

Correspondence



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Anemia of Chronic Disease in Patients with Rheumatoid Arthritis — Use of Zinc Protoporphyrin (ZPP) Levels

To the Editor:

We read with interest the editorial by Swaak¹ on anemia of chronic diseases in patients with rheumatoid arthritis (RA). The article points out that the anemia of chronic disease is the most frequent cause of anemia in RA, and that the most reliable indicator for the detection of iron deficiency is stainable iron content in bone marrow aspirate. In practical terms, however, this procedure may not be routinely performed in patients suspected clinically to have iron deficiency. We wish to draw attention to the role of measuring zinc protoporphyrin (ZPP) concentrations.

Chronic disorders are frequently accompanied by impairment of iron metabolism². There are various blood tests that can be done to elucidate iron deficiency in RA, including serum ferritin, mean corpuscular volume (MCV), and serum transferrin receptor levels, as reviewed by Swaak. The serum ferritin level is not a reliable indicator of iron deficiency, as it is an acute phase reactant and the level may be elevated in RA. MCV can also be affected by the second-line treatment for RA (e.g., azathioprine, salazopyrin, methotrexate), which can increase the MCV. Coexisting morbidity (e.g., hypothyroidism, B12, folate deficiency, and alcohol abuse) could also influence results.

The use of ZPP level in blood to diagnose iron deficiency anemia in RA has received limited attention. Red cell precursors normally synthesize slightly more protoporphyrin than is needed for heme synthesis. The excess remains with the cell throughout its lifespan and has been called free erythrocyte protoporphyrin (FEP). When iron is not available for heme synthesis protoporphyrin accumulates in excess as zinc protoporphyrin. The level of FEP increases dramatically in iron deficiency and is a sensitive laboratory abnormality².

The ZPP determination is simple and also appears to provide a sensitive index of iron-deficient erythropoiesis³. Currently it is used to differentiate between iron deficiency, beta thalassemia, and lead poisoning⁴. ZPP level is also used as a screening tool for iron deficiency anemia in hospitalized patients⁵.

ZPP levels are elevated in iron-deficient erythropoiesis, which can be associated with iron deficiency and anemia of chronic diseases.

In one study the ZPP level returned to normal after successful treatment of the underlying disease, which included polymyalgia rheumatica⁶. Those patients had typical laboratory findings of iron deficiency including low iron, decreased transferrin saturation, and decreased bone marrow sideroblasts, and also strongly elevated ZPP level.

As the editorial points out, anemia appears to be associated with poor outcome in patients with RA. We believe that further work in assessing the role of measuring ZPP in patients with RA to give a noninvasive indicator of the degree of poor iron utilization and heme synthesis would also be merited. This would particularly be helpful when the response to treatment is being assessed. The cost of testing ZPP level is also relatively low.

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Dr. Swaak replies

To the Editor:

I read with interest the letter by Saravana and Rai in reaction to the editorial Anemia of Chronic Disease in Patients with RA. The question raised by Saravana and Rai is very important, related to which test is the best method for detection of iron-deficiency erythropoiesis (IDE) in patients with RA. Next to the question, which test could also predict the eventual effect on iron supplementation in restoring the anemia. In the past different methods were proposed and investigated: the measurement of the percentage of hypochromic red blood cells, content of hemoglobin in reticulocytes, soluble transferrin receptor, ferritin levels, and zinc protoporphyrin (ZPP) levels.

Presently, serum ferritin levels are the most common test in daily practice. The remark by Saravana and Rai that serum ferritin level is not a reliable indicator of iron deficiency, because it behaves as an acute phase reactant, is partly correct. However, by defining a cutoff $< 50 \mu\text{g/l}$ we were able to show that this value correlated with the results obtained in bone marrow smears (no stainable iron), but also with the effect of iron supplementation. In this way the use of serum ferritin levels in RA was validated. In a recent study¹ ZPP, the soluble transferrin receptor, and the hemoglobin content of reticulocytes were investigated as a diagnostic and prognostic parameter in RA patients with anemia of chronic disease. In our study the value of serum ferritin was confirmed, and no additional benefit of the other measures for predicting or monitoring IDE was shown. To claim that a test can

be used for the diagnosis of IDE, the test has to be validated in the defined disease. For example, in patients with renal disease no significant correlation could be demonstrated between ZPP levels and IDE²⁻⁴. In these studies it was concluded that ZPP could not be used to predict the erythropoietic response to iron supplementation.

The same holds true for serum ferritin levels; however, in these studies a cutoff value of < 100 µg/l was defined for IDE. But it should be stressed that patients undergoing dialysis often showed raised serum ferritin levels, which is not explained. Still, a weak correlation could be demonstrated in another study⁵. Therefore, it should be stressed that for every disease the defined measure has to be validated. In this way the ZPP levels are not investigated in a prospective way in RA patients with anemia of chronic disease and IDE.

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Tumor Necrosis Factor (TNF) Can Paradoxically Increase on Etanercept Treatment, Occasionally Contributing to TNF-Mediated Disease

To the Editor:

Sari, *et al*¹ described a 34-year-old woman with a 3 year history of rheumatoid arthritis (RA), who developed psoriasis when given etanercept; the psoriasis resolved on cessation of etanercept. When etanercept was restarted the psoriasis returned. The psoriasis again resolved on cessation of etanercept. Etanercept is a treatment approved by the US Food and Drug Administration for RA, juvenile RA, ankylosing spondylitis, psoriatic arthritis (PsA), and psoriasis itself². Tumor necrosis factor- α (TNF- α) is a signaling molecule, 17 kDa in its soluble form (sTNF), 26 kDa as a transmembrane form (tmTNF). TNF maps to chromosome 6p21.3. TNF has emerged as an important inflammatory cytokine implicated in a number of inflammatory diseases or diseases with significant inflammatory component, including Crohn's disease, congestive heart failure (CHF), RA, and psoriasis, among a number of others. In psoriasis, TNF is abnormally released from cells in the skin in a constitutive manner — inducing production of other cytokines and chemokines that act to mediate an overly active autoimmune response³.

Etanercept is a 934 amino acid wholly-human protein, roughly 150 kDa total. It consists of an IgG Fc portion fused to 2 TNF receptor molecules (specifically, TNF-R2, synonymous with p75). It was introduced in late

1998 as the first drug in its class — TNF antagonizing agents — for the treatment of RA. Since then, its use has only expanded. We describe the apparent paradox of a drug, approved for treating psoriasis, apparently causing it.

In 1999, Moreland, *et al* reported from a randomized controlled trial that etanercept had significant benefit in improving signs and symptoms of RA⁴. Another study in 2004 showed equally impressive results, with RA patients significantly improving after starting etanercept treatment⁵. Etanercept was first reported to have had benefit in patients with PsA in 2000, in a 12 week study, where 73% of patients responded to etanercept therapy compared with only 13% of placebo-treated controls. This study also reported 25% of patients with psoriasis achieved a 75% improvement in psoriasis activity score compared with none in the placebo group⁶. It is important to note that PsA and psoriasis often occur together; about a third of patients with psoriasis have PsA, and most patients with PsA have coincident skin involvement. PsA represents an arthropathy that follows any of a number of specific patterns. Nail lesions, pitting edema, and ocular involvement are common⁷. Psoriasis is largely confined to the skin, with large silvery and scaly plaques; small, guttate lesions; pustular lesions (the most life-threatening form, associated with fever, malaise, diarrhea, hypocalcemia, leukocytosis, and liver failure); inverse psoriasis (extensor surfaces — knees, elbows, lower back, and scalp — spared; covered surfaces — axillary, inguinal, perineal, genital, gluteal — involved); and nail psoriasis⁸.

While etanercept is widely, and we believe correctly, understood to be an anti-TNF agent, it is possible that it may, at times, be increasing the levels of the very cytokine that it is designed to downregulate. At least 7 studies have shown an increase in serum TNF levels during etanercept treatment⁹⁻¹⁵.

Tsimberidou, *et al*⁹ administered 25 mg of subcutaneous etanercept twice weekly to 10 patients with refractory multiple myeloma, and TNF concentrations were shown to rise significantly; it was concluded that etanercept had no anti-multiple myeloma activity.

Suffredini, *et al*¹⁰ studied etanercept's effects on endotoxemia in 18 healthy volunteers (6 given placebo, 6 given low-dose etanercept, 6 given high-dose etanercept) and concluded that the drug markedly increased TNF levels in a dose-dependent fashion.

Zou, *et al* described upregulation of TNF secretion on administration of etanercept¹¹. They studied¹² cytokine effects of etanercept in 10 patients with ankylosing spondylitis and found upregulation of serum TNF levels even in those patients achieving clinical benefit.

Madhusudan, *et al*¹³ investigated the effects of etanercept in patients with progressive metastatic breast cancer that was refractory to conventional therapy, and determined that TNF levels were elevated within 24 hours of etanercept therapy — an elevation that persisted throughout the course of etanercept treatment in all patients who received the drug.

Nowlan, *et al*¹⁴ studied etanercept as a potential treatment for TNF-receptor associated periodic syndrome (TRAPS), a type of hereditary periodic fever, and found that 8 patients with TRAPS who were given etanercept had increased levels of TNF.

Finally, Eason, *et al*¹⁵ studied the use of etanercept in 6 patients given OKT3, an immunosuppressive agent that targets the T cell receptor (TCR/CD3) complex and works to prevent activation of T lymphocytes, helping to mitigate the potential for rejection after transplantation. They found that TNF levels were elevated post-etanercept, although they also observed clinical benefits of preserved renal function and less OKT3-mediated side effects in those who had elevation of circulating TNF.

Although Sari, *et al* did not monitor their patient's serum TNF levels, we believe studies cited above indicate that etanercept could well have caused an increase in TNF that contributed in generating her psoriatic symptoms.

It is important to note that in all of these studies, TNF that is biologically or immunologically active, that is active in immune and cellular signaling, is not necessarily the same as that detectable by anti-TNF antibodies by ELISA. TNF bound to etanercept or other carrier molecules can still

be present and detectable in the circulation but be unable to mediate biological, physiological, immunological, or inflammatory effects. The half-life of natural sTNF in circulation is variously estimated to be between 3 and 30 minutes. By administering etanercept it has been shown that this half-life is lengthened. Although sTNF bound by etanercept is not usually able to exert its physiological signaling effects, it may sometimes do so, either by dissociation from or while still retained by etanercept.

De novo generation of TNF mediated disease is not unheard of during etanercept treatment, and other published cases will be reviewed below. A third possibility is reviewed below, where etanercept, simply by removing sTNF signaling, can increase TNF mediated effects.

An explanation of the mechanism of etanercept increasing TNF has been reviewed¹⁶. Briefly, sTNF or tmTNF mediates its action through 2 outer cell-membrane receptors, TNF-R1 (weighted toward proapoptotic and antiinflammatory actions) and TNF-R2 (weighted toward antiapoptotic and proinflammatory actions). sTNF preferentially binds TNF-R1 over TNF-R2, while tmTNF binds and stimulates TNF-R1 and TNF-R2 equally well. Etanercept preferentially binds sTNF, preventing it from binding to TNF receptors, but shows little binding to, and therefore little inhibition of, signaling by tmTNF¹⁷. Since sTNF mediated downstream actions tend to be preferentially proapoptotic and antiinflammatory via the TNF-R1 pathway, tm-TNF is therefore left unopposed. A state of relative shift of weighting from TNF-R1 toward TNF-R2 occurs, resulting in a shift toward an antiapoptotic, proinflammatory state. By this mechanism, it is conceivable that etanercept actually increases TNF levels, and in some cases, as Sari, *et al* learned, may even cause the afflictions it is designed to treat.

TNF signaling is central to the pathology of Crohn's disease and is thought to play a part in CHF. A double-blinded placebo-controlled study¹⁸ showed that etanercept was not effective for treatment of Crohn's disease. However, at least 2 studies describe cases of initial presentation of Crohn's disease after administration of etanercept for other reasons^{19,20}; in neither case were TNF levels monitored.

From 1999 to 2001, etanercept was evaluated in 2 large randomized double-blinded placebo-controlled trials in CHF, where TNF and other inflammation related cytokines were seen to be elevated. Both studies concluded that etanercept was not efficacious, and one found etanercept use was associated with worsened mortality and increased hospitalizations. This association was dose related but did not reach statistical significance²¹.

There have been a number of case reports of CHF associated with etanercept use; Kwon, *et al* reviewed 29 cases of etanercept use that were associated with CHF onset: 4 of these patients were less than 50 years of age and had new-onset heart failure²². They concluded that TNF antagonists may indeed induce new-onset heart failure in a fraction of patients.

We conclude that elevated levels of biologically active TNF can occasionally occur with etanercept therapy. Three possible mechanisms for this are described. Etanercept induced elevation of TNF signaling may at times generate TNF mediated disease. Etanercept has benefit in lowering pain, increasing energy level, and improving quality of life in patients with RA and ankylosing spondylitis. But use of etanercept can be a concern because of an associated increase in TNF. We would advocate at least monitoring TNF levels detectable by ELISA, if not biologically active TNF. The former is easily available through specialized testing laboratories. The use of etanercept with caution is warranted, another example that understanding all effects of an administered drug should be kept in mind when treating the patient.

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Drs. Sari and Akkoc reply

To the Editor:

We appreciate Bhatia and Kast's interest in our case report and welcome their valuable comments. They argue that etanercept treatment can sometimes lead to increased tumor necrosis factor- α (TNF- α) concentrations that may occasionally contribute to occurrence of TNF mediated disease, as in the case we described¹.

They state there have been at least 7 studies showing an increase in TNF levels during etanercept treatment²⁻⁸. One report⁷ actually reviewed the results of another study that was cited by them and also in our case report⁶. This study suggested an increase in the number of interferon- γ (IFN- γ) and TNF- α -secreting T cells after nonspecific antigen stimulation after etanercept therapy in patients with ankylosing spondylitis. However, no data of serum TNF levels were given in that study.

The rest of the studies were mostly performed in patients with non-rheumatic conditions including myeloma⁵, breast cancer², or renal transplant⁸, or in healthy volunteers given endotoxin⁴. These studies and another³ conducted in patients with TNF-receptor associated periodic syndrome (TRAPS)³ all reported increased levels of immunoreactive TNF. In 3 of these studies TNF bioactivity was measured by cytotoxicity assays and was found not to be increased^{3,4,8}. Preclinical and clinical studies have demonstrated that etanercept prolongs the half-life of TNF^{8,9}, and increased TNF levels observed in these studies are probably due to the carrier effect of etanercept.

Bhatia and Kast claim that etanercept-bound soluble TNF may sometimes exert its physiological signaling effects either by dissociation from etanercept or while still retained by it. However, this is very unlikely considering that TNF must be present for extended periods of time to achieve maximal biologic activity¹⁰. The development of psoriasis in our patient in the presence of marked improvement of arthritic symptoms (which are certainly also TNF mediated) also contradicts their hypothesis, suggesting a role for increased TNF levels in the circulation in the occurrence of psoriasis in our patient¹. Occurrence of psoriasis or psoriasiform lesions after anti-TNF therapy, despite a good clinical response in arthritic symptoms, has also been observed by others^{10a}.

Psoriasis has been reported not only with etanercept therapy, but also with infliximab and adalimumab, which have not been shown to lead to increased TNF levels in the serum. Interestingly, our patient who developed psoriasis after etanercept therapy did not develop any psoriatic lesion after infliximab within a followup of 15 months. We pointed out in our report that etanercept⁶, but not infliximab¹¹, has been shown to upregulate local secretions of TNF- α and IFN- γ , and proposed that this differential effect of the 2 TNF inhibitors could provide an explanation for the occurrence of psoriasis in our patient under treatment with etanercept, but not infliximab. However, there are reports of other cases that developed psoriasis with infliximab but not with etanercept¹. It is likely that different mechanisms may play a role in different patients.

We agree that etanercept treatment may be associated with other TNF mediated diseases, such as Crohn's¹², in which infliximab is efficacious¹³. Uveitis is another condition that can be successfully treated with infliximab, but that can occur as an adverse effect of etanercept¹⁴. However, worsening of congestive heart failure (CHF) has been reported with both

TNF inhibitors¹⁵. The review Bhatia and Kast cite describing 4 cases of new-onset CHF associated with etanercept use in patients under age 50 also reports 6 cases associated with infliximab therapy¹⁶. Moreover, a randomized controlled trial with infliximab for treatment of CHF was also stopped early due to increased morbidity and mortality¹⁷.

We believe the increased TNF levels reported in some studies cannot alone explain the occurrence of the paradoxical adverse effects such as psoriasis that have been reported not only with etanercept, but also with the other TNF inhibitors. We believe monitoring patients under etanercept therapy for detectable TNF levels is of questionable clinical value at best, and probably not necessary.

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Whiplash and Widespread Pain

To the Editor:

We understand that Sterling, as a physiotherapist, in her discussions of hypersensitivity and whiplash¹, would find clinical tests of a subjective nature (i.e., perceptions of pain responses to stimuli and pain thresholds) useful in daily practice. That is the very nature of much of current physiotherapy practice — focusing on pain levels and attempting to quantify pain. As physicians, our training encourages us to ask different questions of the chronic pain problem, such as how patients' environment (litigation, compensation), expectations of recovery, and psychosocial characteristics shape their clinical presentation and prognosis. This approach is increasingly important in many medical conditions, and can be no less so in a condition that is defined less by injury (no one, not even physiotherapists, know of what whiplash injury consists) than by widespread, systemic illness inexplicable by pathology alone². The concern with focusing on a theory that links hypersensitivity and outcomes is that this focuses clinicians and their patients on injury.

Sterling, in reviewing risk factors for chronic pain following a motor vehicle accident (MVA) appears to have missed the boat (for an Australian this could be a long sentence). The most single important factor determining whether or not chronic whiplash-associated disorder (WAD) develops after an MVA is where one lives, something that could not be tested in the Manchester study. Some cultures are the Petri dishes for chronic pain. Although the studies are few, and more are needed to extend the results, results from Germany, Lithuania, and Greece, when examined in detail in relation to similar studies conducted in whiplash cultures (i.e., North America and Australia), clearly define culture, not crash, as the chief determinant of outcome³. Still, it could be argued that, within a whiplash culture, not all collision victims develop chronic pain. It is thus worthwhile to identify prognostic factors. Yet, here too, we feel the most globally important factors, such as expectation of recovery, are being overlooked by

researchers who cling to injury-based theories because their training and experience do not allow them to step out of those unidimensional models.

Current work in Saskatchewan (data in submission), for example, where litigation has been eliminated, and more than 100 variables are accounted for in multivariate analysis, indicates that what the injured person expects in terms of recovery in turn determines time to self-reported recovery. We find this approach at identifying predictors of outcomes much more compelling, being based on large, unselected populations, without the selection bias that the small sample size of Sterling, *et al* introduces. Many more factors are accounted for and there is a more extensive inclusion of those at risk for chronic pain. We find research on hypersensitivity has been conducted without any population based approaches, without a defined gold standard for hypersensitivity, and with no known sensitivities or specificities for any of the tests conducted (Ferrari³, p. 112). This narrowly focused, rudimentary research strays into metaphysics and moreover smacks of the 19th century explanation for chronic pain — nervous irritation⁴. With railway spine in the 19th century, and then in 2 separate occasions with whiplash earlier in our history, the diagnosis of nervous irritation has been championed in one form or another⁴. Whatever medicine has learned over the years about the importance of psychological factors in chronic pain tends to be ignored or downplayed as nonetiologic. What seems most tempting about concepts like nervous irritation then, and hypersensitivity now, what places these terms in the theorist's spotlight, is the emotional connotations of these terms, making them ideal to use with laypeople, and gaining ready acceptance (almost as terms of empathy) in a suffering patient.

Hypersensitivity is, quite plainly, a distraction to the truth, and a disservice to our patients, as we cause them to focus on an unidentifiable problem within their nervous system arising from an unidentifiable injury, rather than focusing on how their beliefs (and those of our society), expectations, and victimization within the litigation and treatment industries have led them to chronic pain.

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Dr. Sterling replies

To the Editor:

Once again we hear from Ferrari and Russell, who cite only their opinion-based papers, thereby negating any attempt to engage them in valid scientific debate in a prestigious peer-reviewed journal such as this. They believe that, "[T]he most single important factor determining whether or not chronic WAD develops after an MVA is where one lives."

At odds with this belief is a recent systematic review on prognosis following whiplash injury that failed to identify culture as a predictor of poor outcome¹. The Greek study² quoted by Ferrari and Russell was included in this review, but was not rated as a particularly high quality study. The

German study to which they refer comprised 43 subjects with acute whiplash injury, of whom only 32 (74%) participants attended for followup assessment³ — which can hardly be considered as a population based study!

While a full and clear picture of these “whiplash” conditions is yet to be elucidated, one fact is quite apparent. They are remarkably complex, with diverse clinical manifestations that can include motor dysfunction, psychological distress, and, in some patients, evidence of sensory dysfunction.

The phenomenon of sensory hypersensitivity to a series of stimuli, both noxious and non-noxious, has been unequivocally demonstrated in numerous cohorts, in the acute and chronic contexts, by researchers from many disciplines involved in pain medicine (including physiotherapists)⁴⁻¹⁰.

Two studies, one conducted in Denmark and the other in Australia, have shown that sensory hypersensitivity, often in association with other prognostic indicators such as pain intensity and some psychosocial factors, is predictive of poor recovery^{6,11}.

While it is thought that the sensory hypersensitivity is a reflection of altered nociception, interpretation of many of the quantitative sensory tests used in clinical research is necessarily dependent upon the patients’ cognitive responses. However, evidence of spinal cord hyperexcitability as measured by reflex muscle responses following direct electrical stimulation to a peripheral nerve has been demonstrated in both chronic whiplash and other painful musculoskeletal conditions^{12,13}. This reflex response is robust in the presence of anxiety and catastrophization and provides what can be considered as “objective” evidence of central hyperexcitability¹⁴⁻¹⁶.

As a side issue, it is disappointing that Ferrari and Russell have chosen to launch an ad hominem attack upon the physiotherapy profession from their self-appointed position as “trained physicians” who are apparently custodians of the truth in these matters. They would be better advised to heed the words of William J. Mayo, who wisely said: “Scientific truth which I formerly thought of as fixed, as though it could be weighed and measured, is changeable. Add a fact, change the outlook, and you have a new truth. Truth is a constant variable. We seek it, we find it, our viewpoint changes, and the truth changes with it”¹⁷.

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Alberta Rodeo Riders Do Not Develop Late Whiplash

To the Editor:

We were surprised to see that Shannon, *et al*'s paper regarding the comparative rates of chronic whiplash in Alberta rodeo athletes versus members of the rodeo audience merited publication¹. Despite these authors' claim that “we have no reason to believe that the distribution of such injuries should be strikingly different in these 2 groups”, we would have surmised that the peer reviewers of this article would have easily discovered the reason that escaped Shannon, *et al* and yet would have been readily apparent to most lay readers of the study. We find the authors' conclusions just as publication-worthy as those of a study of the average height of NBA basketball players versus game attendees, with the conclusion that the difference of more than a foot in height is best explained by the theory that the attendees must be lacking in nutrition. In a similar vein, Shannon, *et al* explained the difference in symptom duration between rodeo athletes and audience members as the result of a specious biopsychosocial theory that sidesteps the enormous amount of literature indicating an organic etiology of most chronic whiplash symptoms, instead blaming the chronic symptoms on an irrational fear of whiplash injury in the patient²⁻¹⁰.

In arriving at their biopsychosocial explanation for their findings, Shannon, *et al* managed to overlook the fact that rodeo athletes are self-selected ultra-hardy members of the population, located at the furthest right extreme of the injury susceptibility bell curve. While few laypeople are aware of the definitions of the epidemiologic terms “bias” and “confounding,” most are aware of the intuitive concept that professional athletes should not be compared to nonprofessional athletes for the characteristics that make them most likely to become professional athletes: physical prowess and injury resistance. It is rather surprising that the reviewers who green-lighted this paper for publication were not more attentive. In our opinion, this paper should not have been published in its current form.

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Drs. Ferrari and Russell reply

To the Editor:

Drs. Centeno and Freeman seem to “get” the point of our study: there is a significant psychosocial difference between athletes and nonathletes, and this may lead to vastly different whiplash injury outcomes. Whiplash injury is thus not like a leg fracture: while coping style may assist in some aspects of rehabilitation from a fracture once it is healed, being an athlete probably does little else to speed recovery from a fracture. A form of “mental toughness” or other psychosocial differences between athletes and nonathletes is more likely to be relevant in whiplash injury recovery, and this aspect is apparent from our study. As even Drs. Centeno and Freeman managed to get this, we are not surprised the reviewers should as well.

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RS₃PE Syndrome: Bad or Good Prognosis?

To the Editor:

We read with great interest the article by Russell regarding the potential relationship between remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) syndrome and neoplasia¹. As the author concluded, prospective followup studies would help clarify longterm risk of neoplasia in patients with RS₃PE syndrome.

Since 1988 we have followed 15 cases of RS₃PE syndrome in a standardized manner at a single university institution. Reports on 12 cases have been published, and we describe here the clinical, immunogenetic, and development characteristics of the whole cohort, adding 3 new cases seen in the last 3 years². All cases fulfilled the main features of RS₃PE syndrome given in the seminal article by McCarty, *et al*³. Our study protocol for these cases has been published, and these 3 new cases were followed according to it².

The main results are shown in Table 1. No patient needed disease modifying antirheumatic drugs to achieve remission.

Although initially RS₃PE syndrome appeared to be a well characterized entity with a good prognosis, in the last few years several groups have questioned this view, as the syndrome has been associated with several solid tumors, hematological diseases, immunostimulants, infections, and rheumatic conditions⁴. Since its initial description, most cases have shown clinical, developmental, and immunogenetic features that distinguished RS₃PE from the 2 most closely related conditions, late-onset rheumatoid arthritis (RA) and polymyalgia rheumatica (PMR)³. In that sense, an association between RS₃PE and HLA-DR antigens has not yet emerged, whereas both RA and PMR are correlated with HLA-DR4, although the putative epitopes responsible for these 2 conditions differ in location⁵. In our view, RS₃PE syndrome may be seen from 3 different perspectives. The first plausible explanation is that this entity may be a type of reactive arthritis favored by some HLA antigens, such as B27 and B7-CREG antigens. In the present series, 46% showed at least one of these antigens, but we did not investigate the presence of habitual pathogens for this type of arthritis. Also favoring this notion, a late-onset undifferentiated spondyloarthropathy syndrome resembling the features of RS₃PE has been described in men over 50 years of age, and over time some of them developed ankylosing spondylitis⁶. A second conception has been supported by some authors, that both PMR and RS₃PE syndrome are similar conditions, emphasizing the idea that the presence of distal edemas only indicates a better prognosis and not a real difference between the 2⁷. However, we must keep in mind that the HLA profile of these 2 conditions is quite different, as we cited above and also show here. Finally, a third conception is that the condition could involve a type of paraneoplastic syndrome linked to the synthesis of a factor such as interleukin 6, among others⁸. This view is supported by some recent case reports and small series, but we found no case of neoplasia in the present report. We found one patient who presented an IgG-kappa monoclonal paraproteinemia, but he has developed neither multiple myeloma nor malignant disease over a followup of 9 years. Two of our patients died, one with acute myocardial infarction and one with a cerebral hemorrhage.

In our opinion, RS₃PE syndrome is a well characterized entity with a spectrum of severity ranging from the less severe and most common forms,

represented by cases with one attack and no relapse; then an intermediate form, in which there are relapses successfully treated with corticosteroids (20% of the present series); and in the extreme of the spectrum, cases associated with neoplasia, which fortunately represent a minority among RS₃PE cases.

In our context, RS₃PE still remains a definite condition with an excellent prognosis, but some questions remain unsolved. For example, which patients will have a benign, self-limiting course and which will have more protracted disease, and more importantly, whether the disease course and the risk of neoplasia can be predicted on the basis of the initial presentation or the HLA profile.

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