Another look at Wegener's granulomatosis-associated pachymeningitis.

Peer Malte Aries, Eva Reinhold-Keller and Wilhelm Lugwig Gross

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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.
Still a Blind Spot for Osteoporosis Prevention and Treatment for Rheumatoid Arthritis

To the Editor:

In the September issue of The Journal, Drs. Zochling and March commented on our editorial in which we noted the absence of recommendations for the prevention and treatment of osteoporosis in patients with rheumatoid arthritis (RA).

They referred to the American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines update 2002, which, they state, addressed the issue of osteoporosis prevention for patients with RA. However, these guidelines contain only the following sentence within the text of the article: “RA is associated with an increased risk of osteoporosis independently of glucocorticoid therapy.” There is a recommendation for bone mineral densitometry as well as vitamin D and calcium supplement only for RA patients who are taking glucocorticosteroids. But these recently published guidelines, like the 2 we reviewed, as well as the recent consensus statement on pharmacological management of early RA, failed to deal with the need for osteoporosis prevention in RA patients in general. Only the recent article of Haugeberg, et al also raised the question of identifying RA patients at high risk for osteoporosis, identifying 5 criteria: age, weight, inflammation, immobility, and ever-use of corticosteroids.

The role of corticosteroids in RA was the principal focus of Drs. Zochling and March, and this was well described in this Guidelines update. However, every patient undergoing glucocorticoid treatment needs bone mineral densitometry evaluation and consideration of treatment for osteoporosis, as recently reiterated by Saag, et al, so this is not specific to patients with RA.

This unfortunately reinforces our contention that the prevention and treatment of osteoporosis in patients with RA continues to be insufficiently addressed in published guidelines for management of RA. Our colleagues who work on the osteoporosis side are doing better — as evidenced by the Guidelines on Osteoporosis Management recently published by the Osteoporosis Society of Canada, which list RA as a risk factor for the development of osteoporosis.

REFERENCES


Dr. Zochling and Dr. March reply

To the Editor:

Drs. Jolles and Bogoch have highlighted an important shortcoming of current rheumatoid arthritis (RA) guidelines, in the lack of direction for prevention and management of associated osteoporosis. We agree wholeheartedly, and suggest it is perhaps a result more of the lack of good scientific evidence on which to base such guidelines than a lack of recognition. Little is known about the natural history of bone loss and associated fracture risk in steroid-naïve RA. Corticosteroid therapy is renowned for causing bone loss in other disease states, but in RA the association of osteoporosis and disease activity complicates the picture.

It may well be that with more aggressive use of disease modifying agents and biologic therapies, improved control of disease activity will bring with it an opportunity to more adequately assess the progression of osteoporosis in RA independent of corticosteroids in prospective studies, and to define the most appropriate management strategies.

Until that time, any guidelines must make it clear they are based on evidence that is incomplete. We agree that the management of any patients with RA should include assessment of the risk of osteoporosis, including underlying disease activity, demographics, and potential corticosteroid use.

JANE ZOCHLING, MBBS, FRACP, MMED (ClinEpi), Research Fellow in Rheumatology, Institute of Bone and Joint Research, Department of Rheumatology, Royal North Shore Hospital, Pacific Highway, St. Leonards, NSW, Australia 2065 (E-mail: jzochlin@med.usyd.edu.au);
LYN MARCH, MBBS, MSc, PhD, FRACP, FAFPHM, Associate Professor of Medicine, Senior Staff Specialist in Rheumatology and Clinical
Fatigue and Psychological States and Traits in Systemic Lupus Erythematosus: Association or Causation?

To the Editor:

We read with interest the article by Omdal and colleagues, with results from a study of psychological characteristics of fatigued patients with systemic lupus erythematosus (SLE). Applying a cross-sectional design, they found that fatigue, as measured by the Fatigue Severity Score, was correlated with measures of depression, hysteria, anxiety, and social dysfunctioning. The authors have previously reported a lack of association between fatigue and biological markers of disease activity in the same population. They conclude that psychological factors like response and adaptation to a chronic disease appear to be the most important determinant of fatigue, and the high prevalence of fatigue is probably caused by personality traits common in patients with SLE.

The study seems nicely performed, and the applied statistical methods seem appropriate. The authors, however, seem to mistake correlation with causation. The correlation between fatigue and symptoms of depression is based on the Beck Depression Inventory (BDI). Fatigue is one of the key symptoms of depression and fatigue/energy questions are therefore embedded in most diagnostic instruments. Consequently, a fatigued population will necessarily score higher on a depression scale, clinically depressed or not. It has been suggested that the only way to overcome this methodological problem is to discharge fatigue/energy items from the depression inventory. The authors themselves deliver an argument for this point of view, since no correlation was found with the “depression” factor in the General Health Questionnaire (GHQ-30) and the Fatigue Severity Score. The GHQ-30, and consequently the depression factor derived from GHQ-30, does not include that psychological factors like response and adaptation to a chronic disease appear to be the most important determinant of fatigue, and the high prevalence of fatigue is probably caused by personality traits common in patients with SLE.

The reported correlation between fatigue and hysteria is based on the Hysteria-axis in the Multiphasic Personality Inventory (MMPI). The MMPI claims to detect stable personality traits. However, as Creed and Ash point out, the MMPI includes several items that rheumatologists commonly attribute to disease rather than change in psychological status; for example, “I have few or no pain”. With respect to fatigue, the instrument includes a significant number of fatigue/energy items (Table 1). Again, any fatigued population would score higher on this scale, disregarding present psychopathology or not. It has been suggested that the MMPI for this reason should not be used in patients with rheumatological diseases because “their elevated score on some dimensions, e.g., hypochondriasis, depression and hysteria, may reflect the disease rather than psychopathology”.

Many aspects of the etiology and pathogenesis of SLE still remain to be solved, and no single valid biomarker for disease activity or organ involve-

Table 1. Examples of fatigue-related items in the “Hysteria-axis” from the MMPI. Numbers refer to item numbers in MMPI-2.

<table>
<thead>
<tr>
<th>Item</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>My sleep is fitful and disturbed (true)</td>
</tr>
<tr>
<td>175</td>
<td>I feel weak all over much of the time (true)</td>
</tr>
<tr>
<td>3</td>
<td>I wake up fresh and rested most mornings (false)</td>
</tr>
<tr>
<td>10</td>
<td>I am about as able to work as I ever was (false)</td>
</tr>
</tbody>
</table>

In conclusion, we agree with the authors that fatigue in chronic disease is a complex phenomenon, but with the lack of valid biomarkers it is important to ask if cross-sectional studies add to our understanding of causal and modifying factors for the development and course of fatigue in SLE and other chronic diseases.

NIELS HENRIK HJOLLUND, MD, PhD, OLE NØRBY HANSEN, MSc, PhD. Department of Occupational Medicine, Herning Central Hospital, Gl. Landevj 61, DK-7400 Herning, Denmark. E-mail: hhjol@akh.aaa.dk

REFERENCES

Dr. Omdal, et al reply

To the Editor:

We thank Drs. Hjollund and Hansen for their interest in our report. Their letter contains important views on the topic of fatigue in autoimmune diseases, and is written with insight concerning fatigue and psychology. With a few exceptions, we have no problem agreeing with most of their arguments, but would like to comment on them.

Considering mistaking correlation with causation, we cannot quite understand that the message from our study should be interpreted as that. It is clear from the text that this is a cross-sectional study, and it should also be emphasized that we use the word association throughout. This word does not imply any specific causation, only that some variables covariate correlation — as Hjollund and Hansen call it. Having said that, the procedure for unveiling the mechanisms of fatigue in these diseases would include prospective studies, intervention studies, and search for biomarkers of the fatigue phenomenon, as emphasized by Hjollund and Hansen.
Their comments regarding fatigue and depression are important. Mutually related factors may cause "circular arguments" leading to conclusions of associations that do not exist. This is a well known phenomenon, but sometimes hard to exclude since the associations may be unknown, or the researcher unaware of relationships among the variables.

Hjollund and Hansen argue that the Beck Depression Inventory (BDI) contains several items related to fatigue, while the General Health Questionnaire (GHQ-30) does not. They also argue that we find no association between fatigue and the depression factor (Factor C) in the GHQ-30, while such a relationship is evident in the BDI.

Factor C in the GHQ-30 is significantly associated to fatigue ($R^2 = 0.24$, $p = 0.0001$) by simple regression analysis. It is only in a stepwise regression model that Factor C does not significantly contribute to fatigue. This does not imply lack of association between fatigue and the items of Factor C, but indicates that Factor C does not independently contribute enough to the association with fatigue to be maintained in a multivariate model. To some extent, we can therefore agree with Hjollund and Hansen’s argument.

Further, the BDI is a 21 item questionnaire pertaining to cognitive/emotional and somatic manifestations of depression. The first 13 items assess cognitive/affective symptoms of depression; the final 8 items evaluate defenses seem to score high on both clusters. Indeed, it is not possible to reasonably independent in normal subjects, persons displaying hysterical and of discomfort in social situations. Although these 2 clusters of items are involved a rather general denial of psychological or emotional problems, while such a relationship is evident in the BDI.

It has been suggested that the Multiphasic Personality Inventory (MMPI) should not be used in patients with rheumatological diseases. This may be true for arthritis and other joint-related diseases, but our patients with SLE are characterized by few or no joint manifestations and have features more related to systemic disease. In this context, we see no reason for not applying the MMPI instrument in SLE.

Also, the Hysteria-axis in the MMPI-2 includes 60 items. Almost all items on Scale 3 are scores on other clinical scales; only 10 items are unique to Scale 3. Some of the items deal with a general denial of physical health and some specific somatic complaints. Another group of items involves a rather general denial of psychological or emotional problems and of discomfort in social situations. Although these 2 clusters of items are reasonably independent in normal subjects, persons displaying hysterical defenses seem to score high on both clusters. Indeed, it is not possible to obtain a T score above 65 on Scale 3 without endorsing both kinds of items. Patients with bona fide medical problems lacking any evident psychological component tend to obtain T scores of about 55–60 on this scale.

However, Hjollund and Hansen’s concern about the BDI and MMPI-2 versus fatigue reflects to a considerable extent the problem of mutually related variables — a matter in which we fully agree.

Finally, Hjollund and Hansen refer to the study by Gladman, et al where 5 health status instruments in SLE were compared by correlation analysis, and suggest that health status assessment as measured by the Medical Outcomes Study Short Form (SF-20) is a valid independent outcome measure in SLE. Applying correlation statistics for comparing different instruments (measuring agreement between 2 methods) is in our opinion questionable. A more adequate approach is estimation of limits of agreement. The results of such a comparison between the health instruments are unknown, as far as we know. Whether the SF-20 is superior in evaluating fatigue in patients with SLE therefore remains to be seen.

ROALD OMDAL, MD, PhD. Clinical Immunology Unit, Rogaland Central Hospital, N–4068 Stavanger, Norway; KNUOT WATERLOO, PsyD, Department of Neurology; WENCHE KOLDINGSNES, MD, Department of Rheumatology, University Hospital of North Norway; GUNNAR HUSBY, MD, PhD, Department of Rheumatology, National Hospital, Oslo; SVEIN MELLGREN, MD, PhD, Department of Neurology, University Hospital of North Norway; BJORN STRAUME, MD, Institute of Community Medicine, University of Tromsø. E-mail: romdal@online.no

REFERENCES

Hands-on Treatment in Rheumatology

To the Editor:

The editorial by Fitzcharles regarding “hands-on” treatments in rheumatology is timely and balanced. She noted the seemingly low frequency of side effects of spinal manipulation and wonders whether this is due to underreporting or the rarity of complications.

We recently surveyed all UK neurologists asking them to note all neurological adverse effects of spinal manipulation seen within the last year. Our response rate was 74% and 35 cases of often serious complications were reported. None of these had been published in the medical literature. It follows that, in our case, underreporting was exactly 100%. I therefore agree with Fitzcharles that (chiropractic) manipulation (particularly of the upper spine) is associated with serious complications of unknown frequency. The incidence rates reported by chiropractors are pure speculation and, in view of huge underreporting, even nonsensical. The inescapable conclusion is that we need conclusive incidence figures. Until they are available, caution seems well advised.

EDZARD ERNST, MD, PhD, FRCP, FRCPEd, Director, Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, 25 Victoria Park Road, Exeter, EX2 4NT, UK. E-mail: Edzard.Ernst@pms.ac.uk

REFERENCES

Dr. Fitzcharles replies

To the Editor:

The comments of Prof. Ernst are appreciated. Once again caution in the use of manipulation therapies is advocated. Good medical practice requires that a physician should be fully aware of risks associated with a treatment before prescription. We do not currently have accurate information regarding risks related to “hands-on” or manipulation therapies. Prof. Ernst and colleagues have recently demonstrated the high rate of underreporting of neurological events following spinal manipulation. This survey of physicians, which is likely reflective of usual practice, raises further concerns about the true frequency of side effects due to any treatment without a formal monitoring procedure. The literature abounds with anecdote, case reports, and polls from physicians, none sufficient to give reliable estimates of risk.
Attempts at systematic review or metaanalysis of manipulation therapies concede that the quality of clinical trials, mostly examining efficacy, but also reporting on risks, is generally poor. Risk of harm is clearly of importance to prescribers. Although a recent metaanalysis reported that spinal manipulation was no better than other commonly used treatments for low back pain, advantages or risks associated with various treatments were not addressed. In a population-based study examining the relationship of stroke and chiropractic manipulation, the rates for chiropractic visits were similar in the preceding year for both patients and the population controls. However, differences only emerged when the groups were divided according to age of 45 years, with younger stroke patients reporting more chiropractic visits.

Once again there is a strong call for rigorous scientific evidence before these treatments can be universally endorsed.

MARY-ANN FITZCHARLES, MB, CHB, MRCPUK, FRCP, Associate Professor of Medicine, Division of Rheumatology, Montreal General Hospital, McGill University Health Centre, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4, Canada

REFERENCES

Another Look At Wegener’s Granulomatosis–Associated Pachymeningitis

To the Editor:

Fam, et al recently described an unusual manifestation of Wegner’s granulomatosis (WG) with cranial pachymeningitis and reviewed the literature. We read their report with great interest, as we had reported 3 cases of severe central nervous system (CNS) manifestations in generalized WG and reviewed the literature ourselves. In contrast to Fam, et al, we found 18 patients with meningeal involvement, all proven by biopsy. Yet Fam, et al did not mention that 9 out of 20 patients (45%) with meningeal involvement and known antineutrophil cytoplasmic antibodies (ANCA) results were found to be ANCA negative. Although the sensitivity for cANCA/PR3-ANCA approaches almost 100% in acute generalized WG, there are published reports of about 12 patients with generalized WG and negative ANCA in the English literature. On top of that, out of these 12 patients with ANCA-negative WG, 83% (10 patients) had cerebral and/or meningeal involvement.

Fam, et al did not point out that according to the literature, 83% of patients with WG and cerebral involvement are persistently ANCA-negative versus just 10% with “classic” WG, as shown in larger cohorts. In addition to broader awareness of this data, further studies and other initiatives are needed to distinguish this subset of ANCA-negative WG with predominant CNS involvement from others.

PEER MALTE ARIES, MD, EVA REINHOLD-KELLER, MD, WILHELM LUDWIG GROSS, MD, Universitätsklinikum Schleswig Holstein, Poliklinik für Rheumatologie, Rheumaklinik Bad Bramstedt, Oskar Alexander Strasse 26, 24576 Bad Bramstedt, Germany. E-mail: aries@rheuma-zentrum.de

REFERENCES

Dr. Fam replies

To the Editor:

We appreciate the comments by Aries, et al and their interest in our study. In its classic generalized form, WG chiefly affects the upper and lower respiratory tracts and kidneys. In the limited or partial form, the pathological findings of necrotizing granulomatous vasculitis are similar but the upper respiratory tract, orbit, or lung are primarily affected, in the absence of renal disease.

Measurement of serum cytoplasmic antineutrophil cytoplasmic antibody (cANCA/PR3-ANCA) is highly specific for WG, with a sensitivity greater than 90% for active generalized WG, but only 67% for those with active limited disease. Thus, ANCA is absent in one-third of patients with limited WG.

Reinhold-Keller, et al described 3 patients with active, ANCA-negative WG and severe neurologic manifestations: leptomeningitis in 2 and cerebrospinal lesions in one. However, the absence of renal disease in all 3 patients raises some question whether these subjects had limited rather than generalized WG. Review of reported patients with WG-associated meningeal disease revealed that 45% of cases were ANCA-negative.

Our study, which focused on meningeal inflammation in WG, showed that most reported cases occurred early (within 6 months of onset) in the course of active, limited WG, and that about one-third of patients were ANCA-negative. In accord with other studies, our patient developed pachymeningitis in the setting of active, limited WG. ANCA was repeatedly negative initially, but she subsequently developed pANCA/myeloperoxidase (MPO) antibodies, which disappeared following successful immunosuppressive therapy for WG. A possible association between limited WG, pANCA/MPO antibodies, and pachymeningitis has recently been described by Japanese investigators.

Thus an association between active limited WG and pachymeningitis with variable ANCA results, but a trend toward cANCA negativity and pANCA positivity, is proposed but remains unproven. To confirm these clinical observations, further case-control studies of this rare manifestation of WG, and new insights into the pathogenetic roles of cANCA and pANCA antibodies, are required. Greater awareness, early recognition, and timely therapy of WG-associated pachymeningitis are important to minimize permanent neurologic damage.

ADEL G. FAM, MD, FRCP. Division of Rheumatology, Sunnybrook and Women’s Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Room M1-402, Toronto, Ontario M4N 3M5, Canada. E-mail: Adel.Fam@Sunnybrook.on.ca

REFERENCES
I’m confused how the fatal methodological flaws in this study were not uncovered in editorial review, and that this study was allowed to be published.

The most glaring problem, the “treatment” group used a topical product that contained a known active ingredient, camphor, while this was absent from the placebo group. This does not support the author’s conclusion that “Topical application of glucosamine and chondroitin sulfate is effective in relieving the pain from OA of the knee.” The proper conclusion should be that camphor was effective in short term pain relief, or better yet, no conclusion could be drawn on glucosamine and chondroitin because the “active” group contained 3 variables compared to the placebo-treated group.

This is not the only flaw. Subjects in the study were apparently allowed to apply treatment or placebo “ad lib” and were not required to “dab” the product, as is often the standard in study of topical agents. The act of rubbing the joint alone may help reduce symptoms. The camphor-containing “active” product may have been used more often by the subjects, further biasing the results. Finally, camphor has a burning sensation not found with the “active” product, as is often the standard in study of topical agents. The act of rubbing the product, both the subjects and investigators were naive to any slight difference between the creams due to the presence of camphor in the active preparation, both the subjects and investigators were naive to any contamination occurred. Further, blinding was formally checked with subjects being asked at each visit which group they thought they had been allocated to. The data from these assessments indicate that blinding was maintained (see Table 1).

It is unlikely that the method of application influenced the results of this study. Having the subjects rub rather than dab the cream may have contributed to the observed pain reduction seen in the placebo group; however, this effect would not have led to the observed difference between the groups. Over the course of the trial the active group used a total of 5.5 tubes, while the placebo group used 5.7 tubes.

Finally, the contribution of glucosamine and chondroitin to the observed pain reduction in the active group is open to speculation and cannot be determined by the current study. Unfortunately, the doses of these ingredients were overstated in the original article by a factor of 10. Thus the active intervention actually contained glucosamine sulfate (3.0 mg/g), chondroitin sulfate (7.2 mg/g), and shark cartilage (14 mg/g), of which 10–30% is chondroitin sulfate, along with camphor (32 mg/g) and peppermint oil (9 mg/g).

The effective dose of glucosamine and chondroitin delivered to a painful joint is uncertain. Based on animal studies it is evident that even though there is active uptake of glucosamine by articular cartilage, only around 0.4% of an administered oral dose is delivered to cartilage tissue. Extrapolating this to humans would equate to approximately 6 mg of a 1500 mg oral dose. This is in the range delivered by topical administration in our study, and the observed gradual and progressive improvement is consistent with studies using oral administration of these agents. Thus while the study title refers to glucosamine, chondroitin, and camphor, the exact mechanisms of action of the cream used in our study are yet to be determined, and it is premature to discount the therapeutic effect of topical glu-
and other infectious diseases and abandon his pioneering studies, which Ehrlich’s namesake, a century ago, did not dismiss syphilis, tuberculosis, mias and curses and other causes which were entertained. Fortunately, Dr. sis2, but I do remember historic terms such as consumption and the mias-

rheumatologists were too busy and too important to waste their time with patients with FM. I am distressed at the disinterest and lack of compassion by the editorial blitzkrieg you have unleashed against that common, unfor-
thin the diagnosis of FM4, but he is the one who devised the criteria, published the information, and has since been widely quoted. The problem is that the ACR has a long history of describing diagnostic criteria for their various diseases of interest which have been constructed after many committee meetings. Such criteria and medical algorithms are sloppy methods to use in the practice of sound medicine and merely encourage the uninformed to render diagnoses which he is not competent to make. They do not serve any purpose other than in research and should otherwise be abandoned.

It may be helpful to understand how these criteria came about. Almost 50 years ago, I directed the Streptococcal Disease Laboratory at Western Reserve University, a group of investigators who were given the Lasker Award for studies in strep infections and rheumatic fever. One of my consultants was Dr. T. Duckett Jones, who headed the House of the Good Samaritan in Boston and was a member of the Streptococcal Disease Commission. Dr. Jones undoubtedly had seen more patients with rheumatic fever than anyone before or since. He was also acutely aware of the problems in the diagnosis of rheumatic fever; particularly studies in prevention and therapy such as we were then conducting (I hate to think what he would do with the current problems with Lyme disease). So that we were all on the same wavelength, he devised the widely quoted Jones Criteria2, but its sole purpose was for epidemiologic and clinical research and not to help a physician in individual patient care. Those of us who knew Duckett Jones will confirm this. The ACR over the past few decades has seen fit to copy Dr. Jones’s effort in composing such criteria for many of the illnesses seen by rheumatologists, but these have been distributed to help the non-rheumatologist physician rather than as a research tool. Dr. Wolfe, his colleagues, and their predecessors have produced a litany of such shortcut diagnostic aids to enable the non-rheumatologist to arrive at a correct conclusion. But as Dr. Wolfe states, there is considerable overlap between the findings in FM and rheumatoid arthritis and although not mentioned, probably all forms of polyarthritis and perhaps other illnesses. The same is probably true of all diagnostic criteria for other illnesses which have been devised. In brief, Dr. Wolfe implies that such criteria are near-worthless and I would not disagree.

As a practicing rheumatologist, I must agree with much of what Drs. Ehrlich and Hadler state3, 4. I do not have the foggiest idea what FM and chronic fatigue syndrome are, and the diagnosis is essentially made on a basis of the history and an absence of abnormal physical findings and laboratory tests. In my practice, most have had the diagnosis of FM made prior to my examination, by another physician, a relative or friends, or by exploring the Internet. At best, the diagnosis is correct in perhaps half of them. Without a specific physical or laboratory finding and with no knowledge of its cause or pathophysiology, I do not know how to explain this condition to the patient. I can only paraphrase Justice Potter Stewart, who, in describing pornography, said he doesn’t know how to define it but he knows it when he sees it. In contrast to your experts, I find it difficult to believe that this is an iatrogenic disease. We saw such patients when I was a house-offi-

<table>
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<tr>
<th>Actual Group Allocation</th>
<th>Subject’s Assessment of Allocation at 4 Weeks</th>
<th>Subject’s Assessment of Allocation at 8 Weeks</th>
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<td>Active group</td>
<td>14 Active</td>
<td>17 Active</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td>6 Don’t know</td>
<td>2 Don’t know</td>
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Fibromyalgia — Real or Imagined?

To the Editor:

It seems that editorials in medical journals are designed principally to identify problems rather than find solutions. With this in mind, I am intrigued by the editorial blitzkrieg you have unleashed against that common, unfortunate malady we call fibromyalgia (FM). It would appear that your purpose is to ban FM once and for all from rheumatology practices, research endeavors, and training programs and to exile these ladies to a medical limbo and into the clutches of con men, charlatans, and the expert advice of the Internet. Just one year ago, one of our leaders was widely quoted1 that there is no evidence to support the active cream containing camphor, glucosamine, and chondroitin is safe and effective in reducing the pain from osteoarthritis of the knee. The relative contribution of these ingredients is now the subject of ongoing research.

REFERENCES

cism must be understood according to the ideas of the philosophers, like
published in the August 2003 issue of
This essay refers to the editorials by Gordon, Ehrlich, Hadler and Wolfe,
To the Editor:
Fibromyalgia. Reflections About Empirical Science and Faith
ALTON MORRIS, MD, Kingsport, Tennessee 37660, USA.
At least one female physician to join this group of male chauvinists. I believe
ably dislike ladies with FM, it would have been more fair if you had had at
least one female physician to join this group of male chauvinists. I believe
that there would have been a more valid conclusion.

ALTON MORRIS, MD
Kingsport, Tennessee 37660, USA.

REFERENCES
1. Wolfe F. Stop using the American College of Rheumatology criteria
2. Ehrlich P, Hata S. Die experimentelle Chemotherapie der
3. Ehrlich G. Pain is real. Fibromyalgia isn’t [editorial]. J Rheumatol
4. Blann EF, Jones TD. The natural history of rheumatic fever: a 20
available.
5. Jones TD. The diagnosis of rheumatic fever. JAMA
1944;126:481-4.
7. Gordon DA. Fibromyalgia. Real or imagined? [comment]

Fibromyalgia. Reflections About Empirical Science and Faith
To the Editor:
This essay refers to the editorials by Gordon, Ehrlich, Hadler and Wolfe,
As medicine, rheumatology is an empirical science. In science, empiri-
cism must be understood according to the ideas of the philosophers, like
Hume and Berkeley1,2, who conclude that knowledge could only be
acquired through sensory experience. In other words, the object of knowl-
edge must be perceptible through one’s senses.
When a scientist is looking for T CD4 lymphocytes in a human tissue,
he or she is looking for empirical evidence. To achieve this, he or she
works with a visible and tactile piece of tissue; stains it with visible, tactile, and
smelly chemical substances, and gets something that can be visible with a
microscope and that can be photographed. This is the empirical part of sci-
cific work and the facts that are produced in it are empirical facts and
empirical knowledge. They are visible, tactile, perceptible, and real.
However, when T CD4 lymphocytes are detected in a human tissue,
what does this mean? To answer this, we need a different kind of knowl-
edge, an abstract knowledge. This is a “theoretical” knowledge and it is
expressed with words. It can be based on empirical facts or faith.
When a patient has clinical manifestations of tuberculosis, like cough
and sputum, fever, weight loss, and radiographically visible pulmonary
lesions, the person really only knows that he or she has tuberculosis after a
sequence of empirical facts. First, a laboratory test of tissue or secretion
from that person has to show a structure, conventionally named
Mycobacterium tuberculosis, which is visible by staining methods. Second,
the result of the laboratory test is written on paper. Finally, a physician
reads the result and translates into one word: tuberculosis.
One who gets M. tuberculosis, gets tuberculosis. This is a form of cir-
cular reasoning, which is scientifically acceptable because it is the presence
of the bacillus (empirical fact) that defines the disease (theoretical knowl-
edge). The same is true for cancer, of which the empirical basis is the
malignant cell.
The development of criteria for fibromyalgia (FM) classification was
an attempt to give empirical support to a common situation in medical prac-
tice. A patient who complains of body pain over a long period of time rep-
resents this situation. When the complaint persists longer than 3 months
and is diffuse, it is conventionally named widespread chronic pain.
Without empirical or specific evidence to define that clinical situ-
ation, the committee takes 2 additional items of evidence, which are the
complaint of widespread chronic pain and the finding of tender points in a
physical examination. I say “the complaint of widespread chronic pain” and
not “widespread chronic pain” because “the complaint” is the only empiri-
cal form describing the phenomenon. When one says “widespread chronic
pain,” one is accepting the pain as being real, but that is an act of faith and
causes judicial consequences.
The idea behind the development of the criteria attempts to define the
word fibromyalgia as being the empirical evidence of someone complain-
ing of widespread chronic pain and the finding of 11 or more tender points in
a physical examination. The reasoning used is the passage of empirical
evidence (complaint of widespread chronic pain and tender points) to a ver-
bal significance (fibromyalgia). A mental process known as induction leads to
this. Personally, I call it an inductive jump. The jump is from empirical
effects to words. Induction is a process of thought where an act of faith turns
empirical evidence into words, words into meanings, meanings into feel-
ings, and feelings into realities. These realities reinforce the initial faith.
When someone jumps from a malignant cell to cancer or from M. tuber-
culos to tuberculosis, those acts are accepted as scientific truth because
there is no evidence showing there is tuberculosis without M. tuberculosis
and cancer without a malignant cell. The association of these words is spec-
cific and complete. Even if in these cases there are inductive jumps from
one word to another, they represent the same reality, in spite of using
“malignant cell” for the isolated cell and “cancer” for the clinical expres-
sion of the disease; we are saying in an empirical way, malignant cell is
cancer and cancer is a malignant cell. This “scientific tautology” is the basis
of the meaning of words in science.
But this is not true for FM. Tender points are not specific for the com-
plaint of widespread chronic pain, and the complaint of widespread chron-
ic pain is not specific for FM, so the combination of tender points and the
complaint of widespread chronic pain is not sufficient to construct a scien-
tific tautology with the word fibromyalgia. The result is a concept that is
not empirical, that is not verifiable. But it is useful.
It is useful because the construct has initiated scientific efforts to prove
its veracity or deny its existence. These works have produced meaningful
scientific knowledge of anatomical and biochemical phenomena involved
in perception and modulation of pain. It is useful because it explains to
patients that pain does not mean lesion or deformity, does not mean arthri-
tis or cancer, does not mean disability or incapacity. And the prognosis of
someone complaining of widespread chronic pain is not hopeless. There are
patients that even complain of widespread chronic pain for a long time,
who stop complaining after some time. If those patients had pain and the
pain disappeared, it is a conclusion that current medicine cannot explain;
there is no empirical evidence to do so. But if there are patients that com-
plain of widespread chronic pain for some time and at the same time have sleep disturbance, fatigue, and tender points, and then stop complaining and these manifestations disappear, we can say that there is hope for someone complaining of widespread chronic pain.

However, while the construct is useful in some aspects, it has failed in others because it is not empirical. Because FM is not verifiable, it cannot be denied, and this is more important than proving its existence. Nobody will go to court to request compensation for cancer without showing the malignant cell that defines the disease. Without the empirical proof, a claim for cancer cannot be defensible. But someone with bad intentions can claim compensation for FM because this complaint cannot be overturned by present-day knowledge. Astute lawyers certainly have perceived that, and the scientifically useful construct has been abused in legal proceedings, taking advantage of the law’s inexactness and subjective determinations of incapacity and compensation.

Physicians who have testified that patients complaining of widespread chronic pain really felt the pain, were moved by faith in words, but not by empirical evidence to support the scientific statement. Yet giving testimony, the physician is called to answer empirically, perhaps as follows:

Does the patient complain about widespread chronic pain?

“Yes.”

Does the patient feel the pain?

“I can’t affirm that.”

Does the patient have fibromyalgia?

“No one can have fibromyalgia. Fibromyalgia is just a word we use to represent the situation of someone complaining about widespread chronic pain, fatigue, and sleep disturbance who has tender points on physical examination. It is not a disease, it’s a description.”

That’s the difference between scientific tautology and pleonasm.

LUIZ CLAUDIO da SILVA, MD, Rheumatologist, Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Brazil.
E-mail: lclaudiosilva@terra.com.br

REFERENCES

Systolic Blood Pressure in Patients with Osteoarthritis and Rheumatoid Arthritis

To the Editor:
The recent article by Singh, et al raises an increasingly important issue: with the advent of cyclooxygenase-2 (COX-2) inhibitors, doctors seem to have forgotten that nonsteroidal antiinflammatory drugs (NSAID) have important adverse effects. The effects on blood pressure are often more severe than the few mm Hg that they highlight. I frequently see patients whose blood pressure has been significantly aggravated by NSAID, including COX-2 inhibitors. However, like many, they seem to have forgotten that not all NSAID are created equal with respect to effects on blood pressure.

We showed that in contrast to other NSAID, sulindac does not raise blood pressure, and that this difference was due to sparing of renomedullary vasodilator prostaglandins. I have suspected for some time that the (to me) surprising neglect of our report may have been related to the apparent small size of the sample (30 patients). However, because it was a 4-way complete-crossover design, the study had a greater power than would a parallel-group study in 120 patients. It was also more relevant to the clinical situation than some other negative studies at the time done in healthy volunteers, in that we studied patients with hypertension, stabilized on beta-blocker and diuretic.

As Santayana pointed out, those who forget history are doomed to repeat the mistakes of the past. Patients with hypertension, congestive heart failure, or other conditions aggravated by retention of salt and water will do better taking sulindac than other NSAID.

J. DAVID SPENCE, MD, Stroke Prevention and Atherosclerosis Research Centre, 1400 Western Road, London, Ontario N6G 2V2, Canada. E-mail: dspence@robarts.ca Phone 519-663-3113; fax 519-663-3018

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Acute Polymyositis Related to Once-Weekly Alendronate in a Woman with Osteoporosis

To the Editor:
In regard to reports of alendronate therapy, we describe our experience treating a woman for postmenopausal osteoporosis with a once-weekly formulation of bisphosphonate, who, 12 hours after each intake, developed severe myalgia and symmetrical polyarthritis. She recovered spontaneously without sequelae.

A 63-year-old woman had a history of total hysterectomy at the age of 42 years and of recurrent episodes of lumbar pain since the age of 60. She also had pains involving the base of both thumbs and the right big toe, related to osteoarthritis (OA). Lumbar radiographs showed mild signs of OA of the zygapophyseal joints of the last 2 lumbar vertebrae. Densitometry dual energy x-ray absorptiometry evaluation revealed reduced mineral density in both vertebral (T score –3.6) and femoral neck (T score –2.02) sites. Postmenopausal osteoporosis was diagnosed.

For therapy, she was given once-weekly alendronate (70 mg) in addition to oral calcium (1 g daily) and vitamin D3 (800 IU daily). Twelve hours after the first ingestion of alendronate, she started to have severe diffuse myalgia and pains of both hands, feet, and knee joints; the pain was so severe that she was confined to her bed for one day. There was no fever, chills, cutaneous erythema, or esophageal irritation. After the second dose of alendronate, who, 12 hours after each intake, developed severe myalgia and symmetrical polyarthritis. She recovered spontaneously without sequelae.

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For therapy, she was given once-weekly alendronate (70 mg) in addition to oral calcium (1 g daily) and vitamin D3 (800 IU daily). Twelve hours after the first ingestion of alendronate, she started to have severe diffuse myalgia and pains of both hands, feet, and knee joints; the pain was so severe that she was confined to her bed for one day. There was no fever, chills, cutaneous erythema, or esophageal irritation. After the second dose of alendronate 70 mg, one week later, she experienced the same symptoms. Clinical examination after 3 days revealed swelling of both wrists, index fingers (Figure 1), forefeet, and the right knee. Flexion of the fingers was limited bilaterally. The grip strength was very weak. Aspiration of the right knee yielded 4 ml of synovial fluid, which contained 6800 leukocytes/mm3 (30% polymorphonuclears, no eosinophils); no birefringent crystals were seen. C-reactive protein (CRP) was 14 mg/l. Erythrocyte sedimentation rate (ESR; Westergren) was 16 mm/h. Rheumatoid factor was negative. Radiographs of the hands and knee joints revealed mild signs of OA. There was no chondrocalcinosis. Sacroiliac joints were normal on pelvic radiographs. Alendronate was discontinued. During the 6 month followup
myalgia and symptoms of arthritis did not reappear. CRP values returned to normal (3 mg/l) after 10 days. ESR after one month was 6 mm/h.

To our knowledge, this is the first report of acute polyarthritis that can be related to therapy with alendronate. In a series of 476 patients receiving glucocorticoids treated with oral daily alendronate, no case of arthritis as an adverse event was reported. In a series of 38 children treated with daily alendronate during 1 year, one dropped out of the study after the first 2 days of therapy because of severe bone pain. With pamidronate given intravenously to patients with osteoporosis or conditions related to cancer, Thiébaud, et al. have reported bone pains, arthralgia, and flu-like syndrome in 12.5%. These authors postulated that this reaction, which resembled the acute phase response, could be mediated by release of cytokines after bisphosphonate therapy. In an in vitro study, the same authors found an increase of tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) in blood incubated with 2 aminobisphosphonates, pamidronate and zolendronate. In a collagen-induced arthritis model in mice, the aminobisphosphonates showed an exacerbating effect on development of the arthritis. Alendronate, also an aminobisphosphonate, has been found to favor cytokine release by macrophages (IL-1β, IL-6, and TNF-α); however, this effect was not observed with a non-nitrogen-containing bisphosphonate, clodronate. These findings suggested to the authors that amino-containing bisphosphonates such as alendronate could have proinflammatory properties. However, in chronic inflammatory arthritides, the effect of longterm treatment with bisphosphonates is still controversial.

Our observation suggests that not only arthralgia but also transient true polyarthritis may be a rare side effect of alendronate given to patients with primary osteoporosis. Whether this compound could also occasionally aggravate articular manifestations in patients with preexisting chronic arthritis such as rheumatoid arthritis should be assessed in prospective studies.

JEAN C. GERSTER, MD, Professor of Rheumatology, Division of Rheumatology, Centre Hospitalier Universitaire Vaudois, Av. Pierre Decker 5, CH 1011 Lausanne; FRANÇOIS NICOLE, MD, General Practitioner, Lausanne, Switzerland.
E-mail: jean-charles.gerster@chuv.hospvd.ch

REFERENCES


ment. Differential diagnosis included other autoimmune diseases with common skin manifestations: polyarteritis nodosa, microscopic polyangiitis, cutaneous leukocytoclastic vasculitis, giant cell arteritis, and angiocentric lymphomas, along with diseases referred to as ANCA-associated vasculitis (microscopic polyangiitis, Churg-Strauss vasculitis, necrotizing pauci-immune glomerulonephritis). Our patient fulfilled clinical and laboratory criteria for the diagnosis of WG, supported by a good response to cyclophosphamide. Further, absence of the necrotic core and violaceous border speak against pyoderma gangrenosum. The patient did not receive coumarins, a potential cause of skin necrosis.

Since he presented with extensive necrosis, a skin biopsy was not performed for ethical reasons (risk of provoking new ulcers at the biopsy site). In this case, rapid initiation of aggressive immunosuppression and wound care led to therapeutic success.

Our case illustrates that skin necrosis, although rare, could be a potentially devastating manifestation of WG that requires a rapid diagnosis and vigorous treatment.

REFERENCES

Juvenile Polyarteritis: Is It a Different Disease?
To the Editor:

In 1897, Still suggested that the rheumatoid arthritis of children was different than that of adults. He contended that the disease in children started in childhood and had an insidious onset. He also pointed out the marked differences in clinical features and sex distribution, and suggested it might
include more than one disease. Today, juvenile (idiopathic) arthritis is still evolving in terms of nomenclature and classification.

Küssmaul and Maier had described polyarteritis nodosa (PAN) some 30 years before Dr. Still’s report. The description was based on pathology, where necrotizing arteritis characterized the disease. In 1994, PAN was separated into 2 subtypes according to the vessel size involvement, on the basis of the classical presentations in adults: classic PAN and microscopic polyangiitis.

The peak frequency of PAN in adults is in ages 40s and 50s, whereas in children the peak age of onset is before puberty, around 10 years. Both classic PAN and microscopic polyangiitis in adults are known to be more common in males; however, in children the frequency is roughly equal. In adults the disease has a poor outcome. In children, however, the outcome is better. In adults the reported survival rates are around 80%. On the other hand mortality is very rare in children after the 1990s; indeed there were no deaths reported in the 2 recent series published after 1997. The disease in children has a rather insidious onset as in juvenile idiopathic arthritis.

Clinical features of the disease in children are also different than in adults. The pulmonary-renal involvement that characterizes microscopic polyangiitis is very rare in children; the typical cases with high myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) have been rarely reported. In adults there are large series of reports with classic PAN associated with hepatitis B surface antigen (HBsAg). This group is very rare in children, which may partially be due to the increased vaccination in children. Although we had described a number of patients associated with HBsAg in our series before 1990, we have seen only 2 cases since 1990. However, when present it necessitates a different treatment regimen.

Thus the typical presentation in children is of isolated one or 2 organ involvement, with constitutional symptoms, and the diagnosis is often based on pathology. Further, the disease does not necessarily confine itself according to vessel size.

As well, a large group of child patients are characterized by cutaneous PAN, which is rare in adults and is not even included in the Chapel Hill nomenclature criteria. Thus, similarly to juvenile arthritis, we may talk about subtypes in childhood PAN. These may be: (1) Cutaneous PAN: this will be disease confined to the skin. These patients may describe accompanying myalgia, arthralgia, and sometimes arthritis. (2) Systemic PAN with organ involvement other than the skin, regardless of the vessel size (both small and middle size). Constitutional symptoms and elevated acute phase reactants are almost always present. (3) Microscopic polyarteritis as in adults associated with MPO-ANCA: this would be the typical pulmonary-renal syndrome with a guarded prognosis. Some patients may just present with renal disease (pauci-immune, crescentic necrotizing glomerulonephritis) or, rarely, just pulmonary disease. (4) Hepatitis B associated classic PAN of adults: this is an immune complex disease characterized by aneurysms in the renal arteries.

These 4 groups have different etiology: cutaneous PAN is associated with streptococci, whereas the last group is associated with HBsAg. They have different disease courses. They also require different treatment regimens, which remain to be proven. As pediatricians, we need to validate our own classification criteria and severity scores, and to develop treatment protocols for the disease subtypes. These subtypes may well be different parts of the spectrum of the same disease process, which vary in their manifestations according to the modifier genes/factors. In the future we may be able to define these factors; for the time being the features noted here may justify a subclassification.

Infantile PAN has not been included as a separate subtype, since probably all the cases reported in the literature fit with the classification of Kawasaki’s disease. Since the disease has different features and perhaps different subtypes, it might be time that we recognize PAN in children as a different entity, and call it “juvenile PAN.”
In Section I, the roles of all cell types, including T and B cells, dendritic cells, mast cells, macrophages and fibroblast-like synoviocytes and cell surface receptors with their inherent pathways relevant to rheumatic disorders are reviewed. What is known of pathogenetic and pharmacologic concepts from the known basic science is discussed.

In addition to chapters on the roles of chemokines and cytokines such as tumor necrosis factor-α, the pertinent interleukins, and osteoprotegerin, Section II reviews their effector molecules and the roles they play in the immune response of rheumatic diseases. Their functions are analyzed in terms of the Th1/Th2 and pro-/anti-inflammatory balance in both experimental models and human disease. Using both models, Section III goes on to explore the physiology and roles for the transcription factors nuclear factor-κB, STATs, and JAKs (Janus kinase and signal transducer and activator of transcription), the signaling factors inducible nitric oxide synthase, cyclooxygenase, inhibitors of complement, and matrix metalloproteinases.

In Section IV, the knowledge of the response to biotherapeutics is explored in a spectrum of rheumatic disease including rheumatoid arthritis, early rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, systemic lupus erythematosus, myositis, and vasculitis. Additional chapters are devoted to ethical issues in rheumatologic investigation and practice, randomized controlled trials, longer observational controlled trials, and regulatory issues.

This work is of sufficient scope to be recommended for those wanting a review of the basic science behind biotherapeutics, for translational researchers bringing targeted therapies to human rheumatic diseases, and for interested clinicians using them in practice.

Vivian P. Bykerk, BSc (Hons), MD, FRCPC, Assistant Professor of Medicine, University of Toronto, Consultant, Mount Sinai Hospital, Toronto, Ontario, Canada M5G 1X5

Correction

Kötter I, Stübiger N. Therapeutic implications for interferon-α in arthritis [letter]. J Rheumatol 2004;31:624-5. Fish EN [reply]. The second paragraph, fourth sentence of Dr. Fish’s reply should read: “It is the very nature of IFN-alphas as pleiotropic biological response modifiers that suggests their therapeutic potential: their ability to target different cell populations, thereby affecting cellular communication and immunological control at multiple levels.” We regret the error.