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The Rise and Fall of Chemonucleolysis

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INTRODUCTION

The past four decades have witnessed the arrival of numerous interventional procedures for the treatment of sciatica and back pain. Some have failed to gain general acceptance and have simply faded away, and others continue to be used without evidence of efficacy. What is unique about chymopapain is that it has fallen out of favor despite convincing evidence of its utility and efficacy in the treatment of sciatica from lumbar disc protrusion. It has been shown to be superior to placebo in no less than three double-blind, randomized controlled trials *(1,2)*, and to be cost-effective with low morbidity when compared with open surgery *(3)*.

This chapter describes the circumstances and events leading to the rise and fall of chymopapain, exploring how commercial interests and emotional influences have overridden substantial scientific evidence of efficacy and safety *(4–7)*. Much of this account describes information that has already been published extensively, but some of it emphasizes details not well known but considered important in the overall context, particularly from a historical perspective.

The attraction for the use of chymopapain as a proteolytic agent for the treatment of herniated nucleus pulposus (NP), is readily understandable and its introduction and rise to prominence are covered in some detail in this chapter. On the other hand, the factors leading to the demise of chemonucleolysis are less well documented in the literature but are equally apparent in light of events to be described.

The use of chymopapain B in the treatment of problems related to the disc is probably one of the most critically appraised invasive procedures involving a pharmaceutical drug that we as clinicians have dealt with. However, in spite of extensive evidence that supported safety and efficacy leading to worldwide use, the product suffered a demise that occurred without a satisfactory official explanation. What follows is an account of the history of chymopapain followed by an assessment of the factors leading to its removal from clinical use.

Eugene Jansen and Arnold Balls isolated chymopapain in 1941 from the crude latex derived from the fruit of carica papaya by "milking" the green papaya fruit while on the plant prior to harvest *(8)*.

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Lewis Thomas was seeking an enzyme that would reduce circulating protein in blood that clogged the renal tubules resulting in renal shutdown, as enzymatic activity cannot be produced by known chemical methods and has to be obtained by way of naturally occurring biologicals. In 1956, he injected rabbits intravenously with crude papain and noticed that their ears drooped. Forty-eight hours later, the rabbits'ears resumed their erect posture. This indicated a reversible action on the chondral intracellular substance of the ears. It was also noted that the trachea softened, but there was no effect on any other tissue in the rabbit. It was particularly of interest that

> apart from the unusual cosmetic effect, the animals exhibited no evidence of systemic illness or discomfort. The ears had replenished their basophilic chondroid matrix allowing them to regain their original shape. Larger doses of papain were injected and had an impact on joint cartilage, epiphyseal growth plates, and tracheal and bronchial cartilage; however, no systemic problems were found to be present *(9)*.

Lyman Smith first thought that could papain might be of value in treating chondroblastic tumors. Although this did not prove worthy, he found that intradiscal injections in rabbits removed the NP, leaving the annulus largely intact *(10)*.

Prior to this, Carl Hirsch had the concept of injecting a specific enzyme into the intervertebral disc but not specifically for the treatment of disc herniation *(11)*. He reasoned that an intradiscal injection of a chondrolytic enzyme would cause the disc to become stable and asymptomatic by accelerating the process of disc degeneration. He had envisioned an enzyme similar to that produced by bacteria as is seen in infectious processes. Other proteolytic enzymes were investigated and found to have a similar effect on the disc tissue, but toxicological studies revealed chymopapain to be the least toxic and to have the most specific action on the mucopolysaccharide of the intervertebral disc. Other proteolytic enzymes such as collagenase were advocated *(12)*. Extensive research with collagenases proved it not to be "safe and effective."

Subsequently, Smith sold the patent for chymopapain to Baxter-Travenol for $. The company then formulated a product called Discase, which was a combination of chymopapain B, cysteine sodium sulfite, and EDTA in lyophilized form. During the period of the first phase of investigation, it was used in 10 patients in Switzerland in 1963, and by 1975, 35 of us as investigators in a phase 3 trial had injected approx 17,000 patients.

A controversial study done at Walter Reed Army Medical Center in 1975 triggered the withdrawal of the New Drug Application that had been filed with the Food and Drug Administration (FDA) for the use and treatment of intervertebral disc disease with Discase *(13)*. The study reported no statistical difference in instance or quality of improvement between the placebo group (29% success rate) and the group treated with Discase (58% success rate). Baxter-Travenol voluntarily withdrew the drug, rather than take the chance of rejection by the FDA. Although Brown and Daroff *(14)* criticized the Walter Reed Army Medical Center study because of the early code break, the lack of inert placebo, the insufficient dose of Discase, and the lack of technical experience, the drug continued to be unavailable for use in indicated patients. Physicians in the United States who had been using the drug with excellent results were disheartened that no effort appeared to be being made toward an FDA approval. Investigational use continued throughout most of the world, particularly in Australia and in England. Yugoslavia had produced a product (Lekopain) that was basically a chymopapain B and was widely used in the Eastern bloc countries and, to a lesser extent, in France and Italy with favorable results.

On October 15, 1975, Baxter-Travenol withdrew its new drug application for chymopapain from the FDA, effectively removing the drug from use in the United States *(15)*. Patients desiring chemonucleolysis with chymopapain were forced to seek treatment in Canada, where the drug was commercially available. In early 1977, a coalition of American physicians interested in making chymopapain available to patients was formed and chartered the Committee Advocating the Development and Use of Chymopapain to Eliminate Unnecessary Surgery (CADUCEUS). This group pursued legislative approaches to reactivate the withdrawn new drug application and even considered submitting its own application. For several years, the group worked diligently to gain national approval. However, in the late 1970s, other groups seeing little progress in the national trust began to explore state legislative approval to allow the production and use of chymopapain at the suggestions of CADUCEUS. Illinois, Indiana, and Texas all had legal vehicles to allow such interstate use, but of these states only Texas had the environment that would support growth of the raw materials. This was of critical importance, because according to FDA regulations all materials had to be available within the state and not cross-state boundaries. Subsequently, the State of Texas was granted approval for local manufacture of chymopapain preparation under the Food, Drug & Cosmetic Act. The product Chemolase produced in Texas was used from January 1980 until approval by the FDA of Chymodiactin® in 1982. Although the Texas group attempted to get FDA approval of Chemolase, it was apparent that only Chymodiactin would be approved. Without FDA approval for national distribution, the production of Chemolase was discontinued.

During the use of Chemolase *(16,17)*, orthopedic surgeons and neurosurgeons and 919 patients participated in an open-label uncontrolled clinical trial involving the use of chymopapain (Chemolase) in Texas from 1980 to 1982. Patients admitted to the study had persistent low-back pain or sciatica owing to protrusion, extrusion, or degeneration of the lumbar intervertebral disc that was not responsive to conservative management. Although the study was not specifically designated to assess safety and efficacy, it did allow retrospective analysis of these entities following intradiscal administration of chymopapain. Patients were considered candidates for the study if a myelogram or computed tomography scan suggested lumbar disc disease and specific clinical signs of lumbar disc disease were present. The dose of chymopapain most frequently used ranged from 3000 to 4000 U/disc. Responses to chemonucleolysis were assessed at 1, 3, or 6 mo after injection, depending on patient and physician adherence to the protocol. Patients' responses were assessed by point reduction systems that were deducted from an initial patient score of 10, based on the presence of various levels of discomfort or limitations of daily activities. Based on the point scores, patients' responses were categorized as poor, fair, good, or excellent. Fair, good, and excellent responses were considered treatment successes. Of the 919 patients who underwent chemonucleolysis with chemolase (chymopapain B), 408 were evaluated 1, 3, or 6 mo after injection by a physician. An independent biostatistician reviewed all of the data and performed the statistical analysis. Fifty-five percent of patients received injections in a single intervertebral disc, and the remainder in two to four discs. Success rates were 93% 1 mo after injection, 92% at 3 mo, and 93% at 6 mo. An unusual finding was observed when the effect of different variables on treatment efficacy was analyzed. Significantly lower response rates were found for Hispanics,

blue-collar workers, and patients covered by workers'compensation insurance in the categories of race, occupation, and type of insurance coverage, respectively. In the other 511 patients, either the patient did not report for follow-up examinations or the follow-up evaluation was not recorded appropriately for evaluation of efficacy. For the 919 patients who received chymopapain by intradiscal injection, 70 adverse reactions were noted in 46 patients (5.0%). Erythema was the most common side effect, occurring in 1.8% of patients. The most serious reaction was anaphylaxis, which occurred in 1.1% of patients; however, based on the individual physician assessment, severe anaphylactic reactions were reported in only 0.54% of patients. All patients were managed medically without lasting effects. Giant urticaria, hypotension, and paraspinal muscle spasm occurred at similar frequency. Back pain was reported in only 0.4% of the treated patients. No deaths occurred. Although more sophisticated studies have since been done, the Texas study provides additional support for the safety and efficacy of chymopapain chemonucleolysis in the treatment of low-back pain and sciatica of discogenic origin that do not respond to more conservative management.

In 1979, Baxter-Travenol began a blinded study of chymopapain vs cysteine-edetate-iothalamate (CEI) or saline control, which allowed patients to have a laminectomy in the United States or go to Canada as a control. Patients during that period had a choice of having a laminectomy in the United States, going to Canada for chemonucleolysis, or going to Canada for chemonucleolysis if they had a placebo failure. It was apparent that significant difficulty was encountered in accumulating adequate numbers of trial participants. The results were finally published in 1998. One hundred seventy three participants at 25 locations reported 71% success with Discase compared with 45% with CEI *(13)*. More sophisticated studies were being done in Australia. Immunological, vascular, and neurological complications as well as discitis have all been discussed scientifically in detail, along with the risk of mortality *(18)*.

Was the fall from favor of chymopapain simply the result of adverse reports about complications, even though as reported in this chapter such reports were not well founded? If the answer to this question is "yes" it is a sad misconception on the part of the treating physicians as well as the patient population. Could it have been an administrative decision? We know that the FDA license to produce and sell Chymodiactin went from Smith to Baxter-Travenol and was separated off later into a company called Omnis. Boots Pharmaceutical acquired Omnis, thereby obtaining the license from Baxter-Travenol, and the next step in this procession was for Knoll Pharmaceuticals to purchase the license from Boots *(19)*. The license to manufacture and sell chymodiactin was subsequently sold to Abbott along with other pharmaceutical products. It was Abbott'decision, in about 1999, to discontinue the manufacture of Chymodiactin, thereby making it unavailable for use.

The official explanation for the discontinuation of the manufacture of Chymodiactin has yet to be obtained. However, the factors influencing the downfall can be summarized as follows:

- *Income*: Chemonucleolysis with chymopapain competed with discectomy, a surgical procedure that was the main source of income for many surgeons. This led, unfortunately, to biased and unfavorable comments being made by those with a vested interest in its demise.
- *Inappropriate patient selection*: It is apparent that chymopapain was being used to treat patients who were not good candidates for discectomy. To quote Ian Macnab (*personal communication, 1977*), a leading authority on the treatment of lumbar disc disease in the

1970s, "If a surgeon cannot get good results with chymopapain he should not be operating on the spine!"

- *Poor technique leading to complications*: In 1984, during the first few months following the release of Chymodiactin in the United States, approx 8000 orthopedic surgeons and neurosurgeons attended 1-d training courses. It is apparent that this alone was inadequate training for a percutaneous interventional technique that demanded precision for its safety and efficacy.
- *Fear of litigation*: This was generated to a large degree by the much-publicized complications that resulted in part from poor training in technique.
- *Competition from the introduction of the automated nucleotome*: This is a device that allowed removal of disc tissue; hence, the procedure achieved greater initial acceptance by surgeons.
- *Change in attitude to early rehabilitation following disc surgery*: The practice of early ambulation and early hospital discharge after disc surgery, first introduced in the early 1990s, reduced the advantage in cost-effectiveness of chemonucleolysis.
- *Use of targeted epidural steroids*: Posterior epidural steroids were of lesser therapeutic value in the treatment of lumbar disc prolapse and did not greatly compete with chemonucleolysis. The increased success of foraminal epidural steroids *(20)*, whereby the solution was delivered to the affected root canal with image intensifier guidance, greatly lessened the number of patients being considered for chemonucleolysis.

In all probability these factors combined to reduce dramatically the use of Chymodiactin to the point where the manufacturer made a commercial decision to remove the product from the market.

Dr. Lyman Smith addressed most of the questions and doubts regarding the use, safety, and efficacy in the following three personal communications:

In April 1987, a report on chemonucleolysis was aired on the ABC program *20/20*. Timothy Johnson, MD, ABC News medical editor, conducted this report, and the following is quoted from a letter written to Dr. Johnson by Lyman Smith, MD, dated August 27, 1990, in response to his report.

> Chemonucleolysis is widely used in Europe. The explanation for this is that surgeons in Europe are commonly on salaries and contingency fees for plaintiff lawyers are illegal. Clearly, the health care crisis in this country today has reached extraordinary proportions. We cannot afford to overlook effective alternatives to dangerous and costly invasive surgery.
>
> Your report on Chemonucleolysis, which aired on the "20/20" program, in April 1987, condemned thousands of individuals suffering from disc disease in the United States to unnecessary major surgery. Due to your blasted and inaccurate report, very little of which was substantiated by facts, use of Chymopapain fell precipitously (40% in the two months following the program).
>
> The result was that either more invasive laminectomy or the percutaneous automated discectomy procedure, touted on the program (and since proven a therapeutic failure), were utilized far more often than the less dangerous and less costly Chemonucleolysis.
>
> Further, your reference to Chemonucleolysis causing acute transverse myelitis (ATM) has been proven to be unfounded. The appearance of these reported six cases of alleged acute transverse myelitis was devastating. As with other severe conditions following any procedure in the United States, the patient records were sealed and access to them denied. Rumors were the natural consequences. Symptoms in all but one of the cases appeared two to three weeks after apparently successful treatments with Chymopapain. In that one case, symptoms appeared shortly after treatment and got worse as time went on. All had flaccid paralysis and none developed signs of spastic paralysis, a characteristic of transverse myelitis. At the time

of diagnosis, one patient had a suggestive history of multiple sclerosis and another later developed clear evidence of this disease. One had a history of viral infection before treatment and another was diabetic. The other, Mr. Devletsah, who appeared on "20/20", only developed paralysis after laminectomy following Chemonucleolysis. This, the causes of paralysis in these six patients are far from certain. Some could have been due to inept injections and others to causes other than the enzyme or the procedure. Finally, it may interest you to know the ATM has been reported in Australia after intradiscal injection of saline and another, in this country, following removal of an intramedullary nail. Other causative agents were sought in these and other comparable cases. Why should this not have been done in the case of a useful and effective therapeutic agent such as Chymopapain?

Statistics show that Chemonucleolysis is a valid and effective alternative to surgery. I would be delighted to review these data with you. These findings are certainly newsworthy and something your audience will be interested in."

On August 27, 1990, a telephone conversation was held between Dr. Lyman Smith and Dr. Helene M. Cole, senior editor of *JAMA*. After their conversation, Dr. Smith sent Dr. Cole his rebuttal to the Diagnostic and Therapeutic Technology Assessment (D.A.T.T.A.) *(21)* on chemonucleolysis, published in *Clinical Orthopaedics and Related Research*.

D.A.T.T.A. Statement #3: "Even small intrathecal leaks of Chymopapain have a potential for damage to the central nervous system."

REBUTTAL: Chymopapain will cause bleeding from the capillaries of the pia arachnoid, which are not protected by collagen, as are larger blood vessels. Large doses will cause enough bleeding to raise C.S.F. pressure to unacceptable levels and the animal will die. The toxic effect is purely a pressure phenomenon. If a spinal tap is done early to relieve the pressure, the animal will survive without a following neurological deficit. Small amounts do not damage the central nervous system. The L.D. 50 in Rhesus monkeys, for example, is 1000 units per kilogram. Fifty units are therapeutic. *(22)*

The following is a quote from a letter dated September 4, 1990, to Prof. Alf Nachemson, Department of Orthopaedics, Gothenburg University, Sweden, from Dr. Lyman Smith, in response to statements made by Prof. Nachemson during a symposium published in *Contemporary Orthopaedics (23)*.

I have just been saddled with a sever diagnosis leaving a poor prognosis; so I wish to clear the air with you. You are basically a great scientist, however, some of your biased statements on Chemonucleolysis throughout the years have bordered on the ridiculous.

In 1961, I began work with Baxter Laboratories on the ceramics and after awhile, I told the Director of Research about the rabbits. He was interested and we formed a research team—the million-dollar question to be pursued: "Was papain the best enzyme and was it safe? You know the rest of the story!

In the British Journal of Bone and Joint Surgery, February 1959, Carl Hirsch theorized as follows: "Sooner or later a substance may be found by which a degenerated disc could be transformed. It might be possible to create a chemolytic enzyme that, injected into a disc, would cause a connective tissue reaction." As you know, Chymopapain does not act in that sclerosing fashion. Carl came to my hospital in Elgin on November 6, 1968, with Jorge Galante and we examined some patients and viewed the x-rays of the first 80 patients I had injected. The only other investigators at the time were Lee Ford and Leon Wiltse. Carl seemed favourably impressed; it's a shame that impression did not wash off upon you!

You continue to quote your poor results with Chymopapain obtained with partially inactivated DISCASE, "Surgery versus Chemonucleolysis for Herniated Lumbar Discs," Clinical Orthopaedics, No. 174, April 1983. I pointed out to you then that the Chymopapain had been shipped to you from the United States without being refrigerated. DISCASE, unlike the present version, CHYMODIACTIN, was sensitive to heat. Mulholland

> of Nottingham received the same shipment and complained that laminectomies on the failed patients showed little or no action of the enzyme. Active enzyme would have led to an accurate study!
>
> Chemonucleolysis is neater, quicker, safer, cheaper, and if performed on an ideal patient, as effective as any invasive mechanical procedure. Prove me wrong!"

A citizens' petition was made to the FDA February 8, 2002, to determine whether the drug was withdrawn from sale for reasons of safety and effectiveness. A response to the citizens' petition was received January 27, 2003, stating that

> the FDA has reviewed its records and has determined that Chymopapain 10,000 units/vial injections (Chymodiactin), NDA 18-663, was not withdrawn from sale for reasons of safety or effectiveness. FDA will maintain Chymopapain 10,000 units/vial injections in the "discontinued drug product list" of approved drug products with therapeutic equivalence evaluations (the orange book). *(24)*

Whatever the reasons for discontinuation of the manufacture of Chymodiactin, it was not for safety and effectiveness. "The results of Chemonucleolysis depend not only on the enzyme, but more importantly on the diagnostic acumen of clinician. If you can't get a good result from Chemonucleolysis you shouldn't really be allowed to operate on backs." Chymopapain continues to be unavailable for use in the United States *(25)*.

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