Correspondence

INSTRUCTIONS FOR LETTERS TO THE EDITOR

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

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

Opioids for Osteoarthritis of the Hip and Knee: Which Opioids for Which Patients?

To the Editor:

I read with interest the editorial by Dr. Peloso regarding the role for opioids in the management of chronic pain related to osteoarthritis (OA) of the hip and knee. Dr. Peloso concluded that it would be unwise to discount this class of medications over unfounded fears and incomplete knowledge of their benefits[1].

For practical purposes, however, opioids should be divided into "weak opioids" and "strong opioids," this distinction being primarily based on the existence or absence, respectively, of a ceiling effect for analgesia[2]. In fact, weak opioids, including codeine, dihydrocodeine, dextropropoxyphene, and tramadol, are largely used either alone or in combination with non-opioid analgesics, especially acetaminophen (paracetamol) for treating OA pain, at least in European countries. Of note, some combination products that contain low doses of weak opioids (e.g., 20 mg codeine phosphate) are available as nonprescription drugs in France. Thus it does not appear that physicians are reluctant to consider weak opioids for the management of OA.

Whether these compounds are more effective analgesics than nonsteroidal antiinflammatory drugs (NSAID) is, however, debatable[2]. Dr. Peloso based that assertion on the results of 2 studies that indicated that a weak opioid (namely codeine) with or without acetaminophen, combined with an NSAID (ibuprofen) provided significantly better pain relief than that NSAID alone[3,4]. On the other hand, controlled clinical trials that directly compare an NSAID and a weak opioid suggest that the former is at least as effective as the latter[2]. Ketoprofen 150 mg daily has been reported to result in significant reduction in mean joint tenderness score compared to paracetamol 1.95 g plus dextropropoxyphene 195 mg daily in patients with OA[5]. Patient preference strongly favored ketoprofen, although there was no superiority of the NSAID with respect to day pain score and night pain score[5]. Tramadol 200 to 400 mg/day and ibuprofen 1.2 to 2.4 g/day have been found to be equally effective for symptomatic treatment of OA of the hip or knee[6]. Similarly, a mean daily dose of 164.8 mg tramadol and 86.9 mg diclofenac showed comparable efficacy in such patients[7]. However, patients receiving tramadol experienced substantially more adverse effects including nausea, constipation, and drowsiness than those receiving NSAID in both studies[6,7]. Accordingly, NSAID and weak opioids should not be regarded as step 1 and step 2 analgesics, respectively[8]. Weak opioids may be considered for use in OA patients who have contraindications to NSAID, including COX-2 selective inhibitors, or who do not respond to or tolerate NSAID[8,9]. Weak opioids may also be useful as adjunctive therapy in patients whose symptoms are inadequately controlled with acetaminophen or NSAID[8,9].

Finally, physicians are still reluctant to prescribe strong opioids (e.g., morphine, hydromorphone, levorphanol) because of uncertainty about their true risk-benefit ratio in patients with OA hip or knee pain. Few clinical trials have examined the use of strong opioids in chronic nonmalignant pain[2]. They showed that both the incidence of adverse effects and the number of withdrawals due to adverse effects were high in the opioid groups in spite of slow dose titration[2]. It is well known that tolerance to constipation develops very slowly or not at all. Unfortunately, other side effects, especially sedation, may persist in some patients while taking longterm opioid therapy[2]. I agree with Dr. Peloso that the risk of addiction or drug abuse is low among individuals who truly have pain, but it exists. Further, the diagnosis of addiction is rarely straightforward[2] and there are "no obvious predictors of drug seeking"[1].

All in all, the available data suggest that properly selected, informed, and monitored patients with OA hip or knee pain may benefit from the use of opioids, including strong opioids, without requiring rapidly escalating doses or developing intolerable side effects or drug addiction[2]. In this respect, prescribing guidelines have been developed to assist practitioners in selecting the appropriate patients and monitoring them[2]. A subcommittee of the French Society of Rheumatology provided recommendations on the use of morphine in chronic rheumatic pain[10]. According to them, morphine may be a valid treatment option in patients with advanced hip or knee OA who fail to respond to other pharmacological and nonpharmacological modalities and who are waiting for surgery or are not surgical candidates[10].

BERNARD BANNWARTH, MD, Department of Rheumatology, Groupe Hospitalier Pellegrin, Division of Therapeutics, University Victor Segalen, Bordeaux, France.

REFERENCES

1. Peloso PM. Opioid therapy for osteoarthritis of the hip and knee: use it or lose it? [editorial]. J Rheumatol 2001;28:6-11.
2. Bannwarth B. Risk-benefit assessment of opioids in chronic noncancer pain. Drug Safety 1999;21:283-96.
3. Quiding H, Grimstad J, Rusten K, Stubhaug A, Bremnes J, Breivik H. Ibuprofen plus codeine, ibuprofen, and placebo in a single and multiple cross-over comparison for coxarthrosis pain. Pain 1992;50:303-7.
4. Vlok GJ, Van Vuren JP. Comparison of a standard treatment with a new ibuprofen/paracetamol/codeine combination in chronic osteoarthritis. S Afr Med J 1987; Suppl 1:4-6.
5. Doyle DV, Dieppe PA, Scott J, Huskisson EC. An articular index for the assessment of osteoarthritis. Ann Rheum Dis 1981;40:75-8.
6. Dalgin P. Comparison of tramadol and ibuprofen for the chronic pain of osteoarthritis [abstract]. Arthritis Rheum 1997;40: Suppl:S86.
7. Katz WA. Pharmacology and clinical experience with tramadol in osteoarthritis. Drugs 1996;52: Suppl 3:39-47.
8. Bannwarth B. Is the WHO analgesic ladder for cancer pain management appropriate for rheumatology patients? [editorial]. Rev Rhum Engl Ed 1999;66:277-80.
9. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. Arthritis Rheum 2000;43:1905-15.
10. Perrot S, Bannwarth B, Bertin P, et al. Use of morphine in nonmalignant joint pain: the Limoges recommendations. Rev Rhum Engl Ed 1999;66:651-7.

To continue

please scroll

to next page

Dr. Peloso replies

To the Editor:

I certainly agree with Dr. Bannwarth that reasoned debate is necessary regarding the role of opioids in the management of osteoarthritis (OA), and musculoskeletal pain in general. These debates ought to be based on best available evidence. The intent of the editorial[1] was to describe, in part, that evidence. It is instructive to learn that Europeans may be more open to opioids in musculoskeletal pain management.

Should opioids be classified as weak versus strong? This concept proposes an analgesic limit for "weak" opioids. Many of the drugs listed as weak opioids, such as codeine and oxycodone, are in fact agonists, not mixed agonists-antagonists[2] whose doses are limited by the drugs they are combined with (principally acetaminophen) and not by the properties of the drugs themselves. That is, the maximum daily dose of acetaminophen at 4000 mg artificially limits the analgesic potential of some less potent opioids. Complicating this fact, an insufficient number of dose response studies are available to judge potency among analgesic classes.

Dose response studies comparing acetaminophen/codeine combination tablets (600 mg/60 mg) to Codeine Contin showed that 4 combination tablets (2400 mg acetaminophen/240 mg codeine daily) provided pain relief equivalent to Codeine Contin 150 mg every 12 hours (300 mg codeine), with equivalent side effect profiles[3]. That study also showed 400 mg/day and 600 mg/day of Codeine Contin provided superior analgesia to the combination product. Our study in hip and knee OA also showed a dose response relationship for both pain and function with increasing doses of controlled release codeine[4].

Potent opioids, in lower doses, may be as rational for moderate pain as are higher doses of less potent opioids. However, physicians may view prescription of a less potent opioid as more acceptable practice[5]. In a survey of physiatrist members of the AAPM&R, 95.6% treated OA, with 90% willing to prescribe codeine, hydrocodone, and oxycodone in combination with acetaminophen, but only 65% willing to prescribe hydromorphone and 75% short acting morphine.

The principle ought to be that opioid doses should be increased until analgesic goals are met, or patients experience limiting side effects. Where opioids are indicated, if one opioid proves insufficient, an alternative opioid should be tried.

Where do opioids fit in management of OA? In contrast to hundreds of trials of NSAID versus placebo or other NSAID[6], there is a limited pool of studies comparing NSAID to acetaminophen and NSAID to opioids. While current evidence suggests that NSAID are superior to acetaminophen in the management of moderate to severe OA pain[7,8], the data are less certain for opioids versus NSAID. The Medline search[1] from 1966 to March 2000 identified 15 trials. Of these 15 trials, 2 were direct comparisons against opioids, while 4 trials compared opioid to placebo against a background of stable NSAID therapy. For the 2 trials of NSAID versus opioid, codeine combination tablets or codeine was superior to ibuprofen. When the 4 trials of opioid versus placebo on a background of NSAID are reviewed, opioid is superior to placebo plus background NSAID. These 6 trials in total suggest opioids are superior to NSAID. Metaanalysis and comparison of effect sizes would better allow us to judge the magnitude of the differences.

Dr. Bannwarth describes another published study that was not identified in the Medline search[9]. This crossover trial with a one week evaluation period, without a washout period, evaluated 25 patients with OA in unspecified areas who received either paracetamol 650 mg plus dextropropoxyphene 65 mg tid or ketoprofen 50 mg tid. Outcome measures included an observer recorded articular index, observer recorded pain including nighttime pain and daytime pain, inactivity stiffness, morning stiffness, urate granuloma size, and patient preference for the 2 drugs. Of these 7 outcome measures, 3 favored ketoprofen, including the articular index, size of the urate granuloma, and patient preferences. The clinical relevance of differences in the articular index and urate granuloma size are not interpretable based on data provided in the paper. Given the lack of differences in the pain scores, the differences in patient preferences favoring ketoprofen suggests preferences were influenced by factors other than pain relief. The report's authors suggest the articular index is a measure of inflammation, and that ketoprofen is a better antiinflammatory than dextropropoxyphene.

The abstract by Dalgin contains insufficient information to judge the comparison of tramadol and ibuprofen in knee OA and a complete article would contribute to the debate[10].

Dr. Bannwarth's statement that "weak opioids may be considered for use in OA patients who have contraindications to NSAID, including COX-2 selective inhibitors, or who do not respond to or tolerate NSAID" is remarkably close to my suggestions for opioid use in OA: [for] "those with moderate to severe OA pain...where acetaminophen is insufficient, and for whom NSAID or COX-2 specific inhibitors are contraindicated...and when NSAID or COX-2 specific inhibitors are not useful, or are insufficient on their own."

His view that "properly selected, informed, and monitored patients with OA hip or knee pain may benefit from the use of opioids, including strong opioids, without requiring rapidly escalating doses or developing intolerable side effects or drug addiction"[11] is supported by the available evidence. The debate has begun. Now we must insist that the evidence needed to fully inform the debate is made available.

PAUL M. PELOSO, MD, MSc, Associate Professor of Medicine, University of Iowa, Iowa City, Iowa 52242, USA. E-mail: paul-peloso@uiowa.edu

REFERENCES

1. Peloso PM. Opioid therapy for osteoarthritis of the hip and knee: Use it or lose it? [editorial]. J Rheumatol 2001;28:6-11.
2. Portenoy RK. Cancer pain management. Semin Oncol 1993;20: Suppl 1:19-35.
3. Chary S, Goughnour BR, Moulin DE, Thorpe WR, Harsanyi Z, Darke AC. The dose-response relationship of controlled-release codeine (Codeine Contin) in chronic cancer pain. J Pain Symptom Manage 1994;9:363-71.
4. Peloso P, Bellamy N, Bensen W, et al. A double blind, randomized, multicenter placebo controlled trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. J Rheumatol 2000;27:764-71.
5. Greenwald BD, Narcessian EJ, Pomeranz BA. Assessment of physiatrists' knowledge and perspectives on the use of opioids. Review of basic concepts for managing chronic pain. Am J Phys Med Rehabil 1999;78:408-15.
6. Dieppe PA, Frankel SJ, Toth B. Is research into the treatment of OA with non-steroidal anti-inflammatory drugs misdirected? Lancet 1993;341:353-4.
7. Eccles M, Freemantle N, Mason J. North of England Evidence Based Guideline Development Project: summary guideline for non-steroidal anti-inflammatory drug versus basic analgesic in treatment of pain of degenerative arthritis. BMJ 1998;317:526-30.
8. Tannenbaum H, Peloso PM, Russell AS, Marlow B. An evidence-based approach to prescribing NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis: The Second Canadian Consensus Conference [review]. Can J Clin Pharmacol 2000;7 Suppl A: 4A-16A.
9. Doyle DV, Dieppe PA, Scott J, Huskisson EC. An articular index for the assessment of osteoarthritis. Ann Rheum Dis 1981; 40:75-8.
10. Dalgin P and the TPS-OA Study Group. Comparison of tramadol and ibuprofen for the chronic pain of osteoarthritis [abstract]. Arthritis Rheum 1997;40 Suppl:S86.
11. Bannwarth B. Risk-benefit assessment of opioids in chronic noncancer pain. Drug Safety 1999;21:283-96.

Clinical Improvement in Osteoarthritis

To the Editor:

Ehrich and colleagues report estimates of the minimal perceptible clinical improvement (MPCI) — also termed minimal detectable change (MDC) — for the WOMAC[1]. The authors suggest it is possible for MPCI to be greater than a clinically important change (CIC): "It may be less than, the same or possibly even greater than the clinically meaningful difference or change"; however, they do not elaborate on this rather curious statement. How is it possible for a patient to declare important a change that cannot be perceived? In attempting to answer this question, we can only imagine that inappropriate comparisons are being made. We will provide a brief outline of our thoughts and are interested in having the authors clarify their statement concerning this issue.

Comparison of estimates from groups and from individuals could lead to the conclusion that MPCI is greater than CIC. Goldsmith, *et al*[2] demonstrated that estimates of CIC for groups are substantially less than estimates of CIC for individual patients. Accordingly, if one compares an estimate of MPCI for an individual patient to an estimate of CIC for a group, it is possible for MPCI to be greater.

A second factor that could influence estimates of MPCI and CIC is the scale or method used to classify patients on the comparison standard (pseudo-criterion). Ehrich, *et al* used a 5 point global rating of change to estimate MPCI. The estimate would likely be different if a 7 point scale were used even if the adjectives on the 5 point scale were a subset of those appearing on the 7 point scale. Moreover, two 7 point global rating scales may provide different estimates of change if the adjectives associated with the scale points differ.

A third explanation is that the estimates of MPCI and CIC being compared may have been obtained from different analytic methods. Estimates can be obtained from distributions of change scores in persons who are stable (reliability) and/or in persons who have truly changed (MPCI) or have changed by an important amount (CIC). In the case of stable patients, a true change is defined as a difference score that has a low probability of being associated with stable patients. For example, consider a distribution of difference scores obtained from a group of stable patients as part of a reliability study. Suppose the difference scores are normally distributed with a mean of zero and a standard deviation of 2 points on the measure of interest. If one chooses 2 standard deviations as a low probability of being associated with the stable group, a change of 4 points represents a true change.

Alternatively, one could focus on a distribution of patients who have either truly changed or have changed an important amount depending on whether MPCI or CIC is being estimated. Here, MPCI (or CIC) is defined as a value that has a low probability (e.g., 10%) of being associated with that group. For example, consider a distribution of patients who have truly changed. For the purpose of illustration we will assume that the change scores are consistent with a normal distribution with a mean of 7 and standard deviation of 2. Once again we choose 2 standard deviations at the point defining true change. Accordingly, a 3 point change ($7 - 2 \times 2$) on the measure of interest is defined as a true change.

A third approach is to consider the distributions of stable patients and truly changed patients simultaneously. Using this method the change score that places a patient closer to the mean of the improved group than to the mean of the stable group defines a true change. For example, if one considers the stable and truly changed distributions mentioned above, a change score of 3.5 represents a true change. When a score of 3.5 change points is used to define a true change, 4% of patients in the stable group will be classified as having improved (i.e., the area in the upper tail of this distribution) and 4% of the patients in the changed group will be classified as not having changed (i.e., the area in the lower tail of this distribution).

A fourth method is to define a true (or important) change as the difference between the mean scores of the stable and changed groups. In the cited example, this difference is 7 points. However, using 7 points as an estimate of true change results in labeling 50% of truly changed patients as not having changed. Less than 1% of stable patients would be classified as having changed.

We do not know the circumstances that have prompted Ehrich, *et al* to suggest important change can be less than perceptible change. However, our view is that their conclusion might be the result of an inappropriate comparison.

PAUL STRATFORD, PT, MSc; JEAN WESSEL, PT, PhD, McMaster University, Hamilton, Ontario, Canada.

REFERENCES

1. Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. J Rheumatol 2000;27:2635–41.
2. Goldsmith CH, Boers M, Bombardier C, Tugwell P. Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. J Rheumatol 1993;20:561–5.

Dr. Ehrich, *et al* reply

To the Editor:

We respectfully acknowledge the comments of Mr. Stratford and Dr. Wessel. In our report[1], however, we did not suggest that it is possible for the minimal perceptible clinical improvement (MPCI) for a patient *population* to be greater than a clinically important change (CIC). Indeed, we highlighted the very opposite to be evident: "Our estimates of minimal perceptible clinical improvement are smaller in magnitude than estimates of minimally important clinical change (i.e., CIC)... The difference is not necessarily an inconsistency but rather may highlight that what is minimally perceptible to patients may still be less than a clinically meaningful improvement."[1]

We do agree with Stratford and Wessel that MPCI for an individual patient could possibly be larger than a CIC based on a population mean.

ELLIOT EHRICH, MD; Cambridge, Massachusetts; GLENN DAVIES, DrPH; DOUGLAS WATSON, PhD; JAMES BOLOGNESE, MStat; Rahway, New Jersey; BETH SEIDENBERG, MD; Princeton, New Jersey, USA; NICHOLAS BELLAMY, MD, Brisbane, Queensland, Australia.

REFERENCE

1. Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. J Rheumatol 2000;27:2635–41.

A Multicase Family with Primary Sjögren's Syndrome

To the Editor:

We read with interest the report of Bolstad, *et al*[1] about a case of monozygotic twins with primary Sjögren's Syndrome (SS). Primary SS is a common connective tissue disease, affecting 0.2–0.6% of the population in Europe[2], with a female to male ratio of 9:1. Although the trend of autoimmune diseases to aggregate in families is well known[3], the event of several cases of primary SS in the same family is uncommon. We report a case of familial aggregation (3 dizygotic siblings — 2 female and one male — and their mother) of primary SS[4] examined in the Systemic Autoimmune Disease Unit, Virgen de las Nieves University Hospital.

Case 1. The brother was diagnosed with primary SS in 1992, at the age of 38. At the time of diagnosis he presented fever, fatigue, odynophagia, aphthous oral lesions, arthralgias in his hands, knees and ankles, and pain and enlargement of parotid glands. He had a history of xerostomia and corneal ulcers and 2 other episodes of fever and pain in parotid glands. Rose-Bengal and Schirmer tests were pathologic, and histological examination of lower labial salivary glands showed an intense lymphocytic infiltration.

Polyclonal hypergammaglobulinemia, rheumatoid factor (RF), and antinuclear antibody (ANA) titers were persistently present or positive. However, he was negative for Sm, RNP, anti-Ro/SSA, anti-La/SSB, Scl 70, and anti-dsDNA; C3 and C4 complements were 0.87 and 0.08 g/l, respectively. The HLA-type was DR3, 8.

Case 2. A sister was diagnosed in 1993, at the age of 35. She had a history of oral and ocular symptoms (xerostomia and keratoconjunctivitis sicca), intermittent non-erosive oligoarthritis, and pain in dorsal and lumbar spine and heels. General symptoms were not present. Schirmer test and Rose-Bengal were abnormal and histological examination of lower labial salivary glands showed a nongranulomatous inflammatory infiltration of lymphocytes. RF was 64 U/ml and ANA, anti-Ro/SSA, and anti-La/SSB were positive. The HLA-type was DR3, 8.

Case 3. The second sister was diagnosed in 1994, at the age of 40. She also presented xerostomia, xerophthalmia, and keratitis several years before. She had polyarthralgias and a history of asthma (IgE 403 µg/l). Enlargement of parotid glands was not observed. Schirmer test and the Rose-Bengal were abnormal and the immunological study showed ANA positive (1:80, speckled pattern), an elevated RF, and positive anti-Ro/SSA and anti-La/SSB. The biopsy of lower labial salivary glands was compatible with SS. The HLA-type was DR3, 8.

Case 4. The mother was diagnosed in 1999, at the age of 70. She had pain and enlargement of submaxilar salivary glands 2 months before and she had dry mouth and eyes at least 20 years before. No fever, arthralgias, arthritis, Raynaud's phenomenon, enlargement of parotid glands, or general symptoms were present. She showed a polyclonal hypergammaglobulinemia and an elevated RF, but she was negative for ANA, anti-Ro/SSA, and anti-La/SSB. Schirmer test and the Rose-Bengal were abnormal and the scintigraphic study of salivary glands showed a relevant dysfunction of submaxilar glands with unaffected parotid glands. Histological examination of lower labial salivary glands showed a lymphocytic infiltration compatible with SS. The HLA-type was DR3, 14.

Primary SS is a chronic autoimmune disease predominantly characterized by oral and ocular dryness due to an inflammatory process in the exocrine glands, with frequent systemic complications. These patients produce specific autoantibodies termed Ro/SSA and La/SSB. Anti-Ro/SSA is found in 50 to 80% of the patients and anti-La/SSB in 30 to 60%, similar to our results (Table 1). In addition, ANA and RF are commonly found. Although the cause of primary SS is unknown, HLA genes have been implicated and the association of HLA-DR3 with primary SS in Caucasians is well established[3]. In this regard all our patients were HLA-DR3 (Table 1). This could explain, at least in part, the trend of primary SS and other autoimmune diseases to aggregate within families. For this reason, the investigation of other family members starting from an index case diagnosed with primary SS could provide worthwhile insights.

JOSE MARIO SABIO, ENCARNACION MILLA, JUAN JIMÉNEZ-ALONSO, Virgen de las Nieves University Hospital, Granada, Spain.

REFERENCES

1. Bolstad AI, Haga HJ, Wassmuth R, Jonsson R. Monozygotic twins with primary Sjögren's Syndrome. J Rheumatol 2000;27:2264-6.
2. Silman AJ, Rooney BK. Epidemiology of Sjögren's syndrome. In: Eriksson E, Jonsson R, editors. The 100-year anniversary of Henrik Sjögren. Hygiea 1999;108 Suppl 1:53-7.
3. Foster H, Stephenson A, Walker D, Cavanagh G, Kelly C, Griffiths I. Linkage studies of HLA and primary Sjögren's syndrome in multicase families. Arthritis Rheum 1993;36:473-84.
4. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340-7.

Dr. Bolstad replies

To the Editor:

I read with great interest the report by Dr. Sabio, *et al.* The patients they describe have salivary gland biopsy results compatible with Sjögren's syndrome (SS) and a histologic picture showing a nongranulomatous lymphocytic infiltration. Since focus score has been found to be the most useful histologic index when evaluating the salivary component[1], it would have been of interest to see the scoring values in this set of patients.

It would also have been nice if the antinuclear antibody (ANA) titers had been recorded for all ANA positive patients, or the limit for regarding ANA as positive had been noted.

Henrik Sjögren in his classical thesis[2] carefully described a method to stain the damaged cells in the conjunctiva and cornea by using 1% Bengal rose, and he invented the expression "keratoconjunctivitis sicca" as a designation for an abnormal condition. In the present case report, commendably both Schirmer test and Rose Bengal staining were used for eye examination. However, the term xerophthalmia was used to describe the status. Since xerophthalmia is defined as dryness of conjunctiva and cornea due to vitamin A deficiency, it might have been preferable if the expression "keratoconjunctivitis sicca" had been applied instead.

Table 1. Patients' clinical characteristics.

Patient/ Sex/Age	Xerostomia	Xerophthalmia	Schirmer Test/ Rose-Bengal	Immunological Studies	LLSG Histology	Associated Symptoms	HLA
1/M/38 yrs	Yes	Yes	+	ANA + Ro/SSA– La/SSB– RF > 80	Compatible with SS	Fever, fatigue, arthralgias, enlargement of parotid glands	DR3,8
2/F/35 yrs	Yes	Yes	+	ANA+ Ro/SSA+ La/SSB+ RF > 60	Compatible with SS	Lumbar and dorsal pain. No general symptoms	DR3,8
3/F/40 yrs	Yes	Yes	+	ANA+ Ro/SSA+ La/SSB+ RF > 80	Compatible with SS	Polyarthralgias, asthma. No general symptoms	DR3,8
4/F/70 yrs	Yes	Yes	+	ANA– Ro/SSA– La/SSB– RF > 40	Compatible with SS	Chronic submaxilitis. No general symptoms	DR3,14

LLSG: lower labial salivary glands; ANA: antinuclear antibody; RF; rheumatoid factor.

The HLA-DR3 association with patients with primary SS is well documented. In a very recent study on HLA markers and clinical characteristics in Caucasian patients with primary SS, we found that the association of HLA class II markers with primary SS may concern the anti-Ro/La response rather than the disease itself[3].

As pertinently reported by the authors, observations of accumulation of autoimmune diseases in families are common, although large families with several cases of primary SS probably are scarce[4,5]. The number of available single case patients with primary SS in each country is also limited. This indicates that to be able to generate valid genetic data in this category of patients, collaboration across country borders to achieve greater primary SS cohorts may be necessary when searching for genes in such complex diseases. This has proven valuable for mapping of systemic lupus erythematosus, another disease with complex genetic traits[6,7].

ANNE ISINE BOLSTAD, DDS, PhD, University of Bergen, Bergen, Norway.

REFERENCES

1. Daniels TE. Labial salivary gland biopsy in Sjögren's syndrome. Assessment as a diagnostic criterion in 362 suspected cases. Arthritis Rheum 1984;27:147-56.
2. Sjögren H. Zur kenntnis der keratoconjunctivits sicca. Acta Ophthalmol 1933; Suppl 11:1-151.
3. Bolstad AI, Wassmuth R, Haga H-J, Jonsson R. HLA markers and clinical characteristics in Caucasians with primary Sjögren's syndrome. J Rheumatol 2001;28:1554-62.
4. Reveille JD, Wilson RW, Provost TT, Bias WB, Arnett FC. Primary Sjögren's syndrome and other autoimmune diseases in families. Prevalence and immunogenetic studies in six kindreds. Ann Intern Med 1984;101:748-56.
5. Bolstad AI, Haga H-J, Johannesen A, Thomassen E, Jonsson R. Norwegian families multiplex for primary Sjögren's syndrome. In: The 100-year anniversary of Henrik Sjögren. Eriksson P, Jonsson R, editors. Hygiea 1999;108:98.
6. Magnusson V, Lindqvist A-KB, Castillejo-López C, et al. Fine mapping of the SLEB2 locus involved in susceptibility to systemic lupus erythematosus. Genomics 2000;70:307-14.
7. Gray-McGuire C, Moser KL, Gaffney PM, et al. Genome scan of human systemic lupus erythematosus by regression modeling: Evidence of linkage and epistasis at 4p16-15.2. Am J Hum Genet 2000;67:1460-9.

Catastrophic Antiphospholipid Syndrome: Need for a Reappraisal

To the Editor:

In 1992 Asherson first described in *The Journal* a small number of patients with antiphospholipid syndrome (APS) exhibiting certain unique characteristics such as (1) clinical evidence of multiorgan involvement (3 or more) and/or (2) histopathological evidence of multiple vascular occlusions that he named "catastrophic antiphospholipid syndrome" (CAPS)[1]. In a subsequent publication it was alluded that this term may only apply to a small subset of patients at one end of the spectrum of the APS[2].

The literature on this topic over the past several years is confusing and there are a number of issues that we would like to raise. First, although the exact prevalence of this complication is unknown, an increasing number of reports suggest that this complication or syndrome may not be that rare after all. Attesting to this is the recent report by Asherson, *et al* describing the clinical and laboratory features in 50 patients[3]. It is possible that this could be secondary to increasing recognition of the syndrome. However, it is also likely that due to the lack of classification criteria some published reports may not have been "catastrophic." The latter is plausible, and further review of published reports including a few of those patients initially reported by Asherson may not have fulfilled the characteristics ascribed to the syndrome[2,4]. A case in point is the report by Dosekun, *et al*[5] describing a woman presenting with clinical evidence of renal and neurologic involvement but with only renal histopathologic evidence of arteriolar and arterial thromboses. This patient was successfully treated with Ancrod IV, but firm documentation of involvement was seen in 2 organs, and histological evidence was presented only in one.

It has become obvious that as the number of patients exhibiting CAPS increases in the literature, there has been a tendency to ignore the second point made in the original report, that is, histological evidence of vascular thrombosis at multiple levels. This, however, might be remedied by the use of newer imaging techniques to confirm the presence of thrombosis.

It is also our impression that the original definition of this subset of patients with APS has been the subject of multiple changes and interpretations by the rheumatology community, including Asherson, who in his most recent publication[6] defines this syndrome as characterized by "rapidly recurring thrombotic events involving many organs, with involvement of predominantly small vessels." Only 2 years earlier, analyzing 50 cases, Asherson defined the syndrome as an acute multisystemic failure associated with positive antiphospholipid antibodies involving multiple organs simultaneously or over a very short period of time (days to weeks). The latter, we believe, requires better definition.

It is our impression that over the past several years this subset of the APS has been overdiagnosed, and this is primarily the result of a lack of precise definition and/or lack of classification criteria. There is a real need to establish consensus criteria, as has already been done for the APS[7].

LOURDES OLGUIN-ORTEGA, MD; LEONOR BARILE-FABRIS, MD, Hospital Especialidades C.M. La Raza, Mexico DF 02990, Mexico; LUIS R. ESPINOZA, MD, LSU Medical Center, 1542 Tulane Avenue, New Orleans, LA 70112-2822, USA.

REFERENCES

1. Asherson RA. The catastrophic antiphospholipid syndrome [editorial]. J Rheumatol 1992;19:508-12.
2. Asherson RA. On the catastrophic antiphospholipid syndrome [letter]. Alarcon-Segovia D [reply]. Clin Exp Rheumatol 1994;12:343-6.
3. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine 1998;77:195-207.
4. Alarcon-Segovia D. On the catastrophic antiphospholipid syndrome [editorial]. Clin Exp Rheumatol 1993;11:587-8.
5. Dosekun AK, Pollak VE, Glas-Greenwalt P, et al. Ancrod in systemic lupus erythematosus with thrombosis. Clinical and fibrinolysis effects. Arch Intern Med 1984;144:37-42.
6. Asherson RA, Shoenfeld Y. The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome-molecular mimicry? [editorial] J Rheumatol 2000;27:12-4.
7. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary criteria for definite antiphospholipid syndrome. Report of an international workshop. Arthritis Rheum 1999;42:1309-11.

Dr. Asherson replies

To the Editor:

I thank Dr. Olguin-Ortega and colleagues for their opinions regarding reappraisal of the catastrophic antiphospholipid syndrome (CAPS) and the need to establish consensus criteria. My original observations on this dramatic, and often fatal, "subset" of the antiphospholipid syndrome, as well as the preliminary criteria I attempted to establish, were predicated on a small number of cases, the majority of whom seem to conform to these preliminary criteria[1]. Since then, increasing recognition of this syndrome has led to more than 130 such cases[2]; I and several colleagues [including Professors Cervera (Spain), Shoenfeld (Israel), Piette (France), and Triplett (USA)] have collaborated closely, not only in publishing several important contri-

butions on the clinical presentation of patients with CAPS[3-6], but have also speculated on the possible pathogenesis[4,7].

There is no doubt that consensus criteria are now necessary — this has been done with the APS[8] — and I shall be taking steps to include this topic in the program of the next Biannual Antiphospholipid Meeting to be held in Israel in 2002. At the Third European Forum on Antiphospholipid Antibodies a CAPS registry was established, and information can be seen at the website — www.med.ub.es.mimmun/forum/caps.htm

To briefly comment on several of the points raised. Dr. Olguin-Ortega and colleagues are certainly correct in stating that newer imaging techniques might obviate the need for histopathological confirmation of the diagnosis of small vessel occlusive disease, and clinicians have indeed used these diagnostic methods to establish the diagnosis. Brain or cardiac biopsies are certainly not possible! Regarding the question of involvement of 3 or more organs as a basic criterion, several patients (a minority only) had only 2 organs involved but still demonstrated the typical features of CAPS.

Chronologically (days to weeks usually), most patients exhibited all the diagnostic features of a "multiorgan" or "multisystem" failure, with severe cardiopulmonary involvement [including the adult (acute) respiratory distress syndrome predominantly] and cerebral manifestations (deterioration of consciousness or frank coma). This time period obviously requires a clearer definition. Small vessels are certainly predominantly affected.

Renal involvement, as we have stressed, although commonly present (with or without hypertension) does not usually cause demise. Some features of disseminated intravascular coagulation are present in many. Is this really DIC or are these simply markers of endothelial damage affecting small vessels? This also has to be clarified, as well as the major diagnostic differences between patients with CAPS and those with the other, very similar condition, thrombotic thrombocytopenic purpura.

And what of patients, for example, who exhibit rapidly recurring skin or central nervous system involvement, affecting *one* organ only, occurring over days, weeks, or months? Is this another "subset," and should these patients too be given the benefit of plasmapheresis, as has been advised for patients with CAPS? These questions too are without answers at the present time.

There are also reports of patients with typical CAPS who at the time of presentation test negative for antiphospholipid antibodies, as has been seen with simple/classic APS. Do we include these as examples of the condition? Continued testing of survivors may show antiphospholipid antibody positivity or past serology might indeed have been positive. A major difficulty with the latter is that many of the CAPS patients (about 50%) suffer from the primary antiphospholipid syndrome. CAPS may be the first manifestation of their illness.

In our opinion, the condition has been *underdiagnosed* rather than overdiagnosed, many of these patients being admitted to intensive care units with multiorgan failure.

No doubt, with time and the application of many minds, the answers to these questions will slowly emerge.

RONALD A. ASHERSON, MD, FACP, FCP(SA), FRCP(Lond), FACR, The University of Cape Town School of Medicine and The Groote Schuur Hospital, Cape Town, South Africa.

REFERENCES

1. Asherson RA. The catastrophic antiphospholipid syndrome [editorial]. J Rheumatol 1992;10:508-12.
2. Asherson RA, Cervera R, Shoenfeld Y, Piette J-C. The catastrophic antiphospholipid syndrome — a review of 130 patients. Possible clues to pathogenesis. Medicine (Baltimore) 2001; (in press).
3. Asherson RA, Cervera R, Piette J-C, et al. The "catastrophic" antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine 1998;77:195-207.
4. Asherson RA. The pathogenesis of catastrophic antiphospholipid syndrome. J Clin Rheumatol 1999;6:242-52.
5. Asherson RA, Cervera R. Catastrophic antiphospholipid syndrome. Curr Opinion Haematol 2000;7:325-9.
6. Triplett D, Asherson RA. Pathophysiology of the catastrophic antiphospholipid syndrome. Am J Haematol 2000;65:154-9.
7. Asherson RA, Shoenfeld Y. The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome — molecular mimicry? [editorial]. J Rheumatol 2000;27:12-4.
8. Wilson WA, Gharavi AW, Kioke T, et al. International consensus statement in "preliminary criteria for definite antiphospholipid syndrome." Report of an international workshop. Arthritis Rheum 1999;42:1309-11.

Sigmoid Diverticular Abscess Perforation in 2 Patients with Rheumatoid Arthritis Treated with High Dose Corticosteroids. A Cautionary Tale

To the Editor:

We describe 2 cases of diverticular abscess perforation in patients with rheumatoid arthritis (RA) following treatment with corticosteroids. We have reviewed the literature (Medline 1966–2000) and we suggest that there is an important association between corticosteroid therapy and diverticular abscess perforation.

Case 1 was a 62-year-old woman with longstanding seropositive erosive RA, admitted to hospital for induction of remission of her disease. She had a 6 week history of a significant relapse, with numerous swollen and tender joints. She also had a recent history of rectal bleeding, anorexia, and weight loss. Her medication consisted of intramuscular gold, 25 mg every 2 weeks, prednisolone 5 mg daily and voltarol 150 mg daily. On examination she was apyrexial and specifically, the abdominal examination was normal. Investigations revealed an accelerated acute phase response, C-reactive protein 85, plasma viscosity 1.8 in keeping clinically with her active RA. In view of the history of rectal bleeding she was investigated further with a barium enema, which revealed extensive sigmoid diverticular disease. Her active RA was treated with 2 pulses of methylprednisolone (1 g) on alternate days. She was discharged, well, 5 days later. Fourteen days following the methylprednisolone she presented to the emergency department with a 4 day history of lower abdominal pain and fever. On examination she was pyrexial, 39°C, and there was tenderness and guarding in her lower abdomen. On investigation there was a moderate leukocytosis (white blood cell count 12,000) and erect abdominal radiography revealed no free gas. A laparotomy was performed that day and a Hartmann's procedure performed for a perforated diverticular abscess of the sigmoid colon. The patient made an uneventful recovery.

Case 2 was a 77-year-old woman with longstanding RA, admitted to hospital with a dry cough and severe shortness of breath. There was no history of diverticular disease. She had recently commenced methotrexate (MTX) and her regular medication included naproxen 250 mg bid and prednisolone 7.5 mg daily. A high resolution computerized tomographic scan of the chest revealed a ground glass appearance and a diagnosis of MTX pneumonitis was made. MTX was stopped and 60 mg of prednisolone was commenced. She was discharged on a reducing dose of corticosteroid. One month following discharge she presented to the emergency department with a 2 week history of epigastric pain. On examination she was pyrexial, 38°C, and diffusely tender in the abdomen, but exhibited no guarding. Investigations revealed leukocytosis (WCC

15,000) and free intraperitoneal gas on the chest radiograph. A laparotomy was performed and a Hartmann's procedure undertaken for a perforated sigmoid diverticular abscess. Postoperatively she failed to recover and died one month later.

Diverticular abscess perforation is a rare, but serious complication of diverticular disease. An audit over 5 years of complicated diverticular disease in a district general hospital[1] observed 80 admissions per year with an overall mortality rate of 6%. On average 25 patients per year required surgery, the majority having a perforated diverticular abscess, and in this group the mortality rate was 18%. In a further audit of 73 patients with complicated diverticular disease there were 6 hospital deaths (8%), and half of these deaths were associated with steroid therapy[2]. A study of neurosurgical patients receiving high dose corticosteroids preoperatively (mean dose 4 g) showed a significantly higher prevalence of perforated diverticular disease in these patients, in contrast to patients who underwent similar neurosurgical procedures, but did not receive corticosteroids[3].

There are 6 patients with arthritis and perforation of a sigmoid diverticular abscess reported in the literature, all taking corticosteroids at the time of perforation. One of these patients had received pulsed high dose corticosteroid[4] and the others had received oral corticosteroid[5-7]. There were 2 deaths reported in this group.

The reasons for the association between corticosteroid therapy and diverticular abscess perforation are not clear, although it is possible that diverticular perforations result from inhibition of synthesis of prostaglandins, which have the beneficial property of cytoprotection, and from the immunosuppressive action of glucocorticoids that may favor development of abscess formation. It is not known if patients with RA have an increased prevalence of diverticular disease, but nonsteroidal antiinflammatory drugs (NSAID) are associated with increased diverticular complications[8], and interestingly patients with RA are reported to have a 6-fold increased risk of death secondary to diverticular disease[9]. We feel this excess mortality is due to the high prevalence of corticosteroid and NSAID therapy in RA. Symptoms and signs of a perforated diverticular abscess may be masked by relatively small doses of prednisolone, i.e., 10 mg per day[7], and patients with severe RA, even when not receiving corticosteroids, may respond abnormally to infection, because they will lack fever or leukocytosis[10]. The physician or surgeon attending a patient with RA with a recent history of corticosteroid therapy should be alert to the possibility of a perforated diverticular abscess in those with nonspecific abdominal symptoms. We suggest this complication is more common than the literature would suggest and we are aware of 7 further rheumatological patients with this serious complication. Both the patients reported here were taking NSAID and these may have acted synergistically with the corticosteroids, resulting in the diverticular perforation.

Another possible explanation for the excess mortality resulting from diverticular disease observed in RA is that active diverticular disease could induce a flare in arthritis symptoms, and as a result of this corticosteroids are prescribed, resulting in perforation of the abscess. To support this hypothesis there is a report of a case of seronegative oligoarthritis in association with a diverticular abscess, the treatment of which led to a complete resolution of joint symptoms[11]. Further, 3 patients are reported with diverticulitis in association with arthritis and pyoderma gangrenosum. Segmental resection of the involved colon promptly and completely resolved all symptoms, without recurrence after surgery[12]. It is noteworthy that in the first case described here there was extensive diverticular disease revealed on the barium enema study and a history of bleeding per rectum around the time of the RA flare. It is likely that her diverticular disease was active and then was further exacerbated by the methylprednisolone.

We feel that that the important association reported here between corticosteroid therapy and perforation of a sigmoid diverticular abscess should be known and recognized by rheumatologists.

DAVID HUTCHINSON, MRCP; MICHAEL LYNCH, FRCP, University of Liverpool, Liverpool, England.

REFERENCES

1. Elliott TB, Yego S, Irvin TT. Five-year audit of the acute complications of diverticular disease. Br J Surg 1997;84:535-9.
2. Shephard AA, Keighley MR. Audit on complicated diverticular disease. Ann Roy Coll Surg Engl 1986;68:8-10.
3. Weiner HL, Rezai AR, Cooper PR. Sigmoid diverticular perforation in neurosurgical patients receiving high-dose corticosteroids. Neurosurgery 1993;33:40-3.
4. Candelas G, Jover JA, Fernandez B, Rodriguez-Olaverri JC, Calatayud J. Perforation of the sigmoid colon in a rheumatoid arthritis patient treated with methylprednisolone pulses. Scand J Rheumatol 1998;27:152-3.
5. Durieux S, Rozenberg S, Bourgeois P. Complications of colonic diverticular disease during rheumatoid polyarthritis: 7 cases. Rev Med Interne 1999;20:50-3.
6. Oehler U, Bulatko A, Jenss H, Helpap B. Lethal complications in a case of sigmoid diverticulitis. A case report. Gen Diagn Pathol 1997;142:231-4.
7. Brooks PM, Stephens WH Jr, Stephens MEB, Buchanan WW. How safe are anti-rheumatic drugs? A study of possible iatrogenic deaths in patients with rheumatoid arthritis. Health Bulletin (Scottish Home and Health Department) 1975;33:1-4.
8. Campbell K, Steele RJ. Non-steroidal anti-inflammatory drugs and complicated diverticular disease: a case-control study. Br J Surg 1991;78:190-1.
9. Myllykangas-Luosujarvi R. Diverticulosis — a primary cause of life threatening complications in rheumatoid arthritis. Clin Exp Rheumatol 1995;13:79-82.
10. Brooks PM, Stevenson RD, Buchanan WW. Septic arthritis in patients with rheumatic diseases: a still underdeveloped complication. J Rheumatol 1976;3:124-33.
11. Averns HL, Cheung NT, Dawes PT. Painful knees associated with a septic focus. Br J Rheumatol 1995;34:862-4.
12. Klein S, Mayer L, Present DH, Youner KD, Cerulli MA, Sachar DB. Extraintestinal manifestations in patients with diverticulitis. Ann Intern Med 1988;108:700-2.

Rhabdomyolysis and 3,4 Methylenedioxymethamphetamine in Rheumatological Practice

To the Editor:

Rhabdomyolysis is defined as a syndrome resulting from the injury of skeletal muscle with subsequent release of intracellular content from myocytes into the plasma[1-4]. This disorder is caused by many factors, especially toxicologic[1,2], and might also simulate a rheumatic disease[5]. The rapid escalation of psychostimulant abuse has led to the recognition of many cases of amphetamine derivative abuse associated rhabdomyolysis[6-15].

Many authors have emphasized the severe complications of this disorder, resulting in: (1) acute renal failure in about one-third of patients[1]; (2) electrolyte abnormalities (potassium, calcium) eventually resulting in cardiac arrest[1-4]; (3) compartmental syndrome and disseminated intravascular coagulation[2], life threatening conditions requiring early intensive treatment in emergency departments.

There are, however, mild forms of rhabdomyolysis related to substance abuse, which have been less commonly described and could also be found in rheumatologic practice, as indicated by this case report.

A 20-year-old man, a waiter, was referred for assessment because of presence of muscle pain in his lower limbs. He had no family or personal history of rheumatic or muscle disease. His history reported in the last 3 years intravenous heroin and cocaine use; because of needle sharing he had acquired hepatitis C virus, but not human immunodeficiency virus infection. He was treated with methadone for heroin withdrawal 3 times during the last year. Two months after finishing the last methadone treatment, he began to ingest 3,4-methylenedioxymethamphetamine (MDMA), commonly known as "ecstasy."

Two days before evaluation he took 2 tablets of MDMA (about 100 mg) before going to a dance party. He developed subjective fever, sweating, agitation, muscle pain in his legs, and emission of dark red-brown urine some hours later. He remembered some similar episodes after prior use of MDMA. He denied any use of alcohol beverages, drugs, or other substances during the last 2 months.

No clinical condition known to be associated to rhabdomyolysis[1-4] was reported: the only etiologic factor remembered by the patient was vigorous dancing in a hot environment for several hours. The quadriceps, gastrocnemius, and soleus were tender to palpation bilaterally, but there was no weakness or swelling of these muscles. The remainder of the examination was unremarkable. Laboratory studies revealed creatine kinase (CK) 1345 IU (normal 37–200) with CK-MB 15 IU (0–16), myoglobin 110 ng/ml (19.0–92.0), AST 88 IU (8–47), ALT 208 (8–60), gamma-GT 37 IU (8–78). Erythrocyte sedimentation rate, c-reactive protein, triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), protein electrophoresis, blood cell count, serum creatinine, blood urea nitrogen, cryoglobulin, and electrolytes were normal. Toxicologic screening of urine could only identify MDMA use.

Although informed about potential life threatening complications of rhabdomyolysis, he refused to undergo any further laboratory investigation or hospital treatment. On the next clinical examinations, after a week and then after 2 months, he abstained from this drug and fully recovered.

Although further laboratory study could have been useful for diagnosis and followup, the aspects of this patient's history and the examination, together with the results of laboratory investigation, seem to indicate the presence of rhabdomyolysis. In particular, increased serum CK level — which most authors feel must be elevated at least 5 times above the upper limit to be diagnostic[1,3,4] — is the most suggestive laboratory abnormality in rhabdomyolysis[1-3]. This biochemical test could also be useful for evaluation of the prognosis; recently, some authors reported that the incidence of acute renal failure and electrolyte disturbances was higher in patients with CK levels exceeding 15,000 IU/l[18].

Other important diagnostic indicators, especially for early diagnosis, are increased serum myoglobin level and myoglobinuria, but their absence several days after the development of rhabdomyolysis does not exclude this muscle disorder[1,3].

In recent years, the awareness of the association of psychostimulant abuse and rhabdomyolysis has increased, so that many case reports have been described[6-15]. These usually represent cases that are so severe that hospitalization and eventual intensive care treatment are needed, while many other cases with mild clinical expression have probably been overlooked in literature descriptions.

The frequency of drug abuse related rhabdomyolysis in clinical ambulatory practice is probably underestimated for various reasons. (1) The great variability of its clinical presentation: Gabow, *et al*[1] found that at least 50% of patients did not complain of muscle pain or weakness at the time of admission; muscle swelling was even less frequently reported; according to other authors, less than 10% of patients complained of any muscle pain[2]. This aspect causes great difficulty in the diagnosis of this disorder. (2) The mildness of symptoms frequently leads the patient to avoid medical attention. (3) Patients are often reluctant to disclose abuse of drugs to their doctor.

It is not unlikely that the MDMA user, who does not consider himself a drug addict, experiencing symptoms suggesting rhabdomyolysis may search for medical attention from specialists in other fields.

To avoid delayed diagnosis, the rheumatologist must keep a high index of suspicion when patients report muscle pain, weakness, and/or dark red-brown urine after drug and alcohol abuse. It must also be remembered that, on initial assessment, rhabdomyolysis in many patients has no clinical expression[1,2]: in this case, toxicologic history should be emphasized. The importance of recognizing this clinical entity lies in the prevention of more severe and occasionally life threatening complications due to MDMA and other amphetamine derivatives sold as "ecstasy," occurring in young people who have used the drug previously without problems[12]. The pathophysiology of this muscle disorder is not yet understood.

Some authors[7] have hypothesized that hyperpyrexia caused by MDMA serotonergic stimulation[16] may be a cause of rhabdomyolysis.

However, the increased muscle activity that occurs during prolonged vigorous dancing in a hot environment as reported in this case report or associated with dysphoric agitation, as well as a direct toxic effect of MDMA on muscles as proposed for methamphetamine[17], could not be excluded as important etiologic factors.

The spread of drug abuse and addiction, particularly of psychostimulants, is dramatically increasing. In view of MDMA's wide recreational misuse[19], it is not surprising that the rheumatologist may be involved in treating patients who develop rhabdomyolysis.

FLORINDO VERDONE, MD, Local Health Unit 9, 10015 Ivrea, Italy.

REFERENCES

1. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. Medicine 1982;61:141–52.
2. Curry SC, Chang D, Connor D. Drug- and toxin-induced rhabdomyolysis. Ann Emerg Med 1989;18:1068–84.
3. Poels PJE, Gabreëls FJM. Rhabdomyolysis: a review of the literature. Clin Neurol Neurosurg 1993;95:175–92.
4. Grob D. Rhabdomyolysis and drug-related myopathies. Curr Opin Rheumatol 1990;2:908–15.
5. Lie JT. Medical complications of cocaine and other illicit drug abuse simulating rheumatic disease. J Rheumatol 1990;17:736–7.
6. Chadwick IS, Curry PD, Linsley A, Freemont AJ, Doran B. Ecstasy, 3,4 methylenedioxymethamphetamine (MDMA), a fatality associated with coagulopathy and hyperthermia. J Roy Soc Med 1991;84:371.
7. Screaton GR, Singer M, Cairns HS, Thrasher A, Sarner M, Cohen SL. Hyperpyrexia and rhabdomyolysis after MDMA ("ecstasy") abuse. Lancet 1992;339:677–8.
8. Woods JD, Henry JA. Hyperpyrexia induced by 3,4-methylenedioxyamphetamine ("Eve"). Lancet 1992;340:305.
9. Henry JA, Jeffreys KS, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). Lancet 1992;340:384–87.
10. Campkin NTA, Davies UM. Another death from ecstasy. J Roy Soc Med 1992;85:61.
11. Green AR, Cross AJ, Goodwin GM. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA) or "Ecstasy." Psychopharmacology 1995;119:247–60.
12. Bodenham AR, Mollick A. New dimensions in toxicology: hyperthermic syndrome following amphetamine derivative. Intens Care Med 1996;22:622–4.
13. Lora-Tamayo C, Tena T, Rodriguez A. Amphetamine derivative related deaths. Forensic Sci Int 1997;85:149–57.
14. Cunningham M. Ecstasy-induced rhabdomyolysis and its role in the development of acute renal failure. Intensive Crit Care Nurs 1997;13:216–23.
15. Fineschi V, Centini F, Mazzeo E, Turillazzi E. Adam (MDMA) and Eve (MDEA) misuse: an immunohistochemical study on three fatal cases. Forensic Sci Int 1999;104:65–74.
16. Gordon CJ, Watkinson WP, O'Callaghan JP, Miller DB. Effects of 3,4-methylenedioxymethamphetamine on thermoregulatory responses of the rat. Pharmacol Biochem Behav 1991;38:339–44.
17. Kendrick WC, Hull AR, Knochel JP. Rhabdomyolysis and shock after intravenous amphetamine administration. Ann Intern Med 1977;86:381–7.
18. Veenstra J, Smith WN, Krediet RT, Arisz L. Relationship between elevated creatine phosphokinase and the clinical spectrum of rhabdomyolysis. Nephrol Dial Transplant 1994;9:637–41.
19. Stocker S. Overall teen drug use stays level, use of MDMA and steroids increases. NIDA Notes 2000;15:5.

The Role of Colchicine in *Helicobacter pylori* Prevalence and Gastric Mucosal Changes in Behçet's Disease

To the Editor:

Behçet's disease (BD) is prevalent among people living in areas adjacent to the ancient Silk Route. Mucosal ulcerative lesions of the mouth and other regions of the gut are a distinctive feature of the disease[1]. Increased leukocyte activity and adhesiveness is another aspect of its physiopathological characteristics[2] that may relate to the beneficial effects of colchicine as a therapeutic modality[3]. *Helicobacter pylori* infection, on the other hand, is associated with mucosal lesions of the stomach or duodenum that resemble neutrophilic gastritis microscopically[4].

We investigated the effects of colchicine on mucosal lesions and on *H. pylori* prevalence among a group of patients with BD. Forty patients (17 men, 23 women, mean age 37.2 ± 6.7 yrs) with dyspeptic complaints, of which 31 were receiving colchicine, classified according to International Study Group criteria[5] were studied. Forty patients (19 men, 21 women, mean age 37.6 ± 10.6 years) with dyspeptic complaints but without BD were evaluated as controls. All patients referred to the outpatient department with dyspepsia were included in the corresponding groups. A physician guided questionnaire and physical and laboratory examinations were performed for each subject in the study and control groups to determine if another disease might have led to the gastrointestinal lesions. Subjects were also asked about antibiotics, immune modulator, or ulcerogenic medications used in the previous 3 months. All subjects gave informed written consent.

Endoscopic examinations were performed on all subjects and controls using a fiberoptic endoscope (Pentax EG 2940). Duplicate mucosal biopsy specimens from the antrum and corpus of the stomach were obtained from each subject. The results of histopathologic findings were classified in 3 categories as "ulcer," "gastritis," and "normal." *H. pylori* was identified by bedside CLO test[6] and by microscopic examination of formol/alcohol fixed, paraffin embedded, and hematoxylin-eosin stained specimens.

The mean duration of disease and colchicine therapy was 5.4 and 3.7 years, respectively. The rate of *H. pylori* positive subjects by CLO testing and histologic examination was 72.5%, 82.5% in the BD group and 75%, 77.5% in the control group, respectively ($p > 0.05$). In contrast, the proportion of BD patients with *H. pylori* was significantly associated with colchicine therapy. Specifically, the percentages of *H. pylori* positive patients by CLO test or histological examination were 87.0% and 94.0%, respectively, in the BD group taking colchicine, but 22.0% and 44.0% in the BD group not taking colchicine ($p < 0.05$). Table 1 also shows there is a difference in *H. pylori* infection between the BD group not taking colchicine and control subjects ($p < 0.05$).

Neutrophils have a fundamental role in nonspecific defence against extracellular bacteria[7]. *H. pylori* is an extracellular pathogen that has a particular tropism for the gastric mucosa. Colonization on the gastric mucosa leads to neutrophilic gastritis and peptic ulcer[4,8]. Colchicine, on the other hand, has well known antimitotic[9] and suppressive effects on leukocytes[10] that may impair host defence. Whether colchicine also directly causes gastritis-like mucosal lesions is unknown. According to the results of this study, it seems reasonable to consider that Behçet's disease may prevent *H. pylori* colonization, possibly because of increased activity of leukocytes. Colchicine treatment, in contrast, may suppress this beneficial effect and promote more *H. pylori* colonization.

CENGIZ PATA, MD; KAMURAN KONCA, MD; AZIZ YAZAR, MD, Department of Internal Medicine, Medical School of Mersin University, Içel, Turkey.

REFERENCES

1. Ehrlich GE. Behçet's disease: current concepts. Compr Ther 1989;15:27-9.
2. Sahin S, Akoglu T, Direskeneli H, Sen LS, Lawrance R. Neutrophil adhesion to endothelial cells and factors affecting adhesion in patients with Behçet's disease. Ann Rheum Dis 1996;55:128-33.
3. Mangelsdorf HC, White WL, Jorizzo JL. Behçet's disease. Report of twenty-five patients from the United States with prominent mucocutaneous involvement. J Am Acad Dermatol 1996;34:745-50.
4. Kirchner T, Steininger H, Faller G. Immunopathology of *Helicobacter pylori* gastritis. Digestion 1997;58:14-6.
5. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078-80.
6. Marshall BJ, Warren JR, Francis GJ. Rapid urease test in the management of the *Campylobacter pyloridis*-associated gastritis. Am J Gastroenterol 1987;82:200-10.
7. Ryan JL. Bacterial disease. In: Stites DP, Terr AI, Parslow TG, editors. Medical immunology. New York: Prentice Hall International; 1997:684-93.
8. Kuipers EJ, Thijs JC, Festen HP. The prevalence of *Helicobacter pylori* in peptic ulcer disease. Aliment Pharmacol Ther 1995; 9:59-64.
9. Ben Chetrit E, Levy M. Colchicine: 1998 update. Semin Arthritis Rheum 1998;28:48-9.
10. Mantzer Y. Neutrophil function studies in clinical medicine. Transfus Med Rev 1987;1:171-81.

Book Review

Principles of Molecular Rheumatology

George C. Tsokos, editor. Totowa, New Jersey: Humana Press, 2000, 545 pages, price $145.00 US.

For those wishing background reading on the basic science of rheumatology, this book is a useful addition to traditional rheumatology textbooks.

Chapters in the first 2 sections outline major topics such as T cell signaling, complement activation, apoptosis, regulation of transcription, and collagen physiology. The development and function of leukocytes, synoviocytes, chondrocytes, and bone cells are covered in detail. There is a useful chapter describing many of the animal models in routine use in rheumatology.

The third section covers the pathogenesis of major rheumatic diseases utilizing the molecular and cellular mechanisms that have already been described. The final section covers the molecular aspects of rheumatic disease treatment. While the majority of disease modifying antirheumatic drugs in use today are covered, a major emphasis is on experimental treatments such as gene therapy and restoration of immune tolerance.

The chapters in this text are largely readable, and important concepts are reinforced from one section to the next. However, there are important limitations. The index is too frequently inadequate for this book to be used as a reference tool. There is unevenness in the amount of detail presented in each chapter. Those with limited science background may find some sections difficult to understand — a problem amplified by the relative paucity of illustrations and the preponderance of acronyms for various proteins. A glossary of acronyms would be helpful. Further, several of the reviews cited for background reading are not in commonly available journals.

Overall, I would recommend this book to those needing more in-depth coverage of the basic science of rheumatology than is available in the traditional rheumatology texts. In particular, those embarking on or returning to basic science rheumatology research will find this an exceptionally useful place to start.

DAVID B. ROBINSON, MD, MSc, FRCPC, Assistant Professor of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.