Chymopapain treatment of intervertebral disc disease

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In the first of a two-part study, the authors review the known biochemical, pharmacological, toxicological, and experimental data concerning chymopapain and the intervertebral disc. They describe the action of this proteolytic enzyme, which apparently disrupts the protein mucopolysaccharide component of disc material, most marked in the nucleus pulposus. A rapid conversion to collagen causes a loss of disc space height; toxicity appears to result from alteration of bonding between capillary endothelial cells that in turn produces hemorrhage. Part 2 reviews significant reported results and complications of clinical chemonucleolysis.

KEY WORDS • chymopapain • chemonucleolysis • intervertebral disc

Part I

Description of Chymopapain

Chymopapain is a proteolytic enzyme first isolated in 1941.17 It has recently attracted interest because of its use in “chemonucleolysis,” a proposed nonsurgical method of treating primary lumbar intervertebral disc disease. It is one of several enzymes prepared from crude papain, which is extracted from the fruit and other juices of a palm-like tree, the Carica papaya. The noncrystalline form of chymopapain is used in chemonucleolysis and is essentially free of papain as demonstrated by electrophoresis on cellulose acetate.45

Physical and Chemical Properties

Chymopapain has a molecular weight which varies from 27,000 to 45,000, depending upon the procedure used for its preparation and the extent of crystallization.7 Its isoelectric point is above 10.0, by virtue of a large content of lysine and other basic amino acids. The optimal pH for its proteolytic activity, measured by casein and hemoglobin digestion, is 7.2 with an active range of 6.5 to 8.5. At pH 2.0 it is quite stable at 0°C. Its stability at temperatures of 75° to 80°C varies, with a half-life of only 2 minutes at pH 2.1 but 75 minutes at pH 7.2. Chymopapain and papain have similar proteolytic effects, but chymopapain’s ratio of milk-clotting power to protein digestion is exactly twice that of crystalline papain.2 It has a lower activity, narrower specificity, higher solubility at neutral pH, and faster electrophoretic mobility than crystalline papain.46 Other minor differences, especially with regard to substrate specificities separate chymopapain and crystalline papain.18
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Chymopapain is a sulfur-containing enzyme. Amino-terminal amino acid analysis indicates that glutamic acid occupies the amino-terminal position. No glycine or isoleucine is present in the molecular configuration. It is activated by reducing agents such as cysteine and cyanide, which are required to maintain the sulfur in sulfhydryl forms. Even though a high level of proteolytic activity is maintained in the presence of reducing agents alone, maximum activity is possible only in the presence of chelating agents such as sodium edetate. These activators may unmask the sulfhydryl groups, thus preventing the poisoning of these groups by substances such as heavy metals.

Effects on Disc Material

The earlier evaluation of crude papain and crystalline papain was made on cartilage in vivo. Crude papain lowered the lactosamine content in cartilage, and isotope studies showed that the remaining chondromucoprotein had lost part of its chondroitin sulfate. With inactivated enzyme the investigators obtained the same results as with crude papain. Further investigation suggested that the activated enzyme reacted with an unidentified component of venous blood, thus neutralizing its effect before it reached the cartilage. Inactivated enzyme reached the cartilage unchanged, where it was then activated. Chymopapain is similar to crystalline papain in this regard.

Chymopapain catalyzes, both in vivo and in vitro, a rapid reduction in the viscosity and hence the molecular weight of the water-insoluble portion of nucleus pulposus. It does not appear to be inhibited by high concentrations of substrate. The dissolution rate is about 1 gm wet tissue/hour/mg chymopapain at pH 7.4. The soluble residue of chymopapain action on the human disc contains keratosulfate, chondroitin sulfate, and protein. Very little hydroxyproline is noted. The primary action of chymopapain appears to be upon noncollagenous protein that connects the long-chained mucopolysaccharides found in the nucleus pulposus. It has little, if any, notable effect upon the annulus.

A temporary rise in urinary acid mucopolysaccharide excretion follows the intradiscal injection of chymopapain. This excretion returns to normal after 1 to 3 days. This occurs after surgical intervention but not following intradiscal cortisone injection. The precipitates of crude urinary acid mucopolysaccharide contain both hexosamine and uronic acid, which are known to make up the bulk of the mucopolysaccharides of intervertebral disc material. Increased urinary mucopolysaccharide excretion probably originates from intradiscal chondromucoprotein.

Digestive activity of chymopapain in human nucleus pulposus in vitro is terminated after the first few hours; after that time, no free enzyme is detectable in extracts of frozen pulverized disc material, even when relatively large quantities of chymopapain are used. However, gross effects of chymopapain digestion of human nucleus pulposus in vivo are not completely apparent until at least 4 to 8 days following injection, suggesting that the gross effects of chymopapain digestion seen in vivo are not related to the digestion per se but to the absorption of the reaction products from the disc space.

A strong anionic-cationic relationship may explain the rapid binding of chymopapain to disc material, since chymopapain has a strong positive charge while acid mucopolysaccharide, at neutral pH, has a negative charge. This binding is more complete in the normal disc than in tissue from prolapsed disc. The decreased mucopolysaccharide content of prolapsed disc compared to that of normal discs further suggests that chymopapain affects or binds the protein mucopolysaccharide portion of the disc. Chymopapain appears to speed up a normal process, possibly by enzymatic induction. This normal process may be the conversion of protein chondromucopolysaccharide to collagen.

Commercial Chymopapain

Commercially available chymopapain (Discase) used in chemonucleolysis is provided in vials containing 10,000 units of the lyophilized agent with 3.5 mg of cysteine hydrochloride monohydrate, 0.37 mg of disodium edetate, and 1.0 mg of sodium bisulfite as stabilizers and activators. The pH is adjusted with sodium hydroxide. A unit of enzyme activity is that amount of enzyme which in 1 minute produces from acid-denatured hemoglobin at pH 4.0 under test conditions.
conditions a hydrolysate with an optical density of 275 nm, equal to that of a tyrosine solution containing 1.0 mcg tyrosine/ml. When reconstituted with 5 ml of sterile water for injection, the solution will contain approximately 2000 units/ml. Five milliliters contain 10,000 units, or approximately 20 mg of chymopapain. Bacteriostatic water for injection cannot be used for reconstitution, since some bacteriostatic agents will inactivate the enzyme.

**Pharmacology**

The effect of chymopapain on intervertebral disc tissues is quite selective and appears to be dose- and time-related both in vivo and in vitro. A selective dissolution of the nucleus pulposus takes place with little significant effect on the anulus fibrosus. Gross changes in the nucleus pulposus are seen at 24 hours when 20 mg or more of chymopapain are injected into the intervertebral disc of the rabbit or dog. However, doses of chymopapain as low as 0.01 mg per disc produce complete dissolution of the nucleus pulposus in some rabbits, while 0.156 mg produces dissolution in all rabbits at 8 days following the injection. The nucleus pulposus is eventually dissolved by doses of 2 mg or less per disc in the dog. These changes occur as late as 10 months following disc injection.

Gross changes in the anulus fibrosus often appear at doses of 5 to 10 mg per disc in the rabbit. These changes, found to be time- and dose-dependent, include thinning of the portion of anulus fibrosus adjacent to the nucleus pulposus. The longitudinal ligaments and bony inplates are not affected. Microscopically, the dissolution of the nucleus pulposus is readily determined. The only change noted in the anulus fibrosus is an occasional loss of metachromatic staining. Hemorrhage is often seen microscopically in the region of the nucleus pulposus in the dog. The peripheral, more fibrous, portion of the anulus fibrosus is unaffected by chymopapain even at the highest doses studied in both the rabbit and the dog. Narrowing of the injected intervertebral disc space as shown by x-ray films has been a consistent finding in rabbits and dogs injected with effective doses of chymopapain.

Only a small amount of data has been accumulated concerning the antigenicity of chymopapain. The minimal anaphylactic dose of chymopapain in guinea pigs following intraperitoneal sensitization is about 0.24 mg/kg. It is 20 times less anaphylactogenic than ovalbumin and 40 times less than horse serum. Serum-precipitating antibody titers are seen in rabbits receiving multiple disc injections of as little as 1 mg/disc. However, no dose-response relationships have consistently been established and individual antibody titers decrease spontaneously over a period of weeks.

Aside from the complications noted under Toxicology, the pharmacological effect of local injections of chymopapain upon man is limited to gross changes in the disc space and to an occasional anaphylactic reaction. The doses used in man range from 2 to 12 mg total with an average of 4 mg/disc. This causes a frequent, but not invariable, loss of intervertebral disc height; no data are available concerning the frequency of disc space narrowing. The average loss of height approaches 50%. Some form of sensitivity reaction occurs in approximately 1% of patients receiving chymopapain intradiscally with the more severe reactions resembling typical anaphylaxis. The symptoms range from a mild hypotension and petechial rash to urticaria, bronchospasm, and severe hypotension. Although the exact nature of this reaction is not clear, the symptoms appear to be reversible by intravenous steroids and epinephrine, and the patients appear to be protected from the anaphylactic reaction by hydrocortisone. A few of these patients either had known allergies to papain-containing commercial food products or recent heavy ingestion of the papaya fruit. Although limited in number, the patients reinjected with chymopapain have not suffered anaphylaxis.

**Toxicology**

**Large Intrascal or Epidural Doses.** Dogs receiving more than 180 mg of chymopapain intradiscally usually die within 24 hours. Autopsy reveals slight dissolution of the nucleus pulposus and varying degrees of systemic hemorrhage involving the lungs, the gastrointestinal tract, the kidneys, the thoracic and abdominal cavities, and the paravertebral muscles about the injection site. Epidural and intrathecal hemorrhage is also occasionally noted. Lesser intrascal doses do not produce death. The surviving dogs

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appear normal when observed for up to 6½ months.

Chymopapain is well tolerated by dogs when injected epidurally at total doses up to 175 mg. No acute or delayed toxic effects are seen during observation periods for as long as 4 months. However, epidural hemorrhage and hemorrhage in the outer layers of the dura are seen in dogs receiving larger epidural doses. In one study, death occurred within 24 hours in seven of eight dogs receiving total epidural doses greater than 200 mg. Autopsy revealed severe epidural and systemic hemorrhage. Intrathecal hemorrhage also occurred in dogs in which the dura had been punctured immediately following the injection of greater than 200 mg of chymopapain into the epidural space.

Conflicting reports concerning the effects of epidural chymopapain in cats have appeared in the literature. Shealy noted that doses of chymopapain in the range of 10 mg, injected epidurally or dripped upon the dural sheath of the cat, resulted in subarachnoid hemorrhage, necrosis, and foreign body inflammatory changes both epidurally and intradurally. However, in repeating Shealy's experiments, was not able to demonstrate any intrathecal pathological changes as the result of the epidural injection of 10 mg of chymopapain.

Intraperitoneal Injection. Rabbits tolerate the intraperitoneal injection of up to 10 mg/kg of chymopapain without difficulty. Death occasionally occurs when 20 mg/kg is injected intraperitoneally; larger doses are consistently immediately fatal. Autopsy reveals generalized hyperemia of the peritoneum with petechial hemorrhages in the serosa of the bowel and the mesentery, as well as bloody fluid in the abdominal and thoracic cavities, and congested lungs.

Intravenous Administration. Rabbits tolerate well the intravenous injection of 2.5 mg of chymopapain. Rapid injection of 5 mg/kg produces immediate convulsions with death; however, 10 mg/kg injected more slowly is well tolerated. Death consistently follows the intravenous injection of 20 mg/kg, regardless of the rate of injection. Autopsy reveals pulmonary hyperemia and congestion, but no other pathological changes. All surviving animals are normal in appearance and behavior when observed for as long as 3 weeks after injection.

Dogs are able to tolerate up to 10 mg/kg chymopapain injected intravenously. However, the larger doses produce hyperpnea immediately after injection with a return to normal in 5 to 10 minutes. Dogs receiving 20 mg/kg of chymopapain intravenously are usually moribund within 2 to 5 hours after injection. Immediate labored respiration and weakness followed by the development of blood-tinged saliva, hematuria, bloody diarrhea, and hemorrhage from needle puncture site are usually observed. Autopsy reveals marked hemorrhage throughout the major abdominal organs; however, the brain, cord, and dura are grossly normal.

The reasons for the bleeding disorder are unknown. However, blood samples drawn 5 minutes after the intravenous injection of 20 mg/kg of chymopapain into dogs did not clot. Even 4 hours following the injection the clotting time was 30 minutes to 1 hour. Prolonged depression of fibrinogen levels and a marked elevation of prothrombin times was noted. A 50% decrease in the platelet count occurred within 5 minutes of the injection. In the surviving animals, all coagulation parameters were normal at 24 hours after the injection.

Intrathecal Chymopapain. Chymopapain is highly toxic when injected intrathecally in the rabbit and the dog. Doses of 0.025 mg/kg cause symptoms of toxicity as soon as 15 minutes after the injection. Death, preceded by hind limb paralysis, labored respiration, and prostration, usually occurs within hours. Autopsy reveals severe subarachnoid hemorrhage, usually extending throughout the length of the cord, as well as petechial hemorrhages on the surface of the cord.

The approximate median lethal dose of chymopapain injected intrathecally in dogs is 2 mg (0.25 mg/kg). Most dogs die or must be destroyed in a terminal condition within 48 hours of the intrathecal injection of this dose of chymopapain. Death is usually preceded by weakness and prostration. Varying degrees of intrathecal hemorrhage with petechial hemorrhages on the surface of the cord extending from the sacral region to the cortex are noted at autopsy. Microscopically, the changes are those of diffuse capillary hemorrhages, diffuse focal hemorrhages in the cord, and capillary hemorrhages in the gray matter. Rarely, intravascular thrombi are noted. Spinal cords of dogs surviving
longer than 24 hours often contain necrotic neurons.

Dogs surviving the intrathecal injection of chymopapain doses equal to or less than the approximate median lethal dose show no signs of acute or delayed neural toxicity during observation for as long as 3 months. At autopsy, no gross pathological changes are seen in the dura, the arachnoid, the spinal cord, or other major organs. Large doses of chymopapain given intrathecally produce an immediate increase in cerebrospinal fluid pressure in both the dog and the rabbit. Venting spinal fluid by a cisternal tap occasionally but not invariably prevents death.

Effects of Chymopapain Upon Extrathecal Nervous Tissue

Limited data concerning the effects of chymopapain upon extrathecal nervous tissue are available, but appear contradictory. The threshold voltage to produce muscle twitch in intact frog sciatic nerve was unaffected by direct exposure of the nerve to a 10% concentration of chymopapain for 160 minutes or a 40% concentration for 35 minutes. Similar findings were noted in the intact and partially-crushed rabbit sciatic nerve exposed to 40% concentration for 95 to 140 minutes. Threshold voltage did not change appreciably even after 180 minutes of observation following the injection of 5%, 10%, or 20% solutions or suspensions of chymopapain directly into the rabbit's sciatic nerve. Microscopic examination of the nerves, however, revealed marked hemorrhage of the adjacent fibroadipose tissue, but the nerve itself inexplicably appeared normal.

Other investigators have reported significantly different results when they studied the effect of chymopapain on the tibial nerve in the rabbit. They noted pathology that appeared primarily related to an effect on the microvasculature of the nerve. A 0.1% solution applied topically caused numerous thromboemboli, but no bleeding; approximately 10% of the vessels in the epineurium were occluded within 3 minutes. A 0.25% solution caused more extensive blockage in more than 50% of the venules and capillaries in the perineurium; the intrafascicular circulation was also affected. Five minutes after treatment of the tibial nerve with a 0.5% solution, microemboli and also microhemorrhages were noted. The intrafascicular circulation was severely affected, and this was apparently not reversible.

Median Lethal Dose of Chymopapain

The median lethal dose of intradiscal or epidural chymopapain has not been accurately determined in all animal species studied. However, in the rabbit, cat, and dog, a margin of safety greater than 300 mg has consistently been recorded (comparing the maximum tolerated dose with the minimum effective dose for discoscopy). Studies in the monkey have been few and incomplete, but this animal can tolerate greater than 90 mg chymopapain in the epidural space. Toxicity studies such as median lethal dose and maximum tolerated dose have, of course, not been performed in man. However, based upon clinical and radiographic responses to chemonucleolysis with chymopapain, a minimum effective dose appears to be 2 to 4 mg/disc space. Extrapolating from animal experiences, the maximum tolerated intradiscal dose in man could conceivably approach 600 mg.

Part 2

Chemonucleolysis: A Clinical Review

Following the description of the syndrome of primary lumbar disc rupture and its surgical treatment, investigators and clinicians focused their attention upon the anatomical and biomechanical nature of the lumbar spine, and particularly the histological and biochemical nature of lumbar disc disease. It was noted that a gradual reduction of intervertebral disc chondromucoprotein and an increase in collagen accompany the aging process; this results in the lessened intervertebral disc resiliency characteristic of the degenerative disc. It soon became obvious that the degradation of chondromucoprotein to collagen, or fibrous tissue, occurring slowly with age and more rapidly following injury or surgery, is synonymous with the process of healing. As degeneration or healing occurs, other changes take place in the biochemical makeup of the intervertebral disc.

Hirsch believed that these biochemical changes might be enhanced by an appropriate enzyme. This suggestion was given impetus by the report of Mitchell, et al., concerning
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the chemical background of intervertebral
disc prolapses and the role of various protein
fractions of the disc in disease and healing.
Thomas found that the intravenous injection
of crude papain in young rabbits altered cer-
tain physical properties of the ear cartilage;
the enzyme was subsequently found to
decompose the mucopolysaccharides of the
intracellular matrix of the cartilage with the
subsequent release of chondroitin sulfates.
Since the biochemical makeup of the nucleus
pulposus of the lumbar intervertebral disc is
very similar to that of cartilage, crude papain
and a number of enzymes isolated from it
were evaluated for their proteolytic activity
upon the intervertebral disc. Smith, et al.,
found that chymopapain was the most potent,
and least toxic, of these enzymes.
Following extensive animal investigations,
Smith commenced his study of the effects of chymopapain on the human disc in 1963 and recorded his first series of patients in 1964. He termed the process of treatment of lumbar, intervertebral disc disease with chymopapain "chemonucleolysis." This induction of more rapid healing in the degenerative or prolapsed disc would theoretically result in decreased pain and disability of individual patients suffering from lumbar disc disease. Since the initial report by Smith, a large volume of literature based on clinical experience has been developed. Most of the clinical experience with chemonucleolysis has been with lumbar disc disease. Results from chemonucleolysis for cervical disc disease have been fragmentary and inconsistent, and chemonucleolysis has been abandoned as a method of treatment of cervical disc disease. Almost 10,000 patients have been treated by lumbar chemonucleolysis. Most studies have dealt with the direct effect of the intradiscal injection of chymopapain upon the symptoms of lumbar disc disease. Truly randomized or double-blind studies have not been reported.

Results

Two major problems immediately confront
the reviewer of reported results of chemonu-
cleolysis. Most of the reported series are
small, containing less than 250 patients in
follow-up. In addition, standardization in the
selection of patients is generally lacking; however, close scrutiny of the method of patient selection makes possible classification of most reported results according to the method of O'Connell, as modified by Macnab, et al.
The "excellent" result is obtained in that
patient who is completely asymptomatic
following treatment. Patients with "good"
results have only minor and intermittent dis-
comfort that does not interfere with normal
activity of work and avocation, while those
with "fair" results continue to have intermit-
tent discomfort of back and/or leg pain which
permits work and avocational activity, but at
a less than normal pace. These patients often
have had to change to a less strenuous job in
order to work regularly. Those whose condi-
tion is virtually unchanged or worse have a
"poor" result; patients requiring open surgery
following chemonucleolysis would fall into
this category. Chemonucleolysis is regarded
as "successful" in the patient with an ex-
cellent or good result and to have "failed" in
those with fair or poor results.

Macnab, et al., reported a series of 100
patients in which 67 patients responded
successfully to chemonucleolysis, including
46 of 52 patients with a classic disc syndrome.
Most of the patients in this group who failed
to respond were found later at surgery to have
either spondylitis or evidence of an extruded
fragment as the primary cause of their dis-
comfort.

Schoedinger and Ford reported a series of
200 patients in which 99 or 49.9% of those
patients had a successful outcome. A total of
101 patients failed to respond satisfactorily
to chemonucleolysis; in some, they also found
extruded disc fragments at laminectomy.
Ford reported another, possibly overlapping,
series of 126 patients, in which chemo-
nucleolysis was successful in 75, or 59%. In
455 patients with a follow-up of greater than
8 months, Widell, et al., noted an overall
success rate of 62.6%. Of these patients, 107
had previously undergone surgery for lumbar
disc disease, and 49% were successfully
treated by chemonucleolysis. In patients who
subsequently underwent laminectomy, a ma-
jor cause of their problem appeared to be
spondylotic spurring. They found no instance
of an extruded fragment as the cause of
disease.

Smith, after previous preliminary clinical
reports, summarized his results in 150
patients in 1969. He used a slightly different
grading system than that described above.
Patients with good results had complete relief
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of sciatica with no limitations in work or avocations. The patient with a fair result had incomplete relief but suffered no limitation in work as a result of his persistent symptoms, and a patient with no improvement was classified as a poor result. Based on this grading system, a successful treatment would include patients with both good and fair results, while a failure of treatment would include only those patients with a poor result. A grading of good was obtained in 125 patients and fair was seen in 11 patients. These 136 patients represented 90.7% of the series treated by chemonucleolysis. Thirty-eight of these 150 patients had previously undergone surgery; 81.9% of this subgroup had good or fair results. Smith subsequently reported a group of over 2000 patients treated by several different groups of investigators with an overall rate of 70% good or fair results.

Other smaller series have been reported. Tibbetts and Javid reported a 65% success rate, with 40 of 61 patients benefiting by treatment. Day noted that 75% of 135 patients successfully responded to chemonucleolysis. Stewart found a success rate of 70% in 40 patients treated and Brown, using the same rating system as Smith, reported 82.5% good or fair results in 40 patients. Parkinson and Shields reported a series of 33 patients; 12 of 20 patients were free of their previous leg and back pain, and an additional four patients free of leg pain and doing their usual work. Three patients who subsequently underwent surgery had completely extruded disc fragments.

Only one previously reported series of any size has compared chemonucleolysis with laminectomy for treating lumbar disc disease. Nordby and Lucas compared the results of 100 patients treated by chemonucleolysis with those of 100 patients treated by laminectomy for disc disease prior to the institution of chemonucleolysis as a form of treatment in their practice. Chemonucleolysis resulted in a success rate of 74% while laminectomy was successful in only 48% of the patients treated. They reported extruded fragments in some patients in whom chemonucleolysis failed, and who subsequently underwent laminectomy. A second series by the author and coworkers comparing chemonucleolysis with laminectomy for treatment of lumbar disc disease appears on pages 397-400 of this issue.

Complications

Several clinical complications, some quite severe, have occurred with chemonucleolysis; the major complications include sensitivity reactions, discitis, and arachnoiditis. Others were less serious.

Sensitivity. There appear to be three types of sensitivity reactions. Transient skin rashes of various descriptions have reportedly occurred several days following chemonucleolysis; these have not been treated and have subsequently disappeared leaving no sequelae. Transient petechial rashes with or without hypotension have occurred within minutes of injection of chymopapain into the intervertebral disc. These invariably have disappeared within moments, especially if intravenous steroids are given at that time. They seem to be associated with no other abnormalities. A more severe sensitivity type of reaction reported by many observers takes the form of a true anaphylaxis. Within minutes of chymopapain injection into the intervertebral disc, generalized urticaria appears, associated with severe hypotension and even bronchospasm. In most instances this has been treated successfully with appropriate anaphylactic regimens including intravenous steroids and epinephrine. However, at least two deaths have occurred.

The etiology of the sensitivity type of reactions during chemonucleolysis is unknown. As a proteolytic enzyme, chymopapain is potentially antigenic. One patient with a known allergy to commercial meat tenderizer (which contains a derivative of the papaya plant) developed an anaphylactic reaction during chemonucleolysis; however, repeated injections in humans have produced no allergic symptoms. The antigenic potential of the protein-polysaccharide combination of the intervertebral disc has been established. Some investigators have postulated that chronic discogenic pain might, in some cases, be an autoimmune phenomenon, although this has not been proven experimentally. Bobechko and Hirsch showed that disc tissue can serve as an antigen in the rabbit, and Feffer reported that almost half of the patients receiving intradiscal hydrocortisone for primary intervertebral disc disease had remission of their symptoms. In some patients, the rapid hydrolysis of intradiscal protein-poly-
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Saccharide by chymopapain might conceivably release into the blood stream large amounts of antigen to which the body had, over a period of time, developed antibodies through a more chronic release of protein-mucopolysaccharide complexes in chronic disc disease.

Discitis. Both aseptic and septic forms of discitis have been recorded following chemonucleolysis.\textsuperscript{2,28,35,48} Most patients with aseptic discitis respond in the usual fashion with a gradual reduction of pain and loss of disc space height over weeks or months. Those patients with septic discitis usually respond to appropriate antibiotics; however, one patient died after developing septicemia.\textsuperscript{28} Whether chymopapain injection is related to the development of an avascular necrosis, or aseptic discitis, is unknown. Simple discography has been followed by aseptic discitis when Hypaque in concentrations greater than 35% has been used.\textsuperscript{29,47} However, Collis\textsuperscript{8} could not attribute observed discography complications to the concentration of contrast material.

Arachnoiditis. Chemonucleolysis has been followed by arachnoiditis in some instances. When associated with inoperable lumbar disc disease, arachnoiditis has been attributed to many factors. The acute and chronic trauma of untreated ruptured intervertebral discs has been incriminated;\textsuperscript{10,34} Pantopaque myelography, especially if it is performed in the presence of blood in the spinal fluid, has also been suspected.\textsuperscript{10,16,33} However, chymopapain has not been directly identified as the cause of arachnoiditis in man. The minimum effective dose of chymopapain for discolysis and its maximum tolerated intradiscal or epidural dose has been determined in several animal species.\textsuperscript{11,12} These doses do not produce subarachnoid pathology if given epidurally.

Although the intradiscal injection of chymopapain probably does not produce arachnoiditis, the widespread use of chemonucleolysis may result in an increased incidence of arachnoiditis associated with lumbar intervertebral disc disease. As has been noted, chronically ruptured lumbar intervertebral discs have been associated with the development of arachnoiditis, and chymopapain does not digest anular material, nor affect the presence of disc material completely extruded into the epidural space.\textsuperscript{12} The chronic presence of this material in the epidural space may lead to arachnoiditis if it is not removed. Macnab, et al.,\textsuperscript{20} reported 10 patients whose symptoms were successfully treated by chemonucleolysis but whose significant myelographic defects did not change.

New Radicular Syndromes. Several patients have been relieved of their original symptoms by chemonucleolysis only to develop new radicular leg syndromes not thought to result from disc disease.\textsuperscript{28,38,50} These disorders have included weakness of dorsiflexion (foot drop), and generally have cleared in a few weeks without specific treatment. However, more severe neurological deficits have been reported. Smith\textsuperscript{35} reported a patient who developed paraplegia secondary to transverse myelitis at T-10, 10 days following lumbar intervertebral disc chemonucleolysis. He attributed this to a complication of Pantopaque myelography, similar to previously reported cases.\textsuperscript{28} He also described a patient who developed a Brown-Séquard syndrome 6 weeks following chemonucleolysis for cervical disc disease. The etiology of that disability was not established.

Causalgia. Postchemonucleolytic syndromes such as causalgia are postulated to be secondary to the accidental spearing of a nerve root during the placement of the needle prior to discography; however, Clark, et al.,\textsuperscript{4} were unable to demonstrate more than a transient change in nerve physiology by the simple procedure of placing a needle in the nerve. A needle might possibly damage the epineurium and thus allow leakage of chymopapain into the nerve; the deleterious effect of chymopapain upon the microvasculature of nerves is well documented.\textsuperscript{2}

Mistaken Diagnosis. Although misdiagnosis is not usually considered a complication, it becomes a factor if the patient undergoing chemonucleolysis has not been properly evaluated. One of the early deaths reported following chemonucleolysis was that of a patient who became quadriplegic following treatment.\textsuperscript{38} Autopsy revealed a cervical hemangioblastoma; this patient had not had a myelogram before chemonucleolysis.

Intraspinal tumors such as meningiomas and neurofibromas can resemble lumbar disc disease, especially in the thoracolumbar region. Discography alone will not demonstrate these conditions, since it cannot reliably separate asymptomatic degenerative
disc disease from symptomatic degenerative disc disease or intraspinal pathology. All patients undergoing lumbar intervertebral disc chemonucleolysis probably should have adequate myelography prior to treatment.

Narrow Disc Space. Up to 50% disc space narrowing has followed chemonucleolysis. This has led to the development of radiculopathy secondary to narrow foramina in some patients who were previously treated for degenerative disc disease without rupture.

Nonspecific Complications. Other major recorded complications not unique to chemonucleolysis include pulmonary embolism, nonfatal cardiac arrest, cerebrovascular accidents, myocardial infarction, and hypovolemic shock. Myocardial infarction and pulmonary embolism following chemonucleolysis have led to death in at least two patients. Minor complications such as transient ileus and urinary retention have also been noted.

As more patients have undergone chemonucleolysis, more complications have been reported. Most of the complications are minor but some are quite severe, particularly the sensitivity reactions, reported at the rate of 2% to 4% in some series. Thus, particularly in this trial period, chemonucleolysis should not be considered as an extension of conservative treatment, but should be evaluated as an alternative operative procedure for intervertebral disc disease with its own share of risks and complications.

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