cosupplementation. In our view, serious shortcomings in the investigation invalidated their conclusion.

The authors analyzed tissue that had been obtained for clinical purposes and found chronically inflamed synovium, giant cells, and a "fluid-like" acellular material that stained pink with hematoxylin and eosin, which they said was Synvisc. However, they never considered the possibility that the material came from an endogenous source, for example, that it might be a piece of the patient's cartilage.

We examined synovial tissue from three patients with grade-IV osteoarthritis who had never been treated with any form of viscosupplementation, and in two cases we noted histopathological findings and pink acellular tissue inclusions identical to those described by the authors (Fig. 1). To be completely certain that our histopathological findings were identical to theirs, it would be necessary for us to see their slides.

The authors stated that the pink material was stained with alcian blue and that the alcian blue material was dissolved by hyaluronidase. Their evidence was in the form of photomicrographs showing a pink material, a blue material, and a tissue section containing holes. However, the images did not form the interlocking chain that the authors asserted because there was no way to know that the pink material would have stained blue, that the blue material would have stained pink, or that the holes in the third photomicrograph once contained material that would have stained pink or blue. Indeed, it is not even clear that the three sections were obtained from the same biopsy specimen or that the sequence of observations in the photomicrographs actually occurred in all six cases.

The proper way to make the argument that the authors sought to make is to cut serial sections of the biopsy specimen and to process adjacent sections in a manner consistent with their hypothesis. We performed this procedure on one of our biopsy specimens and were able to show that a tissue inclusion that stained pink with hematoxylin and eosin and also stained with alcian blue could be dissolved by hyaluronidase (Fig. 2). The authors must present such evidence for each patient to sustain their claim that the three observations applied to the same material.

The authors maintained that their procedure "is diagnostic for hyaluronate material," meaning Synvisc, but this is not true even when the stains and enzyme digestion are performed on serial sections, as we have shown (Fig. 2). The authors should have known that their claim was wrong because the text that they cited[1] indicated that alcian blue stains mucopolysaccharides and glycoproteins and that hyaluronidase has other substrates besides hyaluronate. The text[1] indicates that the procedure followed by the authors can "increase specificity," not, as the authors claim, that it is diagnostic for hyaluronate.

The authors made two other errors that we think are important to recognize because of the central role of implanted materials in orthopaedic practice. The terms "histopathological" and "pathological" were used twelve times in the article and the term "adverse" was used five times, and the context left little doubt that the

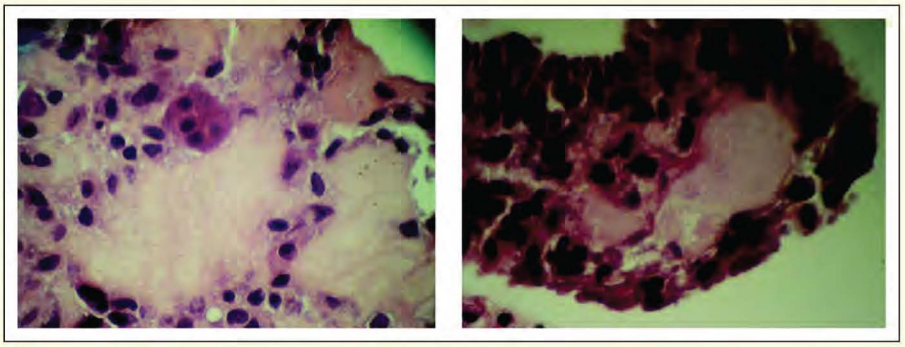

Fig. 1

Synovial tissue from two patients (an eighty-nine-year-old woman [left] and a seventy-year-old man [right]) with grade-IV osteoarthritis (according to the Kellgren Lawrence scale)[3], showing the presence of a pink acellular tissue inclusion. Neither patient had received viscosupplementation (hematoxylin and eosin, ×40).

Granulomatous Inflammation After Hylan G-F 20 Viscosupplementation of the Knee

To The Editor:

The Journal recently published an article entitled "Granulomatous Inflammation After Hylan G-F 20 Viscosupplementation of the Knee. A Report of Six Cases" (2002; 84:1142-7) involving histopathological evaluation of tissue obtained from five patients (six knees) who had received viscosupplementation with Synvisc. The authors concluded that their findings most likely represented a pathological response to vis-

authors thought that Synvisc was responsible for their findings. Unfortunately, these terms were never defined. Almost all of their tissue-pathology terminology could be applied to tissue recovered from the region of a bone implant, fixation device, or bone cement where, from an orthopaedic perspective, the patient had healed splendidly. The point is that analysis of tissue obtained from the trap of an arthroscopic shaver or during an arthroplasty is no reasonable basis upon which, absent suitable controls, to conclude either that the tissue is "pathological" in an orthopaedic sense (in other words, that the tissue appearance is other than that which would be expected when a foreign body is placed in the body) or that a pathology was caused by the implant rather than the underlying disease. When the pathologist states that tissue from a patient who received an implant is "histopathological" because of the implant, the two questions that ought to be asked are, "What do you mean?" and "How do you know?"

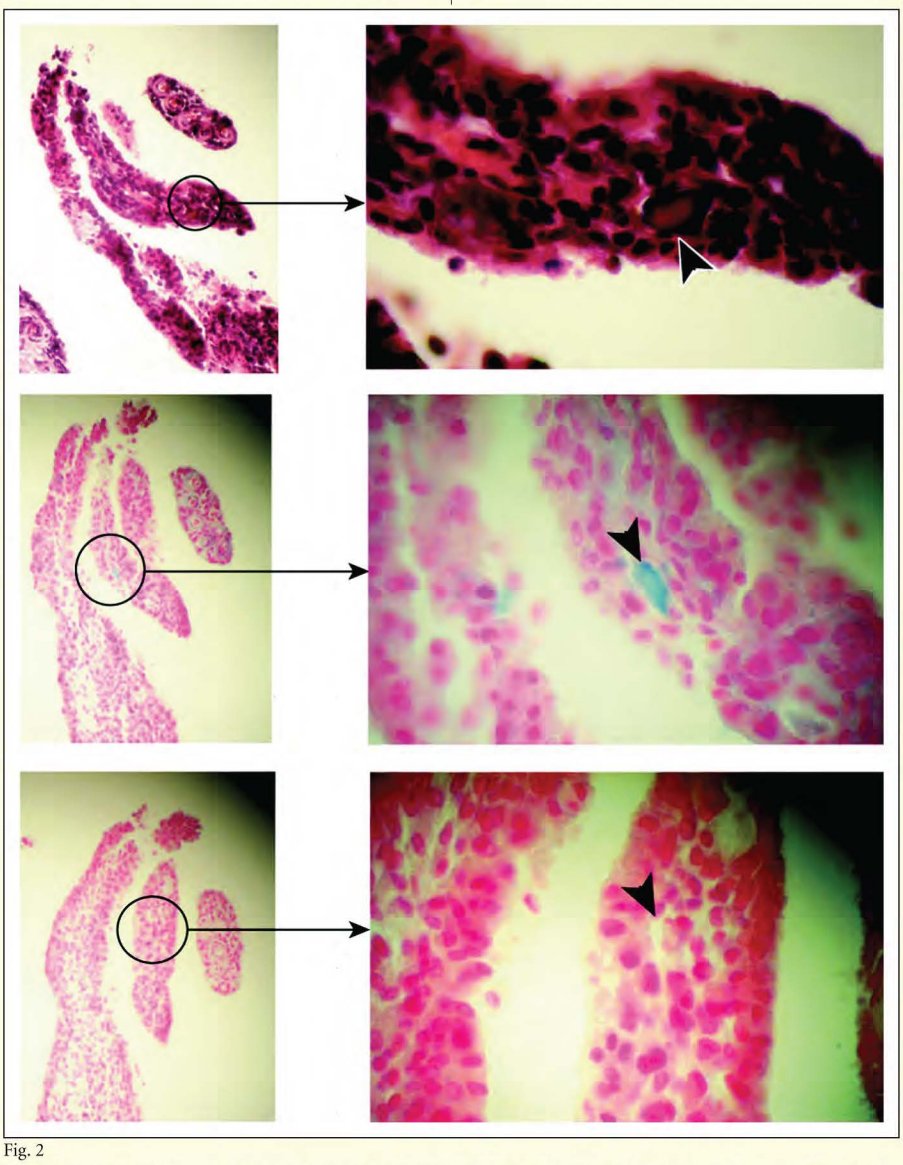

Fig. 2

Histological procedure for the chemical characterization of material in synovial tissue. The synovial tissue was obtained from a seventy-year-old man with grade-IV osteoarthritis. The arrowheads indicate that the tissue contained a material that stained with hematoxylin and eosin and alcian blue and was digestible by hyaluronidase. The material, possibly cartilage, could not have been Synvisc because the patient had never been treated with viscosupplementation (hematoxylin and eosin [top], alcian-blue/fast-red [middle], hyaluronidase digestion followed by alcian-blue/fast-red [bottom]; ×10 [left], ×40 [right]).

Second, the authors failed to indicate the population from which their five patients were drawn. No information was provided regarding the number of patient records that were searched, the number of patients who received Synvisc and did not exhibit synovial inclusions, the number of patients who did not receive viscosupplementation and exhibited the inclusions, or the results for patients who received viscosupplementation with a product other than Synvisc. This information is essential. Otherwise, even if all of the authors' claims are taken at face value, it is simply not possible to evaluate the relative risk associated with the use of Synvisc.

Finally, the authors stated that they were not aware of any studies involving histopathological analysis of the synovium after use of Synvisc. They should have known that histopathological results identical to theirs were described in a report on a case in which Synvisc was injected into the fat pad rather than into the joint[2].

It is important that independent investigators evaluate the safety of commercial products, as the authors intended. But their failure to follow proper procedures made their data uninterpretable. Greater effort is needed to achieve their obviously laudable goal.

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