the title. In most of the recent papers the American College of Rheumatology criteria[2] were used to define the patient groups under investigation. The fact is that chronic pain patients exist and that tender points reflect a decreased pain threshold. The nature and the etiology of these phenomena are discussed controversially. Several authors assume that these patients may suffer, besides a chronic pain disorder, from a depression or an anxiety disorder or a somatization disorder. Others authors think of neuroplasticity.

The aim of our study[1] was to investigate whether or not the clinical symptoms in this patient group may be related to antibodies as reported. In our large cohort of patients recruited for integrated psychological and physical group therapy, we demonstrated that measurement of antibodies against serotonin was not associated with clinical scoring of, for example, pain intensity, depression, or activities of daily living. In addition, antibodies against serotonin showed no diagnostic relevance in these patients at all. Therefore, we only can refuse those unnecessary, even expensive, measurements for routine diagnostics, thus avoiding a fixation on the laboratory data of these patients.

Taking account of these reports we cannot definitely answer the question whether there are angels, or whether FM is a dispensable term, but we are quite sure that serial measurements of the antibodies we investigated have no diagnostic relevance and may, as suggested by Dr. Ehrlich, even have some psychological adverse effects on our patients' lives.

EGON WERLE, MD, PhD; WOLFGANG EICH, MD, PhD, University of Heidelberg, Heidelberg, Germany.

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Polymorphism in the Matrix Metalloproteinase-1 Promoter Gene and Severity of Rheumatoid Arthritis

To the Editor:

In a recent report Constantin, *et al*[1] found no association between collagenase-1 (MMP-1) gene polymorphism and susceptibility to or severity of rheumatoid arthritis (RA). We agree that MMP-1 polymorphism is not involved in RA susceptibility, but have some doubts about the relationship between MMP-1 polymorphism and RA severity.

The search for prognostic markers for early RA is a very important issue. RA is characterized by a variable clinical course, with a poorer prognosis associated with the presence of erosive damage to joints, which is a very early feature of the disease[2]. Therefore, the challenge for the physician is to predict, as early as possible, which patients will have a more disabling course necessitating an aggressive therapy. Identification of RA severity markers is thus urgently required to guide treatment strategies, in particular to avoid overtreating patients who will respond to cheaper and less toxic conventional therapies.

Although a polygenic component in susceptibility and severity of RA is very likely, the bulk of the genetic component is unknown, except for sex and HLA-DRB1 genes that confer susceptibility[1,3].

A strong candidate gene for RA is the MMP-1, since a variant (2G) has been identified in its promoter region, associated with increased transcription and hence with a more aggressive matrix degradation[4], and higher circulating MMP-1 levels have been associated with rapidly progressive erosive RA[5].

We studied polymorphism in the MMP-1 gene promoter in 56 patients with RA (41 women, 15 men, mean ± SD ages 49 ± 16 yrs), all fulfilling the American College of Rheumatology criteria[6]. Patients had symptoms for not more than 6 months at the time of the study and did not take any medication except nonsteroidal antiinflammatory drugs. One hundred sixty-four sex and age matched subjects with no rheumatic complaints served as controls. Patients and controls gave written informed consent. Patients' clinical assessment included counts of tender/swollen joints, measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum rheumatoid factor (RF), and radiographs of the hands. A single observer blinded to clinical features evaluated the presence/number of erosions. Joint erosions were selected as an accepted measure of joint damage[7].

In accord with Constantin, *et al*[1], MMP-1 promoter gene did not contribute to the RA susceptibility (Table 1); but in contrast with their findings, MMP-1 promoter gene polymorphism was significantly associated with erosive RA. Erosive disease was observed in 7 patients, all of whom carried the 2G allele (Table 2). The number of involved joints was significantly higher in the 2G/2G (3 to 21 joints) and 1G/2G (1 to 18 joints) genotypes than in the 1G/1G genotype (1 to 10 joints; p = 0.015 and p = 0.027, respectively). The 2G allele mutation was observed in 12 of the 14 total alleles of patients with erosive RA (86%) and in 45 of the 98 total alleles of those with nonerosive RA (46%) (chi-square 6.252, p = 0.013, OR 7.067, 95% CI 1.382–48.243). No relationship was observed between MMP-1 polymorphism, ESR, CRP, or the presence or titer of RF.

Table 1. Frequency distribution of MMP-1 genotypes in patients and controls.

MMP-1 Genotype	Patients, n = 56	Controls, n = 164
1G/1G	16	42
1G/2G	23	86
2G/2G	17	36

Chi-square 2.45, p = 0.293.

Table 2. Frequency distribution of MMP-1 genotypes in patients with erosive and nonerosive RA.

	Erosive RA, n = 7	Nonerosive RA, n = 49
1G/1G + 1G/2G	2	37
2G/2G	5	12

Chi-square 4.356, p = 0.037, OR 7.708, 95% CI (OR) 1.093–67.252.

The reason for the discrepancy between our results and Constantin's data is not clear. Since the control groups had similar frequency distribution of MMP-1 genotypes, ethnic differences should be ruled out. However, if treatment with disease modifying drugs might have altered the progression of the disease in Constantin's patients, the 6 month period for symptoms might be insufficient for conclusive results. More studies are needed to evaluate whether MMP-1 polymorphism can be considered a reliable prognostic marker of erosive RA.

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Dr. Constantin, *et al* reply

To the Editor:

Dr. Massarotti and colleagues report an association between a MMP-1 gene promoter polymorphism and severity of rheumatoid arthritis (RA), whereas we found no such association in our study[1]. Massarotti used a qualitative approach of RA severity by classifying patients with early RA in erosive or nonerosive disease groups (assessed on radiograph of the hands only), whereas we used a quantitative approach by quantifying RA severity on the basis of a validated radiographic damage score (calculated from radiographs of hands and feet according to the Sharp/van der Heijde method[2]).

Since this methodological difference may account for the discrepancy between these 2 studies, we performed a complementary analysis of our data using the same approach as Massarotti, *et al.* Patients were classified in the erosive disease group if the joint erosion score was ≥ 1 and in the nonerosive group if the joint erosion score equalled 0. Using this qualitative approach, we found no association between MMP-1 gene polymorphism and severity of RA, neither at inclusion of patients in our prospective longitudinal study (Table 1) nor after 4 years of followup (Table 2).

Table 1. MMP1 genotypes in patients with erosive (n = 47) and nonerosive (n = 55) RA at inclusion.

MMP-1 Genotypes	Erosive, n (%)	Nonerosive, n (%)
1G/1G	13 (41.9)	18 (58.1)
1G/2G	23 (54.8)	19 (44.2)
2G/2G	11 (37.9)	18 (62.1)

Chi-square 2.26, p = 0.32.

Table 2. MMP1 genotypes in patients with erosive (n = 74) and nonerosive (n = 21) RA after 4 years of followup.

MMP-1 Genotypes	Erosive, n (%)	Nonerosive, n (%)
1G/1G	23 (76.7)	7 (23.3)
1G/2G	30 (79.0)	8 (21.0)
2G/2G	21 (77.8)	6 (22.2)

Chi-square 0.05, p = 0.98.

Thus, a methodological difference in the assessment of RA severity could not account for the discrepancy between the report of Massarotti and colleagues and our own. Further studies are needed on the value of MMP-1 gene polymorphism as a marker of RA severity.

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Dermatomyositis with Normal Creatine Kinase and Elevated Aldolase Levels

To the Editor:

I read with interest the report by Carter, *et al*[1], and I would like to describe a similar case seen in our hospital.

A 24-year-old man presented in November 2001 with a 3 month history of arthralgias, Raynaud's phenomenon, and rash on his face. On examination, he had a heliotrope rash with associated edema of the upper eyelids, Gottron's papules on metacarpophalangeal, proximal phalangeal, and elbow joints, and digital ulcers. Manual testing of muscle strength revealed minimal proximal muscle weakness of upper and lower extremities. Laboratory evaluation showed an elevation of aspartate aminotransferase (AST) of 203 IU/l, and creatine kinase (CK) was normal (57 IU/l). Anti-dsDNA, human immunodeficiency virus, and renal function tests were negative or normal. Chest radiograph was normal. A muscle biopsy specimen from the right deltoid showed perivascular inflammation, without necrobiotic degeneration or atrophy of the muscle fibers.

He was treated with oral prednisone and vasodilators. On December 10, 2001, AST was 87 IU/l, alanine aminotransferase (ALT) was 69 IU/l, and CK was 59 IU/l. On January 14, 2002, AST was 60 IU/l, ALT 44 IU/l, CK 33 IU/l, and aldolase level was 9.9 IU/l (normal 0–8.1 IU/l). On January 23, 2002, CK was 42 IU/l and aldolase was 11.5 IU/l. A few days later, he was admitted to our hospital because of a possible seizure. On examination, no focal neurologic deficit was found. A lumbar puncture was normal. Electrocardiogram and echocardiogram results were normal. He denied drug abuse. He was discharged 48 h later to continue the prednisone therapy.

CK measurement in serum has remained the best marker for detection and monitoring of inflammatory disease of skeletal muscle. However, of the 3 widely used muscle enzyme measurements (AST, CK, and aldolase), any one may be normal even in an active disease state. Therefore, we recommend that all 3 enzyme tests be performed during evaluation of a patient with myositis.

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Dr. Carter, *et al* reply

To the Editor:

The literature maintains that as many as 10% of patients with active myositis can present with normal creatine kinase (CK) levels[1,2]. Dr. Mercado describes another patient who meets this clinical scenario, i.e., a patient with biopsy proven dermatomyositis who was found to have normal CK concentrations with elevated serum aspartate aminotransferase (AST) and aldolase. He correctly concludes that we must rely on all of the available muscle enzyme results in those patients who have normal CK levels in spite of active myositis. Aldolase is the most specific muscle enzyme after CK.

Clinicians are quick to disregard an abnormal laboratory value if it does not fit the clinical scenario. This reaction is completely justified. A perfect example of this is a patient who presents with mechanical low back pain and a weakly positive antinuclear antibody. A diagnosis of systemic lupus erythematosus is inappropriate in this situation. The clinical picture guides the diagnosis, not a single laboratory test. The converse should also hold true. If your clinical suspicion of a certain disease is very high, a single incongruent laboratory test should not dissuade your opinion. In this instance, it is myositis with a normal serum CK. We must search for other markers of disease activity, i.e., aldolase, AST, lactate dehydrogenase. It is imperative that we use diligence when our laboratory testing does not match our clinical suspicion. If,

after reevaluation, our hypothesis remains the same, it is our duty to find other ways to confirm our suspicion.

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Chronic Nonmalignant Pain

To the Editor:

In a recent research report, Mailis, *et al*[1] investigated nondermatomal somatosensory deficits (NDSD) (nonanatomical sensory deficits) in patients with chronic nonmalignant pain seen for an independent medical examination. They found that 25.3% of the patients had NDSD. In addition, most interestingly, Mailis, *et al* reported that these patients were more likely to have their pain lateralized to one side of the body or worse on one side of the body.

Our group has performed some research that resonates with the data in the report from Mailis, *et al.* First, we reported that 37.8% of patients with chronic pain demonstrated NDSD[2]. Second, in a followup study we reported in abstract form[3] on the relationship between pain location and location of NDSD. We found that there was a strong statistical relationship between location of NDSD and pain location (study in press)[4]. Third, NDSD are important because their presence to some physicians indicates the possible presence of either malingering or conversion disorder[5]. We recently performed a structured evidence based review[5] of studies addressing this issue. It was concluded that nonorganic findings, including NDSD, do not discriminate between organic and nonorganic problems and are not associated with secondary gain, which is a prerequisite for malingering. Overall, this group of studies, including that of Dr. Mailis and colleagues, indicate that NDSD are not psychological phenomena.

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Drs. Mailis and Nicholson reply

To the Editor:

We were interested in Dr. Fishbain's response to our recent report of nondermatomal somatosensory deficits (NDSD) in patients with chronic nonmalignant pain[1]. Several groups have now reported on this phenomenon, which appears to be both prevalent and important. We view the presence of NDSD as a poor prognostic factor associated with a number of other problems. Dr. Fishbain makes reference to an article in press in which a structured based review of the literature concluded that "nonorganic findings, including NDSD, do not discriminate between organic and nonorganic problems...." Unfortunately, we cannot discern what this statement might mean and await publication of the report. He also stated that NDSD are not associated with malingering and, primarily upon this finding, it is concluded that NDSD are "not psychological phenomena."

Although a somewhat crude analogy, this sort of statement (which appears not uncommonly in the literature) is akin to stating that because a person has arms and legs, there is no reason to believe that there are any biomedical factors involved in presentation of some problem such as stroke or cancer. In other words, one negative instance (for example, the absence of malingering) is used to rule out an entire class of events (i.e., all possible psychological, psychosocial, or personality factors). We would here caution about mind-body dualism and consider that psychological phenomena of any description also have an *organic* basis. We strongly suspect that psychological factors are involved in the presentation of NDSD in the context of chronic pain (as well as possible conversion disorders involving sensory deficits independent from chronic pain).

There are several lines of support for this. We have found that certain demographic variables distinguish between chronic pain patients with or without NDSD, i.e., non-Canadian born patients were more likely to have sensory deficits. This may be interpreted as indicating that culture (i.e., the way we view the world) influences the appearance of these deficits. Further, the NDSD subgroup had significantly abnormal pain behaviors, discrepancy between supine and sitting straight leg raising (i.e., behaviors under confrontation and distraction), and much higher levels of disability, as they were all virtually unemployed, as compared with 31% of the non-NDSD group who were employed. Further, Fishbain, *et al*[2] demonstrated that in their study of 247 chronic pain patients, all diagnosed with myofascial pain, 77% of the NDSD subgroup had a workers' compensation claim, while in the group without NDSD, only 40% had such a claim. Could these data be interpreted as showing that the stress associated with a workers' compensation claim or perhaps unusual and therefore contested disability contribute to the generation of NDSD? In the same study 27% of the NDSD group had dependent personality disorder, as compared to 12.9% of the non-NDSD group ($p < 0.01$).

Other groups, as well, have presented evidence that NDSD may be associated with psychological factors. Verdugo and Ochoa reported[3] on a group of patients who responded to administration of placebo with either complete or near complete resolution of pain and sensory deficits. This was interpreted as the result of a psychogenic phenomenon.

We have also seen many patients responding to placebo interventions with resolution of their sensory deficits and pain, at times permanently[4]. To study these phenomena we instituted since 1994 in our unit placebo controlled infusions of sodium amytal in a standardized protocol on patients with chronic pain. Response to inert placebo with "shrinking" or disappearance of the NDSD borders has been seen in many patients, and clearly indicates that the deficits are not structural or anatomical (as in the case of neurectomy or other structural nervous system damage). On some occasions, however, NDSD can be superimposed on definite structural deficits[5].

Our protocols have allowed us to collect a very large database, which is currently under analysis. Preliminary data indicate that personality and psychological factors are indeed associated with the onset, maintenance, severity, or exacerbation of chronic pain *and* with the presence of NDSD.

We also believe that there is an "organic" basis, or better said, a "psy-

chobiological" or "psychophysiological" basis for these NDSD phenomena, as our current magnetic resonance imaging data unequivocally confirm[6]. Beyond our recently published report[1], our group's collective experience shows that NDSD phenomena occur in chronic pain patients (1) with significant psychoemotional factors in the absence of detectable pathology; and (2) superimposed on structural deficits. In the vast majority of cases in both groups, psychoemotional factors do seem to be associated with both chronic pain and the appearance of NDSD.

We would urge researchers not to adopt an either/or approach (i.e., either "organic" or "psychological") to such phenomena, but accept them as bridging the "mind-body interface." Ignoring psychological factors carries the risk of overmedicalizing treatment, while dismissing the phenomena as purely psychological, particularly in the presence of specific detectable peripheral pathology, ignores potential nociceptive or neuropathic sources that are treatable as well.

One contentious point involves patients with diffuse myofascial pain syndromes, often classified as fibromyalgia (FM). These patients do not have detectable peripheral pathology in the form of muscle inflammation, etc. Their proven excessive sensitivity to pressure is more likely the product of sensitization at supraspinal rather than peripheral levels, hence some consider the entity as a manifestation of "hypervigilance" due to attentional switches[7]. Kaziyama, *et al*[8] reported a 38.2% prevalence of hemisensory deficits to pinprick in 76 women fulfilling the American College of Rheumatology criteria for FM[9]. Overall, their patients may not be different than those reported by Fishbain, *et al*[2] (with myofascial pain syndromes) or by Mailis, *et al*[1,10] (most with diffuse pains and the diagnosis of FM).

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Deflazacort in Giant Cell Arteritis

To the Editor:

We read with interest the report by Cacoub, *et al*[1], who found no significant difference between the bone loss for deflazacort versus prednisone in patients with giant cell arteritis. These results are in contrast to results we obtained with low doses[2] and to results obtained with higher doses[3-5]. This apparent lack of effect in their study could be at least partly explained by a randomization leading accidentally to differences in both groups (compare the mean age and presence of symptoms of polymyalgia rheumatica). Even if not statistically significant, potentially clinically relevant differences in erythrocyte sedimentation rate, C-reactive protein, visual loss, and number of positive temporal artery biopsies tend to undermine the blinding of the study and lead to a longer duration of therapy in the group with a more severe condition. Furthermore, the choice of calcidiol as vitamin D supplementation was at least unfortunate, because this drug has been shown several times to interfere with bone metabolism and bone mass in patients treated with glucocorticoids[6-8]. For all these reasons we believe that the conclusions of the authors should be considered as premature, as far as the effects of prednisone and deflazacort on bone mass are concerned.

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Manganese Superoxide Dismutase, Glutathione Peroxidase, and Total Radical Trapping Antioxidant Capacity in Active Rheumatoid Arthritis

To the Editor:

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly occurs in the joints by infiltration of T lymphocytes, macrophages, and plasma cells into the synovium[1]. Inflammation and tissue destruction are initiated by the influx of lymphocytes into the synovium, stimulating plasma cells and macrophages to produce inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin 1 (IL-1). Moreover, mononuclear phagocytes and neutrophils produce large amounts of reactive oxygen species (ROS)[2]. Antioxidant defence of eukaryotic cells is provided by a variety of enzymatic and nonenzymatic systems: copper-zinc (CuZnSOD) and manganese superoxide dismutase (MnSOD) enzymes act in tandem with glutathione peroxidase (GSH-Px), providing the primary enzymatic antioxidant defences. The MnSOD enzyme is inducible under conditions of stress or inflammation[3].

We have described an upregulation of the MnSOD mRNA transcript in lymphocytes of patients with Alzheimer's disease and a significant increase in the enzymatic activity of the cytosolic CuZnSOD enzyme, while the total trapping antioxidant capacity (TRAP) was reduced[4]. Our aim here was to evaluate factors involved in antioxidant protection in the blood of patients with rheumatoid arthritis (RA), such as the concentrations of MnSOD in lymphocytes, cells playing a crucial role in RA, GSH-Px in erythrocytes, and TRAP in plasma, to investigate if active rheumatoid disease may lead to compensatory changes in the level of antioxidant.

We studied 20 consecutive hospitalized female patients, ranging in age from 20 to 73 years (mean 51.2 yrs), with RA according to the 1987 American Rheumatism Association criteria[5]. Mean disease duration was 4.5 years (range 2–10 yrs). All patients had active disease. Criteria for active disease were erythrocyte sedimentation rate > 30 mm/h and/or C-reactive protein > 10 mg/l, duration of morning stiffness > 60 min, > 6 swollen and tender joints, Ritchie index > 16. No patient had been treated with disease modifying antirheumatic drugs in the 3 months before the study. Therapy consisted of nonsteroidal antinflammatory drugs (NSAID). Twelve healthy age matched women made up the control group. All patients and controls provided informed consent to take part in the study.

Venous blood samples were drawn from each patient and control. Mononuclear cells (> 95% lymphocytes) were isolated from heparinized blood by centrifugation on a Ficoll-Hypaque gradient. MnSOD activity was assayed by the method of inhibition of hematoxylin autoxidation to hematein, in the presence of 5 mM cyanide[6]. GSH-Px enzyme assay was based on that of Paglia and Valentine[7], monitored at 340 nm. The TRAP assay, described by Miller, *et al*[8], was based on the quenching of the 2,2'-azinobis(3 thiolbenzothiazoline-6-sulfonic acid) radical cation ($ABTS^{\cdot+}$) by the antioxidants.

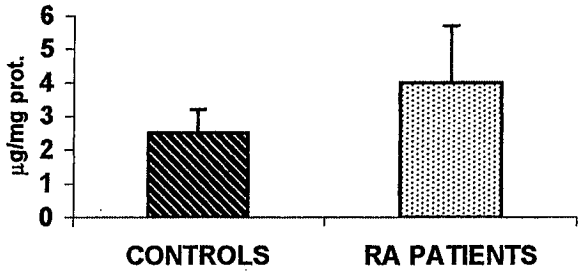

Figure 1. MnSOD activity (µg/mg protein) in lymphocytes of patients with RA and controls. Values are means ± SD.

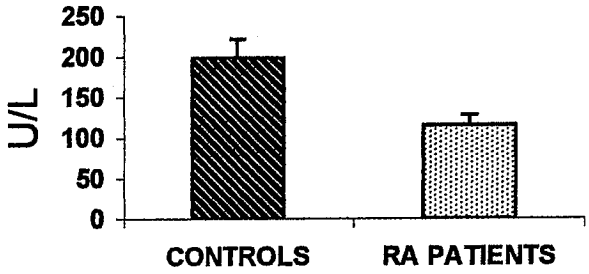

Figure 2. GSH-Px activity (U/l) in erythrocytes of patients with RA and controls. Values are means ± SD.

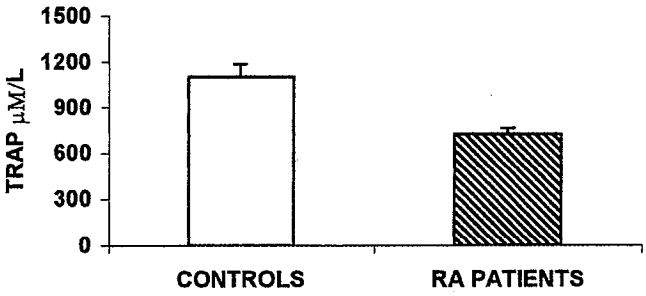

Figure 3. TRAP (µM/l) in plasma of patients with RA and controls. Values are means ± SD.

Data were expressed as the mean ± SD of the indicated number of patients studied. We estimated differences between patients with RA and controls using one way analysis of variance (ANOVA) using Minitab software (Minitab, State College, PA, USA). When a significant effect was found, post-hoc comparison of means was by Fisher's test. Differences were considered significant at $p < 0.05$.

MnSOD levels were significantly higher in patients with RA than in controls (4.20 ± 2.28 vs 2.5 ± 0.73 µg/mg, respectively; $p < 0.05$) (Figure 1). We observed that GSH-Px activity appeared significantly lower in blood of patients compared with controls (115.2 ± 13.6 vs 198.2 ± 23.4 U/l, respectively; $p < 0.01$) (Figure 2). TRAP was significantly reduced compared with controls (723.0 ± 40.5 vs 1100.0 ± 85.0 mmol/l, respectively; $p < 0.002$) (Figure 3).

The presence of T lymphocytes, macrophages, and neutrophils in inflamed joints raises the possibility of a role of ROS in the pathogenesis of RA[9]. Modification of the intracellular redox balance leads to important cellular changes derived from a modification of gene expression. Nuclear

factor-κB and the transcription factor activator protein-1, which together mediate activation of genes involved in host defence, can be activated by oxidants in many cell types[10]. Mitochondrial concentrations of MnSOD enzyme are elevated in response to stimulation with IL-1ß and IL-6, and TNF-α regulates MnSOD mRNA expression[11]. TNF-α plays a central role in regulating lymphokine, chemokine, and growth factor expression in RA joints[12]. ROS are important regulator molecules implicated in the signaling cascade triggered by TNF-α[12]. It has been suggested that enzymatic or nonenzymatic antioxidant systems are impaired in RA[13,14], thus patients with RA are exposed to oxidant. Higher SOD and xanthine oxidase levels and decreased or unchanged GSH-Px levels have been found in RA[15,16].

Our patients were taking NSAID. Recent reports have indicated that NSAID diminished or had no significant effect on serum SOD and TRAP concentrations[17], whereas we found MnSOD enzyme induced by the inflammatory process and TRAP capacity was decreased in patients with RA.

Our findings of elevated lymphocyte MnSOD and reduced erythrocyte GSH-Px concentrations in patients with RA suggest that the intracellular antioxidative system is compromised and peroxidation "reactions" are accelerated in active RA disease. As a result of the excess of H_2O_2 and hydroperoxides formed in these reactions, secondary antioxidant systems measured by TRAP are deficient.

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Influence of Work Related Psychosocial Factors and Psychological Distress on Regional Musculoskeletal Pain

To the Editor:

In a recent interesting research report, Nahit, *et al*[1] attempted to ascertain if there was an association between work related psychosocial factors, such as job demand and control, and reporting of perceived musculoskeletal pain. They demonstrated that those who perceived their work as stressful most of the time were most likely to report pain[1].

As the above study was performed with newly employed workers, I would like to familiarize the readership with a series of studies performed with chronic pain patients (CPP) in a pain facility that also point to the importance of perceived job stress and its importance to pain.

In a series of 4 articles, Fishbain and colleagues have attempted to determine if preinjury job satisfaction influences "intent" to return to work to the preinjury job after pain facility treatment. In the first report, Fishbain, *et al*[2] demonstrated that CPP not intending to return to work after pain facility treatment were more likely to complain of job dissatisfaction. In the second report from this group, Rosomoff, *et al*[3] demonstrated that an association between non-intent to return to work after pain facility treatment and preinjury job dissatisfaction was similarly found across Workers' Compensation and non-Workers' Compensation CPP. In the third report, Fishbain, *et al*[4] looked at actual return to work after pain facility treatment in relation to these variables. They found that actual return to work was predicted at one month "by intent," perceived job stress, and job like (job dissatisfaction) plus other variables. At 36 months, return to work was predicted by "intent" and by perceived job stress plus other variables. In the final study, Fishbain, *et al*[5] attempted to predict "intent" to return to work after pain facility treatment in relation to actual return to work. "Intent" was predicted by perceived preinjury job stress plus other variables. In addition, those CPP who intended to return and did not were predicted by whether there was a job to go back to. Also, CPP not intending to go back to work to the preinjury job initially, but doing so later, were predicted by having a job to go back to. Overall, this series of studies points to a strong relation between preinjury work variables such as job dissatisfaction and "intent" to return to that job after treatment. In addition, these studies indirectly support the findings of Nahit, *et al*[1]. It seems that in trying to understand the

low back pain injury and recovery process, it is important to take into account work related perceptions such as those of perceived job dissatisfaction and job stress.

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Book Reviews

Diagnosis of Bone and Joint Disorders. 4th ed. 5 volumes.
Donald Resnick, Editor, Philadelphia: W.B. Saunders Company, 2002, price $1328 CDN

The White House of the United States is an architectural masterpiece that was originally designed in the late 1790s, and has evolved over the past 200 years to its current state by a series of additions and renovations, as well as a few measured deletions. In my opinion, the 4th edition of Dr. Resnick's textbook on bone and joint disorders is also a masterpiece, and it has evolved in a fashion similar to the residence for the US president.

The core of the first edition is still in evidence, and because a significant portion of that information is still relevant, with its emphasis on anatomic-radiographic-pathologic correlation, there has been no need to overhaul the entire text. Rather, topics that are no longer relevant (e.g., conventional tomography, xeroradiography) have been eliminated, and newer topics (e.g., digital imaging and muscle disorders) have been added. The references for all chapters have also been updated and the text appropriately edited to reflect the new information.

Compared with preceding editions, major revisions and additions of material have also been incorporated, with particular regard to magnetic resonance imaging and musculoskeletal (MSK) ultrasound. In the 3rd edition, for example, internal derangements of joints were covered as a single chapter in a section dealing with trauma. In the most recent edition, internal derangements of joints is a separate section that has been expanded and completely rewritten to reflect the information explosion on this subject.

The original architectural concept for the White House was provided by James Hoban, who still deserves the lion's share of credit; however, the edifice that exists today also reflects the vision and expertise of numerous other individuals over time. Similarly, Dr. Resnick has sought the insights of other authorities on various aspects of MSK imaging to augment his own efforts. The new edition, for example, contains excellent chapters by new contributors discussing "Magnetic Resonance Imaging: Practical Considerations" and "Interventional Spinal Procedures."

We are informed that the newest edition has been streamlined from 6 to 5 "somewhat heavier" volumes, but do not be misled. This work remains encyclopedic in scope and content, and although the text continues to be remarkably readable, it would be the exceptional person who would attempt to read it from cover to cover. Rather, as in the past, I expect to repeatedly use this latest edition as my first line of reference, and to read selectively about many specific subjects in bone and joint disease over the next few years. From my point of view, access to this text is mandatory for rheumatologists, orthopedic surgeons, radiologists, and anyone else who is involved with the full spectrum of musculoskeletal imaging.

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Vasculitis

V.V Ball and S.L. Bridges Jr, Editors. Oxford: Oxford University Press, 2002, 601 pages, price $160 US

This is an overall well written and conprehensive 600 page text on the fascinating topic of vasculitis. The authorship reflects the multisystemic nature and geographic distribution of these diseases and syndromes, as it is written by rheumatologists, immunologists, nephrologists, radiologists, dermatologists, and ophthalmologists from all over the world, including the Middle Ease, Asia, and Africa. The book is divided in 4 sections. The first, which has fewer than 50 pages, focuses on basic sciences, including hypersensitivity, endothelial cell biology, and pathogenesis. Unfortunately, the presentation of these chapters is very bland, and the absence of illustrations is disappointing, as they would have greatly facilitated comprehension and retention of the concepts presented. The second section deals with clinical manifestations common to vasculitis, including individual chapters on cutaneous, ophthalmologic, pulmonary, and renal manifestations, as well as excellent chapters on oral ulcers, neuropathy, and digital ischemia. The chapters in this section are much better illustrated with photographs and figures, most of which are reproduced in color in a separate section. The third section was my favorite, with 2 very well illustrated chapters devoted to imaging studies and percutaneous interventions. These chapters are especially relevant given the increasing role of radiology in the diagnosis and management of patients with medium and large vessel vasculitis. The fourth section constitutes the bulk of the book and includes individual chapters for each vasculitic syndrome and related disorders, including the antiphospholipid syndrome. Most authors follow the same template, and each chapter is very well referenced, except for the unavoidable caveat that no article published after 1999 is cited. Clinicians will appreciate discussions on management that usually include specific recommendations on medication dosage, monitoring, and treatment duration.

Overall, this is a good clinical textbook, although it fell somewhat short of my expectations. I found only a few chapters that I would recommend over recent review articles in journals or even in general rheumatology textbooks. I would have expected a much better presentation of pathophysiology concepts by making use of computer illustration technology. This being said, I believe that Drs. Ball and Bridges have reached their goal and edited a very useful text that will help physicians from all specialties to better care for their patients with these complex diseases.

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Textbook of Pediatric Rheumatology, 4th edition

James T. Cassidy, MD, Ross E. Petty, MD, PhD, FRCPC, Editors. Philadelphia: WB Saunders, 2001, 819 pages, price $284.00 Cdn.

The newly published 4th edition of the *Textbook of Pediatric Rheumatology* is an extremely valuable publication that replaces the 3rd edition as the field's premier text. The primary authors have again produced an outstanding book that is clearly written, well organized, thoroughly researched, and fully referenced.

This edition incorporates extensive revisions of the previous work and several new chapters encompassing the advances in our understanding of the pathogenic mechanisms underlying pediatric rheumatic diseases and the dramatic changes taking place in the area of therapeutics. The textbook now includes contributions from 27 international experts, in addition to the major work by the 2 primary authors. As in previous editions the text includes very readable, in-depth reviews of the major rheumatic diseases affecting children with extensive, up-to-date references. It also includes brief but valuable discussions of uncommon disorders that should be considered in children with features of possible rheumatic disease.

Major changes are found in the first section of the textbook, entitled Basic Concepts. This section now includes not only a fundamental review of the musculoskeletal system, pain, and basic concepts of the immune system, but also has new chapters devoted to mediators of inflammation and genomics, reflecting the increasing importance of these areas. Two new chapters on the subjects of clinical investigations and the assessment of health status and outcome are presented in sufficient detail to give the reader basic working knowledge for the interpretation of the literature. Tables and figures, used frequently throughout the textbook, complement the text, which is usefully organized under various levels of headings. The text's readability is further enhanced by use of larger print and many photographs.

In summary, the authors have succeeded in providing a comprehensive but focused review of the rheumatic diseases of childhood. The *Textbook* is an excellent reference for medical students, postgraduate trainees, as well as all physicians caring for children with rheumatic disease. I most highly recommend it.

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Classic Papers in Rheumatology

P. Dieppe, H.R. Schumacher Jr, and F. Wollheim, Editors. London: Martin Duntz, 2002, 400 pages, price $65.00 US.

In this brightly designed volume the editors selected a group of expert "surveyors" to review 27 topics in rheumatology and to pick out a small group of papers they would then annotate. This included a summary, key message, importance, strength, weakness, and relevance. The scheme works well, except for weakness. Most of the comments were: no weaknesses, too few patients, and crude techniques. What could one expect with "classic" papers? And what would a surveyor do when they list 2/6 and even 5/7 of their own papers? In this latter vein there are few of the "old history," as noted by Eric Bywaters in his pithy foreword. It's not that I miss Hippocrates or Sydenham but I did miss the clear and well written description of juvenile arthritis by George Frederick Still.

There is judicious use of graphs and tables, which distinctly add to the importance of some papers. As would be expected in a multi-author book, some sections stand out because of the expertness of the selection and the comments by the section selector. They are: Sjögren's syndrome, crystal deposition diseases, back pain, association of other systemic diseases with arthropathies, and exercise and rehabilitation in arthritis.

Recently there was a paper questioning the eponymous distinction given Hans Reiter in naming the syndrome of arthritis, urethritis, and/or conjunctivitis. The surveyor's discussion is clear and well considered. It was based on the prior description of this syndrome by the French physicians Feissinger and Leroy, the erroneous description of a spirochaete in his patient by Reiter, and the revelation that Reiter had concealed his past as a war criminal.

The volume is a bit big for bedside reading but deserves to be handy at deskside for a quick dip. It will appeal to rheumatologists from Fellows to those who might say, "I remember that paper!" For physicians contemplating rheumatology, this is a good introduction to a fascinating and wide-ranging specialty, particularly since its cost is not excessive.

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Principles of Bone Biology, 2nd Edition

John P. Bilezikian, Lawrence G. Raisz, Gideon A. Rodan, editors, San Diego: Academic Press, 2002, 1696 pages, price $399.95 US.

This second edition follows the first only 5 years later to incorporate the many advances in this field. It has been expanded to a 2 volume, 4 part text that serves as a comprehensive resource for scientists and clinicians involved in the fields of bone biology, metabolic bone disease, and osteoporosis.

Part I encompasses reviews on the cell biology of osteoclasts, osteoblasts, and their precursors; the biochemistry of collagen, bone matrix proteins; and the role of minerals, hormones, and local regulators of bone remodeling. This is organized into 6 sections with appropriate depth given to each topic. For example, 7 chapters are devoted to parathyroid hormone and its related proteins and peptides, 3 chapters to vitamin D, and 4 chapters to calcitonin.

Nineteen chapters in Part II detail the clinical expression of metabolic bone diseases and their pathophysiology. Twelve chapters in Part III examine the pharmacologic basis of current and new targets for therapeutic strategies. The last 10 chapters in Part IV are dedicated to research tools such as radiographic techniques, molecular approaches to genetics, bone markers, and animal models that have enhanced rapid advancements in bone biology and metabolic bone disease.

The text in each of the 47 chapters is 6 to 12 pages in length in addition to copious references. Chapters are easily understood and organized so that each topic, as intended by the editors, flows well to the next. It is hoped that future editions will incorporate more color diagrams and figures and be available in a CD ROM format to allow portability.

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Correction

Canadian Rheumatology Association Meeting. J Rheumatol 2002;29:1564-73. Abstracts of Podium Presentations given at the Canadian Rheumatology Association Meeting, February 20-23, 2002, were omitted, and they are printed here. We regret the error.

I. Podium Presentations

1

COMPARISON OF MINIMUM MEDIAL JOINT SPACE WIDTH MEASUREMENTS IN THE KNEES OF HEALTHY FEMALES OF TWO AGE GROUPS Beattie K, Boulos P, Duryea J, Jurrianns E, Adachi JD McMaster University, Hamilton Ontario, University of California, San Francisco

To measure the mean medial minimum joint space width (mJSW) in the knees of two age groups of "healthy" females. To compare mJSW measurements of 20-29 year old females with those of 50-59 year old females.

Twenty "healthy" females volunteered to participate in this single knee X-ray study. Of these, 10 were between 20-29 years of age while the others were between 50-69. Each participant completed a consent form and questionnaire prior to having the knee X-ray. Women who had previously been diagnosed with a bone or joint disease were excluded from this study. Individuals were asked to stand for a PA knee radiograph with knees flexed such that their big toes, patellas and thighs were tightly pressed against the Bucky. Feet were externally rotated by approximately 10° and a foot map was traced for each participant to be used in subsequent X-rays. The X-ray beam was directed at a 10° angle to the knee such that it was parallel to the tibial plateau. Using the Kellgren-Lawrence (K-L) scale (0-4), radiographs were graded by a radiologist and rheumatologist to ensure that all knees were, indeed, normal. X-rays were digitized using a Vidar Sierra Plus™ digitizer and measurements of mJSW were made using a knee software package. Statistical analyses were performed using SPSS 10.0.

One knee was excluded from the analyses as it was deemed osteoarthritic on the K-L scale. Thus, 19 X-rays were used in the analysis. Of ten females radiographed in the 20-29 year old age group, mean age (SD) was 24.6 (2.59) and mean BMI was 22.3 kg/m^2 (1.94). For the 9 females in the 50-59 year old age group, mean age was 54.3 (2.63) and mean BMI was 26.7 kg/m^2 (4.06). The mJSW for the 20-29 year olds was 5.11 mm and for the 50-59 year old age group, 4.44 mm. There was a statistically significant difference in BMI between the two groups ($p<0.01$). Thus, in comparing mJSW values between the two groups, BMI was considered a covariate in the analysis. A significant difference in mJSW values was found between the two groups ($p<0.05$).

Although individuals may be considered "normal" by Kellgren-Lawrence standards, females ages 50-59 have significantly smaller minimum medial joint space widths than females ages 20-29.

2

MOLECULAR CHARACTERIZATION OF A NOVEL CYTOPLASMIC PROTEIN GW182 AND THE IDENTIFICATION OF A UNIQUE CYTOPLASMIC COMPARTMENT.

T. Eystathioy[1], E. K. L. Chan[2], K. Griffith[1], and M. J. Fritzler[1], [1]Department of Medicine, University of Calgary, Calgary, Alberta; [2]Department of Molecular and Experimental Medicine, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA, 92037

Autoantibodies from a patient that produced a unique cytoplasmic staining pattern on HEp-2 cells, was used as a probe to isolate a 1.6-kb cDNA insert from a HeLa cDNA library. The *in vitro* translation products of the cDNA yielded a recombinant protein that migrated at 66 kDa in SDS-PAGE. The recombinant protein was immunoprecipitated by the index human serum and by immune rabbit serum, but not by normal human serum or pre-immune rabbit serum. Western blot analysis showed that serum recognized a ~180-kDa protein, suggesting that the isolated clone contained a partial cDNA. Analysis of the cDNA sequence by BLAST search showed that the corresponding human gene is located on chromosome 16p12. The 5' upstream sequence obtained by RACE and the combined 6.6 kb cDNA encoded a protein of 182kDa. The deduced amino acid sequence of the full-length protein showed 39 domains characterized by GW or WG repeats, a single RNA recognition motif (RRM), a nuclear localization signal (NLS), and multiple potential phosphorylation sites. Rabbit antibodies raised against the recombinant protein co-localized at the same cytoplasmic domains recognized by the human antibodies. The human or the rabbit antibodies did not colocalize with markers of the Golgi complex, endosomes, lysosomes, or peroxisomes. Retrospective analysis of the clinical information on the first 20 patients with this novel autoantibody showed that the most common diagnosis is Sjögren's syndrome. This is the first report of a human protein containing multiple GW repeats, and furthermore, the human autoantibody is a marker for a unique cytoplasmic compartment that we have provisionally named GW bodies (GWBs).

3

EVALUATION OF ENDOTHELIAL FUNCTION IN SLE

Sindhu Johnson, Paula Harvey, John Floras, Dafna Gladman, Murray Urowitz. Divisions of Rheumatology and Cardiology. Department of Medicine. University of Toronto

Arterial endothelial function was studied non-invasively by examination of brachial artery responses to endothelium-dependent (post-ischemic reactive hyperemia) and endothelial-independent (sublingual glyceryInitrate) stimuli, using high-resolution external vascular ultrasound. Fifteen lupus patients: 5 with known coronary artery disease (group 1), 5 with subclinical CAD (group 2), 5 with no CAD (group 3), and 5 control subjects (group 4) were assessed. Statistical analysis utilized mean score of rank sums, and p value by Krukal-Wallis test.

Endothelium Dependent and Independent Vasodilation in Lupus Patients and Controls
Mean Score of Rank Sums

	Group 1	Group 2 + 3	Group 4	P value
Baseline	13.00	9.60	9.80	0.55
EDV	3.30	12.55	13.60	0.01
EIV	7.00	12.70	9.60	0.20
EDV/EIV	4.80	11.10	15.00	0.02

Lupus patients with CAD had a EDV/EIV rank score mean of 4.80, whereas the control group score was 15.00. Lupus patients with subclinical CAD and no CAD were similar, and therefore grouped together. They had a mean rank sums score of 11.10.

This test differentiates lupus patients with CAD from controls. The lupus patients with subclinical CAD, and no CAD were also different than controls. Brachial artery ultrasound is a valuable noninvasive tool in assessing endothelial function in lupus patients and controls.

4

CAN INFECTIONS TRIGGER RHEUMATOID ARTHRITIS IN A PREDISPOSED INDIVIDUAL? A CONTROLLED SURVEY OF PATIENTS WITH MUSCULOSKELETAL DISEASE. M Laskin, J Pope, A Krizova, J Goodwin and J Quimet., The University of Western Ontario, London, ON.

The etiology of rheumatoid arthritis (RA) is unknown. Studies suggest that Rubella and Parvo B19 viral infections may predispose to a syndrome that looks like RA. Other immunogenic stimuli such as infections or vaccinations theoretically could be a risk factor for RA. We sent a questionnaire to RA subjects (N = 419) and controls with non-inflammatory musculoskeletal disorders (MSK) (N = 353), to investigate whether viral, bacterial, or other infectious triggers are a risk factor for RA. Questions ascertained past infections, exposure to infectious agents, and subjects' opinions on possible causal factors prior to symptom onset. To date, 243 RA and 196 control subjects (with OA, tendonitis, fibromyalgia) have responded; the groups do not differ in terms of the demographic variables age ($\bar{x}$= 58 years, RA and control) or gender (82% female, RA and control). As expected, RA subjects are less likely than controls to have experienced physical trauma prior to the onset of joint pain (26% versus 44%), $P<0.0001$. RA patients were less likely to report having taken antibiotics one year prior to disease onset (27% RA, 51% controls), $P<0.0001$. Prior to symptom onset, RA patients were less likely to have suffered from Rubella or German measles than controls (43% RA, 58% controls), $P<0.0083$. Similarly, RA subjects were also less likely to have had any infections 12 months prior to symptom onset (22% RA, 35% controls), $P<0.0052$. Though numbers were low (N= 19, total), 3% of RA and 8% of controls reported having ever had Hepatitis A, B or C, $P<0.02$. There were no between groups differences re: having had bacterial infections, $P<0.07$; Strept throat 12 months prior to disease onset, $P<0.21$; Shingles (Herpes Zoster), $P<0.46$; positive TB skin test, $P<0.47$; or Rheumatic fever, $P<0.71$. As well, no one reported Parvo B19 infections. Fifty percent of RA and control subjects reported having received vaccination(s) since age 18. Comparisons within the RA subjects (166 seropositive versus 77 seronegative) were also made. Six seropositive patients and one seronegative patient reported ever having Hepatitis A, B or C, $P<0.0026$. There were no differences re: having suffered from Rubella or German measles, $P<0.44$; having experienced physical trauma prior to onset of joint pain, $P<0.054$; suffering from infections 12 months prior to symptom onset, $P<0.65$; or having taken antibiotics one year prior to disease onset, $P<0.91$. It appears that rates of infections and vaccinations are not higher prior to the development of RA compared to controls.

5

THE PHYTOESTROGEN COUMESTROL DELAYS THE ONSET OF AUTOANTIBODIES IN MURINE LUPUS

L. Schoenroth, D. Hart, M. Fritzler. Faculty of Medicine, University of Calgary

Our objective was to determine whether the phytoestrogen coumestrol can influence disease expression in the NZB/W murine model of SLE. Seventy female NZB/W F1 mice 5-6 weeks of age were fed a soy-free, casein-based diet with or without coumestrol (0.01%). Groups of 10 animals were sacrificed at 16, 24 and 39 weeks. Anti-nuclear antibodies (ANA) were detected by indirect immunofluorescence (IIF), anti-dsDNA by IIF using *Crithidia* substrate, anti-cardiolipin by ELISA, and anti-histone by immunoblotting. Proteinuria was determined by Ames dipstick.

Group	ANA (%)	Anti-dsDNA (%)	Anti-histone (%)	Anti-cardiolipin (%)
Baseline (5-6 weeks)	0	20	100	0
16 weeks Treatment	10	10	90	0
Control	10	0	100	0
24 weeks Treatment	30	0	100	0
Control	60	40	100	10
39 weeks Treatment	80	50	100	20
Control	100	50	100	20

Antibodies to cardiolipin first appeared at 24 weeks of age in 10% of the controls but in none of the coumestrol-treated mice; 20% of both groups were positive by 39 weeks of age. Antibodies to histone (either H1 or core) were present in almost all of the mice; younger mice reacted more weakly and primarily with the H1antigen. At 24 weeks the controls had stronger reactivity with histone antigens: densitometry readings in the controls were twice that of the treatment group ($p>0.05$). Significant proteinuria (>3 g/L) was present in 50% of the controls, vs 20% of the treatment mice at 39 weeks ($p=0.4$). Splenomegaly was significantly greater in the control group at 24 weeks (90 mg vs. 74 mg, $p=0.006$), this difference was not noted later. Survival was not affected by treatment.

Coumestrol ingestion seems to have a transient effect on autoantibody expression, splenomegaly, and development of proteinuria. Antibodies to cardiolipin were not induced by treatment.

6

PERSISTENCE OF CHLAMYDIA IN REACTIVE ARTHRITIS: VIA HOST LIPID TRAFFICKING? S Tse[1,3], R Inman[1,4], B Chiu[1,4] and S Grinstein[2,3]. University of Toronto, Division of Rheumatology[1] and Cell Biology[2], Hospital for Sick Children[3], University Health Network[4], Toronto.

Background: Reactive arthritis, Kawasaki Disease and vasculitis may be caused by the ineffective clearance of microorganisms such as *Chlamydia trachomatis*. *C. trachomatis* is an intracellular parasite that propagates in host cells within an inclusion vacuole where it is capable of evading host cell defenses. The mechanism that generates and maintains the inclusion is not well understood. Lipids, arising from de novo synthesis by *C. trachomatis* or recruited from the host cell, may contribute to the formation and maintenance of the inclusion membrane. The unique composition of the inclusion vacuole may influence the activity of lipid-sensitive cellular enzymes, such as protein kinase C (PKC). PKCs are comprised of three groups: classical(α,β,γ), novel($\eta,\varepsilon,\delta,\theta$) and atypical($\iota,\xi$). All isotypes are activated by phosphatidylserine, but cPKC and nPKC isotypes require diacylglycerol (DAG) for optimal activity. This property is conferred to cPKC and nPKC by a unique DAG-binding domain, the C1 cassette. **Purpose:** To define whether DAG is present in the inclusion membrane of host cells infected with *C. trachomatis* and to determine whether PKC isotypes associate with and are potentially involved in the growth of the inclusion membrane. **Methods:** Human epithelial cells (HELA) were transiently transfected with plasmids encoding GFP-linked full-length PKCs (isotypes $\alpha,\beta\mathrm{I},\delta,\xi$), or the isolated C1 domain of PKCδ (C1δ) or PCKγ(C1γ). The C1 domains were used as probes for DAG. 24 hrs after transfection, the cells were infected with *C. trachomatis* L2 for 20hours. The distribution of DAG or PKCs was assessed by fluorescence digital imaging (FDI). **Results:** Following *C. trachomatis* infection, both C1 constructs (δ,γ) were found to accumulate on or near the inclusions suggesting that DAG is a component of the inclusion membrane. Of all the PKC types studied, only the novel isozyme PKCδ was localized on or near the inclusion membrane. The expression cPKC and nPKC was confined to the cytosol. **Conclusion:** DAG appears to be preferentially accumulated in the *Chlamydial* inclusion membrane, where it is likely collected from host cell sources. This accumulation in turn leads to the selective recruitment and possible activation of the novel PKCδ isotype. Re-routing the traffic of host cell lipids to the inclusion membrane and their subsequent modification therin may be a possible mechanism whereby *Chlamydia* evades host defenses. Interference with the ability of the parasite to modify lipid traffic may prove as a useful therapeutic strategy in reactive arthritis.

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