Eur Spine J (2001) 10 : 192–202
DOI 10.1007/s005860000234

REVIEW

Chemonucleolysis: the state of the art

James W. Simmons
Eugene J. Nordby
Alexander G. Hadjipavlou

Received: 25 September 2000
Accepted: 10 October 2000
Published online: 6 April 2001

This manuscript was created without external sources of support.

J. W. Simmons
Alamo Bone and Joint Clinic,
San Antonio, Texas; and Adjunct Faculty,
Department of Orthopaedics
and Rehabilitation,
The University of Texas Medical Branch,
Galveston, Texas, USA

E. J. Nordby
Madison, Wisconsin

A. G. Hadjipavlou (✉)
Department of Orthopaedic Surgery
and Traumatology,
University of Crete at Heraklion,
University General Hospital
P.O. Box 1352,
71110 Heraklion, Crete, Greece
e-mail: ahadjipa@med.uoc.gr,
Tel.: +30-81-392111, Fax: +30-81-392372

Abstract This review presents the history of chemonucleolysis, the techniques, indications, contraindications, and complications. Presenting an historical overview and comparison of success rates with surgical discectomy may provide a fresh understanding of the controversy surrounding chemonucleolysis and establish its efficacy in relation to more invasive treatments. A review of the literature from 1973 through 1998 for chemonucleolysis, open discectomy, and microdiscectomy provided published success rates for these procedures, and a mean rate with standard deviation was determined. In the experience and opinion of the authors, chemonucleolysis remains a viable alternative for patients who have exhausted all conservative means of treatment. Proper patient selection leads to success rates comparable to open discectomy and microdiscectomy.

Keywords Chemonucleolysis · Open discectomy · Microdiscectomy · Chymopapain

Introduction

Jansen and Balls [43] first isolated chymopapain in 1941 from the latex of the *Carica* papaya fruit. Chemonucleolysis involves the use of chymopapain B, an injectable proteolytic enzyme, for the chemical dissolution of herniated nuclear material. Its mechanism of action is the hydrolysis of noncollagenous protein that interconnects long-chain mucopolysaccharide. The effects of the hydrolysis produced by chymopapain B are similar to those induced by corticosteroids. Chymopapain B also has neurolytic effects on the free nerve endings of the disc. This series of biochemical reactions [28, 39, 62, 63, 90] leads to the depolymerization of the nucleus pulposus, which lowers intradiscal pressure to relieve pain.

Experimentation carried out by Smith and colleagues [87] among 22 dogs demonstrated that paralysis was reversed in 14 canine models following injection of chymopapain into the lumbar intervertebral discs. Autopsy of the dogs revealed no adverse effects attributable to use of the enzyme. These results laid the foundation for the clinical use of chymopapain, which was entered into US Food and Drug Administration (FDA) Phase III trials. The trials

enrolled 17,000 patients to receive chymopapain injections in the United States and Canada during July 1975 [84].

Controversy sparks market withdrawal

Controversy soon surrounded the new treatment, when a later study, conducted at the Walter Reed Army Medical Center in 1975, demonstrated no statistically significant difference in improvement between a placebo group and the experimental group, with success rates of 49% and 58%, respectively [82]. A subsequent critical analysis of the research design applied in the Walter Reed Medical Center's study found fault with the lack of an inert placebo, the insufficient dose of chymopapain, and the lack of technical expertise among the investigators, as well as other issues [12]. Physicians who were already treating intervertebral disc disease with the new substance, and obtaining excellent results, were disappointed to learn that the study at the Walter Reed Medical Center had prompted withdrawal of the FDA's approval for chymopapain use in humans. Chymopapain, however, remained in clinical use abroad – in Canada, Australia, and the UK.

Stymied by the lack of progress in regaining Federal approval, efforts were initiated to bypass the FDA through state legislature authorization. Illinois, Indiana, and Texas won the right to employ chymopapain in intervertebral disc treatment within each state. The papaya fruit is native to the state of Texas, and only Texas had a sufficiently favorable climate to allow its cultivation and, thus, extraction of the crude latex necessary for mass production of the drug. As a result, Chemolase was developed in Texas and legal use began in 1979.

The Texas trial

Between 1980 and 1982, 21 orthopedic surgeons and neurosurgeons enrolled 919 patients in a chymopapain postmarketing, open-label clinical trial. The Texas trial yielded an overall efficacy rate of 93%, and provided additional support for the safety and efficacy of chemonucleolysis in the treatment of low back pain and sciatica of discogenic origin following unsuccessful conservative management [85].

Intradiscal injection of chymopapain produced 70 adverse reactions in 46 patients, or an overall complication rate of 5%. The most common side effect, erythema, occurred in 1.8% of the patient group. Anaphylaxis, the most serious reaction, occurred among 1.1% of the patients. Anaphylactic reactions that qualified as truly severe on the basis of individual physician assessment, however, were reported in only 0.54% of the patient population. Medical management of the anaphylaxis was successful in all patients without sequelae. Other reactions, which occurred at a similar rate, included giant urticaria, hypotension, and paraspinal or muscle spasms. Finally, back pain was reported in only 0.4% of the treated patients. No mortality was associated with the intradiscal application of chymopapain among the 919 enrolled study patients [85].

Renewal of clinical testing

A new formulation of chymopapain, Chymodiactin, was introduced for clinical testing by Smith Laboratories in 1979 [66]. Chymodiactin was tested in 1981 in a randomized, double-blind, FDA-approved study of 108 patients. The clinical success rate was 82% among the Chymodiactin-treated patients; just 41% of the placebo group responded favorably. No complications resulted from this study.

An open study, conducted in Illinois among 1498 patients, yielded a 90% success rate [61]. Four cases of anaphylactic shock, however, produced death in two patients. One case of acute transverse myelitis also was reported, but no causal relationship between Chymodiactin and acute transverse myelitis could be established in an extensive follow-up study [83]. Chymodiactin was granted FDA approval in November 1982.

Of five major double-blind investigations conducted between 1975 and 1987, four trials provided statistically significant evidence in favor of chymopapain treatment. Success rates have ranged from 58% to 80% [18, 23, 25, 44, 82]. By pooling the results of the first three controlled trials, Haines [37] concluded that the "odds of successful outcome are 2.6 times as great with chymopapain as those after placebo injection." Until the 1990s, when reports of percutaneous laser therapy use in humans began to appear in the medical literature [10, 15], chemonucleolysis stood alone as the only conservative treatment modality that could be applied prior to more invasive surgical interventions such as laminectomy, microdiscectomy, and percutaneous discectomy.

Indications

Chymopapain is indicated in the treatment of unremitting sciatica due to a proven herniated nucleus pulposus that has not responded, over a minimum period of 6 weeks, to the typical conservative measures: bed rest, exercise, antiinflammatory drugs, body corset, epidural blocks, physical therapy, and traction [84]. Due to its *in vivo* mode of action, chymopapain will only benefit the patient whose problem has been documented as being of discogenic origin.

Criteria for patient selection

The importance of patient selection as a key factor in the successful outcome of chemonucleolysis cannot be overemphasized. In a study conducted over 25 years ago, patients with severe sciatica of short duration experienced the best results from chymopapain injection. Patients who were obese, diabetic, or afflicted with a psychiatric illness showed the worst results [56]. Other research has examined the impact of pre-existing low back pain (LBP) versus no LBP on the outcome of chemonucleolysis. Those without LBP fared significantly better after the intervention than those already afflicted with LBP (85% success rate versus 52% success rate) [35].

Only patients who have exhausted all conservative measures for sciatica of discogenic origin should be considered for chemonucleolysis. The patient's age also is important. In adults over the age of 60, the situation may often be that age-related degenerative changes have depleted the mucoprotein in the nucleus pulposus [13, 84]. Given this circumstance, the effectiveness of chymopapain would be diminished [3]. By itself, however, advanced age may not always preclude chymopapain treatment. Magnetic resonance imaging (MRI) studies have shown that even octogenarian patients can have normally hydrated discs, thus making them theoretically responsive to chemonucleolysis [84].

Diagnosis of herniated nucleus pulposus should proceed with a complete medical history that includes known allergies, symptom history, total duration of back pain and of leg pain, location of sciatica, other significant medical history, and a listing of current medications. Neurologic and muscle testing also are pertinent to establishing a diagnosis. Testing of muscle strength, deep tendon reflexes, sensation, body mechanics, sciatic stretch, and straight leg raising in the seated and supine positions should be performed. The mechanical and sciatic stretch test should include sitting and supine straight leg raising, and tests for weakness, muscular atrophy, and dermatomal dysesthesia. By way of partial confirmation of the patient's complaints, the straight leg raising test should reproduce the patient's symptoms, as should the bowstring test and the ankle dorsiflexion test [3]. The importance of properly performing and recording these tests lies in the contribution they make to ascertaining the diagnosis of radiculopathy or sciatica, which is secondary to disc herniation – the only condition that warrants a chemonucleolysis procedure.

The ideal candidate should have only single-level disc involvement. Imaging and laboratory studies will aid in determining whether this is so, and should include routine radiographs of the lumbosacral spine, regular and enhanced computed tomography (CT) scans, MRI, myelography, discography, and electromyography. Findings of CT scans and myelography should correlate with the patient's signs, symptoms, and physical examination [3]. Extreme care should be exercised in selecting candidates for chemonucleolysis. Judgment of the patient's suitability for this treatment must be based on complete evaluation of all the compiled subjective and objective data.

Contraindications

Absolute contraindications

A major and absolute contraindication for chymopapain use is allergic sensitivity to papain or papaya. Prior exposure to the chymopapain protein may have occurred from sources of papain that are commonly found in such commercial products as meat tenderizers, papaya fruit, beer, toothpaste, digestive aids, cosmetics, disinfecting solutions for contact lenses, laboratory reagents, and some treated leathers. About 1% of the world's population has the potential for reaction to the injectable form of chymopapain due to prior cross-reactive exposure [92].

Skin testing or direct measurement of IgE antibodies through the radioallergosorbent (RAST) or fluorescent allergosorbent (FAST) tests can be useful in alerting the clinician to the patient's papain sensitivity. Nevertheless, even these tests cannot totally negate the possibility of an anaphylactic reaction, as there have been reports of allergic reactions triggered by epidermal injection for skin testing [55]. Such antigenic responses serve to underscore the importance of proper placement of the needle and localization of chymopapain to the nucleus pulposus [86], which may decrease the probability of anaphylaxis.

Chymopapain treatment is intended strictly for the relief of radiculopathy secondary to a herniated disc. Clearly, if discography or MRI reveal a normal disc, then the need for chemonucleolysis is obviated. Work-up of the patient also must rule out a spinal cord tumor, disseminated malignancy, vertebral osteomyelitis, and disc space infection. Radiographic findings that point to conditions that would interfere with the process of chemonucleolysis, such as mechanical insufficiency, spinal stenosis, advanced spondylolisthesis, blockage by cervical or thoracic disc, inability to reach the disc space via the lateral approach, or intrathecal or intravascular flow of contrast dye upon discography, also would be contraindications to treatment with chymopapain [84]. Cauda equina syndrome, or any major, progressive neurologic condition, is another specific contraindication, because the response to chymopapain is time-dependent and may not offer prompt relief of the neural pressure produced in such urgent cases [67]. The absence of studies on the effects of chymopapain in pregnant women or upon fetal development makes pregnancy another absolute contraindication to chemonucleolysis.

Relative contraindications

There are several relative contraindications to chemonucleolysis that require careful consideration. Osteoarthritis

may obstruct needle insertion. Any history of disc or vertebral infection becomes an important factor due to the potential for activating latent infection. Unsuccessful prior open discectomy may inhibit a favorable outcome due to the presence of fibrosis. Diabetes mellitus, especially with neuropathic changes, presents yet another relative contraindication. The anticipated success of chemonucleolysis could well be diminished by the extent and control of the diabetes. Other reported relative conditions have been medico-legal involvement, psychological problems, or inability to comprehend in English the description of the procedure and its potential outcomes [3, 68, 101].

Operative technique

Preparation of the patient

Chemonucleolysis may be performed by qualified orthopedic surgeons, neuro-radiologists, rheumatologists, neurologists, or similar specialists trained in needle placement procedures, in a facility with suitable radiologic capabilities, where proper sterile techniques can be carried out [84]. Fluoroscopic equipment (radiolucent table, C-arm fluoroscope with image intensifier, and equipment to take anteroposterior lateral X-ray films of the lumbar spine during the procedure) should be available. The procedure begins with presterilized instruments and takes place within a sterile environment.

The patient is placed on a radiolucent operating table in a left lateral decubitus position (Fig. 1). Secure fastening of the patient with adhesive tape will avoid movement from a true lateral position. A portable C-arm fluoroscope is then placed over the stationary table, enabling the surgeon to have biplanar fluoroscopic control. The spine is properly centered; any curvatures can be corrected by a rolled towel placed in the flank above the iliac crest, and by rotating the hips, as needed. Proper positioning allows easier access to the lumbar disc. Both the lateral and anteroposterior views of the spine should be monitored.

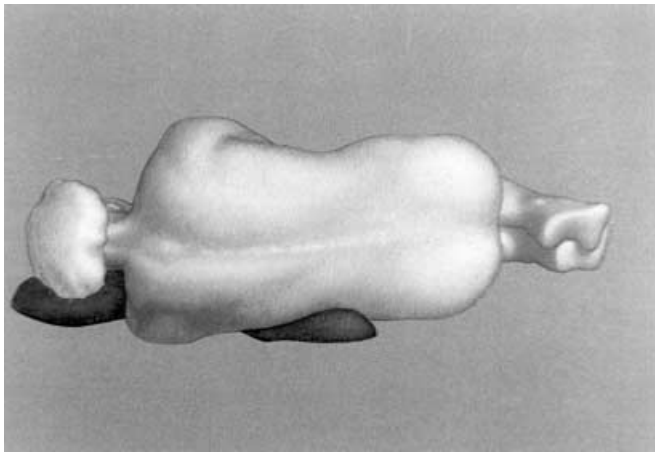

Fig. 1 The patient is placed in the left lateral decubitis position with appropriate padding for comfort, and padding in the flank to help maintain the spine in a horizontal position

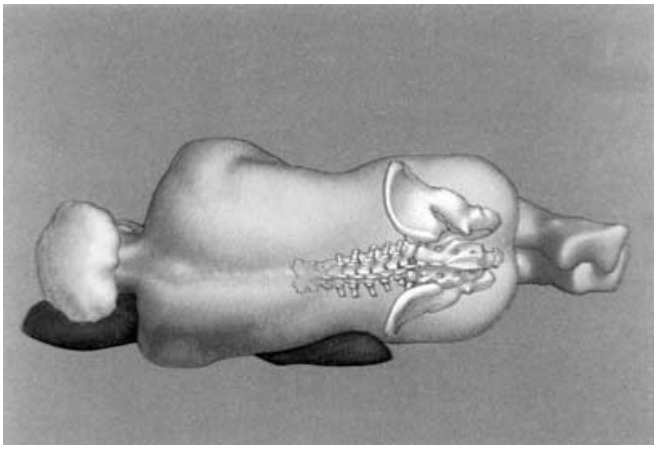

Fig. 2 With the patient in the left lateral decubitus position and properly padded, it is possible to visualize spinal landmarks and their relationship to each other. Note, in particular, the posterior iliac spine, the iliac crest, and the spinous processes

The superior iliac spine, iliac crest, and the spinous process are located (Fig. 2) and identified using a marking pen. Measuring with a ruler, the area 8–10 cm lateral to the tip of the spinous process is marked. This mark is lined up with the intervertebral disc and will be the point of entry through the skin. Surgical preparation and draping of the patient follows.

Technical issues

Several technical considerations deserve attention. First, when the tips of the advancing needles reach a line adjoining the posterior borders of the vertebral bodies, the surgeon should obtain a firm, gritty sensation from the annulus. If the tip of the needle passes anterior to this line before this sensation is obtained, the needle will not bisect the disc, but will pass anteriorly and laterally to it (Fig. 3). If this occurs, the needle should be reinserted at a more acute angle to the sagittal plane. To change the angle, the needle should first be withdrawn close to the skin beyond the lumbodorsal fascia.

There may be bony obstructions near the transverse process, the pars interarticularis, or the facet joint. These structures will be observable on a lateral projection with the C-arm. Obstruction at the level of the upper half of the vertebral body is likely due to the pars interarticularis. When opposite the disc space, the obstruction is probably due to the facet joint. If the transverse process causes obstruction of the L5-S1 disc, the insertion site for the needle is moved in a cephalad direction in order to reach the

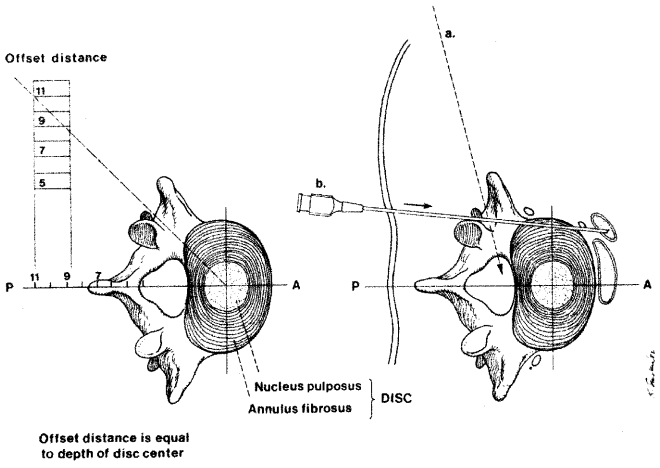

Fig. 3 *Left:* Illustration of the triangulation necessary for three-dimensional perception of correct needle placement. *Right:* The hazards of anterior malplacement of the needle

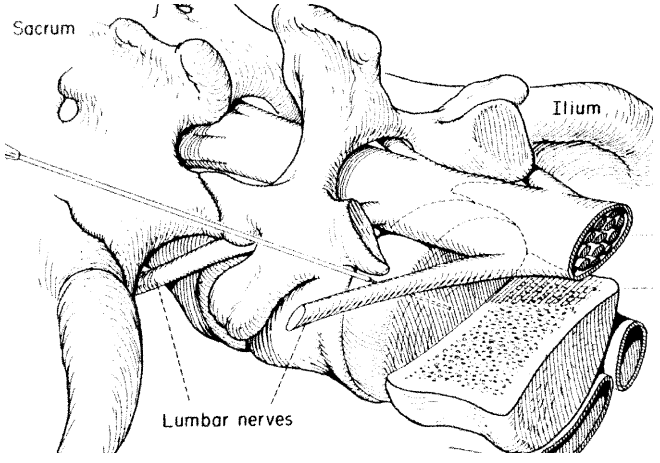

Fig. 4 Three-dimensional conceptualization of correct needle placement

L4 intervertebral disc space. If either of the first two cases is true, the surgeon may angle the tip more posteriorly or anteriorly to gain access.

The angle of needle insertion, however, needs to be considered in conjunction with the overall size and shape of the patient. Having a clear, three-dimensional mental image of the lower lumbar region is important (Fig. 4). It is also helpful to have an articulated spine specimen in the operating room.

For the L5 intervertebral disc space, the image intensifier is repositioned laterally. The L4 needle may serve as a landmark and guide to the position of the L5 disc space. The L5 needle is inserted at the same angle to the sagittal plane; that is, at 30°, but directed approximately 45° caudally. This angle is adjusted until the tip of the needle is level and adjacent to the posterior aspect of the vertebral bodies (the L5 disc

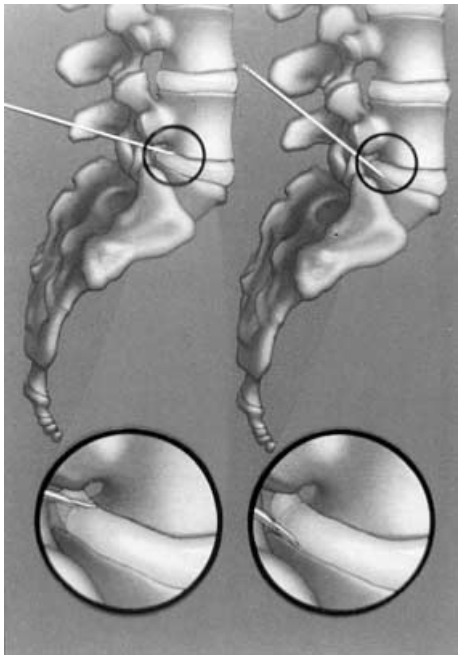

Fig. 5 *Left:* View (background and *inset*) of needle malpositioned slightly cephalad. *Right:* View (background and *inset*) of needle malpositioned slightly caudal

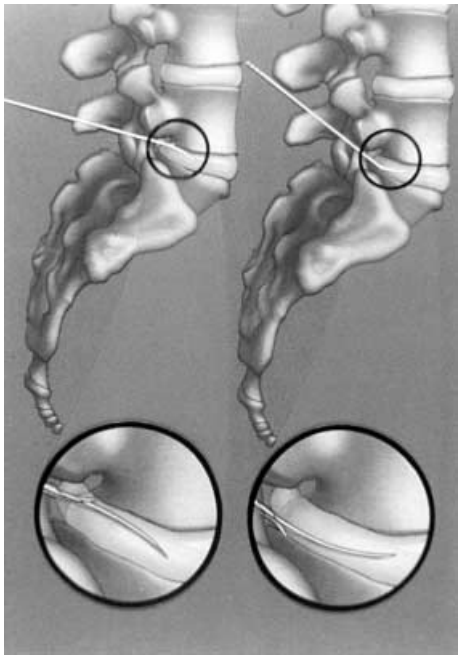

Fig. 6 *Left:* Correction of cephalically malpositioned needle by directing the bevel cephalad. *Right:* Correction of caudally malpositioned needle by placing the bevel in the caudal direction

space). In addition to radiographs, this is of great importance in assessing bony obstruction. Obstruction by the transverse process, for example, necessitates reducing the angle of the needle relative to the sagittal plane.

There may be occasions when a broad transverse process at L5 obstructs this approach. If this occurs, the double-needle technique can be used: A 22-G needle is placed through an 18-G needle, with the tip of the 18-G needle lying just at the inferior level of the L5 vertebral body. By curving the distal half-inch of the 22-G needle with the bevel up, the needle will curve downward into the L5 intervertebral disc space as it passes out of the tip of the 18-G needle (Fig. 5, Fig. 6).

Once the surgeon has visually verified the correct needle tip placement with the aid of the C-arm image intensifier, a deionized, water-soluble contrast medium is injected. Resistance to flow will provide some indication regarding the integrity of the disc. The pattern outlined by the dye will give an indication of the morphology and continuity of the annulus.

Determining the integrity of the disc before chymopapain injection is important. The authors advocate the use of lumbar discography for this purpose. However, in the event that lumbar discography cannot be performed, the water acceptance test is an acceptable methodology for evaluating the integrity of the disc [3].

To begin the lumbar discectomy, an amount of contrast medium adequate to fill the herniated disc is injected, usually 2.0–2.5 ml. An epidural leakage of the dye may occur, but this should not be regarded as a contraindication to chemonucleolysis. The procedure should be abandoned, however, in the rare instance that contrast dye leaks into the subdural or subarachnoid spaces. Resistance to the flow of contrast material is a reliable indicator of the integrity of the disc. A normal disc has a very high resistance to the flow. A prolapsed or herniated disc offers moderate resistance, whereas, a severely degenerated disc poses no resistance whatsoever. Coordination of flow resistance with visual monitoring of the dye allows the surgeon to assess the state of the disc. Radiograms in anteroposterior and lateral views are then taken. At least 10 min should elapse after injection of the dye for evaluation of a possible allergic response.

The amount of chymopapain injected depends on whether the herniation is contained, bulging or prolapsed; generally it should be no more than 1–2 cc. The injection should proceed slowly to allow adequate flow and binding of the enzyme. Three to five minutes after the injection, the needles may be removed. If no reaction occurs and all vital signs remain stable, the patient may be moved to the recovery room.

Complications

Prudent patient selection and correct technique are the most important elements for avoiding complications stemming from the injection of chymopapain. The most frequent complication is that of anaphylaxis, which may be prevented by prior sensitivity testing. The overall incidence of anaphylaxis has been estimated at 0.5%, or 1 out of every 200 patients. Males are slightly less likely to experience anaphylaxis than females (0.3% and 0.9%, respectively). African-American women, however, are at increased risk for anaphylaxis, with a reported incidence of 2.0%. Thus, sensitivity testing is especially indicated for those at increased risk owing to multiple allergies or gender-genetic attributes [3].

The use of general anesthesia is associated with a minimally higher incidence of anaphylaxis (0.6%) over local anesthesia (0.4%) [3]. As the difference bears no statistical significance, however, both general and local analgesia may be used for performing chemonucleolysis [9]. Halogens, however, should be avoided, as they may sensitize the cardiac tissue to epinephrine and cause cardiac arrhythmia, and would preclude the use of epinephrine – the drug of choice for reversal of anaphylaxis [67]. Otherwise, each form of anesthesia brings distinct advantages to the chemonucleolysis procedure [67]. The most important caveat is to be fully prepared in the operating room for the management of anaphylactic shock, should it occur. Alexander presents a comprehensive treatment of this subject [3].

Although anaphylaxis is still the most frequently reported adverse reaction associated with chymopapain, vascular and neurological complications can be equally serious and merit a watchful eye. Possible vascular events include cerebral aneurysm or arteriovenous malformation, intrathecal injection, cerebral accident, subarachnoid hemorrhage, post anti-coagulant, pheochromocytoma, and other vascular complications of unknown etiology. Complications of a neurological nature include acute transverse myelitis, cauda equina syndrome, Guillain-Barre syndrome, seizures, and other neurological complications of unknown etiology [67].

The safety of chemonucleolysis was evaluated on the basis of 121 “serious” and “unexpected” adverse effects among 135,000 patients in the US reported to the Food and Drug Administration between 1982 and 1991. Seven cases of fatal anaphylaxis, 24 cases of infections, 32 cases of hemorrhage, 32 cases of complications of a neurologic nature (clinically expressed as paraplegia, paraparesis, hemiparesis, and foot drop), and 15 cases classified as “miscellaneous events” (cardiac and respiratory complications) were reported. The overall mortality rate was 0.019% [65].

The account concluded that anaphylactic reactions were directly attributable to chymopapain, which is a known immunogen. Infections were the result of the lack of asepsis during the administration of the agent. Investigation of other adverse events did not yield any clear causality, but many were not considered likely to have resulted from chymopapain itself or to its administration [65]. This and similar reports serve to underscore the importance of careful patient selection and the attention to technique required to maximize the chances of a favorable outcome with chemonucleolysis [7].

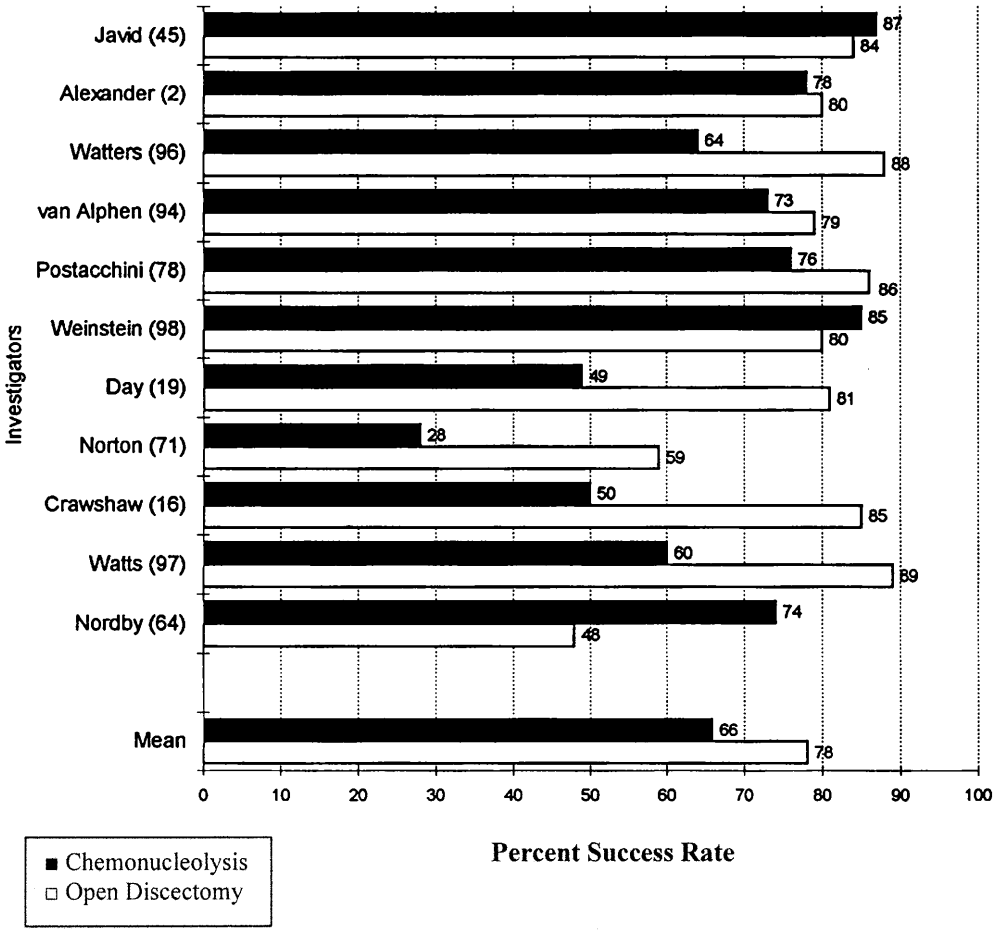

Fig. 7 Success rates published 1973–1992 in studies comparing chemonucleolysis and open discectomy, showing a mean (SD) overall success rate of chemonucleolysis of 66%± 17% versus a mean (SD) of 78%±13% for open discectomy

Pharmacology and toxicology

The work of Simmons and co-workers [86] with animal models helped to define the biochemical and toxicologic profile of chymopapain B (Chemolase) – especially with respect to the immunogenic reactions evoked by its intradiscal injection. Ensuing human clinical trials and clinical experience over more than a quarter of a century have served to further clarify the pharmacologic and toxicologic effects of this agent [25, 27, 30, 44]. Details of the metabolic process and the organic effects of chymopapain are provided in the report by Simmons and Nordby [84]. Borrowing from the work of Stem [91], an overview of chymopapain toxicology follows. Toxicology occurs through the proteolysis of capillaries or the glycosaminoglycan (GAG) structure. Mortality may result from systemic effects such as petechial hemorrhage or emboli, or may be due to intrathecal invasion and the increase in cerebrospinal fluid pressure this produces.

Laser disc surgery versus chemonucleolysis

Reports of a new technique for treatment of sciatica caused by disc herniation have recently surfaced in the medical literature. Automated percutaneous lumbar discectomy utilizes yttrium aluminum garnet (YAG) lasers to lyze the herniated nucleus pulposus. French researchers designed a randomized, multicenter trial to compare this new therapeutic modality with chemonucleolysis. Of 141 patients, 69 were treated with percutaneous lumbar discectomy and 72 underwent treatment with chemonucleolysis. Within 6 months of treatment, 37% of the patients in the automated percutaneous discectomy group required open surgery, in marked contrast to only 7% in the chemonucleolysis group. Observation at 12 months indicated an overall success rate for the percutaneous lumbar discectomy group of 37%. Among those who had undergone chemonucleolysis, the success rate was 66%. Complications rates among both collectives were low, with the exception of postoperative low-back pain, which was experienced by 42% of the chemonucleolysis group [79]. In addition to the evaluation of a new therapy, this trial con-

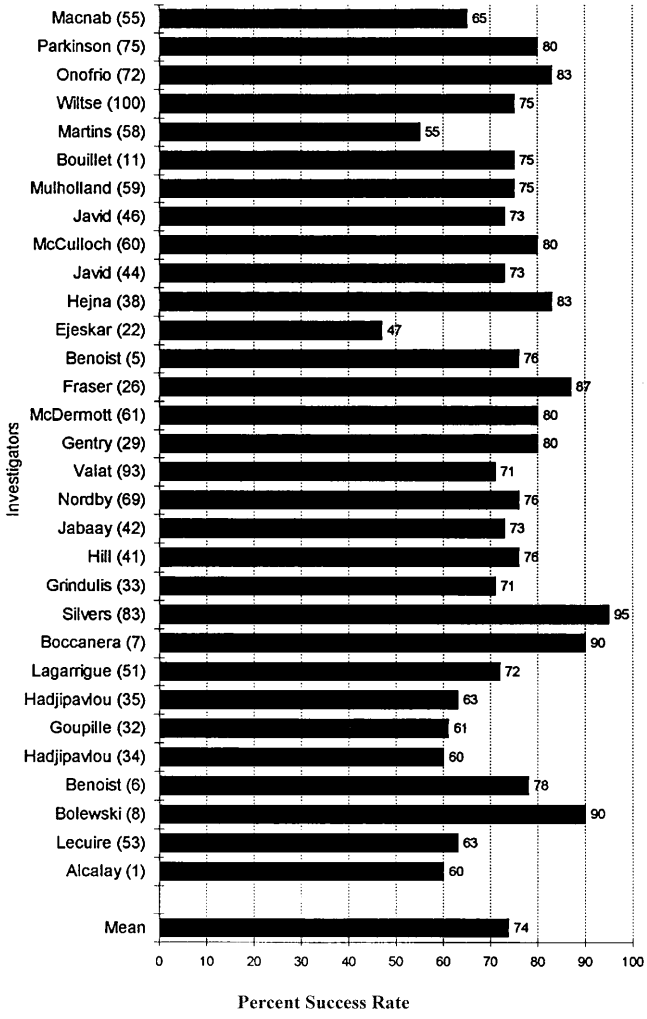

Fig. 8 Chemonucleolysis success rates published 1971–1994, showing an overall mean (SD) success rate of 74%±11%

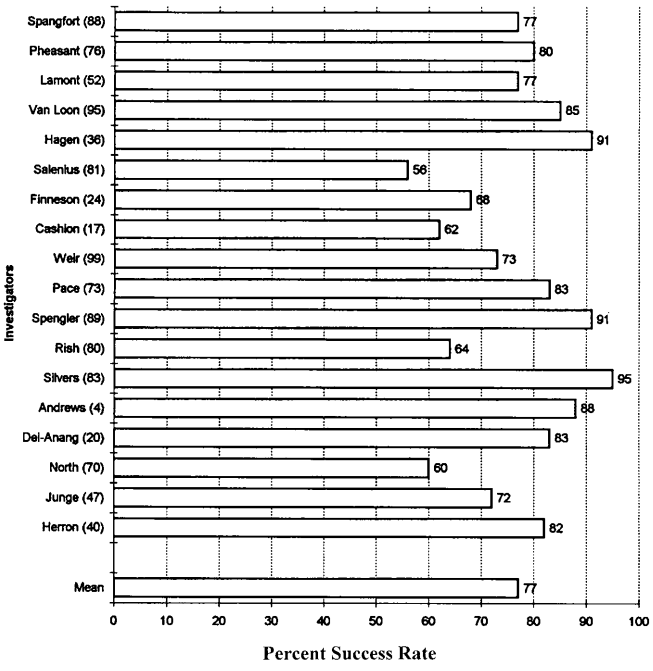

Fig. 9 Open discectomy success rates published 1972–1996, showing an overall mean (SD) success rate of 77%±12%

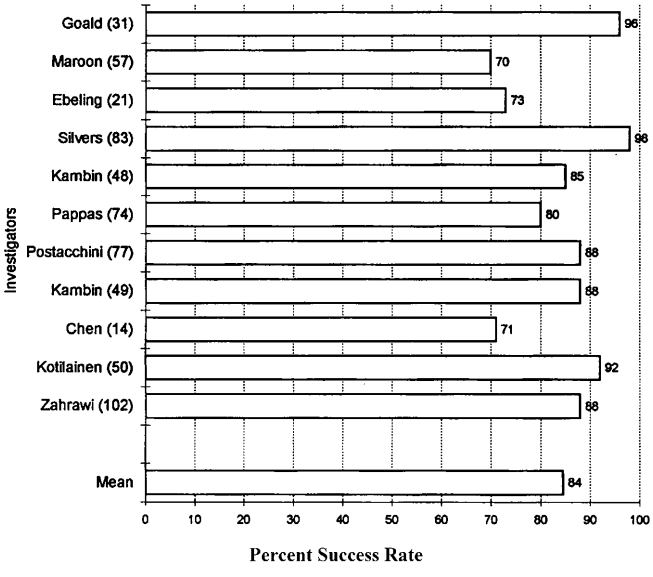

Fig. 10 Microdiscectomy success rates published 1978–1994, showing an overall mean (SD) success rate of 84%±10%

firms the results of previous controlled studies of chemonucleolysis.

Another investigation compared YAG laser discectomy (percutaneous lumbar discectomy, PELD), chemonucleolysis (CN), and automated percutaneous lumbar discectomy (APLD). One hundred patients from the same hospital were assigned to each group (*N*=300). They were assessed at 1 year after surgery by means of physical examination, plain lumbosacral radiographs, CT and MRI studies, and a self-assessment questionnaire. Sixty-eight percent of the patients in the PELD group regarded their outcome as excellent or good; 23% considered their outcome as fair. In the CN group, the corresponding figures were 55% (excellent to good) and 27% (fair); among those in the APLD group, ratings were 48% (excellent to good) and 32% (fair). Nine percent of the patients in the PELD group subsequently underwent open microdiscectomy or continued to suffer from back pain with sciatica, compared with 18% in the CN group and 20% in the APLD group. Better extraction of the herniated mass was possible with PELD than with APLD. PELD also resulted in a lower rate of back pain and a smaller decrease in disc height than CN [54].

Additional, controlled studies of these new therapies will be needed before they can be regarded as additional or replacement strategies in the treatment of sciatica associated with disc herniation.

Open discectomy and microdiscectomy versus chemonucleolysis

In studies comparing chemonucleolysis to open discectomy, the mean success rate (with standard deviation) was 66%±17% as compared with 77%±13% for open surgery (Fig. 7). In separately published studies, the mean success rate for chemonucleolysis was 74%±11% (Fig. 8), with a mean of 77%±12% for open discectomy (Fig. 9). When the two categories of reports were combined, the overall success rates were 72%±13% and 77%±12%, respectively. None of the standard deviations noted were statistically significant. The mean microdiscectomy success rate was higher, at 86%±9%, but nonetheless, this was not significantly different than the mean for the other procedures (Fig. 10).

Conclusion

With more than 30 years of clinical use, chemonucleolysis has become established as a safe, effective procedure for the treatment of sciatica secondary to disc herniation. In comparisons of adverse effects associated with chymopapain injection and open discectomy, chemonucleolysis rates as the safer procedure by far [65]. Experience has shown that the only true complication is anaphylaxis, which can be predicted by sensitivity screening and controlled with appropriate treatment [3]. Thorough consideration of patient selection, widespread testing for immunogenic potential and scrupulous technique remain the key factors to the successful outcome of a chemonucleolysis procedure.

References

1. Alcalay M, Chartier I, Garrouste O, et al (1994) Chemonucleolysis of disk hemiation with low back pain as the single symptom: 20 cases (in French). Rev Rhum Ed Fr 61:839–844
2. Alexander AH, Burkus JK, Mitchell JB, Ayers WV (1989) Chymopapain chemonucleolysis versus surgical discectomy in a military population. Clin Orthop 244:158–165
3. Alexander AH (1993) Chymopapain chemonucleolysis. In: Chapman MW (ed) Operative orthopaedics, 2nd edn. JB Lippincott, Philadelphia
4. Andrews DW, Lavyne MH (1990) Retrospective analysis of microsurgical and standard lumbar discectomy. Spine 15:329–335
5. Benoist M, Deburge A, Heripret G, Busson J, Rigot J, Cauchoix J (1982) Treatment of lumbar disc herniation by chymopapain chemonucleolysis. A report on 120 patients. Spine 7: 613–617
6. Benoist M. Parent H, Nizard M, Lassale B, Deburge A (1993) Hemiation of a lumbar disk in the elderly. Results of chemonucleolysis (in French). Rev Rhum Ed Fr 6:435–439
7. Boccanera L, Laus M (1990) Chemonucleolysis: advantages and disadvantages. Chir Org Mov 75:25–32
8. Bolewski J, Rudnicki SZ (1994) Chemonucleolysis in the treatment of lumbar discopathy (in Polish). Neurol Neurochir Polska 28:681–691
9. Boots Pharmaceuticals (1987) Periodic adverse drug experiences reported to the FDA on Chymodiactin. Boots Pharmaceuticals, Lincolnshire, Ilinois
10. Bosacco SJ, Bosacco DN, Berman AT, et al (1996) Functional results of percutaneous laser discectomy. Am J Orthop 25:825
11. Bouillet R (1990) Treatment of sciatica. A comparison of complications of surgical treatment and nucleolysis with chymopapain. Clin Orthop 251: 144–152
12. Bradford DS, Ocegema TR Jr, Cooper M, et al (1984) Chymopapain, chemonucleolysis, and nucleus pulposus regeneration: biological and biochemical study. Spine 9:135
13. Buckwalter JA (1995) Spine update. Aging and degeneration of the human intervertebral disc. Spine 20:1307
14. Chen ZR (1993) Arthroscopic microdiscectomy (in Chinese). Chun-Hua Wai Ko Tsa Chih [Chinese J Surg] 31:106–108
15. Choy DS (1992) Risks of laser discolysis. J Neurosurg 77:978
16. Crawshaw C, Frazer AM, Merriam WF, Mulholland RC, Webb JK (1984) A comparison of surgery and chemonucleolysis in the treatment of sciatica: a prospective randomized trial. Spine 9:195–198
17. Cashion EL, Lynch WJ (1979) Personality factors and results of lumbar disc surgery. Neurosurgery 4:141–145
18. Dabezies EJ, Langford K, Morris J, et al (1988) Safety and efficacy of chymopapain (disease) in the treatment of sciatica due to a herniated nucleus pulposus. Results of a randomized, double-blind study. Spine 13:561
19. Day AL, Savage DF, Friedman WA, Sypert GW (1986) Chemonucleolysis versus open discectomy: the case against chymopapain. Clin Neurosurg 33:385–396
20. Dei-Anang K, Weigand H, Mader U (1990) Is percutaneous discectomy an alternative to chemonucleolysis? Radiologie 30:70–74
21. Ebeling U, Reichenberg W, Reulen HJ (1986) Results of microsurgical lumbar discectomy. Review of 485 patients. Acta Neurochir 81:45–52
22. Ejeskar A, Nachemson A, Herberts P, Lysell E, Andersson G, Irstam L, Peterson LE (1983) Surgery versus chemonucleolysis for herniated lumbar discs. A prospective study with random assignment. Clin Orthop 174: 236–242
23. Feldrnan J, Menkes CJ, Pallardy G, et al (1986) Double-blind study of the treatment of disc lumbosciatica by chemonucleolysis [translated from French]. Rev Rhum Mal Osteoartic 53:147
24. Finneson BE (1978) A lumbar disc surgery predictive score card. Spine 3: 186–188
25. Fraser RD (1982) Chymopapain for the treatment of intervertebral disc herniation: a preliminary report of a double-blind study. Spine 7:608
26. Fraser RD (1984) Chymopapain for the treatment of intervertebral disc herniation. The final report of a double-blind study. Spine 9:815–818
27. Garvin PG (1965) Chymopapain: a pharmacologic and toxicologic evaluation in experimental animals. Clin Orthop 41:204
28. Garvin PJ, Jennings RB (1973) Long term effects of chymopapain on intervertebral discs of dogs. Clin Orthop 9:281

29. Gentry LR, Strother CM, Turxki PA, Javid MJJ, Sackett JF (1985) Chymopapain chemonucleolysis: correlation of diagnostic radiographic factors and clinical outcome. AJR 145:351–360
30. Gesler RM (1969) Pharmacologic properties of chymopapain. Clin Orthop 67:47
31. Goald HJ (1978) Microlumbar discectomy: follow-up of 147 patients. Spine 3:183–185
32. Goupille P, Cotty P, Fouquet B, Anger C. Betheuil V, Valat JP (1992) Long-term results of chymopapain chemonucleolysis (in French). Rev Rhum Mal Osteo Artic 59:809–812
33. Grindulis KA, Finlay DB, Nichol FE (1987) Chemonucleolysis of lumbar intervertebral disc prolapse with chymopapain: outcome after 1 year. Clin Rheumatol 6:42–49
34. Hadjipavlou A, Lander P, Antoniou J, Levine J, Dupuis P (1993) Chemonucleolysis. Its effectiveness in the treatment of lumbar diskopathies caused by compressive or rotational injuries (in French). Int Orthop 17:148–153
35. Hadjipavlou A, Lander P, Antoniou J (1992) The effect of chymopapain on low back pain. Orthop Rev 21:733–738
36. Hagen R, Engesaeter LB (1977) Unilateral and bilateral partial laminectomy in lumbar disc prolapse. A follow-up study of 156 patients. Acta Orthop Scand 48:41–46
37. Haines SJ (1985) The chymopapain clinical trials. Neurosurg 17:107
38. Hejna WF, Sinkor G (1983) Chemonucleolysis of herniated lumbar discs. Am Fam Phys 27:97–103
39. Hendry NGC (1958) The hydration of the nucleus pulposus and its relation to intervertebral disc degeneration. J Bone Joint Surg Br 40:132
40. Herron L, Turner JA, Novell LA, Kreif SL (1996) Patient selection for lumbar discectomy with a revised objective rating system. Clin Orthop 325:148–155
41. Hill GM, Ellis EA (1987) Chemonucleolysis as an alternative to laminectomy for the herniated lumbar disc. Clin Orthop 225:229–233
42. Jabaay GA (1986) Chemonucleolysis. Eight- to ten-year follow-up evaluation. Clin Orthop 206:24-31
43. Jansen EF, Balls AK (1941) Chymopapain: a new crystalline proteinase from papaya latex. J Biol Chem 137:459
44. Javid MJ, Nordby EJ, Ford LT, et al (1983) Safety and efficacy of chymopapain (Chymodiactin®) in herniated nucleus pulposus with sciatica: results of a randomized, double-blind study. JAMA 249:2489
45. Javid MJ (1995) Chemonucleolysis versus laminectomy: a cohort comparison of effectiveness and charges. Spine 20:2016–2022
46. Javid MJ (1980) Treatment of herniated lumbar disk syndrome with chymopapain. JAMA 243:2043–2048
47. Junge A, Frohlich M, Ahrens S, et al (1996) Predictors of bad and good outcome of lumbar spine surgery. A prospective clinical study with 2 years' followup. Spine 21:1056–1064
48. Kambin P, Cohen LF (1993) Arthroscopic microdiscectomy versus nucleotomy techniques. Clin Sports Med 12:587–598
49. Kambin P (1991) Arthroscopic microdiskectomy. Mt Sinai J Med 58: 159–164
50. Kotilainen E (1994) Microinvasive lumbar disc surgery. A study on patients treated with microdiscectomy or percutaneous nucleotomy for disc herniation. Ann Chir Gynaecol Suppl 209:1–50
51. Lagarrigue J, Lazorthes Y, Verdie JC, Richaud J (1991) Analysis of the results of surgery and nucleolysis using papain in 1085 cases of lumbar disk hernias (in French). Neurochirurgie 37:96–104
52. LaMont RL, Morawa LG, Pederson HE (1976) Comparison of disk excision and combined disc excision and spinal fusion for lumbar disk ruptures. Clin Orthop 121:212–216
53. Lecuire F, Jaffar-Bandjee Z, Basso M, Sorba L, Honore M, Rebouillat J (1994) Long-term result of lumbar disk chemonucleolysis (an 8- to 12-years follow-up (in French). Rev Chir Orthop Reparatrice Appar Mot 80: 468–475
54. Lee SH, Lee SJ, Park KH, et al (1996) Comparison of percutaneous manual and endoscopic laser diskectomy with chemonucleolysis and automated nucleotomy [translated from German]. Orthopade 25:49
55. Lockey RF, Benedict LM, Turkeltaud PC (1987) Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 79:660
56. Macnab I, McCulloch JA, Weiner DS, Hugo EP, Galway RD, Dall D (1971) Chemonucleolysis. Can J Surg 14:280–289
57. Maroon JC, Alba A (1985) Microdiscectomy versus chemonucleolysis. Neurosurgery 16:644–699
58. Martins AN, Ramirez A, Johnston J. Schwetschenau PR (1978) Double-blind evaluation of chemonucleolysis for herniated lumbar discs. Late results. J Neurosurg 49:816–827
59. Mulholland RC, Ravichandran G (1980) Chymopapain chemonucleolysis. A preliminary report. Spine 5: 380–384
60. McCulloch JA (1980) Chemonucleolysis: experience with 2000 cases. Clin Orthop 146:128–135
61. McDermott DJ, Agre K, Brin M, Demma FJ, Nelson J, Wilson RR, Thisted RA (1985) Chymodiactin in patients with herniated lumbar intervertebral discs. An open-label, multicenter study. Spine 10:242–249
62. Naylor A, Smare DL (1953) Fluid content of the nucleus pulposus as a factor in the disc syndrome. BMJ 2: 975
63. Naylor A (1962) The biophysical and biochemical aspects of intervertebral disc herniation and degeneration. Ann R Coll Surg 31:91
64. Nordby EJ, Lucas GL (1973) A comparative analysis of lumbar disc disease treated by laminectomy or chemonucleolysis. Clin Orthop 90: 119
65. Nordby EJ, Wright PH, Schofield SR (1993) Safety of chemonucleolysis. Adverse effects reported in the United States, 1982–1991. Clin Orthop 293: 122–134
66. Nordby EJ (1994) An orthopaedic surgeon's saga. Clin Orthop 307:260
67. Nordby EJ (1991) Chemonucleolysis. In: Frymoyer JW (ed) The adult spine. Principles and practice. Raven, New York, pp 1989–2008
68. Nordby EJ (1985) Diagnosis and patient selection. In: Brown JE, Nordby EJ, Smith L (eds) Chemonucleolysis. Slack, Thorofare, pp 45–60
69. Nordby EJ (1986) Eight- to 13-year follow-up evaluation of chemonucleolysis patients. Clin Orthop 206:18–23
70. North RB, Campbell JN, James CS, et al (1991) Failed back surgery syndrome: 5-year follow-up in 102 patients undergoing repeated operation. Neurosurgery 28:685–690
71. Norton WL (1986) Chemonucleolysis versus surgical discectomy: comparison of costs and results on workers' compensation claimants. Spine 11: 440–443
72. Onofrio BM (1975) Injection of chymopapain into intervertebral discs: preliminary report on 72 patients with symptoms of disc disease. J Neurosurg 42:384–388
73. Pace N, Pace P, Morici D (1980) Clinical valuation of late results of surgical therapy for protruded lumbar intervertebral disc. Arch Orthop Trauma Surg 96:91–94
74. Pappas CT, Harrington T, Sonntag VK (1992) Outcome analysis in 654 surgically treated lumbar disc herniations. Neurosurgery 30:862–866
75. Parkinson D, Shields C (1973) Treatment of protruded lumbar intervertebral discs with chymopapain (Disease). J Neurosurg 39:203–208

76. Pheasant H (1975) Sources of failure in laminectomies. Orthop Clin North Am 6:319–329
77. Postacchini F, Cinotti G, Perugia D (1992) Microdiscectomy in treatment of herniated lumbar disc. Ital J Orthop Traumatol 18:5–16
78. Postacchini F, Lami R, Massobrio M (1987) Chemonucleolysis versus surgery in lumbar disc herniations: correlation of the results of pre-operative clinical pattern and size of the herniation. Spine 12:87–96
79. Revel M, Payan C, Vallee C, et al (1993) Automated percutaneous lumbar discectomy versus chemonucleolysis in the treatment of sciatica. A randomized multicenter trial. Spine 18:1
80. Rish BL (1984) A critique of the surgical management of lumbar disc disease on a private neurosurgical practice. Spine 9:500–504
81. Salenius P, Laurent LE (1977) Results of operative treatment of lumbar disc hemiation. A survey of 886 patients. Acta Orthop Scand 48:630–634
82. Schwetschwenau PR, Ramirez A, Johnston J, et al (1976) Double-blind evaluation of intradiscal chymopapain for herniated lumbar discs. J Neurosurg 45:622–627
83. Silvers HR (1988) Microsurgical versus standard lumbar discectomy. Neurosurgery 22:837–841
84. Simmons JW, Nordby EJ (1995) Chemonucleolysis. In: White AH, Schofferman JA (eds) Spine care. Operative treatment, vol 2. Mosby-Year Book, St. Louis, pp 991–1001
85. Simmons JW, Stavinoha WB, Knodel LC (1984) Update and review of chemonucleolysis. Clin Orthop 183: 51
86. Simmons JW, Upman PJ, Stavinoha WB (1984) Pharmacologic and toxicologic profile of chymopapain B (Chemolase). Drug Chem Toxicol 7: 299
87. Smith L, Garvin PJ, Jennings RB, Gesler RM (1963) Enzyme dissolution of the nucleus pulposus. Nature 198:1311
88. Spangfort EV (1972) The lumbar disc hemiation. A computer aided analysis of 2,504 operations. Acta Orthop Scand Suppl 142:1–95
89. Spengler DM (1982) Lumbar discectomy. Results with limited disc excision and selective foraminotomy. Spine 7:604–607
90. Stem IJ, Smith L (1976) Dissolution of chymopapain in vitro of tissue from normal or prolapsed intervertebral discs. Clin Orthop 50:269
91. Stem IJ (1985) The biochemistry and toxicology of chymopapain. In: Brown JE, Nordby EJ, Smith L (eds) Chemonucleolysis. Slack, Thorofare
92. Tarlo SM, Shaik W, Bell B, et al (1978) Papain-induced allergic reactions. Clin Allergy 8:207
93. Valat JP, Eveleigh MC, Fouquet B, et al (1986) Chemonucleolysis in the treatment of disk lumbo-radiculalgia. Cooperative study of 333 cases (in French). Rev Rhum Mal Osteo Artic 53:467–471
94. Van Alphen HA, Braakman R, Bezemer PD, Broere G, Berfelo MW (1989) Chemonucleolysis versus discectomy: a randomized multicenter trial. J Neurosurg 70:869–875
95. Van Loon L, Hoogmartens M (1977) Results obtained with operative treatment of sciatica. Acta Orthop Belg 43:647–652
96. Walters WC, Mirkovic S, Boss J (1988) Treatment of the isolated lumbar intervertebral disc herniation: microdiscectomy versus chemonucleolysis. Spine 13:360–362
97. Watts C, Hutchison G, Stem J, Dark K (1975) Comparison of intervertebral disc disease treatment by chymopapain injection and open surgery. J Neurosurg 42:397-400
98. Weinstein J, Spratt KF, Lehmann T, et al (1986) Lumbar disc herniation. A comparison of the results of chemonucleolysis and open discectomy after ten years. J Bone Joint Surg Am 68:43–54
99. Weir BK (1979) Prospective study of 100 lumbosacral discectomies. J Neurosurg 50:283–289
100. Wiltse LL (1983) Chemonucleolysis in the treatment of lumbar disc disease. Orthop Clin North Am 14:605–622
101. Wiltse LL, Rocchio PD (1975) Preoperative psychological tests as predictors of success of chemonucleolysis in the treatment of the low-back syndrome. J Bone Joint Surg Am 57: 478–483
102. Zahrawi F (1994) Microlumbar discectomy. Is it safe as an outpatient procedure? Spine 19:1070–1074