



PROLOTHERAPY for Musculoskeletal PAIN

A primer for pain management physicians on the mechanism of action and indications for use.

By Donna Alderman, DO

Prolotherapy is a method of injection treatment designed to stimulate healing.¹ This treatment is used for musculoskeletal pain which has gone on longer than 8 weeks such as low back and neck pain, chronic sprains and/or strains, whiplash injuries, tennis and golfer's elbow, knee, ankle, shoulder or other joint pain, chronic tendonitis/tendonosis, and musculoskeletal pain related to osteoarthritis. Prolotherapy works by raising growth factor levels or effectiveness to promote tissue repair or growth.² It can be used years after the initial pain or problem began, as long as the patient is healthy. Because prolotherapy works to repair weak and painful joint areas, it is a long term solution rather than a palliative measure such as drugs, and should be considered prior to the use of long term drugs or surgery in appropriate patients.

In the April 2005 issue of the *Mayo Clinic Health Letter*, the authors wrote: "In the case of chronic ligament or tendon pain that hasn't responded to more conservative treatments such as prescribed exercise and physical therapy, prolotherapy may be helpful."³ Prolotherapy has been used in the U.S. for musculoskeletal pain since the 1930's, is endorsed by former

U.S. Surgeon General, C. Everett Koop,⁴ and has even made its way into the professional sports world.⁵ In a 2000 issue of *The Physician and Sportsmedicine*, "Are Your Patients Asking About Prolotherapy?" the article starts:

"Prolotherapy, considered an alternative therapy, is quietly establishing itself in mainstream medicine because of its almost irresistible draw for both physicians and patients: nonsurgical treatment for musculoskeletal conditions."

The article states that as many as 450,000 Americans had undergone prolotherapy and that some of the patients reporting benefits from prolotherapy were physicians themselves.⁶ Yet, many physicians have still not heard of or do not know much about prolotherapy.

The purpose of this article is to give the pain management physician an introduction to prolotherapy, how and why it works, and indications for its use.

Background and History

Prolotherapy is based on the premise that chronic musculoskeletal pain is due to inadequate repair of fibrous connective tissue, resulting in ligament and tendon weakness or relaxation (laxity),¹ also

known as connective tissue insufficiency.⁷ When the connective tissue is weak, there is insufficient tensile strength or tightness.⁸ Load-bearing then stimulates pain mechanoreceptors.⁷ As long as connective tissue remains functionally insufficient, these pain mechanoreceptors continue to fire with use.⁹ If laxity or tensile strength deficit is not corrected sufficiently to stop pain mechanoreceptor stimulation, chronic sprain or strain results.² This is the problem that prolotherapy addresses: stimulating growth factors to resume or initiate a connective tissue repair sequence, repairing and strengthening lax ligaments and/or tendons, and ultimately reducing or eliminating pain.

Historically, the use of prolotherapy dates back to Hippocrates who treated dislocated shoulders of soldiers on the battlefields with red-hot needle cautery to stabilize the joint. From 1835 to 1935, injection of sclerosing type agents was used for hernias to proliferate new fibrous tissue. It was during the 1930's that George Hackett, MD, a general surgeon, made the observation — while doing hernia surgery on patients previously treated with proliferant type therapy — that "Injections made (usually in error) at the junction of liga-

ment and bone resulted in profuse proliferation of new tissue at this union.”¹⁰ Hackett then spent many years developing and refining injection therapy for tendons and ligaments, publishing his research and text in 1956. He defined prolotherapy as “the rehabilitation of an incompetent structure [ligament or tendon] by the generation of new cellular tissue,” and concluded that “a joint is only as strong as its weakest ligament.”¹¹

Prolotherapy is sometimes called “Regenerative Injection Therapy” (RIT), “Reconstructive Therapy,” “Non-Surgical Tendon, Ligament, and Joint Reconstruction, or Growth Factor Stimulation Injection.”¹¹ “Sclerotherapy” is an older, inaccurate term for prolotherapy, based on the original theory that scar formation was the treatment mechanism. However, biopsy studies have not demonstrated scar formation with mechanical, inflammatory, or growth factor prolotherapy with the agents and concentrations currently in use.² Rather, studies have shown a proliferation of new, normal, thicker, and stronger connective tissue after prolotherapy injections (thus “prolo” for proliferation).¹²

Why Doesn't Soft Tissue Healing Occur On Its Own?

Ligament and tendon tissues have a poor blood supply, and therefore take longer to heal than other tissues. Incomplete healing is common after an injury to those structures.^{13,14} In fact, it has been estimated that the usual best result of a completed connective tissue repair process is a return to normal connective tissue length, but only 50% to 60% of pre-injury tensile strength.¹⁵ Over time, and multiple injuries, this can result in laxity and connective tissue insufficiency.² Healing can additionally be affected by interfering factors such as smoking, stress, medications, lack of sleep, and poor nutrition. In repetitive trauma, each individual trauma may be insufficient to provide enough stimulus to prompt complete healing, so that even minor injury may be enough to accumulate damage to the point of initiating chronic pain.² Other reasons which have been suggested for incomplete healing are the use of anti-inflammatory medications immediately after an injury.¹⁶ Inflammation is a necessary component of soft tissue healing and the use of anti-inflammatory medication for sports injuries has been questioned and remains controversial. In the January 2003 issue of *The Physician and Sportsmedicine*, a review article examined the physiology and healing of soft tissue injuries and concluded that the use of NSAIDs may interfere with healing and is questionable in the treatment of musculoskeletal injuries.¹⁷

Mechanism of Action

Prolotherapy works by causing a temporary, low grade inflammation at the site of ligament or tendon weakness (fibro-osseous junction) thus “tricking” the body into initialing a new healing cascade. Inflammation activates fibroblasts to the area, which synthesize precursors to mature collagen, and thereby reinforcing connective tissue.² It has been well documented that direct exposure of fibroblasts to growth factors causes new cell growth and collagen deposition.¹⁸⁻²² Inflammation creates secondary growth factor elevation.² This inflammatory stimulus raises the level of growth factors to resume or initiate a new connective tissue repair sequence to complete one which had prematurely aborted or never started.² Animal biopsy studies show ligament thickening, enlargement of the tendinosseous junction, and strengthening of the tendon or ligament after prolotherapy injections^{23,24} (see Figure 1).

Study Results

Over the years since the 1930's, studies and reports have demonstrated the effectiveness of injection prolotherapy for musculoskeletal complaints, including case reports, pilot, retrospective, open face prospective, and double-blind placebo controlled studies.^{25-47,51-60} These studies have clearly indicated the effectiveness of prolotherapy in the treatment of chronic musculoskeletal pain arising from post-traumatic and degenerative changes in connective tissue such as ligaments, tendons, fascia, and intervertebral discs.⁴⁸

Several studies are noteworthy. A double-blind animal study done at the University of Iowa showed significant increase in rabbit bone-ligament-bone junction strength and increase of collagen fibrils after proliferant injections.²³ In a human study of chronic low back patients, biopsy of sacroiliac ligaments 3 months after treatment demonstrated a 60% increase in collagen fibril diameter, as well as decrease in pain and increased range of motion in subjects tested.⁴⁷ And, although not studied in humans, cartilage effects of growth factor stimulation in animals has shown healing of full thickness cartilage defects in injection studies.^{49,50}

Low back studies show improvement in treated groups^{47,51-53} including a randomized double-blind trial which showed statistically-significant improvement in the treated group after 6 months.⁵⁴ A 2004 study showed improvement in two groups of chronic low back patients treated with dextrose or saline injections (both can be used as proliferants). Both groups showed a statistically significant decrease in pain and disability scores at both 12 and 24 months follow-up.⁵⁵ Hackett studied 543 chron-

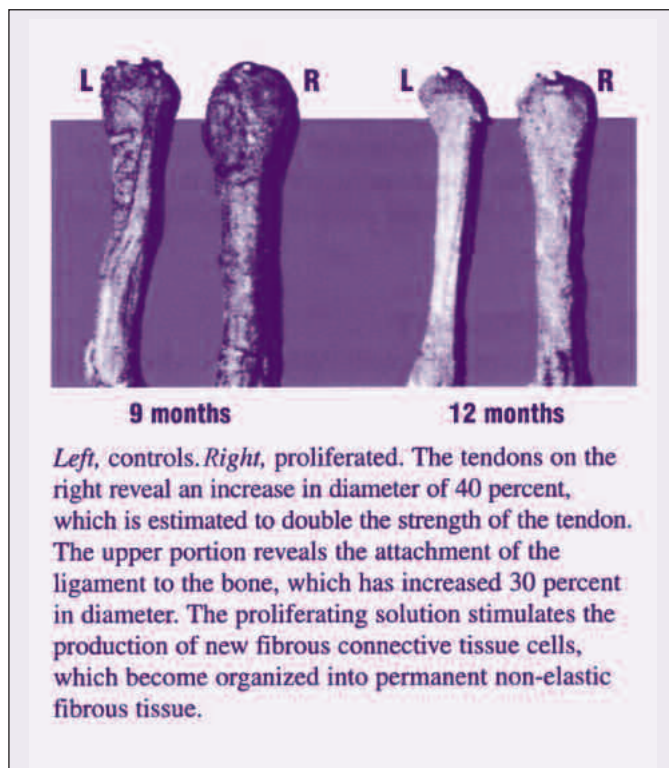


FIGURE 1. Photograph of rabbit tendons at nine and 12 months after three injections of proliferating solution into the right tendons. From Hauser, “Prolo Your Pain Away,” Second Edition. 2004. Beulah Land Press, Oak Park, IL. Used with permission.

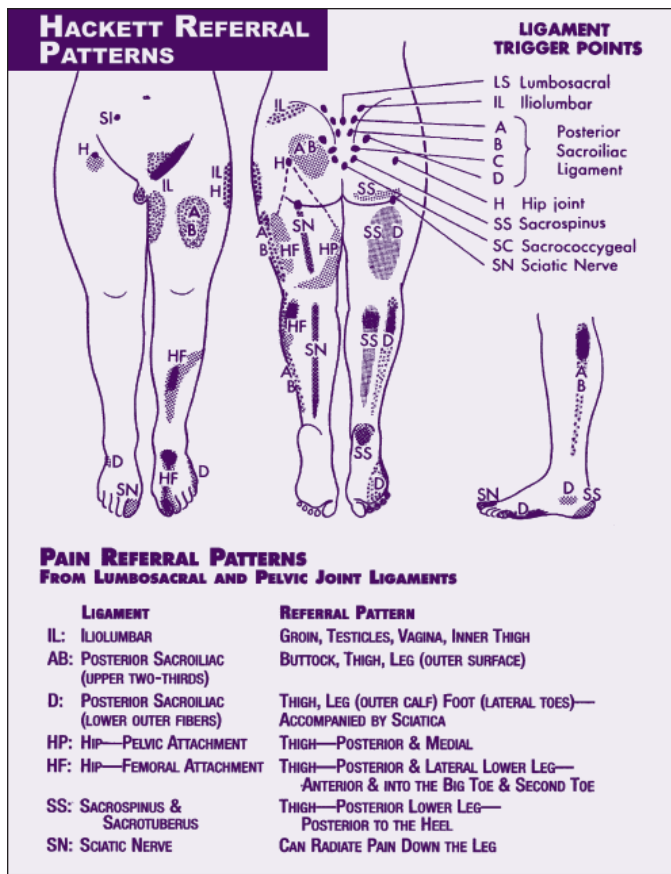


FIGURE 2. Pain referral patterns from lumbosacral and pelvic joint ligaments. From Hauser, “Prolo Your Pain Away,” Second Edition. 2004. Beulah Land Press. Oak Park, IL. Used with permission.

ic low back pain patients ranging in age from 15 to 88, with duration of disability before treatment from 4 to 56 years. Hackett reported that 82% of these patients considered themselves cured over periods ranging up to 12 years of follow-up.³⁷

A 2005 study of elite rugby and soccer athletes with chronic groin pain that prevented full sports participation showed the marked efficacy of prolotherapy. After an average of 2.8 treatments, 20 of 24 athletes reported no pain, and 22 were unrestricted with sports.⁵⁶

Knee injuries have been studied and shown to be successfully treated with prolotherapy. A study involving patients with significant knee ligament laxity and instability showed highly significant tightening of the cruciate and collateral ligaments measured by standard electrogoniometer measurements, as well as subjective improvement in pain and increased activity level 9 months after treatment start.⁵⁷ A double-blind study by Reeves showed that injection prolotherapy resulted in elimination of the knee’s anterior cruciate ligament (ACL) laxity — by machine measurement — in over 60% of patients, with statistically significant improvement at 3 year follow-up, and a larger percentage experiencing reduction in pain, including improvement in symptoms of osteoarthritis even in those who tested loose.⁵⁸

Osteoarthritis pain has also been studied. In a recent double-blind placebo controlled study, there was clinically and statistically significant improvement in knee osteoarthritis symptoms at 1 and 3 year follow-up after prolotherapy injections, with ra-

diographic readings also noting improvement in several measures of osteoarthritis severity. ACL laxity, when present, also improved.⁵⁹ Another study showed improvement in finger and thumb osteoarthritis after prolotherapy injections, with 42% improvement in pain and 8 degree improvement in flexibility after 6 months.⁶⁰

The largest follow-up studies on the pain-reducing effects of prolotherapy treatment involved 1800 patients followed for more than 2 years, and showed marked reduction in upper or lower body pain in 80% of subjects.⁶¹ A review of the medical literature by the Florida Academy of Pain Medicine in 2001 analyzed the medical literature from 1937 to 2000, including case studies, retrospective, prospective, and animal studies. The calculated number of patients reported in those studied exceeded 530,000. Improvement in terms of return to work and previous functional/occupational activities was reported in 48 to 82% of patients, with reduction of pain up to 100%. The Academy concluded that this injection treatment was effective as a type-specific treatment for post-traumatic degenerative, overuse, and painful conditions of the musculoskeletal system related to pathology of the connective tissue.⁴⁸

Pain Referral Patterns

An important concept in musculoskeletal pain is that of ligament referral patterns. Injury in one segment of the body may refer to distant body parts.⁶² Ligament injury may cause severe pain because ligaments are full of nerve endings,⁶³ and may refer nerve-like pain — as in sciatica — which may actually be coming from injured sacroiliac or sacrospinous ligaments (see Figure 2), or headaches which may be referring from the weak cervical ligaments or occipital attachments (see Figure 3). If the ligaments from which the pain is being referred are treated with prolotherapy, the ligaments heal, pain receptors stop firing, and this type of pain resolves. Therefore, knowledge of areas in which individual ligaments may produce referred pain is extremely valuable in diagnosis with prolotherapy treatment.⁶⁴

Common Proliferant Solutions

The most common proliferant used in prolotherapy injections is hypertonic dextrose, 12.5% to 25%, with 15% being the most used. This is a safe solution which works by creating an osmotic gradient in the area of injection, dessicating the local connective tissue cells, initiating an injury response, and activating the inflammatory cascade. Once the cell fluid is able to dilute the dextrose, the inflammation ceases but growth factor activation continues.¹² A local anesthetic such as lidocaine or procaine is also used. Sarapin (extract of pitcher plant) is added in the Hackett-Hemwall-Hauser formula. A saline, rather than dextrose, based formula may also be used as a proliferant. Other solutions in use include non-inflammatory dextrose (10% or less) which has been shown in two double blind studies to be effective in both finger and knee arthritis and also improve knee ACL laxity and pain.^{59,60} Other, more inflammatory formulas in use are phenol-containing-solutions, such as P2G (phenol, glycerin and dextrose).

Appropriate Candidates for Prolotherapy

In the Hackett/Hemwall/Montgomery book on prolotherapy—one of the first texts on the subject—the authors write:

“Criteria For Injection Therapy In New Patients:

1. Appropriate medical problem.
2. Desire for recovery.
3. No underlying medical conditions which would significantly interfere with healing.
4. Ability and willingness to follow instructions.
5. Willingness to report progress.
6. Willingness to receive painful injections in an effort to recover from injury.”¹

These criteria are still true today. The patient must present with an appropriate musculoskeletal problem. The patient needs to have a desire to get better, no known illness which could prevent healing, willingness to follow instructions and to undergo injections. Examples of illnesses which would prevent healing include autoimmune or immunodeficiency disorders, or active cancers. Also, the patient should not be taking drugs which lower the immune system such as systemic corticosteroids or immune suppressants. And, because prolotherapy works to stimulate inflammation, patients should not be taking anti-inflammatory medication during treatment. In fact, as mentioned above and although frequently prescribed for musculoskeletal pain, use of NSAIDs may interfere with healing and is questionable in treatment of musculoskeletal injuries.¹⁷

Age is not a factor as long as the individual is healthy. It also does not matter how long the person has been in pain, or how long ago they injured themselves as long as the person is in good, general health.

MRI's May Be Misleading in Diagnosing Musculoskeletal Pain

When deciding what patients are candidates for prolotherapy, do not be misled by the MRI or use the MRI for diagnosis alone. As many pain practitioners know, an MRI may show nothing wrong and yet the patient is still in pain. And, because MRI's may also show abnormalities not related to the patient's current pain complaint, MRI findings should always be correlated to the individual patient. Many studies have documented the fact that abnormal MRI findings exist in large groups of pain-free individuals.⁶⁵⁻⁷¹ A study published in the *New England Journal of Medicine* showed that out of 98 pain-free people, 64% had abnormal back scans.⁷² Many other studies have also shown abnormal neck MRI scans in asymptomatic subjects,⁷³⁻⁷⁵ and the finding of asymptomatic changes in knee joints during surgery is not uncommon.^{76,77} One study looked at the value of MRI's in the treatment of knee injuries and concluded: "Overall, magnetic resonance imaging diagnoses added little guidance to patient management and at times provided spurious [false] information." So, do not use an MRI alone to determine a treatment course. The MRI should be used in combination with a history of the complaint, precipitating factors or trauma, and a physical exam.

Indications

Prolotherapy has been used to successfully treat a large variety of musculoskeletal syndromes, including cervical, thoracic and lumbar pain syndromes, patients diagnosed with "disc disease," mechanical low back pain, plantar fasciitis, foot or ankle pain, chronic rotator cuff or bicipital tendonitis/tendonsis, lateral and medial epicondylitis, TMJ dysfunction, musculoskeletal pain related to osteoarthritis, and even finger or toe joint pain including "turf toe." It is important to rule out a systemic or non-musculoskeletal origin for the complaints, confirm no underlying



FIGURE 3. Head and neck referral pain patterns. From Hauser, "Prolo Your Pain Away," Second Edition. 2004. Beulah Land Press. Oak Park, IL. Used with permission.

illness which would prevent healing, and also to ensure there are no contraindications to treatment (see section below).

The Florida Academy of Pain Management laid out indications for prolotherapy (Regenerative Injection Therapy or RIT) based on their review of the literature:

1. Chronic pain from ligaments or tendons secondary to sprains or strains.
2. Pain from overuse or occupational conditions known as "Repetitive Motion Disorders," i.e. neck and wrist pain in typists and computer operators, "tennis" and "golfers" elbows and chronic supraspinatous tendinosis.
3. Chronic postural pain of the cervical, thoracic, lumbar and lumbosacral regions.
4. Painful recurrent somatic dysfunctions secondary to ligament laxity that improves temporarily with manipulation. Painful hypermobility and subluxation at given peripheral or spinal articulation(s) or mobile segment(s) accompanied by a restricted range of motion at reciprocal segment(s).
5. Thoracic and lumbar vertebral compression fractures with a wedge deformity that exert additional stress on the posterior ligamento-tendinous complex.
6. Recurrent painful subluxations of ribs at the costotransverse, costovertebral and/or costosternal articulations.
7. Osteoarthritis of axial and peripheral joints, spondylosis and spondylothesis.
8. Painful cervical, thoracic, lumbar, lumbosacral and sacroiliac instability secondary to ligament laxity.
9. Intolerance to NSAIDs, steroids or opiates. RIT (pro-

lotherapy) may be the treatment of choice if the patient fails to improve after physical therapy, chiropractic or osteopathic manipulations, steroid injections or radiofrequency denervation or surgical interventions in the aforementioned conditions, or if such modalities are contraindicated.⁴⁸

Contraindications

Active infection or cancer is a contraindication to treatment, as is any underlying illness which could interfere with healing. Immunodeficiency conditions, acute gout or rheumatoid arthritis, complete rupture of a tendon or ligament, non-reduced dislocations, or severe, unstable spondylolithesis are also contraindications. Other contraindications are allergy to any of the ingredients in the prolotherapy formula or unwillingness to experience possible after-treatment discomfort. Patients should understand the course of the prolotherapy treatment and be participants in their treatment plan.

Relative contraindications include current and long term use of high doses of narcotics as these medications can lower the immune response. Current use of systemic corticosteroids or NSAIDs are also relative contraindications as these are counterproductive to the inflammatory process. Other relative contraindications include central canal spinal stenosis and severe degenerative hip osteoarthritis with loss of range of motion.

Risks

While the most common risk is soreness after treatment, prolotherapy is a medical procedure and, as such, there are risks. While prolotherapy is a low risk procedure, any possible risk should always be fully discussed with a patient prior to treatment and a medical consent signed. Typical risks include bruising around the injected area and the risk of being in more pain — typically for one or two days after treatment — because of the intended inflammation. However, there is a risk that the pain after treatment will continue longer than expected. Other more rare risks include infection, headache, nerve irritation, allergy, puncture of an organ (such as the lungs) if injecting around that region, epidural puncture, or other unexpected risk. There is also the risk that the procedure will not work.

Typical Treatment Course

Treatment intervals are spaced according to how that individual heals. On average, the treatment interval is usually 3 to 4 weeks between treatments. In some people it is shorter, in others it is longer. The average number of treatments for any given area is usually between 4 and 6 total treatments, each treatment involving multiple injections to a particular area. Improvement is sometimes noticed after the initial treatment, however it is more often noticed by the second or third treatment. Some individuals require more than 6 treatments, and, in some cases, less treatments are needed. Individuals with hypermobility often take longer.

How To Get Training In Prolotherapy

Before attempting to use prolotherapy in your practice, it is important to get a solid understanding of prolotherapy basics, as well as approved hands-on and preceptorship training in prolotherapy techniques. Do not attempt to do prolotherapy based on this article or any other article or publication alone. Even if you are adept at injection techniques, you should get specialized training in the technique of prolotherapy and hands-on training experience. While there is no fellowship in prolotherapy available at this time, there are courses given through various associations including the American Academy of Osteopathy; University of Wisconsin School of Medicine — Continuing Medical Education Department; American Academy of Musculo-Skeletal Medicine; American College of Osteopathic Sclerotherapeutic Pain Management; and the American Association of Orthopedic Medicine. It is recommended that you do more than one course. There are also some physicians offering preceptor training through their offices. It is recommended that you read the Hackett/Hemwall/Montgomery primer on the subject (see Reference 1) as well as other books on prolotherapy by Ross Hauser, MD, available at www.beulahlandpress.com.

If your practice is too busy to learn prolotherapy, at least your knowledge and understanding of the technique will allow you to refer appropriate patients for treatment. Since prolotherapy is a treatment modality that provides a long term solution rather than just palliation, it should be considered in appropriate patients prior to resorting to long term narcotic therapy or surgical intervention. ■

Donna Alderman, DO is a graduate of Western University of Health Sciences, College of Osteopathic Medicine of the Pacific, in Pomona, California, with an undergraduate degree from Cornell University in Ithaca, NY. She has extensive training in prolotherapy and has been using prolotherapy in her practice for ten years. She is the author of "Prolotherapy: Freeing Yourself From Chronic Pain," an easy to read primer on the basics of prolotherapy for the lay person, pending publication in 2007. Dr. Alderman is the Medical Director of Hemwall Family Medical Centers in California and can be reached through her website www.prolotherapy.com.

References

1. Hackett GS, Hemwall GA, and Montgomery GA. *Ligament and Tendon Relaxation Treated by Prolotherapy*. (1956 First Edition; Charles C. Thomas, Publisher). Fifth Edition. Gustav A. Hemwall, Publisher. Institute in Basic Life Principles. Oak Brook, IL. 1991.
2. Reeves KD. Prolotherapy: Basic Science, Clinical Studies, and Technique. In Lennard TA (Ed) *Pain Procedures in Clinical Practice*, 2nd Ed. Hanley and Belfus. Philadelphia. 2000. pp 172-190.
3. Alternative treatments: Dealing with chronic pain. *Mayo Clinic Health Letter*. April 2005. 23(4).
4. Koop CE. in Hauser R. *Prolo Your Pain Away!* 1st Edition. 1998. Forward.
5. Hauser R and Hauser M (Eds). *Prolo Your Sports Injuries Away!* Beulah Land Press. Oak Park, IL. 2001.
6. Schnirring, L. News Brief: Are your patients asking about Prolotherapy? *The Physician and Sportsmedicine*. 28(8):15-17.
7. Leadbetter W. Soft tissue athletic injuries. In Fu FH (Ed): *Sports Injuries: Mechanisms, Prevention, Treatment*. Williams & Wilkins. Baltimore. 1994. 736-737.
8. Frank C, Amiel D, Woo SL-Y, et al. Normal ligament properties and ligament healing. *Clin Orthop. Res*. 1985. 196:15-25.
9. Biedert RM, Stauffer E, and Friederich NF. Occurrence of free nerve endings in the soft tissue of the knee joint. A histologic investigation. *American Journal of Sports Medicine*. 1992. 20(4):430-433.
10. Pomeroy KL. *Sclerotherapy, prolotherapy and orthopedic medicine, a historical review*. Presented at American College of Osteopathic Sclerotherapeutic Pain Management seminar. April 2002.
11. Dagenais S, Haldeman S, and Wooley JR. Intraligamentous injection of sclerosing solutions (prolotherapy) for spinal pain: a critical review of the literature. *The Spine Journal*. 2005. 5:310-328.
12. Reeves KD. Prolotherapy: Present and Future Applications in Soft-Tissue Pain and Disability. Injection Techniques: Principles and Practice. *Physical Medicine and Rehabilitation Clinics of North America*. November 1995. (6)4:917-923.
13. Hauser R and Hauser M. *Prolo Your Pain Away!* 2nd Edition. Beulah Land Press. Oak Park, IL. 2004. p 42.
14. Browner, B. *Skeletal Trauma*. Volume 1. WB Saunders. Philadelphia, PA. 1992. p 87-88.
15. Andriacchi T, Sabiston P, DeHaven K, et al. Ligament: Injury and Repair. *Acta Rheum Scand*. 1956. 2:109-116.
16. Banks AR. A Rationale for Prolotherapy. *Journal of Orthopaedic Medicine*. 1991. 13(3).
17. Stovitz, SD and Johnson, RJ. NSAIDs and musculoskeletal treatment - what is the clinical evidence? *The Physician and Sportsmedicine*. 2003. 31:1.
18. Des Rosiers E, Yahia L, and Rivard C. Prolifera-

- tive and matrix synthesis response of canine anterior cruciate ligament fibroblasts submitted to combined growth factors. *J Orthop Res*. 1996. 14:200-208.
19. Kang H and Kang ED. Ideal concentration of growth factors in rabbit's flexor tendon culture. *Yonsei Medical Journal*. 1999. 40:26-29.
20. Lee J, Harwood F, Akeson W, et al. Growth factor expression in healing rabbit medial collateral and anterior cruciate ligaments. *Iowa Orthopedic Journal*. 1998. 18:19-25.
21. Marui T, Niyibizi C, Georgescu HI, et al. Effect of growth factors on matrix synthesis by ligament fibroblasts. *J Orthop Res*. 1997. 15:18-27.
22. Spindler KP, Imro AK, and Mayes CE. Patellar tendon and anterior cruciate ligament have different mitogenic responses to platelet-derived growth factor and transforming growth factor beta. *J Orthop Res*. 1996. 14:542-546.
23. Liu Y. An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. *Connective Tissue Research*. 1983. 11(2):95-102.
24. Maynard JA, Pedrini VA, Pedrini-Mille A, Romanus B, and Ohlerking F. Morphological and Biochemical Effects of Sodium Morrhuate on Tendons. *Journal of Orthopedic Research*. 1983. 3:236-248.
25. Bahme B. Observations on the treatment of hypermobile joints by injections. *The Journal of the American Osteopathic Association*. November 1945. 45:3:101-109.
26. Barbor R. *A treatment for chronic low back pain*. Proceedings from the IV International Congress of Physical Medicine. Paris. September 6-11, 1964.
27. Bourdeau Y. Five-year follow-up on sclerotherapy/prolotherapy for low back pain. *Manual Medicine*. 1988. 3:155-157
28. Chase R. Basic sclerotherapy. *Osteopathic Annals*. December 1978.
29. Coplans C. The use of sclerosant injections in lumbago pain, in *Disorders of the Lumbar Spine* by Heflet A, Grueble L, and David M. 1972. pp 165-169.
30. Dorman T. *Prolotherapy in the lumbar spine and pelvis*. Hanley and Belfus, Inc. Philadelphia. May 1995.
31. Gedney E. Use of sclerosing solution may change therapy in vertebral disk problem. *The Osteopathic Profession*. April 1952. 34, 38, and 39:1113.
32. Gedney E. Progress report on use of sclerosing solutions in low back syndromes. *The Osteopathic Profession*. August 1954. pp. 18-21, 40-44.
33. Gedney E. The Application of Sclerotherapy in Spondylolisthesis and Spondylolysis. *The Osteopathic Profession*. Sept. 1964. pp 66-69; 102-105.
34. Hackett G. Joint stabilization through induced ligament sclerosis. *Ohio State Med J*. Oct 1953. 49:877-884.
35. Hackett G and Henderson D. Joint stabilization: an experimental, histologic study with comments on the clinical application in ligament proliferation. *American Journal of Surgery*. May 1955. 89:968-973.
36. Hackett G. Ligament relaxation and osteoarthritis, loose jointed vs. closed jointed. *Rheumatism*. Lond. April 1959. 15(2):28-33.
37. Hackett G. Low back pain. *Indust Med Surg*. Sept 1959. 28:416-419.
38. Hackett G. Prolotherapy in whiplash and low back pain. *Postgraduate Medicine*. 1960. 27:214-219.
39. Hackett G. Prolotherapy for sciatic from weak pelvic ligament and bone dystrophy. *Clin Med*. December 1961. 8:2301-2316.
40. Hackett G. et al. Prolotherapy for headache: pain in the head and neck, and neuritis. *Headache*. April 1962. 2:20-28.
41. Leedy R et al Analysis of 50 low back cases 6 years after treatment by joint ligament sclerotherapy. 1976. *Osteo Med*. Vol. 6.
42. Linetsky F et al Regenerative Injection Therapy: History of Application in Pain Management, Part I 1930s-1950s and Part II 1930's-1950's. *The Pain Clinic*. April 2000. 2(2):8-13 and April 2001. 3(2):32-36.
43. Matthews J. A new approach to the treatment of osteoarthritis of the knee: Prolotherapy of the ipsilateral sacroiliac ligaments. *American Journal of Pain Management*. 1995. 5(3):91-93.
44. Myers A. Prolotherapy treatment of low back pain and sciatica. *Bull Hosp Joint Disease*. 1961. 22:48-55.
45. Schultz L. A treatment for subluxation of the temporomandibular joint. *Journal of the American Medical Association*. Sept 1937
46. Schultz L. Twenty years' experience in treating hypermobility of the temporomandibular joints. *American Journal of Surgery*. Dec 1956. Vol. 92.
47. Klein RG, Dorman TA, and Johnson CE. Proliferant injection for low back pain: Histologic changes of injected ligaments and objective measurements of lumbar spine mobility before and after treatment. *The Journal of Neurological and Orthopedic Medicine & Surgery*. July 1989. 10(2).
48. Linetsky FS, Botwin K, Gorfine L, et al. *Position Paper: Regenerative injection therapy (RIT) effectiveness and appropriate usage*. The Florida Academy of Pain Medicine. May 24, 2001. http://www.aocomed.org/library/documents/RIT_Position_Paper_052301.pdf
49. Otsuka Y, Mizuta H, Takagi K, et al. Requirement of fibroblast growth factor signaling for regeneration of epiphyseal morphology in rabbit full-thickness defects of articular cartilage. *Dev Growth Differ*. 1997. 39:143-156.
50. Van Beuningen H, Glansbeek H, van der Kraan P et al. Differential effects of local application of BMP-2 or TGF-beta 1 on both articular cartilage composition and osteophyte formation. *Osteoarthritis Cartilage*. 1998. 6:306-317.
51. Ongley MJ, Klein RG, Eek BC, Dorman TA, and Hubert LJ. A new approach to the treatment of chronic low back pain. *The Lancet*. July 1987. pp 143-146
52. Dechow E et al. A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. *Rheumatology*. Oxford. 1999. 38(12):1255-9.
53. Mathews JA et al. Back pain and sciatica: controlled trials of manipulation, traction, sclerosant and epidural injections. *British Journal of Rheumatology*. 1987. 26(6):416-23.
54. Klein RG, Eek BC, DeLong WB, and Mooney V. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain. *Journal of Spinal Disorders*. 1993. 6(1):23-33.
55. Yelland MJ et al. Prolotherapy injections, saline injections, and exercises for chronic low back pain: a randomized trial. *Spine*. 2004. 29(1):9-16.
56. Topol GA, Reeves KD, and Hassanein K. Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain. *Archives of Physical Medicine and Rehabilitation*. 2005. 86:697-702.
57. Ongley MJ, Dorman TA, Eek BC, Lundgren D, and Klein RG. Ligament instability of knees: a new approach to treatment. *Manual Medicine*. 1988. 3:152-154.
58. Reeves KD and Hassanein K. Long term effects of dextrose prolotherapy for anterior cruciate ligament laxity: A prospective and consecutive patient study. *Alternative Therapies*. May/June 2003. 9(3):58-62.
59. Reeves KD and Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. *Alternative Therapies*. March 2000. 6(2):68-79.
60. Reeves KD and Hassanein K. Randomized prospective placebo controlled double blind study of dextrose prolotherapy for osteoarthritic thumbs and finger (DIP, PIP and Trapeziometacarpal) joints: Evidence of clinical efficacy. *Journal of Alternative and Complementary Medicine*. 2000. 6(4):311-320.
61. Reeves KD. Prolotherapy: Present and Future Applications in Soft-Tissue Pain and Disability. Injection Techniques: Principles and Practice. *Physical Medicine and Rehabilitation Clinics of North America*. Nov 1995; (6):4:917-923, citing Hackett GS. Joint stabilization through induced ligament sclerosis. *Ohio State Medical Journal*. 1953. 49:877-884; Hackett GS. Shearing injury to the sacroiliac. *J Int Coll Surg*. 1954. 22:631-642; Hackett GS. *Ligament and Tendon Relaxation Treated by Prolotherapy*, 3rd Edition. Charles C. Thomas. Springfield, IL. 1956; Hackett GS. Prolotherapy in whiplash and low back pain. *Postgraduate Medicine*. 1960. 27:214-219; Hackett GS. Prolotherapy for sciatica from weak pelvic ligaments and bone dystrophy. *Clin Med*. 1962. 8:2301-2316; and Hackett GS, Huang TC, Raftery A. Prolotherapy for headache. *Headache*. 1962. 2:20-28.
62. Hauser R and Hauser M: *Prolo Your Pain Away* 2nd Edition. Beulah Land Press, Oak Park, IL. 2004. p 46.
63. Rhalmi S. Immunohistochemical study of nerves in lumbar spine ligaments. *Spine*. 1993. 18:264-267.
64. Hauser R and Hauser M. *Prolo Your Pain Away*, 2nd Edition. Beulah Land Press. Oak Park, IL. 2004. p 38.
65. Ombregt, Bisschop, and ter Veer. *A System of Orthopaedic Medicine*, 2nd Edition. Churchill Livingstone. 2003. p 59.
66. MacRae DL. Asymptomatic intervertebral disc protrusion. *Acta Radiologica*. 1956. 46-49.
67. Hitselberger WE and Whitten RM. Abnormal myelograms in asymptomatic patients. *Journal of Neurosurgery*. 1968. 28:204.
68. Wiesel SW et al. A study of computer-assisted tomography: 1. The incidence of positive CAT scans in an asymptomatic group of patients. *Spine*. 1984. 9:549-551.
69. Powell MC et al. Prevalence of lumbar disc degeneration observed by magnetic resonance in symptomless woman. *Lancet*. 1986. 13:1366-1367.
70. Boden SD et al., Abnormal magnetic resonance scans of the lumbar spine in asymptomatic subjects. *J Bone and Joint Surgery*. 1990. 72A:503-408.
71. Kaplan PA. MR imaging of the normal shoulder: variants and pitfalls. *Radiology*. 1992. 184:519-524.
72. Deyo R. Magnetic resonance imaging of the lumbar spine-terrific test or tar baby? *New England Journal of Medicine*. 1994. 331:115-116.
73. Matsumoto M et al. MRI of the cervical intervertebral discs in asymptomatic subjects. *Bone and Joint Surgery*. (Br). 1998. 80(1):19-24.
74. Humphreys SC et al. Reliability of magnetic resonance imaging in predicting disc material posterior to the posterior longitudinal ligament in the cervical spine, A prospective study. *Spine*. 1998. 23(22):2468-2471.
75. Kaiser JA and Holland, BA. Imaging of the cervical spine. *Spine*. 1998. 23(24): 2701-2712.
76. Jerosch J, Castro WH, and Assheuer J. Age related magnetic resonance imaging morphology of the menisci in asymptomatic individuals. *Archives of Orthopedic Trauma Surgery*. 1996. 115(3-4):199-202.
77. LaPrade RF et al. The prevalence of abnormal magnetic resonance imaging findings in asymptomatic knees. With correlation of magnetic resonance imaging to arthroscopic findings in symptomatic knees. *Amer J Sports Medicine*. 1994. 22(6):739-745.