Removal of hyaline articular cartilage reduces lymphocyte infiltration and activation in rheumatoid synovial membrane.

Katsuyuki Fujii

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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Use of Prognostic Markers to Guide Biologic Therapies for Rheumatoid Arthritis

To the Editor:

The ATTRACT trial, a landmark study of the combination of infliximab with methotrexate (MTX), provides dramatic evidence of the potential ability of modern pharmacotherapy to arrest the progression of erosive disease in patients with rheumatoid arthritis (RA). At 54 weeks, the mean radiographic score actually improved by 0.7 (SD = 3.8) in the group treated with 10 mg/kg infliximab every 4 weeks and an average dose of 17 mg MTX per week, compared with the score worsening by 7.0 (SD = 10.3) in the MTX group.

This data lends support to the rationale that tumor necrosis factor-α (TNF-α) inhibitors be used as first-line therapy in RA, and etanercept has been FDA approved and is being marketed for use in “DMARD-naïve” patients with moderately to severely active disease. In an editorial on biologic therapies for RA, Dr. John Klippel assessed the case for using TNF-α inhibitors early in the course of all patients with documented RA, citing 3 barriers to adopting this approach: high cost, unavailability of long-term efficacy and safety data, and lack of studies comparing them with other drugs that also slow the rate of erosive disease. We would like to draw attention to a fourth barrier, which has received little attention in the midst of the excitement over the benefits of biologic therapies: a significant percentage of patients diagnosed with RA do not go on to develop joint destruction.

In a study of radiographic progression in 256 patients from a referral-based population with early RA who were followed on average 8.7 years, 15-20% never developed erosions. Follow-up studies from the 1960’s of RA diagnosed in community-based populations suggest that the number with benign disease is even higher. RA is clearly a heterogeneous clinical entity, and a combination of markers, such as C-reactive protein (CRP), DRB1*04/01 HLA alleles, and rheumatoid factor, could prove useful in identifying those patients most likely to develop significant erosive disease.

The study by Listing, et al of 139 patients with early RA demonstrated that only 5% of those who were both negative for DRB1*04/01 HLA class II alleles and had a CRP < 1.5 mg/dl at presentation went on to develop erosions in 5 or more joints at 4 year follow-up.

If rheumatologists were able to risk-stratify patients with RA early in the course of their disease, they could tailor a therapeutic strategy accordingly. It is critical that reliable prognostic markers of erosive disease now be identified as the biologic agents, which show promise of halting the destructive effects of RA, move from bench to bedside.

Christopher A. D’Arcy, MD, Robert F. Willkens, MD, Division of Rheumatology, University of Washington, Seattle, Washington, USA.

REFERENCES


Dr. Listing and Dr. Rau reply

To the Editor:

Several predictors of progressive disease have been described including severe disease activity as measured in swollen joint count and CRP levels, high titer of serum rheumatoid factor (RF), erosive disease, and the presence of HLA-DRB1 0401 alleles. As Drs. D’Arcy and Willkens point out, our study confirmed the important role of CRP, RF, and HLA-DRB1 0401. Indeed, 73% of patients with a double dose of disease related alleles developed erosive disease. In contrast, patients with no disease related alleles, patients with no RF, and patients without erosions at baseline had a good chance that their disease remained non-erosive, especially if their CRP was normal. However, we have to consider that still nearly 40% of patients with 2 alleles had a benign disease with a Ratinin score of less than 5 ( ~ 2.5% of the maximum score) after 4 years. The situation is different when looking at patients with existing erosive disease: in this case, HLA alleles had no influence on radiographic progression, whereas a persistently elevated CRP strongly indicated progressive disease. This is confirmed in another study with early erosive RA followed over 6 years: there was no difference regarding disease progression between soropositive patients with and without disease related alleles. In that study the mean CRP could be reduced from 3.5 mg/dl to < 1 mg/dl after ~18 months, leading to a significant decrease of the slope of progression over time. Forty-six of 109 patients had a radiographic score of < 5% of the maximum possible score after 6 years. This and another study may indicate that early aggressive treatment with conventional DMARD (here, in gold or in MTX) may overcome the predictive value of genetic markers. The importance of effective treatment is underscored by the fact that the time-inte-
Rheumatoid CRP is a better indicator of progression than baseline CRP\(^4\). The best predictor of progressive disease in individual patients may be high disease activity reflected in elevated CRP, because disease activity after a certain time gap translates into destruction\(^6\).

Without any doubt the availability of TNF inhibitors is a great step forward, not only because they have improved our ability to treat many patients unresponsive to conventional DMARD effectively, but even more so because they confirm the theory about the role of cytokines in inflammatory rheumatic disease. On the other hand we must admit that the study comparing MTX with MTX + infliximab consisted of patients who were partial nonresponders to MTX\(^6\). It is also true that a median progression rate of 0 does not mean an arrest of progression in all patients. In a head to head comparison of etanercept with MTX in early active seropositive or erosive disease\(^6\), MTX performed surprisingly well: although the progression rate in the group of patients treated with 2 \(\times\) 25 mg etanercept/week was lower during the first 6 months, there was no significant difference regarding progression between both treatment regimens in the second 6 months; the progression during the second half year had significantly decreased with MTX treatment compared to the first half year. The earlier onset of clinical effect with etanercept translated into earlier inhibition of progression. A similar result could be achieved with prednisolone doses as low as 7.5 or 5.0 mg/day in addition to conventional DMARD\(^6\).

Many patients with active RA can be treated sufficiently with conventional DMARD, including patients with "bad" prognostic markers, and the superiority of TNF blockade is not proven for all patients. Therefore, it seems unnecessary to treat all patients with documented RA with TNF inhibitors, as discussed by Dr. Klippel\(^8\). Instead, we recommend following the consensus statement of an international expert panel\(^11\) to restrict treatment with TNF inhibitors to patients fulfilling certain disease activity criteria in spite of sufficiently dosed treatment with 2 conventional DMARD (one of them MTX) for at least 6 months.

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REFERENCES


Removal of Hyaline Articular Cartilage Reduces Lymphocyte Infiltration and Activation in Rheumatoid Synovial Membrane

To the Editor:

I read with interest the recent article on synovial membrane pathology in chronic arthritis after removal of hyaline articular cartilage\(^4\). Based on immunochemical staining methods and morphometry, it was shown that revision rheumatoid arthritis (RA) or ankylosing spondylitis synovial membranes, in contrast to primary RA samples, did not manifest lymphocyte infiltration and/or activation, "as there would be no antigen there to be processed and presented by the antigen presenting cells to T lymphocytes." As concluded by the authors, autoantigens that perpetuate the autoimmune synovitis might originate from avascular hyaline articular cartilage; this was proved in the article; however, no potential autoantigen was mentioned\(^1\).

Further, the hypothesis that an autoimmune reaction in the articular cartilage initiates the immunopathological events leading to synovial inflammation is not new, and has been already stated in the literature\(^1\). Clinical as well as experimental (collagen induced arthritis mouse) data strongly suggest involvement of the type II collagen degradation peptides in the autoimmune response that occurs in the articular cartilage, primary to pathological changes in synovium. I wonder why Konttinen, et al did not discuss these data in their report.

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REFERENCES


Dr. Konttinen replies

To the Editor:

Thank you for letting us share the comments from Dr. Fujii. The idea about the hyaline articular cartilage being the perpetuating stimulus, containing potential sequestered antigens, is not new. Our observation provides new evidence\(^4\) for this old hypothesis.

Dr. Fujii and his team refer in their hypothesis article\(^4\) to previous work on the early appearance of anti-type II collagen IgG antibody in rheumatoid arthritis (RA). The major antigenic determinants recognized by RA sera have been found to reside in the region represented by cyanogen bromide (CNBr) peptides 11 and 8 (CB-11, CB-8) of human type II collagen molecule. Anti-type II collagen antibody was negative in gout and osteoarthritids (OA). In their work they also describe that although the superficial zone of the hyaline articular cartilage in RA looked healthy, the deep zone con-

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tained less intact type II collagen and intense staining for CNBr derived peptides of type II collagen. Such a reciprocal staining pattern was not seen in OA. Further, islands invading from the subchondral bone into the deep zone of articular cartilage were described and thought to be of relevance for the immune response against type II collagen in RA.

It makes sense to consider sequestrated autoantigens as potential targets for the immune system after some type of injury has damaged the cartilage. This requires suprathereshold concentrations of the autoantigen and a priming context. But it is difficult to prove this hypothesis. One should probably be able to (1) identify the autoantigens involved, (2) demonstrate that these cartilaginous autoantigens are necessary for the development of the disease, (3) demonstrate that specific antigen reactive T lymphocytes and antigen presenting cells are involved in the pathogenesis, and (4) demonstrate that the disease can be transferred by T lymphocytes. Therefore, it is too early to identify any particular candidate antigen by name, and this was not the focus of our work. We discussed this topic when we reported our results on induction of peroral tolerance against (Gly-X-Y), sequences in RA, which is an interesting way to test the collagen autoantigen hypothesis. However, the evidence presented thus far by, for example, Dr. Fuji or by us, although compelling, is far from convincing.

In contrast to the speculations presented by Dr. Fuji and his team, it might well be that the immune response against autologous type II collagen is a late event in disease pathogenesis. Further, degradation of the hyaline articular cartilage and type II collagen are by no means specific for inflammatory arthritides. It is possible that cartilaginous autoantigens are perpetuating factors contributing to the chronicity of the disease rather than initiating early triggers. For example, it has been described that many immunoreactive epitopes in the hyaline articular cartilage need to be revealed by chondroitinase or hyaluronidase pretreatment before they can be confirmed using specific antibodies.

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REFERENCES


Should We Be Reading This Journal?

To the Editor:

I read with great interest the editorial by M. Stanbrook. Medical doctors need to read such articles.

Almost all efficient doctors read medical journals. In the same way, rheumatologists read not one, but 3, 4, or even 5 rheumatology journals, plus one or more internal medicine journals, for the necessary contact with other specialties. They are trying to maintain old knowledge and be informed of all the new data. They wish to miss nothing. The problem in our times is the limited availability of time. We all are tremendously busy with our specialties, research work, patients, and family. As a result, we select the articles we read and in some cases we read only the abstract and the introduction of the article. Many articles seem to be very important and sometimes very impressive.

However, very few original articles, e.g., the initial work about anti-TNF treatment, survive and create a new era in medicine. The problem is that even when you read an article that appears exciting and covers your specific or general interests, you cannot be sure it will prove to be important, that it will survive, or that it is worth reading. And we are talking about thousands of such articles.

In my opinion, the 20,000 medical journals, with few exceptions, do not solve problems, they rather create problems. I don't believe it is a question of which journal we should be reading. Everybody selects a few, depending on many factors including specific interest(s), general knowledge, clinical and/or laboratory practice and/or investigational interest, and country of medical studies. The aim must always be improvement of knowledge and of patient care.

I agree most doctors begin reading journals as a normal educational activity from the time medical training commences. Most of them are influenced by their trainers in choosing journals. Very often doctors choose journals because of coincidence, and so on. In my opinion, the only solution to the cascade of information of our time is the dramatic reduction of the number of medical journals, perhaps through merging. Additionally, the articles should be fewer but of higher quality, which means there must be stricter review before publication, which ultimately will allow acceptance of only very high standard papers. I believe that "publish or perish" or other similar practices concerning career advancement do not favor high quality of articles.

Probably several drug companies and journals will not agree. University hospital clinics receiving grants will not agree either (but they may still be able to publish in internal hospital journals). Still, international medical journals should be very few; only works of the highest level should be accepted for publication.

GEORGE M. PAPADIMITRIOU, MD, Professor, University of Athens, Athens, Greece.

REFERENCE


Dr. Stanbrook replies

To the Editor:

I thank Dr. Papadimitriou for his kind words and thoughtful remarks. His comments, like mine, acknowledge that the conflict between the expanding body of medical knowledge and the limited time available to acquire and process it represents a fundamental dilemma faced by all physician readers. As a solution, he suggests that we should have fewer journals, publishing higher quality articles that have been subjected to a stricter peer review process.

It would certainly make our task easier if all the genuinely important articles could be concentrated into a few journals. However, given the minimal scientific information that exists at present about journals and what they publish, this would raise several difficulties. First, as Papadimitriou admits, it is hard to know what articles will ultimately prove to be important in future, even among those that seem promising now. If it were possible to identify the most important articles easily, readers could just ignore the less important ones, and the volume of material being published might then pose no dilemma. Second, quality and importance are relative, and in practice, their evaluation remains largely subjective. I suspect that many, if not most, journal editors would claim that their own publications already put articles through a strict review process and select only those that are of the highest quality available. Third, some novel and ultimately very important discoveries have been
False Positive Elevation of Cardiac Troponin I in Seropositive Rheumatoid Arthritis

To the Editor:

In a case report, Katwa, et al describe a patient with seropositive rheumatoid arthritis (RA) in whom troponin I, measured with a microparticle enzyme immunassay, was elevated falsely in the absence of acute myocardial infarction.

We report a similar observation. Indeed, we have determined the levels of troponin I in 35 serum samples from patients with seropositive RA. Two immunoassays were tested: TNI and Accu TNI developed by Beckman Diagnostics, Fullerton, CA, USA. Determination of IgM rheumatoid factor (RF) levels was as described. Correlation between IgM RF and troponin I concentration (determined with the TNI test) was assessed using Spearman's rank correlation coefficient: a significant correlation was found (Rho = 0.44, p = 0.01) (Figure 1). No significant correlation was found between IgM RF and troponin I concentrations determined with the Accu TNI test.

When the troponin I concentrations, determined with both tests, were compared, a higher concentration was generally obtained with the TNI test. With the latter method, one sample was found to be positive whereas it was negative with the Accu TNI test (the cutoff values were 100 ng/l for the TNI and 90 ng/l for the Accu TNI test) (Figure 2).

The patient found to be positive for troponin I with the TNI test was a 40-year-old man with seropositive RA complicated with nodules and bone erosions for 15 years. Treatment was initiated with gold salt, then switched to methotrexate (MTX) and low dose prednisone. Five years ago, due to cutaneous vasculitis, MTX was replaced by azathioprine. Due to poor disease control, anti-tumor necrosis factor-α therapy (etanercept, Enbrel®) was added, with a good clinical and radiological effect. This patient also had insulin dependent diabetes for 10 years, with retinopathy and neuropathy. The possibility that he could have had undiagnosed, minor cardiac damage had a low probability, since both the thallium test and the electrocardio-

Figure 1. Correlation between IgM RF and troponin I concentrations determined with the TNI test in serum from patients with RA. Line represents the linear regression (n = 35, Spearman’s rank correlation coefficient = 0.44, p = 0.01).

Figure 2. Comparison of troponin I concentrations determined with Accu TNI and TNI tests; cutoff values were 100 ng/l for the TNI and 90 ng/l for the Accu TNI test.

gram (ECG) were normal. Further, the ECG showed no evidence of previous myocardial injury and when the same serum specimen was reanalyzed using the Accu TNI test, it was negative.

In conclusion, we observed a false elevation of troponin I, associated with high concentration of IgM RF (516 IU/ml). This false positive value probably resulted from IgM RF interference with the assay. The Accu TNI assay did not indicate any false elevation of troponin I concentration in this study.

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Antineutrophil Cytoplasmic Antibodies — A “Red Flag” in Patients with Systemic Sclerosis

To the Editor:

Antineutrophil cytoplasmic antibodies (ANCA) have been described in a number of autoimmune rheumatic diseases but are uncommon in systemic sclerosis (SSc). Although the diagnostic and prognostic significance of these antibodies in SSc is unclear, there have been case reports and a small series of cases of crescentic glomerulonephritis in patients with SSc who were positive for ANCA, usually with antibodies to myeloperoxidase (MPO)\(^1\). Three previous studies, 2 reported in The Journal, have looked for ANCA positivity in cohorts of patients with SSc. Endo, et al found that 6 of 100 patients were ANCA positive with staining in a perinuclear pattern (pANA), all with anti-MPO antibodies\(^2\). All 6 patients had renal failure (5 normotensive), with only one surviving more than 6 months after onset of renal failure, and 2 had pulmonary hemorrhage\(^3\). Locke, et al reported that 2 of 81 patients were ANCA positive (one after treatment with penicillamine), both with a perinuclear staining pattern and with antibodies to MPO, and both had impaired renal function\(^4\). Conversely, Akinomo, et al found that only one of 7 pANCA positive SSc patients (out of a total cohort of 77 patients with SSc) had renal involvement\(^5\).

Because it has been suggested that SSc patients who are ANCA positive might form a specific subset with inflammatory renal disease, we investigated this possibility by reviewing the case records of 168 patients with SSc (27 males, 141 females) attending the Rheumatic Diseases Centre at Hope Hospital, Salford, UK between 1994 and 2000. Forty-three patients had diffuse cutaneous SSc (dSSc) and 125 had limited cutaneous SSc (lSSc). Twenty-two of the 168 patients had an overlap syndrome (4 SLE, 1 subacute lupus erythematosus, 14 inflammatory muscle disease, 1 SLE/Inflammatory muscle disease, 2 rheumatoid arthritis).

ANCA had been tested in 99 patients by indirect immunofluorescence using human neutrophils and were detected in significant titers (>1/132) in the sera of 5 patients\(^6\). Positive sera were further tested for antibodies to serine proteinase 3 and MPO by ELISA. Brief clinical details of these 5 patients are given in Table 1.

Patient 1 is a 61-year-old woman with dSSc. She developed PANC positivity (1/256), with antibodies to MPO, at the time of a pyrexia of unknown origin. She had presented with acute onset of generalized stiffness and aching associated with malaise, weight loss, and night sweats. Hemoglobin was 113 g/l, mean corpuscular volume 86.7 fl, white blood count 14.1×10\(^9\), platelet 349×10\(^9\), and erythrocyte sedimentation rate (ESR) 127 mm/h. She was rheumatoid factor positive (1/256). Renal function was normal. She was treated empirically with antibiotic therapy (all cultures were negative) because of some non-specific shadowing on her chest radiograph and with prednisolone, and her clinical condition improved. While she had received penicillamine in the past, this had been more than 10 years previously.

Patient 2 is a 42-year-old man with dSSc who presented with pulmonary hemorrhage and glomerulonephritis. He was pANCA positive (1/1024) with antibodies to MPO, and was also anti-Ro and anti-La positive; he is described in detail elsewhere\(^7\).

Patient 3 is a 39-year-old woman with ISSc and polymyositis overlap syndrome (anti-PM1 positive); she initially had cytoplasmic pattern of ANCA staining (atypical cANCA, 1/256) but later became pANCA positive (>1/1024). She was anti-MPO negative, and antiproteinase 3 negative. Clinically she had generalized aches and felt lethargic. She responded to treatment with prednisolone 10 mg daily and cyclosporine. Her renal function was normal. Two years later, her pANCA remains greater than 1/1024.

Patient 4 is a 70-year-old woman with ISSc/polymyositis overlap and severe Sjögren’s syndrome, and a history of vasculitic rash, bilateral lower limb amputations (right above knee, left above knee) for peripheral ischemia, and left retinal vein occlusion; she developed upper limb ischemia with vasculitic change. She was pANCA positive (1/512) with antibodies to MPO. Rheumatoid factor was strongly positive 1/2048. Despite treatment with high dose prednisolone, intravenous cyclophosphamide, and anticoagulation, her condition deteriorated and she died, autopsied showing pulmonary edema and bronchopneumonia. Until 3 months prior to her death there had been no impairment of renal function — most recent plasma urea and creatinine were 16.1 mmol/l and 181 mmol/l, respectively. At autopsy the kidneys appeared shrunken (the right weighed 85 g, the left 95 g). No renal histopathology was available.

Patient 5 is a 28-year-old female patient with a dSSc/SLE overlap, who had antibodies to dsDNA and to Sc-IgM; she was also pANCA positive (1/128). Antibodies to MPO were negative. Two years later, after treatment with prednisolone (and about one year’s treatment with penicillinamide), her ANCA was negative. Renal function has been normal.

Although this is a retrospective analysis with the problems inherent in this study design (e.g., ANCA was not checked in all patients), an important clinical point to emerge is that all 5 patients who were ANCA positive were PANC positive (albeit one was initially cANCA positive) and all had

### Table 1. Clinical features.

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<td>61 F</td>
<td>43 M</td>
<td>39 F</td>
<td>70 F</td>
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<td>Disease subtype</td>
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<td>ISSc/PM overlap</td>
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<td>ANCA status</td>
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<td>pANCA 1/1024</td>
<td>Initially cANCA 1/256, then pANCA &gt; 1/1024</td>
<td>pANCA 1/512</td>
<td>pANCA 1/128</td>
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<td>Antibodies to MPO</td>
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<td>Negative</td>
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<td>Plasma creatinine, μmol/l (reference range 60–120)</td>
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<td>92</td>
<td>7</td>
<td>120</td>
</tr>
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<td>0.1</td>
<td>0.5</td>
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</tr>
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<td>Urinalysis or microscopy of urine</td>
<td>WBC 10–19/mm(^3) No RBC</td>
<td>WBC 20–100/mm(^3) RBC &gt; 100/mm(^3)</td>
<td>Urinalysis negative</td>
<td>WBC 6/mm(^3) RBC &gt; 100/mm(^3) Entercoccus infection</td>
<td>Urinalysis negative</td>
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<tr>
<td>Inflammatory features</td>
<td>Fever, high ESR</td>
<td>Glomerulonephritis, pulmonary hemorrhage</td>
<td>PM overlap</td>
<td>PM overlap, vasculitic rash</td>
<td>SLE overlap</td>
</tr>
</tbody>
</table>

features atypical of "classical" SSc. Three had antibodies to MPO. Three had overlap syndromes, 2 had definite clinical features of vasculitis, and all had inflammatory features. Only 2 patients had renal impairment, suggesting that pANCA positivity in a patient with SSc is not necessarily associated with glomerulonephritis. In all patients treatment including prednisolone resulted in clinical improvement, except in the patient who died.

Our experience suggests that ANCA positivity in a patient with SSc indicates an inflammatory component to the illness. Although ANCA positivity in patients with SSc is unusual, it is a "red flag" and should not be ignored. ANCA positive SSc patients need thorough evaluation and follow-up. Although there is concern about using steroids in patients with SSc because of a possible association with renal crisis in patients with early diffuse disease, steroids may be indicated in this ANCA positive cohort. Conversely, if a patient with SSc demonstrates any atypical or inflammatory features, then the ANCA should be checked.

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REFERENCES

Book Review

**Whiplash and Other Useful Illnesses.** Andrew Malleson. Montreal, McGill-Queen's University Press: 2002, 532 pages. $49.95 CDN.

"Whiplash" hangs like an imprecation over North America, and much but not all of Europe. It conjures the image of relentless neck pain consequent to even a minor rear-end motor vehicle accident. That anyone might suffer this fate is deeply embedded in the common wisdom. It is institutionalized by an insurance industry that offers to indemnify us, by the regulators who mandated headrests in personal automobiles, and by a medical establishment that countenanced a certifying acronym, WAD (whiplash associated disorder). Whiplash takes its place among the many untested "truths" that we are wont to accept as part of our social order; whiplash is a social construction. Unlike most social constructions, whiplash was born to be contentious. That is fortunate. If social constructions are not recognized and challenged, they become creeds. Controversy unmask their weaknesses and fuels advances in knowledge.

To exist, whiplash must be indemnified. To qualify for indemnity, others must agree that the patient is a victim of a personal injury that is deemed consequent to the wrongful action of another. That is why the driver whose vehicle is rear ended is at risk for whiplash; the driver whose vehicle commits the rear ending is not, in spite of the first law of thermodynamics. If the driver whose vehicle is rear ended can convince all who question the veracity of symptoms, the victim is entitled to payment of medical care and compensation for loss of income if not compromise in joie de vivre. That is no mean task if whiplash is present in the absence of damage. There are people paid as believers and as doubters at every twist and turn in the indemnity process.

Andrew Malleson is a doughter, unabashedly and unwaveringly so. He is also a keen observer of all aspects of this contest. He is a student of the relevant literatures. And he is an outstanding wordsmith. This monograph is a treat to read. It is a gauntlet for any or all the believers to pick up. It is a model for the way controversy can be marshaled to dissect a social construction. And it is successful in demonstrating the sophistical nature of the whiplash construction.

I would recommend this book for all physicians who seek their primary responsibility as educators of their patients, and for anyone else who feels at risk for medicalization by "whiplash" and its kindred labels.

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Correction

The editors and the authors of the papers submitted to The Journal are grateful for the help of all our reviewers. We here acknowledge, with special thanks, those who reviewed 3 or more papers in 2001–2002.

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