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Prolotherapy: Basic Science, Clinical Studies, and Technique

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Prolotherapy (growth factor or growth factor stimulation injection) raises growth factor levels or effectiveness to promote tissue repair or growth. Growth factors are complex proteins (polypeptides), and their beneficial effects on human ligament, tendon, cartilage, and bone are under intense investigation. Prolotherapy may utilize inflammatory or noninflammatory mechanisms.

NORMAL TENDON AND LIGAMENT HEALING

To understand prolotherapy, a knowledge of the pathology of sprain or strain and the normal healing process is necessary. Sprains (ligaments) and strains (tendons) become chronic when healing does not result in sufficient tensile strength or tightness.[14,50] This condition also is termed *connective tissue insufficiency* (CTI), in which the structure is either too loose or has insufficient tensile strength.[33] Load bearing in CTI stimulates pain mechanoreceptors.[33] Biedert et al. reported that "as long as connective tissue remains functionally insufficient, the pain mechanoreceptors can continue to malfunction."[4] Recent studies show that in chronic pain of soft-tissue origin the pathologic lesion is degenerative rather than inflammatory.[3,33] Therefore, *tendinosis* is a more appropriate description of this tissue state than *tendinitis*.[3,33]

Abnormal ligaments and tendons relate directly to myofascial pain because mechanoreceptors also trigger twitch contractions,[4] which may explain the taut bands observed in myofascial pain. Individual fiber bundles correspond to tight portions of the muscle belly.

Significant sprain or strain results in cell damage, which in turn triggers an inflammatory healing cascade and the appearance of monocytes within hours, fibroblast proliferation and migration within 48 hours, procollagen deposition within one week, and maturation of procollagen to collagen by 8 weeks.[6] In the maturation phase water is lost, causing constriction of the tendon and tightening and allowing for both thickening and tightening of weak or loose ligament, tendon, or joint capsules. After injury, growth factors are elevated enough to stimulate growth only for a matter of days. Thereafter, healing is dependent on maturation of immature repair tissue.

If laxity or tensile strength deficit is not corrected sufficiently to stop pain mechanoreceptor stimulation, a chronic sprain or strain results. Without further stimulation by growth factors, sufficient repair cannot take place. In repetitive trauma, each individual trauma may be insufficient to provide a proliferation stimulus, so that even minor injury may be enough to accumulate damage to the point of initiating chronic pain. Prolotherapy raises the level of growth factors to resume or initiate a repair sequence that has prematurely aborted or never started. Cells in the area of exposure, such as chondrocytes or osteocytes in osteoarthritis (OA), also can be expected to respond if the growth factors are those that proliferate such cells.

The Role of Growth Factors

Growth factors are powerful, hormone-like proteins produced by peripheral cells. Examples include insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor (TGF), bone morphogenetic proteins (BMPs), nerve growth factor (NGF), and hepatocyte growth factor (HGF).[60] Normal cells require growth factors (mitogens) for proliferation; in their absence they withdraw from the cell cycle and stop developing.[62] In order for a

growth factor to work, it needs to be produced, approach the target cell, avoid binding factors, and attach to its receptor. Disrepair factors such as interleukin 1 (IL-1) can interfere with these processes.

SUMMARY OF BASIC SCIENCE AND CLINICAL STUDIES

Chronic sprain and strain pathology consists of decreased tensile strength and often laxity in ligaments and tendons[3,33] (changes are primarily degenerative rather than inflammatory). Osteoarthritis similarly involves primarily degenerative changes in cartilage and cortical and subcortical bone. Polypeptides are growth factors produced in peripheral cells that powerfully initiate growth and repair in connective tissue (fibroblasts) and cartilage (chondrocytes).[60] Direct exposure of fibroblasts to growth factors causes new cell growth and collagen deposition.[9,28,34,36,40,57] Inflammation creates secondary growth factor elevation. Studies of injection of inflammatory proliferant solutions have demonstrated ligament thickening, enlargement of the tendinoosseous junction, and strengthening of tendon or ligament in animal studies.[19,35,44] In humans, inflammatory proliferant injection in two prospective, randomized, double-blind studies of chronic low back pain has resulted in clinically and statistically significant improvement in pain and disability measures.[31,43] Cartilage effects of polypeptide growth factors are considerable: healing of full-thickness cartilage defects in animals has been shown in several injection studies.[45,56,59,61]

Simple dextrose or hyper- or hypoosmolarity exposure causes cells to proliferate and produce a number of growth factors.[2,8,10,32,41,42,47,51,52,58] A recently completed prospective, randomized, double-blind study by this author indicates the ability of simple dextrose injection interarticularly to tighten human ACL ligament.[50a] Two recently completed prospective, randomized, double-blind studies on osteoarthritis (knees and fingers) indicate substantial and statistically significant clinical benefit from dextrose injection as compared with control solution.[50a,50b]

EFFECTS OF PROLOTHERAPY ON LIGAMENTS AND TENDONS

Injection of Growth Factors

Studies involving exposure of fibroblasts from ligaments and tendons have exposed cells to various growth factors, primarily in vitro. Responses to growth factors differ between animal species[9,28,57] and between different tendons and ligaments within the same animal or human.[36,57] Transforming growth factor beta 1 (TGF-β1), erythrocyte growth factor (EGF), PDGF, and basic fibroblast growth factor (bFGF) appear to be particularly important growth factors for either new cell growth or collagen growth in animals and humans.[28,34,36] Application of this information to growth factor injection studies has only been reported in one animal study to date, in which direct injection of injured patellar ligament in rats was performed. The injected material contained a virus altered to produce a key growth factor (PDGF), which resulted in a substantial increase in collagen deposition compared to noninjected controls.[40]

Growth Factor Stimulators

Inflammatory Solutions

The injection of inflammatory solution briefly stimulates the inflammatory cascade to simulate an injury without actually stretching or deforming tissue.[1] Such an approach causes a complex cascade of chemical events, and measurement of individual growth factors and disrepair factors to determine the exact mechanism is not feasible. Dextrose > 10% concentration partially works by this mechanism, as do phenol and sodium morrhuate. *Sclerotherapy* is an older term for inflammatory prolotherapy. It is recommended only in varicose vein injection; sclerosis implies scar induction for therapeutic effect. Biopsy studies have not demonstrated scar formation with mechanical, inflammatory, or growth factor prolotherapy with the agents and concentrations currently in use.

Clinical research on inflammatory prolotherapy has demonstrated an increase in tendon diameter and tendinoosseous junction in animals (Figs. 20-1 and 20-2). Strengthening of knee medial collateral ligament has been demonstrated in a double-blind study in rabbits,[35] and reduction of knee laxity has been suggested by an initial study in humans using an electroarthrometer.[44] Nonblinded studies in whiplash, chronic headache, chronic cervical and low back pain, and temporomandibular joint syndrome have indicated improvement in 70–85% of cases using dextrose-glycerine-phenol, sodium morrhuate, or hypertonic dextrose (≥ 12.5%).[16,29,38,38,49,55]

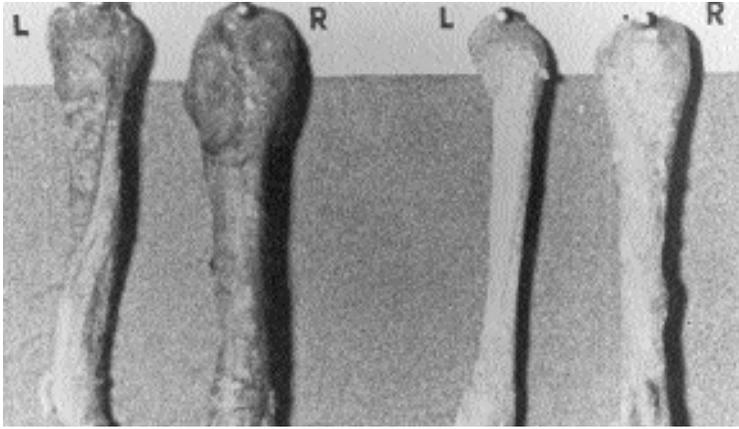Two double-blind studies of inflammatory proliferant injection with 6-month follow-up have

FIGURE 20-1.   Rabbit tendons 9 and 12 months after injection of proliferant; controls (L), treated (R). (From Hackett GS, Hemwall GA, Montgomery GA: Ligament and Tendon Relaxation by Prolotherapy, 5th ed. Oak Park, IL, Gustav A. Hemwall, 1992, p 96, with permission.)

been performed on patients with low back pain. The first study was on 82 patients with chronic back pain for more than 1 year who had failed to respond to conservative treatment.[43] Patients in the active treatment arm received extensive injection throughout the sacroiliac (SI) ligament and lower lumbar attachments with a solution containing 12.5% dextrose + 12.5% glycerine + 1.25% phenol + 0.25% lidocaine. Control patients received injection of saline solution in the same locations. All patients were injected weekly for 6 weeks. Only 1 patient dropped out. Between 0 and 6 months the Visual Analogue Scale pain score improved 60% in the active group and 23%
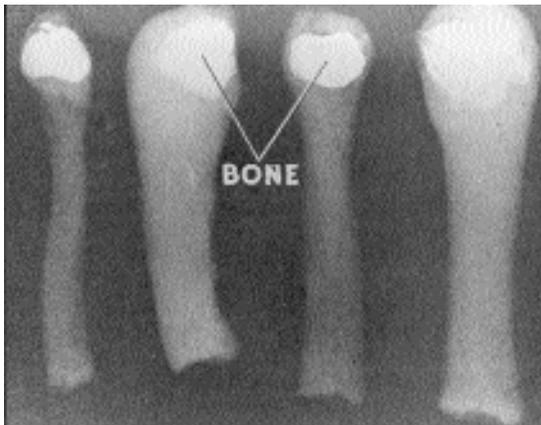

FIGURE 20-2.   Paired radiographs of tendon-to-bone attachment of rabbit tendons 1 and 3 months after injection of proliferant. Controls are on the left side of each pair, treated tendons on the right. (From Hackett GS, Hemwall GA, Montgomery GA: Ligament and Tendon Relaxation by Prolotherapy, 5th ed. Oak Park, IL, Gustav A. Hemwall, 1992, p 96, with permission.)

in the control group with p value for an intergroup difference of < 0.001. A hybrid disability score improved 70% in the active group and 30% in the control group ($p < 0.001$ for intergroup difference).

The second study involved 80 patients with more than 6 months of low back pain and failure to respond to conservative methods.[31] Patients were treated with a solution containing 12.5% dextrose + 12.5% glycerine + 1.25% phenol + 0.25% lidocaine versus a 1-to-1 mixture of 0.5% lidocaine and normal saline. Injections again were given weekly for 6 weeks. Between 0 and 6 months the Visual Analogue Scale pain score improved 53% in the active group and 37% in the control group with p value for intergroup difference of 0.056. The hybrid disability score improved 57% in the active group and 47% in the control group with a p value of 0.068. Therefore, despite similar improvements in the active treatment group in study 2 compared to study 1, the control group in study 2 improved to the point at which the differences between groups were only marginally significant. An examination of the osmolarity of the solutions indicates that in the second study the control solution was hypotonic (which may not be a placebo solution).

Weaknesses of these studies include the use of phenol (whose inflammatory properties may impair blinding), multiple treatment methods applied simultaneously (i.e., all patients also performed back exercises), and a treatment technique that is difficult to duplicate, and the second study included a control group that may have been an active treatment group. On the other hand, the

first study did demonstrate a statistically impressive advantage of proliferant injection versus true placebo solution as well as a substantial and comparable percentage improvement in pain and disability in both studies.

Glucose

A variety of cells, including human gingival ligament cells, promptly produce growth factors or facilitators such as IGF-1, TGFβ, platelet-derived growth factor beta receptor beta (PDGFR-B), TGFα visual analogue scale, and bFGF with resultant proliferation[10,41,47,51] when exposed to elevation of glucose levels to as little as 0.5%.

Gale Borden, M.D., performed a large number of biopsies in the white rat after injection of a variety of dextrose concentrations (unpublished observations). His slides show inflammation with ≥ 12.5% concentration of dextrose (Fig. 20-3), but no inflammation with up to 10% dextrose in 0.5% Xylocaine. This is consistent with the common hospital practice of limiting peripheral venous dextrose concentrations to about the 10% range.

It is not fully understood how elevation of glucose raises growth factor levels. However, even transport of glucose into the cell requires a rise in growth factor(s).[13,47] Two studies have used dextrose injection as a single agent for proliferation.[39,49] The first study used 25% dextrose (D form of glucose in water) injected into the iliolumbar (IL) ligament versus a control of 1% Xylocaine.[39] This study showed a superior outcome in the dextrose-treated patients but had insufficient patient numbers to reach statistical significance. The dextrose concentration was likely in the inflammatory range with potential effect from stimulation of the inflammatory healing cascade. A second study involved 40 patients with severe fibromyalgia injected with 12.5% dextrose solution and demonstrated the ability to inject dextrose solution extensively in patients with severe pain with no significant side effects.[49] That study was consecutive patient-controlled rather than placebo-controlled.

The most recent study involving dextrose as a single agent for treating ligament/tendon was a prospective study of knees with anterior cruciate ligament (ACL) laxity.[50a] An electroarthrometer was used as an objective measure of ACL laxity with anterior displacement difference (ADD), which is the difference in anterior excursion measurement between knees in the same patient. To qualify for the study, patients had to have an ADD
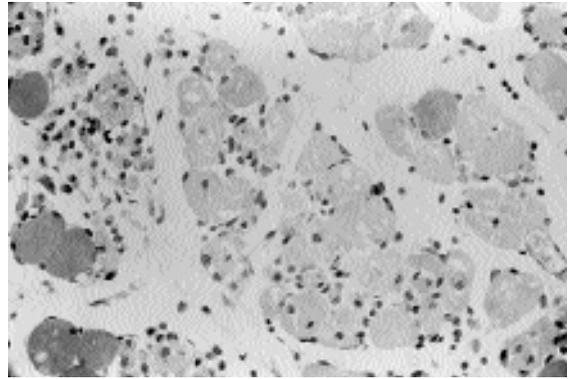

FIGURE 20-3. Photograph of a cross-section of rat muscle 48 hours after injection of proliferant (12.5% dextrose in 0.5% lidocaine) and stained with hemotoxylin and eosin. (Courtesy of Gale Borden, M.D.)

level that was 85% sensitive and 85% specific for ACL laxity. Individual, paired t tests indicated that blinded measurement of goniometric knee flexion range improved by 12.8° (p = 0.005), and ADD improved by 57% (p = 0.025). Eight out of 13 dextrose-treated knees with ACL laxity were no longer lax at the conclusion of 1 year. The rationale for tightening of connective tissue structures is the normal loss of end-to-end length of immature collagen as it dehydrates during the maturation process.

Solutions with Altered Osmolarity

Although hypertonic glucose solution is more effective than equivalently hypertonic mannitol solution, in studies comparing their growth factor stimulation effects, elevation of osmolarity about a cell clearly causes release of growth factors.[47] Osmoregulation, the cellular response to environmental changes of osmolarity and ionic strength, is important for the survival of living organisms. Elevation of osmolarity by as little as 50 mOsm has been found to activate multiple growth factors.[2,8,32,42,52,58] PDGF is among the growth factors activated.[42] Several investigators have demonstrated that hypotonicity also stimulates growth factor release,[8,53] and Sadoshima et al. demonstrated that hypotonicity stimulates a rise in DNA for growth factor production within seconds of cellular exposure.[53] Preventing a cell from shrinking or expanding with changes in osmolarity appears to prevent growth factor release, and stretching a cell without changing osmolarity leads to release of growth factors.[32] These findings imply that cells detect alterations in cell size but not changes in osmolarity or ionic strength.

PROLOTHERAPY EFFECTS ON CARTILAGE OR OSTEOARTHRITIS

Effects of Direct Injection of Growth Factors on Cartilage

Studies on effects of growth factors on human chondrocytes have so far been in vitro.[7,12,25,36] However, in animal studies, results of application of growth factors by infusion or injection have been encouraging. Van Beuningen et al. demonstrated chondrogenesis with single injection of TGF-β1 or BMP-2; TGF-β1 in particular increased proteoglycan synthesis for 3 weeks after injection.[59] Single injection of bFGF into 4-week-old rat knees induced chondrocyte growth and caused a thicker cartilage to develop.[56] Continuous infusion of FGF-2 (fibroblast growth factor-2) and injection of hepatocyte growth factor have both been shown to heal full-thickness lesions (3–4 mm induced injuries) in articular cartilage in rabbit knee and rat knee respectively.[45,61]

Growth Factor Stimulators

Inflammatory Solutions

The injection of inflammatory solutions as a growth factor stimulator has not been studied formally or in a measurable way in terms of effect on cartilage.

Glucose

Two randomized, prospective, placebo-controlled, double-blind clinical trials of dextrose injection of osteoarthritic joints have been conducted.[50a,50b] The first was on 77 patients with 111 knees meeting radiographically confirmed symptomatic knee osteoarthritis.[50a] These patients had an average weight of 193 pounds and pain for more than 10 years in qualifying knees. This study included 38 knees with no cartilage remaining in at least one compartment. Multivariate analysis indicated superior benefit from the dextrose solution over control by 6 months (p =

0.015). Data from 1 year (6 bimonthly injections of 9 ml of 10% dextrose) revealed pain improvement of 44%, swelling improvement of 63%, knee buckling improvement of 85%, and a range of motion improvement in flexion of 14°. X-rays at 1 year showed no progression of osteoarthritis and are being followed for 3 years to further confirm this.

The second study was on 27 patients with finger osteoarthritis and an average age of 64 years.[50b] One hundred fifty joints met the radiographic criteria and the symptom-duration criteria of more than 6 months of pain (average pain duration was more than 4 years). After three injections of 0.5 ml of 10% dextrose on either side of each symptomatic joint, pain with movement of fingers improved significantly in the dextrose group (with a p value of 0.027). Flexion range of motion improved more in the dextrose group (p = 0.003) than in the control group. After six injections of 10% dextrose, pain improvement averaged 53%, and there was a range of motion gain of 8°. X-rays at 1 year again showed no progression of osteoarthritis and are being followed.

Disrepair Factor Blockers

Blocking disrepair factors can promote growth by disinhibiting growth factors. Pelletier et al. demonstrated virus-altered fibroblasts can be made to produce antagonists to IL-1, a key disrepair factor that prevented osteoarthritic changes after the ACL ligament in dogs was cut.[46]

APPROACHES TO PROLOTHERAPY

There are two general approaches to proliferation therapy (Table 20-1). Physicians tend to combine aspects of both methods. The first, known as the Hackett method, is based on the approach of George Hackett with subsequent refinements made primarily by Drs. Gustaff Hemwall and Gerald Montgomery.[17–23] The West Coast method,

TABLE 20-1.   Comparison of Prolotherapy Approaches

	Hackett Method	West Coast Method
Proliferant used	Predominantly dextrose	Predominantly phenol/dextrose/glycerine or sodium morrhuate
Manipulation	Rarely or not used	Used more often
Needle size	Smaller bore	Larger bore
Sedation	Anesthetic gel/blebs + IV sedation	IV sedation less often
Frequency of treatment	Every 6–12 weeks	Weekly
Exercise recommendations	Gentle activity	Fast resumption

popularized by physicians in this region, was promoted by Dorman, Ongley, and others.[11] The comparisons in Table 20-1 result from direct observation of techniques used by Hemwall, Montgomery, and Ongley and the author's personal experience.

In the Hackett method, dextrose is used as the proliferant in the vast majority of cases. Cellular disruption is minimal and nerve damage has not been reported. This method is slower to perform, but is easier to teach and is uniform in distribution of solution. In contrast, the West Coast approach utilizes phenol 1.25%, glycerine 12.5%, and dextrose (D-glucose in water) 12.5%. The needles are generally larger, and needle movements are more rapid and difficult to learn.

PRE- AND POSTPROCEDURE TREATMENT AND SEDATION

In addition to needle insertion and injection method, other considerations include proper patient selection, timing, proliferant solution choice and preparation, identification of injection sites, sedation, positioning and anesthesia issues, postprocedure care, and complications.

Patient Selection

Patients with peripheral joint laxity such as shoulder, knee, metacarpophalangeal joint, and ankle usually will not show clinical laxity on examination. Symptoms related to reflex muscular dysfunction include clicking, popping, or stiffness with reduced range of motion. Symptoms related to more significant soft tissue abnormality with secondary muscle inhibition include feeling a need to self-manipulate the area or benefitting only briefly from manipulation. A feeling of weakness or very easy fatiguability, such as the head feeling too heavy for the neck or immediate pull in the low back when bending over, can occur from either inhibition or laxity origin. Insufficient tautness in cervical ligaments or ankle ligaments can cause a feeling of being off balance from reduced cervical proprioceptive information or repetitive ankle giveway that is resistant to strengthening alone.

Symptoms related to referral from tendons and ligaments include pseudoradicular pain or pseudoradicular or whole extremity numbness. Pseudoradicular referral patterns for selected cervical ligaments are shown in Figure 20-4 and for selected sacroiliac region ligaments in Figure 20-5. In patients with segmental sensitization such as complex regional pain syndrome or fibromyalgia, the pains may be interpreted as burning and hyperalgesia is common. In such cases the normal pulling sensations felt in the lax patient may sometimes be felt as "tearing" sensations.

When prolotherapy is widely practiced, it will be an early choice to alleviate pain from sprain and strain that has lasted more than 2 months and to repair peripheral nociceptors in chronic pain. Basic science clearly points to the entheses as the source of peripheral pathology in chronic sprain and strain. Early treatment may obviate the need for prolonged therapy by providing direct treatment. If treatment does not result in improvement in two
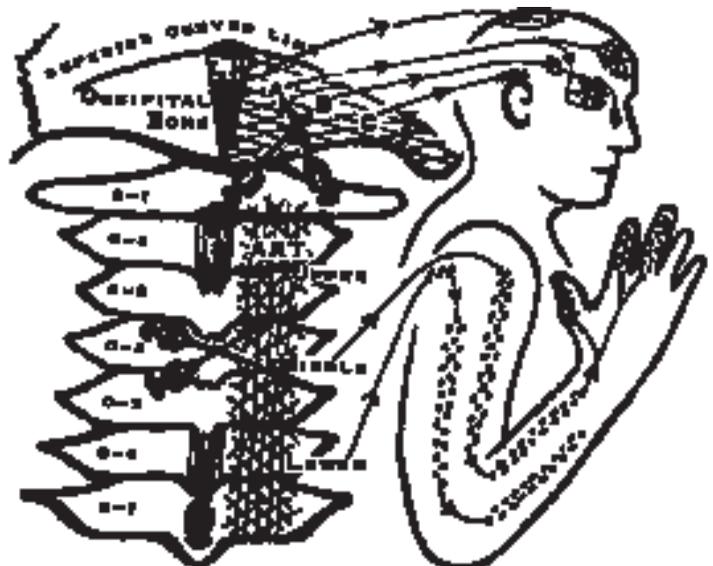

FIGURE 20-4. Common referral patterns of cervical structures. Forehead, eye (A); temple, eyebrow, nose (B); above ear (C); interspinous ligaments (IS); and articular ligaments (ART). (From Hackett GS, Hemwall GA, Montgomery GA: Ligament and Tendon Relaxation by Prolotherapy, 5th ed. Oak Park, IL, Gustav A. Hemwall, 1992, p 70, with permission.)
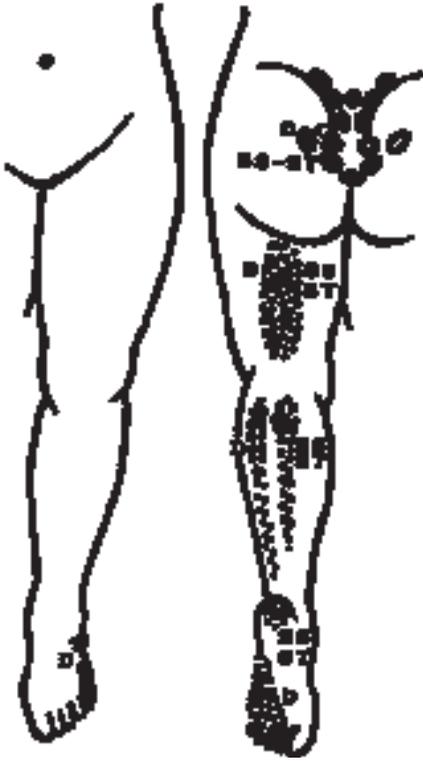
FIGURE 20-5. Common referral patterns of the sacroiliac, sacrospinous, and sacrotuberous ligaments. (From Hackett GS, Hemwall GA, Montgomery GA: Ligament and Tendon Relaxation by Prolotherapy, 5th ed. Oak Park, IL, Gustav A. Hemwall, 1992, p 32, with permission.)

sessions or if symptoms worsen, the diagnosis should be reconsidered.

Timing

In the case of focal pain over the subacromial region, the superior trochanteric bursa, or de Quervain's area, steroid trial may be advisable before initiating proliferant injection because secondary inflammation in these conditions is more prominent.

An 8-week delay after injury is recommended to allow the body to self-repair. If the patient is severely affected after sprain or strain, the pain cycle should be stopped before secondary fibromyalgia syndrome develops. The effectiveness of prolotherapy in aborting conversion of acute pain to chronic pain syndrome is an important topic to research. Reasons for intervening earlier than 8 weeks may include previous chronic sprain and strain in a region in which spontaneous healing is not expected to be efficacious or the patient's inability to work. The success of early intervention depends on a

well-educated patient who understands the extent of the damage; typically this situation arises in a patient previously treated who has another accident.

Pregnant patients generally are not treated during the first trimester (except for focal peripheral joint problems) or the last trimester due to positioning issues.

If inflammatory prolotherapy methods are to be performed, it is preferable to discontinue all nonsteroidal anti-inflammatory drugs (NSAIDs) three days before treatment and 10 days after. The use of anti-inflammatories does not preclude treatment, however; clinical benefit occurs in patients on regular prednisone.

Proliferant Solution Choice and Preparation

Syringes or bags can be prepared using $\frac{1}{4}$ volume of 50% dextrose (i.e., 3 ml in a 12-ml syringe) to make 12.5% soft tissue solution, or $\frac{1}{2}$ volume for 25% joint injection solution. Xylocaine percentage varies between 0.4 and 0.075%, depending on the size of the area to be injected. Bacteriostatic water is recommended for the diluent. Single-use containers should be discarded at the end of each day. Solution made in advance should be refrigerated. Benzyl alcohol can be obtained from the manufacturer for large-volume solution preparation if other than bacteriostatic water is used as diluent.

Bottled phenol is obtainable from the manufacturer, allowing for small amounts to be added to ≥ 250 ml of 12.5% dextrose to convert solution to phenol-dextrose. Concentrations of 0.5–0.75 are alternatives to the 1.25% phenol concentration in the Ongley solution; remember to keep the volume of injection low. The glycerine component function has not clearly been determined or studied individually.

Sodium morrhuate is available as a 5% solution. One to 2 ml per 10-ml syringe makes a 0.5–1% concentration. Again, low volumes should be used. Its advantages over phenol are not established.

For the first treatment, using dextrose is advisable in any patient before using phenol, but particularly in patients with central sensitivity who misinterpret postinjection discomfort as more painful than it should be. Phenol has not been found to create scarring in the maximum prolo concentrations (1.25%), and permanent dysesthesia has not been reported, even with concentrations up to 6% used for nerve block.[48] However, postinjection

stiffness and discomfort are more significant; phenol is best reserved for more local treatment in patients well-known to the treating physician. Small amounts for each injection site should be used. Be especially careful to avoid the spinal canal.

Identifying Injection Sites

Potential pain referral sources for the patient's clinical complaints are palpated with the prolotherapist's fingertip. A knowledge of ligament and tendon referral patterns is essential to determine the sites of injection. Common sites of injection for regions of pain in the upper and lower body are shown in Tables 20-2 and 20-3 respectively. The objective presence of twitch contractions can often be elicited with crossfiber palpation over the tendon or ligament in question and reproduce the patient's pain pattern. After these specific areas are identified, the skin is marked. Trigger points from muscle usually are not marked because the primary pathology in chronic sprain and strain is in connective tissue, and reflex twitch contractions to muscle stimulation are likely a secondary phenomenon.[4] Consistent with this hypothesis, large numbers of twitch contractions in muscle occur during injection of the entheses.

Sedation, Positioning, and Anesthesia

Anesthetic gel (a simple preparation containing benzocaine or an alternative) is applied to diminish skin sensation. Anesthetic blebs are an alternative, especially if IV sedation is not used.

Immediately prior to treatment, prophylactic antinausea medication such as hydroxyzine may be given. The length of the procedure and the patient being treated on his or her stomach create special concerns for sedation hypoventilation. Standard precautions with any sedation include no eating for 6–8 hours and not drinking for 1 hour before treatment. If more than 25 mg of meperidine is given, constant oximetry is recommended with a nasal cannula in place with oxygen ready to initiate. Single-agent sedation is recommended. Midazolam is not recommended for the nonhospital setting unless the patient is constantly monitored by the staff and an alarmed oximeter and the physician is highly familiar with intubation. The physician should routinely inquire if patients have taken any anxiolytics or narcotics before the procedure. Intravenous diazepam may be administered before giving low-dose meperidine, but it should not be given during a treatment to a patient who has already been given IV meperidine, because the tendency for

TABLE 20-2.   Common Sites of Injection for the Upper Body (Regions of Pain)

Referral Source Examples	Head	Head and Neck	Neck	Top of Shoulder	Shoulder	Elbow	Arm	Upper Back
Semispinalis capitis	■	■						
Splenius capitis	■	■						
Rectus capitis	■	■						
TMJ capsule/ligaments	■	■						
Cervical intertransverse ligaments		■	■	■	■		■	
Cervical facet ligaments		■	■	■	■		■	
Anterior/posterior tubercles		■	■	■	■		■	■
Posterior superior trapezius		■	■	■	■			
Costotransverse ligaments			■	■	■		■	■
Longissimus thoracis			■	■	■		■	■
Iliocostalis thoracis			■	■	■		■	■
Shoulder capsule				■	■		■	
Biceps					■		■	
Subscapularis					■		■	
Pectoralis					■		■	
Deltoid					■		■	
Infraspinatus					■		■	
Teres major					■		■	
Teres minor					■		■	
Common extensors						■	■	
Common flexors						■	■	

TABLE 20-3. Common Sites of Injection for the Lower Body (Regions of Pain)

Referral Source Examples	Back	Back and Leg	Buttock	Thigh	Knee	Calf/Shin	Ankles	Heel	Arch	Toes
Facet ligaments	■	■	■	■		■				
Lumbar intertransverse ligaments	■	■	■	■		■				
Sacroiliac ligament/joint	■	■	■	■		■	■	■	■	■
Iliolumbar ligament	■	■	■							
Gluteal insertions			■	■		■				
Sacrospinous ligament			■	■		■	■			
Deep articular ligaments, hip			■	■		■	■	■	■	■
External rotators, hip			■	■						
Distal knee adductors				■	■					
Distal hamstrings				■	■	■				
Knee capsule				■						
Distal vastus medialis			■	■						
Anterior tibialis					■					
Peronei					■					
Talofibular ligament						■				
Calcaneofibular ligament						■				
Tibionavicular ligament						■				
Tibiotalar ligament						■				
Tibiocalcaneal ligament						■				
Achilles tendon							■			
Calcaneonavicular ligament								■		
Calcaneocuboid ligament								■		
Long plantar ligament								■		
Tarsometatarsal ligaments									■	

hypoventilation is substantial. Because both lidocaine and meperidine in the solution cause hypotension and because nausea is related to postural hypotension during and after the procedure, ephedrine, 50 mg intramuscular, and low-dose epinephrine in solutions (0.25 mg per 500–1000 ml) can be quite helpful in limiting hypotension after treatment. Before doing so, blood pressure check or monitoring is advised to confirm that hypertension is not present, and each patient's cardiac status should be known. Oxygen saturation values in the 90s should be maintained, and predrawn naloxone hydrochloride should be available. When a patient falls asleep, this is equivalent to his or her receiving another 50 mg of intravenous meperidine, so keeping the patient in the conscious sedation range is important.

Postprocedure Care

After the procedure, patients generally can be discharged to the care of a responsible driver when they can walk without dizziness. Analgesics are provided for pain, but NSAIDs should be avoided. The inflammatory cascade stimulation of fibroblast migration occurs in the first few days, so three days is a reasonable minimum period to wait. If glucose/osmotic or growth factor proliferation is used, avoidance of NSAIDs may not be necessary. Application of ice or heat in combination with slow, gentle stretching is recommended, and activities should be light for 2–4 days. Resumption of activities that were tolerated before injection should be tolerated after injection, but the patient who has received phenol should be warned that reactions are variable in terms of work tolerance after injection.

Complications

Proliferation therapy is quite safe when used judiciously. The most common complication is an exacerbation of pain that lasts 2–7 days after the injection session. If pain persists beyond this time, residual ligament or tendon trigger points may be present, excess volume injection may have occurred, or a stronger proliferant may have resulted in a central hypersensitivity overreaction. A superimposed inflammatory process also may be present.

Avoiding anaphylaxis is imperative. With sodium morrhuate the risk is real; incidence of anaphylaxis with this solution does not necessarily correspond to a coexisting shellfish intolerance. Preservative-free Xylocaine, bacteriostatic water without methylparabens, and latex-free rubber gloves are recommended. Using chlorhexidine gluconate 2% solution for skin preparation is well tolerated. Nevertheless, epinephrine should be readily available in case of emergency.

Other complications are specific to the injected body part and usually are a result of improper needle placement. Injections around the thorax can lead to pneumothorax, although with proper technique this is rare. Injection into a vertebral artery is rare and safe if ≤ 0.5 ml of standard solution is used.[5] Five cases of substantial neurologic impairment from spinal cord irritation caused by subdural injection above the sacrum have been reported since 1955[26,30,54] and were attributed to strongly inflammatory proliferants that are not in current use.

PROCEDURE PERFORMANCE

Positioning and Volume of Injection

In whole body treatment, the patient begins on his or her stomach with 2–3 pillows under the stomach, with the head above the pillows enough to not have to stretch for the table, and with the mouth and nose clear for breathing. Because gastroesophageal reflux is not uncommon and may increase with length of sedation, performing the back injections first is preferable. Tapping of the bone surface is recommended when the bone is palpated by needle tip, injecting very small amounts of fluid until 0.5–1 ml is injected into the area.

Posterior Neck and Upper Back Injection Techniques

Neck and upper extremity pain often is treated with proliferation therapy. Although understanding common trigger point referral patterns is helpful, as with muscular trigger point, chronic pain often is associated with atypical referral patterns with spread of stimuli from lowered interneuron thresholds. Many cases of upper extremity pain resembling thoracic outlet syndrome or pseudo–reflex sympathetic dystrophy may result from cervical or thoracic nociceptors. This disruption also may affect the posterior cervical sympathetic outflow, resulting in organ dysfunction with chronic sinus drainage problems, ringing in the ears or intermittent hearing loss, swallowing dysfunction, blurry vision, off balance sensation, and nausea (Barré-Lieou syndrome).[15,24] In addition, many tension and migraine headaches unresponsive to medication and other traditional treatments may be treated with injection into the cervical structures.

A nonindenting, reangulation technique is recommended for costotransverse ligament injection because it allows injection of ribs up to 3 inches in depth (patients ≥ 350 lbs) with safety. The nonindenting technique is preferred by the author because it allows the treating physician to know exactly how far from the skin surface the needle is traveling, which is useful for ribs that cannot accurately be palpated. This method begins at about T5–T6 where the ribs are most superficial. Use of a short (i.e., ½ to 1-inch needle) is recommended, palpating, inserting, and searching at ½-inch depth with 5–10° angulation changes of the needle. Redirection is performed by coming out nearly fully to avoid bending of the needle and then reinserting at a different angle. If the rib is not found, re-palpate if the rib is palpable, and then reinsert and search again with a ⅛-inch to ¼-inch increase in depth. Repeat the process until the rib is found. Because of the many reangulations attempted at each depth, passing the rib will seem highly difficult. Nonpublished observations suggest frequency of pneumothorax at 1 per 2,500 to 10,000 needle insertions over the ribs.

After the most superficial costotransverse ligament (CTL) is found, mark that rib and use the depth to find the other levels, inserting at a right angle to the skin surface. Marking as ribs are found is more accurate than premarking. Figure 20-6 demonstrates the row of CTL injection sites on the left about 1½ to 1¾ inches from the midline. Using the superficial rib as a template, inject up and down from that level. Note that depth increases about ¼ inch traveling up to T1 and about ¼ inch traveling down to T12, depending on the size of the patient and varying with the distance from the midline. Slowly increasing the length of the needle may be helpful to the physician. At each level, insert to a level known to be safe from the previous rib, and if the rib is not touched, search in a similar manner to that described previously. This method is used for both CTLs and iliocostalis thoracis, commonly involved in upper back pain and with referral pain as far as the hand or up into the head.

Because the depth for T1 approximates the depth for injection of the posterior cervical vertebral body (cervical intertransversarii), needle insertions
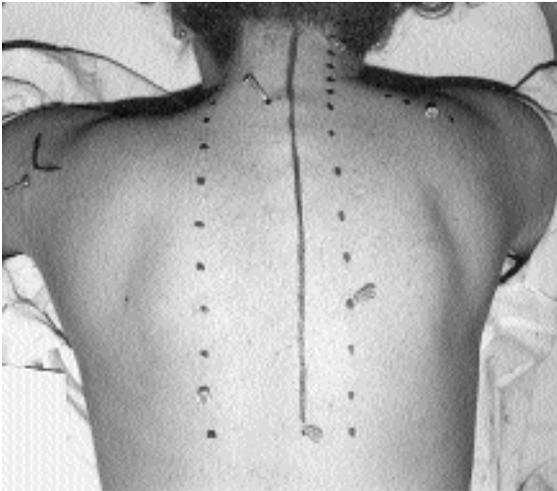
FIGURE 20-6. Injection of posterior neck, upper back, posterior superior trapezius, and shoulder capsule.

for injection along that row are often the most convenient. At cervical levels the needle is directed about 10–20° inferiorly to avoid any possibility of passing between vertebral bodies. The top level injected is C2. This is recognized by palpating the posterior spinous process of C2 about 1 cm below the base of the skull. Note that for C2 injection the same angulation may not be feasible; in this case a shorter and more vertically oriented needle may be used for this level.

Thoracic facet ligament injection depth is usually about ½ inch deeper with the needle directed slightly medially. Figure 20-6 demonstrates marks for a row of facet ligament injections on the right with a point of entry about 1 inch from the midline and needle angulation 10–20° medially and 10–20° inferiorly for safety. Although the distance of the facet articulation from midline varies, spread of solution is satisfactory to achieve the necessary result and uniformity of injection. For each injection a finger is on the spinous process to ensure that the distance from the midline remains about one inch and to rule out or compensate for scoliosis. Carrying the injections up into the cervical region to C2 is again recommended to complete the row of treatments. Note that, with the vertebra prominens varying, it may be difficult to distinguish C7 from T1 level. However, because the depths are constant and an entire row is being injected, this is irrelevant.

Although patients with chronic pain often complain of weakness in the back and the erector spinae, injection of the costotransverse and facet ligaments usually is enough to correct this. However, if the patient continues to complain of weakness or if the

sides of the spinous processes or the interspinous ligament are painful, he or she may be injected in the painful regions. Figure 20-6 shows multifidi injection at vertebra prominens level on the L and insertion into the interspinous ligament at approximately the T9–10 level. The insertion point for multifidi injection is typically ½ inch from the midline. It is not clearly established how critical it is with interspinous ligament to tap bone. The author prefers to inject into the central portion with a 1-inch needle. The injection is done vertically to avoid any chance of entering the spinal canal, which may occur with the use of a 1½ inch-needle in thin patients.

After completing the thoracic and cervical posterior injections, the base of the skull is injected, addressing multiple entheses such as rectus capitis, semispinalis, and splenius capitis. Marks for insertion are made on a line across the width of the neck about 1 fingerbreadth inferior to the base of the skull (about C2 spinous process level) with 4 insertion points along each side, beginning about ½ inch from midline. For safety the midline is again palpated and confirmed visually. Insertion of the needle medially is no closer than ½ inch to the midline. Typically a 2-inch, 25-gauge needle is used. Insertion is at the C2 spinous process level to reach the rectus capitis row (see Fig. 20-6). Insertion is best done aiming slightly laterally and superiorly to be sure the skull is touched and the midline is avoided. After the skull is touched, the needle is redirected inferiorly several times until the depth increases slightly, indicating that the base of the skull has been reached. The first row of injection sites is then complete. Note that an injection here may inadvertently reach the vertebral artery, so aspiration is recommended. The next two rows are located superior to the first at about ½ to ⅔-inch intervals to touch the semispinalis and splenius capitis insertions using a 1-inch needle.

Injection of the posterior superior trapezius is facilitated by bringing the arm up such that the elbow is even with the shoulder (R trapezius area in Fig. 20-6), which elevates the clavicle so that the posterior superior trapezius insertion can be injected posteriorly. If preferred, insertion may be at 90° to the table surface, but because the clavicle travels anteriorly from lateral to medial, angling the needle laterally will find the clavicle with the least distance traveled. Typical insertion points are shown in Figure 20-6.

For the rhomboid and levator scapulae injection, the patient's arm rests either on his or her back or on the leg of the examiner to elevate the scapula so

that distance to the ribs is increased (see right scapulae in Fig. 20-7). Levator scapulae injections travel up to the superior extent of attachment, with depth about ½ inch deeper than that for the rhomboid injection. For teres major and minor and infraspinatus injection (see left scapulae in Fig. 20-7), the arm usually is down at the patient's side. The scapula outline is shown with needle insertion along the lateral border for teres major and minor and in the mid portion of the scapula for the infraspinatus origin.

Low Back and Buttock Injections

Acute and chronic back, hip, buttock, and lower extremity pain often may be attributable to referred pain from trigger points within ligaments or tendon structures around the sacrum or lumbar spine. Failed back syndrome from surgery may be due to instability of ligament and tendon structures. Chronic pain from osteoporotic fractures can be due to traumatic laxity of spinal ligaments with pain from the facet and CTLs or longissimus muscle attachments. Selected ligament referral patterns for the lower back and leg are illustrated previously in Figure 20-5. Sacroiliac (SI) joint referral is similar to the SI ligament pattern depicted.

As in other locations, before performing injections in the lumbar spine, gluteal region, and hips, thorough palpation is necessary to identify abnormal ligaments that appear painful, but the patient with minimally painful palpation may still have SI ligament involvement due to the ligament's depth. Although the posterior superior iliac spine (PSIS) is at the S2 level and the iliac crest corresponds to the L4 level, while palpating it is not uncommon to misjudge the top of the iliac crest as much as 2 cm: thus insertion of a needle vertically is helpful in accurately marking the peak of the iliac crest and potentially in several locations in large individuals.

After the top of the crest is marked, two rows of injection sites can be marked paralleling the top of the crest as shown on the left side of Figure 20-8. The superficial portions of the iliolumbar (IL) and SI ligament are injected from the first row of sites and the deeper portions from the superior row. The medial sites on the top row often will access the SI joint, but this is seldom necessary as long as adequate tapping and instillation is carried out in the ligament. Each insertion site indicated is usually injected with 1.5 ml total volume, for a total volume approximating 20 ml for each IL-SI ligament region.
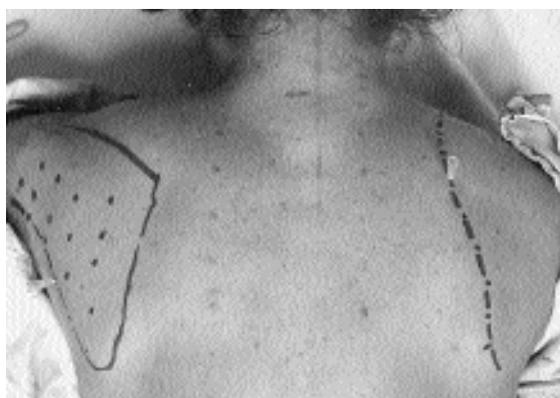

FIGURE 20-7. Injection of the right posterior thromboids/levator and left infraspinatus/teres.

Insertion sites for intertransverse ligaments and facet ligaments are shown in Figure 20-8 on the R. L5 is just below the level of the crest, so usually it is easily approached by inserting a 2–3-inch needle about 2 inches lateral to the midline, about ¼ inch above the top of the crest, touching the top of the crest, and then redirecting medially and inferiorly to slip off the top and down onto L5. The exact tip of L5 may not be touched but spread of solution occurs. Then, L4–L2 are injected, with L4 injection shown in Figure 20-8. The author prefers to inject fairly vertically for L4 and L3 to effectively gauge the distance from midline and then enter on the
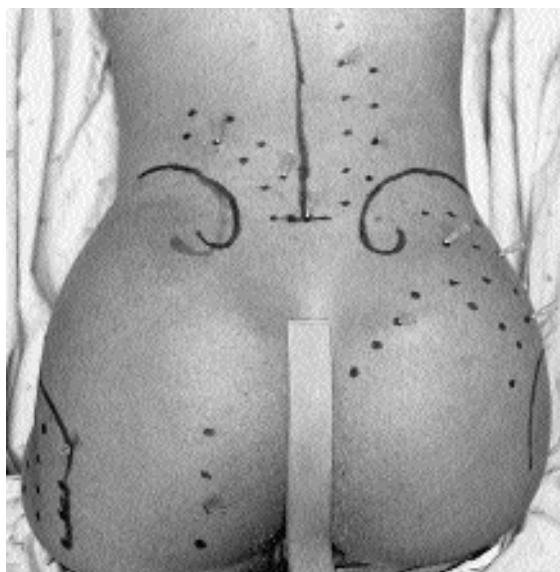

FIGURE 20-8. Injection of the iliolumbar (IL) and sacroiliac (SI) ligaments, intertransverse and facet ligaments, lumbosacral junction, gluteal attachments, deep hip articular ligament, sacrospinous and sacrotuberous ligaments, and multiple insertions on the posterior femur.

same vertical line for L2 and L1 with the needle angled medially to optimize safety. Note that L1 transverse process level is not marked, because novices frequently misjudge the top of the crest. It may be wiser to depend on solution spread to travel from L2–L1 to avoid risk of pneumothorax. The facet ligaments are similarly injected in the thoracic and cervical regions with a slight inferior and medial direction of needle. Note the L5–S1 facet articulation is about ¾ inch above the top of the sacrum. After facet ligament injection, the top of the sacrum usually is injected with a needle short enough (1½ inch) to avoid entering epidural space. The top of the sacrum is injected laterally as well but with inferior direction to avoid inadvertent spinal headache.

In the posterior gluteal region, multiple ligaments and muscular attachments are potential pain generators. Groin or inferior abdominal pain often originates in the IL ligament, pain to the great toe is often from the hip articular ligament, and SI ligament and gluteal attachments can refer pain in a variety of directions into the leg. Figure 20-8 shows needle insertion for gluteal insertions medial to the PSIS, insertions in the mid portion of the gluteus, and insertions for the deep hip articular ligament. Injection volumes in the medial gluteal insertions and hip articular ligament are about 1.5 ml for each site due to redirections with the needle to cover the gluteal insertion and hip ligament region.

The inferior borders of the sacrum are injected for sacrospinous and sacrotuberous insertions that typically radiate posteriorly down the leg. It is important to start on the sacrum and then "walk off" with the needle to avoid excessively deep entry.

Attachments of the gemelli, obturator internus, piriformis, and gluteal muscles at the posterolateral femoral trochanter also can be injected (Fig. 20-8, left side). These attachments are injected in three rows, with the most medial row located ¾ inch off the midline of the posterior thigh. Lateral trochanteric

pain usually resolves with this approach if steroids for bursitis are unsuccessful or as an alternative to steroid injection. The gemelli origin shown above the ischial tuberosity can radiate pain down the back of the leg, and sometimes into the groin and testicular area causing pseudo–tailor's bottom. It is approached directly vertically, finding it first just above the ischial tuberosity and then reinserting vertically, noting that depth typically increases about ¾ of an inch from the first insertion location. Injections are stopped about even with the top of the trochanter to avoid touching the sciatic nerve.

Figure 20-9 shows marks down the lateral thigh with the patient in a side-lying position. At times, injection down the leg appears to address the many slips of the tensor fascia lata as it travels to insert below the knee in patients with resistant lateral thigh pain with weight bearing or persistent difficulty with pain upon side lying. Twitch contractions are particularly large with this injection, especially in distal thigh portion, so sedation may need to be increased.

Foot Injections

Due to substantial pain sensitivity, injections into the feet usually precede knee injections. Medial injection site examples are shown in Figure 20-10. Metatarsophalangeal joints are most comfortably injected from the top of the foot for metatarsalgia; response to this method appears to approximate that of injection directly over the head from the plantar aspect. The needle insertion is lateral to the top of the metatarsal head, which is felt by flexing the toe down or approximated from the metatarsal head through the bottom of the foot, and the needle is directed distally and medially. Entering the joint is not critical—injection under the joint capsule appears to have an equivalent result.

FIGURE 20-9.   Injection of the tensor fascia lata.

FIGURE 20-10. Injection of the metatarsophalangeal (MTP) joints, plantar fascia, and Achilles tendon.

Plantar area insertion point for plantar fasciosis is shown just posterior to the navicular bone and even with its tip. Insertion of a 30-gauge needle in that location to 1-inch depth and injecting 3 ml of lidocaine at the same level and along the needle track is recommended for anesthesia. Wait a few minutes before inserting a 2-inch, 25-gauge needle. A 2-inch needle is required to reach the plantar ligament origins and insertions from one injection site.

If a steroid injection is elected for the first approach to this problem, a similar insertion method can be used to find the origin of the plantar ligament.

Achilles tendonosis (not usually a true "-itis") can be injected over its insertion as shown in Figure 20-10. Usually this is performed on both the medial and lateral aspect. Other insertion points along the tendon for about 2 inches can be injected using a 27-gauge needle, inserting gently through the skin and advancing until slight resistance is met to inject about the peritendinous area. Rupture of the Achilles tendon is not a concern with this as it is with Achilles steroid injection.

Injection of the calcaneofibular and talofibular ligaments (Fig. 20-11) is performed by palpating about the lateral malleolus anteriorly and inferiorly and injecting at tender origins. It is helpful in chronic ankle sprain with inadequate proprioceptive feedback and repetitive sprain tendency. The needle location shown enters the subtalar joint. Filling the subtalar joint with 3–4 ml of 25% dextrose solution has particular merit in chronic ankle strain because it can affect articulations chronically affected about the talus. The lateral talocalcaneal ligament or intercarpal ligaments may be painful to palpation and require injection. Injection of the medial ankle is similar with palpation revealing tenderness in the tibionavicular, tibiotalar, and tibiocalcaneal portion.

Knee Injections

The thigh adductor insertions and vastus medialis insertions are injected from a semicircle about the medial condyle of the femur and the hamstring insertions from several rows oriented vertically below the knee articular line (Fig. 20-12). This is most easily done with the knee bent and the leg in external rotation resting on the examiner's bent leg. The collateral ligament origin and insertion are injected when painful. In addition, the knee capsule often is injected inferomedially with 6 ml of 25% dextrose. Due to tibiotalar-patellofemoral communication, injection of the infrapatellar joint does not appear necessary when 25% dextrose is used.

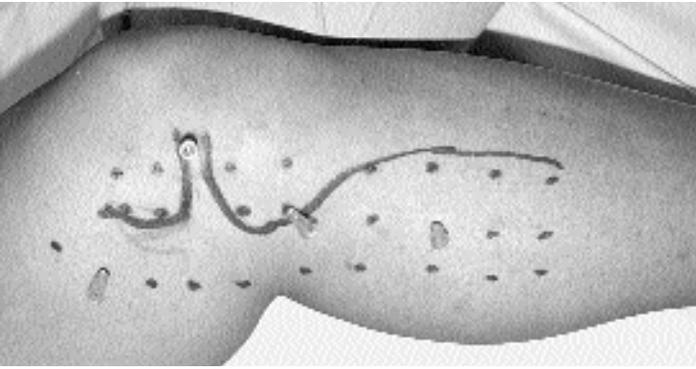**FIGURE 20-11.** Injection of the calcaneofibular and talofibular ligaments and subtalar joint.

FIGURE 20-12.   Injection of hamstring insertions, collateral ligament, and joint capsule.

Forearm, Wrist, and Finger Injection Techniques

Proliferation treatment of medial and lateral epicondylosis is preferable to use of steroids and is best performed before the development of prominent disorientation of tissue. Abundant tapping and low volume (4–6 ml total) proliferant are recommended to avoid excess inflammatory effect, particularly with the first treatment. In lateral epicondylosis, the common extensors are injected starting at the supracondylar ridge, with injections also over the radial head ligament, medial to the condyle, and directly on the lateral condyle (Fig. 20-13). The forearm should be fully supinated to make all attachment sites needle-accessible. Similar spread of fluid about the medial epicondyle is recommended for medial epicondylosis (Fig. 20-14).

Wrist injection is typically in the region of the radial collateral ligament (Fig. 20-13). This is particularly helpful in resistant cases of de Quervain's disease not resolved completely with a single steroid injection (radial wrist strain will mimic this disorder). In cases of marked pain over the first dorsal compartment, initially a steroid injection followed by proliferant injection for connective tissue repair is reasonable. Other common injection sites about the wrist include intercarpal ligaments in cases of wrist hyperextension.

Metacarpophalangeal (MCP) injection for painful function is performed by entering over the palpable joint line with the MCP in flexion, with a 5–10° distal inclination from vertical (Fig. 20-13). PIP and DIP injection is performed from a lateral approach with sufficient capsule infiltration and injection slightly above midline to minimize contact with digital nerves.

Anterior Shoulder and Anterior Chest Injections

The subscapularis, coracobrachialis, and pectoral insertions often are sources of anterior shoulder pain that mimic bicipital tendinitis. The subscapularis and pectoralis major insertion sites are injected with the shoulder in external rotation to expose the anterior insertions (Fig. 20-14). Injection is given in two to three rows over the proximal 3–4 inches of the anterior humerus. Coracobrachialis and pectoralis minor insertions are injected vertically. A chondrosternal ligament row often is helpful for patients with chest pain and pain with palpation of this row.

Scalene Region Injections

Because whiplash and other cervical sprain or strain often affect anterior structures, a safe and effective strengthening of these structures is important.

FIGURE 20-13.   Injection of common extensor origin at elbow, radial collateral ligament at wrist, and metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints.

FIGURE 20-14. Injection of subscapularis, coracobrachialis, and pectoralis attachments on the humerus, chondrosternal ligaments, and scalene origins.

Palpation of anterior and posterior tubercles to inject tender areas may be used, but these structures are normally somewhat tender and palpation may not be sufficiently tolerated for exact determination, especially because the tubercles are often just a few millimeters wide. The author prefers to inject in two rows. The patient's head is rotated 45°–60° away from the side of injection. The first row of injection sites is even with the anterior line of the ear and the second ⅓ inch anterior to the first. The second cervical tubercles are located 1½ fingerbreadths (FB) below the mastoid process. The C6 tubercles correspond to a point three FB above the clavicle (see Fig. 20-7). The needle used usually is a 1¼-inch, 27-gauge with a depth of ⅝ inch, or more, depending on patient size. Injection on bone is again the rule. Note that the C2 level in the anterior row is not injected because there is no C2 anterior tubercle. This is an area in which touching a bone

does not guarantee avoiding a vessel, so aspiration and caution are strongly suggested. Complications from injections into the deep cervical structures may include cervical nerve irritation with temporary paresthesia or vertebral artery injection.

Temporomandibular Joint Injection Techniques

Treatment of temporomandibular joint (TMJ) pain with proliferation therapy is directed at the joint capsule and supportive tendons and ligaments internal to the joint. The objective is to strengthen these structures by thickening and tightening the ligaments, thereby providing joint stability and less pain. With the patient's mouth closed and teeth unclenched (closed-mouth approach), the physician palpates the zygomatic arch adjacent to the condylar process of the mandible

FIGURE 20-15.   Needle placement for the closed-mouth approach when injecting for temporomandibular (TMJ) joint disorders.

with a finger of the injecting hand. A 1-inch, 30-gauge needle or 1¼ inch-, 27-gauge needle is inserted ¼ inch inferior to the apex of this palpable structure, felt as a semicircle (Fig. 20-15). The needle is advanced about 1 inch, and 0.75 ml of 25% dextrose solution is injected.

CONCLUSION

Prolotherapy involves placement by needle of a solution that raises growth factor activity enough to stimulate cell growth or cell production of collagen or matrix. Although inflammatory prolotherapy has been used for many years, noninflammatory prolotherapy methods are rapidly expanding. Two impressive but difficult to reproduce inflammatory prolotherapy studies on low back pain have been performed. Three double-blind studies with simple dextrose are underway in knee, finger arthritis, and knee ACL laxity; one-year data shows statistically and clinically significant results. Future studies on growth factor use should include low-cost options (e.g., growth factor stimulator) as well as more expensive alternatives (e.g., primary growth factor application) to determine cost efficacy factors.

Whole-body treatment of a patient in pain can be tedious and technically difficult. Considerable experience and personal instruction from an experienced prolotherapist is recommended before administering such treatment.

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