TREATMENT OF LUMBAR INTERVERTEBRAL DISC LESIONS BY DIRECT INJECTION OF CHYMOPAPAIN*

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Chymopapain is an enzyme that has the ability to disrupt the mucopolysaccharide-protein complex of an intervertebral disc. It has no apparent effect upon the collagen of the intervertebral disc, of the longitudinal ligaments, or of the dura mater, nor does it have any effect on the lipid of nerve tissue. No deleterious effects have been seen in animals after intrathecal or epidural injection of chymopapain in doses more than sufficient to remove the nucleus pulposus of an intervertebral disc in that animal (Smith, Garvin, Gesler and Jennings 1963; Garvin, Jennings, Smith and Gesler 1965; Stern and Smith 1966).

Our interest was stimulated by the work of Thomas (1956). He reported that minute amounts of crude papain injected intravenously in rabbits had a profound effect on all cartilaginous tissues of the rabbit's body. It occurred to one of us that this action of papain might be useful if the enzyme were applied locally in pathological conditions of cartilage usually requiring surgical excision. The first experiments were carried out by injecting papain directly into a transplantable, osteocartilaginous tumour in mice. The results were not impressive, but subsequent experiments directed at the intervertebral discs of rabbits showed promise. It was soon apparent that collaboration with men working in other fields was essential. This was accomplished with the generous cooperation of two pharmacologists, Dr Robert M. Gesler and Dr Paul J. Garvin; a pathologist, Dr Robert B. Jennings; and a biochemist, Dr Ivan J. Stern. The activity of chymopapain was tested in hundreds of intervertebral discs of rabbits and dogs, as well as its local and systemic toxicity after intrathecal, epidural, intraperitoneal, or intravenous injection. Its effect upon tissues such as the dermis, peripheral nerves, muscles, capillaries and larger blood vessels was also investigated, as well as its influence on the cardiovascular system and the coagulability of blood. Its potential as an antigen was tested in guinea-pigs and rabbits. Twenty-two paraplegic dogs suffering from herniated intervertebral discs were treated and those not recovering were killed and examined. No deleterious effects attributable to chymopapain were detected in these hundreds of experimental animals when the enzyme was applied properly.

In July 1963 we started to investigate in humans the possibility of removing the offending portion of an intervertebral disc by this chemical means. The details of experiences with the first ten patients so treated were published by Smith (1964). The present report concerns the first seventy-five patients treated and followed, up to now, for from four to thirty months.

THE ENZYME

Chymopapain is a major proteolytic enzyme occurring in papaya latex. For these studies, it was prepared by techniques similar to those used for its initial isolation by Jansen and Balls in 1941. It is a sulfhydryl enzyme, stable over a wide range of pH, and is very soluble in water. *In vitro* it has a wide spectrum of activity over a wide range of pH, as shown by the rennin-like precipitation and hydrolysis of casein, and the hydrolysis of haemoglobin. The preparation used by us contained about 500,000 chymopapain-tyrosine unit equivalents per gramme. It was administered at pH 6.5 in water containing 0.01 M cysteine hydrochloride and 0.001 M disodium edetate as activators. Chymopapain acts very powerfully on chondromucoprotein,

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as shown by the fact that 10 micrograms will discretely remove the nucleus pulposus of a lumbar intervertebral disc in an adolescent rabbit. Initial digestion rates obtained *in vitro* indicate that 1 milligram may hydrolyse 1 gramme of wet human nucleus pulposus in one hour. Other proteolytic enzymes tested by us have either not been as effective, or, if as effective, have not shown so favourable a toxicity profile.

CLINICAL MATERIAL

All patients chosen to undergo this method of treatment were considered to be candidates for operation. A presumptive diagnosis of nerve root compression was made from physical findings and radiographs of the lumbar spine. Most patients had typical findings of lumbar list, muscle spasm, and limitation of motion, with reflex, motor and sensory changes in a lower extremity and limitation of straight leg raising. None showed signs or symptoms of a lesion of the cauda equina and in none was there paralysis of a leg.

Twenty-two of the seventy-five patients had previously undergone laminectomy, with temporary or incomplete relief of pain. Four had had spinal fusion in conjunction with the laminectomy. All complained of sciatica and all had pain severe enough to require analgesics. Their conservative treatment had always been prolonged before this method of treatment was instituted. The prime methods used were bed rest and traction, and the usual forms of physiotherapy. Other methods employed by us, or other physicians, were various forms of immobilisation of the lumbar spine; intramuscular, intrathecal and epidural injections of cortisone; spinal manipulations; postural exercises; muscle relaxant drugs given orally; and injections of sclerosing solutions into the ligaments of the low back. The age range was from twenty-two to seventy-four years; there were twenty-one women and fifty-four men. Twenty-six of the seventy-five patients had compensation claims or litigations pending. An attempt was made to choose, if possible, only emotionally stable patients for such an untried procedure.

Myelography was not used by us but had been used previously by others in twenty-one patients. We felt that the possibility of a Pantopaque[†] arachnoiditis could introduce a variable into a clinical experiment. Our thirty-seventh patient, whose case is described in detail later, had had a myelograph that was followed by catastrophic results (Case 37).

The experimental nature of the procedure was explained to all patients and when possible they were required to see or contact previously treated patients. They were also advised that an exploratory laminectomy should be done if their symptoms were not considerably relieved within a few days after the injection.

TECHNIQUE OF INJECTION

The word "chemonucleolysis" was coined to describe the procedure of "injection of chymopapain into an intervertebral disc."

In the first patient the injection was done with local analgesia. In spite of a considerable amount of preliminary medication, she did not obtain relief of pain even with large amounts of novocaine and intramuscular morphine. After this all patients received general anaesthesia.

The technique now used is as follows: The patient is placed on the left side on a transradiant bridge between two tables. The skin is surgically prepared, the back is draped and the surgeon is gowned and masked as for any operative procedure. Needles are inserted into the lower lumbar intervertebral discs by either the lateral or the postero-lateral approach (Fig. 1). The third lumbar disc is not investigated unless clinical findings point to probable nerve root compression at that level. The fourth and fifth lumbar discs are examined routinely. Initially the postero-lateral approach was used exclusively in the belief that penetration of the dura could usually be avoided. At the fifth level the interlaminar space is commonly wider and the dural sheath comparatively narrower; if a needle is aimed to penetrate the disc just

[†] Pantopaque[®] is a trade name for *Iophendylate* injection, U.S.P., a mixture of isomers of ethyl iodophenylundecylate.

medial to the articular facet, it should be lateral to the dura. At the third and fourth levels, however, the interlaminar spaces are narrow or the laminae may even overlap: an approach other than in the midline is difficult and penetration of the dura is common.

A lateral approach at the upper levels is not confounded by these anatomical problems and is usually rapid and easy. A six-inch long, 18-gauge spinal needle with stylet is introduced at an angle of 45 degrees or more, starting about eight centimetres from the midline, and at the level of the third or fourth lumbar disc. One has a tendency to direct the needle posteriorly, rather than anteriorly, to the centre of the disc. A portable image intensifier is used and speeds the procedure. The first needle is introduced gradually with frequent checks of its position on the screen of the intensifier. It should be directed just lateral to the articular facet and just

FIG. 1

The various approaches for injection into the intervertebral disc.

superior to the transverse process. The soft tissues offer little resistance to the passage of the needle in contrast to the complete resistance offered by bone. There is a characteristic sensation when the disc is penetrated, akin to that of pushing a needle into an unripe pear. If the tip of the needle is seen to be anterior to the centre of the disc, yet disc penetration has not been felt, the needle must be directed more posteriorly. If care is taken, penetration of structures anterior to the disc is extremely unlikely (Figs. 2 to 4).

When, on the lateral view, the needles appear to be properly placed in the centre of the discs, their position is checked by rotating the portable intensifier to the antero-posterior position. The needle in the fourth lumbar disc is used as a surface guide to the lateral approach to the fifth lumbar disc. This needle is inserted at approximately the same site as the one in the fourth disc, but is directed slightly more posteriorly and approximately 30 degrees distally. In some patients, either because of a particularly narrow fifth space or because it is deep seated in relationship to the iliac crest, the lateral approach is impossible. In these instances the postero-lateral approach is used. A 4-inch, 20-gauge needle is introduced between the spinous processes of the fifth lumbar and first sacral vertebrae about one inch from the midline. The needle must usually be directed somewhat distally; the degree of angulation is determined by viewing its shadow on the image intensifier screen (Figs. 2 to 4).

The ease of introduction and the time involved vary with the experience of the operator and the anatomical peculiarities of the individual patient.

After the needles appear to be properly placed as seen on the image intensifier, radiographs are taken in two projections for confirmation and record. An injection of 0.5 to 1 millilitre of Hypaque[®]* is made at each level; this amount is sufficient for diagnosis. Much diagnostic weight is given to the degree of resistance experienced with the injection—a normal disc will

FIG. 2

FIG. 3

FIG. 4

The lateral approach. Figure 2—Introduction of needles. Figures 3 and 4—The needles in position.

accept 0.5 millilitre of fluid only if considerable force is applied to the plunger of the syringe, and when the pressure is eased some fluid will stream back into the syringe. A pathological disc will usually accept 1 millilitre of fluid with ease.

Radiographs are taken in two planes. The antero-posterior view is of little value diagnostically and can be omitted. Hypaque diffuses out of the disc space in a few minutes

* Hypaque[®] is a trade name for sodium diatrizoate, U.S.P.

so the films should be taken as soon as possible after injection. Chymopapain, 2 milligrams, dissolved in 0.5 millilitre of sterile distilled water, is then slowly injected into the disc or the discs considered to be causing the nerve root compression. This is followed by 0.1 millilitre of sterile water to ensure that all the enzyme has been delivered into the disc. The needles are left in place for five minutes and are then slowly removed.

COURSE AFTER CHEMONUCLEOLYSIS

Sciatica—Almost all patients were relieved from sciatica within twenty-four hours after chemonucleolysis. Patients who had severe sciatica even when in bed often stated that their leg pain had gone by the time they were alert after light general anaesthesia. The assessment of those who were comfortable before injection if in a flexed position in bed, but were unable to sit or stand without distressing sciatica, was postponed, since they were kept in bed for thirty-six to forty-eight hours after treatment.

Loss of leg pain when a patient first walked was usually incomplete. Mild residual thigh or calf ache was often noted with resumption of activity, but this pain subsided completely within the next few weeks. There were two exceptions: after months of observation, each of these patients estimated that residual sciatica was about half of its former intensity and that it was not incapacitating. These two patients had undergone laminectomies before the chymopapain injection.

Among the early patients in the series three experienced no relief following chemonucleolysis. In two of these discography showed apparent extrusion. All had second injections within a period of three weeks. In all, the sciatica was relieved after the second injection. Shortly after the third of these patients had the second injection we decided to operate, for confirmation of diagnosis, upon any patient who was not markedly relieved of his symptoms within two or three days of the injection. Such a sequel was not, however, encountered among the forty-eight patients treated subsequently.

Back pain—The loss of sciatica after chymopapain injection was similar in pattern to that after successful laminectomy. The same did not apply to back pain. The back pain that a patient experienced following a laminectomy could not be used as a basis to forecast the discomfort we might expect to observe after a few needle tracks had been made for the injection.

In twenty-eight out of seventy-five cases back pain after injection was severe and analgesic drugs were needed. This pain was variously described as a "severe muscle spasm," a "charley horse," "like I was being broken in two," and "worse than having a baby." Its onset was slow; it usually appeared about six to eight hours after injection and usually lasted twelve to twenty-four hours. The spasms were located in the lumbar region, were not necessarily initiated by activity, reached peak intensity lasting a few seconds and then subsided to a dull ache, leaving the patient apprehensive of further attacks. In contrast to such intense reaction, twelve patients had no complaints of back pain or ache after injection. Most patients suffered a few episodes of mild to moderate lumbar muscle cramps and a slowly subsiding lumbar ache and stiffness. This was generally characterised as "different" in site and severity from that present before injection. It was usually described as being at one or both posterior superior iliac spines. The side involved bore no relationship to the side of injection or to the side of the sciatica. The duration of this stiffness and soreness varied. Most patients were free from symptoms three or four weeks after injection. In approximately 20 per cent it persisted beyond a month. In this group the soreness was described as progressively less noticeable at each subsequent visit and was often described as a stiffening after inactivity.

No correlation has been found between the severity and duration of back pain after injection and the number of discs injected or the dose of chymopapain. The patient who typically experienced severe muscle spasms after injection was the stocky, muscular man with a considerable lumbar list before injection who stated that his sciatica was secondary to his

back pain. Conversely, the patient whose complaints before injection were of severe sciatica and negligible backache usually had a smooth course after injection with minimal lumbar pain. **Physical signs**—The diminution of physical signs was comparable to that after successful laminectomy—that is, a return of muscle power, loss of paraesthesiae, increase in range of straight leg raising, improvement or complete return of reflex activity, and recovery of lumbar mobility. Those patients who showed a severe lumbar list before chemonucleolysis did not appear to lose the list after injection any more rapidly than those undergoing laminectomy. Before chemonucleolysis, most of the seventy-five patients showed a constant and circumscribed point of tenderness to pressure on either side of a lower lumbar spinous process. Pressure at this point caused the patient radiating pain or a “funny feeling” in the buttock or some portion of the lower extremity. Commonly, this pressure point was rapidly lost after chemonucleolysis and the point of tenderness was transferred to one or both posterior superior spines of the ilium. At times lumbar tenderness and sciatica were on the right side and the chemonucleolysis was effected on the right side, yet the tenderness after injection was prominent on the left side and absent on the right.

Headache—Headache was a prominent complaint after chemonucleolysis when we were using the postero-lateral approach to the discs. Like that found after lumbar puncture, it was worse in the upright position and at times needed recumbency for a few days. In no case did it persist. In the last thirty-two cases the lateral approach was used and none of these patients has complained of headache.

Walking—Patients treated early in the series were allowed to leave hospital at periods from two to as long as ten days after chemonucleolysis. The three patients who were injected twice were kept in hospital for a month. The average stay was five days. On discharge, the patients were not restricted in their activities, but were advised to attempt whatever they could do without undue discomfort. Those with sedentary occupations usually returned to work within three weeks; those with heavy manual occupations returned to work within five or six weeks.

RESULTS

It is better to use the word *experiences* rather than *results*, because the period of follow-up is short, the number of patients few, and the condition so typically chronic and recurrent.

The first seventy-five patients were assessed four to thirty months after injection (Table I).

TABLE I
RESULTS AFTER CHEMONUCLEOLYSIS

Results	No previous spinal surgery	Previous spinal surgery	Totals
Good .	46	11	57
Fair .	5	6	11
Poor .	2	5	7
Totals .	53	22	75

A “good” result implies complete relief of sciatica and backache, with no residual incapacity for work, sports, or avocations. “Fair” is defined as marked, but incomplete, relief with residual pain not causing incapacity for work. A “poor” result implies no improvement; one patient in this category is actually worse.

One patient of twenty-five years who had not had previous operation obtained a “good” result. He suffered recurrent protrusion of an intervertebral disc at another level twenty-three months after chemonucleolysis (Case 16).

All seventy-five patients were assessed by personal examination by the authors, and by frequent critical analyses by visiting colleagues. Serial lumbar flexion and extension radiographs were a feature of the assessment. None of the patients was assessed by questionnaire.

Among the twenty-two patients who had undergone previous spinal operation one had had three laminectomies and is rated as good. Eight had had two laminectomies; two are rated as good, four as fair and two as poor. Thirteen had had one laminectomy; eight are rated as good, two as fair and three as poor. Four patients had had spinal fusions associated with laminectomy; two of these are rated as good and two as fair. The latter two have lost their sciatica, but a lessened degree of back pain persists, which is not incapacitating for work.

Seven patients are rated as poor results. Two of these had not had previous spinal operation. The details of response to chemonucleolysis of one of these are described later (Case 37); the particulars of the other are as follows:—

Case 1—A forty-year-old woman lost her severe left sciatica four hours after chemonucleolysis, but back pain was severe and unremitting. After three weeks the back pain became localised in the right lumbar area and now was associated with a right sciatica. Laminectomy showed no pathological findings save for a small free fragment of fibrocartilage at the fifth lumbar level on the right. She was relieved of right-sided sciatica, but some back pain persisted. There was gradual return of left sciatica in the following year. Since that time, multiple consultations with many types of specialists, another laminectomy by a neurosurgeon, and all manner of physical therapy and medications have been unavailing in relieving symptoms, which are unsubstantiated by objective findings. This patient was claiming compensation and before injection had received psychiatric treatment. Obviously such a patient was a poor choice as the first candidate for this clinical experiment.

Five of the seven patients whose results were rated as “poor” had undergone previous spinal operation. Two of these patients (Cases 33 and 57) were seventy years of age and had intractable pain following laminectomy. In both cordotomy had been recommended by neurosurgeons. Treating these patients by chemonucleolysis was more compassionate than objective; neither of the two experienced relief. Two other patients (Cases 51 and 52) did not experience significant relief of pain, but did show notable regression of physical signs. Neurosurgical consultation was obtained in each, and myelography was read as negative. In each case a second laminectomy was done by the consultant neurosurgeon. No abnormality was found at any of several levels explored, nor was there evidence of nerve root compression by displaced intervertebral disc tissue. Neither patient experienced relief of symptoms after laminectomy. The fifth patient in this group (Case 38) had not been relieved of low back pain and sciatica by two laminectomies. After chemonucleolysis she was only partly relieved of her sciatica for six months and it then recurred in its original intensity. Eight months later she was found to be suffering from generalised lymphosarcoma.

Radiographic changes after injection—In the seventy-five patients 135 discs were injected. The multiplicity of discs injected is explained by our early scepticism about the infallibility of the discograph. Recently we have been more discriminating in our decisions.

Of the 135 disc spaces injected, many showed appreciable narrowing within five to seven days, and all except thirteen showed some degree of narrowing on radiographs taken within a month of injection. Twelve discs showed slight continued narrowing two months after injection. The degree of narrowing varied from something less than 10 per cent to as high as 60 per cent. We are unable to correlate the degree of narrowing with the amount of enzyme injected, the age and size of the patient, or the apparent pathological state of the injected disc. No adjacent, uninjected discs have shown narrowing.

CASE REPORTS

Case 20—This is an example of the forty-six patients who had had no previous spinal operation and who showed *good* results from chemonucleolysis. A thirty-eight-year-old man did heavy work as lineman for a telephone company. He had suffered intermittent, incapacitating attacks of back pain and left sciatica for four years. The most recent episode had been unrelieved by seventeen days of bed rest,

traction and physiotherapy. The physical findings included a flat back with list to the right, marked limitation of the left straight leg raising, loss of the left ankle jerk, and hypoaesthesia over the lateral aspect of the left foot. He estimated his pain to be 50 per cent in the back and 50 per cent in the left lower extremity.

FIG. 5

FIG. 6

FIG. 7

FIG. 8

Case 20. Figure 5—The discograph showing protrusions at fourth and fifth lumbar levels. Figure 6—Radiograph before injection. Figures 7 and 8—Radiographs one week (Fig. 7) and five weeks (Fig. 8) after injection showing narrowing of spaces after injection.

In October 1963 a discograph was interpreted as showing protrusions at the fourth and fifth lumbar levels (Fig. 5). Chymopapain solution, 9 milligrams, was injected into each disc. The patient's left sciatica disappeared approximately six hours after chemonucleolysis. He complained of a sore, stiff back for four days, but this subsided gradually and he returned to work in four weeks.

Lateral radiographs were taken on the day of injection, a week later, and five weeks later (Figs. 6 to 8). A week after injection there was apparent narrowing of the fourth and fifth spaces. A month

later the narrowing of the fourth space had increased. Subsequent films taken at intervals during the past twenty-four months have shown no further change. The patient has continued to do heavy work without back pain or sciatica.

Case 2—This is an example from the group of eleven patients who had had previous spinal operation and who obtained "good" results after injection. A thirty-two-year-old man had a laminectomy in 1962 for removal of a protruded disc at the fourth lumbar level. He had relief of his right sciatic pain for approximately two months, but then suffered a recurrence. Pain had not been relieved or diminished by two weeks of bed rest and physiotherapy in the hospital. Myelography one week before injection showed indeterminate findings. Physical examination revealed a lumbar list to the left with marked limitation of lumbar extension, slight limitation of right straight leg raising, depression of the right ankle jerk, and hypoaesthesia of the plantar aspect of the right foot. He estimated his pain to be 25 per cent in the back and 75 per cent in the extremity.

FIG. 9
Case 2—Discograph (Fig. 9) and radiographs three months (Fig. 10) and twenty-one months (Fig. 11) after injection. Note the narrowing of the intervertebral spaces.

Figure 9 shows the discograph of July 1963. Chymopapain, 10 milligrams, was injected at the fourth lumbar level and 16 milligrams at the fifth. The patient stated that his right sciatica had gone five or six hours after chemonucleolysis. He returned to his occupation as a police officer three weeks after injection. He has been free from sciatica and back pain for the past two years despite vigorous physical activity. Radiographs of the lumbar spine taken after injection showed narrowing of the fourth and fifth intervertebral spaces (Figs. 10 and 11).

Case 23—A fifty-seven-year-old male dairy worker was incapacitated for two months because of back pain and right sciatica. There was no improvement after one month of bed rest. The physical findings were: complete loss of lumbar lordosis, limitation of lumbar extension, marked limitation of right straight leg raising, and depression of the right knee and ankle jerks. The patient estimated that his pain was 75 per cent in the back and 25 per cent in the right lower extremity. Radiographs showed marked degenerative changes at the lumbo-sacral level (Fig. 12).

In October 1963 a discograph suggested protrusion at the fourth lumbar level (Fig. 13). Nine milligrams of chymopapain were injected at that level only, because we were unable to penetrate the lumbo-sacral disc with a 20-gauge needle. The patient stated that his right sciatica disappeared approximately twelve hours after injection. He was discharged from the hospital one week later with slight low back pain. He returned to work eight weeks after chemonucleolysis and in the past twenty-seven months has had no complaints of back or extremity pain, even though his occupation entails

frequent lifting of milk cans weighing 100 pounds. Figure 14 shows the narrowing at the fourth lumbar space twelve days after injection. Radiographs taken at varying intervals since have shown no further narrowing.

FIG. 12

FIG. 13

FIG. 14

Case 23. Figure 12—Radiographs before injection show marked degenerative changes. Figure 13—The discograph. There is a suggestion of protrusion at the fourth lumbar level. Figure 14—Narrowing of the fourth lumbar space twelve days after injection. Compare with Figure 12.

Case 18—A twenty-six-year-old man suffered recurrent, incapacitating attacks of low back pain over a period of eleven years. When first seen, he complained of right sciatica of five weeks duration, unrelieved by bed rest. Examination showed complete loss of lumbar lordosis with a list to the left, and limitation of lumbar extension. There was a palpable shelf at the fifth lumbar level. Straight leg raising was limited on the right, but the knee and ankle reflexes were equal and active and there were no sensory changes. He estimated his pain to be 75 per cent in the right low back and 25 per cent in the extremity. Radiographs showed a minor degree of spondylolisthesis at the lumbo-sacral level

with a defect in the pars interarticularis at that level (Fig. 15). A discograph was done in October 1963 (Fig. 16). Chymopapain solution, 8 milligrams, was injected into the fourth lumbar disc and 10 milligrams into the fifth. The patient stated that he had complete relief from sciatica six hours after the injection, but a diminishing degree of low back pain and stiffness persisted for six weeks. A radiograph

FIG. 15

FIG. 16

FIG. 17

Case 18. Figure 15—Radiograph before injection. Note the spondylolisthesis with pars interarticularis defect. Figure 16—The discograph. Figure 17—Six weeks after injection. There is marked narrowing of the fourth and fifth lumbar spaces.

taken six weeks after injection showed marked narrowing at both levels (Fig. 17). When assessed in January 1966 the patient had no complaints of back or leg pain. Subsequent radiographs have shown no further narrowing.

Case 16—At the time of writing, one case of recurrent disc protrusion following chemonucleolysis has been encountered. A twenty-five-year-old man was disabled for ten months because of right low back pain and right sciatica. His symptoms were unrelieved by various measures, including a chairback

brace and seven weeks of bed rest, traction and physiotherapy. He estimated his pain to be approximately 50 per cent in the back and 50 per cent in the right lower extremity. The physical findings were compatible with nerve root compression at the fourth lumbar level. In October 1963 discography was done and read as questionably normal at both the fourth and fifth levels. Chymopapain, 9 milligrams, was injected at each of these levels. After injection the patient was not relieved of his back pain or sciatica, and radiographs of the lumbar spine taken ten days after injection showed no evidence of narrowing at either injected level. Accordingly, three weeks later, a second injection was done. At that time radiographs showed 10 to 20 per cent of narrowing at the fifth lumbar level, so chymopapain was injected only at the fourth lumbar level. The patient stated that his sciatica disappeared approximately six hours after the second injection, but back stiffness and soreness subsided slowly and it was three months before he returned to manual work. Radiographs taken in January 1964 showed narrowing at the fourth lumbar space estimated to be 30 to 40 per cent and narrowing at the fifth lumbar space estimated to be 10 to 20 per cent (Figs. 18 and 19). Until September 1965

FIG. 18

FIG. 19

Case 16—Radiograph before injection (Fig. 18) and three months after the second injection (Fig. 19). Note the marked narrowing of the fourth and fifth spaces.

the patient was free of symptoms even with heavy physical activity; then, after a severe lifting strain, he had a sudden onset of pain in the right low back accompanied by right sciatica. His symptoms were unrelieved by three weeks of bed rest, physiotherapy and traction. The physical findings suggested nerve root compression at the fifth lumbar level. A laminectomy was done in October 1965. A large nuclear protrusion was found at the fifth lumbar level and was removed; the posterior longitudinal ligament was intact. Findings at operation were otherwise negative. The fourth lumbar level was not explored. The patient's convalescence was rapid and he returned to light work three weeks after operation. He has been doing heavy work for the past two months.

It is noteworthy that this patient's symptoms were relieved and physical signs lessened by the second injection at the fourth lumbar level. The recurrence of pain and sciatica in 1965 proved at operation to be associated with a herniation at the fifth lumbar level. The fragment of herniated disc removed at operation weighed 2 grammes. The microscopic appearance of the fibrocartilage was no different from that of the same tissue removed from patients who had not had previous chemonucleolysis. Areas of focal degeneration were seen interspersed with areas of apparently normal fibrocartilage with mature chondrocytes.

Histological appearances after injection—We have examined histologically portions of five other human lumbar discs which were removed surgically after chemonucleolysis. The histological appearances have been unremarkable. Chymopapain affects only the chondromucoprotein

of the disc, leaving the collagen intact. The chondrocytes likewise do not appear to be directly affected (Thomas 1956). Chondrocytes synthesise the chondromucoprotein matrix of cartilage, which might, therefore, be replaced to some degree after chemonucleolysis. One might further expect to see widening of intervertebral disc spaces previously narrowed after chymopapain injection. We have not seen this in man, but it has been observed in three experimental animals who had been injected with chymopapain. Chemonucleolysis, like surgical extirpation, can only be expected to relieve the symptoms of disc disease and in no sense can be considered a "cure." We would speculate that the cure of disc disease awaits some biochemical method of preventing or anticipating the hormonal or metabolic influence believed to be responsible for the original breakdown of the chondromucoprotein in the discs of some people (Naylor 1962).

COMPLICATIONS OF CHYMOPAPAIN INJECTION

CASE REPORTS

Case 37—One patient, the thirty-seventh in this series, suffered severe complications after injection. A fifty-six-year-old man endured acute back pain and left sciatica which were unresponsive to conservative measures, including two weeks of bed rest and traction. The physical findings were compatible with nerve root pressure at the fourth or fifth lumbar level. A myelograph revealed a persistent filling defect between the fourth and fifth lumbar vertebrae. It was estimated that approximately 5 millilitres of Pantopaque[®] were left in the subarachnoid space. Five days later discography was done by the postero-lateral approach at the third, fourth and fifth lumbar levels. Difficulty was encountered in gaining entrance to the fifth lumbar disc space and multiple dural punctures were probably made before the needle was properly placed. The discographs were read as showing degeneration at the third and fifth lumbar levels and extrusion at the fourth level with epidural leak of the contrast medium. Chymopapain, 10 milligrams, was injected into each disc. The patient's sciatic pain disappeared six hours after injection, but he complained of severe back and abdominal pain. For the ensuing five days he showed signs of an unlocalised acute abdominal crisis of such severity as to raise the question of exploratory laparotomy. Seven days after the injection, the patient's abdominal distress was subsiding and he had no complaint of back or extremity pain, but some weakness in dorsiflexion of the left foot was noted. On the tenth day he was paraplegic. Laminectomy from the fourth thoracic to the fifth lumbar vertebra showed normal tissue save for a haemorrhagic arachnoiditis centred at the tenth thoracic level. There was no evidence of protrusion or extrusion at the third, fourth or fifth lumbar disc spaces. There was no recovery from the paraplegia.

Discussion—This experience prompted a reassessment of the toxicity of chymopapain when injected intrathecally or epidurally. Experiments in rabbits, cats and dogs were repeated (Garvin and colleagues 1965) and were extended to include the rhesus monkey. These experiments showed that chymopapain injected intrathecally or epidurally in a human could not initiate the clinical events observed in this patient.

In none of the hundreds of animals injected with chymopapain have we found arachnoiditis at necropsy. When chymopapain is injected intrathecally in sufficient quantity to be toxic, it causes bleeding from the poorly supported vessels of the pia-arachnoid and the animal usually dies in a few hours with increased intracranial pressure. The toxicity produced appears to be a haemorrhagic pressure phenomenon and may be alleviated. For example, lethal dose in 50 per cent of dogs after intrathecal injection is 0.25 milligram per kilogram. If 1 milligram per kilogram is injected intrathecally in the lumbar area, a water manometer attached to a needle in the cerebello-medullary cistern will show a rise from a normal of approximately 45 millimetres of saline to more than 400 millimetres in fifteen minutes. If 1 millilitre per kilogram of cerebrospinal fluid is removed by cisternal puncture the pressure will drop and the animal will survive with no neurological sequelae; necropsy done months later shows no abnormal features. This sequence was confirmed by Macnab (1965) in another way. After laminectomy in a rabbit, a one-quarter inch square window was cut in the dura and, with a long, bent needle, 30 milligrams of chymopapain were instilled intrathecally through the window one and a half inches cephalad. This dose was 300 times the lethal intrathecal dose

for such an animal. The laminectomy wound, but not the window, was closed after the injection. The rabbit survived without apparent deleterious effects. The dural window operated as a vent for the resulting increased cerebrospinal fluid pressure. We have confirmed this observation in cats.

Our patient received a chymopapain dosage of 10 milligrams in each of three lumbar discs. Even if this total chymopapain dosage of 30 milligrams had been injected intrathecally, one would have expected the patient to have shown some signs of increased intracranial pressure, but this was not so.

What caused the paraplegia? It has been pointed out by others (Howland, Curry and Butler 1963) and confirmed by us that 2 or 3 millilitres of Pantopaque[®] retained intrathecally for five to seven days in a dog will regularly cause arachnoiditis. If some of the dog's own blood is then injected intrathecally a few days later a more severe reaction will ensue which commonly results in paraplegia. This sequence probably occurred in this patient: a large amount of retained Pantopaque for five days, a difficult transdural needling procedure at the fifth lumbar level, and intrathecal haemorrhage.

Case 31—Another patient caused us considerable concern. He was a fifty-one-year-old engineer who had suffered neck, shoulder and arm pain for more than a year without relief from conservative measures. Discography by the antero-lateral approach demonstrated a "ruptured disc" at the sixth cervical level and this disc was injected with 10 milligrams of chymopapain through the same needle. His pain was partially relieved for two weeks, but then recurred with increasing severity, and in the subsequent six weeks he developed a Brown-Séquard syndrome. An operative exploration was made by a neurosurgeon who found an extramedullary, intradural vascular mass at the sixth cervical level, fed by an artery coming through the dura. A tiny biopsy specimen was read as "consistent with granulation tissue," and he made a clinical diagnosis of pseudoaneurysm, which he apparently felt was caused by lytic action of chymopapain on the artery. Approximately four months after the diagnosis of pseudoaneurysm had been made the patient was operated upon again because of worsening paralysis and, on this occasion, examination of the mass removed showed the lesion to be a malignant haemangioendothelioma.

This case shows the difficulty of diagnosis in the cervical region as compared to that in the lumbar area. For this reason, we have confined all subsequent trials to patients with lumbar pain and sciatica.

Case 27—A forty-three-year-old man suffered intermittent attacks of low back pain with left sciatica for five years. He had been incapacitated for seven weeks by a severe episode of pain unrelieved by bed rest, physiotherapy and traction. Physical findings were considered to be typical of a disc lesion at the fifth lumbar level.

In October 1963 discography was done by the postero-lateral approach and showed a probable extrusion at the fourth lumbar level and a protrusion at the fifth (Fig. 20). Chymopapain, 10 milligrams, was injected at the fourth lumbar level and 7 milligrams at the fifth lumbar level. The course after injection was unusual in that he lost his back pain and lumbar tenderness in a few days, but his left sciatica persisted.

Three weeks after the first chemonucleolysis the findings at discography were unaltered, so a second injection was done. Chymopapain, 9 milligrams, was injected into the fourth and fifth discs. Immediately after the injection the patient manifested anaphylactic shock with a marked fall in blood pressure and a diffuse pilomotor reaction with erythema of the skin. He was treated with intramuscular steroids and vasopressor drugs and recovered within an hour. He lost his sciatica within twelve hours and was discharged from the hospital six days later. Three weeks later his serum was tested for antibodies against chymopapain. None was

FIG. 20

Case 27—The discograph showing epidural leak of the contrast medium.

demonstrated by various agglutination and precipitation tests. Intradermal test to the Hypaque^a used for discography was positive on that occasion but negative a week later.

Chymopapain is a relatively poor antigen, being approximately twenty times less anaphylactogenic for guinea-pigs than ovalbumin and forty times less than horse serum. This patient's serum showed no antibodies against chymopapain three weeks after the injection, so we assumed that the acute hypersensitivity reaction was probably caused by the contrast medium.

Case 56—A thirty-two-year-old furniture mover developed a disc space infection after chemonucleolysis. He had suffered from severe low back pain and left sciatica for seven weeks, which had not responded to bed rest, physiotherapy and traction. His physical findings were considered to be typical of a disc lesion at the fifth lumbar level.

FIG. 21

FIG. 22

Case 56. Figure 21—Area of lysis in the lower part of the body of the fourth lumbar vertebra, secondary to disc space infection—fifteen weeks after injection. Figure 22—Ten months later the lytic area is filling in. The fourth disc space has not narrowed further.

Discography in October 1964 showed apparent degeneration at the fourth lumbar level and protrusion at the fifth lumbar level. These discs were injected with 2 and 4 milligrams of chymopapain respectively. The patient stated that he lost his sciatica about eight hours later. He was discharged from hospital in four days and returned to work in a month. However, two weeks later he noted a gradual onset of low back pain which increased to severe "muscle spasms" without radiation into the buttocks or extremities. This severe pain subsided after three weeks of hospitalisation, but during that time the cause of the pain was obscure. Repeated lumbar radiographs were negative, the blood sedimentation rate was only slightly elevated and only moderate tenderness to palpation was found in the lumbar area. The diagnosis of low grade infection was finally made when radiographs taken fifteen weeks after injection showed an area of destruction in the inferior portion of the body of the fourth lumbar vertebra (Fig. 21). The patient returned to his heavy occupation in February 1965 and has had no complaints of back or extremity pain since then. Radiographs taken in November 1965 showed filling in of the defect in the vertebral body without continued narrowing of the disc space (Fig. 22).

Case 19—A fifty-one-year-old labourer had for several months suffered incapacitating back pain and right sciatica. Discography showed degeneration at the fourth lumbar level and protrusion at the fifth lumbar level. Chymopapain, 8 milligrams, was injected at the fourth level and 10 milligrams at the fifth level. Sciatic pain disappeared in five hours, but back pain persisted although less severe. Seven months later the patient was admitted to hospital because of persistent back pain, localised over the sacrum. This pain and spasm were intermittently present one or two times a day and were severe, but lasted only a few minutes. When they were not present the patient had no symptoms. Neurological examination was negative, but a myelograph showed a block at the fourth lumbar level. Laminectomy by a neurosurgeon revealed a small area of filmy arachnoiditis at the fifth lumbar level. The patient's convalescence was good and he experienced considerable, but incomplete, relief of back pain. For the reasons expressed previously chymopapain was not considered a cause of the arachnoiditis.

Incidental untoward effects—Other non-specific side effects recorded after chemonucleolysis include: giant urticaria ten days after injection (Case 40); a recurrence of acute glaucoma four days after injection (Case 32); unexplained gastrointestinal bleeding one month after injection (Case 24); a Marie-Strümpell type of arthritis one year following injection (Case 43); a massive myocardial infarction fifteen months after chemonucleolysis (Case 11); and lymphosarcoma fourteen months following injection (Case 38). We do not feel that any of these complications are attributable to chymopapain.

DISCUSSION

The symptoms caused by a lumbar intervertebral disc lesion can be relieved by removing the offending disc tissue either surgically, or chemically by the injection of chymopapain into the disc. When protruding or extruding disc material removed at operation is used as a substrate for chymopapain in the test tube, the chondromucoprotein is dissolved whereas the collagenous parts are unaffected (Stern and Smith 1966). The collagen remaining represents 44 per cent of this material by dry weight (Mitchell, Hendry and Billewicz 1961), but its mass is a very small percentage of the total because the water-trapping properties of the chondromucoprotein portion cause it to occupy several thousand times more space (Schubert 1964). The probable action of chymopapain is to disrupt the fine structure of the chondromucoprotein, so removing its water-binding capacity and markedly reducing pressures on contiguous structures. The degraded chondromucoprotein is then of sufficiently small molecular size to diffuse out of the disc. The rapid loss of sciatica in most of our patients can best be explained by this mechanism.

The ultimate fate of the injected enzyme is unknown. When injected into an animal's intervertebral disc, it has not been recovered even at zero time. It apparently bonds immediately to the disc tissue. This may be the result of interaction between the negatively charged acid mucopolysaccharides and the enzyme which is positively charged at pH below 9. The enzyme has been tagged with I^{131} before injection, but recovery studies have been inconclusive. Tagging with C^{14} has not been done. The length of activity of the enzyme *in vivo* is limited by natural antagonists. For example, after intrathecal injection of 20 milligrams of chymopapain in a dog weighing 20 kilograms, 20 per cent of the activity may be found after thirty minutes and none after one hour.

A double-blind study was not conducted during the clinical investigation of chymopapain because the effectiveness of chymopapain was adequately demonstrated in the *in vitro* and *in vivo* experiments. The thousands of intervertebral disc injections done by others with radiopaque agents and cortisone may be considered controls.

We have found the diagnostic accuracy of discography sufficient to differentiate between a degenerated and a normal intervertebral disc. Whether the degenerated disc causes symptoms is another matter. We have assumed that it is whenever the discograph shows a protrusion

into the spinal canal or epidural leak of the dye, compatible with a rent in the posterior longitudinal ligament. We realise that escape of a liquid such as Hypaque[®] through a ligamentous tear does not necessarily indicate that nuclear material also has extruded. Chymopapain injected into the centre of the disc bonds immediately to its preferred substrate, chondromucoprotein. Evidently, in the case of an extrusion with nuclear fragments lying epidurally, chymopapain reaches them, breaks them down, and relieves nerve root pressure. Thus, twenty-two of our seventy-five patients showed epidural leak of dye at discography, and twenty-one of these claimed a rapid loss of their sciatica.

We have no evidence that the rapid narrowing of injected discs causes sciatica by intraforaminal nerve root pressure, or lumbar pain from instability. Alfred (1951), in a study of disc narrowing after laminectomy, found it in 74 per cent of spines studied over a ten-year period after operation. He found no relationship between the degree of narrowing and residual or recurrent symptoms. All our patients have been followed to date by flexion and extension lateral radiographs at frequent intervals. On these films, many show evidence of some instability as described by Harris and Macnab (1954) but none has as yet complained of lumbar pain related to activity and relieved by immobilisation that would indicate the need for a spinal fusion. Thus, our results provide evidence against the argument for routine arthrodesis of lumbar segments in conjunction with laminectomy.

Some of the first patients in this series received doses of chymopapain into the disc as high as 16 milligrams. We have been gradually reducing the dosage to find the minimal amount that is effective. A dose of 2 milligrams per disc is adequate. It is reassuring that 2 milligrams can be injected intrathecally in a five-pound rhesus monkey without acute or chronic ill effects.

Recently, a temporary rise in urinary acid mucopolysaccharide excretion has been detected in our patients after chemonucleolysis. Excretion is increased approximately one or two fold for one to three days after injection, after which it recedes to pre-injection levels. The increase is largely in the chondroitin sulphate C fraction. We believe this substance represents absorption products from the displaced disc material; if this is so, such a comparatively simple method of relieving this disability is most appealing.

Other clinicians are starting investigations in humans with this method of chemical attack upon intervertebral disc lesions. We await their confirmation of our experiences.

SUMMARY AND CONCLUSIONS

1. An account of experiences in seventy-five cases with a new method of treatment of low back pain and sciatica caused by intervertebral disc lesions has been presented. The method is based on the fact that chymopapain, a proteolytic enzyme, can break down displaced intervertebral disc material without deleterious effects upon adjacent tissues.
2. Chymopapain was injected into intervertebral discs by the postero-lateral or preferably the lateral approach. Two milligrams per disc constitute an effective dose. The enzyme was administered to seventy-five patients who were potential candidates for laminectomy. These patients were followed for four to thirty months and results were graded as "good" (76 per cent), "fair" (15 per cent) and "poor" (9 per cent).
3. Although untoward reactions have been encountered, none of these has been attributable to chymopapain.
4. Our investigations have convinced us that enzymatic dissolution of a lumbar intervertebral disc lesion is a safe, effective method of relieving sciatica and low back pain in selected cases.

REFERENCES

- ALFRED, K. S. (1951): Surgical Treatment of Herniated Lumbar Intervertebral Discs. *American Journal of Surgery*, **81**, 390.
- GARVIN, P. J., JENNINGS, R. B., SMITH, L., and GESLER, R. M. (1965): Chymopapain: A Pharmacologic and Toxicologic Evaluation in Experimental Animals. *Clinical Orthopaedics and Related Research*, **41**, 204.
- HARRIS, R. I., and MACNAB, I. (1954): Structural Changes in the Lumbar Intervertebral Discs. *Journal of Bone and Joint Surgery*, **36-B**, 304.
- HOWLAND, W. J., CURRY, J. L., and BUTLER, A. K. (1963): Pantopaque Arachnoiditis: Experimental Study of Blood as a Potentiating Agent. *Radiology*, **80**, 489.
- JANSEN, E. F., and BALLS, A. K. (1941): Chymopapain: A New Crystalline Proteinase from Papaya Latex. *Journal of Biological Chemistry*, **137**, 459.
- MACNAB, I. (1965): *Personal communication*.
- MITCHELL, P. E. G., HENDRY, N. G. C., and BILLEWICZ, W. Z. (1961): The Chemical Background of Intervertebral Disc Prolapse. *Journal of Bone and Joint Surgery*, **43-B**, 141.
- NAYLOR, A. (1962): The Biophysical and Biochemical Aspects of Intervertebral Disc Herniation and Degeneration. *Annals of the Royal College of Surgeons of England*, **31**, 91.
- SCHUBERT, M. (1964): Intercellular Macromolecules Containing Polysaccharides. *Biophysical Journal*, **4**, Supplement 1, 119-138.
- SMITH, L. (1964): Enzyme Dissolution of the Nucleus Pulposus in Humans. *Journal of the American Medical Association*, **197**, 137.
- SMITH, L., GARVIN, P. J., GESLER, R. M., and JENNINGS, R. B. (1963): Enzyme Dissolution of the Nucleus Pulposus. *Nature (London)*, **198**, 1311.
- STERN, I. J., and SMITH, L. (1966): Dissolution by Chymopapain *in vitro* of Tissue from Normal or Prolapsed Intervertebral Discs. *Clinical Orthopaedics and Related Research*, **50**, 269.
- THOMAS, L. (1956): Reversible Collapse of Rabbit Ears after Intravenous Papain, and Prevention of Recovery by Cortisone. *Journal of Experimental Medicine*, **104**, 245.