

**Letters**

**Comments and Response**

**Overviews and Systematic Reviews on Low Back Pain**

**TO THE EDITOR:** In a recent overview of systematic reviews and randomized trials of pharmacotherapy in low back pain, Chou and Huffman (1) concluded that there is good evidence that acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and muscle relaxants provide moderate pain relief in acute low back pain. In the clinical practice guideline (2) in the same issue, the recommendations for acetaminophen and NSAIDs are extended to include chronic low back pain and tramadol, opioids, and benzodiazepines are recommended both in acute and chronic low back pain despite lack of “good” or even “fair” evidence. Chou and Huffman’s method of reviewing literature relies too heavily on preexisting systematic reviews, some seriously outdated. As a result, previous work is reiterated without adequate scrutiny. In fact, methodological issues led to inclusion of studies not meeting the stated eligibility criteria and, more important, to erroneous conclusions.

**Acetaminophen:** No direct evidence shows acetaminophen to be more effective than placebo for treating low back pain. A small (n = 30) trial (3) found acetaminophen to be less effective than NSAIDs in treating acute low back pain. One low-quality trial (4) reported no difference between acetaminophen and no treatment, and another (5) showed ambiguous results. In an outdated Cochrane review (6) cited by Chou and Huffman, 2 low-quality trials (7, 8) found no difference between NSAIDs and acetaminophen. One of these trials (7) was not randomized. Comparative studies (9) of acetaminophen and nonpharmacologic treatments in high-quality randomized, controlled trials (RCTs) have shown that acetaminophen was inferior to superficial heat. In an old trial of lower quality (10), acetaminophen allegedly was slightly inferior to manipulation, but poor reporting of treatment allocation and handling of withdrawals obscured these results. As for evidence of the effectiveness of acetaminophen in non–low back pain scenarios, the authors claim that 3 systematic reviews demonstrate the superiority of NSAIDs over acetaminophen in osteoarthritis, with a standardized mean difference of approximately 0.3. We have previously reported the effectiveness of NSAIDs over placebo in knee osteoarthritis, corresponding to a standardized mean difference of 0.31 (11), whereas acetaminophen had statistically significant but clinically insignificant effects in knee osteoarthritis, with a weighted mean difference for pain of 3.0 mm (95% CI, 1.4 to 4.7 mm) on a visual analogue scale (12). In summary, there is no direct evidence and a paucity of indirect evidence to prove the effectiveness of acetaminophen in low back pain. Chou and Huffman’s claim of “good evidence of a moderate effect” of acetaminophen in this condition is, in our view, unsubstantiated.

**NSAIDs:** The outdated Cochrane review (5, 13) cited by Chou and Huffman has several shortcomings. Most important, the standardized mean difference analysis for pain was statistically insignificant for NSAIDs in acute low back pain (−0.53 [CI, −2.74 to 1.69]). Chou and Huffman state that the Cochrane review included 6 trials in which NSAIDs were superior to placebo in acute low back pain, with a relative risk for benefit of 1.24 (CI, 1.10 to 1.41). Of these 6 trials, 4 found statistically insignificant differences, whereas 2 (14, 15) reported statistically significant positive results. In the first of these studies, groups of patients received intramuscular injections of dipyrone (metamizole), diclofenac, or saline (placebo). Dipyrone, the sodium sulfonate of the obsolete antipyretic agent antipyrine, is not licensed in the United States and many other countries because of serious side effects and is hardly a typical NSAID. However, only data for the dipyrone group in this particular study were entered into the Cochrane analysis. In addition, 1 of the trials (16) was not randomized and thus was not eligible for the overview. Removing this trial and substituting dipyrone data with diclofenac data in the other trial rendered global improvement statistically insignificant, with relative risk for benefit of 1.11 (CI, 0.98 to 1.26). The overview claims ibuprofen was superior to placebo in 1 trial of chronic low back pain, but this trial (17) actually states that both groups received ibuprofen, and additional medication was compared with placebo. Thus, on the basis of the cited material, the conclusion that there is good evidence for moderate effect of NSAIDs in low back pain is erroneous.

**Muscle relaxants, including benzodiazepines:** On the basis of 4 RCTs summarized in a Cochrane review (18), the overview states that there is “good” evidence of a “moderate” effect of muscle relaxants in acute low back pain. However, 3 out of 4 RCTs in this relative risk analysis for pain have statistically insignificant results, with CIs less than 1. The positive overall result rests more or less on a single RCT from 1982 in which Merck & Co. personnel performed the statistical analysis. In the review, 79% of the weight in the statistical analysis came from this trial, which has a methodological quality score at the reviewers’ cutoff value (6 of 11). In other words, if this RCT had been rated 5 instead of 6 out of 11 and thereby was excluded from the analysis for poor methodological quality, the overall result of the meta-analysis would have been negative. The reported relative risks stated in the overview (1.25 and 1.72) differ from those reported in the Cochrane review (0.80 and 0.58), and the reason for this discrepancy remains obscure. Chou and Huffman also claim that tizanidine was efficacious in 8 trials, but according to the cited review (18), only 6 of the trials were placebo-controlled and just 3 of these reported statistically significant results. For benzodiazepines, the positive overall result in the overview rests on 2 RCTs. However, the analyses failed to include 51 patients who dropped out in 1 of these studies (19). The relative risk for pain relief by benzodiazepines became statistically insignificant at 1.38 (CI, 0.99 to 1.92) after inclusion of these withdrawals.

**Low-level laser therapy (LLLT):** Chou and Huffman handled LLLT on a trial-by-trial basis because no suitable reviews of LLLT were identified. The overview states that the LLLT material is heterogeneous, although adequate doses of LLLT with wavelengths ranging from 600 to 1100 nm seem to offer an anti-inflammatory class effect (20), and all trials were performed in participants with nonspecific low back pain. Only a small (n = 20), medium-quality (methodological quality score, 6 out of 11) trial, which used a dose less than 10% of the other LLLT trials, reported negative results. The remaining 4 placebo-controlled trials in participants with nonspecific low back pain (including 3 high-quality trials) found largely statistically significant results in favor of LLLT for pain, global improvement, and the Oswestry disability index. Our analyses show that combined outcomes were statistically significantly better than those with placebo for the LLLT groups regarding pain reduction on a visual analogue scale (11.2 mm [CI, 1.2 to 22.3 mm]), relative risk for global improvement (2.55 [CI, 1.9 to 3.3]), and disability as measured by the Oswestry disability index (5.3 [CI, 0.1 to 10.5]) even if the trial with insufficient dose was included. The overview...
still grades LLLT evidence as “poor.” In our view, these data seem to merit a more positive assessment.

We believe that the examples given are sufficient to support our key message: Overviews of systematic reviews are methodologically inferior to systematic reviews. The degree of transparency is low, errors often remain unacknowledged, and sensitive and unreliable data are propagated. With the small body of RCTs that eventually constitute the critical basis for guidelines, systematic review with updated meta-analyses should be mandatory. If the present overview’s definition of “good evidence” is applied (1, 2), many of the covered therapies should have their evidence strength downgraded to “fair” or even “poor.”

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References
Huffman may have excluded these from their review on low back pain because they occur only after neck manipulation. This could be misleading because chiropractors, who use spinal manipulation more frequently than any other specialist, consider the spine as a separate entity and will manipulate the upper spine if they diagnose a subluxation in this area, even when patients consult them because of low back pain.

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IN RESPONSE: We thank the authors of the letters for their comments on our low back pain guideline (1) and evidence reviews (2, 3). Dr. Bjordal and colleagues note some methodological concerns with our review on medications for acute and chronic low back pain. To clarify, we performed a systematic review of a broad range of systematic reviews and included past systematic reviews when they were available and of sufficient quality. The idea that new systematic reviews of the primary literature should always be conducted when developing clinical practice guidelines is both unsupported by any empirical evidence and could be a poor use of scientific resources (4). Guideline panels need relevant, current, high-quality reviews of the evidence; if existing reviews fulfill those criteria, then it is wasteful to ignore them and conduct new ones. We included systematic reviews published in or after 2000 and identified higher-quality reviews by using a validated, quality-rating instrument (5, 6). Although systematic reviews should be updated, there is no compelling reason to ignore higher-quality Cochrane reviews (7) that satisfied our methodological criteria for inclusion but did not meet an updating deadline (8). Dr. Bjordal and colleagues suggest that we graded evidence for acetaminophen too positively. In their letter, they describe 1 trial as evaluating acute low back pain when it actually evaluated chronic low back pain (9). Otherwise, our descriptions of the evidence are similar (Appendix Tables 10 and 11 [2]). We agree that our evidence ratings for acetaminophen were generous given some inconsistency among trials of acute low back pain, small benefits, and a lack of direct evidence for chronic low back pain. In a subsequent Correction (10), we re-rated evidence for acetaminophen for acute low back pain as fair quality with moderate benefits and evidence for chronic low back pain as fair quality with small benefits. Because of acetaminophen’s favorable safety profile compared with other pharmacologic therapies, these corrections do not change our recommendation to consider it as a first-line option (1).

For NSAIDs, skeletal muscle relaxants, and benzodiazepines, Dr. Bjordal and colleagues’ focus on single outcomes from placebo-controlled trials reported in Cochrane reviews ignores much of the available evidence. Our assessments are based on both placebo- and active-controlled trials; non-Cochrane systematic reviews; data on various outcomes related to pain, function, and global efficacy; and indirect evidence from patients with other pain conditions (Appendix Tables 10 and 11 [2]). We also evaluated consistency between trials and across higher-quality systematic reviews (11). In addition, post hoc analyses, such as those presented by Dr. Bjordal and colleagues, can be misleading and should be interpreted with caution. For example, excluding trials on the basis of small differences in quality scores is problematic because of unpredictable associations between summary quality-rating scores and estimates of effects (12). We did not report data on mean improvement in pain scores from a Cochrane review of NSAIDs because of substantial, unexplained heterogeneity ($P < 0.001$) (7).

As Dr. Bjordal and colleagues surmised, we inverted relative risks (1/relative risk) for “no pain relief” with skeletal muscle relaxants and benzodiazepines (as reported in a Cochrane review [13]) to present results for a positive outcome (achieving pain relief) (2). However, this transformation was incorrect, because relative risks (unlike odds ratios) are not a symmetric statistic. We have corrected the article to show original results as reported in the Cochrane review (10). This correction will not change any conclusions, but we thank Dr. Bjordal and colleagues for noting the error.

We disagree with the assertion that there is enough evidence to establish the efficacy of LLLT and transcutaneous electrical nerve stimulation. In the case of LLLT, there is substantial diversity across trials in doses and types of laser, some inconsistency among high-quality trials, and the possibility of publication bias. Our conclusion of insufficient evidence is similar to a recently published Cochrane review (14). For transcutaneous electrical nerve stimulation, the highest-quality, placebo-controlled trial found no benefit in chronic low back pain (15). In addition, it is inappropriate to pool studies of disparate patient populations and therapies (transcutaneous electrical nerve stimulation and neuromuscular stimulation) as proposed by Dr. Bjordal and colleagues, and 2 of the trials proposed for pooling found no benefits on pain or function with transcutaneous electrical nerve stimulation versus placebo (16, 17).

Dr. Bjordal and colleagues suggest that recommendations for therapy favor pharmacologic over nonpharmacologic options (1). In fact, we recommend either type of therapy (Figure 1, box 9 [1]), and strength of evidence and magnitude of benefits were graded similarly for several pharmacologic and nonpharmacologic therapies (Appendix Tables 5 and 6 [1]). However, recommendation 7 on nonpharmacologic therapies in general was graded “weak” because of relatively weak evidence for some suggested options (Appendix Tables 10 and 11 [3]), higher costs compared with first-line pharmacologic therapies, and less convenience (most nonpharmacologic options involve multiple provider visits). It would be appropriate to select a nonpharmacologic therapy over a pharmacologic one in patients who express such a preference, but the trade-offs should be discussed (20).

Superficial heat is already recommended as a self-care option (Figure 2, Interventions box [1]).

We disagree with Dr. Ernst that our conclusions regarding rare risk for serious adverse events with spinal manipulation are misleading or downplay the risk for cerebrovascular events (3). Our review deals with low back pain and treatment with lumbar spinal manipulation. There are no reports of cerebrovascular events after lumbar
spine manipulation or during treatment for low back pain (18, 19). Cervical manipulation is not a subject of our review or practice guideline.

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References

CLINICAL OBSERVATIONS

Prevalence and Incidence of Viral Infections among Musculoskeletal Tissue Donors and First-Time Blood Donors

Background: Musculoskeletal tissue is second only to blood as the most frequently transplanted human tissue, and there continues to be an enormous demand for these allografts throughout the world. Little information is known about the risks associated with musculoskeletal tissue donation. Viral infection is a potential complication of tissue transplantation, and the prevalence and incidence of infection among tissue donors provides an indication of the relative safety of the tissue supply in different countries.

Objective: To define the prevalence and incidence of markers of HIV, hepatitis B virus, hepatitis C virus, and human T-cell lymphotropic virus (HTLV) in musculoskeletal tissue donors in Australia, and to compare the results with recently published data on rates of viral infection among tissue donors from Canada, Scotland, and the United States (1–3). We also compared the results with blood donors, who are comparable because they have satisfied similar donor selection criteria and have not been previously tested (3).

Methods: We studied blood serum samples from 12 415 consecutive musculoskeletal tissue donors from 3 large musculoskeletal tissue banks in Australia from 1993 through 2004, which encompasses approximately 85% of the total number of musculoskeletal tissue donations in Australia within that period. The total includes 10 973 surgical donations obtained from retrieved femoral heads after primary hip arthroplasty and 1478 donations (including bones, cartilage, tendon, and fascia) obtained from postmortem organ donation patients and cadaveric donors. Donors and next-of-kin provided oral consent for tissue donation and blood sampling for virologic testing (HIV, hepatitis C virus, and HTLV antibody testing and hepatitis B surface antigen testing). We defined prevalence as the number of

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donors with confirmed positive test results divided by the total number of donors tested. We estimated the incidence of new infections among donors by using a method similar to that of Zou and colleagues (1). We then compared the serologic data with those of first-time blood donors obtained during the same period.

Results: Table 1 demonstrates the differences in demographic characteristics among Australian blood donors and tissue donors in different countries. The prevalence of viral markers in Australian musculoskeletal tissue donors was much higher than in Australian first-time blood donors, by factors of about 10 for HIV, 3 for hepatitis B virus, 2.5 for hepatitis C virus, and 35 for HTLV (P < 0.05) (Table 2). The prevalence of viral markers was greater in tissue donors than blood donors in all countries, except for anti-HIV antibody in Scottish tissue donors. The prevalence of viral markers was higher in tissue donors in Australia than in Canada and Scotland. Moreover, the prevalence of anti-HTLV in Australian tissue donors was nearly 2 times higher than that in U.S. tissue donors. Estimated incidence rates of viral infections were also higher among tissue donors than among first-time blood donors in Australia, Canada, and the United States.

Discussion: We report prevalence and incidence estimates for viral infection in Australian tissue donors that are higher than those in blood donors, a pattern also reported in other countries. These data contradict the perception among many clinicians that the risk for transmission of viral infection from a musculoskeletal tissue donor is equivalent to that from a first-time blood donor. However, our findings have limitations. The results are highly dependent on the assumptions inherent in the mathematical risk model we used to estimate incidence and the accuracy of the data used. Musculoskeletal tissue donors usually can donate only once in their lifetime. Therefore, although prevalence rates were calculated directly from tissue donor data, incidence estimates were calculated by extrapolating from rates obtained in first-time donors. Thus, these estimates will be affected by any bias in the underlying data and assumptions. Comparisons of data between countries are also affected by differences in donor selection policies, evolution and differences in screening tests, and differences in the donor profile. Nevertheless, we believe these findings have important implications. Monitoring viral prevalence and incidence among tissue donations is a vital tool for evaluating the safety of the tissue supply and provides important information with which to implement appropriate public health measures and policies.

Table 1. Characteristics of Musculoskeletal Tissue Donors and First-Time Blood Donors

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<tbody>
<tr>
<td>Donors tested, n</td>
<td>12 415</td>
<td>664 686</td>
<td>3372</td>
<td>9616</td>
</tr>
<tr>
<td>Living donors, %</td>
<td>88.10</td>
<td>100.00</td>
<td>84.40</td>
<td>98.00</td>
</tr>
<tr>
<td>Female donors, %</td>
<td>45.58</td>
<td>52.81</td>
<td>52.10</td>
<td>–</td>
</tr>
<tr>
<td>Average age, y</td>
<td>67</td>
<td>27</td>
<td>60</td>
<td>69</td>
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<tr>
<td>Musculoskeletal donations, %</td>
<td>100.00</td>
<td>–</td>
<td>85.02</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Table 2. Comparison of Prevalence and Incidence of HIV, Hepatitis B Virus, Hepatitis C Virus, and Human T-Cell Lymphomatropic Virus among Musculoskeletal Tissue Donors and First-Time Blood Donors*

<table>
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<tr>
<td><strong>Prevalence per 100 000 persons</strong></td>
<td></td>
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<tr>
<td>Anti-HIV</td>
<td>64.44 (27.94–126.58)†</td>
<td>5.12 (3.54–7.02)†</td>
<td>0.00</td>
<td>2.92</td>
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<tr>
<td>HBsAg</td>
<td>407.13 (302.57–536.60)†</td>
<td>135.97 (127.24–145.53)†</td>
<td>89.39</td>
<td>93.59</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>354.63 (413.76–679.95)†</td>
<td>215.29 (203.94–227.09)†</td>
<td>476.04</td>
<td>103.99</td>
</tr>
<tr>
<td>Anti-HTLV</td>
<td>121.88 (66.18–204.55)†</td>
<td>3.46 (2.16–5.37)†</td>
<td>29.79</td>
<td>30.33</td>
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<tr>
<td><strong>Incidence per 100 000 person-years</strong></td>
<td></td>
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<tr>
<td>HBsAg</td>
<td>4.43 (3.39–6.84)</td>
<td>1.48 (0.41–2.79)</td>
<td>24.16</td>
<td>18.32</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>10.04 (8.47–11.95)</td>
<td>4.04 (2.78–5.19)</td>
<td>11.32</td>
<td>10.53</td>
</tr>
<tr>
<td>Anti-HTLV</td>
<td>6.06 (4.93–7.97)</td>
<td>–</td>
<td>–</td>
<td>5.59</td>
</tr>
</tbody>
</table>

* HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HTLV = human T-cell lymphotrophic virus.
† Denotes a statistically significant difference (P < 0.05) between musculoskeletal tissue donors and first-time blood donors in Australia. Assessment of statistical significance was performed by the Fisher exact test and Pearson chi-square test as appropriate. The 95% CIs for prevalence and estimated incidence rates were obtained by the Fleiss quadratic method, which is adapted when proportions are close to zero.
Transfusion-Associated Babesiosis with an Atypical Time Course after Nonmyeloablative Transplantation for Sickle Cell Disease

**Background:** Babesiosis is a tick-borne zoonosis that is increasingly recognized as a transfusion-associated infection (1).

**Objective:** To describe a case of transfusion-associated babesiosis presenting with an atypical time course after nonmyeloablative, peripheral blood stem-cell transplantation.

**Case Report:** A 21-year-old Puerto Rican woman underwent nonmyeloablative peripheral blood stem-cell transplantation at the National Institutes of Health in October 2005 for hydroxyurea-refractory, severe sickle cell disease. Her peritransplant course was unremarkable, hemoglobin level normalized, and hemoglobin electrophoresis revealed donor type (hemoglobin AS). Her last blood product transfusion was in October 2005. She received long-term *Pneumocystis* prophylaxis with trimethoprim–sulfamethoxazole and underwent periodic therapeutic phlebotomy for iron overload.

In April 2006, she returned for evaluation of daily fever to 39 °C for 1 month. She defervesced during a 2-week course of levofloxacin therapy for presumed sinusitis, yet fever returned after completion of treatment and was accompanied by neck pain, arthralgias, lightheadedness, palpitations, and severe fatigue. On examination, she had marked pallor, nuchal rigidity, and a systolic flow murmur. Her hemoglobin level was 6.2 g/dL with an absolute reticulocyte count of 147 × 10^6 cells/L, a lactate dehydrogenase level of 536 U/L, a total bilirubin level of 1.0 mg/dL (17 μmol/L), and an undetectable level of haptoglobin. Although sickle cell disease relapse was suspected, the hemoglobin donor type remained, and myeloid cells were all of donor origin. Cerebrospinal fluid was negative for infections, and blood cultures yielded no growth.

A peripheral blood smear contained intraerythrocytic ring-shaped trophozoites, without gametocyte or Maltese cross forms (Figure, top). Because of initial suspicion for *Plasmodium falciparum* infection, the patient was given a combination of atovaquone (1000 mg/d) and proguanil (400 mg/d) therapy, which led to rapid defervescence and symptom improvement. Serial peripheral smears, however, revealed persistent parasitemia after 6 days of therapy, and polymerase chain reaction (PCR) testing for *Plasmodium* species was negative. *Babesia* species testing was then performed: *Babesia* indirect fluorescent assay was positive at 1:256 and nested PCR was strongly positive for *B. microti*. Antibiotics were changed to atovaquone (750 mg twice daily) and azithromycin (600 mg/d) (2) to complete a

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**References**

10-day course of therapy. She has remained well and had no further evidence of parasitemia by blood films or PCR.

Because the patient neither resided in nor had visited an endemic area, a red cell donor inquiry was initiated for possible transfusion-associated babesiosis. One of her 17 peritransplant blood product donors was found to have a very high Babesia indirect fluorescent assay (1:1024) but negative PCR. The donor was an avid outdoorsman who had periodically visited babesiosis-endemic areas. The implicated unit was transfused to our patient in October 2005, a week before her transplant.

Discussion: Most of the reported U.S. cases of babesiosis have been caused by B. microti, which is transmitted in nature by Ixodes scapularis ticks (2). The sporozoites infect erythrocytes and can pose a serious risk to the donated blood supply. More than 50 cases of transfusion-transmitted babesiosis are reported in the literature, although the first reported case in a human stem-cell transplant recipient (3). In healthy hosts, naturally occurring babesiosis develops 1 to 6 weeks after inoculation as a mild, self-limited, febrile illness. Asymptomatic parasitemia can persist beyond the clinical illness and therefore escape the symptom screening at blood donation (4–6). Infection in asplenic or otherwise immunocompromised patients follows a more severe course and often results in relapse. Signs and symptoms result from hemolysis and include fevers, chills, myalgias, and malaise. The incubation period of 6 months in this case was far longer than the 1 to 9 weeks reported for most episodes of transfusion-associated babesiosis (1). The extent to which host factors, parasite factors, or medications modulated the clinical course in our patient is unknown. Babesiosis remains an underreported disease. This case illustrates the importance of its consideration in non-endemic areas and highlights the potential for transfusion-associated disease presenting with an atypical time course.

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Potential Financial Conflicts of Interest: None disclosed.

References

Correction

Correction: Overanticoagulation with Coumarin and Cutaneous Azole Therapy

In a recent letter (1) describing 6 cases of overanticoagulation in elderly patients, only 2 of the 5 authors were included in print. The letter was written by Jean-François Alexandre, MD, Eric Pautas, MD, Isabelle Gouin-Thibault, PhD, and Virginie Siguret, PhD, from Hôpital Charles Foix (AP-HP), 94205 Ivry-sur-Seine, France; and Marie-Anne Loriot, PhD, from INSERM U775, Université Paris Descartes, 75006 Paris, France.

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