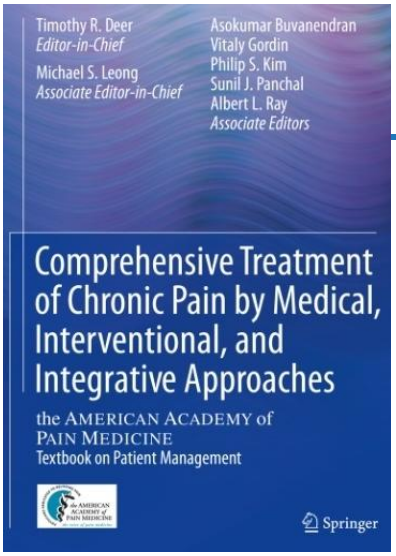

Treatment of Chronic Painful Musculoskeletal Injuries and Diseases with Regenerative Injection Therapy (RIT): Regenerative Injection Therapy Principles and Practice

81

Felix S. Linetsky, Hakan Alfredson, David Crane, and Christopher J. Centeno

Key Points

- Focuses on treatment of pain related to pathology of the connective tissue
- Provides detail explanation of mechanism of action
- Emphasizes neurolytic properties of chemical injectates
- Describes biologic injectates in details
- Compares and explains the significant resemblance of pain maps derived from the interspinous ligaments with those from the spinal and pelvic synovial joints
- Provides a step by step approach to differential diagnosis and treatment
- Describes future directions for regenerative injection therapy

F.S. Linetsky, M.D. (✉)
Department of Osteopathic Principles and Practice,
Nova Southeastern University of Osteopathic Medicine,
Clearwater, FL, USA
e-mail: linetskyom@gmail.com

H. Alfredson, M.D., Ph.D.
Sports Medicine Unit, University of Umea,
Gosta Skoglunds Vag 3, Umea 90738, Sweden
e-mail: hakan.alfredson@idrott.umu.se

D. Crane, M.D.
Regenerative Medicine, Crane Clinic Sports Medicine,
219 Chesterfield Towne Center,
Chesterfield, MO 63005, USA
e-mail: dcranemd@earthlink.net

C.J. Centeno, M.D.
Physical Medicine and Rehabilitation and Pain Medicine,
Regenerative Medicine, Centeno-Schultz Clinic,
403 Summit Blvd, Broomfield, CO 80021, USA
e-mail: centenooffice@centenoclinic.com

Introduction

Regenerative injection therapy (RIT), also known as prolotherapy or sclerotherapy, is a treatment for chronic musculoskeletal pain caused by connective tissue diathesis utilizing chemical or biologic substances [1]. Steroidal and nonsteroidal anti-inflammatory medications are useful in degenerative disease processes with concomitant inflammatory changes or fibrosis which tethers adjacent structures such as nerves or tendons. In such instances, hydrodissection with injectates containing corticosteroid may also prove useful. RIT is a viable, type-specific treatment for chronic conditions that involve collagen destruction or degeneration. Multiple controlled and uncontrolled studies indicated effectiveness of RIT in treating painful degenerative musculoskeletal conditions. Advances in imaging technology such as MRI and diagnostic ultrasound made it possible to visualize soft tissue pathology in the muscles, ligaments, and tendons. Tendinosis is frequently present in the appendicular and axial tendons. The diagnosis of tendinosis requires therapeutic interventions different from corticosteroids. There is literally an army of capable doctors who need biologically active substances to repair or regenerate degenerative pathologic changes. Old and newer injectates used for RIT such as polidocanol, platelet-rich plasma, and stem cells meet these requirements and are rendering impressive results.

The published pain patterns from ligaments, muscles, intervertebral discs, and synovial joints in the cervical thoracic and lumbar regions overlap significantly (Figs. 81.1, 81.2, 81.3, 81.4, 81.5, and 81.6) [2–4, 10–16]. Nonetheless, ligaments and tendons of these regions are rarely included in differential diagnosis. This chapter is addressing the diagnostic and therapeutic approaches to chronic musculoskeletal pain related to the pathology of fibrous collagenous connective tissue that could benefit from RIT.

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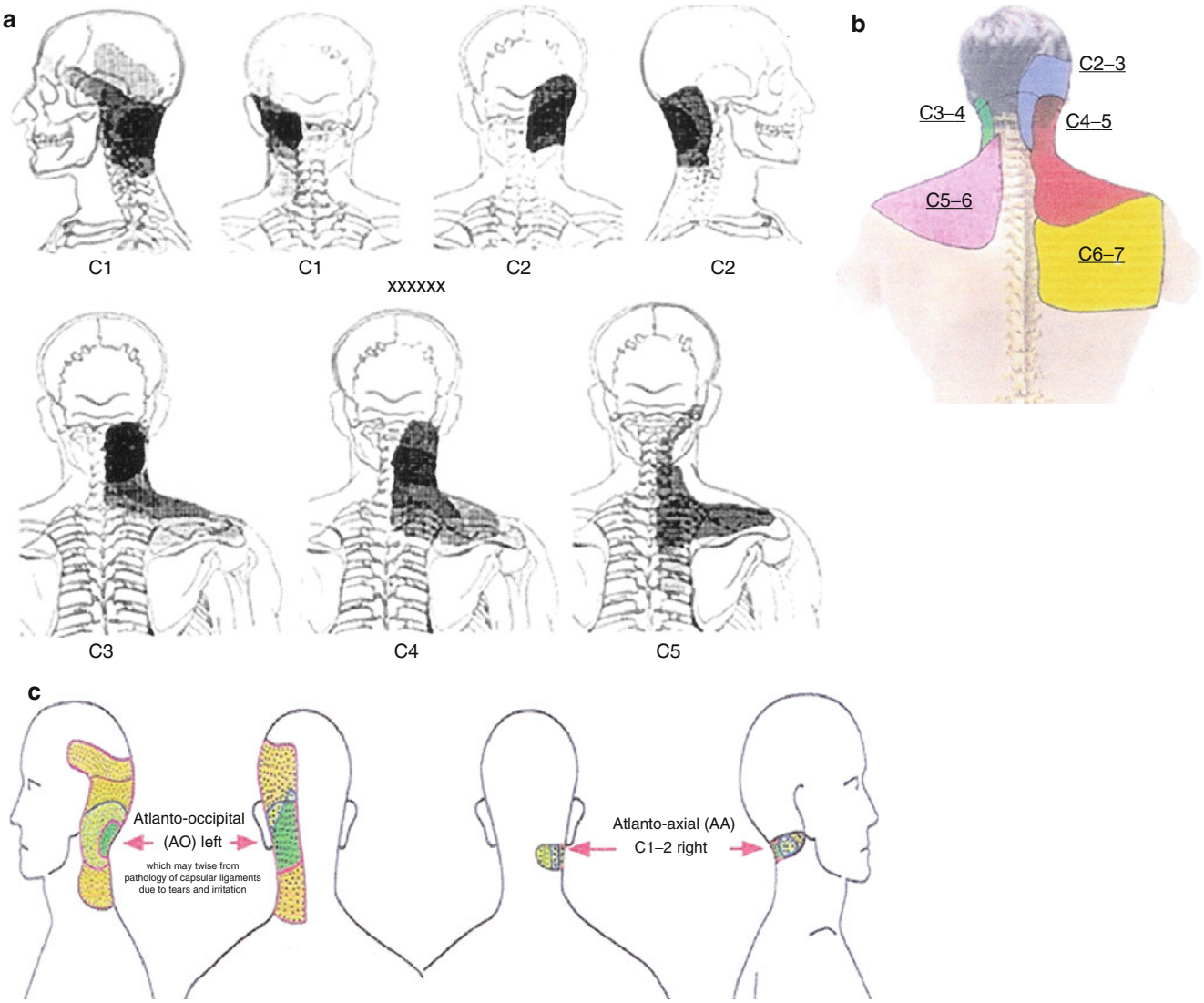

Fig. 81.1 Modified comparative composition of pain distribution in the cervical region provoked by injections of hypertonic saline in to the interspinous ligaments (**a**) Feinstein et al. [2]. Synovial joints: (**b**) (**c**) Significant overlap of these pain maps is due to the fact that injected structures are innervated by the cervical dorsal rami specifically the medial branches (MBDR). Similar relations exist in the thoracic, lumbar, and sacral regions (With permission from Dwyer et al. [3]; and Dreyfuss et al. [4])

Evolution of Terminology

Prior to 1930s, this treatment was called "injection treatment" with addition of a pathologic descriptor such as of injection treatment of varicose veins or injection treatment of hydroceles [17]. Biegeleisen coined the term "sclerotherapy" in 1936 [18].

Concluding that sclerotherapy implied scar formation, Hackett coined the term prolotherapy as "the rehabilitation of an incompetent structure by the generation of new cellular tissue." Hackett's supposition that "… prolotherapy is a treatment to permanently strengthen the 'weld' of disabled ligaments and tendons to bone" led to treatment with injections at the fibro-osseous junctions [11]. More recent work found significant amount of degenerative changes in the midsubstance of the ligaments and tendons as well as ruptures at the fibro-muscular interfaces, and intersubstance changes.

Further, current understanding of the basic science is such that regeneration and repair extend beyond the proliferative stage which is only a short phase of the healing process. More so, proliferation is an integral part of a malignant unsuppressed growth as well as degenerative changes which are present in the bones, synovium, intervertebral discs, ligaments, tendons, and fascial connective tissues. Regenerative injection therapy was coined by Dr. Linetsky because it is a more appropriate nomenclature for the treatment modality which promotes natural healing [1, 19–22].

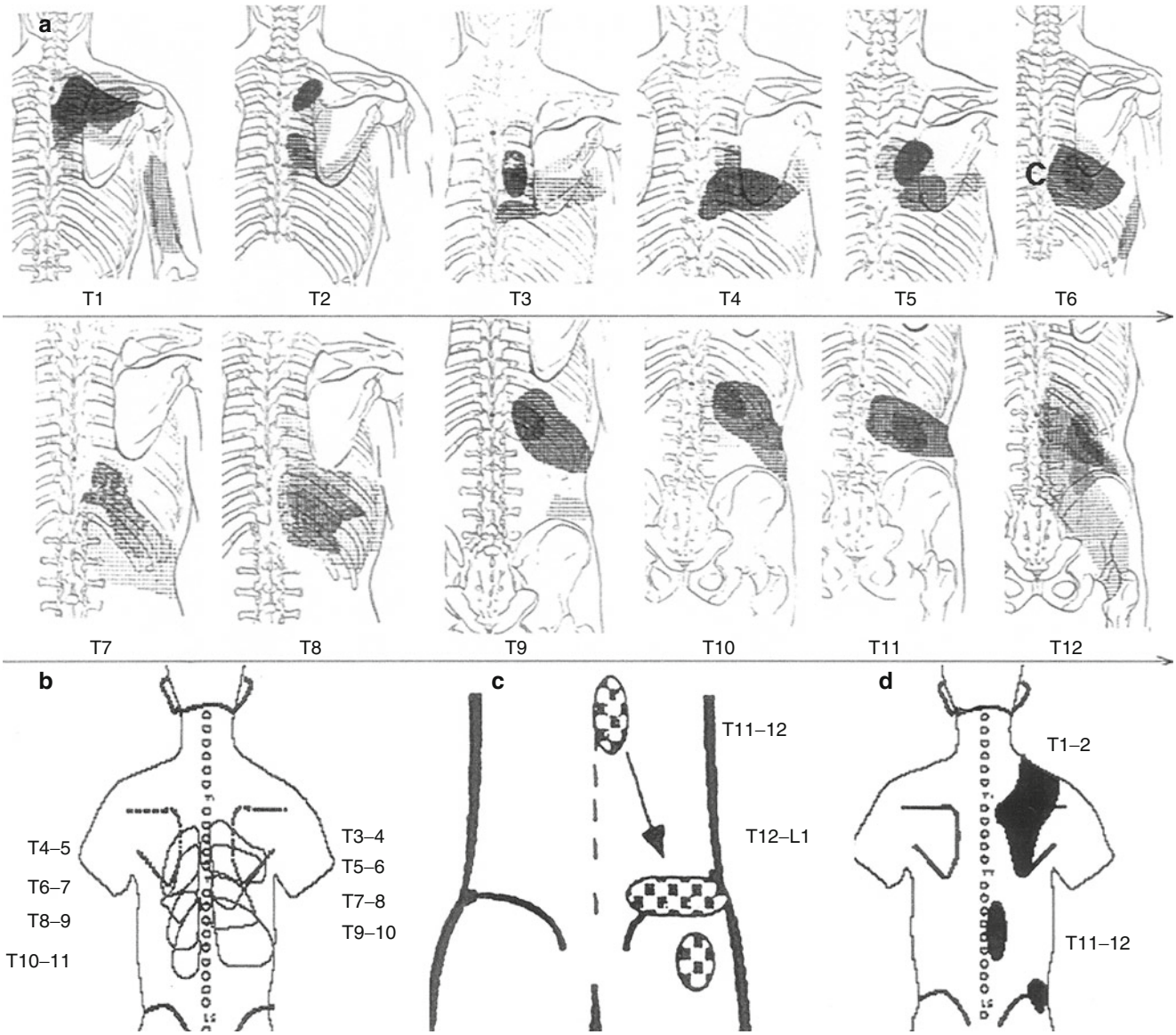

Fig. 81.2 A modified, comparative composition of pain distribution in the thoracic region provoked by injections of hypertonic saline into the interspinous ligaments by Feinstein et al. [2] (Upper two rows – **a**) and thoracic Z-joints (**b**) by Dreyfuss et al. [4], (**c**) by Dussault and Kaplan [5], and (**d**) by Fukui et al. [6]. Significant resemblance of the pain patterns and their overlaps is due to the fact that injected structures receive the same segmental innervated by the thoracic dorsal rami specifically the medial branches (MBDR)

Local Anesthetics in the Diagnosis of Musculoskeletal Pain

Differential diagnosis of musculoskeletal pain based on infiltration of procaine at the fibro-osseous junctions was pioneered in the 1930s by Leriche [16, 19, 22]. Steindler and Luck described that posterior primary rami provide sensory supply to muscles, tendons, thoracolumbar fascia, ligaments, and aponeuroses and their origins and insertions; therefore, no definite diagnosis could be made based on clinical presentation alone. They established the following criteria to prove a causal relationship between the structure and pain symptoms: reproduction of local and referral pain by needle contact, suppression of local tenderness, and referral/radiating pain by procaine infiltration [23]. Haldeman and Soto-Hall [24] infiltrated procaine in to posterior sacroiliac and interspinous ligaments, zygapophyseal joint capsules producing a field block with a marked relaxation of spastic musculature facilitating a routine use of sacroiliac and facet joint manipulations. They have introduced manipulation of axial joints under local anesthesia [24].

The same basic principles have been employed over all of the anatomic areas since the inception of RIT. Local anesthetic diagnostic blocks are still the best available objective confirmation of the precise source of pain in clinical diagnosis [3, 4, 11–17, 22–25].

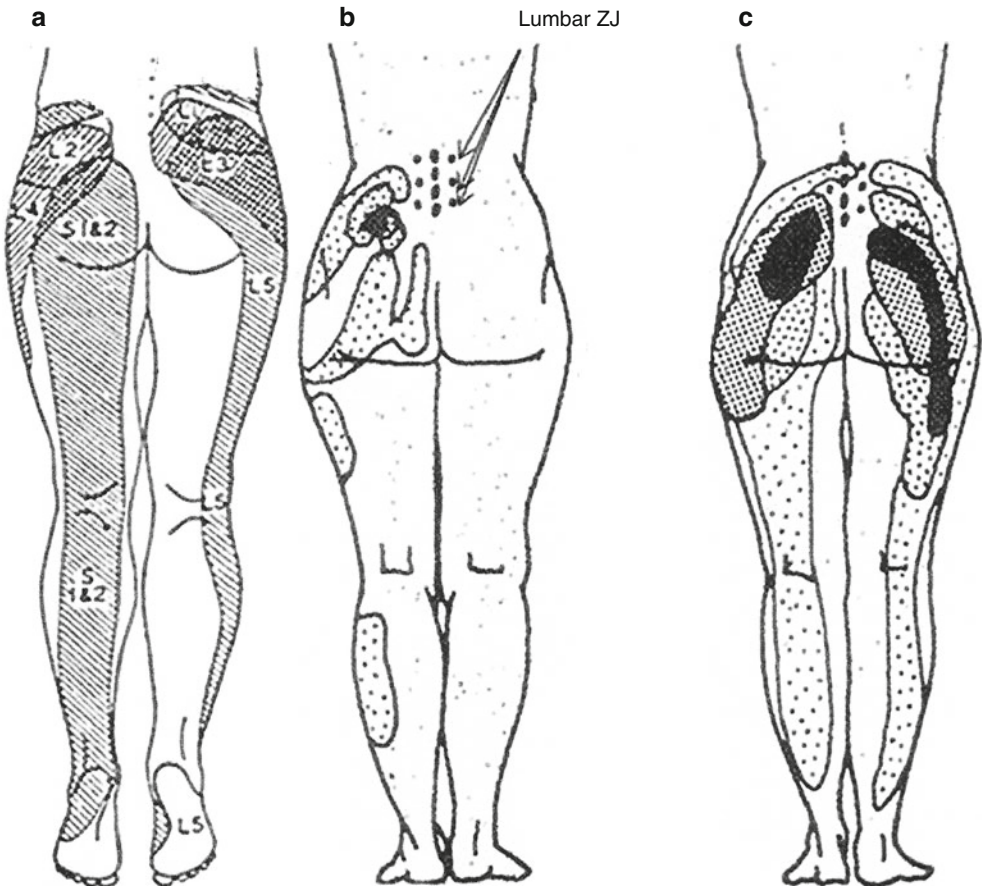

Fig. 81.3 Modified comparative composition of pain distribution in the lumbar region provoked by injections of hypertonic saline into the (**a**) lumbar interspinous ligaments dots in the midline from Kellgren et al. [7], from lumbar Z-joints, Mooney and Robertson [8] (**b**), and from asymptomatic subjects (**c**) of symptomatic patients (*paravertebral dots*); significant resemblance of the pain patterns and their overlaps is due to the fact that injected structures receive the same segmental innervated by the lumbar dorsal rami specifically the medial branches (MBDR)

Anatomic Biomechanical and Pathologic Considerations

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, each of these orientations contains specific cross-linking formations. Such orientations represent adaptation to specific directions in restriction of joint displacements. Under a light microscope, ligaments have a crimped, wavelike appearance which unfolds during initial loading of collagen [22, 26–28]. When elongated up to 4 % of original length, ligaments and tendons return to their original crimped wave appearance. Beyond 4 % of elongation, they lose elasticity and become permanently laxed, causing joint hypermobility. In degenerated ligaments, subfailure was reported at earlier stages of elongation. At its best, natural healing may restore connective tissue to their pre-injury length, but only 50–75 % of its pre-injury tensile strength [22, 27–30].

There are three types of nerve terminals in posterior spinal ligaments: free nerve endings and the Pacini and the Ruffini corpuscles. A sharp increase in the quantity of free nerve endings at the tips of lumbar spinous processes was documented (Fig. 81.7) [29].

Collagenous tissues are deleteriously affected by non-steroidal anti-inflammatory drugs (NSAIDs), steroid administrations, inactivity, and denervation. A single corticosteroid injection into a ligament or tendon has been reported to have debilitating effects on the strength of collagen contained therein [27].

In the presence of repetitive microtrauma with insufficient time for recovery, use of NSAIDs and steroids, tissue hypoxia, metabolic abnormalities, and other less defined causes, connective tissues lose their homeostasis and cycle toward an accelerated degenerative pathway [17, 22, 27, 30, 32–34]. Therefore, a cautious use of anti-inflammatory therapy continues to be a useful, but an adjunctive, therapy [32]. It should be noted that unless homeostasis is reestablished in a joint which the ligament protects, further progressive degenerative changes occur with time when continued laxity is present. A well-known example of this is the development of osteoarthrosis in the knee joint following ACL injury with associated laxity of the joint capsule.

As opposed to ligaments, tendons are glistening whitish collagenous bands interposed between muscle and bone that transmit tensile forces during muscle contraction. There are considerable variations in shape and structure of fibro-osseous attachments and myotendinous junctions. A normal tendon with a cross section of 10 mm in diameter can support a load of 600–1,000 kg [22, 26, 33].

Collagenous tissue response to trauma is inflammatory/regenerative/reparative in nature and varies with the degree

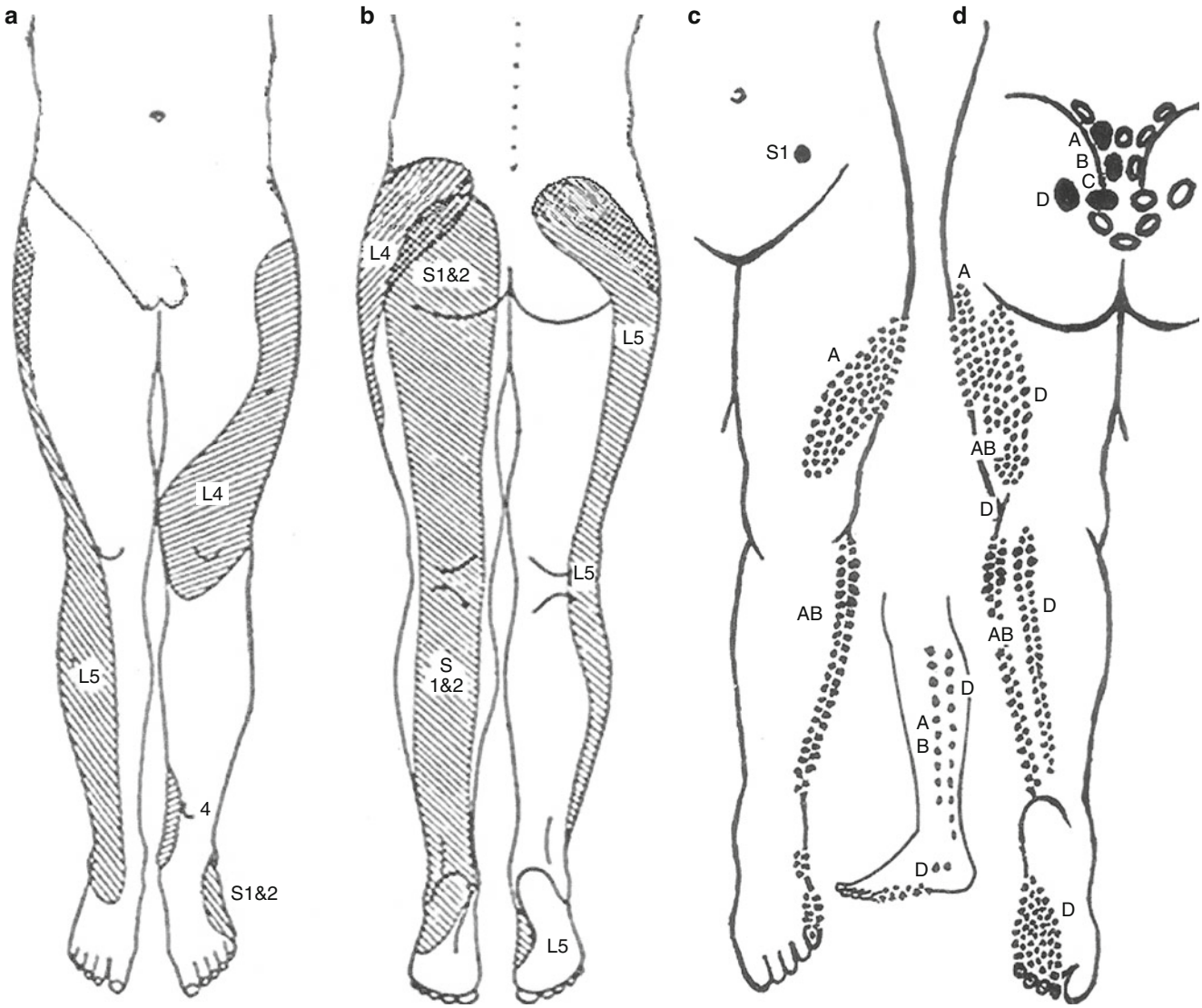

Fig. 81.4 Modified comparative composition of pain distribution from lumbosacral region provoked by injections of hypertonic saline into the (**a**, **b**) interspinous ligaments from L4–5 to S1–2 from Kellgren et al. [7]. (**c**, **d**) Referred pain maps from posterior sacroiliac ligament enthesopathies and sacroiliac joint instability (*AB* from the upper fibers, *CD* lower fibers ileum and sacrum) (Reproduced from Hackett [9]). Hackett published these maps after abolishing pain with local anesthetic infiltration in more than 7,000 injections over 17 years. Significant resemblance of the pain patterns and their overlaps is due to the fact that injected structures receive the same segmental innervated by the lumbar dorsal rami (Prepared for publication by Felix Linetsky M.D.)

of injury. In the presence of cellular damage, regenerative pathway takes place; in the case of extracellular matrix damage, a combined regenerative/reparative pathway takes place. Both are controlled by hormones, chemical, and growth factors [17, 22, 27, 30, 32–34]. Central denervation, such as in quadriplegia, paraplegia, or hemiplegia, leads to a statistically high, accelerated tendon degeneration [33]. Radiofrequency procedures may not be an exception. Corticosteroids do not arrest or slow the course of degenerative process. Neoneurogenesis and neovasculogenesis are also integral components of degeneration.

The presence of vascular and neural ingrowth into degenerated intervertebral discs, posterior spinal ligaments, the hard niduses of fibromyalgia, and tennis elbow tendinopathies have been known for some time. Presence of neuropeptides in the facet joint capsules and articular and periarticular tissue of the sacroiliac joints with the absence of inflammatory markers are also well established, rendering the aforementioned structures nociceptive; nonetheless, corticosteroid injections are still the advocated therapeutic interventions [35–39].

More recently, research dedicated to sports medicine shed light on degenerative changes in tendinosis and tendinopathy as a distinct pathologic and clinical entity [40]. The neurovascular ingrowth was studied extensively in Achilles, patellar, and supraspinatus tendinosis. Intratendinous microdialysis

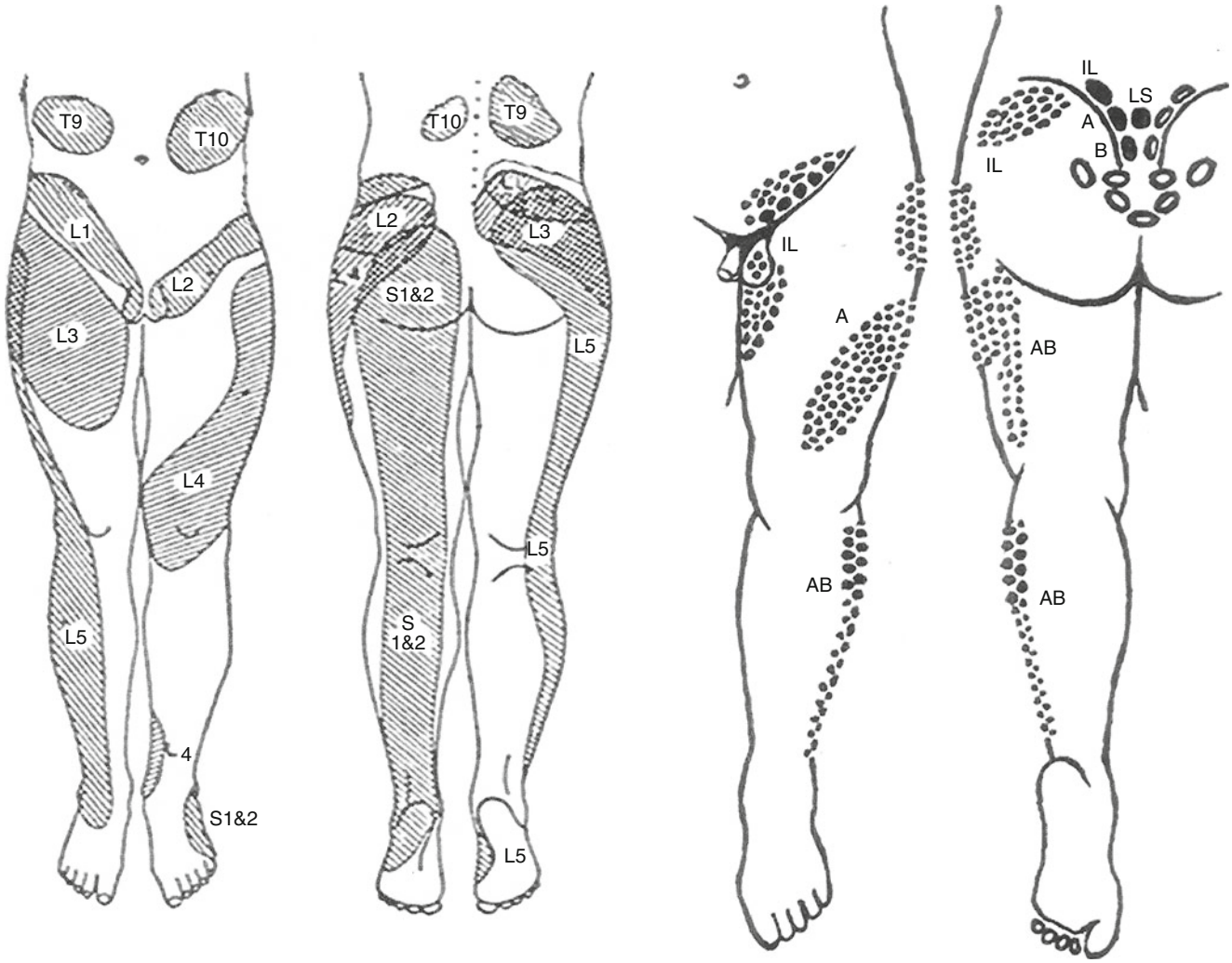

Fig. 81.5 Modified comparative composition of pain distribution from lumbosacral region provoked by injections of hypertonic saline into the (**a**, **b**) interspinous ligaments from L1–2 to S1–2 from Kellgren et al. [7]. (**c**, **d**) Trigger areas and referred pain from iliolumbar (*IL*) and posterior sacroiliac (upper *AB*) ligaments (lumbosacral (*LS*) and sacroiliac joint instability). Hackett published these maps after abolishing pain with local anesthetic infiltration in more than 7,000 injections over 17 years. Significant resemblance of the pain patterns and their overlaps is due to the fact that injected structures are innervated by the same segmental lumbar dorsal rami (From Hackett [9]. Prepared for publication by Felix Linetsky M.D.)

of these tendons found normal prostaglandin E_2 (PGE_2) levels in chronic painful tendinosis. Analyses of biopsies showed no upregulation of pro-inflammatory cytokines. The neurotransmitter glutamate, a potent modulator of pain in the central nervous system, was found in tendinosis. Microdialysis demonstrated significantly higher glutamate levels in chronic painful tendinosis in comparison with pain-free control tendons [41–44]. Significantly, higher lactate levels were found in chronic painful tendinosis in comparison with pain-free normal tendons, implicating either hypoxia or a higher metabolic rate in pathophysiology of tendinosis [45].

Biopsies from the areas with tendinosis and neovascularization followed by immunohistochemical analyses of specimens showed substance P (SP) in the nerves juxtapositioned to the vessels and in the nervi vasorum together with calcitonin gene-related peptide (CGRP) juxtapositioned to the vascular walls [46, 47]. The neurokinin-1 receptor (NK-1R), that is known to have a high affinity for SPP, has been found in the vascular wall [48]. The findings of neuropeptides indicate the presence of a so-called neurogenic inflammation mediated by (SP) – like neuropeptides. The use of diagnostic ultrasound is very helpful in evaluation of tendinosis and

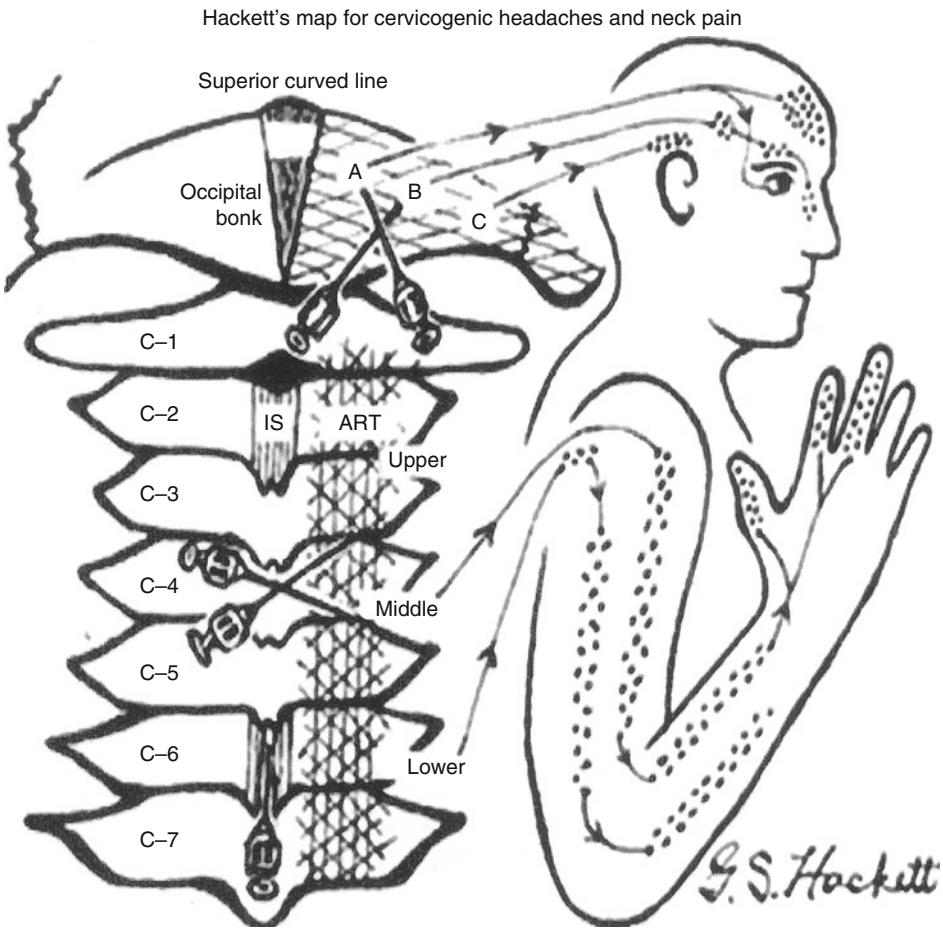

Fig. 81.6 Trigger areas and needle positions for diagnosis and treatment of cervical enthesopathies with small fiber neuropathies and neuralgias with their respective referral pain maps from ligaments and tendons. (*A–C*) Between superior and inferior nuchal lines. *ART* ZJ articular ligaments and periarticular tendons, *IS* Interspinous ligaments (From Hackett [9])

other musculoskeletal pathology and will be described under radiologic evaluation.

Rationale

The rationale for RIT in chronic painful pathology of ligaments and tendons evolved from clinical, experimental, and histological research performed for injection treatment of hydroceles and hernia. In hydroceles, hypertrophied subserous connective tissue layer reinforced capillary walls and prevented further exudate formation. The same principle is employed in the treatment of chronic bursitis. Conversely in hernias, proliferation and subsequent regenerative/reparative response lead to a fibrotic closure of the defect [17–22].

A similar ability to induce a proliferative regenerative repetitive response in ligaments and tendons was demonstrated in experimental and clinical studies, with a 65 % increased diameter of collagen fibers [18, 49–51]. Multiple recent studies demonstrated that injecting polidocanol in to the neovascularity proximal to Achilles, patellar, and supraspinatus tendinosis under color Doppler (CD) ultrasound guidance produced an ultrasound-documented resolution of tendinosis and neovascularity, allowing patients return to a full painless activities. Thus, the sclerosing agent acting directly on neovessels is capable of restoring connective tissue homeostasis by modulation of local hemodynamic [52–55].

Clinical Anatomy in Relation to RIT

The shape of a human body is irregularly tubular. This shape, cross-sectionally and longitudinally, is maintained by continuous compartmentalized fascial stacking that incorporates, interconnects, and supports various ligaments, tendons, muscles, neurovascular, and osseous structures. Collagenous connective tissues, despite slightly different biochemical content, blend at their boundaries and at the osseous

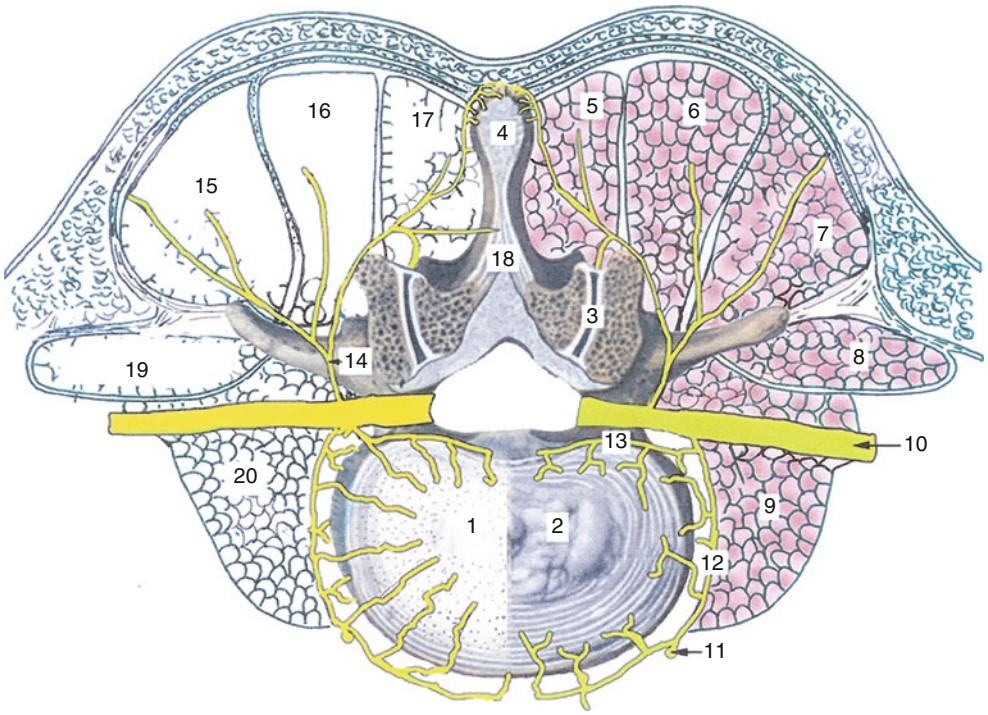

Fig. 81.7 Cross-sectional semi-schematic drawing of lumbar area illustrates *1* vertebral body, *2* intervertebral disc, *3* zygapophyseal joint (*ZJ*), *4* spinous process, *5* multifidus, *6* longissimus thoracis, *7* iliocostalis lumborum, *8* quadratus lumborum, *9* psoas major, *10* ventral ramus, *11* sympathetic trunk, *12* gray ramus communicant, *13* sinuvertebral nerve, *14* dorsal ramus, *15* lateral branch of the dorsal ramus (*LBDR*) in longissimus thoracis compartment, *16* intermediate branch of the dorsal ramus (*IBDR*) in iliocostalis lumborum compartment, *17* medial brunch of the dorsal ramus (*MBDR*) in multifidus compartment, *18* interspinous ligament, *19* quadratus lumborum compartment, and *20* psoas major compartment. MBDR innervates ZJ, multifidi, and interspinous ligaments and forms a several fold increase of the free unmyelinated nerve fibers at the tips of the spinous processes (Modified from Sinelnikov [31]. Modified and prepared for publication by Tracey James. All rights reserved. No part of this picture may be reproduced or transmitted in any form or by any means without written permission from Felix Linetsky M.D.)

structures, functioning as a single unit. This arrangement provides bracing and a hydraulic amplification effect to the muscles, increasing contraction strength up to 30 % (Fig. 81.7) [22, 26, 56–62].

Movements of the extremities, spine, and cranium are achieved through various well-innervated articulations, which are syndesmotic, synovial, and symphysial. For the ease of radiologic evaluation, spinal joints were allocated to the anterior, middle, and posterior columns. Syndesmotic joints are anterior and posterior longitudinal ligaments, anterior and posterior atlantooccipital membranes (ALL and PLL), supraspinous and interspinous ligaments (SSL and ISL), and ligamentum flavum (LF).

Symphysial joints are the intervertebral discs (IVD), which are absent at the cranio-cervical and sacral segments, but present from the sacrococcygeal segments caudally.

Spinal synovial joints are the atlantoaxial (AA), atlantooccipital (AO), zygapophyseal (ZJ), costotransverse (CTJ), and costovertebral (CVJ); sacroiliac (SI) joint is a combined synovial–syndesmotic joint [22, 26, 56, 57].

Differential diagnosis is based on understanding of the regional and segmental anatomy, pathology, as well as segmental, multisegmental, and intersegmental innervation of the compartments and their contents around the spine; this is provided by ventral rami (VR), dorsal rami (DR), gray rami communicants (GRC), sinuvertebral nerves (SVN), and the sympathetic chain (SC) (Fig. 81.7) [22, 26, 56, 57].

Lumbar interspinous ligaments receive innervation from the medial branches of the dorsal rami (MBDR). Three types of nerve terminals in posterior spinal ligaments have been confirmed microscopically. They are the free nerve endings and the Pacini and Ruffini corpuscles. These nerve endings arise from lumbar MB [29]. A sharp increase in the quantity of free nerve endings at the lumbar spinous processes attachments (enthesis) was documented, rendering them putatively nociceptive (Fig. 81.7) [29]. Experimental and empiric observations suggest that a similar arrangement exists at the cervical and thoracic spinous processes, especially at the C2, C7, and T1, rendering them putatively nociceptive (Fig. 81.8) [2, 10, 28, 56]. Willard demonstrated that cervical, thoracic,

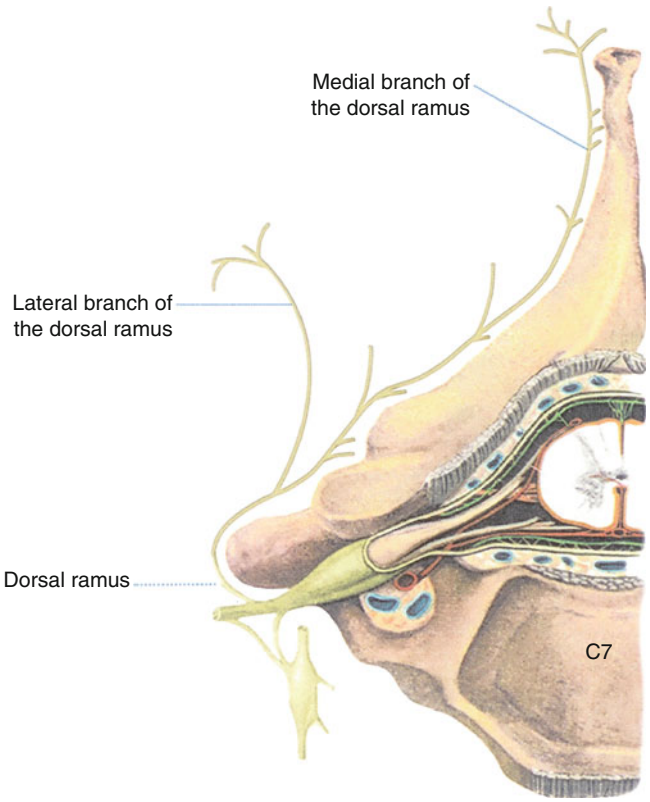

Fig. 81.8 The course of the dorsal ramus proper and its lateral (LBDR) and medial branches (MBDR) represented semi-schematically at the level of C7 (Modified from Sinelnikov [31]. Modified and prepared for publication by Tracey James. All rights reserved. No part of this picture may be reproduced or transmitted in any form or by any means without written permission from Felix Linetsky M.D.)

and lumbar MBs on their distal course are located very close to the bone descending to the very apex of the spinous process, innervating the multifidus and cervical interspinales muscles [28, 56]. A formal recent anatomic study by Zhang et al. reconfirmed these observations in the cervical region [62]. Proximal to the origin, cervical MB is located in the gutter formed by the neighboring ZJ capsules under the semispinalis capitis (SSCa) tendon and supplies twigs to ZJ capsules. Thereafter, MB continues dorsomedially supplying on its course the semispinalis cervices (SSCe) and SSCa. At the mid-lamina level, MB innervates the multifidi and continues adjacent to every spinous process bilaterally below C2 to become a

Thus, MBs do not exclusively supply innervation to the cervical, thoracic, and lumbar ZJ but also to the structures that have enthesis at the spinous processes. This explains the similarity of clinical presentations and the significant overlap of the known pain patterns (Figs. 81.1, 81.2, 81.3, 81.4, 81.5, 81.6, 81.7, and 81.8) [2–4, 10–13, 28, 56, 62].

Current prevailing trends in diagnostic efforts address discogenic, facetogenic, and neurocompressive components of spinal pain. The therapy is directed toward neuromodulation or neuroablation with radiofrequency generators or corticosteroid injections [25]. Example, cervical ZJ is responsible for 54 % of chronic neck pain after whiplash injury; the prevalence may be as high as 65 % [58]. In patients with headaches after whiplash, more than 50 % of the headaches stem from the C2 to C3 z-joint [25, 58]. Intra-articular corticosteroid injections are ineffective in relieving chronic cervical z-joint pain [59]. These statistical data strongly suggest the presence of nociceptors other than ZJ and IVD [22, 25, 58, 59].

Spondyloarthropathies with enthesopathies and muscular, ligamentous, and tendinous pain are rarely, if ever, included in the differential diagnosis or therapeutic plan. The unspoken reasons for this are economical. Major insurance carriers identify the MBDR block as a ZJ block. Any other injections are considered trigger point or ligament injections, and only two ligament or tendon injections or a maximum of three trigger point injections with corticosteroids are reimbursed during the same office visit at a very low rate. The fact that there may be several nociceptors in the same area in the same patient at the same time is disregarded.

The other reason can be explained by the spinal uncertainty principle. In a simple example of two motion segments, the disc, facets, and musculotendinous compartments are 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.

In the majority of cases, RIT can be done without radiologic guidance, taking innervation into account. Therefore, it can afford evaluation of many putative nociceptors from the variety of pain presentations and offers a practical advantage that can be accomplished during the same procedure (Fig. 81.9). The syndromes and conditions treated with RIT are listed in Table 81.1 [11, 17–22, 39, 52–55, 57, 60–84].

Clinical Presentation and Evaluation

The list of syndromes and conditions gives the reader the idea that there is a wide variety of presenting complaints including headaches, neck pain, low back pain, pain between the shoulders, mid-scapular pain, pain mimicking pleurisy or various radiculopathies, thoracolumbar area pain, occipital and suboccipital pain, low back and hip pain, neck and shoulder pain, sharp pain with difficulty breathing, tail bone pain with difficulty seating, and any combination of these symptoms. The intensity, duration, and quality of pain are variable, and the onset may be sudden or gradual. The evaluation may reveal postural abnormalities, functional asymmetries, and combinations of kyphoscoliosis, flattening of cervical

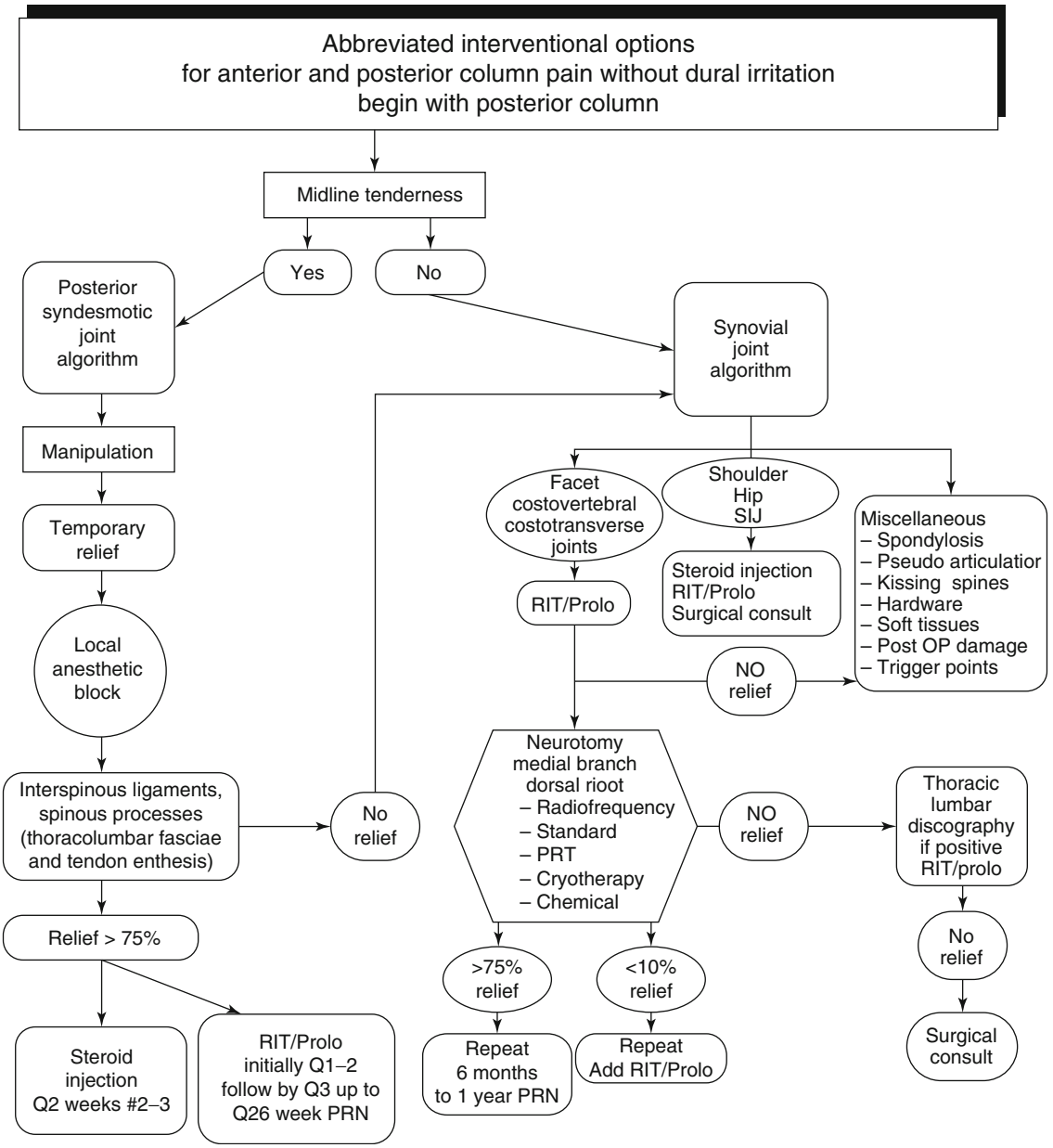

Fig. 81.9 Self-explanatory, modified, abbreviated excerpt from interventional options for spinal and paravertebral pain without dural irritation including large synovial joints (From Linetsky et al. [57])

and lumbar lordosis, and arm or leg length discrepancies. A wide range of increased or restricted passive and active range of motions as well as frank deformities of axial or peripheral joints may be present.

Contractions against resistance usually denote a tendon-related pain, whereas passive attempts to bring a joint to the anatomic range indicate a ligament-related pain. The most reliable, objective clinical finding is tenderness which may be present at the fibro-osseous junction (enthesis) or at the midsubstance of a muscle, ligament, or tendon. Such areas of tenderness are identified and marked and become the subject of ultrasound investigation and eventually needle probing "needling" and local anesthetic block. The needle placement at the areas of maximum tenderness usually reproduces the pain that becomes temporarily worse during infiltration of local anesthetic and usually subsides within 10–15 s after infiltration. Such diagnostic blocks may be performed with or without fluoroscopic or ultrasound guidance. Abolishment or persistence of tenderness and or local or referred pain concludes the clinical examination and becomes the basis for clinical diagnosis (Figs. 81.9 and 81.10) [11, 22, 57, 63–65].

Table 81.1 The syndromes and conditions treated with RIT

Barre–Lieou syndrome	Acromioclavicular sprain/arthrosis
Cervicocranial syndrome (cervicogenic headaches)	Scapulothoracic crepitus
Temporomandibular pain and dysfunction syndrome	Rotator cuff syndrome: supraspinatus, infraspinatus, subscapularis tendinosis, or impingement
Whiplash injury syndrome, spasmodic torticollis	Proximal and distal biceps tendinosis
Cervical and cervicothoracic spinal pain of "unknown" origin	Tennis and golfer's elbow
Cervicobrachial syndrome (shoulder/neck pain)	Baastrup's disease – kissing spine
Snapping scapulae syndrome or scapulothoracic crepitus	Recurrent shoulder dislocations
Hyperextension/hyperflexion injury whiplash syndromes	Myofascial pain syndrome
Cervical, thoracic, and lumbar facet syndromes	Ehlers–Danlos syndrome
Cervical, thoracic, and lumbar sprain/strain	Marie–Strumpell disease
Cervical, thoracic, and lumbar disc syndrome	Internal disc derangement
Slipping rib syndrome	Failed back surgery syndrome
Costotransverse and costovertebral joint arthrosis pain and subluxations	Low back pain syndrome
Sternoclavicular arthrosis and repetitive sprain and subluxations	Iliac crest syndrome
Acromioclavicular arthrosis and instability	Friction rib syndrome
Repetitive thoracic segmental dysfunction	Sacroiliac joint sprain/strain and instability
Costosternal arthrosis/arthritis	Groin pull/sprain/strain
Tietze's syndrome/costochondritis/chondrosis	Coccydynia syndrome
Interchondral arthrosis	Groin sprains
Xiphoidalgia syndrome	Snapping hip syndrome
	Gluteus minimus and medius tendinosis
	Trochanteric tendinosis
	Patellar tendinosis
	Osgood Schlatter disease
	Achilles tendinosis

Radiologic Evaluation Relevant to RIT

Plain Radiographs

Plain radiographs are of limited diagnostic value in painful pathology of the connective tissue, but may indirectly suggest the presence of such pathology by detecting structural or positional osseous abnormalities, like anterior or posterior listhesis on flexion/extension lateral views and degenerative changes in general with deformities of the osseous and articular components such as osteophyte formations in various parts of the skeleton, ectopic calcifications, and improperly healed fractures [66].

Magnetic Resonance Imaging (MRI)

MRI may detect the pathology of intervertebral disc, ligamentous injury, interspinous bursitis, enthesopathy, ZJ disease, SIJ pathology, neural foramina pathology, bone contusion, infection, fracture, or neoplasia. Magnetic resonance imaging may exclude or confirm spinal cord disease and pathology related to extramedullary, intradural, and epidural spaces. MRI detects cartilage abnormality, degenerative tendon and ligament pathology, tendinosis, joint effusions, bursitis, soft tissue edema, hematoma, ligament tendon and muscle rupture, and vascular abnormalities [66, 67].

Computed Tomography Scans (CT)

CT scan may detect small avulsion fractures of facets, laminar fracture, fracture of vertebral bodies and pedicles, and neoplastic or degenerative changes in the axial or appendicular skeleton [66].

Bone Scan

Bone scans are useful in assessing entire skeleton to evaluate for metabolically active disease processes [66].

Diagnostic Ultrasound

Gray scale (GS) ultrasound can detect in real time joint effusions, bursitis, cystic formations, synovial hypertrophy, cartilage abnormality, muscle atrophy, attenuation or partial

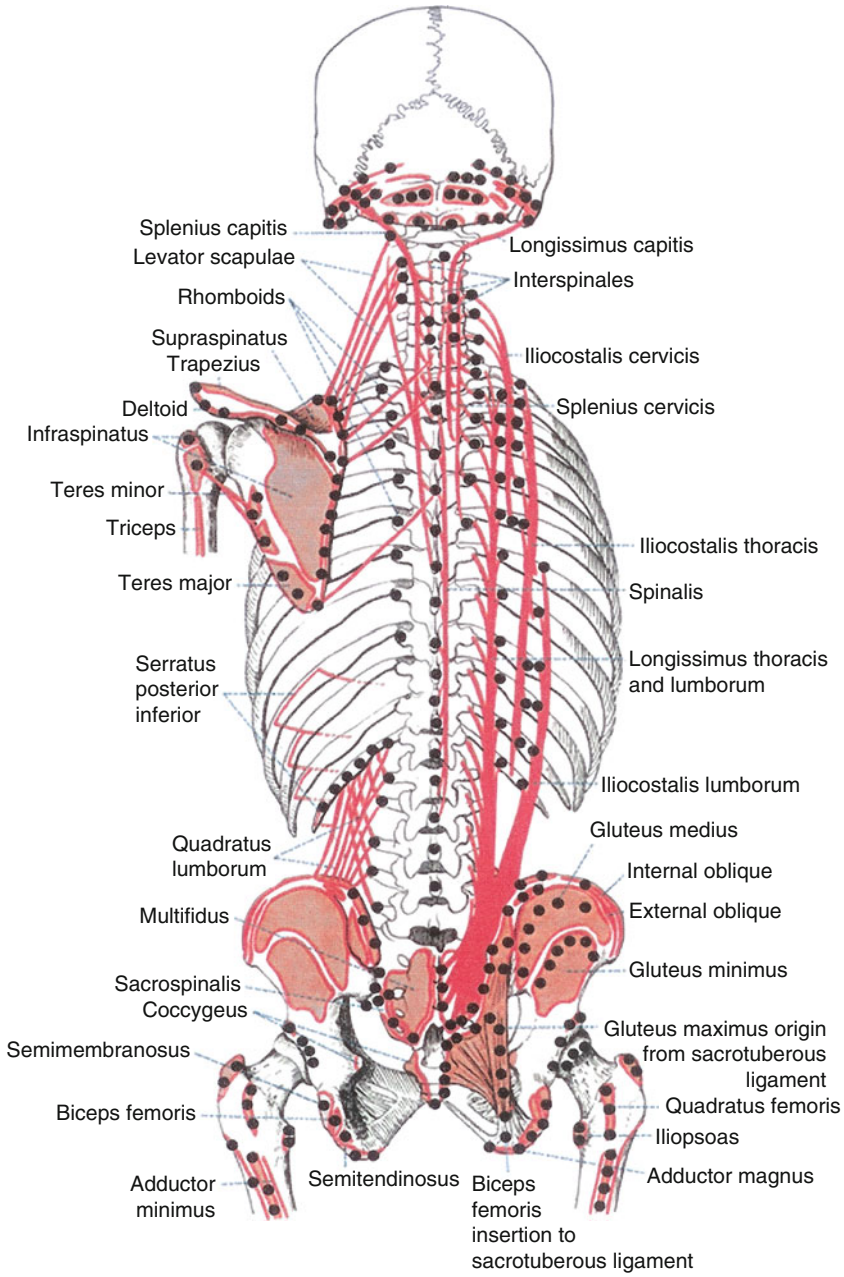

Fig. 81.10 Schematic drawing demonstrating sites of tendon origins and insertions (enthesis) of the paravertebral musculature in the cervical, thoracic, lumbar, and pelvic regions with parts of the upper and lower extremities. Clinically significant enthesopathies with small fiber neuropathies and neuralgias are common at the locations identified by *dots*. *Dots* also represent most common locations of needle insertion and RIT injections (Note: Not all of the locations are treated in each patient) (Modified from Sinelnikov [31]. Modified and prepared for publication by Tracey James. All rights reserved. No part of this picture may be reproduced or transmitted in any form or by any means without written permission from Felix Linetsky M.D.)

disruptions of ligaments, tendons or muscles, ectopic calcifications, tendon enlargement, inhomogeneity in tendinosis, and nerve hypertrophy like in carpal tunnel syndrome. Nerve and tendon subluxations or impingements are evaluated with dynamic ultrasound. GS ultrasound provides real-time needle guidance during various diagnostic or therapeutic injections including aspirations, nerve blocks, and percutaneous needle tenotomy. Ultrasound is becoming a more useful tool in the assessment of myofascial and osseous pain sources because it allows a dynamic pattern recognition as well as direct evaluation and patterning in superficial collagenous structures. Ultrasound is now a preferred method to evaluate rotator cuff pathology in the office setting and is gaining popularity in knee joint evaluation prior to arthroscopy.

The color Doppler (CD) ultrasound can detect neovascularities to be injected, when present, in tendinosis or synovitis and delineate positions of large vessels and nerves to be avoided during injections [52–55, 68, 69]. Unless the practitioner is very experienced in MSK, ultrasound correlations with plain radiographs, MRI, CT scans, and palpation are highly advisable. There are a multitude of weekend courses in musculoskeletal ultrasound; the industry is promoting the methodology, but the high quality hands on supervised training is not yet available at the academic institutions for the practicing physicians. Gaining a supervised high-quality experience takes time.

Solutions for Injections

Local anesthetics are an important component of the solutions used for RIT and were described under the heading of *Local Anesthetics in the Diagnosis of Musculoskeletal Pain*. When contemporary local anesthetics are combined with hyperosmolar injectates, they provide long-lasting diagnostic/therapeutic blocks, and the reasons for this scientifically proven effect will be described below.

Five types of injectates are used for RIT, and they are:

1. Osmotic shock agents such as hypertonic dextrose, glycerin, or distilled water
2. Chemical irritants such as phenol
3. Chemotactic sclerosing agents such as sodium morrhuate, Sotradecol, or polidocanol
4. Particulates such as pumice suspension
5. Biologic agents such as whole blood, platelet-rich plasma (PRP), autologous conditioned serum (ACS), platelet-poor plasma (PPP), adipose-derived and bone marrow aspirate concentrates with their mesenchymal and hematopoietic biocellular components, and isolated and cultured mesenchymal stem cells

The injectates in groups 1–4 have been used as a single agent in various concentrations or in various combinations with other chemical agents, and their concentrations are mixed with local anesthetics, by the virtue of being injected into connective tissue, all of them become irritants [57, 60, 61, 63–65, 71–74]. Injectates in group 5 are also used as a single injectate agent in various concentrations or in various combinations of the agents and their concentrations.

Experimental studies demonstrated that any solution with osmolality greater than a 1,000 mOsm/l is *neurolytic*, causing separation of the myelin lamellae in myelinated nerve fibers and total destruction in unmyelinated fibers, after soaking for 1 h in solutions with osmolality greater than 1,000 mOsm/l or a distilled water. Hypoosmolar solutions produce a reversible conduction block of rabbit vagus nerve and potentiate the local anesthetics. C fibers showed evidence of axonal damage characterized by accumulation of macrophages and proliferation of Schwann cells. Osmotic fragility of axons is similar to that of erythrocytes after exposure to 0.4 and 0.5 dilutions of normal saline. When administered intrathecally, local anesthetics are more effective in hypobaric solution than in hyperbaric solution [85–88]. In humans, intrathecal hypertonic saline produced good results in chronic intractable pain and is currently used in epidurolysis of adhesions [17, 89–91]. Hypertonic/hyperosmolar dextrose has been successfully used for treatment of enthesopathies with small fiber neuropathies, spondyloarthropathies, and internal disc derangements [1, 11, 17, 19–22, 57, 73, 74].

Pharmacologic *properties of phenol*, *glycerin*, *and hypertonic dextrose are both neurolytic and inflammatory*. Various concentrations of water- and glycerin-based phenol solutions have been used to treat pain. The literature suggests that perineural phenol glycerin combinations produce a better regenerative/reparative response; these experimental findings support the use of phenol glycerin or phenol glycerin dextrose solutions in treatment of axial and peripheral enthesopathies with small fiber neuropathies and neuralgias [92–102].

Neurolytic intra-articular injections of a 10 % aqueous phenol, diluted to 5 % with omnipaque or omniscan contrast and local anesthetic, are used in the Pain Management Department of Mayo Clinic to facilitate nursing care in severely debilitated patients [103].

Diluted 5 % phenol in 50 % glycerin solution is used for the treatment of spinal enthesopathies and injections at donor harvest sites of the iliac crest for neurolytic and regenerative/reparative responses. Prior to injection, 1 ml of this solution is mixed with 4 ml of local anesthetic 1,086 mOsm/l [63, 64]. The most common solutions contain lidocaine/dextrose mixtures in various concentrations. Lidocaine is available in 0.5–2 %; dextrose is available in a 50 % concentration.

To achieve a 10 % dextrose concentration, dilution is made with lidocaine in 4:1 proportions (i.e., 4 ml of 1 % lidocaine is mixed with 1 ml of 50 % dextrose) and will produce a 0.8 % lidocaine with osmolality of 555 mOsm/l (*hyperosmolar block*).

To achieve a 12.5 % dextrose concentration, dilution is made with lidocaine in 3:1 proportions (i.e., 3 ml of 1 % lidocaine mixed with 1 ml of 50 % dextrose) and will produce a 0.75 % lidocaine with osmolality of 694 mOsm/l (*hyperosmolar block*).

To achieve a 20 % dextrose concentration, dilution is made with lidocaine in 3:2 proportion (i.e., 3 ml of 1 % lidocaine mixed with 2 ml of 50 % dextrose) and will produce a 0.6 % lidocaine with osmolality of 1,110 mOsm/l (*hyperosmolar neurolytic block*). In two studies, this solution produced a 50 % reduction in low back pain lasting for 2 years.

A 1:1 dilution makes a 25 % dextrose concentration with 0.5 lidocaine solution with osmolality of 1,388 mOsm/l (*hyperosmolar neurolytic block*). In two studies, this solution was used for intradiscal injections.

Dextrose/phenol/glycerin (DPG) solution is referred to as DPG or P2G and contains dextrose and glycerin in equal 25 % amounts, 2.5 % phenol and water. Prior to injection, DPG is diluted in concentrations of 1:2 = 1,368 mOsm/l, 1:1 = 2,052 mOsm/l, or 2:3 = 1,641 mOsm/l with a local anesthetic.

When dextrose-containing solutions are not controlling pain and dysfunction, progression to stronger solutions such as sodium morrhuate, Sotradecol, or polidocanol has been used in various dilutions up to a full strength.

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

This is very well tolerated in selective patients with rheumatoid arthritis or ankylosing spondyloarthropathies, personal observation of the senior author.

Sotradecol® (sodium tetradecyl sulfate injection) is a sterile nonpyrogenic solution for intravenous use as a sclerosing agent. Three percent (30 mg/ml) with 2 % benzyl alcohol: Each mL contains sodium tetradecyl sulfate 30 mg and benzyl alcohol 20 mg. It can be used interchangeably with sodium morrhuate; clinical results are similar, but there is a lesser possibility of allergic reactions.

Polidocanol is a nonionic detergent, containing a polar hydrophilic (dodecyl alcohol) and an apolar hydrophobic (polyethylene oxide) chain as active ingredients. On March 31, 2010, the US Food and Drug Administration (FDA) approved polidocanol injection for the treatment of small varicose veins. Polidocanol is a local anesthetic and antipruritic component of ointments and bath additives. The substance is also used as a sclerosant, an irritant injected to treat varicose veins. Professor Alfredson has extensively used 1 % polidocanol in 1–2 ml increments for the treatment of tendinosis [52–55].

Pumice suspension: Pumice is a substance of volcanic origin consisting chiefly of complex silicates of aluminum, potassium, and sodium. Pumice is insoluble in water and is not attacked by acids or alkali solutions. It is used in this preparation as a material irritant to stimulate the fibrosing process. Extra fine grade is defined as one that passes a 325 mesh sieve at 84 % or more, and only a trace is retained by a 200 mesh sieve:

- Pumice (extra fine grade) – 1.0 g.
- Glycerin – 5.0 ml.
- Polysorbate 80–0.09 ml (2 standard drops).
- Preservatives q.s.
- Lidocaine 1–2 % q.s. ad 100 cc.
- Place in a multidose bottle, sterilize, and shake well before use.

Two to three milliliter of this suspension is drawn in a 10-ml syringe mixed with dextrose formula of a choice or alone. Drawing in to the syringe should be done through the same gage needle that will be used for injection. Suspension was developed by Dr. Gedney for injections of sacroiliac ligaments to stabilize SI and lumbosacral joints [19–22].

Biocellular autografts include whole blood, platelet-rich plasma (PRP), autologous conditioned serum (ACS), platelet-poor plasma (PPP), and adipose- and bone marrow-derived aspirate concentrates with mesenchymal and hematopoietic components [104–109]. Widely popularized and accepted in recent years, these autografts are composed of three ingredients used separately or together:

1. PRP or ACS provides platelet concentrates with cytokines and growth factors.
2. Autologous fat cells provide a living collagen bioscaffold with its intrinsic stromal vascular tissue transferred in the form of a graft or a lyophilized collagen in the form of an injectate which may be utilized as a cellular bioscaffold matrix.
3. Lipoaspirates or adipose tissue plus/minus bone marrow aspirate concentrate provides stromal vascular fraction with supporting mesenchymal stem cells.

PRP is a platelet concentrate of four- to eight-fold above baseline levels that contain signal proteins, platelet-derived growth factors, chemokines, and cytokines that control inflammatory cascade. Autologous conditioned serum (ACS or ACP) contains platelet concentrations of two to three-fold baseline levels, and whole blood contains platelet levels at baseline. It remains a point of debate in the literature which autograft provides a superior collagen growth. It may depend on the structure to be regenerated which level of chemokine and cytokine concentration or MSC concentration or pure scaffold regeneration proves most helpful.

PRP is a reach source of important signal proteins (cytokines) and a variety of growth factors (GF) critical to initiation and maintenance of the entire inflammatory cascade in vivo. Many studies have shown the effectiveness of these GFs in healing.

Bone marrows concentrate with or without supporting matrix releases chemokines and cytokines. Growth factors are known to be a major player in vascular remodeling. The platelets in a bone marrow concentrate upon activation secrete stromal-derived factor (SDF-1). This supports primary adhesion and migration of progenitor cells to the site of injury. Bone marrow stroma contains plastic adherent cells (colony-forming unit fibroblast, CFU-F) that can give rise to a broad spectrum of fully differentiated connective tissues [105–107].

Adipose-derived mesenchymal stem cells (AD-MSCs) also contribute to the growth factor load through direct secretion of growth factors (autocrine amplification system), such as vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), IGF-2, and hepatocyte growth factor. Additional benefits of adipose tissue comparing to bone marrow are greater concentration of mesenchymal stem cells, ready availability, ease and rapidity of harvesting, lower morbidity, and diminished cost. In addition, adipose tissues possess properties which serve as an ideal living bioscaffold or matrix [106, 107].

PRP concentrates are obtained by venous blood draw of 20–120 cc. Centrifugation produces the buffy coat fraction. Various manufacturers utilize proprietary techniques to remove the neutrophils with the intent of maintaining the monocyte fraction along with the platelet fraction of spun cells. The amount of cytotoxicity of neutrophils in vivo is currently a point of contention in the literature. It is therefore up to the practitioner to decide if they wish to manufacture platelet concentrates via a two spin centrifugation technique or utilize a proprietary solution on the market [108, 109].

Bone marrow aspirates are obtained via 12-ga. multiport aspiration needle with a stylet placed within the iliac crest or other appropriate marrow cavity, and 60–120 cc of marrow is aspirated in small aliquots obtained from multiple positions within the marrow cavity. This gives variable numbers of

CD34+ cells in a matrix of total nucleated cells. The total number of cells is based on the aspiration and centrifugation technique. Manufacturer and independent tests are available to measure cell counts [105].

Lipoaspirates, or autologous fat grafting (AFG), are used extensively in aesthetic and reconstructive surgery over the past 20 years. A closed syringe system (Tulip Medical) and cell-friendly microcannulas allow a safe and effective harvest of volumes ranging from 10 to 20 cc. Combined with thrombin-activated PRP, this injectate is accurately placed by guided ultrasonography into damaged muscular, tenoligamentous, and cartilaginous tissue [107].

Practical note: The physician should examine the state and federal laws of their respective practice location to determine what level of cellular processing is permissible under current law.

Isolated and Expanded Stem Cells

Mesenchymal stem cells (MSCs), also known as marrow stromal cells, derive from mesodermal tissues and are pluripotent adult stem cells with therapeutic potential in regenerative medicine [110–116]. It has been shown recently that MSCs are a heterogeneous population of similar cells rather than one distinct cell type [117]. As a result, outside of the ability to select cells via adhesion culture and a handful of hallmark surface markers, there is still no uniformly accepted definition of an MSC [118].

As stated above, MSCs can be easily isolated from many different tissues, including a whole bone marrow aspirate, marrow mobilized whole blood, muscle biopsy, adipose liposuction aspirate, and other tissues [110]. As a rule, the closer the graft source to the treated tissue, the more efficient are the MSCs to differentiate into to the treated tissue type. For example, Vidal compared equine MSCs derived from the bone marrow to ones derived from adipose tissue for their chondrogenic potential and found that bone marrow MSCs produced a more hyaline-like matrix and had improved glycosaminoglycan production [119]. Animal studies demonstrated that bone marrow MSC produced better repair of a tibial osteochondral defect when compared to adipose MSCs [120]. Yoshimura determined that MSCs derived from the synovial tissue of the knee (closest to the target tissue of cartilage defect) produced a better chondrogenesis than bone marrow MSCs [121].

MSC Culture Expansion

A limited amount of cells can be obtained from any tissue. In many instances, the number that can be harvested from the source tissue is less than the quantity of cells needed for tissue repair. One method to obtain larger numbers of cells is to culture them. A delicate balance exists between length of time in culture (which produces more cells) and adverse consequences to the cells (such as genetic transformation).

MSCs are usually expanded in a culture via monolayer. MSCs are placed into a specialized flask and allowed to attach to a plastic surface and fed with a nutrient broth. Because MSCs are contact inhibited, they will grow on this surface until they become confluent at which point they abruptly stop growing. To keep MSCs proliferating in culture, when the colonies are near confluence, the nonadherent cells in the media are discarded and an enzyme is used to detach the MSCs from the plastic surface. The MSCs are then replated in a similar flask, and fresh media is added. Most MSCs are grown in culture for 11–17 days, because some studies have shown decreased differentiation if MSCs are grown for prolonged periods in culture with a higher chance of genetic mutation [122–125].

How Do the MSCs Affect Tissue Repair?

Animal studies have demonstrated the multipotency of MSCs and their ability to differentiate into muscle, bone, cartilage, tendon, and various cells of internal organs. However, these cells also act via paracrine mechanisms to assist in tissue repair. In this context, paracrine is defined as the production of certain growth factors and cytokines by the MSCs which can assist in tissue repair [126].

Donor Versus Autologous MSC Sources

Obviously, autologous stem cells do not have the risk of communicable disease transmission as donor allogeneic cells. However, there are reasons why donor cells are attractive. For example, some studies have shown a decreased differentiation potential for MSCs obtained from older patients [127]. In addition, somatic genetic variants (i.e., trisomy V and VII) have been demonstrated in the MSCs and osteoprogenitors of some patients with osteoarthritis [128].

Use of MSC in Musculoskeltal Diathesis

MSCs have been used in animal and early clinical studies to repair meniscal tissue, cartilage, and intervertebral discs. Izuta et al. demonstrated meniscus repair after MSCs transplant on a fibrin matrix [129]. Horie reported that synovial-derived MSCs after injection into massive rat meniscus tears were able to differentiate and repair meniscal tissue [130]. Yamasaki et al. repopulated devitalized meniscus with MSCs and demonstrated biomechanical properties approximating the normal meniscus [131].

The earliest models of cartilage repair used autologous, cultured chondrocytes [132]; others used MSCs because MSCs have shown innate cartilage repair properties through both differentiation and paracrine signaling [133]. In these studies, an osteochondral defect (OCD) was created, and the MSCs were implanted into the lesion, often in a hydrogel or other carrier or at times through local adherence [134–137]. Partial to robust healing of the OCD takes place over weeks to months [110]. The cartilage produced by these cells was very much like native hyaline cartilage, but subtle differences have been observed [138].

Traditional spinal surgery on degenerated intervertebral discs (IVDs) continues to show disappointing results [139–141]. Conversely, animal studies have shown robust repair of acutely injured IVDs [142–148]. For example, Sakai et al. have published animal models whereby MSCs are combined with atelocollagen and achieved disc repair with improvements in hydration, height, and disc morphology demonstrated on MRI [149]. Richardson et al. and Risbud et al. investigating the coculturing of MSCs with cells from the nucleus pulposus (NP) demonstrated that this technique can produce partially differentiated cells that are capable of repopulating the NP in an animal model [150, 151]. Finally, Miyamoto et al. recently demonstrated that intra-discal transplantation of synovial-derived MSCs prevented disc degeneration through suppression of catabolic genes and perhaps proteoglycan production [152].

Biocellular injectates such as whole blood and PRP are extremely irritating immediately upon injection. Regional pain blocks have therefore become an important adjunct in the treatment paradigm with biocellular autografts. If used with inadequate or improperly placed local anesthesia, even under US guidance, these agents produce overwhelming non-localized deep somatic pain lasting for up to 10 min which subsides to a tolerable level after about 30 min and which follows a typical primary, secondary, and tertiary curve for collagen maturation with the pain levels inherent therein. Thus, pain subsides over the secondary cellular maturation time frame of 6–8 weeks resulting in a pain-free state. Intra-articular hip injections of PRP with or without bioscaffold, in the presence of significant degenerative changes, when used with local anesthesia under US guidance produce a significant pain that subsides to a preinjection level in about 2 weeks.

Clinical Effectiveness

Multiple publications on RIT include randomized trials [63, 72, 75–77, 153], non-randomized publications, and prospective and retrospective clinical studies as well as case reports [65, 78] and systematic reviews [78]. In one of the systematic reviews of prolotherapy injections for chronic low back pain, Yelland et al. [78] included four randomized high-quality trials with a total of 344 patients. Two of these four studies [72, 76] demonstrated significant differences between the treatment and control group. However, Yelland et al. [78] could not pooled their results because in the study of Ongley et al. [76], manipulation allegedly confounded independent evaluation of results. And in the other study by Kline et al., there was no significant difference in mean pain and disability scores between the groups [72]. The third study was demonstrated no improvement in either group [77]. The fourth study was the earlier one of Yelland et al. reporting only mean pain and disability scores of 40 patients in each group [75] showed no difference between groups. But in each group, there was more than 50 % improvement maintained for more than 2 years. Therefore, Yelland et al.'s [75] study clearly demonstrated that relatively large volumes of normal saline injected in the low back ligaments are therapeutic and are not a placebo. The conclusions of this systematic review were confusing and unrealistic such as that there was conflicting evidence regarding the efficacy of prolotherapy injections in reducing pain and disability in patients with chronic low back pain or that in the presence of co-interventions, prolotherapy injections were more effective than controlled injections, more so when both injections and co-interventions were controlled concurrently.

Another controlled trial is eliminated from the systematic review because it could not be pooled by Wilkinson [63] who demonstrated that when specific diagnosis is applied, the positive results approach 89 %. There is substantial evidence from non-randomized prospective and retrospective studies as well as case reports that cannot be discussed here due to a limited size of this publication [17–22, 65]. Similar results were demonstrated by Alfredson et al. in peripheral tendinosis [52–55] and Topol et al. in groin strains [79–83].

The growing use of biologic agents deserves a special attention. The clinical translation of MSCs from the lab to the bedside is already taking place; Centeno et al. published early case studies in which positive MRI changes were observed in knees and hip joints after MSC injections [143–145]. They have also noted that the complication rate of expanded MSC injection procedures is no greater than other needle-based interventional techniques [146]. Their submitted publication data on 339 patients demonstrated a safety profile better than surgical techniques such as total knee arthroplasty. They have recently submitted for publication a large case series of 250 knee and hip osteoarthritis patients treated with percutaneous injection of MSCs. Prior to MSC injections, two-thirds of the knee patients were total knee arthroplasty (TKA) candidates, only 6 % of the patients opted for TKA after the injections; additionally, both treated groups reported better relief than an untreated comparative group.

Other authors have described similar safety profiles using more invasive surgical implant techniques. Wakatani published an 11-year prospective study of 45 knees (in 41

patients) treated with autologous bone marrow-derived MSCs, with results indicating both safety and efficacy [147]. Nejadnik recently described a comparison between surgically implanted chondrocytes versus MSCs placed by needle in 72 knees [153]. The MSC-treated knees demonstrated good safety, less donor site morbidity, and better efficacy when compared with an autologous chondrocyte implantation procedure. Haleem has noted that autologous, cultured bone marrow MSCs reimplanted into articular cartilage defects in platelet-rich fibrin demonstrated evidence of healed cartilage in some patients [148].

While very little has been published on intervertebral disc repair in humans, some clinical data is available. Yoshikawa recently published on two patients who were treated with surgically implanted MSCs that showed less vacuum phenomenon on follow-up imaging [142]. The only other human data of which we are aware is produced by Centeno's group from 2005 to 2010, under IRB supervision and now being prepared for publication (unpublished data). Replicating the Sakai study [149] wherein cultured MSCs were placed into the disc produced little measureable results, their experience was similar. However, a third case series performed with changes in culture, injection technique, and diagnostic criteria (changed from degenerative disc disease DDD to chronic disc bulge with lumbar radiculopathy). The last model showed encouraging clinical and imaging results. Presented literature, especially newer publications, does offer convincing evidence of RIT efficacy in carefully selected patients, when specific diagnostic entities are treated and strict diagnostic criteria and injection techniques are applied [52–55, 63, 78–84, 142–148].

Mechanism of Action of Chemical Injectates

Based on literature review [11, 12, 17–22, 49–55, 57, 63–65, 71–104] and the above described pharmacologic properties of the injectates, current understanding of the mechanism of action is complex and multifaceted. Obviously, *phenol- and glycerin*-containing solutions, depending on concentration, produce *temporary neurolysis or neuromodulation* of peripheral nociceptors and provide modulation of antidromic, orthodromic, sympathetic, and axon reflex transmissions. Modulation of sympathetic transmission via nervi vasorum leads to modulation of local hemodynamics in tendons, ligaments, and bone; this in turn decreases blood pressure which leads to pain reduction. Hyper-/hypoosmolar injectates provide the same initial action; purple discoloration of the skin is frequently observed after injection of several adjacent interspinous ligaments.

Conversely, sclerosants act initially on modulation of hemodynamics with subsequent regression of neoneurogenesis. When sclerosant was deposited into pathologic neovascularities ventral to Achilles tendon, restoration of normal longitudinal microcirculation was documented by power Doppler. Chemomodulation of collagen through inflammatory, proliferative, and regenerative/reparative response is induced by the chemical and pharmacologic properties of all injectates and mediated by cytokines and multiple growth factors.

A relatively large volume of osmotically inert or active injectate assumes the role of a space-occupying lesion in a relatively tight, slowly equilibrating, extracellular compartment of the connective tissue. Inert injectates are also used to disrupt adhesions that have been created by the original inflammatory attempts to heal the injury or for hydrodissection of fibrotic bands.

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.

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. Cellular and extracellular matrix damage induced by mechanical transection with the needle stimulates inflammatory cascade, governing release of growth factors [11, 12, 17–22, 49–55, 57, 63–65, 71–104].

Indications for regenerative injection therapy are listed in Table 81.2. General contraindications are those that are applicable to all of the injection techniques. A list of general contraindications is presented in Table 81.3.

Vertebral and Paravertebral Injection Sites and Techniques

Any innervated structure is a potential pain generator. The same nerve usually supplies several structures; therefore, there is a significant overlap of all known pain maps (Figs. 81.1, 81.2, 81.3, 81.4, 81.5, and 81.6). The main question is, "How to navigate in this sea of unknown?" For the purpose of RIT, the following step by step approach is implemented. Patients' "pain and tenderness" is accepted for face value without dismissal or allocation to a distant "proven" source. The *knowledge of clinical anatomy*, *pain patterns*, *and pathology guiding the clinical investigation* is based on clinical experiments of many researchers over decades. Diagnostic ultrasound may reveal tendinosis and neovascularities in the tender areas.

Tenderness over posterior column structures is an objective finding, especially in the midline, as is the rebound tenderness in any abdominal quadrant [17, 22, 57, 63–65, 104]. The tender areas are identified by palpation and marked.

Table 81.2 Indications for regenerative injection therapy

Cervicogenic headaches	Osteoarthritis, osteoarthrosis/arthritis, spondylolysis, osteochondrosis and spondylolisthesis
Unhealed fractures, pseudoarthrosis	Rheumatoid arthritis with osteoarthritis
Chronic enthesopathies, tendinosis or ligamentosis with small fiber neuropathies and neuralgias after sprains/strains or overuse occupational and postural conditions known as repetitive motion disorders (RMD)	Peripheral nerve and tendon entrapments
Small unhealed painful intersubstance ruptures of muscles ligaments and tendons	Osgood Schlatter disease
Internal disc derangement (cervical, thoracic, lumbar)	Postsurgical cervical, thoracic, and low back pain (with or without instrumentation)
Painful hypermobility and instability of the axial and peripheral joints due to capsular laxity	Other posterior column sources of nociception refractory to steroid injections, nonsteroidal anti-inflammatory therapy (NSAID), and radiofrequency procedures
Vertebral compression fractures exerting stress on adjacent joints and soft tissue	Enhancement of manipulative treatment and physiotherapy

Table 81.3 Contraindications for regenerative injection therapy

General contraindications	Specific contraindications
Allergy to anesthetic solutions	Acute arthritis (septic, gout, rheumatoid, or posttraumatic with hemarthrosis)
Bacterial infection, systemic or localized to the region to be injected	Acute bursitis or tendonitis
Bleeding diathesis secondary to disease or anticoagulants	Acute non-reduced subluxations, dislocations, or fractures
Fear of the procedure or needle phobia	Allergy to injectable solutions or their ingredients such as dextrose (corn), sodium morrhuate (fish), or phenol
Neoplastic lesions involving the musculature and osseous structures	
Recent onset of a progressive neurological deficit including but not limited to severe intractable cephalgia, unilaterally dilated pupil, bladder dysfunction, bowel incontinence, etc.	
Requests for large quantity of sedation and/or narcotics before and after treatment	
Severe exacerbation of pain or lack of improvement after local anesthetic blocks	

Confirmation is obtained by needle tapping the bone and local anesthetic block of the tissue at the enthesis keeping the innervation in perspective.

Using palpable landmarks for guidance, experienced practitioners have been safely injecting, with or without fluoroscopic guidance, the following posterior column elements innervated by the dorsal rami: tendons and ligaments enthesis at the spinous process, lamina, posterior ZJ capsule, and thoracolumbar fascia insertions at the transverse process.

Theoretically, 0.5 % lidocaine solution is an effective, initial diagnostic option for pain arising from posterior column elements when utilized in increments of 0.5–1.0 ml injected after each bone contact; in practice, hyperosmolar lidocaine/dextrose in 4:2 or 3:2 dilution is used initially blocking the structures innervated by terminal filaments of the MB with the sequence as follows:

Step A: In the presence of midline pain and tenderness, enthesis of ligaments and tendons at the spinous process are blocked initially in the midline at the previously marked level(s).

Step B: The blocked area is reexamined about 1 min after each injection for tenderness and movements that provoked pain.

If tenderness remains at the lateral aspects of the spinous processes, injections are carried out to the lateral aspects of their apices, thus continuing on the course of medial branches or dorsal rami. Step B is repeated.

Persistence of paramedial pain is calling for investigative blocks of ZJ capsules (cervical, thoracic, and lumbar) and costotransverse joints. Step B is repeated.

Perseverance of lateral tenderness dictates investigation of the structures innervated by the lateral branches of the dorsal rami, such as the enthesis of iliocostalis or serratus posterior superior/inferior at the ribs, the ventral sheath of thoracolumbar fascia at the lateral aspects of the lumbar transverse processes, or at the iliac crests. Step B is repeated. In this fashion, all potential nociceptors on the course of MB and LB are investigated from their periphery toward their origins. Thus, the differential diagnosis of pain arising from vertebral and paravertebral structures innervated by MB and LB is made based on the results of the

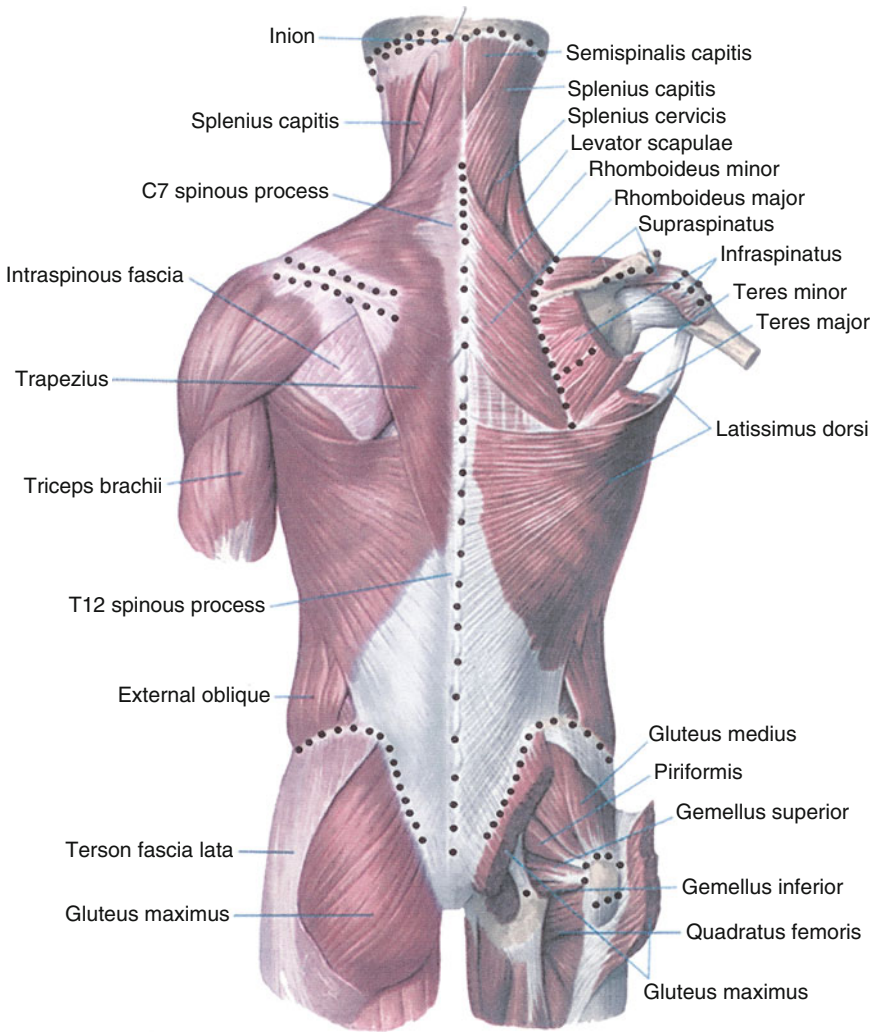

Fig. 81.11 Drawing demonstrating sites of tendon origins and insertions (enthesis) of the paravertebral musculature in the cervical, thoracic, lumbar, and pelvic regions with parts of the upper and lower extremities. Clinically significant enthesopathies with small fiber neuropathies and neuralgias are common at the locations identified by *dots*. *Dots* also represent most common locations of needle insertion and RIT injections (Note: Not all of the locations are treated in each patient) (Modified from Sinelnikov [31]. Modified and prepared for publication by Tracey James. All rights reserved. No part of this picture may be reproduced or transmitted in any form or by any means without written permission from Felix Linetsky M.D.)

blocks (Figs. 81.9, 81.10, and 81.11). Manipulation under local anesthesia can be performed after anesthetic has taken effect, and the musculature is sufficiently relaxed [154]. Pain from the upper cervical synovial joints presents a diagnostic and a therapeutic challenge; therefore, it is a diagnosis of exclusion.

The possibility of serious complications dictates that all intra-articular injections of the axial synovial joints, specifically atlantoaxial and atlantooccipital, ZJ, costovertebral, and intervertebral discs, should be performed only under fluoroscopic guidance by an experienced practitioner [3, 4, 14–16, 25, 58–61, 73, 74]. Conversely, the intra-articular injections of SJ joint are grossly overemphasized [39, 51, 57, 63, 64, 72]. This was recently proven again by Murakami et al. [155].

Most commonly injected sites of painful spinal enthesopathies of the posterior column are innervated by the medial (MB) and lateral (LB) branches of the dorsal rami:

- Enthesis of ligaments and tendons at the superior, inferior, and lateral surfaces especially at the apex of the spinous processes
- Enthesis at the occipital bone at and between inferior and superior nuchal lines
- Enthesis at the thoracic and lumbar transverse processes
- Capsular ligaments and periarticular enthesis at the cervical thoracic and lumbar ZJs
- Costotransverse joints and capsules
- Tendons and ligaments at the posteromedial, superior, inferior, and lateral surfaces of the iliac crests and spines
- Posterior tubercles and angles of the ribs

Multiple other common peripheral enthesopathies are depicted in Figs. 81.10 and 81.11 and described below:

- Proximal and distal portions of the clavicle specifically superior acromioclavicular (AC) ligament and AC joint, sternoclavicular (SC) ligament and joint, etc.
- Greater and lesser humeral tuberosities and medial and lateral epicondyles
- Sternum, xiphoid, and anterior ribs
- Pubic tubercles, superior and inferior rami, and ischial spines, tuberosities, and rami
- Greater and lesser femoral trochanters and medial and lateral femoral epicondyles

Side Effects and Complications of RIT

Several types of statistically rare complications occur with regenerative injection therapy [156]. The most recent statistical data on complications came from a survey of 171 physicians providing RIT in 2006 [157].

Responders to the survey had been providing this treatment for a median of 10 years and described treating a median of 500 patients each, giving a median of 2,000 injections each.

The following complications were reported: 164 spinal headaches, 123 pneumothoraxes, 73 temporary systemic reactions, and 54 temporary nerve damage. Sixty-nine adverse events required hospitalization, among them 46 patients with a pneumothorax and none with the spinal headache. Five cases of permanent nerve damage were reported. Only three surveyors included information on the specific injury: one case of mild to moderate leg pain, one case of persistent numbness in a small area of the gluteal region, and one case of persistent numbness in the quadriceps region [157]. These findings were similar to an earlier survey by Dorman of 450 physicians performing RIT/prolotherapy [158]. At that time, 120 respondents revealed that 495,000 patients received injections. Among them, 29 instances of pneumothorax were reported, two of them requiring chest tube placement. Also, 24 of non-life-threatening allergic reactions were reported [158].

Stipulating that each patient had at least three visits and during each visit received at least ten injections, the occurrence of pneumothorax requiring a chest tube was 1 per 247,500 injections. Thus, self-limited pneumothoraxes were 1 per 18,333, and allergic reactions were 1 per 20,625 injections [158].

In the 1960s, five cases of postinjection arachnoiditis were reported [159]. Two were fatal; one was a direct sequence of arachnoiditis and another was a sequence of incompetent shunt and persistent hydrocephalus with increased intracranial pressure. Of the other three cases, the first one with mild paraparesis recovered after a ventriculojugular shunt. The second recovered spontaneously with a mild neurological deficit, and the third patient remained paraplegic.

Three other cases of intrathecal injections known to the first author have not been reported in the literature because of medicolegal issues. Two of them resulted in paraplegia. The first occurred after injection at the thoracic level and the second after a lumbar injection. The third case was performed by an untrained person who injected zinc sulfate solution, which is hardly used in today's practice, at the cranio-cervical level, resulting in immediate onset of severe neurologic deficit, quadriplegia, and subsequent hydrocephalus. One case of self-limiting sterile meningitis after lumbosacral sclerosing injections was reported in 1994. Adjacent endplate fractures associated with intradiscal dextrose injections were recently reported [160].

Postspinal puncture headaches have been reported after lumbosacral injections. Two such cases occurred in the first author's practice during the past 20 years. Both patients recovered after 1 week with bed rest and fluids.

Overall, pneumothorax is the most commonly reported complication. Injections of anterior thoracic synovial joints, such as sternoclavicular, costosternal, and interchondral, may also result in pneumothorax.

Conclusions

Double-blind, placebo-controlled, and retrospective studies clearly indicate the effectiveness of RIT in painful degenerative posttraumatic conditions of fibrous connective tissue.

Literature suggests that degenerative cascade is a multietiologic disease process. NSAIDs and steroid preparations have limited use in chronic painful overuse conditions and degenerative painful conditions of ligaments and tendons. Microinterventional regenerative techniques and proper rehabilitation up to 1 year supported with mild opioid analgesics are more appropriate.

Cervical thoracic and lumbar discogenic pain continues to be a therapeutic challenge. Encouraging positive results were published after regenerative injections for lumbar discogenic pain with dextrose-based solutions, methylene blue, and mesenchymal stem cells. The work in this direction continues. It appears that cervical and thoracic discogenic pain may be addressed similarly in the near future.

The future is such that, instead of indirect stimulation of growth factors through inflammatory cascade, specific growth factors or their combinations may be available. The challenge will continue to determining which specific growth factors should be used. The other viable possibility is injection of engineered, type-specific tissue derived from stem-cell research [83, 84, 154]. Some variations of nanotechnology will be also added.

As stated by the late Professor Mooney, "The ideas of regeneration and controlled proliferation are slowly moving from the fringe to the frontier of medical care" [161]. A physician versatile in diagnostic and therapeutic injection techniques may have ample opportunity to implement RIT in the treatment of chronic musculoskeletal pain. More information regarding RIT can be found on linetskymd.com and aarom.org. Full texts of many original articles text books and chapters are available on these websites. The individual training with CME credits is available by the American Academy of Regenerative Orthopedic Medicine (AAROM) at Drs. Linetsky, Centeno, Crane, and Hirsch offices.

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References

1. Linetsky F, Willard F. Use of regenerative injection therapy for low back pain. Pain Clin. 1999;1:27–31.
2. Feinstein B, Langton J, Jameson R, et al. Experiments on pain referred from deep somatic tissues. J Bone Joint Surg Am. 1954;36A:981–96.
3. Dwyer A, Aprill C, Bogduk N. Cervical zygapophyseal joint pain patterns: a clinical evaluation. Spine. 1990;15:458–61.
4. Dreyfuss P, Michaelsen M, Fletcher D. Atlanto-occipital and lateral atlanto-axial joint pain patterns. Spine. 1994;19:1125–31.
5. Dussault RG, Kaplan PA. Facet joint injection: diagnosis and therapy. Appl Radiol. 1994;23:35–39.
6. Fukui S, Ohseto K, Shiotani M. Patterns of pain induced by distending the thoracic zygapophyseal joints. Reg Anesth Pain Med. 1997;22(4):332–336. http://dx.doi.org/10.1016/S1098-7339(97)80007-7
7. Kellgren JH. Observations on referred pain arising from muscle. Clin Sci. 1939;4:35–46.
8. Mooney V, Robertson J. The facet syndrome. Clin Orthop Relat Res. 1976;115:149–156.
9. Hackett G. Ligament and tendon relaxation treated by prolotherapy. 3rd ed. Springfield: Charles C. Thomas; 1958.
10. Kellgren J. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. Somatic Pain. 1939;4:35–46.
11. Hackett G, Hemwall G, Montgomery G. Ligament and tendon relaxation: treated by prolotherapy. 5th ed. Springfield: Charles C. Thomas; 1991.
12. Simons DG, Travell JG, Simons LS. Myofascial pain and dysfunction: the trigger point manual, vol. 1. Baltimore: Williams & Wilkins; 1991.
13. Bonica J, Loeser J, Chapman C, et al. The management of pain. vol I, 2nd ed. Malvern: Lea & Febiger; 1990; 7:136–139.
14. Dreyfuss P, Tibiletti C, Dreyer S. Thoracic zygapophyseal joint pain patterns: a study in normal volunteers. Spine. 1994;19:807–11.
15. Dussault RG, Kaplan PA, Anderson MW. Fluoroscopy-guided sacroiliac joint injections. Radiology. 2000;214(1):273–7.
16. O'Neill C, Kurgansky M, Derby R, et al. Disc stimulation and patterns of referred pain. Spine. 2002;27:2776–81.
17. Linetsky F, Trescot A, Manchikanti L. Regenerative injection therapy. In: Manchikanti L, Singh V, editors. Interventional techniques in chronic non-spinal pain. Paducah: ASIPP Publishing; 2009. p. 87–98.
18. Biegeleisen H. Varicose veins, related diseases, and sclerotherapy: a guide for practitioners. Fountain Valley: Eden Press; 1994.
19. Linetsky F, Mikulinsky A, Gorfine L. Regenerative injection therapy: history of application in pain management: part I 1930s–1950s. Pain Clin. 2000;2:8–13.
20. Linetsky F, Botwin K, Gorfine L, et al. Position paper of the Florida Academy of Pain Medicine on regenerative injection therapy: effectiveness and appropriate usage. Pain Clin. 2002;4:38–45.
21. Linetsky F, Saberski L, Miguel R, et al. A history of the applications of regenerative injection therapy in pain management: part II 1960s–1980s. Pain Clin. 2001;3:32–6.
22. Linetsky F, Derby R, Saberski L, et al. Pain management with regenerative injection therapy (RIT). In: Boswell M, Cole E, editors. Weiner's Pain management: a practical guide for clinicians. 7th ed. Boca Raton: CRC Press; 2006. p. 939–66.
23. Steindler A, Luck J. Differential diagnosis of pain low in the back: allocation of the source of pain by the procaine hydrochloride method. JAMA. 1938;110:106–13.
24. Haldeman K, Soto-Hall R. The diagnosis and treatment of sacroiliac conditions by the injection of procaine (Novocain). J Bone Joint Surg Am. 1938;3:675–85.
25. Bogduk N. Post-traumatic cervical and lumbar spine zygapophyseal joint pain. In: Evans RW, editor. Neurology and trauma. Philadelphia: WB Saunders; 1996. p. 363–75.
26. Williams P. Gray's anatomy, 38th British edition. Philadelphia: Churchill Livingston, Pearson Professional Limited; 1995.
27. Best T. Basic science of soft tissue. In: Delee J, Drez D, editors. Orthopedic sports medicine principles and practice, vol. 1. Philadelphia: WB Saunders; 1994.
28. Willard F. Gross anatomy of the cervical and thoracic regions: understanding connective tissue stockings and their contents. Presented at the 20th American Association of Orthopedic Medicine annual conference and scientific seminar; a common sense approach to "hidden" pain generators, Orlando, 2003.
29. Yahia H, Newman N. A light and electron microscopic study of spinal ligament innervation. Z Mikrosk Anat Forsch. 1989; 102:664–74.
30. Leadbetter W. Cell-matrix response in tendon injury. Clin Sports Med. 1992;11:533–78.
31. Sinelnikov RD. Atlas of anatomy, vol. 1. Moscow: Meditsina; 1972.
32. Leadbetter W. Anti-inflammatory therapy and sport injury: the role of non-steroidal drugs and corticosteroid injections. Clin Sports Med. 1995;14:353–410.
33. Jozsa L, Kannus P. Human tendons, anatomy, physiology, and pathology. Champaign: Human Kinetics; 1997.
34. Cotran R, Vinay K, Collins T, et al. Robbins pathologic basis of disease. Philadelphia: WB Saunders; 1999.
35. Freemont A. Nerve ingrowth into diseased intervertebral disc in chronic back pain. Lancet. 1997;350:178–81.
36. Ashton I, Ashton B, Gibson S, et al. Morphological basis for back pain: the demonstration of nerve fibers and neuropeptides in the lumbar facet joint capsule but not in the ligamentum flavum. J Orthop Res. 1992;10:72–8.
37. Tuzlukov P, Skuba N, Gorbatovskaya N. The morphological characteristics of fibromyalgia syndrome. Arkh Patol. 1993;4:47–50.
38. Nirschl R, Pettrone F. Tennis elbow. The surgical treatment of lateral epicondylitis. J Bone Joint Surg Am. 1979;61(6A):832–9.
39. Fortin J, Vilensky J, Merkel GJ. Can the sacroiliac joint cause sciatica? Pain Physician. 2003;6(3):269–71.
40. Khan KM, Cook JL, Taunton JE, Bonar F. Overuse tendinosis, not tendinitis part 1: a new paradigm for a difficult clinical problem. Phys Sportsmed. 2000;28(5):38–48.
41. Alfredson H, Thorsen K, Lorentzon R. In situ microdialysis in tendon tissue: high levels of glutamate, but not prostaglandin E2 in chronic Achilles tendon pain. Knee Surg Sports Traumatol Arthrosc. 1999;7:378–81.
42. Alfredson H, Ljung BO, Thorsen K, Lorentzon R. In vivo investigation of ECRB tendons with microdialysis technique: no signs of inflammation but high amounts of glutamate in tennis elbow. Acta Orthop Scand. 2000;71(5):475–9.
43. Alfredson H, Forsgren S, Thorsen K, Lorentzon R. In vivo microdialysis and immunohistochemical analyses of tendon tissue demonstrated high amounts of free glutamate and glutamate NMDAR1 receptors, but no signs of inflammation, in Jumper's knee. J Orthop Res. 2001;19:881–6.
44. Alfredson H, Forsgren S, Thorsen K, Fahlström M, Johansson H, Lorentzon R. Glutamate NMDAR1 receptors localised to nerves in human Achilles tendons. Implications for treatment? Knee Surg Sports Traumatol Arthrosc. 2000;9:123–6.
45. Alfredson H, Bjur D, Thorsen K, Lorentzon R. High intratendinous lactate levels in painful chronic Achilles tendinosis. An investigation using microdialysis technique. J Orthop Res. 2002; 20:934–8.
46. Bjur D, Alfredson H, Forsgren S. The innervation pattern of the human Achilles tendon: studies of the normal and tendinosis tendon with markers for general and sensory innervation. Cell Tissue Res. 2005;320(1):201–6. Epub 2005 Feb 9.

47. Ljung BO, Forsgren S, Fridén J. Substance-P and Calcitonin gene-related peptide expression at the extensor carpi radialis brevis muscle origin: implications for the aetiology of tennis elbow? J Orthop Res. 1999;17(4):554–9.
48. Ljung BO, Alfredson H, Forsgren S. Neurokinin 1-receptors and sensory neuropeptides in tendon insertions at the medial and lateral epicondyles of the humerus. Studies on tennis elbow and medial epicodylalgia. J Orthop Res. 2004;22:321–7.
49. Liu Y, Tipton C, Matthes R, et al. An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. Connect Tissue Res. 1983;11:95–102.
50. Maynard J, Pedrini V, Pedrini-Mille A, et al. Morphological and biochemical effects of sodium morrhuate on tendons. J Orthop Res. 1985;3:234–48.
51. Klein R, Dorman T, Johnson C. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measurements of lumbar spine mobility before and after treatment. J Neurol Ortho Med Surg. 1989;10:2.
52. Öhberg L, Alfredson H. Ultrasound guided sclerosis of neovessels in painful chronic Achilles tendinosis: pilot study of a new treatment. Br J Sports Med. 2002;36:173–7.
53. Alfredson H, Ohberg L. Neovascularisation in chronic painful patellar tendinosis – promising results after sclerosing neovessels outside the tendon challenge the need for surgery. Knee Surg Sports Traumatol Arthrosc. 2005;13(2):74–80. Epub 2004 Nov 26.
54. Alfredson H, Öhberg L. Sclerosing injections to areas of neovascularisation reduce pain in chronic Achilles tendinopathy: a double-blind randomized controlled trial. Knee Surg Sports Traumatol Arthrosc. 2005;13(4):338–44. Epub 2005 Feb 2. PMID:15688235.
55. Alfredson H, Harstad H, Haugen S, Ohberg L. Sclerosing polidocanol injections to treat chronic painful shoulder impingement syndrome-results of a two-centre collaborative pilot study. Knee Surg Sports Traumatol Arthrosc. 2006;14(12):1321–6. Epub 2006 Oct 7.
56. Willard F. The muscular, ligamentous and neural structure of the low back and its relation to back pain. In: Vleeming A et al., editors. Movement stability and low back pain. New York: Churchill Livingston; 1997. p. 1–35.
57. Linetsky F, Parris W, et al. Regenerative injection therapy. In: Manchikanti L, editor. Low back pain. Paducah: ASIPP Publishing; 2002. p. 519–20.
58. Lord S. Chronic cervical zygapophyseal joint pain after whiplash: a placebo-controlled prevalence study. Spine. 1996;21:1737–45.
59. Barnsley L, Lord S, Walis B, et al. Lack of effect of intra-articular corticosteroids for chronic pain in the cervical zygapophyseal joints. N Engl J Med. 1994;330:1047–50.
60. O'Neill C. Intra-articular dextrose/glucosamine injections for cervical facet syndrome, atlanto-occipital and atlanto-axial joint pain, combined ISIS AAOM approach. Presented at the 20th AAOM annual conference and scientific seminar, Orlando, April 30–May 3, 2003.
61. Stanton-Hicks M. Cervicocranial syndrome: treatment of atlanto-occipital and atlanto-axial joint pain with phenol/glycerin injections. Presented at the 20th AAOM annual conference and scientific seminar, Orlando, April 30–May 3, 2003.
62. Zhang J, Tsuzuki N, Hirabayashi S, et al. Surgical anatomy of the nerves and muscles in the posterior cervical spine. A guide for avoiding inadvertent nerve injuries during the posterior approach. Spine. 2003;28:1379–84.
63. Wilkinson H. Injection therapy for enthesopathies causing axial spine pain and the "failed back syndrome": a single blinded, randomized and cross-over study. Pain Physician. 2005;8:167–74.
64. Wilkinson H. The failed back syndrome etiology and therapy. 2nd ed. New York: Springer; 1992.
65. Kayfetz D, Blumenthal L, Hackett G, et al. Whiplash injury and other ligamentous headache: its management with prolotherapy. Headache. 1963;3:1.
66. Resnick D. Diagnosis of bone and joint disorders, volumes 1–6. 3rd ed. Philadelphia: WB Saunders; 1995.
67. Stark D, Bradley W. Magnetic resonance imaging, volumes 1 and 2. 3rd ed. St. Louis: Mosby; 1999.
68. European Society of Musculoskeletal Radiology. http://www.southstaffordshirepct.nhs.uk/policies/clinical/Clin55_DiagnosticUltrasoundProcedures.pdf. Approved 27 Apr 2009. http://www.essr.org/html/img/pool/shoulder.pdf; http://www.essr.org/html/img/pool/elbow.pdf; http://radiology.rsna.org/content/252/1/157.full.pdf.
69. McNally E. Ultrasound of the small joints of the hands and feet: current status. Skeletal Radiol. 2008;37(2):99–113. Epub 2007 Aug 22.
70. Linetsky F, Stanton Hicks M, O'Neil C. Prolotherapy. In: Wallace M, Staats P, editors. Pain medicine & management – just the facts. New York: McGraw-Hill; 2004. p. 318–24.
71. Linetsky F, Saberski L, Dubin J, et al. Letter to the editor. Re: Yelland MJ, Glasziou PP, Bogduk N, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized study. Spine, 2003; 29:9–16. Spine. Spine. 2004;29(16):1840–1; author reply 1842–3.
72. Klein R, DeLong W, Mooney V, et al. A randomized, double-blind trial of dextrose-glycerin-phenol injections for chronic, low back pain. J Spinal Disord. 1993;6:23–33.
73. Miller M. Treatment of painful advanced internal lumbar disc derangement with intradiscal injection of hypertonic dextrose. Pain Physician. 2006;9(2):115–21.
74. Klein R, O'Neill C, Mooney V, et al. Biochemical injection treatment for discogenic low back pain: a pilot study. Spine J. 2003; 3(3):220–6.
75. Yelland M, Glasziou P, Bogduk N, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. Spine. 2004;29:9–16.
76. Ongley M, Klein R, Dorman T, et al. A new approach to the treatment of chronic low back pain. Lancet. 1987;2:143–6.
77. Dechow E, Davies R, Carr A, et al. A randomized, double-blind, placebo controlled trial of sclerosing injections in patients with chronic low back pain. Rheumatology. 1999;38:1255–9.
78. Yelland M, Yeo M, Schluter P. Prolotherapy injections for chronic low back pain – results of a pilot comparative study. Australas Musculoskelet Med. 2000;5:20–3.
79. Yelland M, et al. Prolotherapy injections for chronic low back pain: a systematic review. Spine. 2004;19:2126–33.
80. Kon E. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc. 2010;18(4):472–9.
81. Mishra A, et al. Platelet-rich plasma compared with corticosteroid injection for chronic lateral elbow tendinosis. P M R. 2009;1(4):366–70.
82. Topol G, et al. Efficacy of dextrose prolotherapy in elite make kicking-sport athletes with chronic groin pain. Arch Phys Med Rehabil. 2005;86(4):697–702.
83. Topol G, Reeves K. Regenerative injection of elite athletes with career-altering chronic groin pain who fail conservative treatment: a consecutive case series. Am J Phys Med Rehabil. 2008;87:890–902.
84. Kon E, et al. Platelet-rich plasma: new clinical application: a pilot study for treatment of jumper's knee. Injury. 2009;40(6):598–603.
85. Robertson J. Structural alterations in nerve fibers produced by hypotonic and hypertonic solutions. J Biophys Biochem Cytol. 1958;4:349–64.
86. Jewett D, Kind J. Conduction block of monkey dorsal rootlets by water and hypertonic saline solutions. Exp Neurol. 1971;33:225.
87. Barsa et al. Functional and structural changes in the rabbit vagus nerve in vivo following exposure to various hypoosmotic solutions. Anesth Analg. 1982;61(11):912–6.
88. Fink et al. Osmotic swelling effects on neural conduction. Anesthesiology. 1979;51(5):418–23.
89. Hitchcock E, Prandini MN. Hypertonic saline in management of intractable pain. Lancet. 1973;1(7798):310–2.

90. Racz GB, Heavner JE, Trescot A. Percutaneous lysis of epidural adhesions – evidence for safety and efficacy. Pain Pract. 2008; 8(4):277–86. Epub 2008 May 23.
91. Westerlund T, et al. The endoneurial response to neurolytic agents is highly dependent on the mode of application. Reg Anesth Pain Med. 1999;24(4):294–302.
92. Westerlund T, Vuorinen V, Roytta M. The effect of combined neurolytic blocking agent 5 % phenol -glycerol in rat sciatic nerve. Acta Neuropathol (Berl). 2003;106:261–70.
93. Bodine-Fowler SC, Allsing S, Botte MJ. Time course of muscle atrophy and recovery following a phenol-induced nerve block. Muscle Nerve. 1996;19:497–504.
94. Birch M, Strong N, Brittain P, et al. Retrobulbar phenol injection in blind painful eyes. Ann Ophthalmol. 1993;257:267–70.
95. Garland DE, Lilling M, Keenan MA. Percutaneous phenol blocks to motor points of spastic forearm muscles in head-injured adults. Arch Phys Med Rehabil. 1984;65:243–5.
96. Viel E, Pellas F, Ripart J, et al. Peripheral neurolytic blocks and spasticity. Ann Fr Anesth Reanim. 2005;24:667–72.
97. Raj P. Practical management of pain. 3rd ed. St. Louis: Mosby Inc.; 2000.
98. Zafonte RD, Munin MC. Phenol and alcohol blocks for the treatment of spasticity. Phys Med Rehabil Clin N Am. 2001;12:817–32.
99. Kirvela O, Nieminen S. Treatment of painful neuromas with neurolytic blockade. Pain. 1990;41:161–5.
100. Wilkinson HA. Trigeminal nerve peripheral branch phenol/glycerol injections for tic douloureux. J Neurosurg. 1999;90:828–32.
101. Robertson D. Transsacral neurolytic nerve block. An alternative approach to intractable perineal pain. Br J Anaesth. 1983;559:873–5.
102. Trescot A. HansenH. Neurolytic agents: pharmacology and clinical applications. In: Manchikanti L, Singh V, editors. Interventional techniques in chronic non-spinal pain. Paducah: ASIPP Publishing; 2009. p. 53–8.
103. Lamer T. Neurolytic peripheral joint injections in severely debilitated patients. Presented at the annual meeting of the Florida Academy of Pain Medicine, Orlando, 30 July 2005.
104. Broadhurst N, Wilk V. Vertebral mid-line pain: pain arising from the interspinous spaces. J Orthop Med. 1996;18:2–4.
105. Kevy S, Jacobson M. Point of care concentration and clinical application of autologous bone marrow derived stem cells. Presented at the Orthopedic Research Society, 52nd annual meeting. 19–22 March 2006.
106. Aust L, Devlin B, Foster S. Yield of human adipose-derived adult stem cells from lipoaspirates. Cytotherapy. 2004;6:7–14.
107. Alexander R. Use of PRP in autologous fat grafting. In: Shiffman M, editor. Autologous fat grafting. Berlin: Springer; 2010. p. 140–67.
108. Crane D, Everts P. Platelet rich plasma matrix grafts. Pract Pain Manag. 2008;8:12–26. http://www.prolotherapy.com/PPM_JanFeb2008_Crane_PRP.pdf
109. Everts P, Knape J, Weibrich G, et al. Platelet-rich plasma and platelet gel: a review. J Extra Corpor Technol. 2006;38:174–87.
110. Alhadlaq A, Mao JJ. Mesenchymal stem cells: isolation and therapeutics. Stem Cells Dev. 2004;13(4):436–48.
111. Barry FP. Mesenchymal stem cell therapy in joint disease. Novartis Found Symp. 2003;249:86–96; discussion 96–102, 170–4, 239–41.
112. Bruder SP, Fink DJ, Caplan AI. Mesenchymal stem cells in bone development, bone repair, and skeletal regeneration therapy. J Cell Biochem. 1994;56(3):283–94.
113. Cha J, Falanga V. Stem cells in cutaneous wound healing. Clin Dermatol. 2007;25(1):73–8.
114. Gangji V, Toungouz M, Hauzeur JP. Stem cell therapy for osteonecrosis of the femoral head. Expert Opin Biol Ther. 2005;5(4):437–42.
115. Becker AJ, Mc CE, Till JE. Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells. Nature. 1963;197:452–4.
116. Friedenstein AJ, et al. Precursors for fibroblasts in different populations of hematopoietic cells as detected by the in vitro colony assay method. Exp Hematol. 1974;2(2):83–92.
117. Zhou Z, et al. Comparative study on various subpopulations in mesenchymal stem cells of adult bone marrow. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2005;13(1):54–8.
118. Schauwer CD, et al. Markers of stemness in equine mesenchymal stem cells: a plea for uniformity. Theriogenology. 2011;75(8):1431–43. Epub 2010 Dec 31.
119. Vidal MA, et al. Comparison of chondrogenic potential in equine mesenchymal stromal cells derived from adipose tissue and bone marrow. Vet Surg. 2008;37(8):713–24.
120. Niemeyer P, et al. Comparison of mesenchymal stem cells from bone marrow and adipose tissue for bone regeneration in a critical size defect of the sheep tibia and the influence of platelet-rich plasma. Biomaterials. 2010;31(13):3572–9.
121. Yoshimura H, et al. Comparison of rat mesenchymal stem cells derived from bone marrow, synovium, periosteum, adipose tissue, and muscle. Cell Tissue Res. 2007;327(3):449–62.
122. Frisbie DD, et al. Evaluation of adipose-derived stromal vascular fraction or bone marrow-derived mesenchymal stem cells for treatment of osteoarthritis. J Orthop Res. 2009;27(12):1675–80.
123. Banfi A, et al. Proliferation kinetics and differentiation potential of ex vivo expanded human bone marrow stromal cells: Implications for their use in cell therapy. Exp Hematol. 2000;28(6): 707–15.
124. Crisostomo PR, et al. High passage number of stem cells adversely affects stem cell activation and myocardial protection. Shock. 2006;26(6):575–80.
125. Izadpanah R, et al. Long-term in vitro expansion alters the biology of adult mesenchymal stem cells. Cancer Res. 2008;68(11): 4229–38.
126. Ladage D, et al. Mesenchymal stem cells induce endothelial activation via paracine mechanisms. Endothelium. 2007;14(2): 53–63.
127. Zhou S, et al. Age-related intrinsic changes in human bone-marrow-derived mesenchymal stem cells and their differentiation to osteoblasts. Aging Cell. 2008;7(3):335–43.
128. Broberg K, et al. Polyclonal expansion of cells with trisomy 7 in synovia from patients with osteoarthritis. Cytogenet Cell Genet. 1998;83(1–2):30–4.
129. Izuta Y, et al. Meniscal repair using bone marrow-derived mesenchymal stem cells: experimental study using green fluorescent protein transgenic rats. Knee. 2005;12(3):217–23.
130. Horie M, et al. Intra-articular Injected synovial stem cells differentiate into meniscal cells directly and promote meniscal regeneration without mobilization to distant organs in rat massive meniscal defect. Stem Cells. 2009;27(4):878–87.
131. Yamasaki T, et al. Meniscal regeneration using tissue engineering with a scaffold derived from a rat meniscus and mesenchymal stromal cells derived from rat bone marrow. J Biomed Mater Res A. 2005;75(1):23–30.
132. Brittberg M, et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med. 1994;331(14):889–95.
133. Caplan AI. Mesenchymal stem cells. J Orthop Res. 1991; 9(5):641–50.
134. Angele P, et al. Engineering of osteochondral tissue with bone marrow mesenchymal progenitor cells in a derivatized hyaluronan-gelatin composite sponge. Tissue Eng. 1999;5(6):545–54.
135. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. Instr Course Lect. 1998;47:487–504.
136. Johnstone B, Yoo JU. Autologous mesenchymal progenitor cells in articular cartilage repair. Clin Orthop Relat Res. 1999; 367(Suppl):S156–62.

137. Minas T, Nehrer S. Current concepts in the treatment of articular cartilage defects. Orthopedics. 1997;20(6):525–38.
138. Katakai D. Compressive properties of cartilage-like tissues repaired in vivo with scaffold-free, tissue engineered constructs. Clin Biomech (Bristol, Avon). 2009;24(1):110–6.
139. Fritzell P, Hagg O, Nordwall A. Complications in lumbar fusion surgery for chronic low back pain: comparison of three surgical techniques used in a prospective randomized study. A report from the Swedish Lumbar Spine Study Group. Eur Spine J. 2003; 12(2):178–89.
140. Deyo RA. Lumbar spinal fusion. A cohort study of complications, reoperations, and resource use in the Medicare population. Spine. 1993;18(11):463–70.
141. Elias WJ, et al. Complications of posterior lumbar interbody fusion when using a titanium threaded cage device. J Neurosurg. 2000;93(1 Suppl):45–52.
142. Yoshikawa T. Disc regeneration therapy using marrow mesenchymal cell transplantation: a report of two case studies. Spine (Phila Pa 1976). 2010;35(11):E475–80.
143. Centeno CJ, et al. Regeneration of meniscus cartilage in a knee treated with percutaneously implanted autologous mesenchymal stem cells. Med Hypotheses. 2008;71(6):900–8.
144. Centeno CJ, et al. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. Pain Physician. 2008;11(3):343–53.
145. Centeno CJ, et al. Partial regeneration of the human hip via autologous bone marrow nucleated cell transfer: a case study. Pain Physician. 2006;9(3):253–6.
146. Centeno CJ, et al. Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. Curr Stem Cell Res Ther. 2010;5(1):81–93.
147. Wakitani S, et al. Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. J Tissue Eng Regen Med. 2011;5(2):146–50.
148. Haleem AM, et al. The clinical use of human culture-expanded autologous bone marrow mesenchymal stem cells transplanted on platelet-rich fibrin glue in the treatment of articular cartilage defects: a pilot study and preliminary results. Cartilage. 2010;1(4):253–61.
149. Sakai D, et al. Transplantation of mesenchymal stem cells embedded in Atelocollagen gel to the intervertebral disc: a potential therapeutic model for disc degeneration. Biomaterials. 2003;24(20):3531–41.
150. Richardson SM, et al. Intervertebral disc cell mediated mesenchymal stem cell differentiation. Stem Cells. 2006;24(3):707–16.
151. Risbud MV, et al. Differentiation of mesenchymal stem cells towards a nucleus pulposus-like phenotype in vitro: implications for cell-based transplantation therapy. Spine. 2004;29(23): 2627–32.
152. Miyamoto T, et al. Intradiscal transplantation of synovial mesenchymal stem cells prevents intervertebral disc degeneration through suppression of matrix metalloproteinase-related genes in nucleus pulposus cells in rabbits. Arthritis Res Ther. 2010; 12(6):R206.
153. Nejadnik H, et al. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. Am J Sports Med. 2010;38(6): 1110–6.
154. Dreyfuss P, Michaelsen M, Horne M. MUJA: manipulation under joint anesthesia/analgesia: a treatment approach for recalcitrant low back pain of synovial joint origin. J Manipulative Physiol Ther. 1995;18:537–46.
155. Murakami E, et al. Effect of periarticular and intraarticular lidocaine injections for sacroiliac joint pain: prospective comparative study. J Orthop Sci. 2007;12(3):274–80.
156. Peng B, Pang X, Wu Y, et al. A randomized placebo-controlled trial of intradiscal ethylene blue injection for the treatment of chronic discogenic low back pain. Pain. 2010;149(1):124–9.
157. Dagenais S, Ogunseitan O, Haldeman S, et al. Side effects and adverse events related to intraligamentous injections of sclerosing solutions (prolotherapy) for back and neck pain: a survey of practitioners. Arch Phys Med Rehabil. 2006;87:909–13.
158. Dorman T. Prolotherapy: a survey. J Orthop Med. 1993;15: 49–50.
159. Keplinger J, Bucy P. Paraplegia from treatment with sclerosing agents. JAMA. 1960;173:1333–5.
160. Whitworth M. Endplate fracture associated with intradiscal dextrose injection. Pain Physician. 2002;5:379–84.
161. Mooney V. Prolotherapy at the fringe of medical care, or is it the frontier? Spine J. 2003;3:253–4.