CHEMONUCLEOLYSIS

ANATOMICAL, RADIOLOGICAL AND CLINICAL ASPECTS

J.G. Konings

CHEMONUCLEOLYSIS
Anatomical, radiological and clinical aspects

STELLINGEN

I

De lichamelijke toestand van patiënten enkele jaren na een radiculair syndroom op basis van een hernia nucleï pulposi lumbalis is, behoudens complicaties, onafhankelijk van de voorafgaande behandeling.

II

Epidurale fibrose na chemonucleolysis is zeldzaam.

III

De exacte wijze waarop chemonucleolysis het radiculaire prikkelingsbeeld kan doen verdwijnen, is tot dusver niet opgehelderd.

IV

In geval van een recidief radiculair syndroom na discectomie is beeldvorming door middel van magnetische resonantie (MRI) met gebruik van gadolinium het onderzoek van keuze om littekenweefsel van een hernia te kunnen onderscheiden.

V

Bij instabiliteit van het glenohumerale gewricht met onduidelijke etiologie dient een stabiliteitsonderzoek en arthroscopie van de schouder vooraf te gaan aan een stabiliserende operatieve reconstructie.

VI

De biologische waarde van de osteochondrale "allograft" is nog onduidelijk.

VII

Histologisch onderzoek alleen kan niet leiden tot een goed gefundeerd oordeel over het resultaat van een meniscustransplantatie.

VIII

Voor de detectie van meniscuslaesies is MRI een zeer sensitief maar weinig specifiek onderzoek.

IX

Een dilemma in de transplantatie chirurgie van pancreas of van eilandjes van Langerhans is het feit dat enerzijds de huidige risico's van de ingreep het uitvoeren van een transplantatie bij jeugdige diabetes patiënten niet rechtvaardigen, terwijl anderzijds bij patiënten met lang bestaande diabetes de late complicaties door een transplantatie niet kunnen worden ongedaan gemaakt.

X

Ook voor de Westeuropese landen geldt, dat het medisch denken en (be)handelen niet alleen op zuiver wetenschappelijke gronden berust, maar in belangrijke mate beïnvloed wordt door nationale geaardheid en denkwijze.

XI

Het rekruteren van werkloze vrouwen met HAVO-diploma, al of niet met "bijspijker"cursus wiskunde, om in een slechts twee jaar durende deeltijd opleiding te worden omgeschoold tot lerares wiskunde tweede graads, teneinde het tekort aan gekwalificeerde leerkrachten te compenseren, moet als een noodsprong worden beschouwd en zal de kwaliteit van het wiskunde onderwijs niet ten goede komen.

XII

Het grootste milieuprobleem is, dat velen het milieu nog niet serieus genoeg nemen.

XIII

In het kader van gezondheidsbevordering, milieubescherming en filebestrijding verdient het overweging om een forfaitaire reiskostenaftrek alleen voor het gebruik van de fiets te laten gelden.

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To Els
Saskia, Leonie
and Jorrit

Table of contents

1. Introduction and objectives

1.1. GENERAL INTRODUCTION

Degenerative changes in the lumbar spine and its sequelae are the cause of many problems and much discomfort for patients and society. The degenerative aging process of the spine is a normal natural development in every person (Kirkaldy-Willis et al. 1978) but the beginning of this process may vary and can even start in childhood (Russwurm et al. 1978, Gibson et al. 1987). There is general agreement about its multi-factorial etiology, but the relative contribution of single factors is often hypothetical. Although all the anatomical structures in the spine may show degenerative changes, more and more evidence has been gathered that pathology of the intervertebral disc is the most important factor in low back pain (Vanharanta et al. 1988). Disc degeneration may cause symptoms, as has been shown in recent studies using provocative CT-discography (McCutcheon and Thompson 1986, Vanharanta et al. 1987, Calhoun et al. 1988). Except for (single level) spinal fusion in some selected cases of primary disc degeneration, treatment is mainly conservative (exercises, ergonomic measures, etc.). Compression of dural sac or nerve roots by a prolapsed disc is a secondary consequence of this degenerative process and often leads to a radicular syndrome and rarely to a cauda syndrome (Spangfort 1972).

In most patients, the radicular symptoms resolve spontaneously or respond favourably to conservative measures. In the small group of patients whose symptoms persist or are very severe and hard to bear, an attempt can be made to alleviate or abolish the pain using a number of different treatment modalities. Lumbar discectomy, which was introduced by Mixter and Barr (Mixter and Barr 1934), has withstood the test of time. However, the consequences of fibrotic changes in the epidural space and back pain due to muscle trauma and/or laminectomy, led to the introduction of microdiscectomy by Williams in 1973, in an attempt to reduce the surgical trauma to these delicate structures (Williams 1978).

Hirsch was the first to suggest using a 'chondrolytic enzyme' for intradiscal therapy in order to accelerate disc degeneration and resolve the secondary symptoms (Hirsch 1959).

In 1963, it was Smith who introduced enzymatic discolysis with chymopapain ('chemonucleolysis') to clinical practice, as an alternative to lumbar disc surgery (Smith et al. 1963). Over the following twenty-five years this method of treatment became the subject of many chemical, biomechanical and clinical studies in numerous publications and books (Ford 1977, Braun 1981, McCul-

lough and McNab 1983, Brown 1983, Simmons et al. 1984, Nordby 1986, Dekker 1987).

As a result of adverse reactions caused by incorrect use, chemonucleolysis fell into disfavour for some years, but is presently receiving renewed interest as an alternative to surgery (Leary 1989).

Recently, percutaneous (automated) discectomy, another method of treatment for lumbar disc herniation, has gained some degree of popularity because it avoids the risk of epidural fibrosis after surgery and the risk of anaphylaxis in chemonucleolysis.

However, this method, which was introduced by Hijikata in 1975 (Hijikata 1975) and improved by Onik (Onik et al. 1985), seems to have only limited indications (Castro 1989).

Consequently, at present it appears that we can only offer patients a choice between (micro)discectomy and chemonucleolysis in the second phase of treatment for the (uncomplicated) lumbar disc herniation.

Despite the numerous studies which have already been performed on the possible modes of action of chymopapain, the mechanism by which it resolves radicular symptoms is still unclear. Discussions on the effectiveness of chemonucleolysis have not subsided completely, but the overwhelming number of publications showing its efficacy cannot be ignored (Simmons et al 1984, Van Leeuwen 1989).

As many questions still remain unanswered, we initiated various studies in 1984 to investigate the field of technique, the fate of the disc herniation after chemonucleolysis and the clinical results in the long term.

1.2. AIMS

The objectives of the three studies reported in this thesis are:

I. To study the needle position in the lateral approach to lumbar discs in postmortem lumbar spines and to make recommendations for optimal needle placement.

II. A. To perform a prospective study using CT on patients with a herniated lumbar disc treated with chymopapain and to discover possible changes after chemonucleolysis that can be demonstrated by CT.

B. To establish correlations between the clinical outcome, conventional radiological changes and CT changes after chemonucleolysis.

III. To answer the following questions:

A. What has been the effect of chemonucleolysis treatment in a large consecutive group of (Dutch) patients?

B. What is the condition or situation of these patients in the short-term (1.5 - 4 years) and long-term (5.5 - 8.5 years) after chemonucleolysis?
C. What are the residual complaints after chemonucleolysis in the long-term and are they comparable to the residual symptoms after other treatment modalities reported in the literature?

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2. Topographic anatomical aspects of lumbar disc puncture

2.1. INTRODUCTION

In recent years, more complications besides anaphylactic reactions have been attributed to chemonucleolysis (Buchman et al. 1985, Dyck 1985, Cusick et al. 1987). Some of the neurological complications may be the result of an incorrect needle placement technique during lumbar disc puncture (Smith Laboratories 1984), with violation of the subarachnoid space or nerve root sheaths.

In 5% to 10% of the patients, conjoined roots, cyst-like conditions and dilatations of lumbosacral nerve root sleeves are observed, located especially in the lower lumbar and sacral roots at the level of the posterior root ganglion in the foramen (Capesius and Babin 1978, Kadish and Simmons 1984). It is very important not to penetrate the intervertebral foramen, because puncture of the dural sac or nerve root sheath can lead to communication between the disc and subarachnoid space (Dabezies and Murphy 1985, Houser et al. 1986). Additionally, it is also important not to puncture the nerve root (Watts 1977), the lumbar plexus, spinal artery and the visceral contents, such as the colon. Therefore, disc puncture in chemonucleolysis as well as in percutaneous discectomy, requires a thorough knowledge of topographic anatomy.

The purpose of this study was to arrive at recommendations regarding how to avoid puncturing nerve roots and/or penetrating the foramen, by assessing the needle position in the lateral approach in relation to the foramen, facet joint, and nerve root.

2.2. MATERIAL AND METHODS

2.2.1. **Dissection and microplaning study**

Firstly, the parameters of needle placement were studied on three postmortem lumbar spines. The needles were inserted under fluoroscopic control in cadaveric discs L4-L5 and L5-S1 at 8 cm and 10 cm from the midline.

Two lumbar spines were studied by dissection. In one lumbar spine specimen, the needles were replaced by small catheters (Fig. 2.1) and this specimen was studied using CT (Fig. 2.2) and microplaning techniques (Laboratory for Anatomy and Embryology, University of Groningen, The Netherlands).

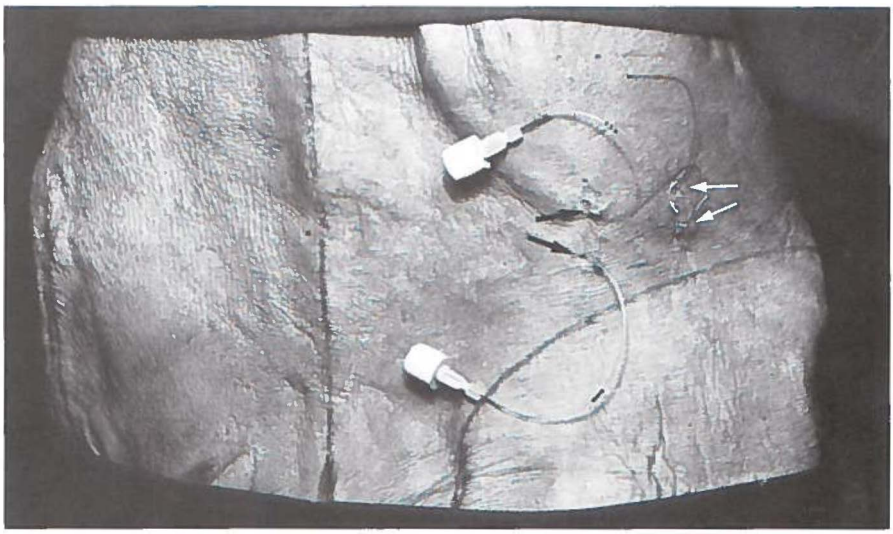

Fig. 2.1. Lumbar spine specimen. Needles inserted at 8 cm (arrows) and at 10 cm (white arrows) from the midline in discs L4-L5 and L5-S1 were replaced by small catheters.

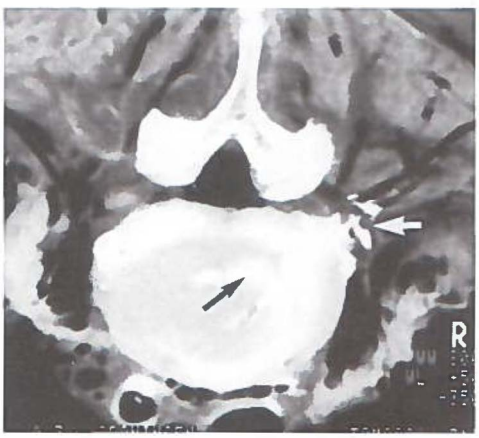

Fig. 2.2. CT scan of lumbar spine specimen at disc level L4-L5. Discography (arrow) and leakage of contrast after injection (white arrow).

2.2.2. **CT study of needle placement**

In the second part of the study, the parameters of lumbar intervertebral disc puncture were measured on the CT scans of 30 patients, taken in the disc plane at disc level L4-L5 and L5-S1 (Fig. 2.3 and Fig. 2.4). The projected needle direction on the scan was chosen in such a way that trauma to the colon, lumbar plexus, nerve root and penetration of the foramen were avoided. In this position, the site of insertion and the angle of approach were measured, as well as the distance to the centre of the nucleus in that particular patient.

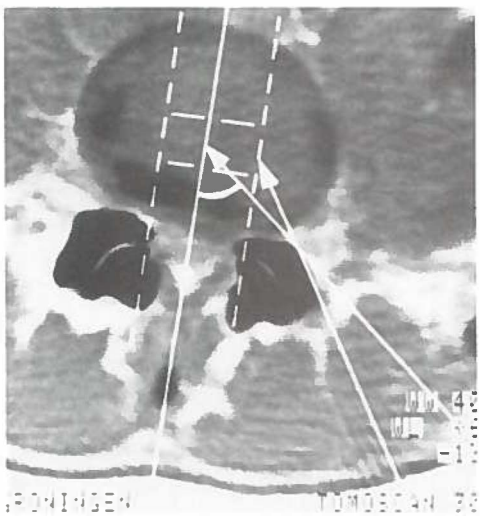

Fig. 2.3. CT scan in the plane of disc level L4-L5. Two needle placements are outlined: one with the tip of the needle in the exact centre of the nucleus, the other just in the margin of the nucleus.

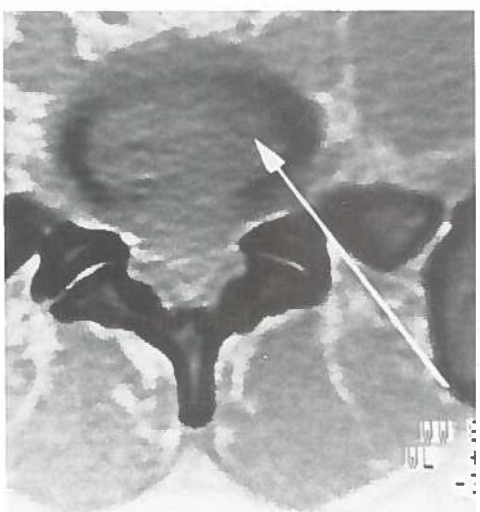

Fig. 2.4. CT scan in the plane of disc level L5-S1. If a high iliac crest is present, needle placement with a straight needle often occurs in the margin of the nucleus.

2.3. RESULTS

2.3.1. **Topographic anatomical aspects**

In the lateral approach, the needle pierces the thoracolumbar fascia and the erector spinae muscles, passes laterally to the multifidus muscle and pierces the lateral intertransverse muscles. In this intertransverse plane, as well as at the posterior angle of the disc, puncture of the ascending and intervertebral veins is often inevitable. The ventral ramus of the spinal nerve leaves the spinal canal via the superior part of the foramen and runs obliquely forwards, downwards and laterally, anterior to the intertransverse muscles and between the interspaces of the psoas muscle fibers.

The nerve root passes the level of the disc at the posterolateral border of the intervertebral disc. At disc level L4-L5, the branches of the lumbar plexus lie 1 cm anterolateral to this root and aside of the disc.

Fig. 2.5. In this lumbar spine specimen of a woman of slender build, the needle inserted at 8 cm from the midline at disc level L4-L5 punctured a branch of the lumbar plexus (arrow).

In one of the three lumbar specimens (a woman of slender build), it was observed that the needle which had been inserted 8 cm from the midline at disc level L4-L5, had punctured a branch of the lumbar plexus (Fig. 2.5). In a second specimen of a person of average build who was studied using microplaning, the findings were similar at disc level L4-L5 after needle insertion at 10 cm from the midline, whereas the needle which had been inserted at 8 cm, had punctured the emerging L4 nerve root (Fig. 2.6).

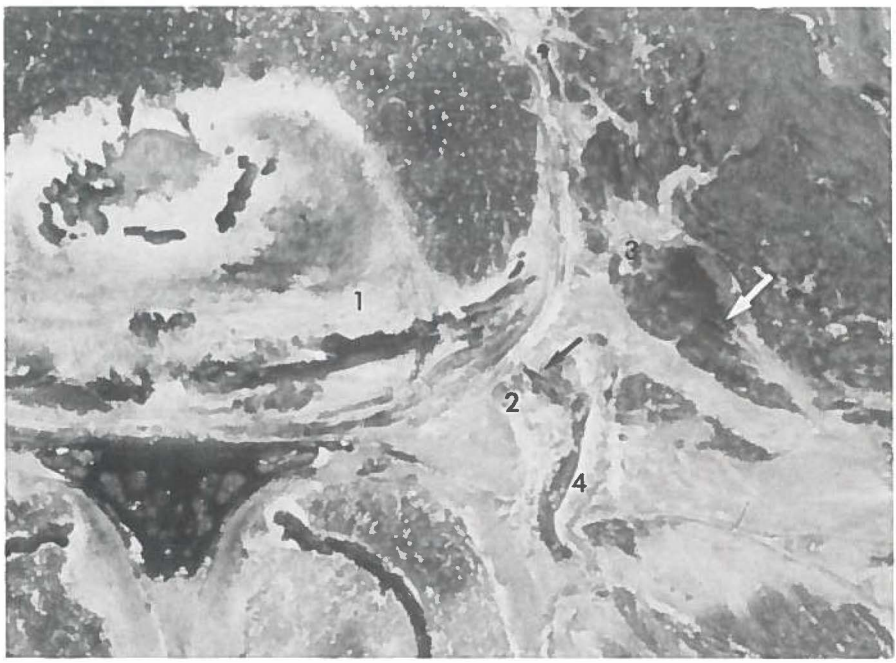

Fig. 2.6. Microplaning section at disc level L4-L5. The sectioned catheter is seen in nerve root L4 (black arrow); the outer catheter will penetrate the lumbar plexus (white arrow). 1. disc L4-L5; 2. nerve root L4; 3. lumbar plexus; 4. radicular vein.

At disc level L5-S1, the most lateral needle had pierced the L5 nerve root, whereas the needle, inserted at 8 cm from the midline, had passed just lateral to the superior articular process of S1 and medial to the L5 nerve root (Fig. 2.7).

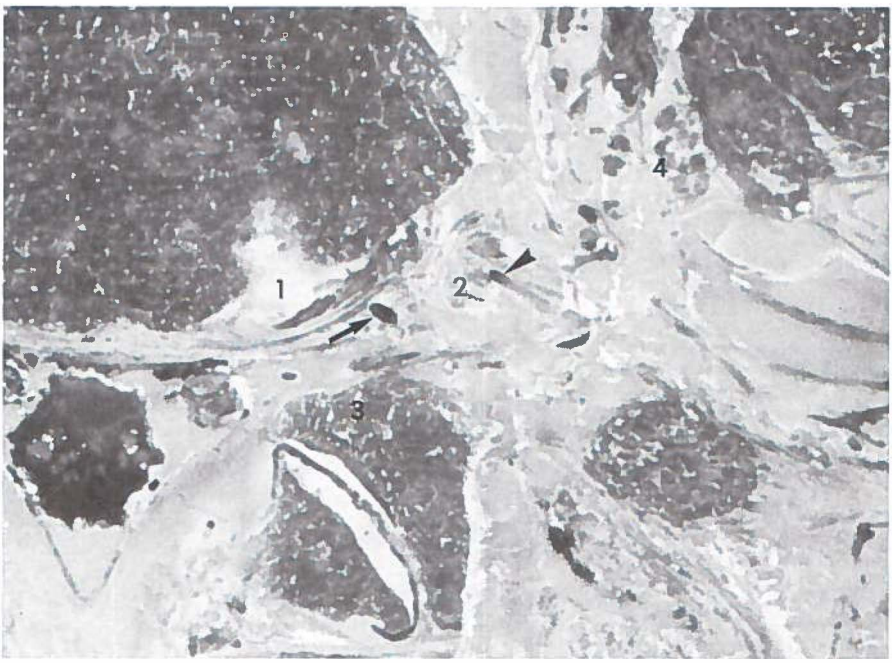

Fig. 2.7. Microplaning section at disc level L5-S1 shows catheter penetrating nerve root L5 (arrowhead) and catheter entering disc L5-S1 (arrow). 1. disc L5-S1; 2.nerve root L5; 3. superior facet S1; 4. lumbar plexus.

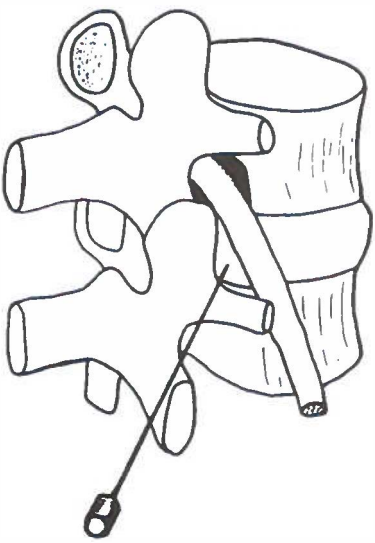

Fig. 2.8. Optimal needle placement in lumbar disc puncture, which avoids puncture of the lumbar plexus and nerve root, while the facet protects against erroneous penetration of the foramen.

In a third (fresh, not fixed) lumbar spine specimen needle placement in discs L4-L5 and L5-S1 was successful without puncturing any nerve structures. Further exploration of all three specimens showed that the tip of the needle had been placed in the centre of the nucleus.

On the basis of the results of the dissection and microplaning studies, we can conclude that the best method to avoid puncturing the nerve root or lumbar plexus is to direct the needle just lateral to the facet and enter the disc as far caudally as possible (Fig. 2.8). In this way, the facet will also prevent erroneous entry of the foramen.

2.3.2. **Parameters for optimal needle placement**

With these directives, parameters for optimal needle placement were measured in the second part of the study on 30 CT scans taken in the plane of the disc (Table 2.1).

Table 2.1. CT-scan, parameters of calculated (straight) needle placement: distance to centre of nucleus, angle of approach, needle insertion from midline, percentage of exact placement.

	Disc L4-L5	**Disc L5-S1**
Mean depth from skin to centre nucleus (range)	8.6 cm (7.7-9.6)	8.8 cm (7.7-10.2)
Mean angle of approach (range)	47.7° (45°-50°)	41.5° (35°-50°)
Mean needle insertion from midline (range)	9.5 cm (8-11)	7.5 cm (6.5-9.5)
Placement in exact centre nucleus achieved	93%	30%
Placement in nucleus impossible according to CT	0%	10%

At disc level L4-L5, the distance from the skin to the centre of the nucleus varied from 7.7 to 9.6 cm. The needle was inserted 8 to 11 cm from the midline, depending on the patient's body build, with an approaching angle of 45° to 50° from the sagittal plane (Fig. 2.3). Projected placement of the tip of the needle in the L4-L5 nucleus was successful in all cases.

Measurements of these parameters in the L5-S1 disc plane showed that with a straight needle, it was often impossible to place the tip of the needle exactly in the centre of the nucleus (Fig. 2.4). This was usually caused by a high iliac crest.

In the AP projection, the final position of the tip of the needle must be medial to the pedicles; in the lateral view it must be located in the middle third of the disc. Measured on the CT scan, this was (theoretically) possible when the needle was inserted 6.5 to 9.5 cm from the midline at an approach angle of 35° to 50° from the sagittal plane. The needle then passed just lateral to the superior articular process of S1 and usually entered the disc from a low point (Fig. 2.9 and Fig. 2.10). In this way, it was possible to reach the nucleus without the risk of penetrating the foramen and puncturing the L5 nerve root.

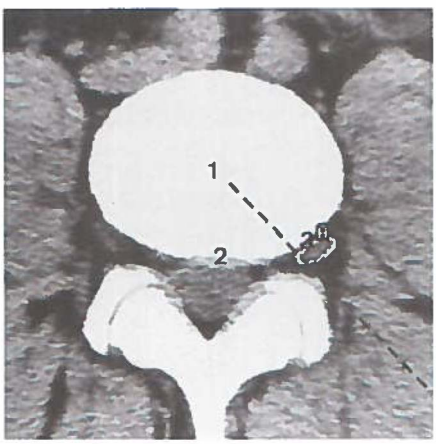

Fig. 2.9. CT scan at a high level through the disc L4-L5 and the inferior endplate of vertebra L4. Needle placement high in disc L4-L5 (represented by dotted line) will puncture the L4 nerve root. 1. inferior endplate vertebra L4; 2. disc L4-L5; 3. L4 nerve root outlined. (Photograph: Dr. J.T. Wilmink, Department of Neuroradiology).

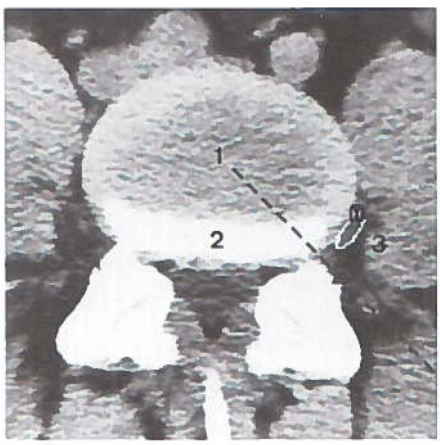

Fig. 2.10. CT scan at a low level through disc L4-L5 and the superior endplate of the vertebra L5. Needle placement low in disc L4-L5 (represented by dotted line) clearly avoids the emerging L4 nerve root. 1. disc L4-L5; 2. superior endplate vertebra L5. 3. L4 nerve root outlined (Photograph: Dr. J.T. Wilmink, Department of Neuroradiology).

2.4. DISCUSSION

Incorrect needle placement or difficulties with needle positioning can cause serious damage to neurovascular structures during lumbar disc puncture.

The direct or indirect introduction of contrast media and chymopapain into the subarachnoid space can cause cerebral haemorrhage or paraplegia (Smith Laboratories 1984, Buchman et al. 1985, Dyck 1985, Cusick et al. 1987). There is general agreement regarding the superiority of the lateral approach for needle placement (Day 1969, McCullough and Waddell 1978, Crawshaw 1984).

However, there is still some controversy surrounding the question of how far the needle should be inserted laterally (Sutton 1983, McCullough 1984). Of course, this also depends on the size and build of the patient. In general, for obese patients, the needle should be inserted half the skin-fold thickness more laterally.

Even then, some physicians advocate needle insertion at up to 12 cm from the midline (Benoist 1984, McCullough 1984). As shown in this study, this can easily result in damage to the lumbar plexus or nerve root. The possibility of penetrating the colon has even been reported (Benoist 1984, Cauchoix 1982, Helms et al. 1989).

At the level of the lumbosacral disc, needle insertion so far from the midline will usually be impossible, because of the iliac crest.

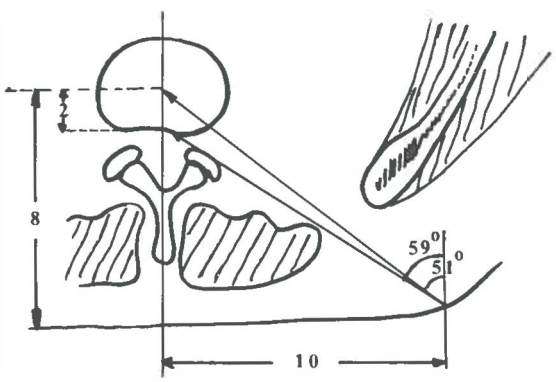

Fig. 2.11. Representation of planned disc puncture in the plane of disc L4-L5. If the centre of the nucleus lies at 8 cm and the needle is inserted 10 cm from the midline, the approaching angle amounts to 51° (=arctg 10/8). A small error of 8° in needle direction (=arctg 10/6) could result in penetration of the foramen.

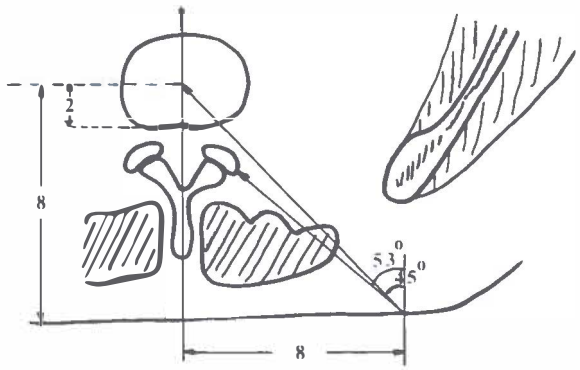

Fig. 2.12. The same situation as in Fig. 2.11, but with needle insertion at 8 cm from the midline, resulting in an approaching angle of 45°. If the same small error of 8° in needle direction is made, the facet joint will prevent erroneous penetration of the foramen.

When a small error in needle direction is made, penetration of the foramen is more likely to occur in the far lateral insertion with an angle of approach of 60° from the sagittal plane, as is shown in Fig. 2.11 and Fig. 2.12. With a more medial insertion, at an approach angle of 45°, the superior articular process will prevent erroneous penetration of the intervertebral foramen if the needle is angled too steeply in a medial direction. However, this protection can only be expected with needle placement in the disc plane.

If the C-arm image intensifier is directed at the chosen angle of approach in relation to the sagittal plane, it is facilitated to insert the needle just lateral to the facet and to graze it with low entrance of the disc, in order to avoid puncturing the emerging nerve root (Fig. 2.13).

Sometimes needle placement in the L5-S1 disc is very difficult. If the needle is angled too far cranio-caudally in the sagittal plane, the protection from the facet may be lost and lead to penetration of the foramen. In such cases it is safer to stay in the disc plane and use a smaller angle of approach. Under these circumstances, one can be content with a less optimal position of the tip of the needle in the nucleus, because the fluid injected will spread through the interspaces in the nucleus and be able to reach the prolapsed part of the disc (Adams et al. 1986, Dolan et al. 1987).

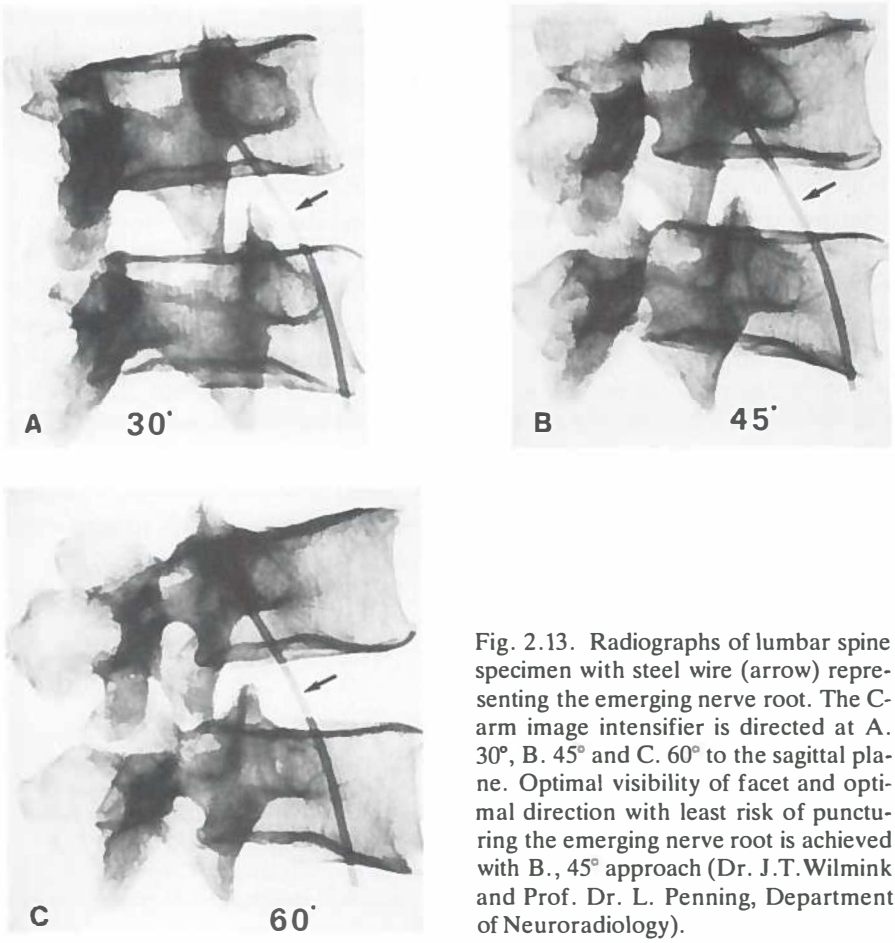

Fig. 2.13. Radiographs of lumbar spine specimen with steel wire (arrow) representing the emerging nerve root. The C-arm image intensifier is directed at A. 30°, B. 45° and C. 60° to the sagittal plane. Optimal visibility of facet and optimal direction with least risk of puncturing the emerging nerve root is achieved with B., 45° approach (Dr. J.T.Wilmink and Prof. Dr. L. Penning, Department of Neuroradiology).

Developmental variations in the nerve roots and thecal sac are sometimes obscure on a CT scan. Myelography is more suitable for visualizing the intrathecal portion of the nerve root and the position of the thecal sac (Wilmink 1988), but will not show all the root anomalies (Kadish and Simmons 1984).

If conjoined roots are demonstrated by myelography, with extension of the dural and arachnoid diverticulum into the foramen, a contralateral approach to the disc is preferable, in order to avoid inadvertent penetration of the subarachnoid space (Houser et al. 1986, Onofrio and Edgerton, 1990).

If CT scans of the level(s) to be treated are available, this will facilitate the planning and positioning of needle placement by allowing measurement of the site of insertion and the angle of approach (Nazarian 1985).

In cadaver studies it is assumed that vessels and nerves will sometimes allow a grazing needle to penetrate, because of the fixative and rigor mortis, in contrast to the more mobile structures in the in vivo situation. However, it is easy for a sharp needle to penetrate a nerve root, especially when the procedure is carried out under general anaesthesia. Little is known about the effects of puncture of nerve roots. Presumably, a single puncture will have no clinical consequences, in contrast to multiple punctures of the nerve root. This situation can only be prevented if the puncture is carried out under local anaesthesia, so that the patient is able to tell the surgeon if he feels radiating pain.

In addition, the safest way to avoid puncturing the nerve root or the lumbar plexus and to avoid penetrating the intervertebral foramen, is to direct the needle just lateral to the facet, with a low point of entry to the disc.

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3. Computed tomography (CT) analysis of the effects of chemonucleolysis

3.1. INTRODUCTION

The technique of chemonucleolysis, using intradiscal injection of chymopapain, is now well established in the 'conservative' treatment of lumbar disc herniation (Smith 1964, JAMA 1983). The prime mode of action of chymopapain is hydrolysis of the glycoproteins of the nucleus pulposus (Garvin et al. 1965, Krempen et al. 1975). Some believe that the degradation of the nucleus pulposus results in a reduction in intradiscal pressure and also in a reduction in the inflammatory reaction of the nerve root (Braun 1981).

No prospective studies were reported prior to 1984 in which computed tomography (CT) had been used to demonstrate the changes produced by chemonucleolysis. Such a study would demonstrate the changes in both the soft tissue and bony anatomy of the lumbar spine (Haughton et al. 1980, Genant et al. 1982). The accuracy of CT for imaging diseases of the lumbar spine is comparable to, or better than, lumbar myelography, particularly at the lumbosacral junction (Haughton et al. 1982).

MRI is the most sensitive method of all for demonstrating disc degeneration (Modic et al. 1984, Gibson et al. 1986).

We initiated a prospective study to determine what changes could be demonstrated by computed tomography in patients with herniated discs who had been treated with chymopapain. The changes were subsequently correlated with the clinical results.

3.2. MATERIAL AND METHODS

3.2.1. **Protocol**

Thirty patients (25 males, 5 females; mean age 39 years, range 22-70 years) who had been referred in connection with suspected lumbar disc herniation were evaluated with CT at the appropriate level before chemonucleolysis treatment and were followed-up at 3 and 12 months.

Patients were included in the study at random. They all had the clinical symptoms of a herniated disc, which persisted despite conservative therapy. None had previously undergone disc surgery or chemonucleolysis.

Before chemonucleolysis, all the patients underwent standard anteroposterior and lateral radiographs of the lumbosacral spine, a lumbar myelogram using water-soluble contrast and plain CT scans of the suspected levels. At follow-up, 3 and 12 months after chemonucleolysis, the plain radiographs of the lumbosacral spine and the CT scans of the treated levels were repeated. At the same time, a clinical assessment was made using McNab's grading (McNab 1971).

Where relevant, statistical analysis was performed using the chi- square test (Siegel and Castellan 1988). In advance, we decided to use $p= 0.05$ as our level of significance.

The percentage disc height reduction was measured on superimposed radiographs using Hurxthal's method (Pope et al. 1977).

Informed consent was obtained from all patients.

The patients were examined with a Philips Tomoscan 310 CT scanner, using angulated consecutive slices parallel to the disc space. The slice thickness was 6 mm through the vertebral bodies and 3 mm through the discs. Optimal matching of anatomical landmarks on pretreatment and posttreatment scans was attempted.

The digitized images were examined in detail using enlargements, attenuation measurements and the blink method (Fig. 3.1-3.4).

The slice angulation was not suitable for the construction of sagittal computer reformats, therefore this was not attempted.

All the scans were reviewed by an experienced independent neuroradiologist (F.J.B. Williams, FRCR). Without prior knowledge of the clinical response, he made a comparison between the baseline CT-scan and the two follow-up CT-scans at 3 and 12 months.

The following criteria were used to make a CT diagnosis of a herniated disc (Lee et al. 1983):

1. Focal abnormality of the posterior or posterolateral disc margin.
2. A soft-tissue shadow, usually of (slightly) increased density.
3. Displacement of epidural fat, the dural sac or nerve root.
4. Swelling of the distal portion of the nerve.

Criteria 1 and 2 represent the size and nature of the *focal abnormality* (herniated disc) and criteria 3 and 4 represent its effect i.e. the *compression or displacement* of nerves and surrounding structures.

The presence of these features and their subsequent degree of alteration were noted together with the condition of the annulus as well as the appearance of the posterior intervertebral joints and associated bony structures.

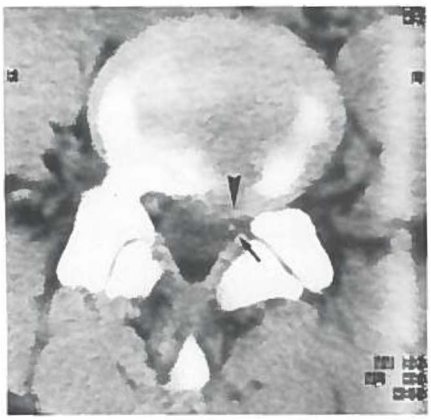

Fig. 3.1. CT scan of disc level L4-L5, demonstrating a left sided posterolateral herniated disc. Note asymmetrical disc protrusion (arrowhead) with displacement of epidural fat and S1 nerve root (arrow).

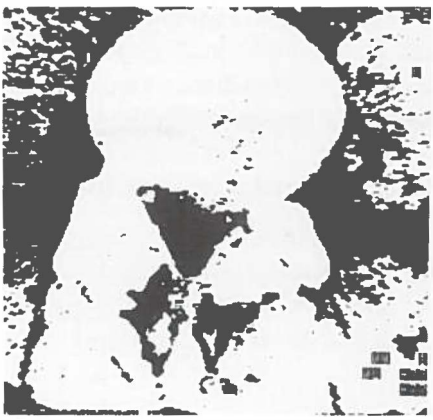

Fig. 3.2. The same situation as in Fig. 3.1, but with maximum contrast (blink method) at density level of disc material, highlighting the disc herniation.

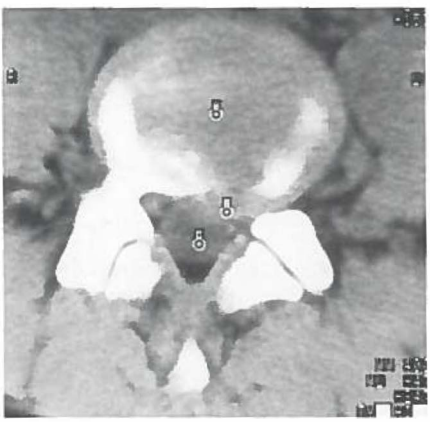

Fig. 3.3. The same situation as in Fig. 3.1, measuring the densities of different structures in Houndsfield Units.

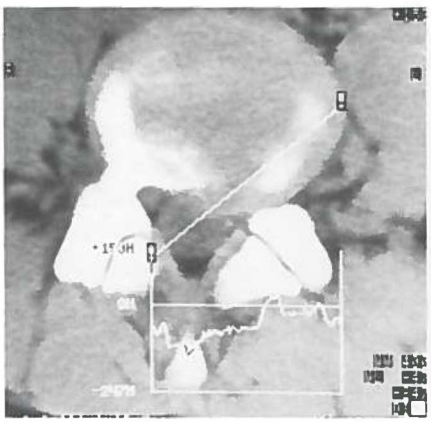

Fig. 3.4. The same situation as in Fig. 3.1; line graphic of density pattern.

A discogram was performed as part of the chemonucleolysis procedure to show the type and site of the disc pathology and to confirm the position of the tip of the needle in the nucleus.

A follow-up CT examination was carried out at three months in 30 patients and at 12 months in 27 patients. In the interval, one patient had undergone discectomy elsewhere. Two patients refused the CT examination at 12 months, although at that time their clinical result was assessed as excellent.

3.2.2. **CT, lumbar myelography and discography**

The CT findings before chemonucleolysis are summarized in Table 3.1. The CT scan showed a herniated disc in 28 patients. On account of the partial volume effect, CT also demonstrated some (increased?) diffuse annular bulging of the disc in 13 patients.

Table 3.1. Computed Tomography findings before chemonucleolysis.

Herniated disc	15
Herniated disc and annular bulging	13
No convincing disc pathology	2
Concomitant findings	
Asymmetrical facet joints	3
Minor degenerative changes	3

Both patients without clear CT evidence of a herniated disc had asymmetrical facet joints and one of them displayed slight degenerative changes. These patients were treated because of their convincing clinical symptoms as well as the abnormal discographic findings.

The radiological findings on the CT scan, lumbar myelogram and discogram before chemonucleolysis are shown in Table 3.2.

In 26 patients, all three examinations were abnormal. In two patients the CT scan demonstrated a herniated disc at L5-S1, while the myelogram was normal. In one patient the CT scan disclosed no abnormalities but the myelogram and an epidural venogram were abnormal: this patient, with a convincing clinical history, underwent discography which confirmed a ruptured disc. In a second patient an equivocal CT appearance was later interpreted as normal, although the discogram had been abnormal.

One patient showed herniation of disc L2-L3 without CT evidence of compression of the thecal sac or nerve roots.

No evidence of the migration of disc fragments was found in this series.

Four thousand units of chymopapain were injected at the appropriate levels. Chemonucleolysis was carried out in one patient at L2-L3, in 12 patients at L4-

Table 3.2. Before chemonucleolysis: number of patients with normal (–), equivocal (±) or abnormal (+) findings on CT, lumbar myelography and discography.

	CT-scan	Myelogram	Discogram
26 patients	+	+	+
2 patients	+	–	+
1 patient	–	+	+
1 patient	±	–	+

L5 and in 14 patients at L5-S1. Three patients with a herniated disc at L5-S1 were also treated at L4-L5 because of an abnormal discogram, although only the lower level was included in the study, as only this level had been examined by CT.

3.3. RESULTS

3.3.1. **Disc height reduction**

At follow-up, 3 and 12 months posttreatment, the lateral radiograph of the lumbar spine showed an average reduction in disc height of 26% (range 5% - 50%). No relation was found between the degree of reduction and the clinical result. In two patients, disc height re-expansion took place from an initial 50% reduction at 3 months to 15% disc height reduction at 12 months.

3.3.2. **Size of focal disc abnormality**

Two aspects of disc herniation were discriminated: the focal abnormality of the posterior or posterolateral disc margin and the (apparent) compression or displacement of epidural fat, the dural sac, or nerve root.

Table 3.3. Effect of chemonucleolysis on the size of the focal abnormality at 3 and 12 months.

	At 3 months N=30	At 12 months N=27
Hernia disappeared	12	19
	2	no CT
Hernia reduced	8	5
Hernia unchanged	5	1
	1	discectomy
No hernia on CT	2	2

The focal disc abnormality had disappeared at three months in 14 patients (50%) and at 12 months in 19 out of the 27 patients (70%), see also Table 3.3.

At 3 months follow-up, the focal abnormality on the CT scan was still present in 14 of 28 patients (50%), but a reduction in its size was seen in 22 of 28 patients (78%). At 12 months follow-up, the focal abnormality still existed on the CT scan in 6 out of the 25 patients (24%), but it was reduced in size in 24 of them (96%).

3.3.3. **Annular bulging**

At three months follow-up, an increase in annular bulging was noted in 23 out of the 28 patients with a herniated disc on their CT scan and also in one patient without a visible hernia on the CT scan, i.e. in a total of 24 out of the 30 patients (80%).

In the course of one year, the degree of annular bulging remained unchanged in all but one patient who showed a decrease in annular bulging and disc height re-expansion at the 12-month follow-up examination (see also Fig. 4.5).

3.3.4. **Compression or displacement of nerve structures**

The increase in annular bulging had caused different patterns or combinations of focal abnormalities and apparent compression, as was demonstrated by deformation or displacement of the dural sac or the extradural nerve root segment. Fig. 3.5 and Fig. 3.6 show two examples of reduced focal abnormalities, while the net compression effect on the dural sac and the root appears to be the same.

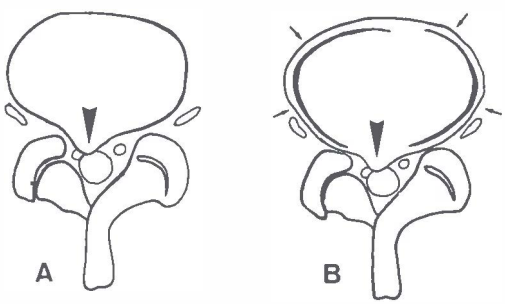

Fig. 3.5. A. Drawing of a right posterolateral herniated disc (arrowhead). B. After chemonucleolysis diffuse annular bulging increased (small arrows); although compression remained the same, the focal abnormality decreased in size (arrowhead).

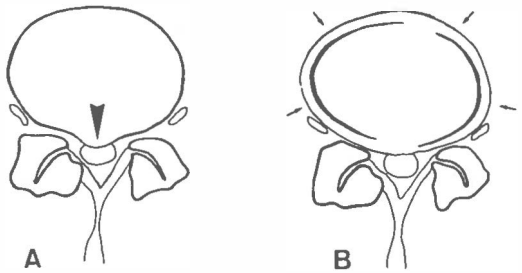

Fig. 3.6. A. Drawing of a midline herniated disc (arrowhead). B. After chemonucleolysis, diffuse annular bulging increased (small arrows). There is no more evidence of a hernia, but compression of the dural sac appears to be the same.

A focal abnormality may also remain after chemonucleolysis without giving rise to displacement or deformation of the dural sac or nerve root structures.

A slight decrease in apparent compression could be inferred from an increase in the amount of visible epidural fat, a reduction in the asymmetry of the dural sac, or less displacement of the nerve root (see also Figs. 3.11-3.14). The changes in apparent compression as judged by CT, are reported in Table 3.4.

Table 3.4. Effect of chemonucleolysis on apparent compression at 3 and 12 months.

	At 3 months N=30	At 12 months N=27
Compression disappeared	9	20
	2	no CT
Compression reduced	9	0
Compression unchanged	6	4 *
	1	discectomy
No compression on CT	3	3

* In three patients the apparent compression was caused by increased annular bulging at disc level L4-L5 (Fig. 3.6).

Although the CT scan still demonstrated displacement of nerve structures in 16 out of the 27 patients (59%) at three months follow-up, signs of a reduction in apparent compression were seen in 20 out of the 27 patients (74%). In three patients the CT examination at 12 months showed apparent compression of

the dural sac due to increased annular bulging at disc level L4-L5 (Fig. 3.6). In an obese woman with an unsatisfactory clinical result at 3 and 12 months follow-up, the CT examination of disc level L5-S1 still showed disc herniation with apparent compression of the nerve structures.

3.3.5. **Spinal canal**

No change was detected in the facet joints in any of the patients at the follow-up CT examinations. In two patients a minimal retroposition of L4 in relation to L5 was seen on the lateral radiograph of the lumbar spine at three months. One of them had disc height re-expansion and the lateral radiograph at 12 months did not show persistent retroposition (see also Fig. 4.5).

None of the patients showed evidence of epidural fibrosis after chemonucleolysis.

3.3.6. **Correlation of the clinical result with the CT findings**

The clinical results of the follow-up examinations at 3 and 12 months are shown in Table 3.5.

Table 3.5. Clinical results assessed 3 and 12 months after chemonucleolysis.

Clinical result:	At 3 months N=30	At 12 months N=27
Hernia demonstrated by CT:		
Satisfactory result	19	20
Satisfactory result	2	2(no CT)
Unsatisfactory result	6	5
Unsatisfactory result	1	discectomy
No hernia demonstrated by CT:		
Satisfactory result	1	2
Unsatisfactory result	1	0
	Satisfactory 22/30 (73%)	Satisfactory 24/30 (80%)

At three months follow-up, the apparent *compression* had not changed in 7 patients; in 4 of them the clinical result was assessed as unsatisfactory (57%). In 18 out of the 20 patients with CT findings of a reduction in compression, the clinical result was assessed as satisfactory (90%). This difference was found to

be statistically significant using the chi-square analysis with Yates' correction for continuity ($\chi^2=4.22;\upsilon=1; p<0.04$).

Therefore, clinical improvement was correlated with an improvement on the CT scan.

At 12 months follow-up, the clinical outcome in patients with or without remaining *focal abnormalities* showed no statistical difference: the result was satisfactory in 4 out of the 6 patients with remaining focal abnormalities and in 16 out of the 19 patients without remaining focal abnormalities ($\chi^2=0.12; \upsilon=1; p=0.73$).

In other words, the clinical improvement was correlated with CT findings of a decrease in apparent compression of the nerve structures and not with (residual) focal disc abnormalities per se.

3.3.7. **Case reports.**

Some case reports are presented to illustrate the CT findings:

Case 1. A 40-year-old teacher had suffered from back problems since the age of 17. During the preceding year he had sciatic pain in the right leg and examination demonstrated a positive right straight leg raising (SLR) test at 25°. The myelogram, CT scan (Fig. 3.7) and discogram showed disc herniation at L4-L5 and chemonucleolysis was performed at this level.

At three months follow-up, he only occasionally experienced a numb feeling on the lateral side of the leg and foot. The reduction in disc height was 42%. The CT scan at three months showed no remaining herniation of the disc (Fig. 3.9). He was free from pain, returned to work four months after chemonucleolysis and was classified as an excellent result.

At 12 months follow-up, he mentioned only occasional pain in the right leg during sporting activities. Physical examination showed no abnormalities. At that time, CT examination showed no disc herniation and the images were not different from those obtained at three months follow-up (Fig. 3.10).

In a questionnaire six years after chemonucleolysis, he reported incidental periods of leg pain and an occasional need for physiotherapy because of stiffness in his back. He was satisfied with his actual condition and could perform his work without limitations.

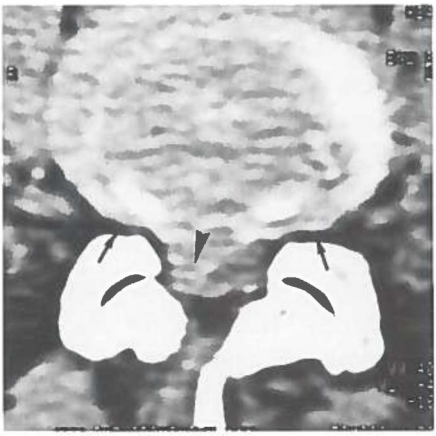

Fig. 3.7. Case 1. CT scan of a right sided posterolateral hernia of disc L4-L5 (arrowhead). Note the symmetrical fat in the neural foramina (small arrows).

Fig. 3.8. Case 1. Blink method, outlining disc herniation.

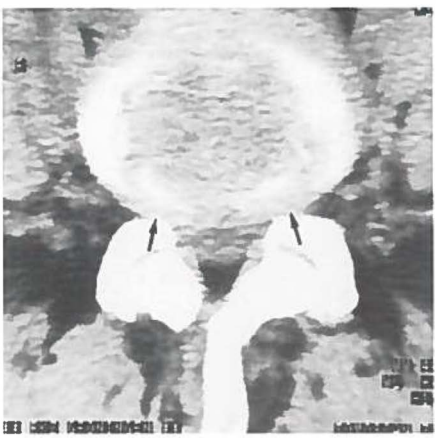

Fig. 3.9. Case 1. CT scan at the same level three months after chemonucleolysis. No visible evidence of hernia, but increased diffuse bulging of the annulus, with obliteration of the foraminal fat at this level (small arrows).

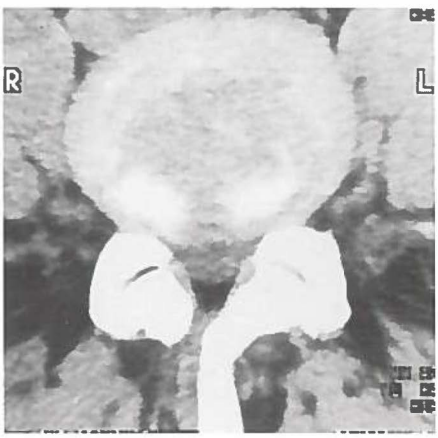

Fig. 3.10. Case 1. CT scan at the same level 12 months after chemonucleolysis. No hernia, no change compared to the CT scan at three months.

Case 2. A 22-year-old male student had suffered from sciatic pain in the right leg with mild backache for six months. Bed-rest gave initial relief of symptoms but these returned after two months. Examination showed some restricted movement of the lumbar spine, no weakness, a reduced ankle jerk on the right and a positive straight leg raising test at 50°. Myelography, performed two months earlier, had shown a herniated disc at L5-S1 on the right. CT scans (Fig. 3.11) and discography confirmed the diagnosis and chemonucleolysis was performed at this level.

Three months after chemonucleolysis, he still had some stiffness in the back and some cramp-like sensations in the right leg. He rated his degree of improvement at 70% and had resumed sports. Examination showed no neurological abnormalities. The lateral radiograph of the lumbar spine showed a reduction of 50% in disc height. The CT scan at three months follow-up still demonstrated a herniated disc at L5-S1 (Fig. 3.13), but with some reduction of compression when compared to the CT scan before chemonucleolysis. The clinical result was assessed as good. At 12 months follow-up, he was completely symptom-free and the physical examination was normal. At that time, the CT examination showed no more signs of disc herniation, but annular disc bulging had increased (Fig. 3.14).

In a questionnaire 6½ years after chemonucleolysis, he reported some back pain during heavy lifting, but no limitations in work or sporting activities.

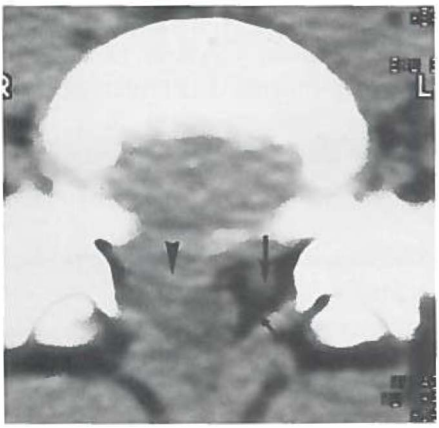

Fig. 3.11. Case 2. CT scan of a right sided posterolateral herniation of disc L5-S1. Note the asymmetrical disc protrusion on the right (arrowhead) with posterior displacement of the right S1 root. The epidural fat is replaced in contrast to normal epidural fat on the left (small arrow) and the sharply defined left S1 root (arrow).

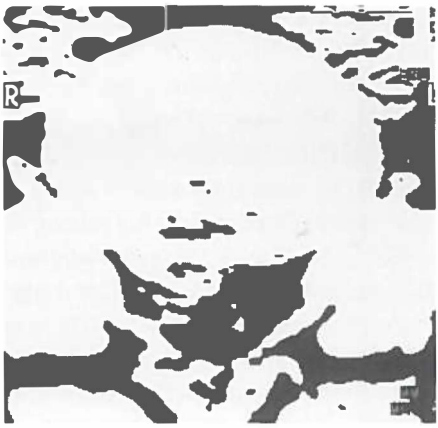

Fig. 3.12. Case 2. Blink method, outlining disc herniation.

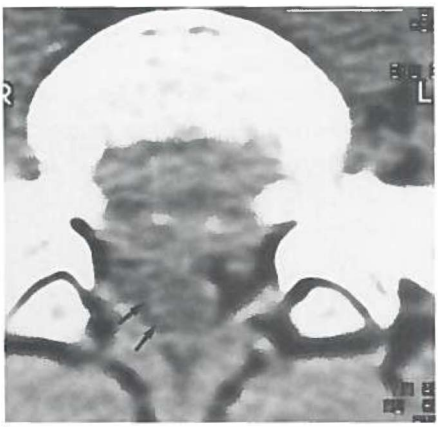

Fig. 3.13. Case 2. CT scan at the same level three months after chemonucleolysis. There is still some asymmetrical disc prorusion on the right with posterior displacement of the right S1 nerve root, but there is more epidural fat (small arrows) and better definition of the dural sac and nerve root on the right.

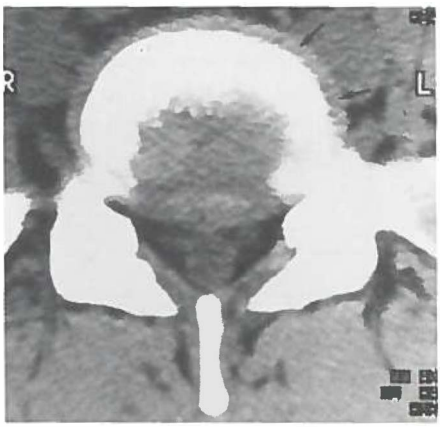

Fig. 3.14. Case 2. Twelve months after chemonucleolysis; no visible herniated disc, but annular bulging has increased (small arrows).

Case 3. A 42-year-old storekeeper had a six-month history of right sciatic pain following a period of backache. After clinical investigation at another hospital, a myelogram was performed, which demonstrated a herniated disc at L4-L5. He was referred to our department three months later after conservative treatment had failed. Clinical examination showed signs and symptoms consistent with a mild radicular syndrome, with pain radiating to the right calf on straight leg raising to 70°.

CT scans (Fig. 3.15) and discography confirmed the diagnosis of a herniated disc at L4-L5, and chemonucleolysis was performed at this level.

At three months follow-up, there was only slight relief of the sciatic pain. He was not using analgesics and had not been able to resume work. Examination showed improved mobility of the lumbar spine and no neurological signs. Disc height reduction amounted to 22%.

The CT scan showed increased bulging of the annulus and the same appearance of compression of the dural sac and nerve root as before chemonucleolysis (Fig. 3.17). Surgery was not felt to be indicated at that time and the result was assessed as fair on account of the objective clinical improvement. Because of persistent complaints, the patient consulted a neurosurgeon at another hospital and underwent surgery 10 months after chemonucleolysis: some disc protrusion at L4-L5 was found. After the laminectomy, the symptoms persisted and remained unchanged in the short-term and long-term. He was not able to resume work and was receiving a disability pension because of continuing back and leg pain.

According to his answers to a questionnaire six years after chemonucleolysis, he was suffering from limitations in his activities caused by back and leg pain and was still receiving a disability pension.

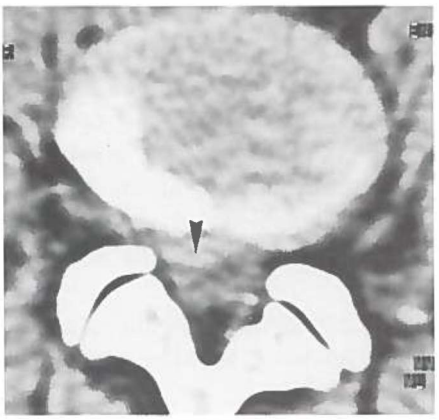

Fig. 3.15. Case 3. CT scan of a right sided posterolateral herniation of disc L4-L5 (arrowhead).

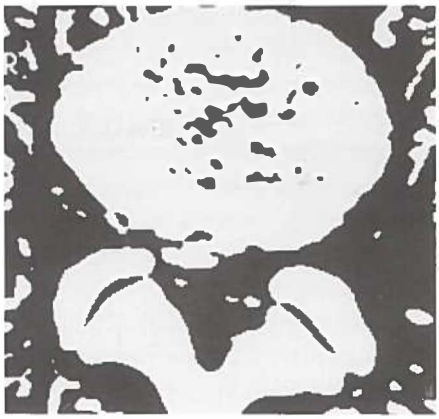

Fig. 3.16. Case 3. Blink method, outlining disc herniation.

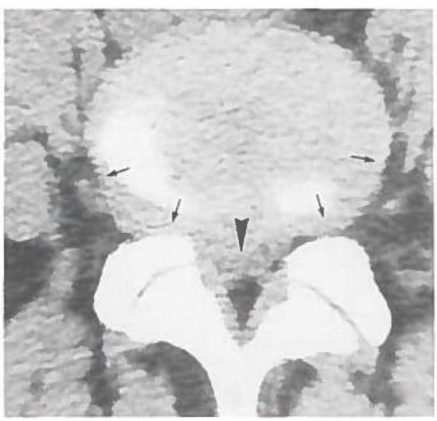

Fig. 3.17. Case 3. CT scan at the same level three months after chemonucleolysis, showing asymmetrical protrusion of the disc (arrowhead) apparent on the right, the obvious increased diffuse bulging of the annulus with obliteration of foraminal fat at this level (small arrows).

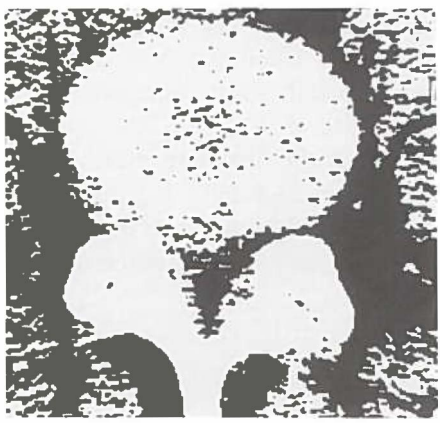

Fig. 3.18. Case 3. Same CT scan as in Fig. 3.17; blink method, with the same window width and window level adjustments as in Fig.3.16, demonstrating unchanged disc protrusion and increased annular bulging at three months.

Case 4. A 32-year-old former director of a shoe factory was already suffering from long-standing back pain, for which he had consulted a rheumatologist, before he experienced the gradual onset of right-sided sciatica over a period of six months. No improvement was achieved with conservative treatment. Examination showed restricted lumbar motion, wasting of the quadriceps muscle and a positive straight leg raising test on the right at 50°. Lumbar myelography as well as CT scans (Fig. 3.19) demonstrated a right-sided, postero-lateral herniated disc at L5-S1 and chemonucleolysis at that level was performed.

After an initial period of improvement, the back and leg pain returned, although no objective symptoms of a radicular syndrome could be found. Disc height reduction amounted to 45%.

CT examination at three months follow-up (Fig. 3.21) revealed a clear reduction in the size of the focal abnormality and complete relief of the compression of nerve root structures. Because of continuing complaints and despite the clear objective clinical and radiological improvement, his clinical result was assessed as only fair. His disability pension was continued. No change in the clinical picture has occurred since.

The CT examination at 12 months follow-up (Fig. 3.22) showed a wide spinal canal, some increased bulging of disc L5-S1 but no signs of disc herniation at all.

During the following years, he continued to have subjective complaints of back pain and mild leg pain without any objective symptoms. Physical examination showed only minor limitation of mobility in the lumbar spine, but objective radicular symptoms did not return.

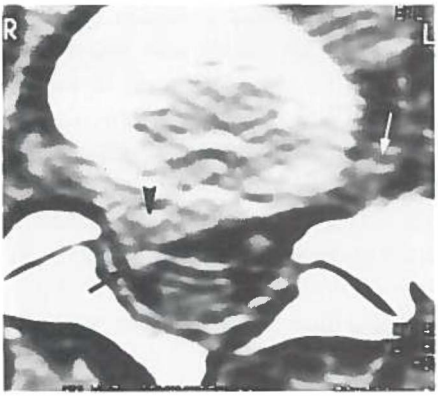

Fig. 3.19. Case 4. CT scan at disc level L5-S1, demonstrating a wide spinal canal and a right sided posterolateral herniated disc (arrowhead) with displacement of the right S1 nerve (arrow). Note the position of the L5 nerve root (white arrow).

Fig. 3.20. Case 4. Blink method, outlining disc herniation.

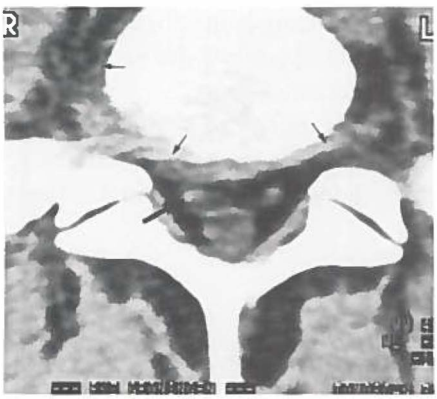

Fig. 3.21. Case 4. CT scan at the same level three months after chemonucleolysis. No obvious hernia visible anymore and the position of the S1 nerve root is normal (arrow); slightly increased diffuse annular bulging can be demonstrated (small arrows). The gantry angulation of the CT scanner was slightly different from Fig. 3.19 due to the disc height reduction.

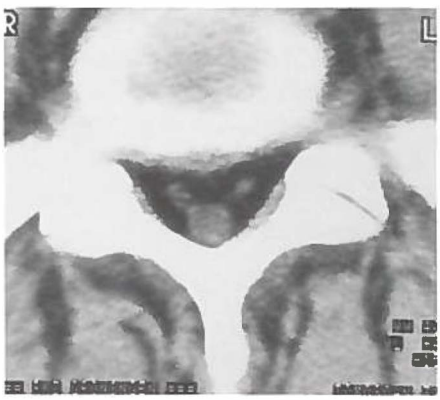

Fig. 3.22. Case 4. CT scan at the same level 12 months after chemonucleolysis. No change, compared with the CT scan at three months. There was a discrepancy between his subjective complaints and the normal objective examination.

Case 5. A 43-year-old assistant production manager had a sudden onset of severe right-sided sciatica. Bed-rest proved to be impossible because it increased the pain. There were no problems in bladder or bowel function. Examination showed severe disturbance in posture and restricted lumbar motion, sensory disturbances in dermatomes L5 and S1, weakness of extensor hallucis and reduced ankle jerk. The straight leg raising test was positive at 50° on the right. Lumbar myelography and CT scans (Fig. 3.23) showed a herniated disc at L4-L5, which was confirmed by discography. Disc level L5-S1 was normal. Chemonucleolysis of disc level L4-L5 was performed. Four months after an initial period of improvement, mild leg pain and some back pain returned. Disc height reduction was 28%.

CT examination at three months follow-up, showed considerable annular bulging with apparent compression of the dural sac (Fig. 3.24).

Some time later, mild left-sided sciatic symptoms developed as well. These symptoms slowly diminished and he resumed work seven months after chemonucleolysis.

At 12 months follow-up, physical examination showed normal function of the lumbar spine, minor sensory disturbances, no motor weakness and a normal ankle jerk. The CT examination (Fig. 3.25) did not show any focal abnormalities, but the annular bulging had not changed and there was little epidural fat. He regularly experienced periods of mild right-sided sciatica, but these did not interfere with his work or leisure activities.

In June 1988 he was examined again by a neurologist and neurosurgeon and CT-myelography was performed, which did not demonstrate a herniated disc (Fig. 3.26). On a lumbar radiograph, severe spondylosis at levels L2-L3 and L3-L4 was observed.

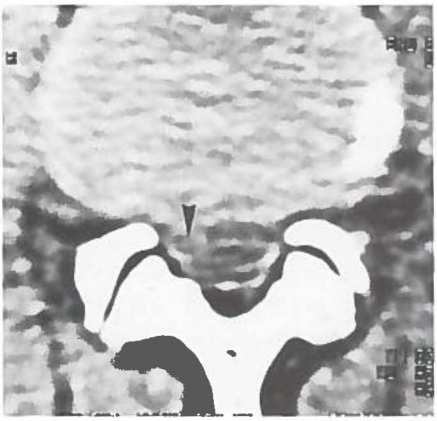

Fig. 3.23. Case 5. CT scan of disc level L4-L5, demonstrating a small right sided posterolateral herniated disc (arrowhead).

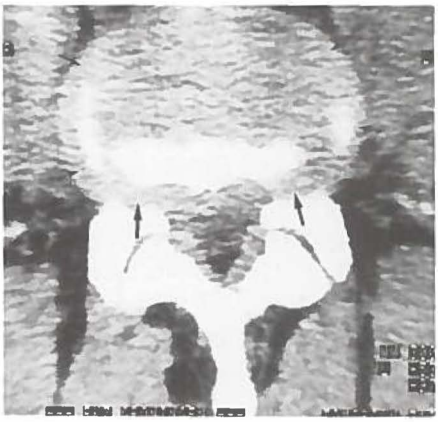

Fig. 3.24. Case 5. CT scan at the same disc level. Three months after chemonucleolysis there is no focal abnormality, but the diffuse annular bulging has increased (small arrows) with obliteration of foraminal fat at this level (arrows).

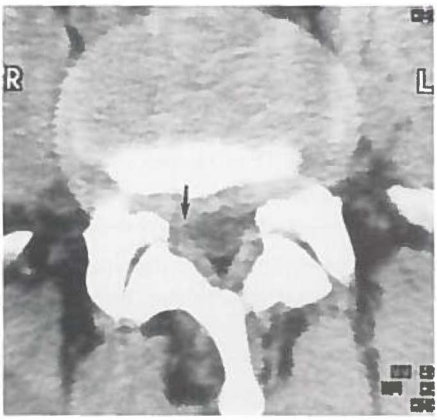

Fig. 3.25. Case 5. CT scan at the same disc level, 12 months after chemonucleolysis: it is not clear whether there is still slight disc protrusion on the right (arrow), compared with the CT scan at three months. The interpretation of the focal abnormality may be complicated by the increased annular bulging (compare to Fig. 3.5).

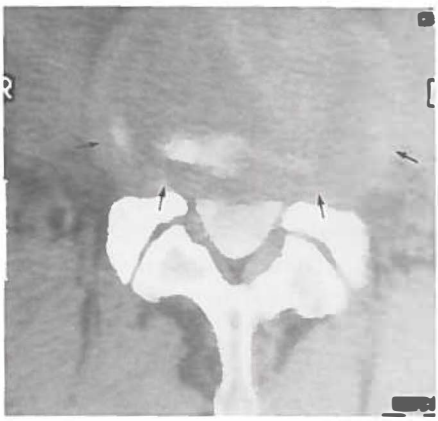

Fig. 3.26. Case 5. CT-myelography at disc level L4-L5, six years after chemonucleolysis: no focal abnormality. Note the unchanged annular bulging (small arrows).

3.4. DISCUSSION

3.4.1. **Specificity of CT**

The radicular syndrome is primarily a clinical concept. If conservative treatment has failed and invasive treatment is being considered, supplementary radiological investigation is necessary to confirm (or reject) the existence and cause of nerve root compression.

Although myelography better visualizes the intrathecal nerve root than CT (Wilmink 1989), CT demonstrates lumbar disc herniation as effectively as myelography (Haughton et al. 1982). Moreover, myelography is invasive and can be complicated by untoward reactions (Wilmink 1984), whereas CT is noninvasive and can be performed on an outpatient basis (Wiesel et al. 1984).

At present, MRI is not routinely available and it is also more expensive than CT for studying the herniated lumbar disc syndrome.

With the availability of all these excellent imaging techniques, it is important to realize that they must not be assessed in isolation from the clinical picture.

From the literature it is known that the specificity of myelography and CT is not very high. It has been reported that 24% of a group of subjects who had never experienced sciatica, showed a defect on the myelogram (Hitselberger and Witten 1968). Similarly, 36% of an asymptomatic population examined with CT were found to have a significant abnormality in the lumbar spine and over 19% of the study subjects under the age of 40 years were diagnosed as having a herniated disc (Wiesel et al. 1984). Abnormal CT scan findings are more frequent with increasing age. In the younger age group, there is a better correlation between the pathology visualized in the CT scan and the clinical picture than in the older age group (Wiesel et al. 1984).

Therefore, the correlation of radiological signs with the clinical symptoms is very important. Treatment initiated on account of an abnormal myelogram or CT scan, without an appropriate clinical indication, often leads to 'failed back surgery'.

Leaving aside these considerations in treatment planning, CT is nevertheless of value for follow-up examinations after surgery or chemonucleolysis, because it reveals the soft tissue anatomy in the spinal canal (Haughton et al. 1980), it is noninvasive, readily available nowadays and lends itself well to the objective comparison of the pretreatment and posttreatment situation in order to study possible changes.

CT examinations performed within several weeks of lumbar discectomy, have shown a soft tissue mass on the operated side in 75%-95% of the

symptomatic and asymptomatic patients, which apparently consisted of blood and scar tissue (Teplick and Haskin 1983, Braun et al. 1984, Ilkko et al. 1988). In time, the mass appeared to diminish in size, but it rarely disappeared completely. In cases where the clinical symptoms persist or recur, it is very difficult to differentiate between symptomatic scarring and small clinically significant recurrent disc herniation using CT, even when contrast enhancement is used (Teplick and Haskin 1984, Braun et al 1984, Ilkko et al 1988, Wilmink 1987).

3.4.2. **Prospective CT studies in chemonucleolysis**

It has been shown that myelographic studies after chemonucleolysis on asymptomatic patients (McNab et al. 1971) and on patients with persistent or recurrent complaints (Gentry et al. 1985) do not demonstrate any significant change in the size of the myelographic defect.

The comparison of CT studies performed at various time intervals after chemonucleolysis sometimes gives rise to contradictory findings concerning the changes observed in the extent of disc herniation (Table 3.6). Although it seems obvious that the symptoms are caused by compression of nerve structures, while (residual) focal abnormalities do not necessarily cause compression, the literature is mainly concerned with the effect of the treatment on the extent of herniation.

According to these studies, there is no consistent correlation between the observation of a decrease in HNP size on the CT scan and the degree of clinical improvement. In the study by Brown et al. however, the level of improvement in terms of objective clinical findings at six weeks, agreed closely with the CT findings of a decrease in HNP size. The authors stated that an absolute decrease in HNP size of 1-3 mm, was not obvious on cursory visual inspection but required careful measurement.

The controversial data in these studies can perhaps be explained by differences in:

1. CT scanning technique: slice thickness (Van Leeuwen: 8 mm!), precise matching of preinjection and postinjection scans, differences in degree of detailed interrogation of the scans.
2. Patient selection (Mall and Kaiser, N=17, several hospitals); small sample size (Brown, N=9).
3. Judgement criteria: a general judgement of the CT scan in grades from normal to abnormal (Boumphrey); grading the change in HNP size (most studies); grading the change in compression.

Table 3.6. Prospective CT studies examining the changes in HNP size after chemonucleolysis.

	Interval	Number of patients	decrease in size of HNP	Clinical correlation
Mall and Kaiser 1984	- 3-15 weeks (av. 3 months)	17	in 47%	yes
Weinstein et al. 1984	- 24 hours	15	no	
	- 3 months	15	yes	yes
	- 6 months	15	yes	yes
Brown et al. 1985	- 6 weeks	9	in 90%	yes
Gentry et al. 1985	- 6 weeks	21	in 8%	no
	- 6 months	21	in 59%	some
Konings et al. 1984, 1986	- 3 months	30	in 78%	yes *
	-12 months	25	in 96%	no
Boumphrey et al. 1984, 1987	- 3 months	50	in 12%	no
	- 6 months	10	in 70%	?
v. Leeuwen 1989	- 3 months	91	in 57%	no
	-12 months	27	in 85%	no

* Correlation with decrease in compression or displacement of nerve structures.

These CT data give the general impression that a slow, but progressive decrease in HNP size and signs of compression will usually be observable macroscopically several months after chemonucleolysis.

Changes in the disc after chemonucleolysis can also be demonstrated using MRI. Serial sagittal MRI scanning after chemonucleolysis has shown a gradual reduction in nuclear signal intensity due to the loss of water content (Fig 3.27). A complete loss of signal took at least six weeks and corresponded with the maximum reduction in disc height (Szypryt et al. 1987).

As with CT, some studies using MRI demonstrated that a decrease in the size of the defect correlated with a successful outcome (Huckman et al. 1987); in other studies no correlation was found (Masaryk et al. 1986).

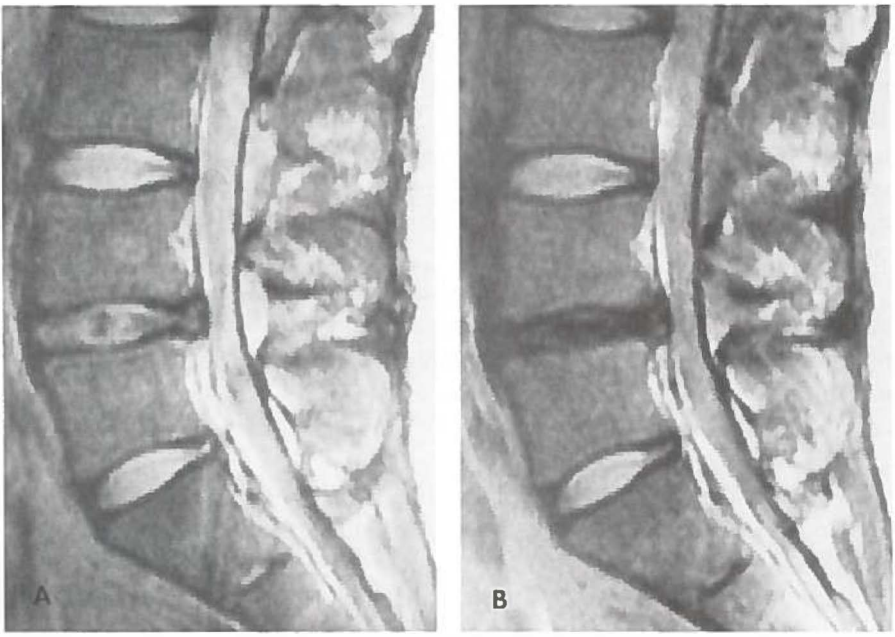

Fig. 3.27. A. MRI scan of a 23-year-old male, demonstrating a herniated disc L4-L5. B. Three months after chymopapain injection of disc L4-L5, the MRI scan demonstrated a marked decrease in signal intensity at that level, consistent with loss of water content.

Our findings show that the degree of clinical improvement is correlated with the decrease in compression of the root or thecal sac (Brown 1985, Weinstein et al. 1984) and not with the presence or absence of residual focal abnormalities which sometimes remain visible for quite a long time after chemonucleolysis.

A slight decrease in radiologic evidence of compression can be compatible with a good clinical result. This relief of compression after chemonucleolysis can be demonstrated using CT, but it is necessary to perform detailed examinations, measurements and comparisons of consecutive CT scans.

3.4.3. **Mode of action of chymopapain**

Gentry et al. observed no visible decrease in the size of the hernia at six weeks follow-up, although a successful outcome was noted in 76% of their patients. They found the same discrepancy at six months follow-up: CT changes in 59% and a successful outcome in 91%. They concluded that to

achieve pain relief in most patients, it was apparently unnecessary to achieve a marked decrease in size of the hernia and that the persistence of disc protrusion at follow-up should not be used as an indicator of chemonucleolysis failure. On the basis of their CT study, Gentry et al. suggested that early improvement after chemonucleolysis might be mediated by chymopapain-induced disc-space narrowing, influencing the degree of nerve-root compression and tension, as has also been suggested by others (Bertolini et al. 1982, Spencer et al. 1983).

The above-mentioned effects of chemonucleolysis need some time to develop and cannot explain the immediate relief of sciatica that is often observed. Other modes of action cannot be excluded, such as the direct interference of chymopapaine with an inflammatory reaction secondary to root compression (Krempen et al. 1975) or interference with a chemical mediator of pain (McNab and McCullough 1971).

Dolan et al. studied the short-term effects of chymopapain on cadaveric lumbar discs (Dolan et al. 1987). They found that although chymopapain had a negligible effect on the mechanics of the disc, it could reduce the size of any prolapsed nuclear material with which it came into contact. In their in vitro experiment, chymopapain reduced the size of the nuclear fragment by about 24% in one hour and by 80% after 48 hours. Such a reduction in vivo would certainly cause a detectable change in HNP size on a CT scan, but this has never been observed or reported.

Thus the exact mode of action of chymopapain has still not been clarified; perhaps all the above-mentioned factors, in a time sequence, are responsible.

3.4.4. **Annular bulging**

A slight bulging of the annulus is a normal physiological phenomenon, necessary to permit mobility in the motion segment. In our study, increase in annular bulging after chemonucleolysis was noted in 80% of the patients. This feature has not been reported in other CT studies, although they all mentioned a decrease in disc height. Three months after chemonucleolysis the reduction in apparent compression was to some degree offset by this increase in annular bulging (Fig. 3.5, Fig. 3.6, Fig. 3.24, Fig. 3.25).

At the 12-month follow-up examination, the CT showed complete relief of compression in most of the patients, although the annular bulging had not changed and a (reduced) focal abnormality was still visible in some cases.

Chymopapain degrades the proteoglycans and matrix proteins in the nucleus pulposus, but it also has a dose-related effect on the degradation of the proteoglycans and matrix proteins in the annulus and the cartilaginous end-plates (Bradford et al. 1983, Stern 1969).

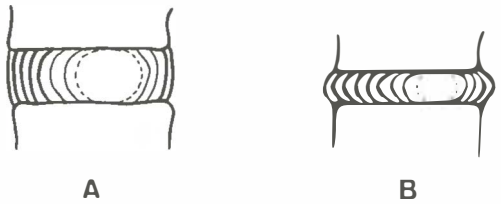

Fig. 3.28. A. Representation of a disc before chemonucleolysis. B. After chemonucleolysis, annular bulging increased by the collapse of the nucleus.

The results of a recent study have indicated that there is no dose-response relationship in the sense of an increasing response with increasing dose, but rather an all or nothing response and a minimum enzyme level needed to obtain that response (Kiester et al. 1989).

A standard dose of chymopapain mainly dissolves the nucleus pulposus and causes the decrease in disc height. Because the collagen is not degraded by the chymopapain, the fibers of the annulus will retain their original length. The reduction in disc height then induces annular bulging (Fig. 3.28). Owing to the fact that annular bulging increased in the majority of patients, chemonucleolysis is not indicated in the treatment of dural sac or nerve root compression caused by diffuse annular bulging alone as this would only increase the problems. Chemonucleolysis should be applied with caution in cases of narrowing of the spinal canal, where annular bulging may further reduce the available space within the canal.

It is difficult to differentiate between a broad based or midline disc herniation and diffuse annular bulging. CT scanning is superior to lumbar myelography for distinguishing between diffuse annular bulging and a midline herniated disc (McCullough and McNab 1983), although this distinction can also be suspected on careful inspection of the myelogram (Kieffer et al.1982) and by taking flexion-extension radiographs during lumbar myelography.

No evidence of epidural fibrosis was seen on the CT examinations of our group of patients after chemonucleolysis. This appears to be a major advantage of chemonucleolysis, because epidural fibrosis is a recognized complication of disc surgery and, as such, is a cause of recurrent symptoms (Benoist et al. 1980, McNab 1977).

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4. Clinical evaluation of long-term results of chemonucleolysis

4.1. INTRODUCTION

Few treatment modalities for the herniated lumbar disc syndrome have been as thoroughly studied as chemonucleolysis.

Since the introduction of chymopapain for the treatment of lumbar disc herniation by Lyman Smith in 1963, probably all the serious complications and deaths related to chemonucleolysis have been recorded in figures and percentages. Its clinical efficacy has been studied in a few small double-blind studies, in many short-term studies and recently also in long-term follow-up studies. Although favorable results were reported in most of these studies, controversy and disagreement continue regarding the indications for chemonucleolysis and its efficacy.

Chemonucleolysis was introduced to the Netherlands in April 1980 by Sutton and Deutman. An increasing number of orthopaedic surgeons and also some neurosurgeons have been using chemonucleolysis ever since. Nevertheless only a few reports have appeared by Dutch authors on the clinical results (Dekker 1987, Van Alphen et al. 1988, Van Leeuwen 1989). In general, it is of value to know whether a particular therapy is giving the same result in different countries, as these results are also influenced by socio-economic factors, cultural factors and patterns of health care delivery (Nachemson 1989, Payer 1988). Therefore we were interested to ascertain not only the short-term effects of chymopapain treatment on Dutch patients, but also the situation of these patients in the long-term after this treatment and to compare these results to other studies and other treatment modalities.

The questions adressed in this study are:

1. What is the effect of chemonucleolysis in a consecutive series of patients with the herniated lumbar disc syndrome?
2. What is the condition or situation of these patients in the short-term and long-term after chemonucleolysis?
3. Are there any residual complaints? How do they compare with those associated with other treatment modalities reported in the literature.

4.2. MATERIAL AND METHODS

4.2.1. **Protocol**

In the period from April 1980 to January 1989, 900 patients with the herniated lumbar disc syndrome were treated using chemonucleolysis at the Orthopaedic Department of the Roman Catholic (RK) Hospital in Groningen (Dr. R. Deutman).

A consecutive series of the first 200 patients, treated between April 1980 and February 1983, was studied.

In the summer of 1984, all the patients answered a detailed questionnaire (Appendix A) and 173 of them agreed to undergo a physical (Appendix B) and radiological examination.

In september 1988, 195 patients were reassessed using a detailed questionnaire (Appendix C). The remaining five patients had died in the meantime of causes unrelated to chemonucleolysis. So, none of the patients were lost to follow-up.

The data (105 items per patient) were studied and processed by means of a computer.

The effect of chymopapain treatment was established retrospectively from the information recorded in the patients' files and from the information obtained during the first follow- up examination. The grading of the treatment effect depended on the situation or condition of the patient that was obtained within a certain time period. McNab's grading system (McNab 1971) was used to assess the situation or condition of the patients (Table 4.1).

Table 4.1. Grading the situation of a patient according to McNab.

Satisfactory	Excellent . .	No pain, no limitations in work and sport
	Good	Occasional back and/or leg pain, minor limitations
Unsatisfactory	Fair	Intermittent pain interfering with work and leisure activities
	Poor	No improvement, severe limitations, regular analgesics

In general, the judgement of the effect (Table 4.2) was based on the situation which had been reached within 6-12 months after the treatment. If a patient had undergone surgery within (an arbitrary period of) three years because of a recurrence, this judgement was adjusted. If a patient had been operated on because of persisting symptoms, the effect of chemonucleolysis was considered to be poor. If it took more than 6-12 months to reach a

satisfactory situation, the effect of the treatment was considered fair, because it may be assumed that by this time other factors, such as the natural history of the disease, might have been responsible and not chemonucleolysis.

Table 4.2. Grading of the effect of chemonucleolysis.

Satisfactory	Excellent . .	Satisfactory situation < 3 months
	Good	Satisfactory situation < 6-12 months (provided continuing improvement)
Unsatisfactory	Fair	Satisfactory situation > 1 year
	Poor	Unsatisfactory situation > 1 year, operation

At the follow-up examinations in 1984 and 1988, the situation (condition ratings) of the patients was established and compared. But, it must be born in mind that the answers to a questionnaire only indicate the state of affairs at a given moment and are not always representative of the judgement of the treatment per se.

The outcome (effect) of chemonucleolysis was examined in relation to age, sex, duration of symptoms, McCullough's criteria (McCullough 1980), and the type and level of herniation. The situation of the patients at the second follow-up examination in 1988 was compared to that which had been established at the first follow-up examination in 1984 and also to the pretreatment factors.

When relevant, statistical analysis was performed by means of the chi-square tests. In advance we decided to use $p=0.05$ as our level of significance.

4.2.2. **Demographic variables**

The patient group studied consisted of 135 males and 65 females. Their ages at the time of chemonucleolysis ranged from 14 - 72 years, with an average of 37.5 years (Table 4.3 and Fig.4.1).

Table 4.3. Age distribution of male and female patients.

Age	10-19	20-29	30-39	40-49	50-59	>60	total
Males	6	27	46	40	11	5	135
Females	5	7	29	15	7	2	65
Total	11	34	75	55	18	7	200

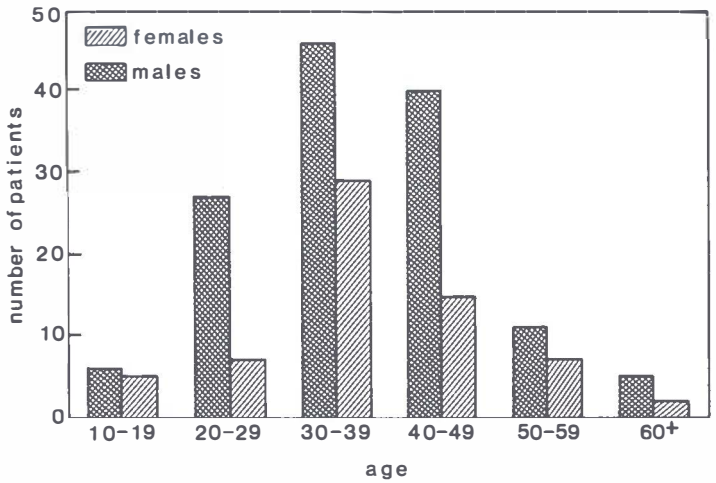

Fig. 4.1. Age distribution.

Fifty-three patients were engaged in heavy (back straining) labour, 49 in administrative work, or driving or school work, 82 in varied light manual work (e.g. housewife) and 16 in standing light work.

Thirteen patients were receiving a disability pension. The mean duration of chronic symptoms, attributable to their degenerative disc disease, was 43 months (range 1 month to 25 years), in males 40 months, in females 51 months.

The mean duration of the most recent symptoms or acute exacerbation which eventually prompted medical treatment, was 15 months.

In 141 patients (70.5%), back pain was the first symptom followed by sciatica at a later stage. In 23 patients (11.5%), the first symptom was unilateral sciatica.

Left-sided sciatica was present in 107 patients (53.5%), right- sided sciatica in 85 patients (42.5%) and bilateral leg pain in 8 patients (4%).

Pain predominantly ($\geq$50%) irradiating into the leg was reported in 170 patients (85%).

Seventy-nine patients reported paraesthesia in a typically dermatomal pattern, 45 patients reported loss of sensation and 65 patients reported muscle weakness (Table 4.4).

Table 4.4. Subjective neurological symptoms before treatment.

Paraesthesia	79	(39.5%)
Loss of sensation	45	(22.5%)
Muscle weakness	65	(32.5%)

Eighty-eight patients (44%) had used analgesics because of the radicular pain.

Before their referral to the Orthopaedic Department, all but 4 patients had already had some form of conservative treatment: 5 patients bed-rest only, 37 patients physiotherapy only and 154 patients bed-rest and various forms of physiotherapy (Table 4.5).

Table 4.5. Conservative treatment before chemonucleolysis.

Bed-rest and physiotherapy	154	(77%)
Bed-rest only	5	(2.5%)
Physiotherapy only	37	(18.5%)
None	4	(2%)

4.2.3. **Physical and radiological examination**

On physical examination shortly before treatment, 52 patients (26%) had difficulty with walking or could hardly walk at all. In the standing posture, 24 patients (12%) showed scoliosis and 81 patients (40.5%) showed flattened lordosis.

The *dynamic* examination showed slight restriction in forward bending in 109 patients (54.5%) and severe restriction in 75 patients (37.5%). In 128 patients (64%) there was a raised centre of rotation on lateral bending.

Table 4.6. Function of lumbar spine.

Severe static and dynamic disturbances	30	(15%)
Minor static and dynamic disturbances	153	(76.5%)
Normal stature and lumbar motion	17	(8.5%)

On *neurological* examination, sensory deficits were present in 42 patients (21%), motor deficits in 40 patients (20%) and reflex changes in 68 patients (34%).

It must be realized that in the disc herniation syndrome, symptoms and findings may vary somewhat over time, especially lumbar motion and

provocation tests. The values for the straight leg raising test (SLR) were noted shortly before treatment. In 89 patients (44.5%), SLR was less than 50% of normal. In 41 patients (20.5%), the pain crossed over into the affected leg when the asymptomatic leg was raised (crossed SLR test).

Supplementary *radiological* examinations were carried out in all patients to establish the level of disc herniation (Table 4.7).

CT as a diagnostic procedure for lumbar disc herniation was introduced to the RK Hospital in 1982. Before that time, lumbar myelography was performed on 11 patients with the clinical suspicion of a herniated disc but the results were equivocal or normal and the diagnosis had to be confirmed by discography, which showed disc degeneration or disc protrusion. In six patients with a normal or equivocal lumbar myelogram, CT showed a herniated disc at L5-S1.

Table 4.7. CT and lumbar myelography.

		Lumbar myelography				
		Not done	Herniated disc	Equi-vocal	Normal	Total
CT	Not done	0	116	6	5	127
	Herniated disc	8	53	1	5	67
	Equivocal	1	0	0	1	2
	Normal	0	3	1	0	4
	Total	9	172	8	11	200

EMG studies were performed in 64 patients and abnormalities were found in 29 of them. EMG findings did not contribute greatly to the diagnosis, so this investigation was discontinued.

4.2.4. **Findings summarized**

The 'rule of five' presented by McCullough and McNab (McCullough and McNab 1983), gives a set of criteria describing the classic patient with a herniated disc.

These criteria are composed of two symptoms (dominant leg pain, paraesthesia in dermatomal pattern), two signs (SLR changes, neurological

signs) and one investigation (lumbar myelogram, CT). To relate the outcome of the treatment in the short-term and long-term with the situation before treatment, the number of positive criteria per patient was noted (Table 4.8).

Table 4.8. Number of positive pretreatment criteria.

	Number of positive criteria					
	5	4	3	2	1	total
Patients	43	63	55	29	10	200

On the basis of all the pretreatment information, a final diagnosis was made for the cause of the radicular syndrome (Table 4.9).

Table 4.9. Final pretreatment diagnosis.

Herniated disc L2-L3	1
Herniated disc L3-L4	2
Herniated disc L4-L5	79
Herniated disc L5-S1	80
Herniated discs L3-L4 and L4-L5	8
Herniated discs L4-L5 and L5-S1	18
Lumbosacral anomaly: hernia at last mobile level (L4-L5)	8
hernia at last formed level (L5-S1)	2
Spondylolysis L5: herniated disc at L4-L5	1
Spondylolisthesis L5-S1: herniated disc at L5-S1	1
	200

The ultimate reasons for performing chemonucleolysis as the next step in the 'conservative' treatment (McNab 1977) for lumbar disc herniation in these patients were: very severe pain on walking as well as with bed-rest in 11 patients; severe pain and limitations in activities of daily living and inability to work in 95 patients; regular pain and limitations in 93 patients; no pain at present but frequent relapses in 1 patient.

4.2.5. **Discography and chemonucleolysis**

The procedure was carried out under general anaesthesia at the radiological department. The patients received promethazine (25 mg) together with the usual premedication and intravenous hydrocortisone during the procedure to prevent a possible anaphylactic reaction.

Needle placement was performed using the right lateral approach in all cases, in accordance with the well-known recommendations (Sutton 1983, McCullough 1980). Discography with jotalaminic acid (Conray 60) at the clinically and/or radiologically suspected levels was always performed to establish the abnormal disc level and to check the exact position of the tip of the needle in the nucleus as well as for documentation purposes.

The contrast injection was recorded on video tape.

Until June 1983, Discase (Baxter-Travenol) was used and since then, Chymodiactin (Smith Laboratories). So, all the patients in this group had received Discase for their treatment.

Chemonucleolysis, usually with 4000 units of chymopapain (Discase), was performed at one level 139 times, at two levels 54 times and at three levels 7 times (Table 4.10).

Table 4.10. Levels of chymopapain treatment (N=200 patients).

L2-L3	1 patient
L3-L4	
L4-L5	55 patients
L5-S1	83 patients
L2-L3 and L3-L4	1 patient
L3-L4 and L4-L5	9 patients
L4-L5 and L5-S1	44 patients
L3-L4, L4-L5 and L5-S1	7 patients

No serious anaphylactic complications were observed in this group of patients, only two mild (type 1 sensitivity) allergic reactions: one patient with a rash over the chest and one patient with angioneurotic oedema.

The day after the procedure, the patient was routinely mobilized and received diazepam and ibuprofen for one to two weeks. A few patients used a brace for some weeks.

Hospitalisation ranged from 1 to 13 days, average 4 days.

The course after chemonucleolysis can be very variable. In general, patients were advised to restrict their activities during the first two or three weeks. After that period, they were allowed to resume light work and they were advised to go swimming and/or cycling in order to improve their condition. If necessary, an exercise program was started under physiotherapy supervision.

At 6 weeks and at three months, they were re-examined routinely.

4.3. EARLY RESULTS

4.3.1. **Complications**

In one patient a serious complication developed, consisting of discitis at level L5-S1, demonstrated on serial radiographs, a bone scan and raised sedimention rates. This patient was treated with bed-rest, analgesics and antibiotics until the pain subsided and the sedimentation rate normalized, after which she was mobilized uneventfully with a brace.

4.3.2. **Relief of sciatica**

Sixty-eight patients (34%) noticed immediate relief of sciatica following the chemonucleolysis. Fifty patients noticed relief of sciatica within one week, 34 patients within one month, 23 patients within three months, 8 patients within six months and 5 patients within 1 year. Eleven patients had no relief of their sciatica. One patient had been treated because of many relapses of his sciatica, but at the time of treatment he had no pain; his sciatica and back pain never returned after the chemonucleolysis. The cumulative index of improvement of sciatica is shown in Fig. 4.2.

After treatment, 27 patients did not experience any back pain. Twenty-one patients complained of stiffness of the lumbar spine. In the remaining 152 patients, the relief of back pain was somewhat slower than the relief of sciatica (Fig. 4.2) and 29 of them even complained of constant and severe backache.

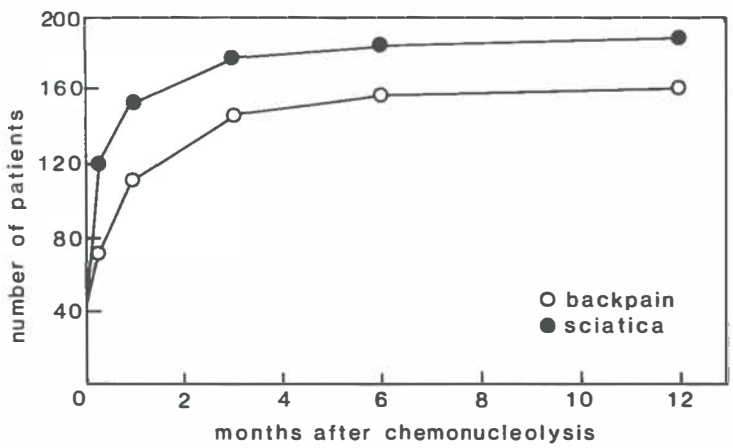

Fig. 4.2. Improvement of sciatica and back pain after chemonucleolysis.

4.3.3. **Treatment in the case of relapse**

Sixty-eight patients had an uneventful, straight forward recovery in connection with chemonucleolysis. More frequently, however, a slow but gradual improvement occurred, often with a temporary relapse of symptoms. This relapse of sciatica and/or backache occurred in 78 patients within a few weeks of the initial improvement (Table 4.11).

Table 4.11. Duration and complaints in the case of relapse after initial improvement.

	Duration of relapse			
	<1 month	1-3 months	3-6 months	>6 months
Back pain only	13	4	7	1
Sciatica only	9	6	3	1
Back pain and sciatica	10	9	4	2
Pain in other leg	5	2	1	1

The treatment of these complaints was usually conservative: physiotherapy in 54 patients, bed-rest in 8 patients and epidural steroids in 3 patients.

Five patients were operated on because of persisting symptoms: two patients had complete relief of sciatica, but suffered from severe backache with clinical and radiological signs of segmental instability. One level spinal fusion at L5-S1 was performed at 9 and at 16 months after chemonucleolysis.

Three patients underwent a laminectomy at another hospital because of persisting radicular symptoms, 8, 10 and 21 months after chemonucleolysis, respectively.

A special problem was encountered in a 31-year-old male with the signs and symptoms of a herniated disc at level L4-L5. The discogram at that level was completely normal, whereas the discogram at level L5-S1 showed leakage of contrast to the symptomatic side. It was decided to treat only the L5-S1 level with 4000 units of chymopapain. His initial recovery was uneventful, but the symptoms returned within 5 months and the CT scan still showed a large herniated disc at level L4-L5. Chemonucleolysis at L4-L5 with 4000 units of chymopapain was then performed. Again, recovery was uneventful. His situation at both follow-up examinations was established as excellent and, despite the early second procedure, the effect of the chemonucleolysis was considered as excellent as well.

A 16-year-old patient with spondylolisthesis L5-S1 had the signs and symptoms of a herniated disc at the same level. He underwent chemonucleolysis at this level with an excellent result. Although disc L5-S1 had collapsed, no increase in slip was noticed on short-term and long-term examination.

4.3.4. **Effect of chemonucleolysis**

The effect of chemonucleolysis was graded in accordance with the critera shown in Table 4.2 and is summarized in Table 4.12.

Table 4.12. Effect of chemonucleolysis treatment (N=200).

Excellent	83	Satisfactory effect in 70% of the patients
Good	57	
Fair	39	Unsatisfactory effect in 30% of the patients
Poor	21	

4.3.5. **Effect in relation to age and sex**

The effect of chemonucleolysis was further analysed for age and sex (Table 4.13 and Fig. 4.3).

Table 4.13. Percentage of satisfactory effect of chemonucleolysis in relation to age and sex.

Age	10-19 (N=11)	20-29 (N=34)	30-39 (N=75)	40-49 (N=55)	50-59 (N=18)	>60 (N=7)	Average (N=200)
Males	100	93	65	70	64	5 of 5	75
Females	100	71	45	67	57	1 of 2	60
Average	100	88	57	69	61	6 of 7 (86%)	70

The best results of chemonucleolysis were seen in adolescents (100% satisfactory effect) (Fig. 4.4) and in males in their third decade (93% satisfactory effect). The worst results were seen in females in their fourth decade (only 45% satisfactory effect). A distinct difference in the results between the sexes was noted: in males 75% satisfactory effect and in females only 60% satisfactory effect ($\chi^2=4.58$, $\upsilon=1$, $0.02<p<0.05$).

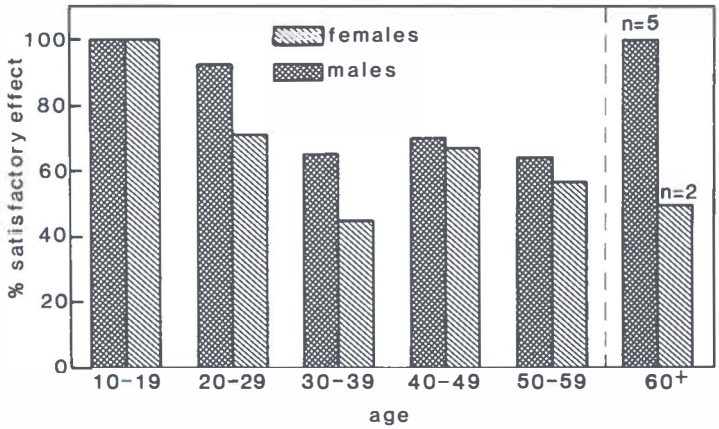

Fig. 4.3. Effect of chemonucleolysis in relation to age and sex.

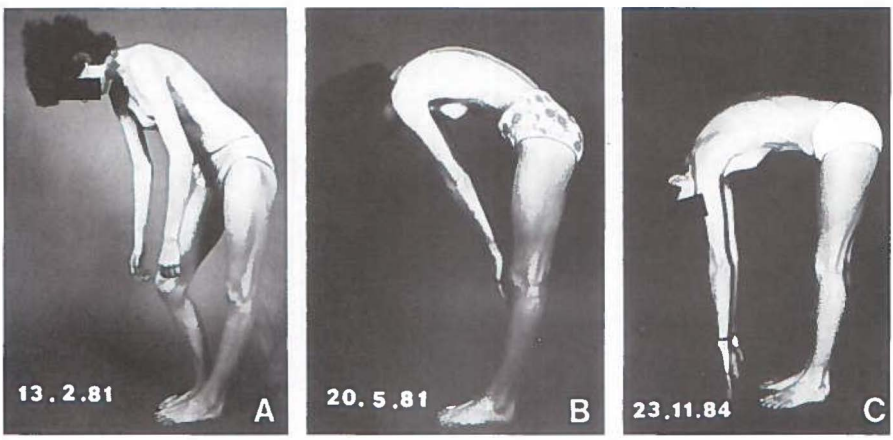

Fig. 4.4. A. Severely restricted forward flexion in a 14-year-old girl with right sided sciatica due to a herniated L5-S1 disc.
B. Three months after chemonucleolysis L5-S1: excellent effect; only some restriction of lumbar mobility.
C. Three years after chemonucleolysis: excellent situation and normal mobility of lumbar spine.

4.3.6. **Effect in relation to the findings before treatment**

The relation between the findings before treatment and the outcome of chemonucleolysis are displayed in Table 4.14.

As we might expect, the more symptoms and signs before chemonucleolysis, the better the effect of this treatment (chi-square analysis: $p<0.01$).

Table 4.14. Effect of chemonucleolysis and the findings before treatment (Rule of five, McCullough and McNab).

Number of positive criteria	Effect of chemonucleolysis (% satisfactory)
< 3	54% (N= 39)
= 3	69% (N= 55)
> 3	78% (N=106)

The most important findings during the physical examination of patients with the herniated disc syndrome include a distinctly positive SLR test, bowstring test or pain crossing over on straight leg raising.

In cases where the initial pretreatment examination showed that the pain crossed over into the affected leg on straight leg raising, the ultimate effect of chemonucleolysis was satisfactory in 81 % of the patients.

The ultimate effect of the treatment was satisfactory in 80% of the patients with a SLR less then 50% of normal and in 62% of those with a SLR more then 50% of normal (Table 4.15).

The difference between these groups was statistically significant with the chi-square analysis ($\chi^2=7.28$; $\upsilon=1$; $p<0.01$): a clear SLR test on the initial examination gives a better chance of a successful outcome of chemonucleolysis.

Table 4.15. SLR and the effect of chemonucleolysis (N=200).

	satisfactory effect	unsatisfactory effect	Total
SLR ≤ 50%	71 (80%)	18 (20%)	89
SLR > 50%	69 (62%)	42 (38%)	111

The influence of the disc level and the number of levels treated is dealt with in chapter 4 section 5.3.

4.4. RESULTS OF THE FIRST FOLLOW-UP EXAMINATION

4.4.1. **Information obtained from first questionnaire**

In the summer of 1984, the whole group was assessed by means of a detailed questionnaire (Appendix A). Patients were asked about pain relief, type and frequency of residual back and/or leg pain, limitations in work and sporting

activities, presence of disturbances in sensibility or motor weakness, need for analgesics and adjuvant therapy.

One hundred seventy-three of these patients also agreed to participate in a physical and radiological examination.

At that time, the duration of follow-up ranged from 16 to 51 months, averaging 25 months.

One hundred and thirteen patients had returned to their normal or comparable working activities; 22 women had resumed the task of housewife. In 28 patients, some adaptations had been made in the work situation.

Four patients had retired, one patient had become unemployed and one was still on sickleave. Thirty-one patients were receiving a disability pension; 28 of them because of their lumbar disc disorder.

The patients had returned to work an average of 14.7 weeks (1-90 weeks) after chemonucleolysis.

Return to sporting activities was possible without limitations in 60 patients, with some limitations in 40 patients. Eleven patients stated that previous sport activities were impossible. Eighty-nine patients had never participated in any form of sport.

If the patient had indicated in the questionnaire that the pain had improved by more than 50% in comparison with the pain before treatment, we assumed the residual pain in back and/or leg to be minor or moderate. If the patient indicated that the pain had improved by less than 50%, we assumed that the pain was still considerable. Seventy-four patients (37%) had no pain at all, 34 patients (17%) had some or considerable backache, 18 patients (9%) had some or considerable sciatica and 74 patients (37%) had some or considerable backache and sciatica.

Neurological symptoms, like the sensory disturbances or the muscle weakness had (subjectively) disappeared in 75 patients, had improved in 70 patients, had not changed in 17 patients and had never been present at all in 35 patients. Three patients stated that their sensory loss had increased: one patient with vascular obstructive disease, one patient with radicular symptoms on physical examination and one patient without any objective symptoms.

Patients were also asked if the chemonucleolysis had come up to their expectations: 132 patients (66%) answered yes, 22 patients (11%) answered no and 46 patients (23%) answered yes, but they had expected more of the treatment.

As mentioned above, at this time 5 patients with a follow-up from 22 to 41 months, had been operated on (8-21 months after chemonucleolysis) because of persisting symptoms.

At the time of the 1984 examination, the *situation* of 66 patients was considered excellent, of 87 patients good (76.5% satisfactory), of 30 patients fair and of 17 patients poor (23.5% unsatisfactory). The comparison of the situation of the treated patients at the follow-up examinations in 1984 and 1988 is reported in Table 4.19.

4.4.2. **Physical examination**

One hundred and seventy-three patients agreed to participate in a physical examination and have one lateral lumbar radiograph taken. The protocol for the physical examination is reported in Appendix B and the results are summarized in Table 4.16.

Table 4.16. Physical examination at first follow-up (N=173).

Mild restricted lumbar motion	24 pat.
Severe restricted lumbar motion	8 pat.
Severe restricted lumbar motion and radicular signs	4 pat.

The relationship between the effect of the treatment and the findings on physical examination are reported in Table 4.17.

Table 4.17. Effect of treatment and findings on physical examination (N=173).

Physical examination	Satisfactory effect	Unsatisfactory effect	Total
- Normal	107 (78%)	30 (22%)	137
- Mild lumbar restrictions	12 (50%)	12 (50%)	24
- Severe lumbar restrictions	2 (25%)	6 (75%)	8
- Radicular signs and symptoms	0	4 (100%)	4
	121 (70%)	52 (30%)	173

As expected, there was a clear relationship between restricted lumbar motion with residual radicular signs and the treatment outcome. The effect of the treatment in two patients was good despite severely restricted lumbar motion; one of them had undergone surgery six months before because of a femoral fracture.

4.4.3. **Radiological examination**

At the time of the first follow-up examination in 1984, a standing lateral radiograph of the lower lumbar spine was taken. Complete radiological records were available on 171 patients.

The disc height reduction, 16-51 months after chemonucleolysis, was compared to the initial disc height reduction and possible disc height re-expansion and development of degenerative changes were studied (Table 4.18).

Table 4.18. Disc height reduction (three months after treatment and at follow-up) and re-expansion at follow-up in % of the initial disc height; N=171, 233 discs injected.

171 complete exam.	L2-L3 (N=2)	L3-L4 (N=16)	L4-L5 (N=98)	L5-S1 (N=117)
- Mean % disc height reduction (at 3 months)	12	31	30	27
- Mean % disc height reduction (at follow-up)	12	26	27	25
- Average % disc height re-expansion	0	20 (N=4)	15 (N=25)	15 (N=17)

In 25% of disc levels L3-L4 and L4-L5 and in 15% of disc level L5-S1, disc height re-expansion was found at the follow-up examination conducted in 1984, 16-51 months after chemonucleolysis (Fig. 4.5). Some degree of degenerative change was noticed after treatment at 23 of these 233 injected disc levels. In another 4 patients, the degenerative changes were more severe.

4.5. RESULTS OF THE SECOND FOLLOW-UP EXAMINATION

4.5.1. **Information obtained from second questionnaire**

In september 1988, a second questionnaire (Appendix C) was sent to 195 patients. In the meantime, 5 patients (follow-up 3-7.5 years) had died of causes unrelated to chemonucleolysis.

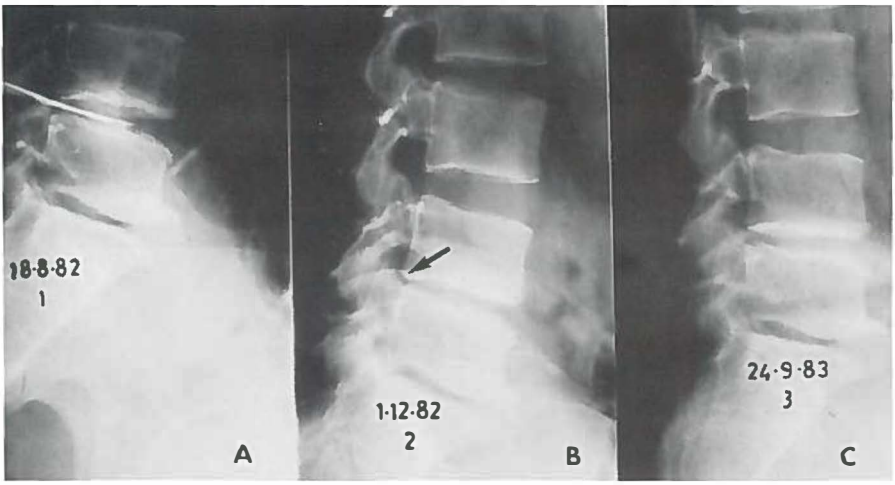

Fig. 4.5. A. Chemonucleolysis of disc L4-L5 in a 42-year-old male with herniated disc at that level.
B. Three months later: a disc height reduction of 50% has developed with slight retroposition of L4 in respect to L5 (arrow).
C. One year after chemonucleolysis: (incomplete) disc height re-expansion has occurred and the retroposition can no longer be demonstrated.

We succeeded in reaching all 195 patients and obtaining their response, in some cases with the aid of civil registration. The follow-up of these 195 remaining patients ranged from 5.5-8.5 years, average 6.5 years.

The condition or situation of the 195 patients was again assessed according to the criteria presented by McNab and compared to the situation at the first follow-up study in 1984 (Table 4.19).

In the course of time the situation of 16 patients (8%) improved from an unsatisfactory situation to a satisfactory one. However, during the same interval, the situation of 17 patients (8.5%) had deteriorated from satisfactory to unsatisfactory.

In 1984, 149 out of the 195 patients (76%) were in a satisfactory situation; at the second follow-up examination in 1988, 148 were in a satisfactory situation (76%).

The differences in the results between the sexes also remained similar: in 1984, 81% of the males and 67% of the females were in a satisfactory situation, as compared to 80% and 68% in 1988, respectively.

Table 4.19. Comparison of the situation of the treated patients at the follow-up studies in 1984 and 1988 (N=195).

		1988				
SITUATION		satisfactory		unsatisfactory		
		excellent	good	fair	poor	total
1984	satisfactory	excellent 40	20	3	1	64
		132		*17*		
		good 23	49	9	4	85
	unsatisfactory	fair 3	13	12	2	30
		16		*30*		
		poor 0	0	7	9	16
total		66	82	31	16	195

During the activities of daily living, 27% of the patients experienced some degree of restriction (for instance, during vacuum cleaning). Nineteen per cent of the patients experienced more severe limitations and were restricted in lifting, household activities and/or gardening.

Changes in employment circumstances were observed when the patients who have (had) a job were taken into consideration (Table 4.20).

Table 4.20. Changes in employment circumstances, housewives omitted (N=195-20=175).

		1984					
		Normal	Adjust-ments	Sick	Disability pension	Retired	Total
1988	Normal	98	11	0	3	0	112
	Adjustments	6	12	1	2	0	21
	Sick	5	1	0	0	0	6
	Disability pension	2	4	0	23	0	29
	Retired	1	0	0	2	4	7
	Total	112	28	1	30	4	175

Of the 31 patients receiving unemployment benefits in 1984, one patient had died because of vascular disease, 2 patients had retired and 5 patients had resumed their work. Six patients, still working in 1984, were receiving a disability pension at the time of the second follow-up examination, in 5 patients because of backache. At the time of the second examination, 3 patients were on sick leave because of back pain, one patient had a tumor of the pituitary gland, one patient had motor neuron disease and one patient was recovering from total hip arthroplasty.

As mentioned above, 13 patients were already receiving a disability pension before chemonucleolysis. A satisfactory treatment result was reached in only two of them. Curiously enough, both these patients retired in the period between the two examinations.

Patients were also asked about residual pain in their back and leg (Table 4.21).

Table 4.21. Back and/or leg pain (N=195).

	Some	Considerable	Total
Back only	47	5	52
Back and leg	42	34	76
Leg only	19	4	23
No pain			44

In the follow-up examination performed in 1988, 52 patients (26.6%) reported some or considerable backache, 76 patients (39%) reported some or considerable pain in back and leg and 23 patients (11.8%) reported some or considerable pain in one leg (Fig. 4.6).

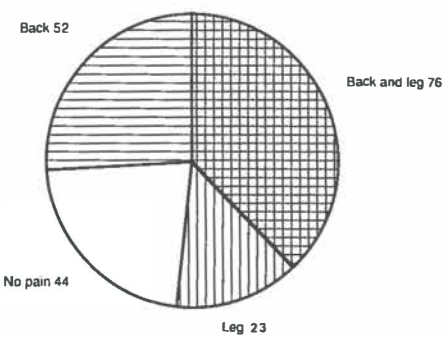

Fig. 4.6. Number of patients with residual minor or considerable back and/or leg pain at second follow-up examination (N= 195).

After chemonucleolysis, 57 patients (29%) had been treated by a physiotherapist, because of pain in the back and/or leg.

Thirty patients (15%) used analgesics incidentally, 17 patients (9%) used analgesics regularly and 6 patients (3%) used analgesics daily.

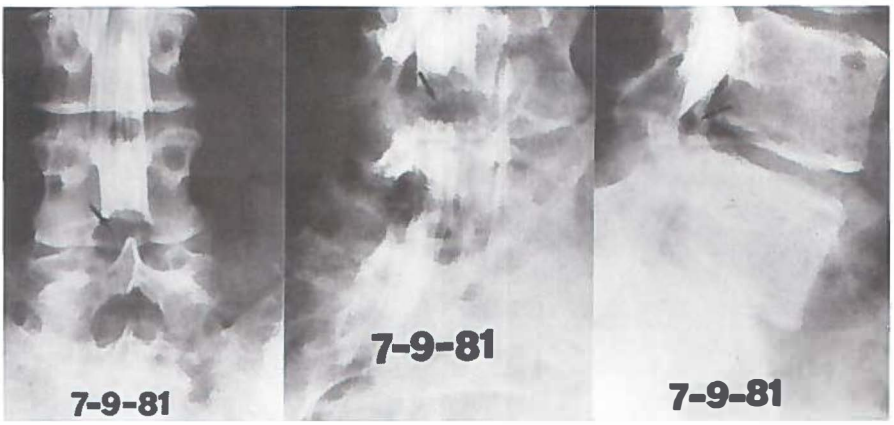

Fig. 4.7. Lumbar myelogram in an 18-year-old woman with *right* sided sciatica due to a large herniated L4-L5 disc (arrows). Discography demonstrated disc protrusions at L4-L5 and also at L5-S1. Chemonucleolysis of both discs was performed with excellent clinical effect.

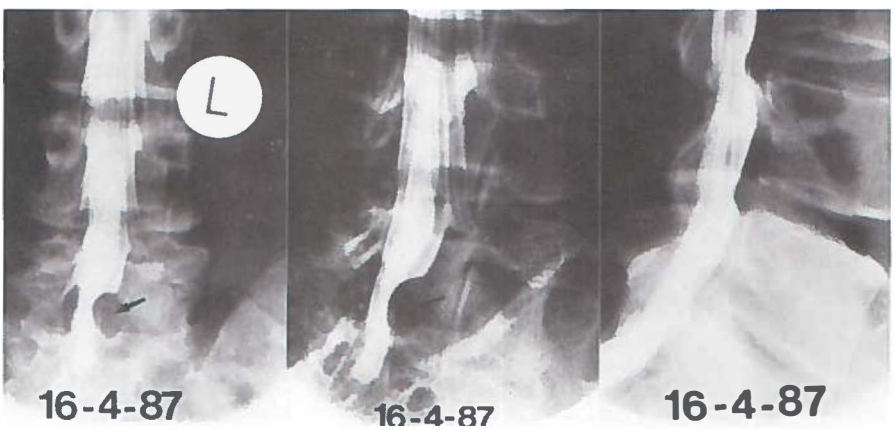

Fig. 4.8. Lumbar myelography of the same patient as in Fig. 4.7 (5½ years after chemonucleolysis L4-L5-S1). *Left* sided sciatica due to a herniated disc L5-S1 (arrows). Repeat chemonucleolysis L5-S1 was performed with good effect. Note 1: normal findings with caudography at L4-L5. Note 2: development of herniated disc L5-S1 despite chemonucleolysis performed earlier at L5-S1.

4.5.2. **Secundary procedures**

Until september 1988, a total of 26 patients had undergone a second procedure (24 times at the same level, twice at a different level). Prior to the first examination in 1984, this had occurred in 5 patients because of persistent symptoms and in one patient, who had a false normal discogram, because of early relapse. After the first follow-up examination, another 4 patients who had persistend complaints (without clear objective symptoms in 3 cases) underwent surgical exploration; an unsatisfactory situation still existed at the second follow-up study. Three patients had a relapse of the herniated disc after a short symptom-free interval, within three years of chemonucleolysis (effect of first chemonucleolysis was assessed as unsatisfactory according to the protocol); two of these patients underwent repeat chemonucleolysis and one underwent a laminectomy; all were in a satisfactory situation at the second follow-up examination.

Thirteen patients had a relapsed herniated disc after an interval of at least three years without symptoms (Fig. 4.7 and Fig. 4.8). In 6 of these patients, a laminectomy was performed (all in a satisfactory situation) and in 7 of them, a repeat chemonucleolysis was performed (6 patients in a satisfactory situation).

At the time of the first follow-up examination, the situation of these patients, who had been symptom-free for at least three years, had been considered satisfactory, as was also the effect of the (first) chemonucleolysis.

The situation at the time of the second follow-up examination in the group of 26 patients who had undergone a second procedure is shown in Fig. 4.9.

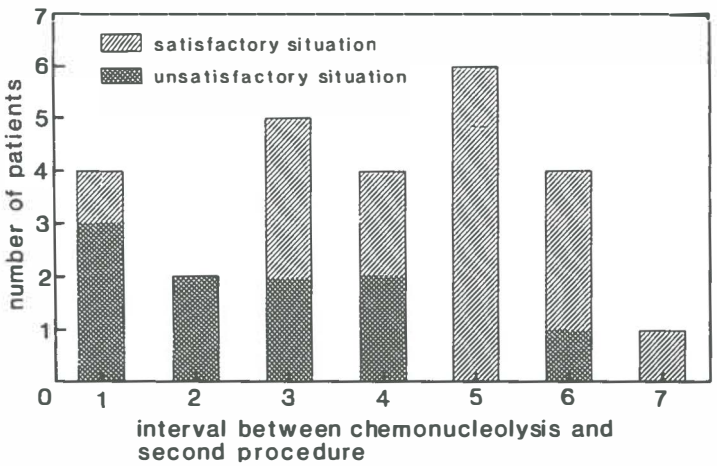

Fig. 4.9. Situation at second follow-up examination in 1988 and interval between second procedure and chemonucleolysis (N=26).

The satisfactory situation that was present in patients who had undergone a second procedure, in case of relapse after a long symptom-free interval, is in contrast to the unsatisfactory situation of the 7 patients who underwent a laminectomy in another hospital because of persistent complaints since the chemonucleolysis.

4.5.3. **Results in relation to disc level(s)**

The effect of chemonucleolysis in relation to the number of pretreatment findings is shown in Table 4.14. At the second follow-up, 56% of the 39 patients who had less than 3 positive criteria before treatment were in a satisfactory situation regarding their lumbar spine disorder, as were 81% of the 102 patients with more than three positive criteria (chi-square analysis: $p<0.01$).

The correlation between the effect of the treatment and the situation of the patients after a long interval, in association with the number of pretreatment criteria, did not change: the more probable the diagnosis of a herniated disc, the better the short-term effect and long-term situation.

The influence of the disc level and the number of levels treated was studied with respect to the ultimate effect of chemonucleolysis and the situation of the 195 patients at the time of the follow-up examination in 1988 (Table 4.22).

Table 4.22. Influence of disc level and number of injected levels on effect of treatment and situation in 1988 (N=195).

		Satisfactory effect of chemonucleolysis	Satisfactory situation at second follow-up
L2-L3 and L2-L3-L4	(N=2)	0	0
L3-L4-L5	(N=8)	3 (38%)	3 (38%)
L3-L4-L5-S1	(N=7)	5 (71%)	5 (71%)
L4-L5	(N=53)	33 (62%)	35 (66%)
L4-L5-S1	(N=43)	33 (77%)	37 (86%)
L5-S1	(N=82)	62 (77%)	66 (80%)

Better results were seen when disc level L5-S1 was involved, but the difference in clinical outcome between single level chemonucleolysis at L4-L5 or at L5-S1 was not statistically significant ($\chi^2=3.33$; $\upsilon=1$; $0.05<p<0.10$).

The number of disc levels injected did not seem to be of much importance. There was hardly any difference between the clinical outcome of patients who had single level chemonucleolysis at L5-S1 and patients with multilevel treatment at L4-L5-S1 or L3-L4-L5-S1 ($\chi^2=0.004$; $\upsilon=1$; $p \geq 0.95$).

No relationship could be demonstrated between residual back pain at the long-term follow-up examination and the number of disc levels injected ($\chi^2=0.008$; $\upsilon=1$; $p>0.90$).

No significant difference could be demonstrated between the frequency of back pain after earlier chymopapain injection at disc level L4-L5 or disc level L5-S1 ($\chi^2= 1.68$; $\upsilon=1$; $p>0.10$).

4.6. DISCUSSION

4.6.1. **Short-term and long-term follow-up studies**

Over the years, there has been much debate about the effectiveness of chemonucleolysis (Brown 1983). In the USA, the method gained a widespread acceptance initially. However, owing to reports on deaths occurring secondary to anaphylaxis and adverse neurological reactions, many neurosurgeons and orthopaedic surgeons abandoned the procedure. In recent years, there have been no more deaths after anaphylaxis and the number of neurological complications has decreased, presumably because of better patient selection for chemonucleolysis and an improved technique for disc puncture.

In Europe, regular surveys (Bouillet 1983, 1989) have indicated no deaths after chemonucleolysis and a lower frequency of allergic reactions than in the USA. From April 1980 until January 1989 an estimated ten thousand chemonucleolysis procedures were performed in the Netherlands; recently, about 1500 procedures were performed each year (±1.5% of the procedures for herniated lumbar disc disease).

The *short*-term results of chemonucleolysis, studied in a few double blind studies and in many retrospective studies, are well documented in the literature (Brown 1983, Simmons 1984, Van Leeuwen 1989):

- 5 double-blind studies on chemonucleolysis versus placebo: N=422 patients.
  Satisfactory result with chemonucleolysis in 58-80%, mean 72%; satisfactory result with placebo in 42-57%, mean 50%.
- 43 retrospective studies: N=7858 patients.
  Satisfactory result with chemonucleolysis in 40-98%, mean 74%.

In the meantime, *long*-term results of chemonucleolysis treatment have become available, mainly from the USA and Canada (Javid 1985, Nordby 1986, Flanagan and Smith 1986, Weinstein 1986, Sutton 1986):

- 13 retrospective long-term studies (Nordby 1986) N=3130 patients. Satisfactory long-term 'result' after chemonucleolysis in 66-93%, mean 77%.

Ours is the first report from the Netherlands which includes the long-term results of chemonucleolysis.

But, what is the definition of long-term (Nordby 1986)? Is it two years or at least ten years?

Weber, in his well-known study (Weber 1983), compared conservative and operative treament for the herniated lumbar disc syndrome. He found a distinctly better result in the operated group at one year, no statistically significant difference at four years and no difference at ten years follow-up. So, perhaps four years is sufficient for long-term evaluation as has been advocated by Weber.

When considering the long-term judgement, it is confusing to speak of the *result* of the treatment when one judges the *situation* of the treated patients at the time of the follow-up examination at, for instance, four or ten years. We must differentiate between the effect or efficacy of the treatment in the short-term and the situation at the moment of the follow-up examinations (Jabaay 1986). Only then can we compare the situation at both follow-up examinations (condition status).

4.6.2. **Data compared**

In the literature, there is great variation in short-term and long-term 'results' of chemonucleolysis treatment (Simmons et al. 1984, Crawshaw 1984, Nordby 1986).

There are several reasons for these differences, such as bias because of incomplete follow-up data, no judgement by independent observers (Javid 1985, Sutton 1986, etc.), different criteria for success/no success (Nordby 1986, Simmons 1984,), no comparable patient population, no comparable after-treatment etc.

The effects of questionnaire design on the determination of end results is considerable (Howe and Frymoyer 1985). This has always been a problem and, apparently, no strongly confident classification can be made.

In contrast to nearly all the studies reported, we were able to achieve a 100% follow-up of our treated patients.

In general, our short-term and long-term conclusions were very comparable to those reported in other studies in the literature. A satisfactory effect was obtained with chemonucleolysis in 100% of the 11 adolescents (9 excellent, 2 good) and in 93% of the 27 males in their third decade (13 excellent, 12 good, and 2 fair). In the adolescent group and in 23 out of the 26 males (one of whom died of unrelated cause) in their third decade, their situation remained satisfactory over the course of time.

A striking feature was the better treatment effect in males (average 75%) than in females (average 60%). Also the condition ratings or situation at the second follow-up examination (195 patients) showed better ratings for males (79% satisfactory) then for females (69% satisfactory). Such differences between the sexes regarding the treatment effect and the long-term condition ratings, have also been found by others (Nordby 1986, Sutton 1986) in their long-term studies.

Nordby found better results in adolescents and in young males similar to those in our group of patients. Sutton did not find age to be a significant factor when analysing his results.

In contrast to these authors, we found the poorest results in females in their fourth decade. In 9 out of the 15 females in this group, we found some indication for the presence of psychosocial or work-related problems, but this was not investigated further.

As might be expected, more disappointing results were found in patients with a less 'classic' clinical presentation:
preoperative SLR >50% of normal and with less than three positive criteria according to McCullough and McNab's rule of five. The long-term unsatisfactory condition-status rating at the second follow-up examination in 44% of these patients, underscores the opinion that we were probably dealing with a degenerative disc problem without a true herniation at the time of treatment in many of these patients.

To examine the possible effect of experience gained with the chemonucleolysis treatment method over the years, we compared the results of treatment and the further course of the patients (1- 100) treated between April 1980 and June 1982 to those (101-200) treated between June 1982 and February 1983. No differences were found.

4.6.3. **Multi-level treatment**

The question of single versus multiple disc injections still gives rise to much controversy (McCullough and McNab 1983, Nordby 1986, Sutton 1989).

At the RK Hospital in Groningen , chemonucleolysis was introduced by Sutton. When it appeared appropriate, multi-level injections were carried out in accordance with his protocol.

The presence of nerve root involvement caused by more than one herniated disc does exist, but is rare. Multi-level discography, performed as part of the chemonucleolysis procedure, will often reveal multiple degenerated discs, especially with increasing age. Performing discolysis at all the abnormal disc levels in a more or less prophylactic manner is not logical nor is it harmless. Besides an increased risk of complications, chemonucleolysis causes further disc degeneration and disturbs the shock-absorbing properties of the injected disc (Wakano 1983, Kahanovitz 1985).

On the other hand, however, like many other authors, we could not demonstrate any detrimental effects in the short-term or long- term after patients had received multi-level injections (Mansfield 1986, Sutton 1989, Wiltse 1975, Nordby 1985, Benoist 1985). In our study, the effect of chemonucleolysis and the residual complaints in the long-term were not related to the number of disc levels injected nor to the disc height reduction or even to disc height re-expansion.

When we consider the patients in whom chemonucleolysis had been performed at one level (N=135), better short-term and long-term results were found at disc level L5-S1 than at disc level L4-L5. However, the difference was not statistically significant using the chi-square analysis ($\chi^2=3.33$, $\upsilon=1$, $0.10>p>0.05$).

In the literature, only a few reports mention this difference (Houser et al. 1986).

The effect of low-dose chymopapain injection appears to lower the incidence of back spasm and back pain in the short-term, with less shrinkage of the disc, but long-term studies are needed to confirm its efficiency (Bonneville et al. 1989).

4.6.4. **Relative contra-indications**

Many relative contra-indications for chemonucleolysis have been mentioned in the literature (McCullough 1983, Brown 1983). In the meantime, however, satisfactory results have been reported on spondylolisthesis (Nordby 1986), repeat chemonucleolysis (Sutton 1986) and adolescent patients (Lorenz 1984, Sutton 1985, Wilms et al. 1986).

In our study group, chemonucleolysis was performed in one patient with spondylolisthesis and in 11 adolescent patients. The short- term and long-term results were satisfactory in all cases. In 9 patients, chemonucleolysis was re-

peated. In 8 of them, a satisfactory effect and satisfactory condition rating was observed at the second follow-up.

It is generally agreed that a free sequestrated disc fragment, which has lost contact with the disc, forms a contra-indication for chemonucleolysis. The diagnosis of a free sequestrum is hard to make on the basis of clinical symptoms alone and is rarely visualized on preoperative radiologic examination. Perhaps MRI would be a more suitable technique for identifying sequestrated disc fragments (Masaryk et al. 1986, 1988), especially with the further improvement in image resolution.

Free sequestrated fragments were found in only ±12% of the patients who underwent surgery because of persistent symptoms or early relapse after chemonucleolysis (Deburge et al. 1985, Jabaay 1986). This percentage is about the same as that found with primary surgery. Therefore, a free fragment does not seem to form a real contra-indication for chemonucleolysis. On the other hand, this observation could provide support for the theory of the anti-inflammatory action of chymopapain (Braun 1981, Taylor and Akeson 1971, Krempen et al. 1975, McNab and McCullough 1971).

4.6.5. **Return to work**

In the USA, some authors consider 'returned to work within six weeks' as the important factor in their judgement of whether the treatment was successful (LeBlanc 1989, Weinstein 1986). This criterium alone is not satisfactory as an outcome measure (Roland 1983, Waddell et al.1988, Waddell 1989) because it depends very highly on the social security system and, as such, is not relevant in this country with an advanced social security system. It is possible that the social security factor was partly responsible for the unsatisfactory results in the 13 of our patients who were already receiving a disability pension before treatment. It appears to be very difficult to return to the employment process after (many) years of sickleave or unemployment. Only two patients (15%), who had retired at the time of the second follow-up, showed a satisfactory effect of the chemonucleolysis. In other studies performed in Canada and the USA, success rates of chemonucleolysis in worker's compensation cases varied from 40-62% (Javid 1988, Jabaay 1986, Sutton 1986, Dabezies 1978).

4.6.6. **Secondary procedures after chemonucleolysis or surgery**

In the 9 patients who underwent surgery because of persistent symptoms and the 3 patients with an early relapse, chemonucleolysis was considered to have failed (6%).

One patient needed a 'two-stage' treatment because, initially, the discogram of the symptomatic L4-L5 disc was interpreted as normal which later appeared to be a false-negative discogram.

False-negative discograms are more frequent when a protrusion involves the degenerated annulus fibrosus rather than the nucleus pulposus (Yasuma et al. 1988).

Thirteen patients (6.5%) had a relapse of their herniated disc after at least three symptom-free years.

In some long-term follow-up studies on chemonucleolysis, the percentage of early secondary procedures varied from 10% -12.7% and for late relapse from 9% - 32% (Table 4.23). In comparison, figures for late relapse of lumbar disc herniation after surgery, varied from 17% - 39% in some studies (Table 4.24).

Table 4.23. Percentage of early and late secondary procedures after chemonucleolysis (long term studies, 1986).

	Follow-up (in years)	Early %	Late %	Total %
Maciunas and Onofrio	10	11	9	20
Weinstein et al.	10	10	32	42
Sutton	6-11	12.7	9.5	22.2
Nordby	8-13			17.3
Mansfield	10-14			29
Present study	6-8.5	6.5	6.5	13

Table 4.24. Percentage of repeat operations after surgery for lumbar disc herniation (long term studies).

	Number of patients	Follow-up (in years)	Repeat operations (in %)
Weber (1983)	54	10	10
Weinstein et al. (1986)	71	10	39
Lewis et al. (1987)	83	5-10	18
Dvorak et al. (1988)	371	4-17	17

4.6.7. **Residual complaints**

Our long-term satisfactory condition status rating/result of 76% agrees with the long-term data given in the literature, which varies from 66-93% (Nordby 1986), average 77%, for a total of 3130 patients.

Many patients experience mild or severe pain in the back and/or leg after chemonucleolysis which has also been reported after surgery (Spangfort 1972, Dvorak et al. 1988, Habbema et al. 1989) for lumbar disc herniation. The pain may occur infrequently, once or twice a year, but can take on a chronic form (Table 4.25).

Table 4.25. Low back pain and radiating pain after different forms of treatment for lumbar disc herniation in some long-term studies.

	Follow-up (in years)	Low back pain	Radiating pain
Weber, conservative treatment (N=49)	4	35% some 12% considerable	26% some 10% considerable
	10	24% some	2% some
Weber, operative treatment (N=56)	4	27% some 11% considerable	14% some 9% considerable
	10	16% some	2% some
Dvorak, operative treatment (N=362)	4-17	48% intermittent 23% constant	47%
Lewis, operative treatment (N=83)	5-10	29% no relief 9% same/worse	27% no relief 11% same/worse
Flanagan, chemonucleolysis (N=191)	10-20	23% mild 20% severe	31% mild 26% severe
Present study, chemonucleolysis (N=195)	6-8.5	46% some 20% considerable	30% some 19% considerable

Because of recurrent complaints, 29% of our patients had undergone some form of treatment recently or had conservative treatment in the years after chemonucleolysis. The literature gives sparse information about this aspect and about the residual complaints in the leg and back in the long-term after chemonucleolysis or surgery.
Flanagan and Smith reported additional treatment in 37% of their patients because of back pain, 10-20 years after chemonucleolysis. Dvorak et al. reported that 37% of their patients were undergoing some form of treatment for back and/or leg pain, 4-17 years after surgery.

At the time of our second follow-up examination, 26 patients (13%) were receiving a disability pension. In Dvorak's (Swiss) series, 14% of the patients were receiving a disability pension; in Weinstein's series (USA), this was the case in 10% of the chymopapain and in 11% of the surgical patients.

The long-term follow-up findings have shown that a large proportion of patients still suffer from the sequela of their degenerative disc disease for many years, irrespective of whether the treatment for their disc herniation was conservative, operative or chemonucleolysis. The degree of improvement of neurological symptoms and signs (muscle weakness, sensory changes, reflex changes) is comparable after the different forms of treatment (McCullough 1980, Weber 1983, Flanagan 1986, Javid 1988), although Braakman et al. have reported an increase in or the development of neurological signs in a number of their patients, assessed one year after surgical treatment (Braakman et al. 1988).

Except in the case of the rare cauda equina syndrome (Spangfort 1972), persistent, intolerable sciatic pain is the most important reason to end conservative treatment. Surgery as well as chemonucleolysis may eliminate or modify the pain a little sooner than nature does (Nordby 1989). Our 'therapeutic' intervention then causes an acceleration in the degenerative process and transforms the initially unstable disc situation (Kahanovitz 1985, Wakano 1985) into a more or less stable and asymptomatic situation, as has already been suggested by Hirsch (Hirsch 1959).

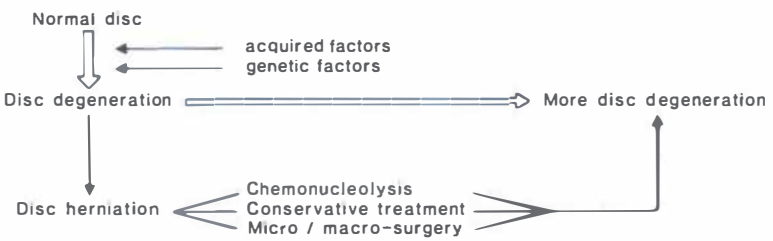

Fig. 4.10. The fate of the lumbar disc.

Therefore, we should be modest when expressing what we can achieve with our different forms of treatment for the uncomplicated lumbar disc syndrome (Fig. 4.10). If conservative treatment fails, we have to choose a treatment which has a reasonable chance of success and offers the least risk of complications in the short-term and long-term. From our own experience as well as from that of many other authors, we can conclude that chemonucleolysis meets these requirements.

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Summary

In this thesis the findings and results are reported of three studies on the anatomical, radiological and clinical aspects of chemonucleolysis for the treatment of lumbar intervertebral disc herniation.

The objectives of these studies are described in Chapter 1.

Many experimental studies on the pharmacology, toxicology and biomechanical effects of intra-discal chymopapain administration have elucidated part of its (possible) mode of action, but many questions relevant to clinical practice still remain.

Some of the complications related to chemonucleolysis have been attributed to an incorrect needle placement technique during lumbar disc puncture, which leads to the intrathecal administration of the drug and subarachnoid haemorrhage. Also damage to nerve roots may occur during lumbar disc puncture, especially in percutaneous discectomy.

In Chapter 2, the needle track position in the lateral approach to lumbar disc puncture is described in relation to the nerve roots, lumbar plexus and intervertebral foramen. With the aid of microplaning techniques and by replacing the needles by small catheters, an undistorted anatomical dissection was obtained and meticulous observation was possible. Damage to the lumbar plexus or nerve root, as well as penetration of the foramen, is more likely to occur when the needle is inserted further away from the midline.

CT scans taken in the plane of the disc will facilitate the planning of safer needle insertion, by allowing measurement and plotting of the site of insertion and the angle of approach.

From this study, it can be concluded that the safest method to avoid puncturing the nerve root or lumbar plexus is to direct the needle just lateral of the facet and to enter the disc from a low point. In this way the facet will also protect against erroneous needle penetration of the intervertebral foramen.

The fate of the herniated disc after chymopapain injection is described and discussed in Chapter 3.

In a prospective study, 30 patients with the herniated lumbar disc syndrome were examined by Computed Tomography before chemonucleolysis and at 3 and 12 months follow-up. Careful inspection and measurements of the CT scans were performed by an experienced neuroradiologist who was unaware of the clinical response to the treatment.

At three months follow-up, the degree of compression of the dural sac and/or nerve root was reduced in 74% of the patients and was found to correlate

with the clinical result. At that time, a focal abnormality still existed in 50% of the patients. However, the reduction in compression of the dural sac and/or the nerve root, proved to be a better guideline to judge the effect of chemonucleolysis than the prolonged existence of a focal abnormality.

An increase in diffuse annular bulging, as judged on CT scans, was noted in 80% of the patients. Chemonucleolysis is certainly not indicated for the treatment of dural sac or nerve root compression due to annular bulging alone, because it would only increase the amount of bulging.

After chemonucleolysis, no evidence of epidural fibrosis was seen on the CT scans of these patients.

The effect of chemonucleolysis treatment and the situation or condition ratings in the short-term and long-term are described in Chapter 4. The study was performed on a consecutive group of 200 patients, who were followed-up for at least 5.5 years.

None of the patients were lost to follow-up!

Data on socio-demographic variables, history, physical examination and supplementary radiologic examinations are presented in Chapter 4 section 2.

The early results are presented in Chapter 4 section 3.

Thirty-four per cent of the patients had an uneventful, straight forward recovery following the chymopapain injection. In some cases, recovery often took many months; 39% of the patients had a (temporary) relapse of symptoms some weeks or months after an initial period of improvement.

The treatment effect (with correction if the patient underwent disc surgery within three years) was satisfactory in 70% of the patients. A distinct difference was noted between the sexes: the effect of the treatment was satisfactory in 75% of the males and in 60% of the females.

Reports have shown that disc surgery in adolescents with a herniated disc is often very successful; chemonucleolysis treatment in all 11 adolescent patients in our group was satisfactory too.

The follow-up findings in the short-term (1984) and long-term (1988) are reported in Chapter 4 sections 4 and 5.

The condition rating of 75% of the patients was considered to be satisfactory over the years.

In agreement with the literature, a better treatment effect and better short-term and long-term condition ratings were seen in patients with the 'classic' radicular symptoms. Unsatisfactory short-term and long-term results were encountered in patients receiving a disability pension. Patients who underwent surgery because of persistent symptoms after chemonucleolysis had poor results.

No correlation was found between the clinical short-term and long-term condition ratings and the degree of disc height reduction or the number of disc levels injected.

In the long-term, the frequency of persistent back and/or leg pain, the need for physiotherapy, disability pensions and the frequency of secondary procedures, appears to be very similar for the various treatment modalities for lumbar disc herniation. The long-term follow-up findings have shown that a large proportion of patients still suffer from the sequelae of their degenerative disc disease for many years, irrespective of whether the treatment for their disc herniation was conservative, operative or chemonucleolysis.

Surgery as well as chemonucleolysis will accelerate the degenerative process and eliminate or modify the pain a little sooner then nature does.

Samenvatting

In dit proefschrift worden de bevindingen en resultaten beschreven van drie studies over anatomische, radiologische en klinische aspecten van chemonucleolysis in de behandeling van de hernia nucleï pulposi lumbalis.

Door vele experimentele studies over pharmacologie, toxicologie en biomechanische effecten van de intra discale chymopapaïne toediening is een deel van de (mogelijke) werkingen en bijwerkingen van het chymopapaïne duidelijk geworden. Echter vele vragen met betrekking tot de klinische praktijk zijn gebleven. De vraagstukken en doelstellingen van de drie uitgevoerde studies zijn geformuleerd in Hoofdstuk 1.

Enkele van de aan chemonucleolysis toegeschreven complicaties zijn een gevolg van een onjuiste techniek van de discuspunctie, waardoor het enzym intrathecaal is terechtgekomen en subarachnoïdale bloedingen heeft veroorzaakt. Bij de lumbale discuspunctie en vooral bij percutane discectomie kan ook beschadiging optreden van de uittredende zenuwwortel(s).

In Hoofdstuk 2 wordt de positie van de punctienaald in de laterale benadering van de lumbale discus beschreven in relatie tot zenuwwortels, lumbale plexus en foramen intervertebrale. Om een ongestoorde anatomische dissectie te verkrijgen en een gedetailleerde bestudering van de lumbale discuspunctie mogelijk te maken, is gebruik gemaakt van microplaning. De naalden zijn daartoe vervangen door kleine catheters.

Indien de punctieplaats te ver uit de mediaanlijn wordt gekozen is de kans groter dat wortels en plexus kunnen worden getroffen, terwijl bij het maken van een geringe hoekfout reeds binnendringen van het foramen kan optreden. Indien CT scans, genomen in het vlak van de discus, aanwezig zijn, kan door meting van insteekplaats en benaderingshoek, een veiliger discuspunctie mogelijk worden.

Uit deze studie kan de conclusie worden getrokken dat punctie van uittredende zenuwwortel en/of lumbale plexus kan worden vermeden door de punctienaald in het vlak van de discus, juist lateraal van het facetgewricht, te richten en de discus laag te penetreren. Op deze manier zal het facet ook een accidentele penetratie van het foramen intervertebrale kunnen belemmeren.

Het beloop van de lumbale discusherniatie na chemonucleolysis wordt beschreven en besproken in Hoofdstuk 3.

In een prospectief opgezette studie zijn 30 patienten met een radiculair syndroom op basis van een lumbale discushernia vòòr en respectievelijk 3 en 12 maanden nà chemonucleolysis onderzocht met Computer Tomografie van

het (de) behandelde discusniveau('s). Een zorgvuldige beoordeling van de CT scans werd verricht door een ervaren neuroradioloog, die onkundig was van het klinische beloop bij de betreffende patient.

Op het CT beeld werden oorzaak (focale uitpuiling van de discus) en gevolg (compressie of verdringing van dura, wortel en epidurale vet) onderscheiden en bestudeerd.

Drie maanden na chemonucleolysis kon bij 74% van de patienten. een afname worden geconstateerd van de compressie van durale zak en/of zenuwwortels. Op dat moment was op de CT scan bij 50% van de patienten echter nog wel een focale uitpuiling van de discus te zien. De afname in compressie bleek goed te correleren met het klinische resultaat en leek een betere maatstaf te zijn om het effect van de chemonucleolysis vast te stellen dan het persisterend aantoonbaar zijn van een focale discusuitpuiling.

Na chemonucleolysis werd bij 80% van de patienten een toename geconstateerd in de 'bulging' van de annulus fibrosus.

Chemonucleolysis is dus zeker niet geïndiceerd bij patienten waarbij compressie van durale zak of zenuwwortels alleen lijkt te worden veroorzaakt door de diffuse 'bulging' van de annulus fibrosus, aangezien dit door chemonucleolysis alleen maar zal verergeren.

In deze groep patienten werden met CT geen aanwijzingen gevonden voor de ontwikkeling van epidurale fibrose. Dit is een voordeel van chemonucleolysis, aangezien epidurale fibrose de oorzaak kan zijn van recidiverende (en slecht te behandelen) klachten.

In Hoofdstuk 4 wordt het klinisch effect van de chemonucleolysis behandeling beschreven, alsmede de resterende klachten, beperkingen en situatie-score op korte en lange termijn.

Een aaneengesloten groep van 200 patienten werd onderzocht, met een follow-up duur van 5,5-8,5 jaar en een respons van 100%!

Het onderzoeksprotocol, de patientengegevens en demografische gegevens van vòòr de behandeling, alsmede gegevens van anamnese, lichamelijk onderzoek en aanvullend radiologisch onderzoek, staan vermeld in Hoofdstuk 4.2.

Het resultaat van de chemonucleolysis behandeling in deze groep patiënten staat beschreven in Hoofdstuk 4.3. In 34% van de patienten was de radiculaire pijn direct na de chemonucleolysis verdwenen en volgde er een voorspoedig herstel zonder complicaties. Vaak echter verliep de genezing trager, of ging soms gepaard met tijdelijke toename van klachten, en vergde het herstel meerdere maanden.

Het effect van de chemonucleolysis (met correctie indien alsnog binnen drie jaar een discectomie werd verricht) kon bij 70% van alle patienten als bevredigend worden beschouwd (75% van de mannen en 60% van de vrouwen). Alle 11 adolescenten in deze groep hadden een goed resultaat van de chemonucleolysis en een goed beloop op lange termijn.

De bevindingen van de vervolg onderzoeken op korte (1984) en lange (1988) termijn staan beschreven in Hoofdstuk 4.4 en Hoofdstuk 4.5.

De situatie op korte (16-51 maanden na chemonucleolysis) en lange termijn (5.5-8.5 jaar na chemonucleolysis) was bij 75% van de behandelde patienten bevredigend te noemen.

In overeenstemming met gegevens uit de literatuur werden betere resultaten op korte en lange termijn bereikt naarmate de symptomatologie vóór de behandeling meer 'klassiek' radiculair was geweest. Onbevredigende resultaten op korte en lange termijn werden gezien bij patienten, die voor de behandeling reeds een WAO uitkering genoten. Ook bij patienten, die in verband met persisterende klachten werden geopereerd, bleef de situatie in de loop der jaren slecht.

Er kon geen correlatie worden vastgesteld tussen het klinische beloop op korte en lange termijn enerzijds en het verlies van discushoogte na chemonucleolysis en het aantal geïnjiceerde disci anderzijds.

Als op de lange termijn de diverse behandelingsmethoden voor een radiculair syndroom ten gevolge van een HNP met elkaar worden vergeleken, blijken vergelijkbare frequenties te bestaan van persisterende rug en/of beenklachten, behoefte aan fysiotherapie, arbeidsongeschiktheid, en secundaire invasieve ingrepen.

Uit deze lange termijn studies leren wij dat vele patienten nog vaak de gevolgen ondervinden van hun degeneratieve discus'ziekte' en dat dit onafhankelijk is van het feit of de behandeling van de opgetreden discusherniatie indertijd conservatief, dan wel operatief of chemonucleolysis is geweest.

Zowel operatieve therapie als chemonucleolysis versnellen de discusdegeneratie en kunnen de ischialgie wat eerder doen verdwijnen c.q. doen afnemen dan volgens het natuurlijk beloop zou geschieden.

Appendix A

Questionnaire 1, 1984

Patient number:

Name:
Date of birth:
Address:
Telephone:

A. Before treatment:

1. What is your profession? .....
   (also student, housewife etc.)

2. For how long had you been experiencing back pain and/or leg pain before the chymopapain injection? .....

3. For how long were you unable to perform your occupation because of these complaints (before treatment)? .....

4. Please give the ratio between back pain and leg pain on the scale below (encircle):

Back pain	100	90	80	70	60	50	40	30	20	10	0
Leg pain	0	10	20	30	40	50	60	70	80	90	100

5. Did you experience any sensory disturbances or muscle weakness in the affected leg? .....

6. What treatment did you have before chemonucleolysis (e.g. bed-rest, physiotherapy, etc.)? .....

B. After treatment:

7. Improvement in leg pain appeared within (encircle):
   1 day / 1 week / 1 month / 3 months / 6 months / 1 year /
   no improvement / worse

8. Improvement in back pain appeared within (encircle):
   1 day / 1 week / 1 month / 3 months / 6 months / 1 year /
   no improvement / worse

9. Did the pain recur? yes / no
   if yes: 9a. How long after chemonucleolysis? . . . weeks
   9b. How long did it last? . . . . . weeks/months
   9c. Localization of pain (encircle):
   back / same leg / other leg
   9d. Did you receive any treatment for these complaints?
   yes / no
   If yes, what treatment . . . . . .

10. Please indicate the pain at this moment in comparison with the pain before treatment (encircle the relevant description):

no pain anymore	excellent > 85% improved	good 50-85% improved	fair 25-50% improved	no improve-ment	worse

11. Localization in the case of persistent pain (encircle):
back / leg / back and leg / no pain

12. Do you experience any limitation with activities of daily living because of these complaints (encircle)?
yes / no / some
Comment .....

13. Do you experience any limitation with sports (encircle)?
yes / no / some / no sport
Comment .....

14. Can you perform your normal occupation?
If yes (encircle): normal / adaptations / other work,
namely .....
If no: sickleave / disability pension / unemployment / other,
namely .....

15. How long after the treatment did you resume your work? . . . . . weeks / . . . . . months

16. After chemonucleolysis, the sensory disturbances or the muscle weakness (encircle): disappeared / improved / did not change / increased / irrelevant

17. Do you still need analgesics because of back and/or leg pain? (encircle): yes, almost every day / yes, incidentally / no

18. Did you need any other form of treatment after chemonucleolysis because of back pain or radiating pain in the leg (e.g. operation, acupuncture, manipulation, physiotherapy)?
    yes, ...
    no, ...

19. Did the chemonucleolysis treatment came up to your expectations (encircle): yes, completely / yes, but not completely / no

20. Do you have any remarks about your chymopapain treatment?
    .....
    .....

Appendix B

Physical examination, May/June 1984

Patient number:

Name:
Date of birth:

Encircle the relevant description

1. Walking: Normal / disturbed / cannot walk

2. Examination lumbar spine (static):
   Normal
   Leg length discrepancy . . . . cm
   Scoliosis (functional / structural)
   Desequilibration
   Lordosis (flattened / increased)

3. Examination lumbar spine (dynamic):
   Forward flexion: fingertips from the floor . . . .cm
   Schober minor . . . . . cm
   Lateral bending: normal / symmetrical reduced / asymmetrical reduced

4. Strength abdominal muscles: Normal / reduced / weak

5. Kemp test: Negative / positive

6. Hip function: Normal / abnormal left / right
   Knee function: Normal / abnormal left / right

7. Sensory changes: None / L3 / L4 / L5 / S1 left / right

8. Motor deficit: None / L3 / L4 / L5 / S1 left / right

9. Reflex changes: Patellar tendon reflex Normal / abnormal left / right
   Achilles tendon reflex Normal / abnormal left / right

10. Provocation tests:

Straight leg raising right leg . . .degrees
Straight leg raising left leg . . . .degrees
Crossed straight leg raising yes / no
Bowstring test positive / negative

11. Muscle wasting: Quadriceps muscles, difference . . . cm
Calf muscles, difference . . . . . cm

12. Palpation: Muscle tone and spasm: Normal / abnormal
Tenderness localization: L1 / L2 / L3 / L4 / L5 / S1 / sacrum / iliac crest

Appendix C

Questionnaire 2, september 1988

Patient number:

Name:
Date of birth:

Please encircle the relevant description.

1. Please indicate the pain at this moment in comparison with the pain before treatment:

No pain anymore	Excellent > 85% improved	Good 50-85% improved	Fair 25-50% improved	No improve-ment	Worse

2. Localization in the case of persistent pain:
   back / leg / back and leg / no pain

3. Do you experience any limitation with activities of daily living because of these complaints?
   yes / no / some
   Comment .....

4. Which sports do you practise? .....
   Do you experience any limitation with sports?
   yes / no / some / no sport
   Comment .....

5. My profession is (also housewife, student) .....
   Can you perform your normal occupation?
   If yes (encircle): normal / adaptations / other work,
   namely .....
   If no: sickleave / disability pension / unemployment / other,
   namely .....

6. Do you still need analgesics because of back and/or leg pain?
   yes, almost every day / yes, incidentally / no

7. Did you need any other form of treatment after chemonucleolysis because of back pain and/or radiating pain in the leg
(e.g. operation, acupuncture, manipulation, physiotherapy)?
yes, ...
no, ...
N.B. In the case of operation, please report: when, where, treating physician and the result of the operation:
.....

8. Remarks
.....
.....

Appendix D

PUBLICATIONS on CHEMONUCLEOLYSIS

Konings, J.G., Williams, F.J.B., Deutman, R.
The effects of chemonucleolysis as demonstrated by computerised tomography.
J. Bone Joint Surg., 66-B, 417-21, 1984

Wilms, T.S., Konings, J.G., Deutman, R.
Chemonucleolysis ter behandeling van hernia nuclei pulposi bij jeugdige patienten.
Ned. Tijdschrift Geneeskunde, 130, 680-4, 1986

Konings, J.G., Williams, F.J.B., Deutman, R.
Computed Tomography (CT) Analysis of the effects of Chemonucleolysis.
Clin. Orthop., 206, 32-6, 1986

Konings, J.G., Veldhuizen, A.G.
Topographic Anatomical Aspects of lumbar disc puncture.
Spine, 13, 958-61, 1988

PAPERS presented on the subject of CHEMONUCLEOLYSIS

'Prospective CT-study of the effects of chemonucleolysis'
Autumn Meeting British Orthopaedic Association, Nottingham, England, September 21, 1983
Abstract in J. Bone Joint Surg., 66-B, 277, 1984

'CT-scan onderzoek naar de effekten van chemonucleolysis'
NOV-meeting, Dijkzigt Ziekenhuis, Rotterdam, October 8, 1983
Abstract in Acta Orth. Scand., 55, 399, 1984

'Chemonucleolysis ter behandeling van de lumbale HNP bij jongeren'
NOV-meeting, Academisch Ziekenhuis, Utrecht, May 14, 1985
Abstract in Acta Orthop. Scand., 57, 282, 1986

'Topographic anatomical aspects of lumbar disc puncture'
Orthopaedica Belgica Congres, Brussel, Belgium, May 22, 1986

'CT-Analysis of the effects of chemonucleolysis'
Orthopaedica Belgica Congres, Brussel, Belgium, May 22, 1986

'Anatomical aspects of lumbar disc puncture'
Second Annual Meeting, International Intradiscal Therapy Society, Orlando, Florida, USA, March 10, 1989

'Chemonucleolysis, six year follow-up'
Second Annual Meeting, International Intradiscal Therapy Society, Orlando, Florida, USA, March 11, 1989

'Lange termijn resultaten van chemonucleolysis'
NOV-meeting, Ned. Zeehospitium, The Hague, June 3, 1989

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Curriculum vitae

The author, Joop G. Konings, was born on the 22th of October 1948 in Nieuw-Helvoet, The Netherlands. He attended Grammar school (H.B.S.-B) in Brielle before embarking on technical studies in 1966 at the University of Technology in Delft. He showed special interest in holography and in theoretical aspects of electronics and he obtained his Masters degree in Electrical Engineering at the Department of Theoretical Electro-technics in 1974 (Prof. Dr. Ir. A.T. de Hoop).

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During this time, different studies about certain aspects of chemonucleolysis were initiated. His training was continued and completed in the Department of Orthopedics in the University Hospital of Groningen (head: Prof. Dr. H.K.L. Nielsen), where he remained as an orthopedic surgeon after his qualification in May 1988.