PAIN MANAGEMENT WITH REGENERATIVE INJECTION THERAPY (RIT)

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"The whole of science is nothing more than a refinement of everyday thinking" Einstein

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INTRODUCTION

The purpose of this chapter is to provide the pain management clinicians with a review of the pertinent literature, clinical and anatomic considerations in relation to a interventional regenerative treatment for chronic musculo-skeletal pain.

There is an omnipresence of the connective tissue throughout the body. Structurally and biomechanically they represent a heterogenous group with variations in collagen orientation, cross linking, shape, cell properties, and presence of synovial lining in various locations. Without connective tissue the "musculo-skeletal system" will cease to exist. Great variety of functions depend on proper homeostasis of connective tissue. For example, without the storage and release of energy in connective tissue during locomotion, much higher energy requirements would be encountered. [1,2] On the other hand, many dysfunctional and painful syndromes may arise from pathologic conditions of the connective tissue.

The injury occurs when the internal or external forces exceed the threshold of failure for the specific connective tissue. This may be in the form of a ruptured or strained ligament, tendon, fascia, bone fracture or a prolapsed disc.

Pain arising from connective tissue pathology, such as

degenerative & post-traumatic changes in the intervertebral disc, ligaments, tendons, aponeuroses, fasciae, sacroiliac and facet joint capsular ligaments, is often difficult to differentiate based solely on clinical presentation. Individual variations in innervation further complicate the differential diagnosis. Left untreated, posttraumatic and overuse injuries of ligaments and tendons can linger indefinitely, leading to the progression of degenerative changes, loss of function, deconditioning and perpetuate disability and chronic pain. [3-9]

Interventional Regenerative Modalities for painful musculo-skeletal pathologies have been described for more than two millenniums. For example, the technique of collagen thermomodulation now known as thermocapsulorrhaphy was originally described by Hippocrates, who had created thermocoagulation of the anteroinferior capsule for treatment of recurrent shoulder dislocations "with red hot slender irons". [6,10] It is currently recognized that sufficient thermomodulation of collagen can be achieved with lower temperatures to stimulate a proliferative and regenerative/reparative response. This concept has lead to development of intradiscal electrothermal (IDET) procedures, currently utilized with the intent to achieve nuclear shrinkage, seal annular fissures and thermocoagulate nociceptors. [11-13]

Coexistence of physical and chemical methods is well demonstrated in the contemporary practice of dermatology and plastic surgery, where chemical (carbolic acid=phenol) and laser induced facial peels are utilized for regeneration and

rejuvenation by chemo and thermomodulation of the skin collagen.

One of the less known but a long practiced method of interventional regenerative modalities is Regenerative Injection Therapy (RIT), also known as prolotherapy or sclerotherapy. [14,15] It was originally described by Celsus for treatment of hydrocele, with injections of saltpeter. [16,17] Its current technique combines addressing the affected connective tissues with diagnostic local anesthetic blocks followed by injection of solutions that, by virtue of their chemical properties, are able to stimulate regenerative reparative process in the injured tissues.

Application of RIT for low back pain has been described in numerous textbooks and articles, comparatively adequate applications for cervical and thoracic pain are lacking. We choose to emphasize cervicothoracic pain problems treated with RIT. [5,10,18-21]

ETYMOLOGY OF SOME TERMINOLOGY

Biegelesen first used the term "sclerotherapy" in 1936. 'Sclero': [derived from the word skleros (Greek)-hard]. [22]

Hackett felt that sclerotherapy implied scar formation, therefore he coined the term "prolotherapy" and defined it as: "the rehabilitation of an incompetent structure by the generation of new cellular tissue". [4] [derived from the word 'proli' (Latin)-offspring. 'Proliferate': to produce new cells in rapid succession] The former, however, is an integral attribute of a malignant unsuppressed growth. Moreover with

advance of basic science and the contemporary understanding of the healing process these authors prefer RIT because it is recognizes that regeneration extends beyond the proliferative stage. On a cellular level RIT induces chemomodulation of collagen through repetitive stimulation of the inflammatory and proliferative phases in a sophisticated process of tissue regeneration and repair, mediated by numerous growth factors leading to the restoration of tensile strength, elasticity, increased mass and load bearing capacity of the affected connective tissue. [23-26] The above capabilities make RIT a specific treatment for degenerative chronic painful conditions such as enthesopathy, tendinosis, and ligament laxity, versus commonly utilized steroid injections and denervation procedures. [27,28]

LOCAL ANESTHETICS IN DIAGNOSIS OF MUSCULOSKELETAL PATHOLOGY

BRIEF HISTORY

In 1930 Leriche introduced application of procaine for differential diagnose and treatment of ligament and tendon injuries of the ankle and other joints at their fibroosseous insertions. [29]

In 1934 Soto-Hall & Haldeman reported on the benefits of procaine injections in the diagnosis and treatment of painful shoulders. Subsequently in 1938 they published a study on diagnosis and treatment of painful sacroiliac dysfunctions with Procaine injections. After infiltration of posterior sacroiliac

ligaments, interspinous ligaments at L4-5 & L5-S1 levels and zygapophyseal joint capsules with procaine they observed a marked relaxation of spastic musculature and added the routine use of sacroiliac joint manipulations, establishing manipulation of axial joints under local anesthesia. (30)

In 1938 Steindler and Luck made a significant contribution to currently validated approaches in the diagnosis and treatment of low back pain based on Procaine injections. Authors pointed out that posterior divisions of the spinal nerves provide the sensory supply to the musculature, tendons, supraspinous, interspinous, iliolumbar, sacroiliac, sacrotuberous and sacrospinous ligaments and origins and insertions of aponeurosis of tensor fascia lata, gluteal muscles and thoracolumbar fascia. They emphasized that based on clinical presentation alone, no definite diagnosis could be made, and postulated that five criteria have to be met to prove that a causal relationship exists between the structure and pain symptoms. See table 1. (3)

TABLE 1 Radiating/referral pain postulates

"1) Contact with the needle must aggravate the local pain.
2) Contact with the needle must aggravate or elicit the radiation of pain
3) Procaine infiltration must suppress local

tenderness.

4) **Procaine infiltration must suppress radiation of pain.**
5) **Positive leg signs must disappear."**

Subsequently, in 1948, Hirsh demonstrated relief from sciatica following intradiscal injection of procaine. (31)

Local anesthetic diagnostic blocks are currently the most reliable and objective confirmation of the precise tissue source of pain and clinical diagnosis. (8,32-34)

HISTORY AND EVOLUTION OF RIT

The scientific rationale for implementing regenerative injection therapy in chronic painful pathology of ligaments and tendons evolved from clinical and histologic research performed for injection treatment of hernia, hydrocele and varicose veins. The therapeutic action of the newly formed connective tissue was different in each condition. In hernias, the proliferation and subsequent regenerative/reparative response lead to fibrotic closure of the defect. (35-37) In hydrocele, hypertrophied subserous connective tissue reinforced capillary walls of serous membrane and prevented further exudate formation. (16,17) The latter mode of action was employed in the treatment of chronic olecranon and pre-patellar bursitis by Poritt in 1931. He

drained the fluid from the sac and injected 5% sodium morrhuate. In cases of persistence he injected a 5% phenol solution into the bursae. (38)

In 1935 Shultz, while searching for a better way to treat painful subluxations of TMJs, conceived the idea that strengthening of the joint capsule by induced ligament fibrosis would lead to capsular contraction and prevent subluxations. Animal experiments were conducted with several solutions, among those, Sylnasol provided the best outcomes and, therefore was chosen for the clinical trials. (Note: Sylnasol-sodium psyllate was an extract of psyllium seed oil produced by Searle pharmaceutical and discontinued in 1960s.) A clinical study of 30 human subjects after bi-weekly injections of 0.25 to 0.5ml of Sylnasol demonstrated "entire patient satisfaction". Shultz concluded that the principle of induced hypertrophy of the articular capsule by injecting a fibrosing agent might be applied to other joints capable of subluxations or recurrent dislocations. He also concluded that Sylnasol was a dependable agent. Injections restored normal joint function and the method was within the scope of treatment of a general practitioner.(39) Twenty years later, Schultz presented the positive results of

Sylnasol injections on several hundred patients, successfully cured from painful hypermobility of TMJs. [40]

Also in 1937 Gedney reported some details of collateral ligament injections for painful unstable hypermobile knees and posterior sacroiliac ligaments of unstable painful sacroiliac articulations. Small amounts of sclerosant solutions were injected along the entire affected structures. Six months later, he extended this treatment to recurrent shoulder dislocations, acromioclavicular separations and sternoclavicular subluxations. [41,42]

In 1939, Kellgren, injected volunteers with hypertonic saline and implicated interspinous ligaments as a significant source of local and referred pain. He published maps of referred pain from deep somatic structures including interspinous ligaments.[43]

In 1940 Riddle included a chapter on "The injection treatment of joints" in his text and described the injection treatment of TMJ's and shoulders in great details, giving Shultz the appropriate credit for initiation of this treatment.[37]

Shuman described injection treatment of recurrent shoulder dislocations via strengthening of the inferior capsular

ligaments with Sylnasol in 1941.[44] Subsequently in 1949 he adopted the term sclerotherapy for this injection modality, modifying it later that year to Joint Sclerotherapy. [45,46]

In 1945 Bahme published the first retrospective study of 100 patients who improved after injection of Sylnasol to the sacroiliac ligaments. Patients were under his care for an average of 4 months. The average number of injection treatments was five, 80% reported complete resolution of symptoms. He also found these injections to be very helpful in the treatment of unstable ribs, and reported improvement in 12 patients. He described a significant co-existence of painful hypermobile ribs with hypermobile sacroiliac joints explaining the phenomenon by concomitant functional scoliosis. [47]

By 1944 Lindblom demonstrated radial annular fissures during cadaveric disc injections and later described nucleographic patterns of 15 discs in 13 patients. [48] Thereafter, in 1948, Hirsch relieved sciatic pain with intradiscal injection of procaine. [31] These two articles prompted Gedney and subsequently Shuman to explore therapeutic applications of sclerosants for pain related to intervertebral disc (IVD) pathology.

By 1951 Gedney extended treatment with sclerosant injections to painful degenerative lumbar disc syndromes and described the detailed technique of Sylnasol injections into the lateral annulus of the lumbar disc without fluoroscopic guidance.(49) He reported L4 disc involvement in 95% of cases and a 50% clinical improvement after treatment of this disk alone.(50) In treatment of hypermobile sacroiliac joints he emphasized that the amount of solution and quantity of treatments were highly individual and depended on the patient's response.(51) In retrospective study he emphasized significant statistical coexistence of sacroiliac pathology with disk pathology at L3, L4 & L5 levels.(52) By 1954 he completed a prospective study of 100 patients. 65 were treated initially with the injections into the disc. 35 were initially treated with injections into the posterior sacroiliac ligaments. The latter group required less intradiscal injections. Thus, he concluded that, in the presence of sacroiliac pain and hypermobility, adequate stabilization of the sacroiliac joint should be achieved in all cases prior to addressing discogenic pain. (52) He emphasized the importance of interspinous & iliolumbar ligament injections in the treatment of lumbar spondylolisthesis. (53)

In 1954 Shuman evaluated the effectiveness of sclerosant injections to the sacroiliac joints, intervertebral discs, spondylolisthesis, zygapophyseal joint capsules, knees and shoulders in 93 respondents to a retrospective survey. Improvements ranged from 75 to 98%. Only those patients who were able to perform their usual occupations were considered to have positive results. (54) Later he detailed many aspects of treatment with integration of manipulative techniques, including manipulation under local anesthesia (Introduced 20 years earlier by Haldeman & Soto-Hall). Shuman stated that zygapophyseal joint pathology emphasized by Hackett in 1956 and disc pathology were the more common causes of lower back pain than the sacroiliac joint pathology. (6)

Hackett, the inventor of prolotherapy postulated in 1939 that ligaments were responsible for the majority of back pain.(55) By 1958 he came to the conclusion that tendons at the fibroosseous junctions were another significant source of chronic pain syndromes. (4) In a retrospective study he reported on 84 patients with sacroiliac pain treated by sclerosant injections of Sylnasol, 5-7 times to each affected area. 82% reported themselves entirely symptom free for a duration of 6-14

years.[56] In the initial animal experiments he demonstrated 30 to 40% increase in tendon size, after injections of Sylnasol. [57] **(Figure 1 & 2)** Unsatisfied with the term sclerotherapy, because it implied hardening of the tissue and scar formation, he introduced the term "prolotherapy" in 1956. He did this because the results of his experimental study did not support scarring but rather hypertrophy induced by proliferation of connective tissue in linear fashion.[57] Hackett employed and emphasized the importance of the earlier referenced postulates of Steindler. He confirmed the ligament or tendon involvement as pain generators reproducing local and referred pain by "needling" and abolishing the pain by infiltration of local anesthetic prior to injecting the proliferants. [57] He published maps of referred pain from ligaments and tendons, initially of the lumbopelvic region. There were derived from 7000 injections in over 1000 patients treated over 17 years. He subsequently developed maps of the cervicothoracic region.[4] **(Figure 3)** Later he pointed out that loose-jointed individuals had lesser ability to recuperate from sprains because of the congenital laxity of their ligaments, and, have a predisposition to chronic lingering pain for decades. He emphasized their positive

response to prolotherapy. [58]

In many subsequent publications, Hackett emphasized the common pathogenesis of impaired local circulation in chronic conditions such as neuritis, headaches, whiplash, osteoporosis, bone dystrophy, bronchospasm and arteriosclerosis. Excess of antidromic, sympathetic and axon reflex stimulation caused local vasodilatation and edema with a perpetuating vicious cycle, of "tendon relaxation", the condition now understood as degenerative changes, enthesopathy, tendinosis, and laxity. [58-69]

Extended subsequent animal experiments with multiple solutions conducted by Hackett revealed that the strongest fibroosseous proliferations were achieved with Sylnasol, zinc sulfate solutions and silica oxide suspension. The strongest acute inflammatory reaction was obtained with Sylnasol and zinc sulfate followed by silica oxide, whole blood moderately stimulated fibroosseous proliferation. Hydrocortisone used alone or in combination with proliferants inhibited proliferation for 3-4 weeks. At the fracture sites proliferants increased callus formation in 3 weeks, whereas used in combination with steroids the callus formation was markedly inhibited. [62]

Hackett's positive results were initially corroborated by Green, Compere, Neff and Myers. [70-75] In fact Myers reported improvement in 82% of his patients. [75]

By 1961 Blasche reported the first prospective study of 42 patients treated with prolotherapy for lower back pain. Thirty-two of them were workmans compensation cases, notoriously the most difficult cases to treat and 10 were private insurance. Complete recovery was achieved in 20 patients observed for 3 years. Thirteen patients reported no change in their condition, 9 underwent surgery. Four patients with clinical presentation of acute herniated disc, in whom prolotherapy was utilized without hope of success, had better results than any other patients in this study. In three instances of surgical intervention specimens were obtained from the sites of injections and were reported as "normal fibrous tissue". [76]

A multicenter study conducted by Kayfetz at al was published in 1963. 264 patients were treated by prolotherapy for headaches, 78% had headaches of traumatic origin, 58% had non-traumatic headaches and 56% had symptoms of Barre Lieou syndrome. 86% had symptoms longer than 1 month and 46% had symptoms longer than 1 year. Traumatic group reported

satisfactory results in 79%, with excellent results in 60%. Non-traumatic group reported satisfactory results in 47% and excellent results in 29%. 60% of patients were followed by over 1 year and 27% were followed up to 3-5 years. There were no infections or other complications following prolotherapy. [77]

Also in 1963 Kayfetz reported a 5 year follow up study of 189 cases with (whiplash injuries) treated by prolotherapy. 149 cases (79%) were due to automobile accidents. 153 (81%) had associated injuries to thoracic and lumbar areas. 98 (52%) had an associated Barre-Lieou syndrome. 55% had symptoms longer than 1 months duration and 21% longer than 1 year duration. Majority of patients received 6 to 30 injections in one setting and were treated on 1 to 10 occasions. Duration of treatment was from 1 to 6 months. Excellent results, in terms of pain, were obtained by 113 (60%), good by 15 (8%) and fair by 34 (18%). Seventy-five percent of patients were considering themselves cured from pain. [78]

In response to adverse effects published after alleged incidental intrathecal injections of zinc sulfate Hackett conducted experiments with intrathecal injections of this solution in rabbits. [79-81] Clinical doses (4-5 drops) did not

produce a noticeable effect. Those animals received increased doses that produced spinal anesthesia, completely recovered after the anesthetic wore off. "It was necessary to use much greater than clinical dosage to induce paraplegia for a few weeks duration, which also cleared up." (62)

In 1967 Coleman brought medicolegal aspects of prolotherapy to the attention of the medical community. He pointed out that Hackett's technique was accepted as a standard of care. It was declared by the California court that a physician treating a patient had deviated from the method as described by Hackett. Conclusion was made that one did not have to follow the method of treatment followed by majority of the physicians in the community. A physician is permitted to follow a method or a form of treatment followed by minority of physicians if they are reputable and of good standing. But if he varies from the minority method of treatment he does so in violation as if he deviated from the generally accepted method of treatment.

The court concluded: "...as a matter of law that prolotherapy as a method of treatment can not be said to be inappropriate or to be malpractice even though it has not been accepted as a common method of treatment by the medical

profession generally". [82]

Abroad, positive results with Hackett's method were obtained by Ongley, Barbor, Cyriax and Coplans.[18,20,83,84] Barbor presented a study of 153 patient with back pain for up to 20 years duration. 111 of them (74%) reported relief to their satisfaction. 17 (11%) failed to improve. 25 (16%) were lost for follow up. 31 patients (23%) required periodic booster injection for relief. Solution utilized was dextrose, phenol, glycerine (DPG) mixed in proportion of 2cc of DPG to 3cc of local anesthetic. [83]

Cyriax included detailed description of "sclerosant injections" to interspinous and facet joint capsular ligaments of the cervical, thoracic and lumbar regions in his texts. [18-20]

Further he described *"a clinical blind study of 'sclerosant therapy' presented by Sanford in 1972. Of 100 patients only 3 were lost for follow up."* The following 3 solutions were compared: I) 2 ml of DPG sclerosant mixed with 8ml of saline; II) 10ml of 0.5% procaine; III) 10ml of normal saline. The diluted sclerosant and Procaine solutions were almost equally effective, by relieving pain in more than 50% of cases. Procaine and normal saline were equally ineffective by

not helping in 50% of cases. Saline solution helped less than a third of patients. The dilution of DPG sclerosant down to 20% of the original strength significantly impaired its proliferant action. (18-20)

In 1974 Blumenthal reported 2 cases of migraine headache and one case of cluster headache successfully cured by prolotherapy and a minor modification of Hackett's technique in the treatment of cervicodorsal pain. (85)

By 1976 Leedy reported a 70% improvement in the condition of 50 low back pain patients treated with sclerosant injections and followed for 6 years. He also published several descriptive articles of the method. (86,87)

Also in 1976 Vondershot compared prolotherapy with acupuncture in treatment of chronic musculoskeletal pain, and concluded that prolotherapy has a faster onset of action and a longer lasting pain relief. (88,89)

In 1978 Chase reported up to 70% or better improvement in long standing cases of painful head, neck/shoulder and low back syndromes. (90,91)

Also in 1978 Koudele reported findings of Haws and Willman on histologic changes in human tissue treated up to five times

with sclerosant injections for low back pain. The following changes were observed and documented on slides. DPG solution produced early coagulation necrosis, followed by early collagen formation. By six months a small zone of residual inflammatory cells were documented in an area of a very dense collagen. In two other specimens, treated with DPG, a dense collagen with fibrosis, occluded blood vessels and a dense whirl of scar was observed.

After injection of pumice suspension an area of dense collagen and fibrosis surrounding a "lake" of pumice was documented, without foreign body reaction but with a capsule formation. (91)

In 1982 Hirshberg reported a prospective study of 16 patients with the iliolumbar syndrome. Nine were treated with infiltration of Lidocaine at the insertion of the posterior iliolumbar ligament to the iliac crest and 7 were injected with a mixture containing equal amounts of 50% Dextrose and 2% Xylocaine, a total of 5cc. Significant recovery was reported by 10 patients. Six out of the 7 treated with Dextrose/Xylocaine recovered whereas only 4 out of 9 treated with Xylocaine recovered. (92)

In 1983 Liu, in a double-blind study, injected rabbit medial collateral ligaments (MCL) and demonstrated that repeated injections of 5% sodium morrhuate at the fibroosseous attachments (enthesis) significantly increased its bone-ligament-bone junction strength by 28%, ligament mass by 44% and thickness by 27%, when compared with saline controls. Morphometric analysis of electron micrographs demonstrated a highly significant increase in the diameter of collagen fibrill in the experimental ligaments versus controls. These findings confirmed that sodium morrhuate had a significant regenerative influence on dense connective tissue at the insertion sites. (23)

By 1985 Maynard reported decrease in collagen fibrils and hydroxyproline content & overall increased mass of tendons in experimental animals injected with sodium morrhuate. The average tendon circumference increased up to 25%. (24)

In 1987 Ongley in a double blind, randomized study of chronic low back pain in 81 subjects demonstrated statistically significant improvement greater than 50% in patients injected with a DPG solution versus saline. By disability scores the experimental group demonstrated a greater improvement than the control group: ($p<0.001$);($p<0.004$); and ($p<0.001$)

respectively.[25] Subsequently he demonstrated a significant statistical improvement in five patients treated for painful instability of the knees with prolotherapy. Ligament stability data was obtained by a three dimensional computerized goniometry, integrated with force measurements [93]

In 1988 Bourdeau published a five year retrospective survey on patients with low back pain treated with prolotherapy. 17 patients or 70% had reported excellent to very good results. [94]

By 1989 Klein histologically documented proliferation and regeneration of ligaments in human subjects in response to injections of DPG solution accompanied by decreased pain and increased range of motion documented by computerized inclinometry. [26]

In 1991 Roosth described gluteal tendinosis as a distinct clinical entity and Klein described the treatment of gluteus medius tendinosis with proliferant injections. [95,96]

Also in 1991 Schwartz reported a retrospective study of 43 patients with chronic sacroiliac strain who received 3 series of proliferant injection at bi-weekly intervals. Improvement was reported by all but 3 patients, and ranged from 95% reported by 20 patients to 66% reported by 4 patients. Ten patients

reported recurrence. He concluded that induced proliferation of collagen and dense connective tissue of the ligament is associated with reduction of painful subluxations. (97)

In 1992 Hirschberg reported positive results in treating iliocostal friction syndrome in the elderly with proliferant injections and a soft brace. (98)

In 1993 Klein & Eek reported a double-blind clinical trial of seventy-nine patients with chronic low back pain that had failed to respond to previous conservative therapy. Subjects were randomly assigned to receive series of six injections in a double-blind fashion at weekly intervals of either lidocaine/saline or lidocaine/DPG solution into the posterior sacroiliac and interspinous ligaments, fascia, and facet capsules of the low back from L4 to the sacrum. All patients underwent pretreatment MRI or CT scans. Patients were evaluated with a visual analog, disability, and pain grid scores, and with objective computerized triaxial tests of lumbar function 6 months following conclusion of injections. Thirty of the 39 patients randomly assigned to the proliferant group achieved a 50% or greater decrease in pain or disability scores at 6 months compared to 21 of 40 in the group that received lidocaine

(p=0.042). Improvements in visual analog (p=0.056), disability (p=0.068), and pain grid scores (p=0.025) were greater in the proliferant group. [99]

In 1993 Massie & Mooney reported that it was possible to stimulate fibroplasia in the intervertebral discs with proliferant injections. [100] Also in 1993 Mooney advocated proliferant injections for chronic painful recurrent sacroiliac sprains if the clinician was skilled. [101,102]

In 1994 Grayson reported a case of sterile meningitis after injection of lumbosacral ligaments with proliferating solutions.[103]

By 1995 Matthews found significant improvement in painful osteoarthritic knees after injection of the ipsilateral sacroiliac ligaments with proliferant solutions. [104]

Also in 1995 Reeves pointed out that degenerative changes of enthesopathy may be painful and prolotherapy with a less aggressive solution such as 12% dextrose with xylocaine is the only type specific treatment for these pathologic changes of ligaments and tendons. [27]

In 1996 Eek reported on the benefit of proliferating injections for intradiscal pain. [105] In 1997 Klein & Eek

described proliferant injections for low back pain in details. (106)

The clinical anatomy in relation to RIT/prolotherapy for low back pain was reviewed in 1999 by Linetsky & Willard. The presence of the connective tissue stocking surrounding various lumbar structures dictating their function as a single unit in a normal state and necessity to include multiple segmental and extrasegmental structures in differential diagnosis of the low back pain was emphasized. (14)

Subsequently in March of 2000 Reeves demonstrated in a randomized, double-blind, placebo-controlled study beneficial effects of 10% dextrose with lidocaine in knee osteoarthritis with anterior cruciate ligament laxity. Goniometric measurements of knee flexion improved by 12.8% ($p= 0.005$) and anterior displacement difference improved by 57% ($p=0.025$). By 12 months (6 injections) the dextrose-treated knees improved in pain (44% decrease), swelling complaints (63% decrease), knee buckling frequency (85% decrease), and in flexion range (14 degree increase). He concluded that proliferant injection with 10% dextrose stimulated growth factors and regeneration, and resulted in a statistically significant clinical improvements in

knee osteoarthritis.[107] In April of the same year Linetsky reviewed the history of RIT/prolotherapy from 1930 through 1950. [15]

In order to understand the essence of RIT/prolotherapy it is important to review the basic science related to healing process, some anatomical and biomechanical properties of the connective tissue and clinical anatomy.

INFLAMMATORY-REGENERATIVE/REPARATIVE RESPONSE & DEGENERATIVE PATHWAYS

The inflammatory response is intertwined with the regenerative, reparative process. A complex inflammatory reaction induced in vascularized connective tissue by endogenous or exogenous stimuli may lead to two distinct repair pathways. The first is regeneration that replaces injured cells by the same type of cells and second is fibrosis or replacement of injured cells by fibrous connective tissue. Often a combination of both processes contributes to the repair. Initially in both processes a similar pathway takes place,with migration of fibroblasts, proliferation, differentiation and cell-matrix

interaction. The latter, together with basement membrane provides a scaffold for regeneration of pre-existing structures. [108] "...modulation of these cell matrix responses regardless of the method, provides an intriguing challenge." [109] Cell replication is controlled by chemical and growth factors. Chemical factors may inhibit or stimulate proliferation whereas growth factors such as cytokines/chemokines, TGF-ß1 (transforming growth factor ß1), PDGF (platelet derived growth factor), FGF (fibroblast growth factor), VEGF (vascular endothelial growth factor), IGF (insulin-like growth factor), CTF (connective tissue growth factor) and NGF (nerve growth factor) stimulate proliferation. Regenerative potential depends on cell type, genetic information and the size of the defect. In the presence of a large connective tissue defect fibrotic healing takes place. [108,110]

Under the best circumstances natural healing restores connective tissue to its preinjury length but only 50%-75% of its preinjury tensile strength. [27,109] Connective tissues are bradytropic, (their reparative capability is slower than that of muscle or bone). In the presence of repetitive microtrauma, unjudicious use of NSAIDs and steroid medications, tissue

hypoxia, metabolic abnormalities and other less defined causes, connective tissue may divert towards degenerative pathway. [27,109-112] ..." A judicious utilization of anti-inflammatory therapy remains useful, albeit adjunctive therapy..." [111] Biopsies of these tissue demonstrate disorganized collagen, excessive matrix, insufficient elastin, disorganized mesenchymal cells, vascular buds with incomplete lumen, few or absent white blood cells, neovasculogenesis and neoneurogenesis. [112,113] Degenerative changes in tendons may be hypoxic, mucoid, mixoid, hyaline, calcific, fibrinoid, fatty, fibrocartilaginous and osseous metaplasia and any combination of the above. [113]

Similar degenerative changes were found in fibromyalgia syndrome with dense foci of rough frequently hyalinized fibrillar connective tissue. Vascularization occurred at the periphery of these foci, only where thin nervous fibrils and sometimes small paraganglions were seen with severe degenerative changes of the collagen fibers, and marked decrease of fibroblasts. Inflammatory markers were absent. [114]

Repeated eccentric contractions diminish muscle function and increase intramuscular pressure. For instance the intramuscular pressure in the supraspinatus and infraspinatus is

4 to 5 times higher than, that in the deltoid or trapezius at the same relative load.[115] Edema arising in one muscle compartment secondary to overuse does not spread to the adjacent compartments. Prolonged static muscular efforts predispose to edema which leads to a decrease in perfusion pressure and a subsequent reduction of blood flow with granulocyte plugging of the capillaries and further metabolite accumulation and vasodilatation. [112-115]

Further repeated eccentric contractions are notorious for microtraumas with microruptures either at the fibroosseous junctions, in the mid substance of the ligaments and tendons, or at the myotendinous interface.

Repetitive microtrauma with insufficient time for recovery leads to inadequate regenerative process that turns to a degenerative pathway in tendons, muscles, discs, joint ligaments and cartilage.[110-115] Improper posture in combination with eccentric contractions (such as driving with both hands on a steering wheel or typing on a computer with improperly positioned keyboard and monitor) are the most common examples of eccentric contraction. [109-115]

Impaired circulation at the fibromuscular and fibroosseous

interface eventually leads to impaired intraosseous circulation with diminished venous outflow and increase in intraosseous pressure. This in turn stimulates intraosseous baroreceptors and contributes to nociception transmitted through fine myelinated and nonmyelinated fibers that accompany nutrient vessels into bone and located in perivascular spaces of Haversian canals. Decreased circulation leads to hypoxia, effects calcium metabolism and contributes to progression of osteoarthritis.[1,59-69,116-118]

SOME ANATOMICAL & BIOMECHANICAL PROPERTIES OF LIGAMENTS & TENDONS

Ligaments are dull white dense connective tissue structures that connect adjacent bones. They may be intraarticular, extraarticular or capsular. Collagen fibers in ligaments may be parallel, oblique, or spiral. These orientations represent adaptation to specific directions in restriction of joint displacements.

Tendons are glistening white collagenous bands interposed between muscle and bone that transmit tensile forces during muscle contraction. There are considerable variations in shape of fibroosseous attachments from cylindrical, fan shaped to

wide, flat and ribbon shaped. The myotendinous junctions have significant structural variations from end to end to oblique and singular intermuscular fibers. The collagen content of tendons is approximately 30% wet weight or 70% dry weight. (1,119)

Under the light microscope, ligaments and tendons have a crimped, wave form appearance. This crimp is a planar zigzag pattern which unfolds during initial loading of collagen. (1,119) Elongated below 4% of original length ligaments and tendons return to their original crimp wave appearance, beyond 4% elongation they loose the elasticity and become permanently laxed. However, in degenerative ligaments, subfailure was reported as early as at 1.5% of elongation. Laxity of ligaments obviously leads to joint hypermobility. Experimental study confirmed that the medial collateral ligament (MCL) failed more abruptly than either the capsular ligaments or the anterior cruciate. This happened because MCL has more parallel fibers with uniformity in length, therefore, they fail together. The capsular fibers are less organized than MCL or the anterior cruciate, their length and orientation vary. Since fibers are loaded and fail at different time a large joint displacement is needed before capsular failure is complete.

There are three principal failure modes. The first most common is ligament failure. The second, more common, is a bone avulsion fracture, and the third, a less common is a shear or cleavage failure at the fibroosseous interface.

Collagenous tissues are deleteriously affected by inactivity and are favorably influenced by physical activity of an endurance nature. They are also deleteriously affected by NSAIDs and steroid administrations.

In fact "Administration of even a single dose of corticosteroids directly into ligaments or tendons can have debilitating effects upon their strength. Intraarticular injections of methyl-prednisolone acetate given either once or at intervals of several months may be less detrimental to ligament or tendon mechanical properties." (119)

Tendons are strongly attached to the bones by decussating and perforating Sharpey's fibers. Current understanding of OTJ, Osseo Tendinous Junction aka enthesis, aka fibroosseous junction is such that the fibers insert to the bone via four zones: tendon zone, fibrocartilage zone, mineralized fibrocartilage zone and lamellar bone. However, it does not shed much light on the mechanism of tendon avulsion and overuse induced pathology,

as it was emphasized by Hackett. [4,5,61-64,113] The tensile strength of tendons is similar to that of bone and is about half that of steel. A tendon with a cross section of 10mm in diameter may support a load of 600 to 1000kg. [1,113,119]

Three types of nerve endings in posterior ligamentous structures of the spine were confirmed microscopically. They are free nerve endings, Pacini & Ruffini corpuscles. The free nerve endings were found in superficial layers of all ligaments including supraspinous and interspinous with a sharp increase in their quantity at the spinous processes attachments (enthesis). Paciniform corpuscles located in adipose tissue between supraspinous ligaments and lumbosacral fascia and in the deep layers of supraspinous and interspinous ligaments acting as nociceptors in all locations and as mechanoceceptors with a low threshold, stimulated by stretch of the ligaments and muscle actions. Ruffini receptors located in the interspinous and flaval ligaments, respond to stretch and control the reflex inhibitory mechanism. [120]

Neonurogenesis and neuvasculogenesis have been documented in chronic connective tissue pathology. The nerve and vascular tissue ingrowth into diseased intervertebral discs, posterior

spinal ligaments, hard niduses of fibromyalgia, together with neuropeptides in the facet joint capsules, have been observed. (114, 121-123)

During postnatal development tendons enlarge by interstitial growth particularly at the myotendinous junction aka fibromuscular interface where there is a high concentration of fibroblasts. The nerve supplies are largely sensory. (1,113,119,124)

Insertion pathology of the trunk muscles (enthesopathy at the fibroosseous junctions) most commonly affects the following sites: occipital and scapular insertions, the spinous processes especially at the cervicodorsal and thoracolumbar regions, iliac crest, sternum, symphysis pubis. **(Figure 4 & 5)** Histopathologically the following findings were observed: calcium deposits and mineralization of the fibrocartilaginous zone. (113) A large study examined traumatically ruptured tendons from 891 patients in comparison with 445 tendon specimens obtained from similar local sites in similar age and sex group of "healthy" individuals who died accidentally. Degenerative changes were well documented in 865 ruptured tendons (97%) and only in 149 control tendons (27%). Similar

statistical differences were observed comparing tendons of individuals who died 3 years after quadriplegia and those who died accidentally. Irreversible lipoid degenerations at the muscle tendon junctions were documented as early as 3 months after onset of quadriplegia. [113]

Cervical zygapophyseal joints (z-joint) is responsible for 54% of chronic neck pain after "whiplash" injury. The prevalence may be as high as 65%. [125] In populations presenting with headaches after "whiplash" over 50% of the headaches stem from the C2-3 z-joint. [126-129] Intraarticular corticosteroid injections are ineffective in relieving chronic cervical z-joint pain. [125] The above data [125-129] strongly suggests that there is a presence of nociceptors other than z-joints and intervertebral discs. Pain patterns from synovial joints at the cranio-cervical junction overlap with the pain patterns from the lower z-joints and suboccipital soft tissues. [4,5,60,64,130-132] Their contribution to nociception requires confirmation with intraarticular blocks under fluoroscopic guidance by a practitioner with a significant amount of experience. [132,133]

CLINICAL ANATOMY OF CERVICOCRANIAL, CERVICAL AND CERVICODORSAL

REGION IN RELATION TO RIT

It is important to realize that various ligaments, tendons and fasciae of the cervical, thoracic and lumbar regions form a continuous connective tissue stocking incorporating and interconnecting various soft tissue, muscular, vascular and osseous structures. Although each of the connective tissues has a slightly different biochemical content, they blend at their boundaries and function as a single unit. The innervation is generally segmental and posteriorly provided by the respective medial and lateral branches of the dorsal rami. (1,14,134-135)

Differential diagnosis is based on a thorough understanding of the regional and segmental anatomy and pathology. Currently prevailing trends in diagnostic efforts are addressing discogenic, facetogenic and neurocompressive components of spinal pain. Consequently therapy is directed towards neuromodulation or neuro-ablation with radiofrequency generators. Also surgical ablations and fusions correct the mass effects in neurocompressive models, or discogenic pain.

In the mid cervical area blocking the putative medial branches of the dorsal rami at the waist of the articular pillars, as the initial step in differential diagnosis, is

considered diagnostic and prognostic for z-joint pain. [126, 133] However, such approach as an initial step in differential diagnosis may be misleading for two reasons. First, it interrupts orthodromic and antidromic transmission at the proximal segment of the medial branch of the dorsal rami (MBDR), excluding other putative nociceptors located distally on its course from the differential diagnosis. Second, there is significant individual variation in the location of the dorsal rami bifurcations into the medial and lateral branches. [136]

All cervical spinal nerves divide into ventral and dorsal rami. The dorsal rami in turn divide into the medial and lateral branches except the first dorsal ramus, that is also called the suboccipital nerve. The first dorsal ramus supplies the muscles of the suboccipital region: rectus capitis posterior minor and major, inferior and superior oblique, semispinalis capitis and has an ascending cutaneous branch that connects with the greater and lesser occipital nerves and may contribute to the occipital and suboccipital headaches. [1,127,133] The second cervical dorsal ramus also supplies the inferior oblique, connects with the first one and divides into a lateral and medial branch (MBDR). Its medial branch (the greater occipital

nerve) pierces the semispinalis capitis and trapezius at their insertion to the occipital bone on its ascending course. Thereafter it connects with the branches from the third occipital nerve along the course of the occipital artery supplying the skin of the skull up to the vertex. [1,127,133]

Anatomical texts [1,134] indicate that it is the dorsal ramus proper of the lower 5 cervical nerves that is located laterally at the waist of the articular pillars. **(Figures 6 & 7)** On the other hand current trends in therapeutic and diagnostic blocks are based on the assumption that the anatomy and course of the MBDR is constant, that it arises from the intertransverse space and then wraps around the waist of the respective articular pillars. [130,133] However, clinical observations supported by ongoing research and microdisections of Willard indicate that bifurcations into medial and lateral branches are not consistent in their location and may originate in the intertransverse space, projection of lateral and posterior aspects of articular pillars. [136] **(Figure 6 & 7)** Quite often the course of the medial (MB) and lateral branches (LB) is parallel at the waists of the articular pillars with the medial branch being proximal to the osseous structure. [136] Thereafter the medial branch of

the dorsal ramus (MBDR) furnishes twigs to zygapophyseal joint capsules and continues along the lamina and spinous process towards its apex, innervating structures inserting or originating at the lamina and the spinous process on its course. [1,134,136] For example the fourth and fifth cervical MBDRs supply the semispinalis cervices and capitis, multifidi, interspinalis, splenius and trapezius, supraspinous ligaments and end in the skin. The lowest three MBDRs have a similar course. [1,134,136]

(Figure 6 & 7)

Lateral branches supply the iliocostalis, longissimus cervices and longissimus capitis. Similar anatomic relationships are observed in the thoracic region where medial branches of the upper 6 thoracic dorsal rami supply the zygapophyseal joints, semispinalis thoracis, multifidi, piercing trapezius and rhomboid and reach the skin most proximal and lateral to the spinous processes. [1,134]

RIT/PROLOTHERAPY MECHANISM OF ACTION

The RIT mechanism of action is complex and multifaceted.

1) The first is the mechanical transection of cells and matrix by the needle causing cellular damage and stimulating inflammatory cascade.

2) The second is compression of cells by the extracellular volume of the injected solution-stimulating intracellular growth factors. [110]

3) The third is chemomodulation of collagen through inflammatory proliferative, regenerative/reparative response induced by the chemical properties of the proliferants and mediated by cytokines and multiple growth factors.[27,110,137-144] 4) The forth is chemoneuromodulation of peripheral nociceptors and antidromic, orthodromic, sympathetic and axon reflex transmissions. [4,61-68]

5) The fifth is modulation of local hemodynamics with changes in intraosseous pressure leading to reduction of pain. Empirical observations suggest that dextrose/lidocaine combination has a much more prolonged action than lidocaine alone. [58,61-68,116-118]

6) The sixth is a temporary repetitive stabilization of the painful hypermobile joints induced by inflammatory response to the proliferants providing a better environment for regeneration and repair of the affected ligaments and tendons. [4-6,47,50-53]

<u>Putative pain generating structures addressed by</u>

RIT/prolotherapy are : [3-10,14,15,18-28,34,37-47,49-78,83-94,96-107]

1) Ligaments: Intraarticular, periarticular, capsular

2) Tendons

3) Fascia

4) Enthesis: the zone of insertion of ligament, tendon, or articular capsule to bone [28,113,145,146] aka fibroosseous junctions of ligaments and tendons. In orthopaedic literature referred to as OTJ-osseo/tendinous junction. [109-113] For the purpose of this chapter enthesis or fibroosseous junction are interchangeable.

5) Intervertebral discs

TISSUE PATHOLOGY TREATED WITH RIT/PROLOTHERAPY

1) Sprain: *Ligamentous injury at the fibroosseous junction or intersubstance disruption. A sudden or severe twisting of a joint with stretching or tearing of ligaments; also: a sprained condition.* [27,112 147,148]

2) Strain: *Muscle/tendon injury at the fibromuscular or fibroosseous interface. When concerned with the peripheral muscles and tendons sprains and strains are identified as separate injuries and in a*

three stage gradations: first, second & third degree sprain and similarly for strain. In regards to vertebral and paravertebral ligaments and tendons no consensus exists among authors and the definitions are quite vague. [112,145,146]

3) Enthesopathy: *A painful degenerative pathological process that results in deposition of poorly organized tissue, degeneration and tendinosis at the fibroosseous interface and transition towards loss of function.* [14,27,28,112,113]

4) Tendinosis/ Ligamentosis: A focal area of degenerative changes due to a failure of cell matrix adaptation to excessive load and tissue hypoxia with a strong tendency to chronic recurrent pain and dysfunction. [27,28,95,112,113,124]

5) Pathologic Ligament Laxity: a post-traumatic or congenital condition leading to painful hypermobility of the axial and peripheral joints. [4,10,27,87,107,110,145,147]

INDICATIONS FOR RIT/PROLOTHERAPY

1) Chronic pain from ligaments or tendons secondary to sprains or strains. [3-6,8-10,14,15,18-28,34,39-47,49-78,83-94,96-107]

2) Pain from overuse or occupational conditions known as Repetitive Motion Disorders ie neck and wrist pain in typists and computer operators, "tennis" and "golfers" elbows, chronic supraspinatus tendinosis. [5,6,37-47,49-78]

3) Painful chronic postural neck & cervicodorsal junction problems. [5,6,37-47,49-78,83-94,96-107]

4) Painful recurrent somatic dysfunctions secondary to ligament laxity that improve temporarily with manipulation. Hypermobility and subluxation at a given peripheral or spinal articulation or mobile segment(s) accompanied by a restricted range of motion at reciprocal segment(s). [5,10]

5) Thoracic vertebral compression fractures with a wedge deformity that exert additional stress on the posterior ligamento-tendinous complex. [5,10]

6) Recurrent painful subluxations of ribs at the costotransverse, costovertebral and/or costosternal articulations. [5,10,21,47]

7) Spondylolysis and spondylolisthesis [5,10,52,53]

8) Intolerance to NSAIDs, steroids or opiates. RIT may be the treatment of choice if the following modalities are contraindicated or: failure to improve after physical therapy, chiropractic or osteopathic manipulations, steroid injections or radiofrequency denervation, or surgical interventions in aforementioned conditions. [5,10]

THE LIST OF SYNDROMES AND DIAGNOSTIC ENTITIES CAUSED BY LIGAMENT AND TENDON PATHOLOGY THAT HAVE BEEN SUCCESSFULLY TREATED WITH RIT/PROLOTHERAPY

1) Cervicocranial Syndrome (cervicogenic headaches, alar ligaments sprain, atlanto-axial and atlanto-occipital joint sprains)
2) Temporomandibular pain and dysfunction syndrome
3) Barre Lieou Syndrome
4) Spasmodic torticollis
5) Cervical segmental dysfunctions
6) Cervical and Cervicothoracic spinal pain of "unknown" origin
7) Cervicobrachial Syndrome (shoulder/neck pain)
8) Hyperextension/Hyperflexion injury Syndromes
9) Cervical, Thoracic and Lumbar Facet Syndromes

10) Cervical, Thoracic and Lumbar Sprain/Strain Syndrome
11) Costo-transverse joint pain
12) Costovertebral arthrosis/dysfunction
13) Slipping rib syndrome
14) Sternoclavicular arthrosis and repetitive sprain
15) Thoracic segmental dysfunction
16) Tietze's Syndrome/Costochondritis/chondrosis
17) Costosternal arthrosis
18) Intercostal arthrosis
19) Xiphoidalgia syndrome
20) Acromioclavicular sprain/arthrosis
21) Shoulder hand syndrome
22) Recurrent shoulder dislocations
23) Scapulothoracic crepitus
24) Myofacial Pain Syndromes
25) Ehlers-Danlos Syndrome
26) Osgood-Schlatter disease
27) Marie-Strumpell disease
28) Failed Back Syndrome

CONTRAINDICATIONS TO RIT/PROLOTHERAPY

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 sprains or strains of axial and peripheral joints.

4) Acute arthritis (septic or post-traumatic with hemarthrosis)

5) Acute bursitis or tendinitis

6) Capsular pattern shoulder and hip designating acute arthritis accompanied by tendinitis.

7) Acute gout or rheumatoid arthritis

8) Recent onset of a progressive neurologic deficit including but not limited to (ie: severe intractable cephalgia, unilaterally dilated pupil, bladder dysfunction, bowel incontinence, etc).

9) Requests for large quantity of sedation and/or narcotics before & after treatment.

10) Paraspinal neoplastic lesions involving the musculature and osseous structures.

11) Severe exacerbation of pain or lack of improvement after local anesthetic blocks.

13) Relative contraindications: central spinal canal,

lateral recess and neural foraminal stenosis.

CLINICAL PRESENTATIONS

Patients may present with variety of complaints ranging from one area of localized pain and tenderness to any combination of referred pain patterns known with cervical disc, cervicocranial and cervicobrachial or cervical and thoracic facet syndromes. Headaches accompanied by cervical muscle spasms are a common complaint. Exacerbation of pain while standing or sitting in the same position for a given period of time, increased pain after exertion or physical activity are typical complaints. Feeling of weakness in the neck, back or extremities, extreme fatigability are common. Pseudoradicular patterns of change in sensation, such as burning, numbness, tingling. Difficulties maintaining balance, ringing in the ears, blurred vision. Feeling of a need for repetitive self manipulations, chiropractic or osteopathic manipulations. Painful clicking, popping or locking of axial or peripheral joints. Dropping of objects, weakness of the hands and "heaviness of the head". [5,10,27,77,78,110]

PHYSICAL EXAMINATION

Tenderness is the most common finding over the chronically

strained or sprained ligaments or tendons. Provoked tenderness rarely reproduces radiating or referral pain, it is a local phenomenon. However, intensity of such tenderness may be changed or abolished completely after manipulation. Patients are able to point out such pain with their finger in posterior cervicodorsal region.

Such local tenderness as well as referred and radiating pain often can be abolished by infiltration of nociceptors in the involved tissue with local anesthetic. Tenderness is an objective finding especially when elicited at posterior structures. (4,5,14,149,150)

RADIOLOGIC EVALUATION PRIOR TO RIT/PROLOTHERAPY

1) Plain radiographs are of limited diagnostic value in painful pathology of the connective tissue, however they may detect: a) structural or positional osseous abnormalities

b) anterior or posterior listhesis on lateral views (flexion, extension)

c) degenerative changes in general & deformity of zygapophyseal articulation (151-154)

2) Videofluroscopy or digital motion radiography currently is a valuable diagnostic method in evaluation of painful

hypermobility and instability due to posttraumatic and degenerative pathology of capsular and axial ligaments. Evaluation of certain axial and peripheral joints in motion affords noninvasive opportunity to identify specific segments responsible for nociception. At the upper cervical levels this technology is capable of identifying excessive motions at atlanto occipital, lateral and median atlanto axial joints, and indirectly pathology of their respective fibrous articular capsules and periarticular ligaments. **(Figure 8,9,10)** Capsule related pathology with hypo & hypermobility may be identified and documented in caudally situated cervical zygapophyseal articulations. Integrity of the posterior ligamentous complex contributing to listhesis related pathology may be documented. Small avulsion fractures of articular pillars, and vertebral bodies or spinous processes may be identified. Pathology of TMJs is visualized and correlated with audio/video captioning. Painful instability of peripheral joints such as shoulder, elbows, wrists, knees and ankles also has been identified and documented. [155-160]

Such studies have to be performed with high quality

digitalized equipment by well trained technologists in order to produce film quality contrast resolution and to be of diagnostic value, as currently available from VF Works, Inc. Combined with computerized range of motion studies this technology may afford the opportunity to objectively document progress after RIT/prolotherapy, or other procedures directed towards stabilization of axial and peripheral articulations such as facets, shoulders, knees and TMJs.

3) MRI may detect intervertebral disc pathology, enthesopathy, ligamentous injury, interspinous bursitis, zygapophyseal joint disease and sacroiliac joint pathology, evaluation of the neural foraminal pathology, bone contusion, neoplasia, infection or fracture and exclude or confirm spinal cord disease and pathology related to intradural, extramedullary and epidural space. (152,162)

4) CT scan may detect small avulsion fractures of the facets, laminar fracture, fracture of vertebral bodies and pedicles or degenerative changes. (152)

5) Bone scan is useful in assessment of the entire skeleton ruling out metabolically active disease process. (152)

SAFE INJECTION SITES

Common sites for injections are the enthesis of the structures that insert or originate at the spinous processes and are innervated by the medial branches of the dorsal rami. At the cervicodorsal junction, from superficial to deep, those are the supraspinous ligament, superficial layers of the cervico-dorsal fascia, and multiple tendons. The apex of the spinous process may be considered a "spinous rotator cuff". **(Figures 11,12)** At the cervicocranial junction, these are fibroosseous insertions at the superior and inferior nuchal lines, lateral aspects of the apex at the C2 spinous process and C2/3 posterior z-joint capsule.

The following step by step approach to a differential diagnosis is based on knowledge of anatomy and pathology, to investigate all potential nociceptors in the distribution of the medial and lateral branches extending it beyond z-joints, as is currently accepted. (125-130,133,163-165)

Accordingly, in the presence of significant midline tenderness the most painful medial structures innervated by terminal filaments of the MBDRs are blocked initially. If after local anesthetic block, the paramedian pain persists, laminar

enthesis of structures are blocked. If pain still persists the posterior cervical or thoracic facet joint capsules are blocked, because the facet joints are the most proximal structures innervated by MBDRs on their emerging course from the dorsal ramus. Pathology of the capsular ligaments and periarticular tendons is an integral part of the facet joint syndrome.

Laterally positioned structures are innervated by the lateral branches of the dorsal rami. If laterally arising pain persists enthesis at posterior tubercles of the cervical transverse processes and in the thoracic area capsules of costotransverse articulations are injected. If the pain persists the iliocostalis cervices and thoracis tendons, at their respective fibroosseous rib insertions, are blocked.

Regarding z-joints, the intention is to inject the joint capsule posteriorly, initially with lidocaine utilizing the posterior approach, and thereafter with a mixture of bupivacaine and proliferating solution. Patients usually experience slight unsteadiness after injection of C2/3, C3/4 z-joint capsules indicating disturbance of postural tonic reflexes and indirectly successful blocks of the medial branches.

SOLUTIONS UTILIZED

The most common solution is 12.5% dextrose. Dilution is made with local anesthetic in 1:3 proportion, i.e. 1 ml of 50% dextrose mixed with 3 ml of 1% lidocaine. (5,27,110)

For intraarticular injection of the knee Hemwall recommended 25% dextrose solution. (5) Currently Reeves pointed out that 10% dextrose solution may be equally effective. (107) If this proves ineffective, gradual progression to sodium morrhuate full strength has been described. (5,10)

5% sodium morrhuate is a mixture of sodium salts of saturated and unsaturated fatty acids of cod liver oil and 2% benzyl alcohol, which acts as a local anesthetic and a preservative. Note that benzyl alcohol chemically is very similar to phenol.

Dextrose phenol glycerine solution: Originally produced in England by Boots company LTD of Nottingham for treatment of varicose veins, was introduced to pain management by Ongley. (93) The solution consists of 25% dextrose, 2.5% phenol and 25% glycerine and is referred to as DPG aka P2G. Prior to injection it is diluted in concentration s of 1:2; 1:1 or 2:3 with a local anesthetic of the practitioners choice. Some authors exclusively use this solution in 1:1 dilution. (10) Others

modified it, reducing the percentage of glycerine to 12.5%

The 6% phenol in glycerine solution was utilized by Poritt in 1931 [38] and reintroduced in the late 1950s by Maher of England for intrathecal injections in the treatment of spasticity. [166] Subsequently Wilkinson, a neurosurgeon, trained at Massachusetts General Hospital, after gaining sufficient experience with intrathecal use of this solution began injecting it at the donor harvest sites of the iliac crests for neurolytic and proliferative responses. [34]

CONCLUSION

1) RIT/Prolotherapy is a valuable method of treatment for correctly diagnosed chronic, painful conditions of the locomotive systems. [4-6,10,18-22,25-28,34,40-78,83-107]

2) Thorough familiarity of the physician with normal, pathologic, cross-sectional and clinical anatomy, as well as anatomical variations and function is necessary.[1-10,14,18-22,25-30,34,40-78,82-107]

3) Current literature supports manipulation under local joint anesthesia, [165] and a series of local anesthetic blocks for diagnosis of somatic pain.[8,32,166]

4) Use of RIT in an ambulatory setting is an acceptable

standard of care in the community.[1-10,14,18-22,25-30,34,40-78,82-107]

5) The current literature suggests that NSAIDs and steroid preparations have limited utility in chronic painful overuse conditions, and degenerative painful conditions of ligaments and tendons. Microinterventional regenerative techniques and proper rehabilitation up to 6 months or a year supported with mild opiod analgesics are more appropriate.[26,27,99,109-113]

The future is such that instead of indirect stimulation of growth factors through inflammatory cascade specific growth factors will be available. The challenge will remain of what specific growth factors to utilize. Most probably a combination of several growth factors will be utilized together with specific genes responsible for production of these growth factors. It appears that the delivery mode will be injections for deep structures, however, superficial structures probably will be addressed through transdermal delivery systems. [27,110,137-144]

A physician, versatile in manipulation as well as diagnostic and therapeutic injection techniques described above, may have an ample opportunity for RIT use in the practice of

pain management. Readers interested in incorporating RIT/prolotherapy in their pain management practice are referred to the following textbooks containing the bulk of information about this subject, that had been published in 1990s and remain a reliable source of basic principles and information. The "Illustrated manual of Orthopedic Medicine" by Cyriax, is available from Butterworth & Heineman. (19) "The Injection Techniques in Orthopedic Medicine" (10) and "Prolotherapy in the Lumbar Spine & Pelvis" (169) is available from T. Dorman MD at 2505 South 320th St, #100, Federal Way, WA, 98003. Hackett's (5) text is available from the Institute in Basic Life Principles (IBLP), Box 1, Oak Brook, IL 60522-3001. Lennard's text, Pain Procedures in Clinical Practice, is available from Hanley & Belfus. (110) "A system of Orthopaedic Medicine" (21) by Ombergt, is available from W.B. Saunders. "Movement, Stability & Low Back Pain" (170) by Vlemming and Dorman is available from Churchhill Livingstone. "The failed back syndrome etiology and therapy", by Wilkinson is available from Springer-Verlag. (34)

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