

## Correspondence

# Chemonucleolysis for sciatica

### *To the Editor:*

There is no disputing the conclusion of Nachemson and Rydevik<sup>1</sup> that laminectomy is the basic treatment for herniated-disc problems. However, because laminectomy has nine times as many neurologic complications, a four times greater mortality statistics, and a three times greater incidence of discitis than chemonucleolysis, as shown by a review of the literature, many surgeons worldwide are using chymopapain for its specific indications. The injection is not a replacement for discectomy or laminectomy where there is a demonstrable sequestered fragment, a spinal stenosis, or compression of sufficient magnitude to cause a progressive neurologic deficit, such as a cauda equina syndrome<sup>2-9</sup>.

Statistics on laminectomy or discectomy are largely reported from well-run centers, where one would expect a more favorable outcome and fewer complications. Because all the complications of chemonucleolysis in the United States are monitored by the the U.S. Food and Drug Administration and must, by regulation, be reported, statistics are perhaps more accurate for the complications due to chymopapain than any other disc-directed procedure.

The MRI studies of Szupryt et al.<sup>10</sup> showed loss of water content, but no reconstitution over 12 months. Because they used a 10-mg dose of enzyme, which is five times that of a normal dose, it is not likely that any chondrocytes would continue to produce chondromucoprotein—even the end plates were affected.

Neural injury can result if chymopapain is injected into a nerve, but not by mere contact with any nerve that has a fibrous sheath, such as a spinal nerve. Chymopapain will not digest collagen, but it will affect capillaries with no such protective coat, and it will induce bleeding. This in time will affect the microcirculation, denying nutrition to that portion of the nerve supplied by the disrupted capillaries. In the work of Zook and Kobrine et al.<sup>11</sup>, even though they used 15-17 times the normal dose of chymopapain and pathologic studies showed neural changes secondary to interference

with the microcirculation, no clinical evidence of any deficiency was found. Chymopapain has never been shown to be a primary neurotoxin.

Epidural leakage of chymopapain is of no concern beyond these facts, because the alpha-2 macroglobulin in serum promptly neutralizes any enzyme present. Usually, there is only a theoretic presence of enzyme, for it is instantaneously bound by the mucoprotein of the nucleus pulposus upon injection.

Six out of the more than 150,000 patients estimated to have been injected with chymopapain in the United States since 1963 have been reported to have developed acute transverse myelitis. All 6 cases were reported between February 1982 and April 1984, and no other cases have been reported since. Only 1 of these cases has been described in the literature<sup>12</sup>. Intrathecal injections have not been implicated in most of the 6 acute transverse myelitis cases reported. However, no good evidence is known for the true etiology of the acute transverse myelitis of the reported cases.

Multiple-level injections were advised as inappropriate only because of the increased risk of intrathecal injection by inexperienced operators inserting multiple needles. Similarly, discography is only hazardous when extended intrathecally, potentiating the adverse effect when combined with chymopapain. Such a combination is only deleterious when injected intrathecally.

The natural history of discogenic sciatica is not likely to be studied with chymopapain because it is already known from the studies of Weber compared with laminectomy<sup>13</sup>. The fact is that after 10 years the results are pretty much the same whether any definitive treatment is given or not. Definitive treatment is viewed only as an attempt to eliminate or modify the pain a little sooner than nature does, except in those cases of severe neural compression. Engh<sup>14</sup> reported that he followed his patients for 30 years and found, irrespective of treatment, that all the patients had about the same result at the final examination<sup>14</sup>.

Ejeskär et al.<sup>15</sup> reported their prospective ran-

domized study, which included 15 injected patients, half of whom required subsequent discectomy; and half of these patients had a sequestered disc, which is a relative contraindication for chemonucleolysis. Moreover, the enzyme used by them and Crawshaw et al.<sup>16</sup> came from the same depot in Great Britain and is believed to have been inactive, because two batches had been recalled at the time. The new formula has much greater stability, so this should not be a problem. Subjectively, the open, operated-on group of 14 in this study reported only good or excellent results, whereas as regards objective evaluation, only 9 of the 14 could be placed in this category. Thus, there was no statistical difference in the follow-up results between the two types of treatment, neither at 6 months nor at 12 months after the first treatment<sup>16</sup>.

Studies are frequently said to show consistent 80 percent to 90 percent good results after surgical remov-

al of the disc. However, a compilation of all the studies available for both modalities came out with laminectomy at 77 percent and chemonucleolysis at 76 percent<sup>18</sup>.

In spite of discectomy being the "gold standard," this mode of treatment is producing, in the United States, at least 15,000 "failed backs" a year that, for the most part, find no lasting remedial treatment. This is, in great part, secondary to postoperative fibrosis, which does not occur following injection of chymopapain.

I agree with the authors that we need further research on proper patient selection, adherence to the factors already known, and investigation of other substances that may be less hazardous. This work is in progress, and there is hope for the future.

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*To the Editor:*

We would like to thank Dr. Nordby for his comments to our recent review of chemonucleolysis for sciatica<sup>1</sup>. Some of the issues brought up in his response need to be clarified.

Dr. Nordby states that "laminectomy has nine times as many neurologic complications" compared with chemonucleolysis. However, he fails to indicate the complete difference in type and severity of the neurologic complications with the two procedures. Subarachnoid hemorrhage with paraplegia is a reported complication of intradiscal chymopapain injection, but is unlikely to occur following surgical disc removal.

With respect to the issue of neurotoxicity of chymopapain, this matter is obviously still not clear to everyone. Chymopapain causes immediate bleedings if it comes in contact with capillaries<sup>19</sup> and if the enzyme is applied to the surface of a nerve, hemorrhage and edema occur inside the nerve<sup>20</sup>. This has been demonstrated by applying chymopapain to rabbit tibial nerve, in which the nerve fibers are located in fascicles surrounded by a very strong perineurium. Obviously, chymopapain penetrates through such a perineurium if it is applied outside the nerve and may affect the blood supply to the nerve. This leads to long-term changes in nerve structure with Wallerian degeneration and intraneural fibrosis, as well as functional changes. These experimental findings may well explain the neurotoxic reactions that are induced if chymopapain is injected into the subarachnoid space, where it may come in contact with the richly vascularized meninges and nerve-root tissue.

In cases of intradiscal injection, there may be leakage of the injected solution into the epidural space, probably in about 25 percent of the cases as based on experience from discography<sup>21,22</sup>. Chymopapain solution that leaks from the disc is probably of reduced concentration and activity. The fibrous sleeve, which surrounds each spinal nerve root at the foraminal level, probably acts to protect the nerve tissue from leaking chymopapain.

Thus, chymopapain, in itself, has neurotoxic properties and is hazardous to nerve tissue if it comes in direct contact with such tissue. Therefore, subarachnoid injection or injection into a spinal nerve root must be avoided.

In their report on complications to chemonucleolysis, Agre et al.<sup>23</sup> described that all the severe neurologic complications occurred if the chemonucleolysis had been performed in direct combination with discography. We believe that discography, if at all necessary, should be done at least a few days before any planned intradiscal injection procedure.

The age of the patient must also be taken into consideration when discussing enzymatic disc dissolution. Pathoanatomic examination of disc hernias removed at surgery clearly demonstrated that already after the age of 40 more than 80 percent of the tissue removed contains only annulus fibrosus and/or end-plate material<sup>24</sup>. Chymopapain attacks mainly the noncollagenous proteoglycan portion of the disc<sup>25</sup>.

Dr. Nordby must have misunderstood our reference to Weber<sup>13</sup>, which, as stated in our paper, is a "personal communication." This refers to a recently performed investigation by Weber and his group in Norway on the

effects of chymopapain injection on sciatica due to disc herniation. Weber found that only about two thirds of his 80 patients with disc herniation and sciatica responded with good results to chymopapain injection. He was unable to see any benefit of this treatment when comparing this series with his previously reported study on conservative treatment.

Dr. Nordby quotes a study by Ramirez and Javid<sup>18</sup> where comparable results were obtained with laminectomy and chemonucleolysis, both procedures leading to about 76 percent good results. This study is in contrast to several other studies, as listed in our review, where surgical discectomy led to some 90 percent good results, whereas chymopapain injection resulted in about 50-70 percent good results.

Van Alphen et al.<sup>26</sup> recently reported a randomized study of chemonucleolysis with chymopapain versus surgical discectomy. After 1 year, 22 percent of the 151 patients who had undergone chemonucleolysis had required surgery, whereas 3 percent of the surgical cases had been reoperated on. The final results of chemonucleolysis, including secondary treatment, was slightly less favorable than the results of primary

surgery. Increase of radicular pain after 30 days was seen in 22 percent in the chemonucleolysis group as compared with none in the surgical group. This observation on pain response after chemonucleolysis and surgical disc excision accords with recent data from Brown and Tompkins<sup>27</sup>.

Laminectomy with surgical disc removal is a very common procedure in the United States, and it is a several times more frequent procedure for disc herniation in the United States than in countries like Sweden, England, and Israel. If a laminectomy is performed on a correct indication, it is unlikely that the procedure will lead to "a failed back syndrome." Obviously, this matter is a problem in itself, which basically has nothing to do with chemonucleolysis. However, theoretically, enzymatic disc dissolution has the advantage of not creating epidural fibrosis, although there is an incomplete analysis of this matter in the literature.

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