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# Pain Management with Regenerative Injection Therapy

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## INTRODUCTION

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

Connective tissues are ubiquitous throughout the body. Structurally and biomechanically, they represent a heterogeneous group with variations in collagen orientation cross-linking, shape, cell properties, and presence of synovial lining. They constitute the essence of the musculoskeletal system.

A large variety of functions depend on the proper homeostasis of connective tissue. For example, without the storage and release of energy in connective tissue during locomotion, much higher energy expenditure would be required (Bannister et al., 1995; Dorman, 1992). Conversely, 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, or a bone fracture, or a disrupted disc.

Pain arising from connective tissue pathology, such as posttraumatic changes in the intervertebral disc, ligaments, tendons, aponeuroses, fasciae, sacroiliac, and zygapophyseal joint capsular ligaments, is often difficult to differentiate based solely on clinical presentation. Individual variations in innervation further complicate the differential diagnosis. Left untreated, post-traumatic and overuse injuries of ligaments and tendons can linger indefinitely, leading to the progression of degenerative changes, loss of function, deconditioning, and perpetuation of disability and chronic pain (Bogduk et al., 1996a, b; Dreyfuss, 1997; Hackett, 1958, 1991; Merskey & Bogduk, 1994; Shuman, 1958; Steindler et al., 1938).

Interventional regenerative modalities for painful musculoskeletal pathologies have been described for more than two millennia. For example, the technique of collagen thermomodulation, now known as thermocapsulorraphy, was originally described by Hippocrates, who performed thermocoagulation of the anteroinferior capsule for treatment of recurrent shoulder dislocations "with red hot slender irons" (Dorman et al., 1991; Shuman, 1958). 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 led to the development of intradiscal electrothermal (IDET) procedures, currently used with the intent to achieve nuclear shrinkage, seal annular fissures, and thermocoagulate nociceptors (Derby et al., 1998; Saal et al., 1998a, b).

The 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 used for regeneration and rejuvenation by chemo- and thermomodulation of the skin collagen.

Regenerative injection therapy (RIT), also known as prolotherapy or sclerotherapy, is one of the long-practiced methods of pain management. It was originally described by Celsus for treatment of hydroceles, with injections of saltpeter (Hoch, 1939; Linetsky, 1999a). From inception to date, the general principles of injection techniques and differential diagnosis employed in RIT are those advocated by American Academy of Pain Management, American Society of Interventional Pain Physicians, International Spinal Injection Society, and the International Association for the Study of Pain (Aprill et al., 1990; Bogduk, 1982, 1986, 1988, 1996, 1997; Bogduk et al., 1996b; Bonica, 1990; Derby, 2002; Manchikanti, 2002; Merskey & Bogduk, 1994; Steindler, 1938). The difference is that painful chronic tissue bed pathology is the primary target for differential diagnosis and therapeutic application of RIT. Response to the blocks and nerve supply to the tissue are continuously taken into account during procedure. Differential diagnosis encompasses a wide variety of painful tissue including large synovial joints with their components and extends beyond the spinal segmental innervation (Cyriax, 1969, 1982; Dorman et al., 1991; Dorman, 1993; Hackett et al., 1991; Linetsky et al., 2002a, b, c; Ombregt et al., 1995; Waldman, 1998).

Application of RIT for low back pain has been described in numerous textbooks and articles; comparable, adequate applications for cervical and thoracic pain are lacking. We choose to emphasize cervicothoracic pain problems treated with RIT in this chapter (Cyriax, 1969, 1982; Dorman et al., 1991, 1993; Hackett, 1991; Ombregt et al., 1995).

## ETYMOLOGY OF SOME TERMINOLOGY

Biegeleisen (1984) first used the term "sclerotherapy" in 1936. *Sclero* is derived from the word *skleros* (Greek, hard). Hackett (1958) 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" (derived from the word *proli,* Latin, offspring). "Proliferate": to produce new cells in rapid succession. Proliferation, however, is an integral attribute of a malignant, unsuppressed growth. Moreover, with advances in basic science and the contemporary understanding of the healing process, contemporary exponents prefer RIT because it is recognized 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 (Klein et al., 1989; Liu et al., 1983; Maynard et al., 1985; Ongley et al., 1987). These capabilities make RIT a specific treatment for chronic, degenerative, painful conditions such as enthesopathy, tendinosis, and ligament laxity, in place of commonly used steroid injections and denervation procedures (Klein and Eek, 1997; Reeves, 1995).

## LOCAL ANESTHETICS IN DIAGNOSIS OF MUSCULOSKELETAL PATHOLOGY: BRIEF HISTORY

In 1930, Leriche introduced the application of procaine for differential diagnosis and treatment of ligament and tendon injuries of the ankle and other joints at their fibro-osseous insertions. In 1934, Soto-Hall and 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 the posterior sacroiliac ligaments, interspinous ligaments at L4–5 and L5–S1 levels, and zygapophyseal joint capsules with procaine, they observed a marked relaxation of spastic musculature. They added the routine use of sacroiliac joint manipulations, establishing manipulation of axial joints under local anesthesia (Haldeman et al., 1938).

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. The 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 proposed and postulated that five criteria must be met to prove that a causal relationship exists between the structure and pain symptoms (Table 62.1).

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

**TABLE 62.1**
**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.

*Note:* From "Differential Diagnosis of Pain Low in the Back: Allocation of the Source of Pain by the Procaine Hydrochloride Method," by A. Steindler et al., 1938, *Journal of the American Medical Association, 110*, 106–113. Reproduced with permission.

Local anesthetic diagnostic blocks are currently the most reliable and objective confirmation of the precise tissue source of pain and clinical diagnosis (Bonica, 1990; Cousins et al., 1988; Merskey & Bogduk, 1994; Wilkinson, 1992).

## HISTORY AND EVOLUTION OF RIT

The rationale for implementing RIT in chronic painful pathology of ligaments and tendons evolved from clinical and histologic research performed for injection treatment of hernias, hydroceles, 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 led to fibrotic closure of the defect (Riddle, 1940; Warren, 1881; Watson, 1938). In hydroceles, hypertrophied subserous connective tissue reinforced the capillary walls of serous membrane and prevented further exudate formation (Hoch, 1939; Linetsky, 1999c). 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 (Poritt, 1931).

In 1935, Schultz, while searching for a better way to treat painful subluxations of temporomandibular joints (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. (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 biweekly injections of 0.25 to 0.5 ml Sylnasol demonstrated "entire patient satisfaction." Schultz (1937) 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. Twenty years later, Schultz presented the positive results of Sylnasol injections on several hundred patients, successfully cured of painful hypermobility of TMJ (Schultz, 1956). 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. He extended this treatment 6 months later to recurrent shoulder dislocations, acromioclavicular separations, and sternoclavicular subluxations (Gedney, 1937, 1938).

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 (Kellgren, 1939).

In 1940, Riddle included a chapter on "The Injection Treatment of Joints" in his text and described the injection treatment of TMJs and shoulders in great detail, giving Schultz the appropriate credit for initiation of this treatment. Shuman described injection treatment of recurrent shoulder dislocations via strengthening of the inferior capsular ligaments with Sylnasol in 1941. Subsequently, in 1949, he adopted the term "sclerotherapy" for this injection modality, modifying it later that year to "joint sclerotherapy" (Shuman, 1949a, 1949b).

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 coexistence of painful hypermobile ribs with hypermobile sacroiliac joints, explaining the phenomenon by concomitant functional scoliosis.

By 1944, Lindblom demonstrated radial annular fissures during cadaveric disc injections and later described nucleographic patterns of 15 discs in 13 patients. Thereafter, in 1948, Hirsch relieved sciatic pain with intradiscal injection of procaine. 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 had 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. He reported L4 disc involvement in 95% of cases and a 50% clinical improvement after treatment of this disc alone (Gedney, 1952b). In the 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 (Gedney, 1952a). In a retrospective study, Gedney (1954b) emphasized the significant statistical coexistence of sacroiliac pathology with IVD pathology at L3, L4, and L5 levels. By 1954, he had completed a prospective study of 100 patients; 65 were initially treated with the injections into the disc, and 35 were initially treated with injections into the posterior sacroiliac ligaments. The latter group required fewer 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 (Gedney, 1954b). He emphasized the importance of interspinous and iliolumbar ligament injections in the treatment of lumbar spondylolisthesis (Gedney, 1954a).

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 in 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. Subsequently, he detailed many aspects of treatment with integration of manipulative techniques, including manipulation under local anesthesia as introduced 20 years earlier by Haldeman and 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 sacroiliac joint pathology (Shuman, 1958).

Hackett, the inventor of prolotherapy, postulated in 1939 that ligaments were responsible for the majority of back pain (Hackett, 1953). By 1958, he came to the conclusion that tendons at the fibro-osseous junctions were another significant source of chronic pain syndromes (Hackett, 1958). In a retrospective study, he reported on 84 patients with sacroiliac pain treated by sclerosant injections of Sylnasol, five to seven times to each affected area. In this study, 82% reported themselves entirely symptom free for a duration of 6 to 14 years (Hackett & Henderson, 1955). In the initial animal experiments, he demonstrated a 30 to 40% increase in tendon size after injections of Sylnasol (Hackett, 1956; Figure 62.1). Not satisfied with the term "sclerotherapy," because it implied hardening of the tissue and scar formation, Hackett 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 a linear fashion (Hackett, 1956). Hackett employed and emphasized the importance of the earlier referenced postulates of Steindler. He confirmed 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 (Hackett, 1956). He published maps of referred pain from ligaments and tendons, initially of the lumbopelvic region. These were derived from 7,000 injections in more than 1,000 patients treated over 17 years. He subsequently developed maps of the cervicothoracic region (Hackett, 1958; Figure 62.2). Later, he pointed out that loose-jointed individuals have a 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 (Hackett, 1959a).

In several 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 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 (Hackett 1959a, 1959b, 1960a, 1960b, 1961, 1966a, 1966b, 1966c, 1967; Hackett et al., 1961, 1962).

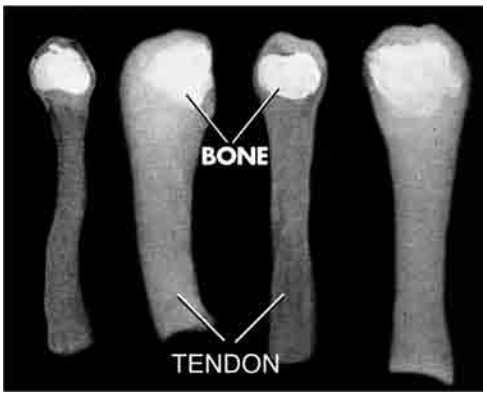


**FIGURE 62.1** Paired radiograph of hypertrophied rabbit tendons, fibro-osseous attachment 1 and 3 months after injection of proliferant. Treated tendons are on the right side of each pair, controls on the left. From *Ligament and Tendon Relaxation (Skeletal Disability) — Treated by Prolotherapy (Fibro-osseous Proliferation)* (3rd ed.), by G. Hackett, 1958, Springfield, IL: Charles C Thomas.

Extended subsequent animal experiments with multiple solutions conducted by Hackett revealed that the strongest fibro-osseous proliferations were achieved with Sylnasol, zinc sulfate solutions, and silica oxide suspensions. The strongest acute inflammatory reaction was obtained with Sylnasol and zinc sulfate, followed by silica oxide. Whole blood moderately stimulated fibro-osseous proliferation. Hydrocortisone used alone or in combination with proliferants inhibited proliferation for 3 to 4 weeks. At the fracture sites, proliferants increased callus formation in 3 weeks, whereas when used in combination with steroids, the callus formation was markedly inhibited (Hackett et al., 1961).

Hackett's positive results were initially corroborated by others (Compere et al., 1958; Green, 1956, 1958; Myers, 1961; Neff, 1959). In fact, Myers reported improvement in 82% of patients.

In 1961, Blaschke reported the first prospective study of 42 patients treated with prolotherapy for lower back pain. Of the patients 32 were workers' compensation cases, notoriously the most difficult cases to treat, and 10 were private insurance cases. Complete recovery was achieved in 20 patients observed for 3 years, 13 patients reported no change in their condition, and 9 underwent surgery. The 4 patients with clinical presentation of acute

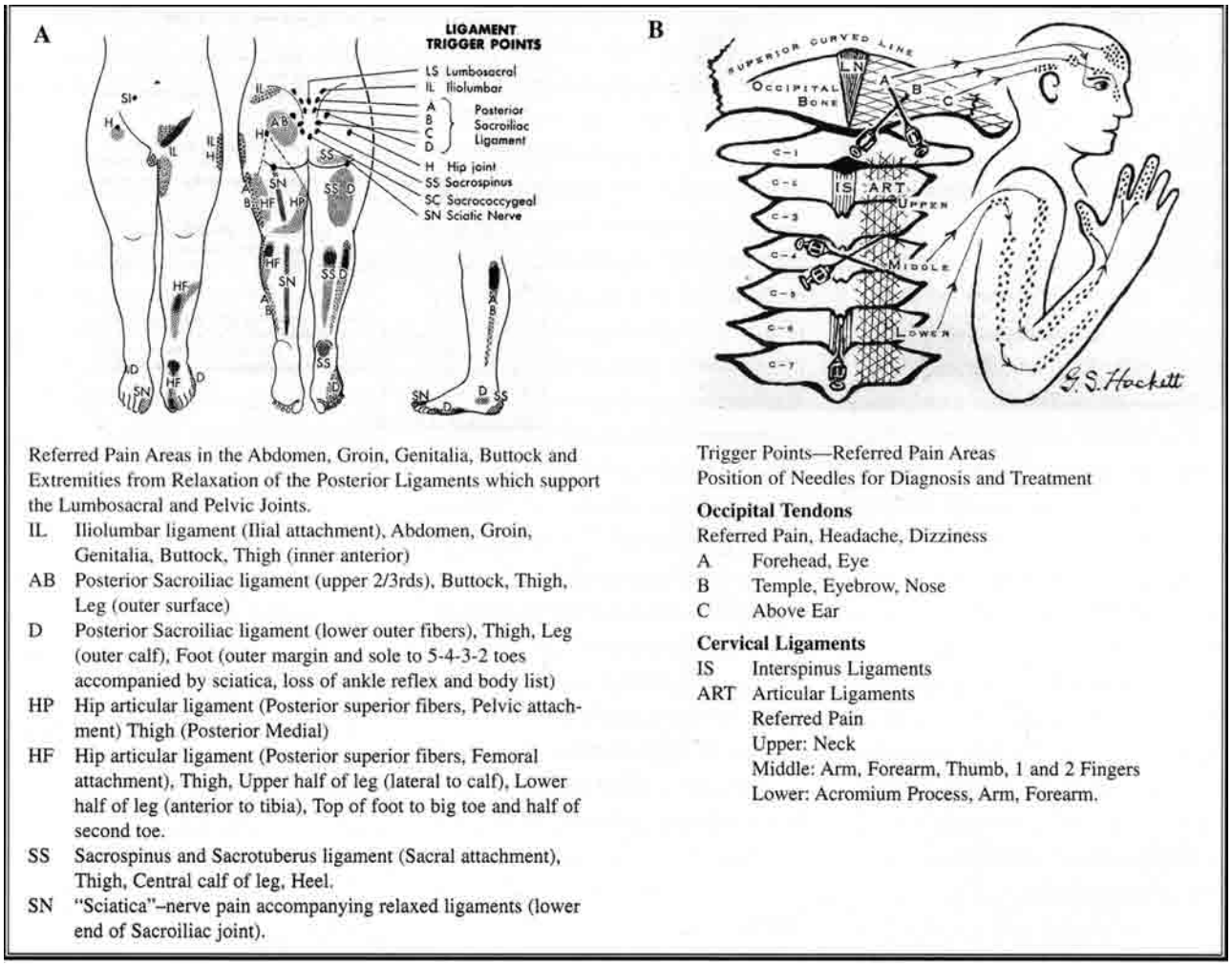


**FIGURE 62.2** Hackett's maps of referred pain from ligaments and tendons. (A) The initial maps of the lumbopelvic region derived from 7,000 injections in more than 1,000 patients treated over 17 years. (B) Subsequent maps were of the cervicothoracic region. From *Ligament and Tendon Relaxation (Skeletal Disability) — Treated by Prolotherapy (Fibro-osseous Proliferation)* (3rd ed.), by G. Hackett, 1958, Springfield, IL: Charles C Thomas. Reproduced with permission.

herniated disc, in whom prolotherapy was used 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."

A multicenter study conducted by Kayfetz et al. was published in 1963. Of 264 patients treated by prolotherapy for headaches, 78% had headaches of traumatic origin, 58% had nontraumatic headaches, and 56% had symptoms of Barre–Lieou syndrome. In addition, 86% had symptoms longer than 1 month and 46% had symptoms longer than 1 year. The traumatic group reported satisfactory results in 79%, with excellent results in 60%. The nontraumatic group reported satisfactory results in 47% and excellent results in 29%. Of 264 cases, 60% of patients were followed for over 1 year and 27% were followed for 3 to 5 years. There were no infections or other complications following prolotherapy.

Also in 1963, Kayfetz reported a 5-year follow-up study of 189 cases with whiplash injuries treated by prolotherapy. Of these, 149 cases (79%) were due to automobile accidents, 153 (81%) had associated injuries to the thoracic and lumbar areas, 98 (52%) had an associated Barre–Lieou syndrome, and 55% had symptoms longer than 1 month duration and 21% longer than 1-year duration. A 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 results by 15 (8%), and fair results by 34 (18%). Some 75% of patients considered themselves cured of pain.

In response to adverse effects published after alleged incidental intrathecal injections of zinc sulfate, experiments were conducted with intrathecal injections of this solution in rabbits (Hunt, 1961; Keplinger et al., 1960; Schneider, 1959). Clinical doses (4 to 5 drops) did not

produce any noticeable effect. Those animals receiving 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" (Hackett et al., 1961).

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 a 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 the majority of the physicians in the community. A physician is permitted to follow a method or a form of treatment followed by a minority of physicians if they are reputable and in good standing. But if physicians vary from the minority method of treatment they do so in violation, just as if they deviated from the generally accepted method of treatment.

The court concluded: "as a matter of law that prolotherapy as a method of treatment cannot 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" (Coleman, 1968, p. 348).

Abroad, positive results with Hackett's method were obtained by Ongley, Cyriax (1969, 1982), Barbor (1964), and Coplans (1972). Barbor presented a study of 153 patients with back pain for up to 20 years duration. Of 153, 111 (74%) of them reported relief to their satisfaction, 17 (11%) failed to improve; 25 (16%) were lost for follow-up, and 31 (23%) required periodic booster injection for relief. The solution utilized was dextrose, phenol, and glycerin (DPG) mixed in proportions of 2 cc DPG to 3 cc local anesthetic.

Cyriax (1969, 1982, 1993) included detailed descriptions of "sclerosant injections" to interspinous and facet joint capsular ligaments of the cervical, thoracic, and lumbar regions in his texts. 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 three solutions were compared: (1) 2 ml DPG sclerosant mixed with 8 ml saline; (2) 10 ml of 0.5% procaine; and (3) 10 ml 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.

In 1974, Blumenthal reported two 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.

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

Also in 1976, Vanderschot compared prolotherapy with acupuncture in the treatment of chronic musculoskeletal pain and concluded that prolotherapy has a faster onset of action and longer-lasting pain relief (Vanderschot, 1976a, 1976b).

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

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 6 months, a small zone of residual inflammatory cells was documented in an area of 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 a 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 (Koudele, 1978).

In 1982, Hirschberg et al. reported a prospective study of 16 patients with the iliolumbar syndrome. Of the patients, 9 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 5 cc). Significant recovery was reported by 10 patients. Of the 7 treated with dextrose/xylocaine, 6 recovered, whereas only 4 of the 9 treated with xylocaine recovered.

Liu et al., in a 1983 double-blind study, injected rabbit medial collateral ligaments (MCLs) and demonstrated that repeated injections of 5% sodium morrhuate at the fibro-osseous 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 fibrils in the experimental ligaments vs. controls. These findings confirmed that sodium morrhuate had a significant regenerative influence on dense connective tissue at the insertion sites.

Maynard and co-workers (1985) reported a decrease in collagen fibrils and hydroxyproline content and an overall increase in the mass of tendons in experimental animals injected with sodium morrhuate. The average tendon circumference increased up to 25%.

Ongley et al. (1987) in a double-blind, randomized study of chronic low back pain in 81 subjects, statistically

demonstrated a significant improvement greater than 50% in patients injected with a DPG solution vs. saline. In terms of disability scores, the experimental groups demonstrated a greater improvement than the control group ($p < 0.001$, $p < 0.004$, and $p < 0.001$, respectively; Ongley et al., 1987). Subsequently, Ongley demonstrated a significant statistical improvement in five patients treated for painful instability of the knees with prolotherapy. Ligament stability data was obtained via three-dimensional computerized goniometry, integrated with force measurements (Ongley et al., 1988).

Bourdeau (1988) published a 5-year retrospective survey of patients with low back pain treated with prolotherapy; 17 patients (70%) reported excellent to very good results.

Klein et al. (1989) 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, as documented by computerized inclinometry.

Roosth (1991) described gluteal tendinosis as a distinct clinical entity, and Klein (1991) described the treatment of gluteus medius tendinosis with proliferant injections.

Also in 1991, Schwartz et al. reported a retrospective study of 43 patients with chronic sacroiliac strain who received three series of proliferant injections at biweekly intervals. Improvement was reported by all but 3 patients, and ranged from 95% reported by 20 patients to 66% reported by 4 patients; 10 patients reported recurrence. Schwartz concluded that induced proliferation of collagen and dense connective tissue of the ligament is associated with a reduction of painful subluxations.

Hirschberg et al. (1992) reported positive results in treating iliocostal friction syndrome in elderly individuals with proliferant injections and a soft brace.

Klein et al. (1993) reported a double-blind clinical trial of 79 patients with chronic low back pain who had failed to respond to previous conservative therapy. Subjects were randomly assigned to receive a 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 L–4 to the sacrum. All patients underwent pretreatment magnetic resonance imaging (MRI) or computed tomography (CT) scans. Patients were evaluated with visual analogue, disability, and pain grid scores, and with objective computerized triaxial tests of lumbar function 6 months following the conclusion of injections. Of the 39 patients randomly assigned to the proliferant group, 30 achieved a 50% or greater decrease in pain or disability scores at 6 months compared with 21 of 40 in the group that received lidocaine/saline ($p = 0.042$). Improvements in visual analogue ($p = 0.056$), disability ($p = 0.068$), and pain grid scores ($p = 0.025$) were greater in the proliferant group.

Massie et al. (1993) reported that it was possible to stimulate fibroplasia in the intervertebral discs with proliferant injections. Also in 1993, Mooney advocated proliferant injections for chronic painful recurrent sacroiliac sprains if the clinician was skilled (Mooney, 1993a, 1993b).

Grayson (1994) reported a case of sterile meningitis after injection of lumbosacral ligaments with proliferating solutions. Matthews (1995) found significant improvement in painful osteoarthritic knees after injection of the ipsilateral sacroiliac ligaments with proliferant solutions. Also in 1995, Reeves pointed out those degenerative changes of enthesopathy may be painful, and prolotherapy with a less aggressive solution such as 12% dextrose with xylocaine is the only type of specific treatment for these pathologic changes of ligaments and tendons.

Eek (1996) reported on the benefit of proliferating injections for intradiscal pain. Klein and Eek have described proliferant injections for low back pain in detail (Klein, 1997).

The clinical anatomy in relation to RIT/prolotherapy for low back pain was reviewed recently. The presence of the connective tissue stocking surrounding various lumbar structures, dictating their function as a single unit in a normal state and the necessity to include multiple segmental and extrasegmental structures in differential diagnosis of low back pain, was emphasized (Linetsky & Willard, 1999; Linetsky et al., 2000).

Subsequently, in March of 2000, Reeves demonstrated in a randomized, double-blind, placebo-controlled study the 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 (six injections), the dextrose-treated knees improved in pain (44% decrease), swelling complaints (63% decrease), knee buckling frequency (85% decrease), and flexion range (14° increase). He concluded that proliferant injection with 10% dextrose stimulated growth factors and regeneration and resulted in statistically significant clinical improvements in knee osteoarthritis (Reeves et al., 2000). The history of RIT/prolotherapy from the 1930s through the 1980s was recently reviewed (Linetsky et al., 2000, 2001).

Two recent pilot studies demonstrated significant pain reduction and return to previous levels of activity in patients treated with intradiscal injections of 25% dextrose and combined dextrose-based solutions (Klein et al., 2003; Matthews et al., 2001). Comparison of intradiscal RIT and intradiscal electrothermal therapy (IDET) demonstrated a statistically significant and better results from intradiscal RIT, 47.8% of IDET patients reported improvement while 65.6% of RIT patients reported the same results. Worsening of the conditions was reported by 35.8% of IDET patients and by none of the RIT patients (Derby et al., 2004).

A retrospective study demonstrated a statistically significant improvement in patients treated with phenol-based solution (Wilkinson et al., 2002). An Australian pilot study demonstrated visual analog scale (VAS) scores of back pain improved 60% and VAS scores for leg pain improved 76% after injection of 20% dextrose/xylocaine solution (Yelland et al., 2000). The randomized study by the same senior author comparing 20% dextrose/xylocaine solution and normal saline demonstrated a sustained, statistically significant improvement in a group of patients with chronic low back pain of up to 14 years duration and post-procedural follow-up for 2 years. The role of volume and concentration in the injectate has been brought to light by this study and appears to be much more complex than previously thought; normal saline injected at 3-cc increments (which had never been done by previous investigators) demonstrated significantly positive results (Yelland et al., 2003). Further studies in this direction may provide a better grasp on the indirectly induced stimulation of growth factors in regenerative reparative cascade. Yelland's study also suggests that the volume of injectate may change the concentration of prevailing catabolic interleukin (IL-1) to anabolic interleukin (IL-8). The latter changes have been demonstrated in the injured porcine discs after percutaneous plasma decompression (O'Neill, 2003). A small group of patients improved after intra-articular injection of 25% dextrose or 2.5% phenol into the cervical synovial joints (Linetsky et al., 2004).

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

## INFLAMMATORY-REGENERATIVE/ REPARATIVE RESPONSE AND 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, which replaces injured cells with the same type of cells; and the second is fibrosis, or the replacement of injured cells with 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 last, together with the basement membrane, provides a scaffold for regeneration of preexisting structures (Cotran et al., 1999). Leadbetter (1992) stated, "modulation of these cell matrix responses regardless of the method provides an intriguing challenge" (p. 572). Cell replication is controlled by chemical and growth factors. Chemical factors may inhibit or stimulate proliferation, whereas growth factors such as cytokines/chemokines, TGF-b1 (transforming growth factor-b1), 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. The 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 (Cotran et al., 1999; Reeves, 2000).

Under the best circumstances, natural healing restores connective tissue to its preinjury length but only 50 to 75% of its preinjury tensile strength (Leadbetter, 1992; Reeves, 1995). Connective tissues are bradytrophic (their reparative capability is slower than that of muscle or bone). In the presence of repetitive microtrauma, injudicious use of nonsteroidal anti-inflammatory drugs (NSAIDs) and steroid medications, tissue hypoxia, metabolic abnormalities, and other less-defined causes, connective tissue may divert toward a degenerative pathway (Leadbetter, 1992, 1994, 1995; Reeves, 1995, 2000). "A judicious utilization of anti-inflammatory therapy remains useful, albeit adjunctive therapy" (Leadbetter, 1995, p. 402). Biopsies of these tissues demonstrate disorganized collagen, excessive matrix, insufficient elastin, disorganized mesenchymal cells, vascular buds with incomplete lumen, few or absent white blood cells, neovasculogenesis, and neoneurogenesis (Jozsa & Kannus, 1997; Leadbetter, 1994). Degenerative changes in tendons may be hypoxic, mucoid, mixoid, hyaline, calcific, fibrinoid, fatty, fibrocartilaginous and osseous metaplasia, and any combination of the above (Jozsa & Kannus, 1997).

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 (Tuzlukov et al., 1993).

Neoneurogenesis and neovascularization always accompanies the proliferative phase of the healing process and regresses during the contraction phase. Neovascularization has been demonstrated by ultrasound in the injured Achilles tendons (Zanetti et al., 2003). The presence of hyaline cartilage in extruded disc material can suppress neovascularization and subsequent size reduction of herniated mass leading to persistent radiculopathy. Modic types of MRI bone marrow changes are highly suggestive of hyaline cartilage defects at the end plates (Schmid et al., 2004). There is a high correlation between gene defects of COL9A3 and intervertebral disc degeneration, Scheuermann disease, Schmorl's nodules, dorsal annular tears,

end plate degeneration, and hyperintense lesions on sagittal T2-weighted lumbar MRIs (Karppinen et al., 2003).

Repeated eccentric contractions diminish muscle function and increase intramuscular pressure. For example, the intramuscular pressure in the supraspinatus and infraspinatus is four to five times higher than that in the deltoid or trapezius at the same relative load (Ranney, 1997). Edema arising in one muscle compartment secondary to overuse does not spread to 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 (Jozsa & Kannus, 1997; Leadbetter, 1994; Ranney, 1997).

Further repeated eccentric contractions are notorious for microtraumas with microruptures at the fibro-osseous junctions, in the mid substance of the ligaments and tendons, or at the myotendinous interface. Repetitive microtrauma with insufficient time for recovery leads to an inadequate regenerative process that turns to a degenerative pathway in tendons, muscles, discs, joint ligaments, and cartilage. 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 (Jozsa, 1997; Leadbetter, 1992, 1994, 1995; Ranney, 1997; Reeves, 2000).

Impaired circulation at the fibromuscular and fibro-osseous interface eventually leads to impaired intraosseous circulation with diminished venous outflow and increased 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, affects calcium metabolism, and contributes to the progression of osteoarthritis (Bannister, 1995; Hackett, 1959b, 1960a, 1960b, 1961, 1966a, 1966c, 1966d, 1967; Hackett et al., 1961, 1962; Shevelev et al., 2000; Sokov et al., 2000; Zoppi et al., 2000).

There is a high coincidence of degenerative changes in syndesmotic, symphyseal (IVD), and uncovertebral joints of the anterior column with degenerative painful changes in synovial and syndesmotic joints of the posterior column. Communications have been reported between the IVD and costovertebral joints (CVJ) through uncovertebral joints. An S-shaped deformity of zygapophyseal joints invariably accompanies disc degeneration with disc height narrowing throughout cervical, thoracic, and lumbar regions (Giles & Singer, 2000, 2001). Degenerative changes in IVD coincide with degenerative changes in tendinous tissue of the posterior spinal syndesmotic joints, i.e., supraspinous, interspinous, and ligamentum flavum representing themselves with disorganization and quantitative decrease of proteoglycan (PG) bonds, chondrifications, and calcifications. Further degenerated spinal ligaments may be a precursor of IVD protrusions (Yahia et al., 1990).

Neoneurogenesis and neovasculogenesis 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 (Ashton et al., 1992; El-Bohy et al., 1988; Freemont et al., 1997; Tuzlukov et al., 1993).

Substance P has been recently identified in chronically painful posterior sacroiliac ligaments, joint capsule, and periarticular adipose tissue. There is a strong possibility that it may be present at chronically painful enthesopathy sites throughout the body (Fortin, Vilensky, & Merkel, 2003).

Insertion pathology of the trunk muscles (enthesopathy) at the fibro-osseous junctions most commonly affects the following sites: occiput, scapulas, spinous processes, especially at the cervicodorsal and thoracolumbar regions; sternum, ribs, posterior lateral and anterior surfaces; iliac crest; and symphysis pubis (Figure 62.3 through Figure 62.9). Histopathologically, the following findings were observed: calcium deposits and mineralization of the fibrocartilaginous zone (Jozsa & Kannus, 1997). 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 gender groups 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 (Jozsa & Kannus, 1997).

There is a high coincidence of degenerative change in syndesmotic and symphyseal joints of the anterior column and uncovertebral arthroses with degenerative painful changes in synovial and syndesmotic joints of the posterior column. Communications have been reported between the IVD and CVJ through uncovertebral joints. An S-shaped deformity of zygapophyseal joints invariably accompanies disc degeneration with disc height narrowing throughout cervical, thoracic, and lumbar regions (Giles & Singer, 2000, 2001). This makes intra-articular needle placement from the posteroinferior pole difficult even with fluoroscopic guidance. Degenerative changes in IVD correspond with degenerative changes in the posterior spinal syndesmotic joints, i.e., supraspinous, interspinous, and ligamentum flavum, where they are represented by disor-

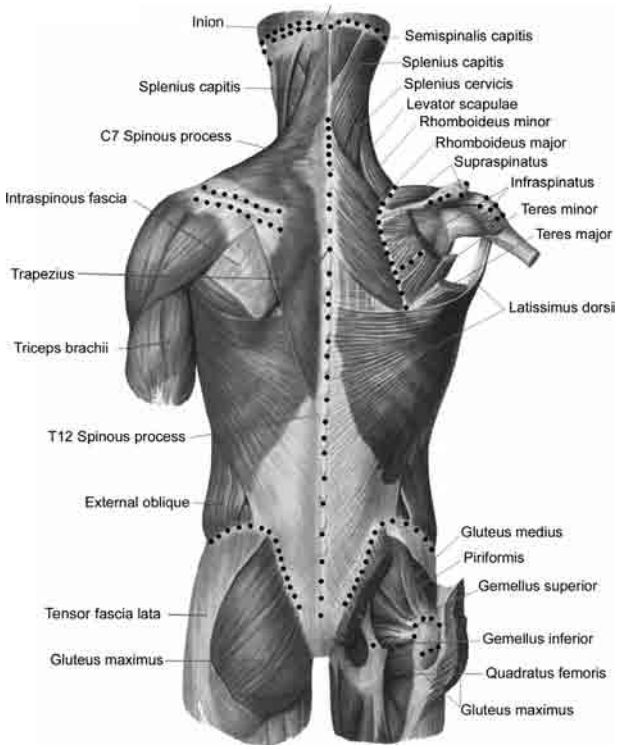


**FIGURE 62.3** Dots represent some of the common enthesopathy areas at the fibro-osseous insertions (enthesis), at the occiput, scapulas, humerus, trochanter, iliac crests, and spinous processes. Dots also represent the most common needle locations during RIT infiltrations. (*Note:* Selected locations are treated at each visit.) From *Atlas of Anatomy* (Vol. 1), by R. D. Sinelnikov, 1972, Moscow: Meditsina. Modified for publication by David M. Paul.

ganization and quantitative decrease of proteoglycan bonds and chondrification (Yahia et al., 1990).

The ability of RIT to regenerate and repair connective tissue has been documented by multiple experimental and clinical studies (Klein et al., 1989; Koudele, 1978; McPheeters et al., 1949; Rice, 1936; Riddle, 1940; Warren, 1881; Yeomans et al; 1939).

## SOME ANATOMICAL AND BIOMECHANICAL PROPERTIES OF LIGAMENTS AND TENDONS

Ligaments are dull white, dense connective tissue structures that connect adjacent bones. They may be intra-articular, extra-articular, 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 fibro-osseous attachments from cylindrical, fan shaped to wide, flat, and ribbon shaped.

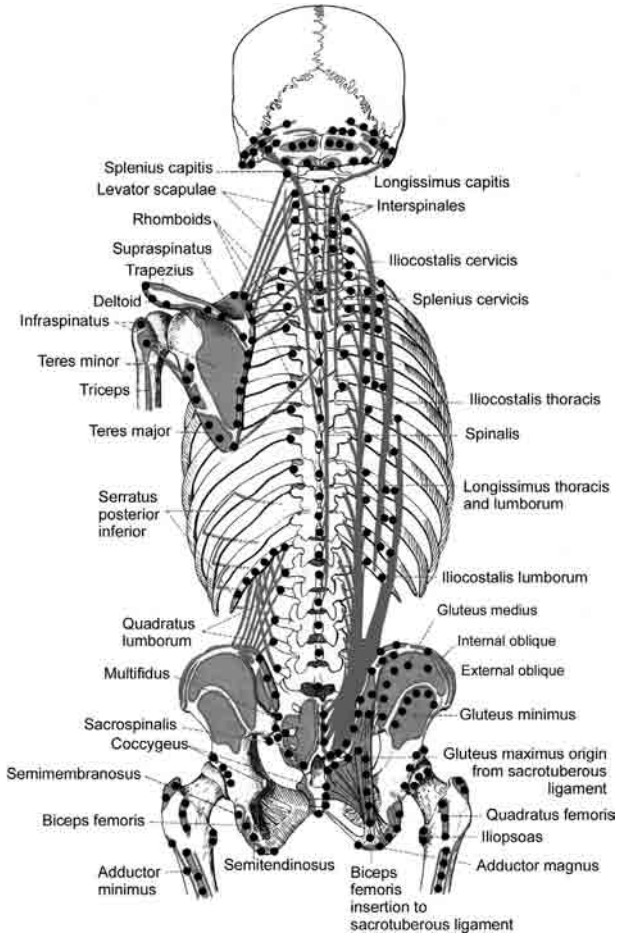


**FIGURE 62.4** Schematic drawing demonstrates sites of tendon origins and insertions (enthesis) of the vertebral, paravertebral, and peripheral musculature in the cervical, thoracic, and lumbar regions and part of the upper and lower extremities. Clinically significant painful enthesopathies are common at these locations defined by dots. Dots also represent most common locations of needle insertions and infiltration during RIT. (*Note:* Selected locations are treated at each visit.) From *Atlas of Anatomy* (Vol. 1), by R. D. Sinelnikov, 1972, Moscow: Meditsina. Modified for publication by David M. Paul.

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, 70% dry weight (Bannister, 1995; Butler et al., 1978).

Under a light microscope, ligaments and tendons have a crimped, waveform appearance. This crimp is a planar zigzag pattern that unfolds during initial loading of collagen (Bannister, 1995; Butler et al., 1978). Elongated below 4% of original length, ligaments and tendons return to their original crimped wave appearance; beyond 4% elongation, they lose the elasticity and become permanently laxed. However, in degenerative ligaments, subfailure was reported as early as 1.5% elongation. Laxity of ligaments obviously leads to joint hypermobility. Experi-

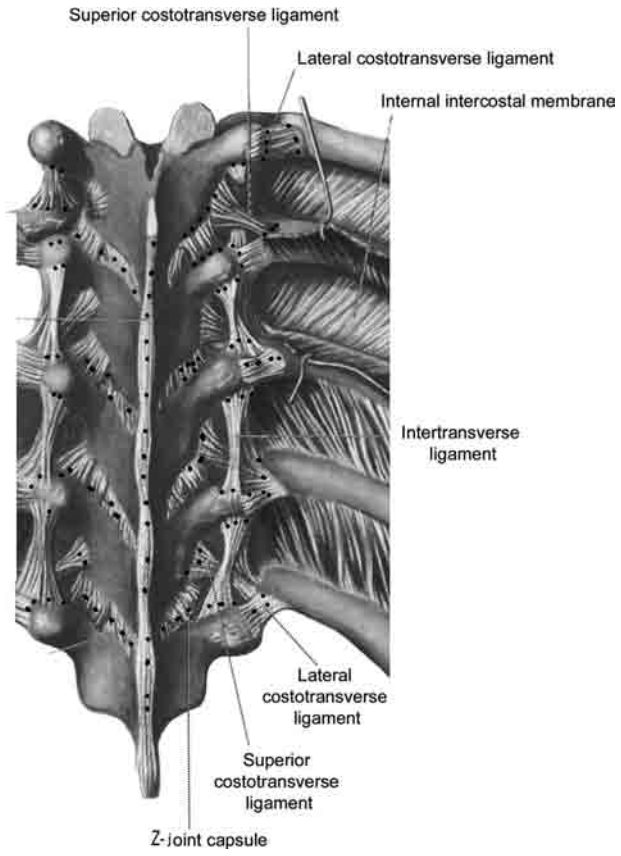


**FIGURE 62.5** Sites of common posterior thoracic vertebral and paravertebral arthropathies and enthesopathies. Dots also represent the most common needle locations during RIT infiltrations. (*Note:* Selected locations are treated at each visit.) From *Atlas of Anatomy* (Vol. 1), by R. D. Sinelnikov, 1972, Moscow: Meditsina. Modified for publication by David M. Paul.

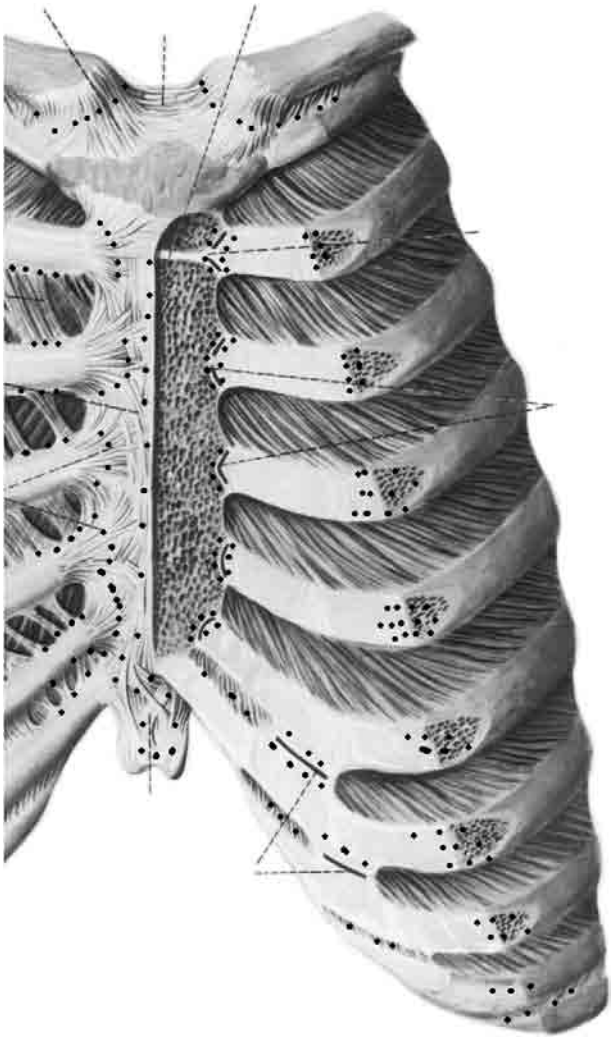

**FIGURE 62.6** Common sites of painful enthesopathies on the anterior thoracic wall, including sternoclavicular, costosternal, interchondral synovial articulations, various syndesmotic joints, and costochondral synchondroses. (*Note:* Selected locations are treated at each visit.) From *Atlas of Anatomy* (Vol. 1), by R. D. Sinelnikov, 1972, Moscow: Meditsina. Modified for publication by David M. Paul.

mental studies have confirmed that the MCL failed more abruptly than either the capsular ligaments or the anterior cruciate ligament (ACL). This happens because the MCL has more parallel fibers with uniformity in length, and therefore, they fail together. The capsular fibers are less organized than the MCL or ACL, and their lengths and orientations vary. Because these fibers are loaded and fail at different times a large joint displacement is needed before capsular failure is complete.

Three principal failure modes exist. The first and most common is ligament failure. The second is a bone avulsion fracture, and the third, the least common, is a shear or cleavage failure at the fibro-osseous 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. Intra-articular injections of methyl-prednisolone acetate given either once or at intervals of several months may be less detrimental to ligament or tendon mechanical properties" (Butler et al., 1978).

Tendons are strongly attached to the bones by decussating and perforating Sharpey's fibers. Current understanding of OTJ (osseo tendinous junction, also called enthesis, fibro-osseous 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 was emphasized by Hackett et al. (1991) and Jozsa and Kannus (1997). The tensile strength of tendons is similar to that of bone and is about half that of steel. A tendon

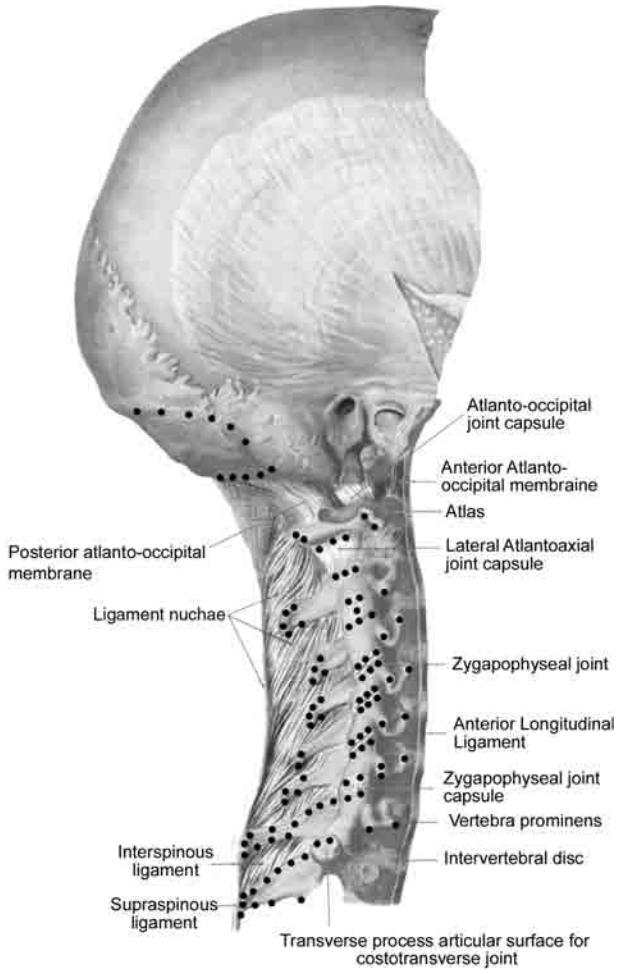


**FIGURE 62.7** Clinically significant painful enthesopathies and arthropathies are common at the locations defined by dots. Dots also represent most common needle locations during RIT infiltrations. (*Note:* Selected locations are treated at each visit.) From *Atlas of Anatomy* (Vol. 1), by R. D. Sinelnikov, 1972, Moscow: Meditsina. Modified for publication by David M. Paul.

with a cross section of 10 mm in diameter can support a load of 600 to 1,000 kg (Bannister, 1995; Butler et al., 1978; Jozsa & Kannus, 1997).

During postnatal development, tendons enlarge by interstitial growth, particularly at the myotendinous junction (also called the fibromuscular interface) where there is a high concentration of fibroblasts. The nerve supplies are largely sensory (Bannister, 1995; Best, 1994; Butler et al., 1978; Jozsa & Kannus, 1997).

## GROSS ANATOMY OF CRANIOVERTEBRAL, CERVICAL AND THORACIC REGIONS IN RELATION TO RIT

The shape of a human body and its components is irregularly tubular. This shape is maintained by continuous compartmentalized connective tissue stocking that incorporates, interconnects, and supports various ligaments, tendons, fascia, muscles, osseous and neurovascular structures. Collagenous connective tissues, despite slightly different biochemical content, blend at their boundaries and at the osseous structures, functioning as a single unit (Agur, 1991; Bannister, 1995; Linetsky et al., 1999, 2002a, 2002b, 2004; Sinelnikov, 1972; Willard, 2003). This arrangement provides bracing and a hydraulic amplification effect to the muscles, increasing contraction strength in the lumbar region up to 30% (Bogduk, 1997). If only the connective tissues were left in place and all other tissue removed, the shape of a human body would not change.

Movements of the spine and cranium are accomplished through various well-innervated joints, located in the anterior and posterior columns. These joints are syndesmotic, synovial, and symphyseal in nature. Syndesmotic joints of the anterior column are anterior and posterior longitudinal ligaments; anterior and posterior atlanto-occipital membranes; and transverse, apical, and alar ligaments. Symphyseal joints are IVDs and their extensions; unique to the cervical and upper thoracic spine are the so-called uncovertebral joints of Luschka, which are lateral and posteriolateral elevations of the uncinate processes. Synovial joints are atlanto-axial (AA), atlanto-occipital (AO), and CVJ. Syndesmotic joints of the posterior column are posterior atlanto-occipital membrane, supraspinous and interspinous ligaments, ligamentum flavum and nuchae. Synovial joints are costotransverse and zygapophyseal (ZJ). The following joints are indirectly related to the spine: costosternal, interchondral, and sternoclavicular (Agur et al., 1991; Bannister, 1995; Giles & Singer, 2000, 2001; Sinelnikov, 1972).

Segmental innervation of the aforementioned compartments and their contents is provided by the spinal nerves and their respective ventral and dorsal rami (VR, DR). The DRs further divide into medial and lateral branches (MBDR, LBDR) providing innervation to the posterior structures. Anteriorly, spinal segments are innervated by sympathetic fibers (SF); laterally, by gray rami communicantes (GRC); and posteriorly, by the sinuvertebral nerve of Luschka (SN). The extrasegmental communications are widely present on the anterior surface of the spine between the SF, laterally between GRCs and posteriorly between branches of SN (Agur et al., 1991; Bannister, 1995; Bogduk, 1986, 1996; Cramer & Darby 1995; Linetsky et al., 2002a, 2002b, 2004; Willard, 1995).

The first dorsal ramus, also called the sub-occipital nerve, supplies the muscles of the sub-occipital region, rectus capitis posterior minor and major, inferior and superior oblique, and semispinalis capitis. It has an ascending cutaneous branch that connects with the greater and lesser occipital nerves and may contribute to the occipital and sub-occipital headaches (Bannister, 1995; Bogduk, 1982, 1986, 1988). The second cervical dorsal ramus also sup-

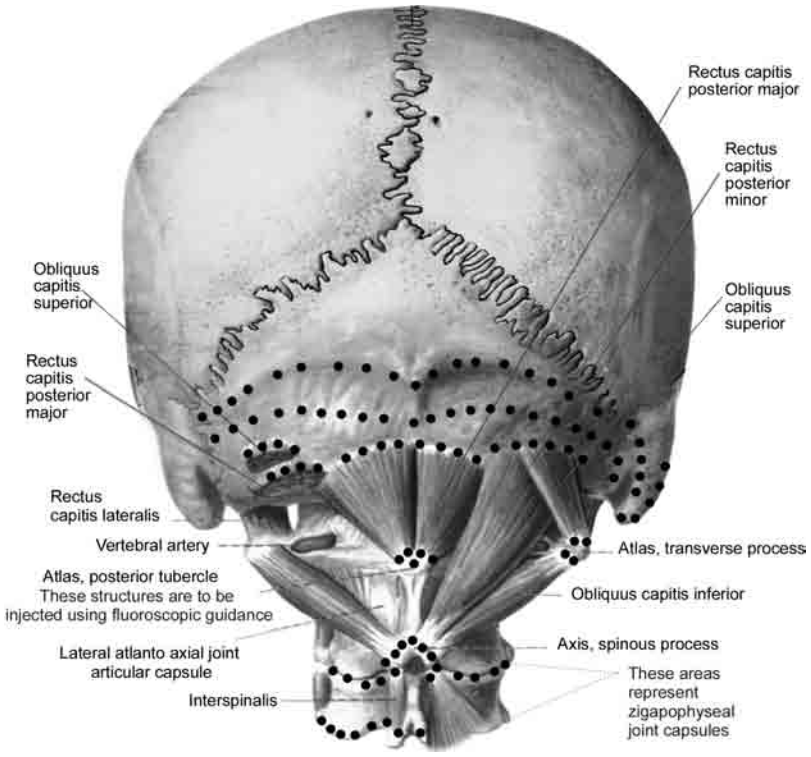


**FIGURE 62.8** Sites of tendon origins and insertions (enthesis) of the vertebral and paravertebral musculature in the upper cervical and occipital region. Clinically significant painful enthesopathies are common at locations defined by dots. Dots also represent most common locations of needle insertions and infiltration during RIT. (*Note:* Selected locations are treated at each visit.) From *Atlas of Anatomy* (Vol. 1), by R. D. Sinelnikov, 1972, Moscow: Meditsina. Modified for publication by David M. Paul.

plies the inferior oblique, connects with the first one, and divides into LMBDR. 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 (Bannister et al., 1995; Bogduk, 1982, 1986, 1988).

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 six 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 (Agur et al., 1991; Bannister et al., 1995; Bogduk, 1982).

Current trends in therapeutic and diagnostic blocks are based on the fact that the anatomy and course of the MBDRs is fairly constant, and that it arises from the intertransverse space and wraps around the waist of the respective articular pillars (Aprill et al., 1990; Bogduk, 1982, 1986, 1988). Recent clinical observations supported by ongoing research and microdissections of Willard (Figure 62.10) concur with the previous investigations (Bogduk, 1982). MBDR furnishes twigs to zygapophyseal joint capsules and continues along the lamina and spinous process toward its apex, innervating structures inserting or originating at the lamina and the spinous process on its course often terminating in interspinalis muscles (Bogduk, 1982, 1988, 1996; Bogduk et al., 1996; Willard, 2003, see Figure 62.10 and Figure 62.11). For example, the fourth and fifth cervical MBDRs supply the semispinalis cervices and capitis, multifidi, interspinalis, splenius and trapezius, and supraspinous ligaments, and end in the skin. The lowest three MBDRs have a similar course (Figure 62.10).

However, variations in innervation occur, their incidence is unknown. Floating dorsal rami have been described in the cervical and thoracic regions, sometimes descending from the level of C5–6, C6–7, or C7–T1 to the level of T3–4, T4–5, T5–6. The latter "so-called" causes of thoracic pain of cervicogenic origin, which may complicate the differential diagnosis, explain failures after MBDR blocks or radiofrequency procedures, and *make tissue nociceptors specific targets for RIT* (Linetsky et al., 2004; Maigne, 1996; Willard, 2003, Figure 62.11).

Three types of nerve endings in posterior ligamentous structures of the spine were confirmed microscopically. They are free nerve endings and Pacini and 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 are

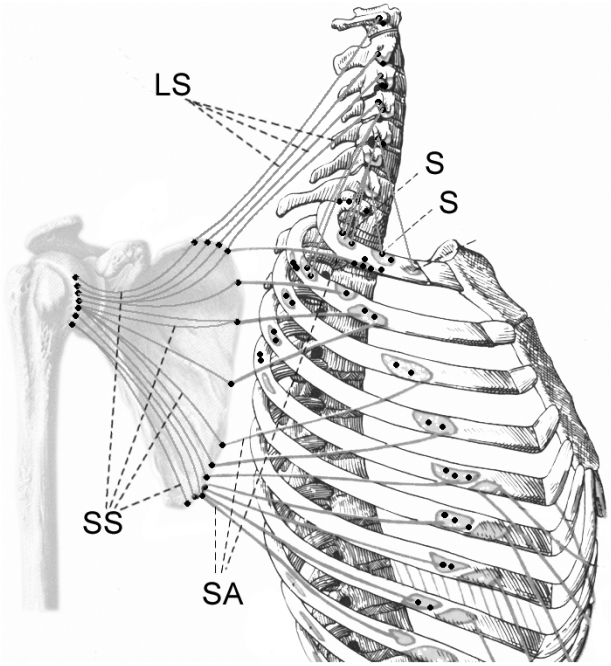


**FIGURE 62.9** Commonly overlooked painful enthesopathies of levator scapula (LS), subscapularis (SS), and serratus anterior (SA) especially superior fascicle often mimic upper trapezial pain. Contribution of rhomboid, scalenes (S), omohyoid (inferior belly), splenius services, posterior and anterior column structures including first costotransverse joint should be considered in differential diagnosis. (*Note:* Selected locations are treated at each visit.) From *Atlas of Anatomy* (Vol. 1), by R. D. Sinelnikov, 1972, Moscow: Meditsina. Modified for publication by David M. Paul.

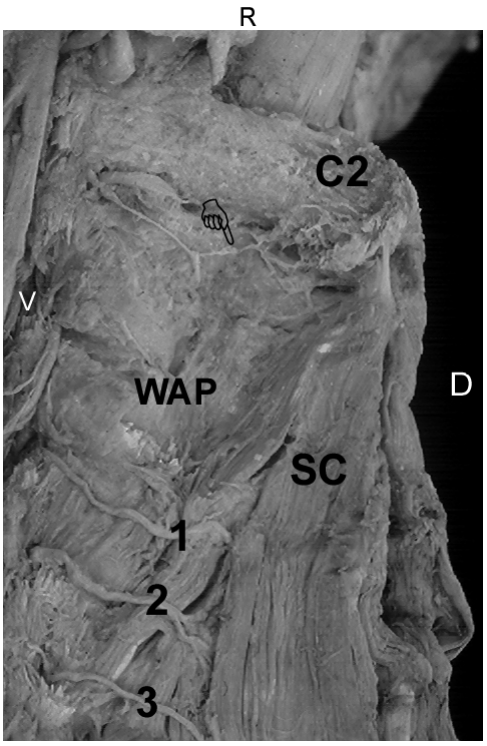


**FIGURE 62.10** Left dorsolateral view of the cervical medial branches of the dorsal rami (MBDRs). C–2 = apex of C2 spinous process, SC = semispinalis cervices, WAP = waist of articular pillar with the medial branch displaced anteriolaterally, 1 2 3 = MBDRs wrapping around the waists of articular pillars ramifying into multifidi. One of the two MBDRs that usually arise separately, innervating structures at the apex of C2. Slide and microdissections are courtesy of Professor Frank Willard, Ph.D. Modified for publication by David M. Paul.

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 mechanoreceptors with a low threshold, and are stimulated by stretch of the ligaments and muscle actions. Ruffini receptors are located in the interspinous and flaval ligaments; they respond to stretch and control the reflex inhibitory mechanism (Yahia et al., 1989).

Variously shaped, synovium-covered menisci composed of adipose, fibroadipose, collagenous, and cartilaginous tissue extend into cervical synovial joint space and anchor at their periphery to the joint capsule where they receive their blood supply. Their shape and position changes with age and degeneration (Mercer & Bogduk, 1993; Yu et al., 1987). The nerve supply to the inferior synovial folds of lumbar z-joints has also been documented (Giles & Taylor, 1987; Giles, 1988).

## CLINICAL ANATOMY OF CRANIOVERTEBRAL, CERVICAL, AND THORACIC REGIONS IN RELATION TO RIT

The subjective nature of pain and especially chronic pain, because of the suffering characteristics, is a major communication problem. Quite often a physician has not had a comparable experience and will have difficulty understanding what the patient is trying to communicate. Physicians, especially those involved in pain management, have to accept patients' "pain and tenderness" at face value without dismissal or allocation to a distant "proven" source. It is the knowledge of clinical anatomy, pain patterns, and pathology that should guide the clinical investigation, versus insurance policies and reimbursement especially in the current mismanaged care environment.

Hilton's law is clear that a nerve passing a joint is also supplying that joint, muscles are moving that joint, and the skin is covering insertions of these muscles (Hilton, 1891). This is in accord with anatomical, histological, experimental, and human studies that followed and are too numerous to count.

Scientifically verified are the following data. Cervical ZJ is responsible for 54% of chronic neck pain after "whiplash" injury. Intra-articular corticosteroid injections are ineffective in relieving chronic cervical ZJ pain (Barnsley et al., 1994, 1995). In cervicogenic headaches after whiplash, more than 50% stem from the C2–3 ZJ

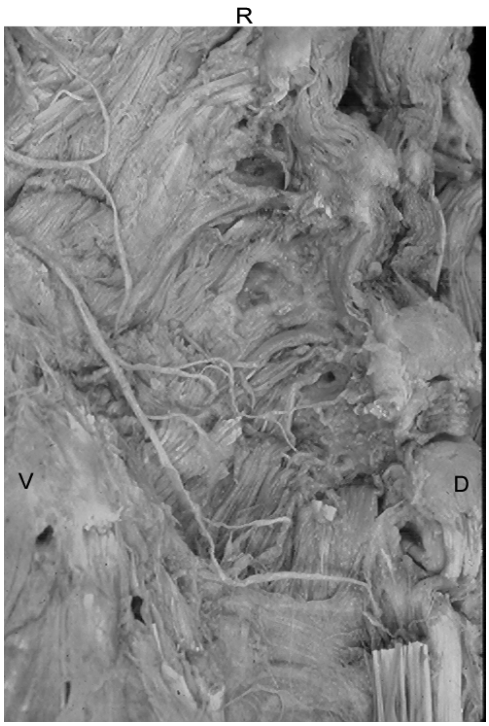


**FIGURE 62.11** Left dorsolateral view of cervical micro-dissection. Descending floating cervical MBDR with multiple branches reaching lateral aspects of the spinous processes at the enthesis of multifidi. Slide and micro-dissections are courtesy of Professor Frank Willard, Ph.D. Modified and prepared for publication by David M. Paul.

(Bogduk, 1986, 1996; Bogduk et al., 1996; Lord, 1996). Prevalence of cervical ZJ pain is as high as 67%; thoracic is 48% (Boswell et al., 2003; Lord, 1996; Manchikanti et al., 2002). The preceding statistical data were obtained by a painstaking adherence to precision protocols and strongly suggest a presence of nociceptors other than ZJ and IVD**.** Lack of statistical data on these "other, hidden, unproven pain generators" could not be misconstrued as their absence. Cervical and thoracic facet syndromes comprise the pathology of capsular ligaments, periarticular tendons with their enthesis, extrapment, and entrapment of menisci, and fractures of the articular pillars, which are not detected by current radiologic modalities. Also S-shaped intra- and periarticular degenerative changes of ZJ predispose intra-articular inclusions and subchondral bone to contusions during trauma (similar to an inadvertent bite on the buccal mucosa). The same changes make intra-articular needle placement from the inferior pole difficult even with fluoroscopic guidance.

Pain patterns resembling those of facet syndromes have been described from structures located distally on the course of MBDRs, lateral branches (LBs), and those receiving extrasegmental innervation. Further, patterns from AO and AA joints overlap with patterns from the lower z-joints (Aprill et al., 1990; Dreyfuss et al., 1994a), as well as sub-occipital and posterior cervical soft tissues (Feinstein et al., 1954; Hackett 1958, 1960a; Hackett et al., 1962, 1991; Kellgren, 1939; Linetsky et al., 2004; Travell et al., 1983). AO and AA contribution to nociception requires confirmation with intra-articular blocks under fluoroscopic guidance by a practitioner with a significant amount of experience (Dreyfuss et al., 1994a). Usually it is a diagnostic procedures of exclusion and is employed after failure of mid-cervical and C2–3 ZJ interventions to provide a relief. (Bogduk, 1988; Dreyfuss et al., 1994a, 1994b). Conversely RIT injections are capsular ZJ injections that provide relief without fluoroscopic assistance in the cervicothoracic region as high as C2–3 ZJ capsule which is the highest palpable ZJ in the cervical spine, at a comparatively much lower cost (Blumenthal, 1974; Cyriax 1969, 1982, 1993; Hackett, 1958, 1962, 1991; Kayfetz, 1993a, b; Linetsky, 2002b, 2004; Maigne, 1996; Waldman, 1998). Current prevailing trends in diagnostic efforts are variable and are as follows. Cervical facetogenic pain is confirmed by MBDR block but AO, AA, CVJ, and sacroiliac joints are diagnosed by intra-articular blocks. Thoracic ZJ pain is diagnosed by both intra-articular and MBDR block, without consideration for chronic degenerative, painful changes in the tissue bed. Neuralgic spinal pain is diagnosed by translaminar or transforaminal block. Discogenic pain is addressed by needle placement and tissue distention with contrast or what is known as tissue bed block (Aprill et al., 1990; Bogduk, 1982; Linetsky & Willard, 1999; Linetsky et al., 2002a, 2004).

Consequently, therapy is directed toward neuromodulation or neuroablation with radiofrequency generators or corticosteroid injections for neuralgic pain. Surgical interventions and fusions are aimed to correct the mass effects in neurocompressive models or discogenic pain. The rest of pain generators are not included in differential diagnosis because of the spinal uncertainty principle. According to the principle even for a simple example of two motion segments, where disc, facets, and musculotendinous compartments, each considered as one putative nociceptive unit, the total number of clinically indistinguishable combinations rises to 63 possibilities. It is practically impossible to address such a magnitude of possibilities under fluoroscopic guidance (Dickey, 2001).

The tissue bed pathology and pain are the primary targets for RIT taking innervation into account. Therefore, RIT affords evaluation of many putative pain generators from the variety of pain presentations in the craniocervicothoracic region in addition to the posterior column. When correctly implemented, RIT offers an attractive, practical alternative that is accomplished at the same office visit.

The apices of the spinous processes (SP) and their entheses are well innervated and considered a "spinous rotator cuff" especially at C2 and C6–T12.

Standard MBDR blocks interrupt orthodromic and antidromic transmission at the proximal segment of MBDR. Other putative nociceptors located distally on MBDR course are excluded from the differential diagnosis without consideration to individual variation in the locations of terminal filaments of MBDR and LB. For RIT purpose, the blocks are performed beginning from the terminal filaments at SP enthesis, towards origins of innervation located proximally on the course of MBDR or LB (Hackett et al., 1991; Linetsky et al., 2002b, 2004; Steindler et al., 1938).

For example, at the cervicocranial junction, lateral aspects of the apex at the C2 spinous process (specifically enthesis of rectus capitus posterior major, obliquus capitus inferior, semispinalis services) are addressed initially. If pain persists, respective enthesis are addressed at the superior and inferior nuchal lines. If pain persists, the C2–3 posterior z-joint capsule is injected (Linetsky, 2002b, 2004; Figure 62.7, Figure 62.8, Figure 62.10, Figure 62.11). At the mid-cervical segments, central tenderness is rare while facet capsular tenderness is more prevalent, which is the reason the posterior ZJ capsules are blocked initially if this is the only presenting pain. Should this fail, subsequent intra-articular fluoroscopically guided injections are indicated. This approach may fail in the presence of paramedian pain and trapezial pain because it does not take into account extrasegmental innervation to some of the cervical and thoracic structures commonly involved in chronic pain syndromes that receive innervation from the cranial nerves or the ventral rami.

Multilevel C6–T9 midline pain with variable degree of tenderness in the projection of posterior syndesmotic joints and rhomboid-shaped trapezius (TR) aponeurosis is by far one of the most common presenting complaints encountered in pain practice (exact prevalence unknown) (Figure 62.3 through Figure 62.5). This is combined with variations of paramedian, lateral, middle and upper TR pain, and tenderness commonly ascribed to "trigger points" (TPs). Injections of these TPs often do not resolve the pain. What to do next? Search for all other tender sites in the region. This usually reveals exquisite tenderness at the superomedial angle of the scapula where levator scapulae (LS) share the insertion site, enthesis, with serratus anterior (SA) and subscapularis (SS). Innervation of these structures is as follows: TR — by the XIth pair, the accessory nerve; LS — by ventral rami (VR) from (C3–C4) and dorsal scapular nerve (C5); SA — by long thoracic nerve (C5–C7 VR); and SS — by superior and inferior subscapular nerves (C5–C6 VR). To base differential diagnosis and treatment of this condition on diagnostic blocks of all these nerves in one setting is impossible (Dickey, 2001).

Conversely, block of the common enthesis at the superomedial scapular angle addressing both dorsal and ventral surface may provide instant relief including disappearance of TPs. The following case will demonstrate the necessity to consider all potential nociceptors in a given presentation (Figure 62.9).

For the purpose of RIT, when trapezial pain is accompanied by midline tenderness at C6–T6, those structures are injected initially. If TR pain persists and is accompanied by paramedian pain and tenderness, ZJ capsules are injected. If TR pain persists, the first CVJs are injected if tender. If not, scalene medius enthesis at the first rib is injected if tender. If pain persists, iliocostalicis services, thoraces, and serratus superior enthesis at the respective ribs are injected. If pain persists, LS and SA enthesis at superomedial angle of the scapula are blocked. This site may be blocked initially if it is the sole area of presenting complaint, pain, and tenderness. If pain persists, the above-described sequence may be initiated.

## MECHANISM OF ACTION

The exact mechanism of action is unknown. The proposed and postulated RIT mechanisms of action are complex and multifaceted.

- Temporary neurolysis with chemoneuromodulation of peripheral nociceptors is achieved by chemical properties of the injectates and provides stabilization of antidromic, orthodromic, sympathetic and axon reflex transmissions.
- Temporary neurolysis is achieved via mechanical transsections of some small myelinated and unmyelinated C fibers by the needle or hydraulic pressure of the injected volume.
- Mechanical transsections of cells and extracellular matrix by the needle causes cellular damage, stimulates inflammatory cascade and release of growth factors.
- Compression of cells by relatively large extracellular volume as well as cell expansion or constriction due to osmotic properties of injectate stimulates the release of intracellular growth factors.
- Chemomodulation of collagen through inflammatory, proliferative, regenerative/reparative response is induced by the chemical properties of the injectates and mediated by cytokines and multiple growth factors.
- Modulation of local haemodynamics with changes in intra-osseous pressure leads to reduction of pain. Empirical observations suggest that dextrose/lidocaine action is much more prolonged than that of lidocaine alone.
- Temporary repetitive stabilization of the painful hypermobile joints, induced by inflammatory response to the injectates, provides a better environment for regeneration and repair of the affected ligaments and tendons.

- The large volume of injectate disrupts adhesions that were created by the original inflammatory attempts to heal the injury, akin to epidural or intra-abdominal lyses of adhesions.
- A relatively large volume of osmotically inert injectate assumes the role of a space occupying lesion in a tight and slowly equilibrating extracellular compartment of the connective tissue. It initiates inflammatory cascade and also irrigates catabolic interleukins

### Putative Pain-Generating Structures Addressed by RIT/Prolotherapy

1. Ligaments: Intra-articular, periarticular, capsular
2. Tendons
3. Fascia
4. Enthesis: The zone of insertion of ligament, tendon, or articular capsule to bone (Anderson, 1988; Jozsa & Kannus, 1997; Klein & Eek, 1997) (also called fibro-osseous junctions of ligaments and tendons). In the orthopedic literature, this is referred to as OTJ (osseo/tendinous junction) (Jozsa & Kannus, 1997; Leadbetter, 1992, 1994, 1995; Linetsky et al., 2002a, b, c, 2004; Reeves, 2000). For the purpose of this chapter, enthesis and fibro-osseous junction are interchangeable.
5. Intervertebral discs

## TISSUE PATHOLOGY TREATED WITH RIT/PROLOTHERAPY

1. *Sprain*: Ligamentous injury at the fibro-osseous junction or intersubstance disruption. A sudden or severe twisting of a joint with stretching or tearing of ligaments; also, a sprained condition (Leadbetter, 1994; Reeves, 1995; Simon et al., 1987).
2. *Strain*: Muscle/tendon injury at the fibromuscular or fibro-osseous interface. When concerned with the 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. With regard to vertebral and paravertebral ligaments and tendons, no consensus exists among authors and the definitions are quite vague (Anderson, 1985; Leadbetter, 1994).
3. *Enthesopathy*: A painful degenerative pathological process that results in the deposition of poorly organized tissue, degeneration and tendinosis at the fibro-osseous interface, and transition toward loss of function (Jozsa & Kannus, 1997; Klein & Eek, 1997; Leadbetter, 1994; Linetsky, 1999b; Reeves, 1995).
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 toward chronic recurrent pain and dysfunction (Best, 1994; Jozsa & Kannus, 1997; Klein & Eek, 1997; Leadbetter, 1994; Reeves, 1995; Roosth, 1991).
5. *Pathologic ligament laxity*: A post-traumatic or congenital condition leading to painful hypermobility of the axial and peripheral joints (Anderson, 1985; Dorman et al., 1991; Hackett, 1958; Reeves, 1995, 2000; Reeves et al., 2000; Simon et al., 1987).

## INDICATIONS FOR RIT/PROLOTHERAPY

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 "golfer's" elbows, chronic supraspinatus tendinosis)
3. Painful chronic postural neck and cervicodorsal junction problems
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. Thoracic vertebral compression fractures with a wedge deformity that exerts additional stress on the posterior ligamento-tendinous complex
6. Recurrent painful subluxations of ribs at the costotransverse, costovertebral, and/or costosternal articulations
7. Spondylolisis and spondylolisthesis
8. Intolerance to NSAIDs, steroids, or opiates and failure of manipulative treatments or physical therapy when corticosteroid injections, RF, and surgery failed or are contraindicated
9. RIT is the treatment of choice

## 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 syndromes
11. Costotransverse 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. Marie–Strumpell disease
27. Failed back surgery syndrome

## CONTRAINDICATIONS TO RIT/PROLOTHERAPY

1. Allergy to anesthetic or proliferant solutions or their ingredients, such as dextrose, sodium morrhuate, or phenol
2. Acute nonreduced 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 severe intractable cephalgia, unilaterally dilated pupil, bladder dysfunction, and bowel incontinence
9. Requests for a large quantity of sedation and/or narcotics before and 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
12. Relative contraindications: central spinal canal, lateral recess and neural foraminal stenosis

## CLINICAL PRESENTATIONS

Patients may present with a 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. Other complaints include (1) exacerbation of pain while standing or sitting in the same position for a given period of time, and increased pain after exertion or physical activity; (2) a feeling of weakness in the neck, back, or extremities and extreme fatigability; (3) pseudoradicular patterns of change in sensation, such as burning, numbness, and tingling; (4) difficulties in maintaining balance, ringing in the ears, and blurred vision; (5) feeling the need for repetitive self-manipulations, or chiropractic or osteopathic manipulations; (6) painful clicking, popping, or locking of axial or peripheral joints; (7) dropping of objects, weakness of the hands, and "heaviness of the head" (Dorman et al., 1991; Hackett et al., 1991; Kayfetz, 1963; Kayfetz et al., 1963; Reeves, 1995, 2000).

### 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 the posterior cervicodorsal region.

Such local tenderness, as well as referred and radiating pain, can often be abolished by infiltration of nociceptors in the involved tissue with local anesthetic. Tenderness is an objective finding, especially when elicited at posterior structures (Borenstein et al., 1996; Broadhurst et al., 1996; Hackett, 1958; Hackett et al., 1991; Linetsky, 1999).

## 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 and deformity of zygapophyseal articulation

(Browner et al., 1998; Harris et al., 1981; Resnick, 1995; Watkins, 1996)

2. Videofluoroscopy has been popularized in the previous edition of this chapter; based on the experience of the last 3 years, our current opinion is that the findings of the interpreting practitioners do not correlate with the findings of clinical evaluation augmented by diagnostic blocks (Fielding, 1957)
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, and neoplasia infection or fracture, as well as exclude or confirm spinal cord disease and pathology related to intradural, extramedullary, and epidural space (Resnick, 1995; Stark et al., 1999)
4. CT scan may detect small avulsion fractures of the facets, laminar fracture, fracture of vertebral bodies and pedicles, or degenerative changes (Resnick, 1995)
5. Bone scan is useful in the assessment of the entire skeleton, ruling out metabolically active disease processes (Resnick, 1995)
6. Ultrasound has been long practiced in Europe for diagnosis of "soft tissue" pathology (Jozsa & Kannus, 1997). It has been widely used in veterinary medicine in the United States (Herthel, 2003). Current radiologic publications also demonstrate the effectiveness of diagnostic ultrasound in soft tissue pathology (Zanetti et al., 2003; Jacobson et al., 2003). A case has recently been reported of trapezius rupture diagnosed by ultrasound and successfully treated with xylocaine/dextrose injections followed by ultrasound confirming the closure of the defect (Saberski, 2003).

## TECHNICAL CONSIDERATIONS AND INJECTION SITES

Painful enthesopathies and arthropathies in the craniocervicothoracic region commonly affect the following sites: apices of spinous processes, occipital bone at inferior and superior nuchal lines, mastoid processes, anterior and posterior tubercles of transverse processes, tubercles, angles and tuberosities of the ribs, proximal and distal portions of the clavicle, superomedial and inferomedial margins and the spine of the scapula, sternum, and xyphoid, capsular ligaments of the cervical and thoracic synovial joints such as AA, AO, z-joints, costovertebral, costotransverse joints, and TMJs. (Figure 62.4 through Figure 62.9).

There is a significant overlap in published pain maps from the structures innervated by the DRs. which have been grouped for practical purposes into the dorsal ramus syndrome (DRS). Consequently, in the craniocervicodorsal area, only structures that receive innervation from DRs are considered potential pain generators. However, there are also many structures receiving extrasegmental innervation that do not fit into DRS. The question is, "How to navigate in this sea of unknown?" The physician continuously follows the main objective of RIT, specifically the painful tissue bed as the primary target of investigation, taking the nerve supply into account. For the purpose of RIT, the following step-by-step approach to differential diagnosis is implemented to investigate all potential nociceptors in the distribution of the medial and lateral branches extending it beyond z-joints.

Initially, pain generators are identified by reproducible tenderness and the areas are marked. Tenderness of the posterior structures is an objective finding, especially in the midline (Broadhurst et al., 1996; Hackett et al., 1991; Kayfetz et al., 1963; Linetsky et al., 2002b, 2002c, 2004; Maigne, 1996; Reeves, 2000; Wilkinson, 1992). Confirmation is obtained by needling and local anesthetic blocks of the tissue at the enthesis, taking the nerve supply into account (Figure 62.3 and Figure 62.4).

The C2 spinous process is the most prominent palpable structure of the upper cervical region, and because of bifurcation, it should be addressed from a lateral approach. C6–T2 are the most prominent structures at the cervicodorsal junction (Figure 62.7, Figure 62.8, and Figure 62.10).

In experienced hands, using palpable landmarks for guidance, the following posterior column elements innervated by the dorsal rami may be safely injected without fluoroscopic guidance: enthesis of ligaments and tendons at the spinous processes, from C2 caudad, lamina, posterior zygapophyseal joint capsule, posterior and anterior tubercles of the cervical transverse processes, and cervicodorsal fascia insertions when palpable. Transverse processes of C1 are rarely palpable and sometimes may be injected without fluoroscopy. It is easier to inject them under fluoroscopic guidance during upper cervical synovial joint injections. Fluoroscopy itself does not prevent intravascular or intraneural needle placement.

Lidocaine is usually used for diagnostic purposes. However, the dextrose/lidocaine solution is also an effective initial diagnostic and therapeutic option for pain arising from posterior column elements when used in increments of 0.2 to 1.0 ml injected at each bone contact, initially blocking the terminal filaments of the MBDRs with the sequence as follows:

1. In the presence of midline pain and tenderness, the superior aspect of the SP is blocked initially in the midline at the enthesis. This is achieved with the caudal direction of the needle.

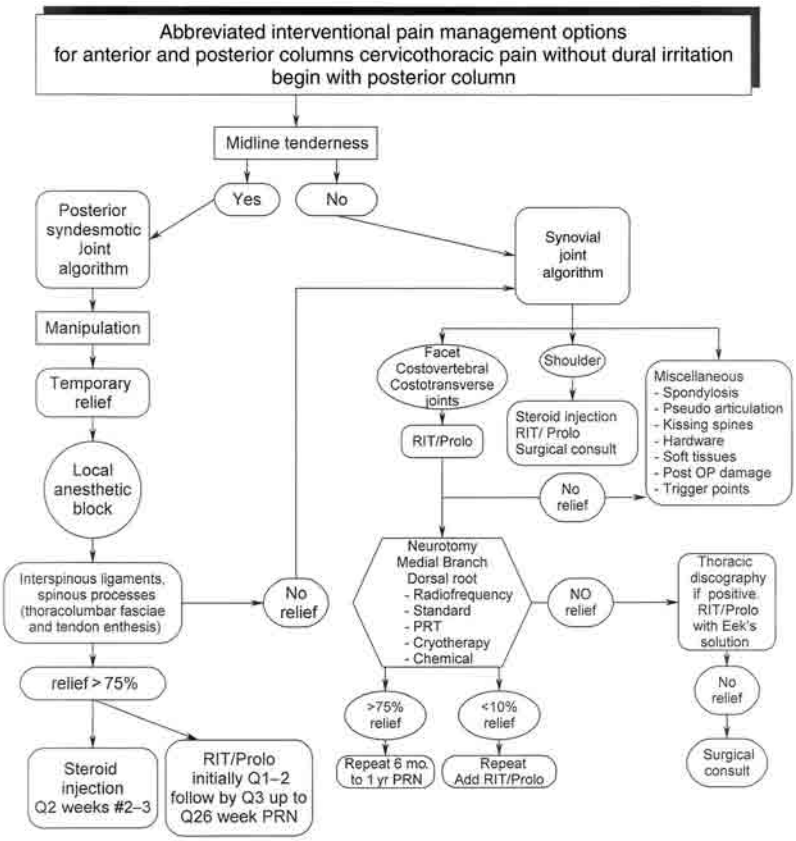


**FIGURE 62.12** Modified excerpt from "Percutaneous Management Options for Cervical and Thoracic Spinal Pain" by Richard Derby, February 9–10, 2002, in *ISIS 9th Annual Scientific Meeting Syllabus, ISIS Presents: The Guidelines* (pp. 1476–1485), Orlando, FL.

2. If tenderness remains at the lateral aspects and the apices of the SP, then injections are carried out to the lateral aspects and the apices of the SPs, thus continuing on the course of MBDR. However, it should be noted that all cervical, and some thoracic, SPs are asymmetrically bifurcated at their apices. Therefore, the needle direction is from lateral to medial to prevent inadvertent intrathecal injections.
3. Persistence of paramedial pain dictates blocks of the facet joint capsules, costotransverse joints, or posterior tubercle of the transverse processes in the cervical region at their respective enthesis.
4. Perseverance of lateral tenderness dictates investigation of the structures innervated by the LBDR (i.e., iliocostalis tendon insertions to the ribs or structures receiving extrasegmental innervation such as serratus anterior and trapezius).

In this fashion, all of the potential nociceptors on the course of MBDR are investigated from its periphery to the origin. Using the previously described sequence, a differential diagnosis of pain developing from vertebral and paravertebral structures innervated by MBDRs and LBDR is made (Figure 62.3 through Figure 62.9). Modified percutaneous management options for cervical and thoracic spinal pain are a broad algorithm to follow while more specific algorithms are being developed.

Pain from the upper cervical synovial joints presents a diagnostic and therapeutic challenge. Because pain patterns overlap, it usually is a diagnosis of exclusion (Figure 62.12).

Intra-articular, atlanto-axial, and atlanto-occipital joint injections of 3 to 4% phenol in the final injectate have secured a long-lasting therapeutic effect in selected patients (Stanton-Hicks, 2003). Positive therapeutic effects with intra-articular injections of 25% dextrose to the same joints and mid-cervical synovial joints also were reported to relieve persistent pain after radiofrequency and capsular injection failure (O'Neill, 2003). All of the synovial intra-articular injections of the spine should be performed under fluoroscopic guidance.

To prevent complications, the following cardinal rules should be followed:

1. Injections should be made only after the needle contacts the bone and the pain is reproduced by the needle placement(s).

2. The needle should be slightly withdrawn to prevent subperiosteal placement of the injectate.
3. Should the needle fail to contact the bone at the expected depth, it must be withdrawn to the level of superficial fascia and redirected.
4. If blood or cerebrospinal fluid appears in the syringe, the injection should be aborted.
5. Should the needle contact the nerve (this may present itself with lancinating, lightening pain), the procedure should be aborted. If pain remains intolerable, infiltrate the area with corticosteroids and local anesthetic.

## SOLUTIONS UTILIZED

The most common solution employed for RIT is dextrose 10%, 12.5%, 16.5%, 20%, and 25%. Dilutions are achieved with local anesthetic in 1:4, 1:3, 1:2, 2:5, and 1:1 proportions (i.e., 1 ml of 50% dextrose mixed with 3 ml of 1% lidocaine will produce a final 12.5% dextrose/lidocaine solution) (Hackett et al., 1991; Linetsky, 2002b, 2002c, 2004; Reeves, 1995, 2000).

For intra-articular knee injections, Hemwall recommended a 25% dextrose solution (Hackett et al., 1991). Reeves et al. (2000) have pointed out that a 10% dextrose solution may be equally effective. If this proves ineffective, gradual progression to sodium morrhuate full strength has been described (Dorman et al., 1991; Hackett et al., 1991).

Sodium morrhuate (5%) 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 is chemically very similar to phenol.

Dextrose/phenol/glycerin solution, originally produced in England by Boots Company Ltd. of Nottingham, England, for treatment of varicose veins, was introduced to pain management by Ongley et al. (1988). The solution consists of 25% dextrose, 2.5% phenol, and 25% glycerin and is referred to as DPG (or P2G). Prior to injection it is diluted in concentrations of 1:2; 1:1, or 2:3 with a local anesthetic of the practitioner's choice. Some authors exclusively use this solution in 1:1 dilution (Dorman et al., 1991). Others modify it, reducing the percentage of glycerin to 12.5%.

The 6% phenol in glycerin solution was used by Poritt in 1931 and reintroduced in the late 1950s by Maher (1957) of England for intrathecal injections in the treatment of spasticity. Subsequently, after gaining sufficient experience with intrathecal use of this solution, Wilkinson (1992), a neurosurgeon trained at Massachusetts General Hospital, began injecting it at the donor harvest sites of the iliac crests for neurolytic and proliferative responses.

## COMPLICATIONS

As with any interventional procedure, complications do occur with RIT, but statistically they are rare. The most recent statistical data are from a survey of 450 physicians performing prolotherapy. In the study, 120 respondents revealed that 495,000 patients received injections. Of the 29 pneumothoraces reported, two of them required chest tube placement; 24 non-life-threatening allergic reactions were also reported. Thus, the occurrence of pneumothoraces requiring chest tube is 1 per 247,500 patients, self-limited pneumothoraces is 1 per 18,333, and allergic reaction is 1 per 20,625. Assuming that each patient receives at least three visits and during each visit receives at least 10 injections, the numbers are relatively miniscule.

In the late 1950s and early 1960s, five cases of post-injectional arachnoiditis were reported (Keplinger et al., 1960). Two of them were fatal (Schneider, 1959; Hunt, 1961). One was a direct sequence of arachnoiditis; another was a sequence of incompetent shunt and persistent hydrocephalus with increased intracranial pressure (Schneider, 1959). Of the three other cases, the first, with mild paraparesis, recovered after a ventriculo-jugular shunt. The second recovered spontaneously with a mild neurological deficit (Hunt, 1961). The third case remained paraplegic (Keplinger et al., 1960). There have been a few recent cases of intrathecal injections not reported in the literature because of medicolegal issues. Two of them resulted in paraplegia. The first occurred after injection at the thoracic level, the second after lumbar injection. A third case was performed by a naturopath who injected solution containing zinc sulfate at the craniocervical level, which resulted in immediate onset of severe neurologic deficit, quadriplegia, and subsequent hydrocephalus.

One case of self-limiting sterile meningitis after lumbosacral sclerosing injections was reported 10 years ago (Grayson, 1994). A more recent report described a case of adjacent end plate fractures associated with intradiscal dextrose injections (Whitworth, 2002). Post-spinal puncture headaches are common, especially after lumbosacral injections (Yelland et al., 2003). Two such cases have occurred in Dr. Linetsky's practice during the past 14 years. Patients recovered after 1 week with bed rest and fluids without sequelae. Among the overall rare complications, pneumothoraces are the most common, occurring during injections of the costovertebral; costotransverse articulations; insertions of the tendons to the ribs such as iliacostalicis, serratus posterior, superior, and inferior, scalene insertions to the ribs, and levator and rhomboid insertions to the scapula especially in very muscular or significantly overweight patients. Anterior synovial joint injections, such as sternoclavicular, costosternal, and interchondral, may also result in pneumothorax in the same subset of patients.

## CONCLUSIONS

As stated recently by Dr. Mooney, this treatment has advanced "from the fringe to the frontier of medical care" (Mooney, 2003).

1. RIT/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 function is necessary.
3. Current literature supports manipulation under local joint anesthesia.
4. The use of RIT in an ambulatory setting is an acceptable standard of care in the community.
5. The 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. Microinterventional regenerative techniques and proper rehabilitation up to 6 months or a year, supported with mild opioid analgesics, are more appropriate.

The future is such that, instead of indirect stimulation of growth factors through inflammatory cascade, specific growth factors will become available. The challenge will remain as to 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 will probably be addressed through transdermal delivery systems (Cook, 2000; DesRosiers et al., 1996; Kang et al., 1999; Lee et al., 1998; Marui et al., 1997; Nakamura et al., 1998; Reeves, 1995, 2000; Rudkin et al., 1996; Spindler et al., 1996).

Physicians versed in manipulation as well as diagnostic and therapeutic injection techniques as described in this chapter may find ample opportunity to use RIT in their pain management practice.

## PRACTICAL SUGGESTIONS

Though Hackett's textbook is used by many as a primary source of information, even the 1991 edition is rudimentary and does not adequately explain the differential diagnosis. Standard anatomical texts are not current regarding innervation; therefore, it behooves physician to familiarize themselves with referral pain patterns and review clinical anatomy from primary sources referenced in this chapter. RIT/prolotherapy is not a panacea but another powerful tool in the armamentarium of many interventional procedures.

Readers interested in incorporating RIT/prolotherapy in their pain management practice may attend the courses and workshops conducted by The Florida Academy of Pain Medicine http://fapm.med.new.net and The American Association of Orthopedic Medicine www.aaomed.org.

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