

Dear Member,

The following is the position paper of FAPM on RIT/prolotherapy. The vote regarding this paper will take place at the FAPM Annual Conference during the business luncheon meeting on Saturday, June 30, 2001, at 1:00 pm.

Position Paper

**Regenerative Injection Therapy (RIT):**

**Effectiveness and Appropriate Usage**

By

The Florida Academy of Pain Medicine (FAPM)

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POSITION PAPER FROM THE FLORIDA ACADEMY OF PAIN MEDICINE (FAPM)  
ON REGENERATIVE INJECTION THERAPY (RIT)

DEFINITION OF RIT

Regenerative Injection Therapy (RIT) is an interventional technique for treatment of chronic pain due to connective tissue diathesis by induction of collagen chemomodulation through inflammatory, proliferative and regenerative/reparative responses mediated by multiple growth factors. (18, 25, 49, 50, 92, 93, 113, 114)

INTRODUCTION

The purpose of this positional paper is:

1. To inform/familiarize the members of FAPM and the medical community at large regarding the validity of an under-utilized, type-specific treatment for chronic musculoskeletal pain related to connective tissue pathology.
2. To outline common indications and conditions treated with RIT, as well as contraindications thereto.
3. To encourage the use of RIT in the treatment of appropriate painful pathology of the connective tissue.

METHODOLOGY

To determine the validity of RIT/prolotherapy, a position paper committee of interventional pain physicians was formed and undertook a comprehensive review of pertinent literature. The committee reviewed 78 specific articles and nine text books, as well as 51 relevant articles and chapters from other text books.

FINDINGS

From 1937 through 2000, more than forty authors reported case studies, retrospective, prospective and animal experiment studies that evaluated the results of treatment with RIT. The calculated number of patients reported in those studies exceeded 530,000. Improvement in terms of return to work and previous functional/occupational activities was reported in 48% to 82% of the patients. The resolution of pain symptomatology was evaluated differently in various studies and ranged from zero to 100%. Complications included 28 pneumothoraces, two requiring chest tubes, 24 allergic reactions, one grand mal seizure, and one aseptic meningitis.

The findings of the FAPM committee substantially contrast with the position of the Department of Health and Human Services (DHHS), Florida Workmen's Compensation, and Medicare guidelines. The committee recommends consideration of the use of RIT as a type-specific treatment for post-traumatic degenerative, overuse and painful conditions of the musculoskeletal system related to pathology of the connective tissue.

For decades, a small group of allopathic and osteopathic physicians has been practicing the methodology known as Regenerative Injection Therapy (RIT), also known as known in the past as prolotherapy. Pilot, retrospective, open face prospective, and double blind placebo controlled studies have clearly indicated RIT's effectiveness 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. <sup>(4, 5, 8-10, 12, 14-17, 20-22, 26-28, 35-36, 38-69, 73-83, 88-99, 101-104, 106-111, 113-118, 120-122, 124-128, 133-135)</sup>

Clinical and experimental electron microscopic studies have proven that structurally the newly formed connective tissue had biomechanical properties similar to those of normal ligaments and tendons. <sup>(78, 94, 99, 110)</sup>

Preliminary results of clinical prospective trials for chemonucleo-annuloplasty with proliferation-causing substances show significant promise. <sup>(35, 36, 81, 97)</sup>

The literature dealing with RIT has been evaluated. This information, in association with extensive clinical experience has found RIT to be an effective therapy for a number of chronic pain conditions. This position paper reviews the clinical and pathophysiological aspects of RIT. The Florida Academy of Pain Medicine endorses RIT when utilized appropriately for the treatment of specific chronic pain entities.

## I. RIT MECHANISM OF ACTION

The RIT mechanism of action is complex and multifaceted. Six identified components include:

- 1) The mechanical transection of cells and matrix induced by the needle, causes cellular damage, stimulating an inflammatory cascade. <sup>(8, 18-20, 93, 113, 114, 118, 119, 132)</sup>
- 2) Compression of cells by the extracellular volume of the injected solution stimulates intracellular growth factors. <sup>(84-86, 93, 113)</sup>
- 3) Chemomodulation of collagen through inflammatory proliferative, regenerative/repairative responses induced by the chemical properties of the proliferants and mediated by cytokines and multiple growth factors. <sup>(7, 18, 24, 45, 49-53, 84-86, 93, 113)</sup>
- 4) Chemoneuromodulation of peripheral nociceptors and antidromic, orthodromic, sympathetic and axon reflex transmissions. <sup>(49, 57-64)</sup>
- 5) Modulation of local hemodynamics with changes in intraosseous pressure leading to the reduction of pain. Empirical observations suggest that a dextrose/lidocaine combination has a much more prolonged action than lidocaine alone. <sup>(57-64, 123, 129, 138)</sup>
- 6) A temporary repetitive stabilization of the painful hypermobile joints, induced by the inflammatory response to the proliferants, provides a better environment for regeneration and repair of affected ligaments and tendons. <sup>(38, 39, 49-55, 120, 121, 124, 127)</sup>

## II. PUTATIVE PAIN GENERATING STRUCTURES ADDRESSED BY RIT

<sup>(1-45, 47-69, 71, 73-86, 89-93, 98-104, 106-111, 113-122, 124-128)</sup>

- 1) Ligaments: Intra-articular, periarticular, capsular
- 2) Tendons
- 3) Fascia
- 4) Entesis: the zone of insertion of ligament, tendon or articular capsule to bone
- 5) Intervertebral discs. Note: outer layers of the annulus represent a typical entesis.

### III. TISSUE PATHOLOGY APPROPRIATELY TREATED WITH RIT

- 1) Sprain: Ligamentous injury at the fibro-osseous junction or intersubstance disruption secondary to sudden or severe twisting of a joint with stretching or tearing of ligaments. (24, 71, 86, 100)
- 2) Strain: Muscle/tendon injury at the fibromuscular or fibro-osseous interface. When concerned with peripheral muscles and tendons, sprains and strains are identified as separate injuries and in three stage gradations: first, second and third degree sprain and similarly for strain. No consensus exists among authors, and the definitions are quite vague, regarding vertebral and paravertebral ligaments and tendons. (24, 71, 86, 100)
- 3) Enthesopathy: A painful degenerative pathological process that results in deposition of poorly organized tissue, degeneration and tendinosis at the fibro-osseous interface and transition towards loss of function. (18, 24, 71, 86, 93, 101)
- 4) Tendinosis/Ligamentosis: A focal area of degenerative changes due to failure of cell matrix adaptation to excessive load and tissue hypoxia with a strong tendency toward chronic pain and dysfunction. (71, 80, 84-86, 93, 112, 114, 119)
- 5) Pathologic Ligament Laxity: a post-traumatic or congenital condition leading to painful hypermobility of the axial and peripheral joints. (7, 8, 38-43, 47-54)

### IV. INDICATIONS FOR RIT

(1-45, 47-69, 71, 73-86, 89-93, 98-104, 106-111, 113-122, 124-128))

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 supraspinatus 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, spondylolysis and spondylolisthesis
8. Painful cervical, thoracic, lumbar, lumbosacral and sacroiliac instability secondary to ligament laxity.
9. Intolerance to NSAIDs, steroids or opiates. RIT 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.

V. SYNDROMES AND DIAGNOSTIC ENTITIES,  
CAUSED BY LIGAMENT AND TENDON PATHOLOGY,  
THAT HAVE BEEN SUCCESSFULLY TREATED WITH RIT  
(4, 5, 8-22, 26-32, 34-70, 74-85, 87-103, 105-115, 119-121, 123-127, 131-134)

- 1) Cervicocranial Syndrome  
(cervicogenic headaches, secondary to ligament sprain and laxity, atlanto-axial and atlanto-occipital joint sprains, mid cervical zygoapophyseal sprains)
- 2) Temporomandibular Pain and Muscle Dysfunction Syndrome
- 3) Barre-Lieou Syndrome
- 4) Torticollis
- 5) Cervical segmental dysfunctions
- 6) Cervicobrachial Syndrome  
(shoulder/neck pain)
- 7) Hyperextension/Hyperflexion injury Syndromes
- 8) Cervical, Thoracic and Lumbar Zygoapophyseal Syndromes
- 9) Cervical, Thoracic and Lumbar Sprain/Strain Syndrome
- 10) Costo-transverse joint pain
- 11) Costovertebral arthrosis/dysfunction
- 12) Slipping rib syndrome
- 13) Sternoclavicular arthrosis and repetitive sprain
- 14) Thoracic segmental dysfunction
- 15) Tietze's Syndrome/  
costochondritis/chondrosis
- 16) Costosternal arthrosis
- 17) Xiphoidalgia syndrome
- 18) Acromioclavicular sprain/arthrosis
- 19) Shoulder hand syndrome
- 20) Recurrent shoulder dislocations
- 21) Scapulothoracic crepitus
- 22) Iliocostalis Friction Syndrome
- 23) Iliac Crest Syndrome
- 24) Iliolumbar syndrome
- 25) Internal lumbar disc disruption
- 26) Interspinous pseudoarthrosis  
(Baastrup's Disease)
- 27) Lumbar instability
- 28) Lumbar ligament sprain
- 29) Spondylolysis
- 30) Sacroiliac joint pain
- 31) Sacrococcygeal joint pain
- 32) Gluteal tendonosis
- 33) Trochanteric tendonosis
- 34) Myofascial Pain Syndromes
- 35) Ehlers-Danlos Syndrome
- 36) Osgood-Schlatter disease
- 37) Ankylosing Spondylitis  
(Marie-Strumpell disease)
- 38) Failed Back Syndrome
- 39) Fibromyalgia Syndrome
- 40) Foot and/or ankle:
  - Sinus Tarsi Syndrome
  - Metatarsalgia
  - Chronic Ankle Sprain
  - Instability
  - Laxity of ligaments

## VI. CONTRAINDICATIONS TO RIT

1. Allergy to anesthetic or proliferant solutions or their ingredients such as dextrose, sodium morrhuate or phenol.
2. Acute non-reduced subluxations or dislocations.
3. Acute arthritis (septic or post-traumatic with hemarthrosis)
4. Acute bursitis or tendinitis
5. Capsular pattern shoulder and hip designating acute arthritis accompanied by tendinitis.
6. Acute gout or rheumatoid arthritis
7. Recent onset of a progressive neurologic deficit including but not limited to (severe intractable cephalgia, unilaterally dilated pupil, bladder dysfunction, bowel incontinence, etc).
8. Requests for a large quantity of sedation and/or narcotics before and after treatment.
9. Paraspinal neoplastic lesions involving the musculature and osseous structures.
10. Severe exacerbation of pain or lack of improvement after local anesthetic blocks.
11. Relative contraindications: central spinal canal, lateral recess and neural foraminal stenosis.

## VII. COMMONLY UTILIZED SOLUTIONS

The most common solutions are dextrose based. Dilutions can be made with local anesthetic, for example, 1 ml of 50% dextrose mixed with 3 ml of 1% lidocaine. A gradual progression to 25% Dextrose solution has also been utilized. <sup>(27, 50, 93, 113, 114)</sup>

For intra-articular injection of the knee, 25% dextrose solution was utilized for decades. <sup>(50)</sup> Recently, a 10% Dextrose solution has been investigated and also proven to be effective. <sup>(115)</sup>

5% sodium morrhuate is a mixture of sodium salts of saturated and unsaturated fatty acids of cod liver oil and 2% benzyl alcohol. Note that the benzyl alcohol chemically is very similar to phenol and acts as a local anesthetic and preservative. <sup>(8, 50, 93, 101, 124)</sup>

Dextrose phenol glycerine solution consists of 25% dextrose, 2.5% phenol and 25% glycerine and is referred to as DPG or P2G. In all referenced studies, it was diluted with a local anesthetic of the practitioner's choice prior to injection. Dilution reported ratios are 1:1, 1:2 and 2:3. <sup>(5, 20-22, 26, 28, 50, 78-80, 108-110)</sup>

6% phenol in glycerine solution was utilized at donor harvest sites of the iliac crests for neurolytic and proliferative responses. <sup>(95, 135)</sup>

Other solutions utilized include pumice suspension, tetracycline, a mixture of chondroitin sulfate, glucosamine sulfate and dextrose. <sup>(14, 36, 37, 42-44, 50, 81)</sup>

### VIII. CONCLUSIONS

(1-138)

- 1) RIT (known in the past as Prolotherapy) is a valuable method of treatment for correctly diagnosed chronic painful conditions of the locomotive systems.
- 2) Thorough familiarity of the physician with normal, pathologic, cross-sectional and clinical anatomy, as well as anatomical variations and functions are necessary to utilize this technique appropriately.
- 3) Current literature supports manipulation under local joint anesthesia and a series of local anesthetic blocks for diagnosis of somatic pain.
- 4) Use of RIT in an ambulatory setting is an acceptable standard of care in the community.
- 5) Current literature suggests that NSAIDs and steroid preparations have limited utility in chronic painful overuse conditions and in degenerative painful conditions of ligaments and tendons. However, they are occasionally helpful to curb a significant inflammatory reaction to proliferants. Microinterventional regenerative techniques and proper rehabilitation up to six months or a year supported with mild opioid analgesics may be more appropriate.

### IX. SUMMARY

RIT is a safe and effective treatment modality that is very useful in a significant number of pain syndromes arising from ligament and tendon diathesis, as well as other clearly delineated pain problems.

Physicians who use RIT must be knowledgeable in clinical anatomy and function and should be properly trained in this technique via a combination of seminars/workshops, apprenticeships or visiting fellowships in order to safely and effectively utilize this treatment. The Florida Academy of Pain Medicine endorses RIT when administered appropriately for the treatment of specific chronic pain entities.

REFERENCES FOR RIT POSITION PAPER

1. **Agur, A.** et al Grant's atlas of anatomy, 9th edition; Williams and Wilkins; 1991
2. **April, C.** et al "Cervical zygapophyseal joint pain patterns II: A clinical evaluation"; *Spine*:15:6; 1990
3. **Ashton, I.** et al "Morphological basis for back pain: The demonstration of nerve fibers and neuropeptides in the lumbar facet joint capsule but not in the ligamentum flavum"; *Journal of Orthopaedic Research*; 10:72-78, Raven Press LTD; New York; 1992
4. **Bahme, B.** Observations on the treatment of hypermobile joints by injections. *The Journal of the American Osteopathic Association*; 45:3; 101-109; Nov 1945
5. **Barbor, R.** "A treatment for chronic low back pain"; *Proceedings from the IV International Congress of Physical Medicine*; Paris; September 6-11, 1964
6. **Barnsley, L.** et al "Lack of effect of intraarticular corticosteroids for chronic pain in the cervical zygapophyseal joints"; *New England Journal of Medicine*; 330:15; 1047-1050; April 14, 1994
7. **Best, T.** "Basic Science of Soft Tissue", in Delee jc, drez, d jr., (eds) *J Orthopedic Sports Medicine Principles and Practice* (Vol 1), Philadelphia, PA, Saunders; 1994
8. **Biegeleisen, H.I.** *Varicose veins, related diseases and sclerotherapy: A guide for practitioners*; Eden Press; 1984
9. **Blaschke, J.** Conservative management of intervertebral disk injuries; *J. of OK State Med Assoc*; 54:9: Sept. 1961
10. **Blumenthal, L.** "Injury to the cervical spine as a cause of headache"; *Postgraduate Medicine*; Vol 56:3; September 1974
11. **Bogduk, N.** *Clinical anatomy of the lumbar spine and sacrum, third edition*; Churchill Livingstone; 1997
12. **Bourdeau, Y.** Five-year follow-up on sclerotherapy/prolotherapy for low back pain: *Manual Medicine*:3:155-157; 1988
13. **Broadhurst, N.** et al "Vertebral mid-line pain: Pain arising from the interspinous spaces"; *The Journal of Orthopaedic Medicine*; 18:1:2-4; 1996
14. **Chase, R.** "Basic sclerotherapy"; *Osteopathic Annals*; December 1978
15. **Coleman, A.** "physician electing to treat by prolotherapy alters the method at his peril"; *J of the National Medical Assoc*; 60:4: 346-348; July 1968
16. **Compere, E.** et al "Persistent Backache", *Med. Clin. of N. Amer.*, 42:299-307; Jan 1958
17. **Coplans, C.** "The use of sclerosant injections in ligamentous pain", pp 165-169, in *Disorders of the lumbar spine* by Heflet, A., Grueble L. and David M. 1972
18. **Cotran, R.S.** et al *Robbins pathologic basis of disease*, W.B. Saunders, Philadelphia, PA; 1999
19. **Cousins, M.** et al *Neural Blockage in Clinical Anesthesia and Management of Pain*, J.B. Lippincott co.; 1988
20. **Cyriax, J.** *Textbook of orthopaedic medicine, Volume one diagnosis of soft tissue lesion*; Bailliere Tindall; London; 1982
21. **Cyriax, J.** *Illustrated manual of orthopaedic medicine, second edition*, Butterworth Heinemann; 1993
22. **Cyriax, J.** *Textbook of orthopaedic Medicine Volume 1, 5th edition*; Williams and Wilkins Co.; 1969
23. **DesRosiers, E.** et al "Proliferative and matrix synthesis response of canine anterior cruciate ligament fibroblasts submitted to combined growth factors"; *J. of Orth Research*; 14: p200-208; 1996
24. **Dorland's Illustrated Medical Dictionary 26th Edition**, W.B. Saunders Co.; 1985
25. **Dorman, T.** et al *Diagnosis and injection techniques in orthopedic medicine*, Williams and Wilkins, publisher, 1991
26. **Dorman, T.** Storage and release of elastic energy in the pelvis: dysfunction, diagnosis and treatment, as published in *Low back pain and its relation to the sacroiliac joint*, San Diego, CA 1992
27. **Dorman, T.** *Prolotherapy: A Survey*, Journal of Orthopaedic Medicine, 15:2, 49-50, 1993
28. **Dorman, T.** *Prolotherapy in the lumbar spine and pelvis*, Hanley and Belfus, Inc, Philadelphia, May 1995
29. **Dreyfuss, P.** et al "Atlanto-occipital and lateral atlanto-axial joint pain patterns"; *Spine*: 19:10; 1125-1131; 1994
30. **Dreyfuss, P.** et al "Thoracic zygapophyseal joint pain patterns: A study in normal volunteers"; *Spine*: 19:7; 807-811; 1994

31. Dreyfuss, P. "Differential diagnosis of thoracic pain and diagnostic/therapeutic-injection techniques"; *ISIS newsletter*, pp 10-29 December 1997
32. Dreyfuss, P. et al "Muja: Manipulation Under Joint Anesthesia/Analgesia: A Treatment Approach for Recalcitrant Low Back Pain of Synovial Joint Origin", *Journal of Manipulative and Physiological Therapeutics*, Vol 18,#8,pp 537-546; Oct. 1995
33. Dussault, R. et al "Facet joint injection: Diagnosis and therapy"; *Applied Radiology*: 35-39; June 1994
34. Dwyer, A. et al "Cervical zygapophyseal joint pain patterns I: A study in normal volunteers"; *Spine*: 15:6; 1990
35. Eek, B. New directions in the treatment of disc pain as in *Diagnosis and treatment of discogenic pain international spinal injection society 4th annual meeting*; Vancouver; BC; Canada; pp 47-48; August 16, 1996
36. Eek, B. Intradiscal Injection Therapy for Chronic Discogenic Pain, a prospective trial, proceedings of the American Association of Orthopedic Medicine Annual Meeting, Memphis, Tennessee, April 2001
37. Freemont, A. et al "Nerve ingrowth into diseased intervertebral disc in chronic back pain"; *Lancet*; 350:178-181; 1997
38. Gedney, E. Special technic hypermobile joint: a preliminary report, *Osteopathic profession*, p 30-31 June 1937
39. Gedney, E. *The hypermobile joint-further reports on injection method*, read before Osteopathic clinical society of Pennsylvania, Feb 13 1938
40. Gedney, E. Disc syndrome, *Osteo prof*, Sept, pp 11-15, 38-46 1951 50.
41. Gedney, E. Use of sclerosing solution may change therapy in vertebral disk problem, *The osteopathic profession*; pp. 34, 38 and 39, 1113 April 1952
42. Gedney, E. Technic for sclerotherapy in the management of hypermobile sacroiliac; *The Osteopathic Profession*; 16-19 and 37-38; August 1952
43. Gedney, E. Progress report on use of sclerosing solutions in low back syndromes. *The Osteopathic Profession*; 18-21, 40-44 August 1954
44. Gedney, E. "The Application of Sclerotherapy in Spondylolisthesis and Spondylolysis", *The Osteopathic Profession*, pp 66-69 and 102-105, Sept. 1964
45. *Gray's anatomy, 38th British edition*, Churchill Livingstone, Pearson Professional Limited; 1995
46. Grayson, M. Sterile meningitis after lumbosacral ligament sclerosing injections; *The Journal of orthopaedic medicine*: 16:3; 1994
47. Green, S. "Hypermobility of joints: causes, treatment and technic of sclerotherapy", *The Osteopathic Profession*; pp 26-27 and pp 42-47; April 1956
48. Green, S. "The study of ligamentous tissue is regarded as key to sclerotherapy"; *The Osteopathic Prof*; pp 26-29; January 1958
49. Hackett, G. *Ligament and Tendon relaxation (skeletal disability)- treated by prolotherapy, (fibro-osseous proliferation), 3rd edition*, Springfield, IL, Charles C. Thomas; 1958
50. Hackett, G. et al *Ligament and tendon relaxation-treated by prolotherapy, 5th edition*; 1991
51. Hackett, G. Joint stabilization through induced ligament sclerosis. *Ohio State Med. J.*; 49:877-884; Oct 1953
52. Hackett, G. and Henderson, D. Joint stabilization: an experimental, histologic study with comments on the clinical application in ligament proliferation, *American Journal of Surgery*; 89:968-973 May 1955
53. Hackett, G. *Joint ligament relaxation treated by fibro-osseous proliferation, first edition*, Charles C. Thomas publisher 1956
54. Hackett, G. Ligament relaxation and osteoarthritis, loose jointed vs. closed jointed. *Rheumatism*, Lond;15:2:28-33, April 1959
55. Hackett, G. "Low back pain", *Indust. Med. Surg.*, 28:416-419; Sept 1959
56. Hackett, G. "Prolotherapy in whiplash and low back pain", *Postgrad. Med.* 27:214-219; 1960
57. Hackett, G. "Prolotherapy in low back pain from ligament relaxation and bone dystrophy", *Clinical Medicine* 7:12, pp 2551-2561 Dec 1960
58. Hackett, G. et al "Back pain following trauma and disease prolotherapy", *military medicine*; pp 517-525; July 1961
59. Hackett, G. "Prolotherapy for sciatic from weak pelvic ligament and bone dystrophy", *Clin, Med.*, 8:2301-2316; Dec 1961

60. **Hackett, G.** et al "Prolotherapy for headache: pain in the head and neck, and neuritis", *Headache*, 2:20-28; April 1962.
61. **Hackett, G.** "Arteriosclerosis, carcinogenesis, neuritis and osteoporosis", *angiology*, Vol 17:109-118, Feb 1966
62. **Hackett, G.** "Cause and mechanism of headache, pain and neuritis", *Headache* 6:88-92, July 1966
63. **Hackett, G.** "Uninhibited reversible antidromic vasodilation in pathophysiologic diseases: arteriosclerosis, carcinogenesis, neuritis and osteoporosis", *Angiology*, Vol 17, #2, February 1966
64. **Hackett, G.** "Uninhibited reversible antidromic vasodilatation in bronchiogenic pathophysiologic diseases", *Lancet* 86:398-404, Aug 1966
65. **Hackett, G.** "Prevention of cancer, heart, lung and other diseases", *Clin. Med.* 74:19, Sept 1967
66. **Haldeman, K.** et al The diagnosis and treatment of sacroiliac conditions by the injection of procaine (novocain), *Journal of bone and joint surgery*, vol. xx, no. 3, July pp. 675-685; 1938
67. **Hirsch, C.** "An attempt to diagnose the level of a disc lesion clinically by disc puncture"; *Acta Orthop. Scand*; 18:131-140; 1948
68. **Hirschberg, G.** et al "Treatment of the chronic iliolumbar syndrome by infiltration of the iliolumbar ligament"; *Western J. of Medicine*; 136: 372-374; Apr 1982
69. **Hirschberg, G.** et al Diagnosis and treatment of iliocostal friction syndromes; *J of Ortho Med*: 14:2: p 35-39; 1992
70. **Hunt, W** "Complications following injections of sclerosing agent to precipitate fibro-osseous proliferation"; *J Neurosurg*; 18:461-465; 1961
71. **Jozsa, L.** Human tendons, anatomy, physiology and pathology, *Human Kinetics*, Champaign, IL; 1997
72. **Kang, H.** et al "Ideal concentration of growth factors in rabbit's flexor tendon culture": *Yonsei medical journal*: 40:1;pp 26-29; 1999
73. **Kayfetz, D.** et al "Whiplash injury and other ligamentous headache-its management with prolotherapy"; *Headache*; Vol III: No I; Apr 1963
74. **Kayfetz, D.** "Occipito-cervical (whiplash) injuries treated by prolotherapy", *Med Trial Tech Quar*, Callaghan and Co; pp.147-167 pp.09-112; 1963
75. **Kellgren, J.H.** "On the Distribution of Pain Arising From Deep Somatic Structures with Charts of Segmental Pain Areas", *Somatic Pain* pp.35-46; 1939
76. **Kidd, R.** "Recent Developments in the Understanding of Osgood-Schlatter Disease: A Literature Review," *The J. of Ortho. Med.*, Vol. 15, No. 3, pp.59-61, 1993
77. **Kidd, R.** "Treatment of Osgood-Schlatter Disease by Prolotherapy – A Case Report," *The J. of Ortho. Med.*, Vol 15, No 3, pp.62-63, 1993
78. **Klein, R.** et al "Proliferation Injections for Low Back Pain: Histologic Changes of Injected Ligaments and Objective Measurements of Lumbar Spine Mobility Before and After Treatment", *J of Neuro and Ortho Med and Surg*, Vol 10, Issue 2, July 1989
79. **Klein, R.** et al "Prolotherapy: An Alternative Approach to Managing Low Back Pain", *The Journal of Musculoskeletal Medicine*, pp.45-59, May 1997
80. **Klein, R.** Diagnosis and treatment of gluteus medius syndrome; *J Orth. Med*: 1373-76; 1991
81. **Klein, R.** Interdiscal injection Therapy for Chronic Discogenic Pain, a prospective trial in progress, presentation at the Amer. Assn. Of Ortho. Med workshop, Daly City, CA, Feb. 2001
82. **Klein, R.** et al. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain; *J of Spinal Disorders*: 6:1; p.23-33; 1993 et al
83. **Koudele, C.** "Treatment of joint pain"; *Osteopathic Annals*: 6:12; 42-45; Dec 1978
84. **Leadbetter, W.** Cell-matrix response in tendon injury; *Clin sports med* 11; 533-578; 1992
85. **Leadbetter, W.** Anti-inflammatory therapy and sport injury: the role of non-steroidal drugs and corticosteroid injections; *Clin sports med* 14; 353-410; 1995
86. **Leadbetter, W.** *Soft Tissue athletic Injuries: Sports Injuries: Mechanisms, Prevention, Treatment*; Williams and Wilkins, pp.736-737; 1994
87. **Lee, J.** et al "Growth factor expression in healing rabbit medial collateral and anterior cruciate ligaments": *Iowa Orthopaedic Journal*:18 pp.19-25; 1998
88. **Leedy, R.** et al "Analysis of 50 low back cases 6 years after treatment by joint ligament sclerothrapy"; *Osteo Med*:6; 1976
89. **Leedy, R.** "Applications of sclerothrapy to specific problems"; *Osteopathic Medicine*; pp.79-81,85,86,89-91, 94-96; Aug 1977

90. **Leriche, R.** Effets de l'anesthesia a la novocaine des ligaments et des insertion tenineuses periarticulaires dans certaines maladies articulaires et dans les vices de positions fonctionnelles des articulations, *Gaz D. Hop.*, 103:1294; 1930
91. **Linetsky, F.** et al "Regenerative Injection Therapy: History of Application in Pain Management, Part I 1930s-1950s"; *The Pain Clinic*; Vol. 2:2; pp.8-13, Apr 2000
92. **Linetsky, F.** et al "Regenerative Injection Therapy: History of Applications in Pain Management, Part II 1930s-1950s"; *The Pain Clinic*; Vol. 3:2, pp.32-36, Apr 2001
93. **Linetsky, F.** et al., "Pain Management with Regenerative Injection Therapy (RIT)", a chapter in *Pain Management: A Practical Guide for Clinicians* (6<sup>th</sup> Ed.) in print
94. **Liu, Y.** et al "An in Situ Study of the Influence of a Sclerosing Solution in Rabbit Medial Collateral Ligaments and its Junction Strength", *Connective Tissue Research*, Vol 11, pp.95-102; 1983
95. **Maher, R.** "Neuron Selection in Relief of Pain. Further Experiences with Intrathecal Injections", *The Lancet*; pp.16-19; Jan 1957
96. **Marui, T.** et al "Effect of growth factors on matrix synthesis by ligament fibroblasts"; *J. or ortho research*: 15:pp.18-23; 1997
97. **Massie, J.** et al Is it possible to stimulate fibroplasia within the intervertebral disc?; *J of Ortho Med*: 15:3; p.83; 1993
98. **Matthews, J.** A new approach to the treatment of osteoarthritis of the knee: Prolotherapy of the ipsilateral sacroiliac ligaments: *Am J of Pain Management*; 5:3; p.91-93; 1995
99. **Maynard, J.** et al "Morphological and Biochemical Effects of Sodium Morrhuate on Tendons", *J of Ortho Research*, 3:234-248; 1985
100. **Merskey, H.** et al *Classification of Chronic Pain, Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms* (2<sup>nd</sup> Ed), IASP Press, Seattle; 1994
101. **Mirman, M.** *Sclerotherapy, 4th Edition*, Springfield, PA 19064; 1989
102. **Mooney, V.** Sclerotherapy in back pain? Yes if clinician is skilled; *J of Musculoskeletal medicine*; p.13; Jan 1993
103. **Mooney, V.** Understanding, examining for, and treating sacroiliac pain; *The Journal of musculoskeletal medicine*; pp.37-49; July 1993
104. **Myers, A.** "Prolotherapy treatment of low back pain and sciatica", *Bull Hosp Joint Disease*: 22:p.48-55; 1961
105. **Nakamura, N.** et al "Early biological effect of in vivo gene transfer of platelet-derived growth factor (PDGF)-B into healing patellar ligament"; *Gene Therapy*; 5: pp.1165-1170; 1998
106. **Neff, F.** "A new approach in the treatment of chronic back disabilities", *The Family Physician*; 9:3; Mar 1959
107. **Neff, F.** Low back pain and disability," *Western Med.*; 1:12 June 1960
108. **Ombregt, L.** et al *A system of orthopaedic medicine*, WB Saunders Co, Ltd; 1995
109. **Ongley, M.** et al "A New Approach to the Treatment of Chronic Low Back Pain", *The Lancet*, July 18, pp.143-146; 1987
110. **Ongley, M.** et al Ligament instability of knees: A new approach to treatment; *Manual Medicine*: 3:pp.152-154; 1988.
111. **Poritt, A.** The injection treatment of hydrocele, varicocele, bursae and nevi, *Proc. Royal Soc. Med.*, 24:81; 1931
112. **Ranney, D.** *Chronic musculoskeletal injuries in the workplace*, W.B. Saunders, Co.; 1997
113. **Reeves, K.D.** Prolotherapy: Basic Science Clinical Studies and Technique as in Lennard *Pain Procedures in Clinical practice*; Hanley and Belfus Inc; Philadelphia; 2000
114. **Reeves, K.D.** "Prolotherapy: Present and Future Applications in Soft-Tissue Pain and Disability", *Physical Medicine and Rehabilitation Clinics of North America*, Vol 6, No. 4, pp.917-926; Nov.1995
115. **Reeves, K.D.** et al Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity, *Altern Ther Health Med*, 6(2) 68-74, pp.77-80, March 2000
116. **Reeves, K.D.** "Randomized, Prospective, Placebo-Controlled Double-Blind Study of Dextrose Prolotherapy for Osteoarthritis Thumb and Finger Joints;" *The Journal of Alter. and Compl. Med.*, 6(4): pp.311-320; 2000
117. **Reeves, K.D.** "Treatment of Consecutive Severe Fibromyalgia Patients with Prolotherapy," *The J. of Ortho. Med.*, Vol. 16, No. 3, pp.84-89, 1994
118. **Riddle, P.** *Injection treatment*, Philadelphia, PA, W.B. Saunders Co.; 1940

119. **Roosth, H.** Low back and leg pain attributed to gluteal tendinosis; *Orthopedics today*; Nov 1991
120. **Schultz, L.** "A treatment for subluxation of the temporomandibular joint"; *Journal of AMA*; Sept 256, 1937
121. **Schultz, L.** Twenty years' experience in treating hypermobility of the temporomandibular joints, *Amer jour of Surg*, Vol 92 Dec. 1956
122. **Schwartz, R.** et al Prolotherapy: A literature review and retrospective study; *J Neurol Orthop Med Surg*; 1991
123. **Shevelev, A.** et al Interosseous receptor system as the modulator of trigeminal afferent reactions; *Worldwide Pain Conference; Pain and Neuromodulation: the new millennium* (hosted by the International and American Neuromodulation societies); Proceedings of The 9th World Congress: The Pain clinic; Hosted by the World Society of Pain Clinicians; San Francisco, CA p 34; 715-21/2000
124. **Shuman, D.** *Low back pain*, Philadelphia, PA, David Shuman publisher; 1958
125. **Shuman, D.** Luxation recurring in shoulder; *Osteopathic Profession* 8:6; p.11-13; 1941
126. **Shuman, D.** Sclerotherapy--injections may be best way to restrengthen ligaments in case of slipped knee cartilage, *Osteopathic profession*, Mar 1949
127. **Shuman, D.** The place of joint sclerotherapy in today's practice. *Bulletin of the New Jersey Association of Osteopathic Physicians and Surgeons*; Oct 1949
128. **Shuman, D.** Sclerotherapy: statistics on its effectiveness for unstable joint conditions, *The osteopathic profession*, July, pp.11-15 and pp.37-38, 1954
129. **Sokov, E.** et al Are herniated disks the main cause of low back pain; *Worldwide Pain Conference; Pain and neuromodulation: the new millennium* (hosted by the International and American Neuromodulation societies); Proceedings of The 9th World Congress: The Pain clinic; Hosted by the World Society of Pain Clinicians; San Francisco, CA p 74; 715-21/2000
130. **Spindler, K.** et al "Patellar tendon and anterior cruciate ligament have different mitogenic responses to platelet-derived growth factor and transforming growth factor b"; *J or Ortho research*: 14:542-546; 1996
131. **Steindler, A.** et al: Differential diagnosis of pain low in the back; allocation of the source of pain by the procaine hydrochloride method, *J.A.M.A.*, 110:106-113; 1938
132. **Vanderschot, L.** The American version of acupuncture. Prolotherapy: coming to an understanding; *Am J Acupuncture*; 4:309-316; 1976
133. **Vanderschot, L.** Trigger pints vs. acupuncture points; *Am J.*
134. **Vlemming, A.** et al *Movement, stability and low back pain: the essential role of the pelvis*, Churchill Livingstone; 1997
135. **Wilkinson, H. A.** *The Failed Back Syndrome Etiology and Therapy, 2nd Edition*, Springer-Verlag; 1992
136. **Willard, F.** "The lumbosacral connection: The ligamentous structure of the low back and its relation to back pain as in *Proceedings of the Second interdisciplinary world congress on low back pain, the integrated function of the lumbar spine and sacroiliac joints; Part I*; pp.29-58; San Diego, CA; Nov 9-11, 1995.
137. **Yahia, H.** et al A light and electron microscopic study of spinal ligament innervation; *Z. mikrosk. - Anat.* 102; 1989
138. **Zoppi, M.** et al From intraosseous pain syndrome to osteoarthritis; *Worldwide Pain Conference; Pain and neuromodulation: the new millennium* (hosted by the International and American Neuromodulation societies); Proceedings of The 9th World Congress: The Pain Clinic; Hosted by the World Society of Pain Clinicians; San Francisco, CA p.412; 715-21/2000.