INSTRUCTIONS FOR LETTERS TO THE EDITOR

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

Contact. **The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M4W 3C7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

Not For Sale, Not Even For Rent: Just Say No. Thoughts About the American College of Rheumatology Adopting a Code of Ethics

To the Editor:

I enjoyed the article and the wonderfully erudite writing of Dr. Richard Panush[1]. I learned from his comments and they were highly germane to our current relationship with the pharmaceutical industry. However, I don't think that we can "just say no" to drug company interactions. Doctors live in two worlds, one that is business and the other that is patient care. The income paying for the business endeavors (such as our salary and overhead) is based upon our medical knowledge that is delivered to patients, performance of laboratory and clinical research, writing of textbooks, teaching rheumatology, and being consultants to drug companies and the business world. Problems arise when patient care intersects with any of the business activities, but especially with pharmaceutical contacts, although that juxtaposition is impossible to avoid or ban. For example, how do I read this esteemed journal and not be influenced by the drug company advertisements? Do I pay someone to rip the glossy pictures out for me? Without the advertisements, it is likely that the journals would be very expensive, and truthfully I learn from many of them. How do I keep up with the introduction of the astoundingly effective new treatments for diseases without allowing the drug companies to tell me about them? My delivery of patient care is influenced by many factors including information from drug companies, journals, word of mouth, and professional meetings, just to name a few, all of which need to be kept in proper perspective. After all, if I only read journals, and wasn't up to date, I would still consider peptic ulcer to be caused by stress. I may become subconsciously beholden to the sponsor of an educational meeting that I attend, as Dr. Panush points out, but I believe that will be counterbalanced by the knowledge that I gained by attending the meeting.

We do need a code of ethics. We all believe in them. We can't allow ourselves to be captives of commercialism. Stop the excesses. Monitor the meetings for inappropriate or wrong information. Don't allow talks or seminars with commercial messages. Continue with educational meetings. Keep them modest. Have drug representatives meet with us only when something is new or needs explanation. Stop the free lunches at the workplace, they are not necessary for us and are demeaning to the drug representatives who bring them. Use these guidelines as the norm for the pharmaceutical industry and their encounters with us, but at the same time realize that the pharmaceutical companies and the doctors need to work together for the advancement of rheumatology.

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1. Panush RS. Viewpoint: Not for sale, not even for rent: Just say no. Thoughts about the American College of Rheumatology adopting a code of ethics. J Rheumatol 2002;29:1049-57.

Dr. Panush replies

To the Editor:

As I know, like, and respect Dr. Ellman, I appreciate his kind and thoughtful comments. My article reflected on the ethics appropriate for American College of Rheumatology (ACR) leadership, and indeed the ACR as an organization regarding relationships with industry. I thought that the highest standards of ethical behavior would be met by eschewing such relationships. I still think so, and believe this applies to physicians generally. There are compelling professional and ethical reasons to reject industry gifts and relationships. I presented these. They include the obligations incurred, the clearly documented and sometimes pernicious influence they have, the unjust spending practice involved, the threat to the physician-patient relationship, and the erosion of the physician's fiduciary role as trustee of patients' welfare. I also acknowledged that individuals and organizations confront imperatives other than ethics and that some will judge there to be circumstances when these trump ethics.

Dr. Ellman raises some specific issues which I did not address in my essay. I am grateful for the opportunity to comment on these. I do not disrespect the contributions of industry or advocate ignoring their advances, information, or representatives; I do suggest recognizing that their agendas are not always ours and that we not accept their "gifts." I do not urge that we avoid attending meetings but rather that educational sponsorship of meetings, when necessary, at least meet the expectations set by governing bodies (i.e., the Accreditation Council for Continuing Medical Education, the American Medical Association, and the American College of Rheumatology). We certainly ought to pay for our attendance at educational meetings and we are certainly able to do so (there should be no expectation that someone else do this for us). We certainly ought to buy our own pens, notepads, coffee mugs, and books, and can surely afford these; accepting such "gifts" is really silly, unnecessary, inappropriate, and morally offensive. Dr. Ellman and I agree that "there is no free lunch" and that these are demeaning to all. I don't defend print/journal advertising (and didn't discuss this in my paper) and would prefer reading the literature without it; but this may be a somewhat special case (e.g., see the correspondence and reply regarding "pharmaceutical advertising in the *Journal*," New England Journal of Medicine 1992;327:1688-9). I understand that many physicians have become dependent on professional and personal income from relationships with industry. I would hope that these relationships are contractually explicit (which is different than a gift), are fully disclosed when appropriate, and that these individuals recuse themselves in situations where conflicts of interest might arise or be perceived to arise (or avoid such situations entirely). I don't think it is enough to "stop the excesses" or "keep them modest." I don't think merely trying to set limits or "draw lines" (Whose line? Where? Under what circumstances?) works well enough. We generally have adapted to the pervasiveness of industry influence and struggled, variably, to tolerate the attendant discomfort. I worry greatly that there is something profoundly wrong with our professional world when/if

we lose perspective about values and relationships, when we expect and accept entitlements for various personal and professional perquisites, and, yes, when/if we let financial incentives cloud our judgment or affect our behavior.

A paradigmatic change in attitude is needed. It's not easy to say "no" to gifts and the relationships they engender. But neither it is inordinately difficult. And, I respectfully suggest, it is the most rigorously ethical approach.

"A people that values its privileges above its principles soon loses both."
— Dwight D. Eisenhower, Inaugural Address, January 20, 1953

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Do Gastroprotective Drugs Prevent NSAID Toxicity?

To the Editor:

We read with interest the recent article by Wolfe and colleagues regarding gastrointestinal ulcers and nonsteroidal antiinflammatory drugs (NSAID)[1]. Their description of channeling bias is very informative and may indeed, explain their results. However, we would like to offer another hypothesis.

Wolfe and colleagues found that patients who are prescribed anti-ulcer treatment (H2 receptor antagonists, proton pump inhibitors, sucralfate, or misoprostol) with a nonselective NSAID or selective cyclooxygenase-2 (COX-2) inhibitor are at a higher risk of future gastrointestinal (GI) ulceration than NSAID users who do not receive concomitant anti-ulcer treatment. The authors suggest that this demonstrates channeling bias — that is, the tendency for physicians to preferentially prescribe anti-ulcer treatment to patients at high risk of GI ulceration. Such patients, despite anti-ulcer treatment, are still prone to GI outcomes; thus, anti-ulcer treatments would paradoxically appear not to confer any safety advantage. They argue that the use of such agents acts as a marker for worse GI morbidity, and that this property can be used to demonstrate the added safety advantage of the selective COX-2 inhibitors.

We agree that this source of bias probably explains part of Wolfe and colleagues' results, but would suggest that another important common pharmacoepidemiologic bias may underlie their results — depletion of susceptibles. This refers to the loss to followup (depletion) of patients with dyspeptic symptoms who are prone to have GI ulceration (susceptibles) and therefore do not complete the full period of observation while taking an NSAID or selective COX-2 inhibitor[2]. One would expect that discontinuation of antiinflammatory treatment would occur less often in patients taking anti-ulcer treatments that limit dyspepsia. These patients are likely to experience fewer GI symptoms and will be able to take an NSAID or selective COX-2 agent at higher dosages and/or for longer periods. Such greater use would put them at a higher risk of GI ulceration. Depletion of susceptibles has been suggested to explain part of the higher rates of complicated ulcers seen at the completion of the CLASS trial in patients randomized to selective COX-2 inhibitors versus traditional NSAID[3].

Thus, the higher rates of GI ulceration reported by Wolfe and colleagues in patients prescribed gastroprotective drugs may not be solely the result of higher baseline patient risk (channeling bias). It may also be caused by depletion of susceptibles: patients taking gastroprotective drugs would be less likely to develop GI symptoms and would therefore continue their antiinflammatory treatments and remain at risk of ulceration. By contrast, those not taking gastroprotective drugs would be more likely to develop GI symptoms, which in turn would cause them to stop their NSAID or selective COX-2 inhibitor. This discontinuation of antiinflammatory treatment seen in patients without a gastroprotective treatment may in fact protect them against future GI ulceration. Consequently, the lower rate of ulceration observed by the authors may also be a result of this differential discontinuation of anti-ulcer drugs by patients, rather than solely the result of differential prescribing by physicians.

DANIEL H. SOLOMON, MD, MPH; JERRY AVORN, MD, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, USA.

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Dr. Wolfe replies

To the Editor:

We appreciate the thoughtful letter of Solomon and Avorn in response to our article[1], in which we suggested that the positive association of proton pump inhibitors (PPI) and gastrointestinal (GI) ulceration was the result of (in the words of Solomon and Avorn) "channeling bias – that is, the tendency of physicians to preferentially prescribe anti-ulcer treatment to patients at high risk of GI ulceration." Solomon and Avorn suggest another "important, common bias may underlie [our] results — depletion of susceptibles." Specifically they suggest that there should be an increased rate of dropouts in our data bank among persons with dyspeptic symptoms. It would follow that data bank dropouts would be decreased among persons who receive PPI, as such drugs would decrease dyspeptic symptoms. The consequence of these effects would be to increase exposure to nonsteroidal antiinflammatory drugs (NSAID) and lead, therefore, to the observed increased rate of GI ulceration among PPI users.

The Solomon/Avorn hypothesis is testable. We performed Cox regression analysis using 16,058 patients with rheumatoid arthritis (RA) in the National Data Bank for Rheumatic Diseases (NDB). Failure was defined as terminating participation in the NDB surveys for any cause. Dyspeptic symptoms were defined as one or more of the following: nausea, vomiting, heartburn, epigastric pain, lower abdominal pain, constipation, or diarrhea. In addition, a count of GI dyspeptic symptoms was calculated. PPI use included any of the following drugs: lansoprazole, omeprazole, pantoprazole, esomeprazole, or rabeprazole.

Of the 54,174 observations, PPI use was noted in 18.3%. Dyspeptic symptoms were noted in 25.2% of observations, and the total dyspeptic symptom score was 1.0 (range 0–7). As shown in Table 1 (univariate analyses), dyspeptic symptoms have a protective effect as a dichotomous variable, but no effect as a continuous variable on the hazard of dropping out. PPI have a non-significant effect on the hazard of dropping out in the univariate analyses.

In multivariate analyses, controlling for demographic and severity factors, dyspeptic symptoms have a modest protective effect on the hazard of dropping out of the study when measured as a continuous variable. PPI have a modest but significant protective effect on this risk, and this protective effect is greatest among patients with dyspeptic symptoms. We also performed these analyses using various sensitivity analyses for the individual component of the dyspeptic variable/count, and noted no meaningful differences from the results presented in Table 1.

The results of these analyses do not confirm the Solomon/Avorn conjecture that dyspeptic symptoms are associated with increased risk of study dropouts in this data set. They do suggest that use of PPI has a small protective effect on study termination. The magnitude of this protective effect

Table 1. Analysis of discontinuations of data bank surveys among 16,058 patients with RA in the National Data Bank for Rheumatic Diseases.

Variable	Hazard Ratio	p	95% CI	95% CI
Univariate analyses				
Dyspeptic symptoms, yes/no	0.94	0.017	0.89	0.99
Dyspeptic symptom count, 0–7	1.01	0.370	0.99	1.03
PPI use, yes/no	0.95	0.083	0.89	1.01
Multivariate analysis				
Dyspeptic symptom count, 0–7	0.94	0.066	0.89	1.00
PPI use, yes/no	0.96	0.000	0.94	0.98
Age, yrs	0.95	0.000	0.94	0.96
Age squared	1.00	0.000	1.00	1.00
Total income, per US$ 1000	1.00	0.004	1.00	1.00
RADAI[2]	1.04	0.000	1.02	1.05
High school graduate, yes/no	0.82	0.000	0.77	0.88
Majority ethnic status, yes/no	0.77	0.000	0.72	0.83
Anxiety (AIMS), 0–10[3]	1.06	0.000	1.04	1.07
Multivariate analysis with PPI and symptom interaction				
No PPI, no dyspeptic symptoms, reference group	1.00	—	—	—
Dyspeptic symptoms, no PPI	0.82	0.000	0.77	0.87
PPI, no dyspeptic symptoms	0.94	0.084	0.87	1.01
Dyspeptic symptoms and PPI	0.80	0.000	0.73	0.88
Age, yrs	0.95	0.000	0.94	0.96
Age squared	1.00	0.000	1.00	1.00
Total income, per US$ 1000	1.00	0.003	1.00	1.00
RADAI[2]	1.04	0.000	1.03	1.05
High school graduate, yes/no	0.82	0.000	0.77	0.88
Majority ethnic status, yes/no	0.78	0.000	0.73	0.83
Anxiety (AIMS), 0–10[3]	1.06	0.000	1.04	1.07

95% CI: 95% confidence interval; PPI: proton pump inhibitor; AIMS: Arthritis Impact Measurement Scale; RADAI: Rheumatoid Arthritis Disease Activity Index.

is small in comparison to the large effect of PPI on the risk of GI ulceration that we have reported[1]. We conclude, therefore, that depletions of susceptibles did not play an important role in the results of our study of PPI and GI ulceration[1].

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Treatment Resistant Ankylosing Spondylitis with Peripheral Joint Involvement — A Case for Infliximab?

To the Editor:

Inhibitors of tumor necrosis factor-α (TNF-α) have been successfully introduced to the treatment of rheumatoid arthritis (RA), juvenile chronic polyarthritis, and Crohn's disease[1-3]. Recently, studies have confirmed their efficacy in other rheumatic conditions, especially in seronegative spondyloarthropathies[4-6]. We read with interest the recent report by Maksymowych, *et al*[7]. In a prospective observational study, they investigated the efficacy and the side effect profile of infliximab in patients with nonsteroidal antiinflammatory drug (NSAID) refractory ankylosing spondylitis (AS). In 17 of 21 patients who completed the study, a significant improvement was seen with respect to all Bath AS indexes, erythrocyte sedimentation rate (ESR), and C-reactive protein. Notably, in 5 of 11 patients with peripheral joint involvement, complete resolution of peripheral arthritis was seen at the 14th week. This matches well with our own experience of the efficacy of infliximab in AS.

We started infliximab therapy in a 55-year-old woman with disabling, treatment resistant AS. Her disease started in 1978 with severe pain in the lumbar spine and peripheral arthritis involving wrist, proximal interphalangeal (PIP), and knee joints. She was initially diagnosed as having RA and treated with NSAID and prednisone (15 mg/day). Although some initial improvement was achieved, her disease progressed rapidly. We saw her first in May 1993; she presented with polyarthritis involving most peripheral joints (wrists, PIP joints, elbows, knees, ankles, and hip joints; Figure 1) and severe spinal deformities highly suggestive of AS (Figure 2).

According to the clinical picture, typical radiographic abnormalities (symmetric ankylosis of the sacroiliac joints, syndesmophytes of the spine), positive HLA-B27, and negative rheumatoid factor, the diagnosis of RA was revised and AS was diagnosed. Unfortunately, continuous use of glucocorticoids led to the Cushing-like appearance of the patient (Figure 2), hypertension, osteoporosis, and secondary diabetes. The dose of prednisone was tapered to 5 mg/day, but all attempts to discontinue the drug failed due to severe exacerbations of disease activity. NSAID therapy was continued and she received sulfasalazine (1.0 g twice daily) over several months, with no noticeable effect. As the peripheral arthritis worsened, arthrocenteses of the knee, wrist, and/or elbow joints with intraarticular glucocorticoid injections

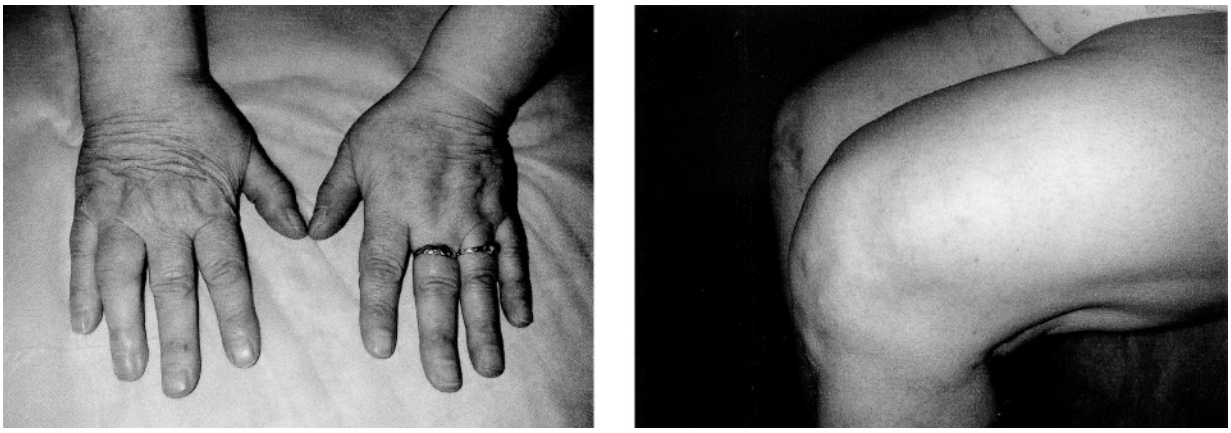

Figure 1. Swelling of some PIP joints and enlargement of the right wrist (left). Enlargement of the suprapatellar recess of the left knee joint due to effusion (right).

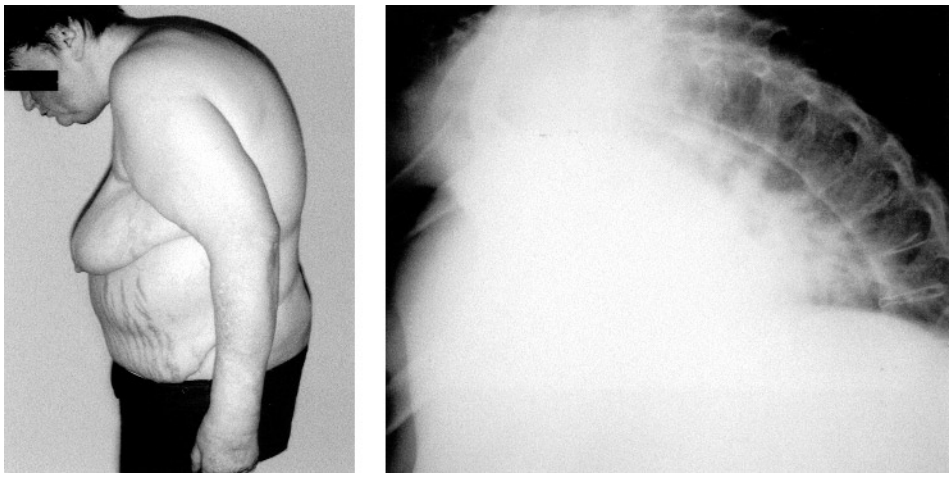

Figure 2. Severe deformity of the spine (left) and complete ankylosis of the thoracic spine on the lateral chest radiograph (right). Note Cushingoid appearance (obesity with typical fat deposition pattern, striae on the lateral aspect of the chest).

were required every 3–4 weeks. After a failure of cyclophosphamide pulse therapy, methotrexate was introduced (20 mg intramuscularly weekly) and then sulfasalazine (1.0 g twice daily) was added. This treatment provided some benefit and was continued over the next few years. In January 1994, she underwent synovectomy of the knee joints with only partial improvement. From 1994 to 2002, several hospitalizations were required due to the exacerbations of disease activity. She continuously suffered severe spinal pain and peripheral arthritis; recently, effusions of the knee joints had to be evacuated every 2nd week. As no improvement could be obtained with a standard approach, we decided to introduce infliximab (5 mg/kg intravenously). An impressive reduction of symptoms was seen 2 weeks after the infusion: duration of morning stiffness fell from 3 h to 1 h, tender joint count decreased from 12 to 1, swollen joint count fell from 10 to 2. ESR decreased from 100 to 17 mm (both values after 1 h). Changes in Bath AS Disease Activity Index (8.2 pre- and 7.3 post-treatment) and Bath AS Functional Activity Index (9.2 pre- and 9.0 post-treatment) were less impressive, most probably due to advanced ankylosis and structural damage of the spine.

We decided not to start the typical induction scheme of infliximab as we feared the increased infection risk due to diabetes and the longterm prednisone treatment. However, we are going to continue the infliximab infusions at longer intervals (5 mg/kg every 12th week). During the 8 weeks of post-infusion observation, no further arthrocenteses nor intraarticular glucocorticoid injections were needed, despite the reduction of the NSAID and oral prednisone intake (now the patient takes 5 mg prednisone every second day). No adverse events occurred during the observation.

The patient's excellent response to a single infliximab dose suggests that introduction of TNF-α inhibitors should always be considered as a therapeutic option in patients with the most severe, refractory AS, especially in those with peripheral polyarthritis. Early introduction of biologic therapies may reduce the need for oral and intraarticular glucocorticoids and prevent serious prednisone related complications in the most severe cases of AS, and the future use of TNF-α inhibitors will greatly improve the outcome of AS.

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Drs. Maksymowych and Russell reply

To the Editor:

We thank Drs. Hrycaj and Lacki for their interest in our report. The response of their patient with treatment refractory AS to a single infusion of infliximab is consistent with our own experience and highlights several issues. First, disease modifying agents traditionally used in RA lack efficacy in AS. Second, systemic steroids are similarly of limited value. Third, although anti-TNF-α therapies are costly, many such patients with NSAID refractory AS would not only be spared the toxicities associated with currently available therapies but also experience substantial symptomatic and functional improvement. The ultimate cost-utility benefits could therefore be significant. Fourth, the apparent lack of change in the BASDAI score despite significant clinical improvement suggests that there is further room for improvement in the development of clinically meaningful outcome measures, especially in late disease.

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Clinical and Immunological Factors Associated with Low Lacrimal and Salivary Flow Rate in Patients with Primary Sjögren's Syndrome

To the Editor:

Salivary gland dysfunction is one of the key manifestations in Sjögren's syndrome (SS), and determining salivary flow rates is of diagnostic and prognostic importance. Collection of unstimulated whole saliva (UWS) is currently used as a sialometrical investigation in the diagnosis of SS[1]. Particularly at the time SS develops, not all salivary glands may manifest dysfunction, rendering whole saliva less valuable as a diagnostic fluid. The collection of glandular saliva, however, reveals sequential involvement of different glands, reflecting the autoimmune process in individual salivary glands. Haga[2] evaluated the association between various clinical and immunological measures and reduced salivary flow. He concluded that only immunological factors (antinuclear antibodies and anti-Ro/SSA) were associated with salivary flow in primary SS, while he did not observe a correlation between UWS and duration of disease. This conclusion may be partly due to his experimental method, as the number of patients with a long duration of symptoms (mean 13.5 years) in his study is rather high. Surprisingly, in spite of this long disease duration, almost half the patients (34/72) have an UWS rate > 1.5 ml/15 min.

We recently defined reference values of several salivary variables, for diagnosing SS[3]. Our study indicated that gland-specific saliva collection and analysis are much more accurate diagnostics than the collection of UWS. Moreover, different sialometrical and sialochemical profiles can be observed, characteristic for either early or late salivary manifestations[4]. Patients with short duration of oral symptoms (less than one year) showed either normal flow rates with changed salivary composition, or reduced stimulated flow rate from the submandibular/sublingual (SM/SL) glands accompanied by (sub)normal flow rate from the parotid glands. It seems that the parotid gland is the last salivary gland to manifest hyposalivation, which has been confirmed in other studies[5,6].

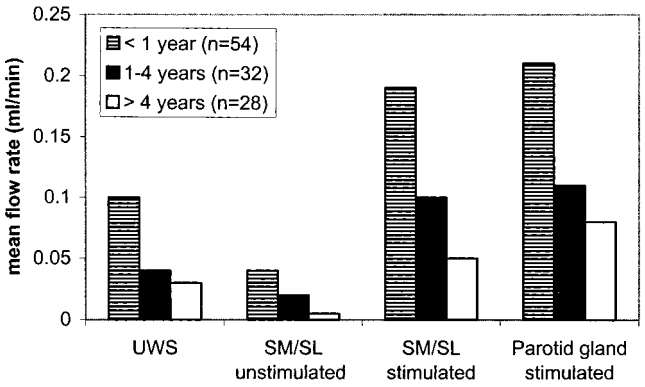

Figure 1. Relation between disease duration, i.e., the time from first complaints induced by or related to oral dryness until referral, and mean salivary flow rates. UWS: unstimulated whole saliva, SM/SL: submandibular/sublingual glands.

Recent data from a longitudinal study indicate that loss of salivary gland function is mainly prominent in early SS, and that the (diminished) function stays relatively stable during the subsequent disease course (Figure 1). Since Haga predominantly evaluated patients with a rather late salivary manifestation, i.e., after long disease duration, the initial normal or selective hypofunction characteristically associated with disease onset will be absent. Further, the use of UWS may lead to underdiagnosing patients with SS of early onset, because a persisting normal function of parotid glands may mask an acquired dysfunction of SM/SL glands. Determination of glandular flow rates is therefore not only important in the diagnosis of SS, but also in identifying patients early after disease onset. These patients in particular, who manifest substantial residual exocrine gland function, may benefit more from (systemic) therapy. A longterm prospective study to clarify the prognosis of salivary gland function is currently in progress.

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Dr. Haga replies

To the Editor:

I enjoyed the comments to our report[1] from Dr. Pijpe and colleagues. They question the use of unstimulated whole saliva collection as a diagnostic tool in primary Sjögren's syndrome. They have demonstrated that gland-specific saliva collection and chemical analysis of saliva are much more accurate diagnostic tools than collection of UWS[2].

Different sialometrical and sialochemical profiles can be observed, characteristic for either early or late salivary manifestations[3]. UWS collection is a crude diagnostic tool that is more practical to perform in a clinical setting than gland-specific saliva collection, which I also believe is of more diagnostic value. Another point is that patients who really "want" the diagnosis of primary SS may swallow the saliva to achieve low saliva volume during the collection time. This is uncommon, but in my clinical practice I have experienced this phenomenon. Dr. Pijpe, *et al* also demonstrated that UWS collection is of less value early in the disease, thereby underdiagnosing patients with primary SS at early onset. Therefore I will look forward to the results of their longterm prospective study to clarify the prognosis of salivary gland function.

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Intrathecal Corticosteroids for Systemic Lupus Erythematosus with Central Nervous System Involvement

To the Editor:

High dose corticosteroids or immunosuppressants are frequently administered systemically for the treatment of systemic lupus erythematosus (SLE) with central nervous system (CNS) involvement. We describe 2 cases of CNS lupus where CNS symptoms and abnormalities in the cerebrospinal fluid (CSF) persisted and corticosteroids were successfully administered intrathecally without serious adverse reactions.

Case 1. A 29-year-old woman was diagnosed elsewhere as having SLE from the presence of facial rash, arthralgia, and serum anti-DNA antibody, and was successfully treated with 40 mg/day prednisolone. Two months later, she was found unconscious with convulsions, and referred to hospital. There was no rash, and no arthritic signs or symptoms. Neurological examination revealed somnolence, but no meningeal or focal signs. Magnetic resonance image (MRI) of the brain was normal. In the CSF, mononuclear cell count was 4/μl; CSF IgG index [(CSF/serum IgG ratio)/(CSF/serum albumin ratio)] was 1.1 and interleukin 6 (IL-6) was 30.5 pg/ml (undetectable normally). Bacterial cultures, serum antibodies to herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and varicella zoster virus were negative. White blood cell (WBC) count was 7800/μl, serum anti-DNA antibody titer was 16 U/ml (normal < 7 U/ml), and complement activity (CH50) was normal. Intravenous administration of 1000 mg methylprednisolone was repeated for 3 days (pulse therapy); then she became alert and the CSF-IgG index (0.6) and IL-6 levels normalized in 4 weeks, and prednisolone was reduced to 30 mg/day. However, headache occurred and the CSF cell count increased to 24/μl, and the CSF IgG level and CSF-IgG index and IL-6 concentration rose to the previous levels. Because the patient had insulin resistant diabetes and there was no evidence for intracranial infection, 20 mg prednisolone was administered intrathecally 3 times with an interval of one week. Headache disappeared in a week, and CSF findings normalized in 3 weeks without recurrence for 8 months.

Case 2. A 39-year-old woman was diagnosed as having SLE without CNS involvement and was successfully treated with corticosteroids plus cyclosporine A. Twenty-eight months later, she had convulsions and was referred to the hospital. There were no systemic findings such as fever, rash, or proteinuria, but she was somnolent without focal or meningeal signs. WBC was 5400/μl, the serum anti-DNA antibody was 20 U/ml, and CH50 was normal. In the CSF, cell count was 754 (polymorphonuclear, 451; mononuclear, 303)/μl, CSF IgG index was 1.7, and IL-6 was 83 pg/ml. There was no evidence for bacterial or viral infections. The serum anti-DNA level and MRI of the brain were normal. Pulse therapy was followed by 100 mg prednisolone/day; she soon became alert and the CSF cell count decreased to 23/μl. However, headache and high CSF IgG indices (1.2–1.6) and intrathecal IL-6 levels (80–99 pg/ml) persisted for a month without extra-CNS symptoms, and the serum anti-DNA and CH50 were normal. Intrathecal injection of prednisolone (20 mg) was done 6 times with an interval of one week; headache subsided in 3 weeks, the CSF findings normalized in 5 weeks, and no remarkable adverse reactions occurred, and the dose of prednisolone was reduced to 15 mg with no flare for 6 months.

It has been reported that lymphocytic activation, local production of immunoglobulins[1,2], or various inflammatory cytokines such as IL-6 or IL-8 are associated in the pathogenesis of CNS lupus[3,4], as well as intrathecal synthesis of various autoantibodies[5]. In the current cases, CSF IgG indices and IL-6 concentrations paralleled the symptoms of CNS lupus.

Intrathecal administration of corticosteroids is often used for prevention of leukemic infiltration in the CNS, but rarely in patients with CNS lupus, while intrathecal administration of dexamethasone and methotrexate has been reported to be effective in SLE[6]. On the other hand, transfer of corticosteroids from blood to CSF is limited if the blood–brain barrier is intact[7]. When 0.8 mg/kg prednisolone was administered intravenously in patients with rheumatoid arthritis, the peak intrathecal concentration was only 55–85 ng/ml after 100–200 min[8]. Since the CSF-serum albumin quotient (Q albumin), an indicator of blood–brain barrier function, was normal in the current cases, administration of 20 mg prednisolone into the intrathecal space of 90–150 ml could cause high concentrations in the CSF. Further, it is expected that doses of corticosteroids will be spared by this method. On the other hand, intrathecal therapy has various complications, such as dural leak, spinal abscess, or thromboembolism[9], and intraorbital hematoma[10] by intrathecal corticosteroids has been reported. Therefore, this therapy should be indicated when systemically administered corticosteroids or immunosuppressants are not effective. Although the possibility exists that improvement of the CNS lupus was a natural course, intrathecal administration of corticosteroids might be useful in some cases of CNS lupus. Evaluation of this therapy, including combination

with immunosuppressants such as methotrexate, should be studied in a larger number of cases.

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Lupus-like Syndrome and Vasculitis Induced by Valpromide

To the Editor:

Valpromide is a thymoregulator drug approved for bipolar disorders and epilepsy. It is a prodrug biotransformed into valproid acid and used as antiepileptic drug, which has been implicated in cases of Stevens-Johnson syndrome and toxic epidermal necrolysis[1]. Rare cases of cutaneous vasculitis or lupus-like syndrome have been described in association with valproid acid but not to valpromide[2-4]. We describe the observations of 2 patients in whom lupus-like syndrome and glomerulonephritis associated vasculitis developed while taking valpromide.

Case 1 is a 34-year-old man hospitalized in March 2000, because of acute polyarthritis. He had a medical history of chronic psychosis treated with haloperidol 7.5 mg/day, levomepromazine 100 mg/day, alprazolam 1 mg/day, and valpromide 600 mg/day for 12 months. He had no family history of autoimmune or connective tissue diseases. He described the occurrence, 2 weeks before hospitalization, of acute and symmetrical polyarthritis of the hands, wrists, shoulders and knees with fever up to 39˚C. Clinical examination was normal except for his polyarthritis. Laboratory data confirmed inflammation (C-reactive protein 259 mg/l) and moderate hyperleukocytosis. Investigations for infectious or tumoral causes were negative (blood and urine cultures, echocardiography, computerized tomographic scan, serologies for cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B and C, HIV, Coxsackies, *Chlamydiae*, *Mycoplasma*, *Rickettsiae*, *Yersinia*, *Salmonella*, *Brucella*, Lyme, polymerase chain reaction detection for EBV, CMV, HCV, HIV, osteomedullar biopsy). Puncture of the right knee showed an inflammatory fluid without infectious agent. Immunologic data found positive antinuclear antibodies at 1/1000 without specificity. Complement levels were normal and we found no cryoprecipitate, rheumatoid factor, or antineutrophil antibodies. According to valpromide metabolism and a previous description of lupus-like diseases under valproate, valpromide was discontinued and nonsteroidal antiinflammatory drugs initiated: the course of the disease was favorable in the following 2 weeks, and antiinflammatory drugs where stopped 6 weeks after. Eighteen months later, no sign of the disease recurred and antinuclear antibodies titer had normalized to 1/250.

Case 2. A 49-year-old woman was hospitalized for purpura of the legs in September 2001. She had a medical history of beta thalassemia, tobacco related chronic bronchopneumonia, and manic-depressive psychosis for 10 years treated with lithium and clomipramine for several years. She had no family history of connective tissue diseases. Twenty days before hospitalization, valpromide, 600 mg twice a day, had been introduced. Four days later she developed a maculopapular rash on her legs, with progressive extension to her trunk and arms. In the same period of time, she described the occurrence of edema of her legs, myalgias, arthralgia, paresthesia of the right foot and constitutional symptoms. The patient was subsequently hospitalized. Clinical examination showed necrotizing purpura. There were extensive soft tissue edemas in both legs. Her temperature was normal. Blood pressure was 140/70 mmHg. Biological data showed anemia (hemoglobinemia 9.4 g/100 ml) with microcytosis (64 μ^3) and hyperleukocytosis from 11,900 to 18,500/mm^3 related to lithium therapy. Baseline creatininemia was 146 µmol/l and progressively increased up to 430 µmol/l 12 days later. Proteinuria was found to be 1.5 g/day with microscopic hematuria (499,500 red cells/min) and aseptic leukocyturia (33,300 leukocytes/min). C-reactive protein was between 50 and 69 mg/l). Immunologic testing (antinuclear, anti-DNA, antineutrophil, and antiphospholipid antibodies, total complement activity and plasma levels of C3 and C4 factors, cryoglobulinemia, rheumatoid factor, electrophoresis, and immunoelectrophoresis of serum protides) did not show abnormality. A cutaneous biopsy of the purpura showed moderate inflammatory infiltration of vessels, and direct immunofluorescence study revealed C3 and IgA deposits. A percutaneous renal biopsy was performed and showed extracapillary glomerulonephritis with epithelial proliferation. Interstitial and tubular lesions (with some eosinophiliac infiltration) were also observed. There was no vasculitis or immunoglobulin or complement deposit on glomerules, but biopsy was performed 4 days after beginning of oral corticosteroid therapy initiated because of the rapid progression of the renal insufficiency. Pulse methylprednisolone (500 mg over 3 days) was then given, followed by oral prednisolone at 20 mg/day. Creatininemia rapidly decreased from 430 µmol/l to 177 µmol/l in 10 days, and purpura disappeared. C-reactive protein decreased to 3.5 mg/l. One and 6 months later, creatininemia was measured at 142 and 120 µmol/l. Proteinuria remained elevated from 1.2 to 1.6 g/day.

Our 2 cases of systemic inflammatory reactions can be reasonably attributed to valpromide, due to the clinical features and the temporal association with drug initiation. Although other therapies could have caused inflammatory reactions in our patients, we do not think they were causative because in our 2 observations, clinical and biological improvement was observed after only valpromide was discontinued, without relapse after 6 and 18 months of followup. Previous descriptions of vasculitis and lupus-like syndrome under valproate, a metabolism product of valpromide, also support the implication of valpromide[2-4]. To our mind, valpromide should be added to the list of drugs that induce vasculitis or lupus-like syndromes.

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Correction

Kalden JR. Expanding role of biologic agents in rheumatoid arthritis. J Rheumatol 2002;29 Suppl 66:27–37. Figure 2 was incomplete, and is printed here as intended. We regret the error.

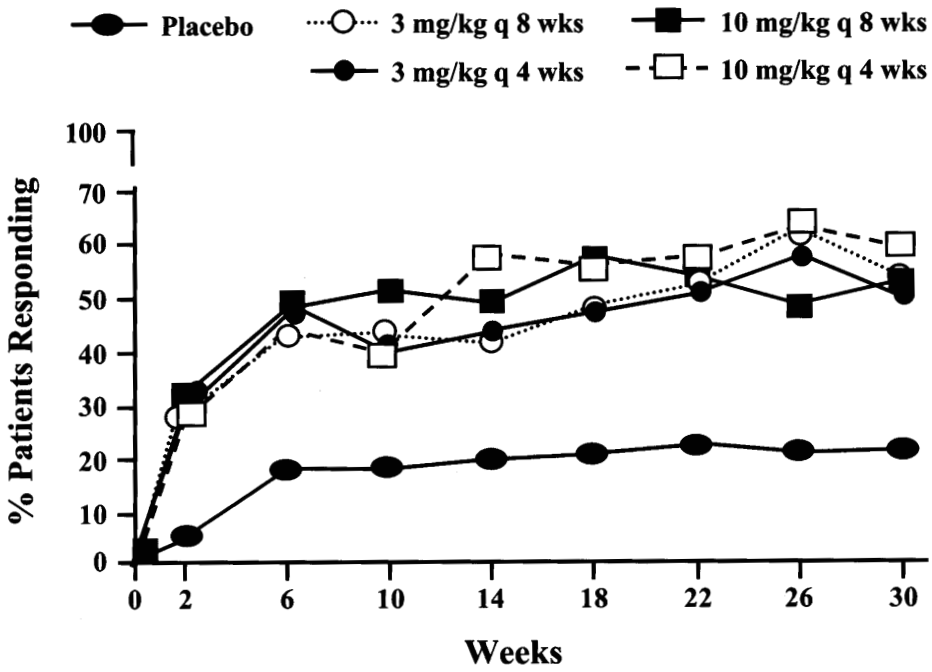

Figure 2. Percentage of patients who achieved an ACR 20% response criteria with combination infliximab/MTX treatment. The dosage and frequency of administration of infliximab varied among groups. All groups received MTX. From Centocor, Inc., with permission.