Regenerative Injection Therapy: History of Applications in Pain Management

Part I 1930s–1950s

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The history of injection treatment and surgery are intertwined from the beginning. The majority of the early innovators were surgeons; therefore, injection techniques were often employed to enhance the outcome of surgical interventions or to replace existing surgical methods. The 1930s and 1940s may be designated as a cumulative stage of knowledge about injection therapy in musculoskeletal pain.

The scientific rationale for implementation of regenerative injection therapy for chronic pain due to pathology of ligaments and tendons has evolved from clinical and histologic research performed for the injection treatment of hernia, hydrocele, prostatitis, and benign prostatic hypertrophy in the 1930s. In all of the aforementioned pathologic conditions, the goal was to stimulate the proliferation of fibrous connective tissue. The therapeutic action of the newly formed connective tissue was different in each condition. In the case of a hernia, the proliferation and subsequent contraction formed a scar that closed the mechanical defect of the abdominal wall. In the case of hydrocele, the serous membrane was intact, but the subserous connective tissue layer demonstrated hypertrophy that in turn reinforced capillary walls of serous membrane and prevented further exudate formation.[1,2] A similar mode of action was employed in the injection treatment of bursitis as the first step in gradual expansion of this treatment modality into musculoskeletal pathology. Thus, in 1931, A.E. Poritt, MD, treated chronic olecranon and prepatellar bursitis.[3] His method was as follows: the fluid was originally drained from the sac with a large-bore needle. With the needle left in place, 1 or

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2 mL (depending on the size of the bursae) of 5% sodium morrhuate was injected. If the bursitis persisted after two or three attempts to cure it with sodium morrhuate, a 5% phenol solution was injected into the bursae.[3]

EARLY USE FOR MUSCULOSKELETAL PATHOLOGY

Shultz

Louis W. Shultz, DDS, MD, Associate Professor of Surgery at the University of Illinois College of Medicine, was searching for a better way to treat painful subluxations of temporomandibular joints (TMJs). His cornerstone research was presented on November 11, 1936, at the Surgical Conference of the Research and Educational Hospital, University of Illinois. In 1935, Shultz conceived the idea that strengthening of the joint capsule by induced ligament fibrosis would lead to capsular contraction and keep the articular surfaces in closer proximity, thereby preventing subluxations. He conducted animal experiments with several solutions; among those used, Sylnasol provided the best results, so it was chosen for clinical trials. In addition, other following important observations and conclusions were made. In all injected animals, the capsule was 5 to 7 mm thicker than in the control animals; the openings between incisor teeth, measured under deep anesthesia,

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were 3% to 5% smaller than before the injections; autopsies revealed normal joint cavities, with a firm fibrous capsule in all dogs; 5 to 20 mL of Sylnasol injected subcutaneously did not cause sloughing, just an area of painless fibrosis; 1 to 2 mL of Sylnasol injected in the mental or infraorbital foramina produced no effect on motor nerves; 60 to 120 mL of Sylnasol injected into the peritoneal cavity produced no effect immediately or subsequently, as was proved by autopsies up to 3 months later, and no changes were observed in the pleural cavity; up to 60 mL of Sylnasol was injected into the left ventricle on 3 successful days, and no ill effects were observed immediately or at the autopsy up to 3 months later; no necrosis occurred in ligaments, just their thickening and strengthening; a clinical study of 30 human subjects who received intra-articular injections of 0.25 to 0.5 mL of Sylnasol at biweekly intervals demonstrated "entire patient satisfaction."[4] Shultz[4] concluded: (1) that the principle of induced hypertrophy of the articular capsule by injection of a fibrosing agent might be applied to other joints capable of subluxations or partial or recurrent dislocations; (2) that Sylnasol was a dependable fibrosing agent to be used in an ambulatory setting; (3) injection treatment restored normal joint function; and (4) the method was within the scope of treatment of the general practitioner. This material was presented a second time before the Illinois State Medical Society Eye Nose and Throat Division on May 18, 1937.[4] Twenty years later, Shultz presented the positive results of this treatment on several hundred patients with painful hypermobility of TMJs at the Annual Meeting of the American Society of Maxillofacial Surgeons, and the results were published in the *American Journal of Surgery*.[5]

Gedney

Earl Gedney, DO, also influenced by the positive results obtained with the injection treatment in herniae, theorized that a similar therapeutic effect may be secured by injecting elongated and sprained ligaments with irritating solutions to produce additional fibrous tissue. The fact that incompetent ligaments were a cause of painful joint hypermobility and instability was already well established.

In June 1937, Gedney[6] reported on injection of several joints. Some details of collateral ligament injec-

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tions for unstable hypermobile knees were described as follows: injections were carried out with the knee in flexion; 1 mL of solution was placed in the center of the ligament, then the needle was redirected along the ligament in the anterior and posterior direction, depositing a total of 3 to 4 mL of solution; posterior sacroiliac ligaments of unstable painful sacroiliac articulations were also injected with neoplasmoid and McDonald's solutions in small amounts along the entire affected structures. Gedney recommended wearing a tight, 2-inch wide, sacroiliac belt until the cure was achieved. The preliminary results were positively encouraging,[6] and, 6 months later, he extended this treatment to recurrent shoulder dislocations, acromioclavicular separations, and sternoclavicular subluxations.[7]

During the next 3 decades, Gedney[8] extended this treatment to painful degenerative lumbar disc syndromes and described the detailed technique of Sylnasol injections into lateral annulus of the intervertebral disc without fluoroscopic guidance. He reported L4 disk involvement in 95% of cases and a 50% clinical improvement, without disclosure of the patient sample size, after treatment of this disk alone.[9] In treatment of hypermobile sacroiliac joints, he emphasized that the amount of solution and quantity of treatments are highly individual and depended on the patient's response.[10] In a retrospective study, he emphasized significant statistical coexistence of sacroiliac pathology with disk pathology at the L3, L4, and L5 levels.[11] By 1954, he completed a retrospective study of 100 patients: 65 were initially treated with injections into the disk and 35 were initially treated with injections into posterior sacroiliac ligaments. The latter group required less intradiscal injections. Thus, he concluded that, in the presence of sacroiliac pain and hypermobility, adequate stabilization of the sacroiliac joint should be achieved in all cases prior to addressing discogenic pain. This corresponds with some of the contemporary views.[11] In addition to other aforementioned structures, he emphasized the importance of interspinous ligament injections in the treatment of spondylolisthesis.[12]

Gedney treated the United States Olympic swimming team in 1968 as well as athletes from the State University of New York. Among his patients were Philadelphia Phillies shortstop Bobby Wine and Pittsburgh Pirates shortstop Gene Alley. Both athletes were the top infielders in the National League during the 1970 season. Among other famous patients of Gedney's was Johnny Weismuller, Hollywood's Tarzan.

Steindler and Luck and Haldeman and Soto-Hall

In January 1938, Arthur Steindler, MD, and J.H. Luck, MD, reviewed differential diagnosis of low back pain based on procaine injections.[13] They pointed out that posterior divisions of the spinal nerves provide the sensory supply to the muscular structures, tendons, posterior ligamentous structures such as supraspinous, interspinous, iliolumbar, sacroiliac, sacrotuberous, and sacrospinous ligaments, and origins and insertions of aponeurosis of tensor fascia lata, gluteal muscles, and thoracolumbar fascia. They emphasized that these structures are interrelated anatomically and functionally. They also stated that, based on the clinical presentations alone, no definite diagnosis could be made and postulated that five criteria have to be met to prove that a causal relationship exists between the structure and pain symptoms (Table).

TABLE Radiating/referral pain postulates.[13]

1) Contact with the needle must aggravate the local pain.

2) Contact with the needle must aggravate or elicit the radiation of pain.

3) Procaine infiltration must suppress local tenderness.

4) Procaine infiltration must suppress radiation of pain.

5) Positive leg signs must disappear.

Later in 1938, Keene Haldeman, MD, and Ralph Soto-Hall, MD, reported on the diagnosis and treatment of painful sacroiliac dysfunctions with procaine injections in 42 consecutive patients.[14] They observed marked relaxation of spastic musculature after injections and added the

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routine use of sacroiliac joint manipulation after infiltration of posterior sacroiliac ligaments, interspinous ligaments at L4-5 and L5-S1 levels, and zygapophyseal joint capsules with procaine. Thus, they have established manipulation of axial joints under local anesthesia.[14] The publications by Steindler and Luck[13] and Haldeman and Soto-Hall,[14] along with many others, together with the successes of herniologists, influenced Hackett to begin his clinical research of ligamentous pain in 1939.

In 1940, Penn Riddle, MD, Assistant Professor of Surgery at Baylor University College of Medicine, included a chapter on "the injection treatment of joints" in his textbook. He described the treatment of TMJs and shoulders, giving Shultz the appropriate credit for initiation of this treatment.[15]

Shuman

David Shuman, DO, along with Gedney, became interested in injection treatment in 1937. In 1941, Shuman[16] described injection treatment of recurrent shoulder dislocations via strengthening of the inferior capsular ligaments with Sylnasol. Early in 1949, he adopted the term sclerotherapy for this injection modality and, later in 1949, added the term joint sclerotherapy.[17,18] In 93 respondents to the retrospective survey, he evaluated the effectiveness of injection treatment of the sacroiliac joints, intervertebral discs, spondylolisthesis, zygapophyseal joint capsules, knees, and shoulders. Improvements ranged from 75% to 98%. Only those patients who were able to perform their usual occupations were considered to have positive results. Such a high percentage of improvement was probably due to a small sample size of each area investigated.[19] In 1958 in his monograph *Low Back Pain,* Shuman[20] detailed many aspects of treatment with integration of manipulative techniques, manipulation under local anesthesia (introduced 20 years earlier by Haldeman and Soto-Hall[14]), and pertinent pharmacotherapy used at that time. Injection techniques and dosages were described in detail. Shuman[20] stated that zygapophyseal joint pathology, emphasized by Hackett in 1956, and disc pathology are the more common causes of lower back pain than sacroiliac joint pathology.

Bahme

In 1945, Basil Bahme, DO, reported the first retrospective survey of 100 patients who improved after injection of Sylnasol to the sacroiliac ligaments.[21] Patients were under his care for an average of 4 months, and the average number of injection treatments was five. Eighty percent of patients reported complete resolution of symptoms, and only two patients reported no improvements. The

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remaining 18 patients improved from 75% to 90%. He also found the injection treatment to be very helpful in treatment of unstable ribs. He reported improvement in 12 patients and found a significant coexistence of hypermobile ribs with hypermobile sacroiliac joints, explaining the phenomenon by coexisting functional scoliosis.[21]

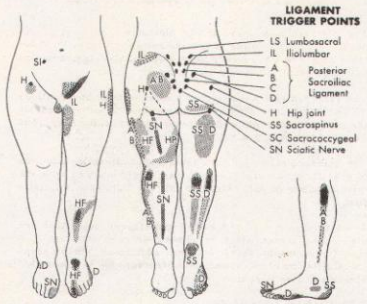
Hackett

In 1953, George Hackett, MD, influenced by some of the researchers mentioned earlier, found that joint "ligament relaxation" is responsible for the majority of back pain.[22] In 1958, he came to the additional conclusion that "tendon relaxation" at the fibro-osseous junctions is another significant source of chronic pain syndromes.[23] In his first report, 82% of 84 patients with sacroiliac pain treated by sclerosant injections of Sylnasol, five to seven times to each affected area, reported themselves entirely cured for a duration of 6 to 14 years.[22] In 1955, Hackett and Henderson[24] demonstrated significant proliferation of tendons in experimental animals after injections of Synasal.

Unsatisfied with the term sclerotherapy because it implied harden-

FIGURE Hackett's maps of referred pain from ligaments and tendons: (A) the initial maps of the lumbopelvic region[25] derived from 7000 injections in over 1000 patients treated over 17 years, (B) subsequent maps were of the cervicothoracic region.[23]

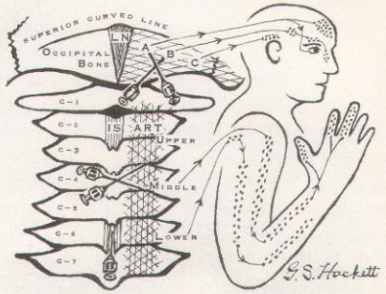
A



Referred Pain Areas in the Abdomen, Groin, Genitalia, Buttock and Extremities from Relaxation of the Posterior Ligaments which support the Lumbosacral and Pelvic Joints.

- IL Iliolumbar ligament (Ilial attachment), Abdomen, Groin, Genitalia, Buttock, Thigh (inner anterior)
- AB Posterior Sacroiliac ligament (upper 2/3rds), Buttock, Thigh, Leg (outer surface)
- D Posterior Sacroiliac ligament (lower outer fibers), Thigh, Leg (outer calf), Foot (outer margin and sole to 5-4-3-2 toes accompanied by sciatica, loss of ankle reflex and body list)
- HP Hip articular ligament (Posterior superior fibers, Pelvic attachment) Thigh (Posterior Medial)
- HF Hip articular ligament (Posterior superior fibers, Femoral attachment), Thigh, Upper half of leg (lateral to calf), Lower half of leg (anterior to tibia), Top of foot to big toe and half of second toe.
- SS Sacrospinus and Sacrotuberus ligament (Sacral attachment), Thigh, Central calf of leg, Heel.
- SN "Sciatica"–nerve pain accompanying relaxed ligaments (lower end of Sacroiliac joint).

B



Trigger Points—Referred Pain Areas
Position of Needles for Diagnosis and Treatment

Occipital Tendons
Referred Pain, Headache, Dizziness

- A Forehead, Eye
- B Temple, Eyebrow, Nose
- C Above Ear

Cervical Ligaments

- IS Interspinus Ligaments
- ART Articular Ligaments
  Referred Pain
  Upper: Neck
  Middle: Arm, Forearm, Thumb, 1 and 2 Fingers
  Lower: Acromium Process, Arm, Forearm.

Unsatisfied with the term sclerotherapy because it implied hardening of the tissue and scar formation, Hackett introduced the term prolotherapy in 1956.

ing of the tissue and scar formation, Hackett[25] introduced the term prolotherapy in 1956. He felt this new term was more appropriate because the results of his experimental study did not support scarring but rather hypertrophy induced by proliferation of connective tissue in linear fashion. Hackett[22] employed and emphasized the importance of the earlier referenced postulates of Steindler and Luck,[13] specifically, confirmation of ligament or tendon involvement as pain generators by reproduction of local and referred pain by "needling" and abolishment of pain by infiltration of local anesthetic prior to injection of proliferating solutions. He published maps of referred pain from ligaments and tendons initially of the lumbopelvic region, which were derived from 7000 injections in over 1000 patients treated over 17 years, and, subsequently, of the cervicothoracic region (Figure).[23,25] Later in the 1950s, Hackett[26] pointed

Hackett's enthusiasm and pioneering spirit brought many capable orthopedists to the field of prolotherapy.

out that loose-jointed individuals have less ability to recuperate from sprains because of the congenital laxity of ligaments and have a predisposition to chronic lingering pain for decades. He emphasized that they respond to the injection treatment positively.[26]

During that same time, Hackett visited London and introduced Cyriax and Barbor to prolotherapy. This gave rise to the spread of this treatment in Europe through Cyriax's disciples. Hackett's enthusiasm and pioneering spirit brought many capable orthopedists to the field of prolotherapy. So convincing were his results that Edward L. Compere, MD, Professor and Chairman, Department of Orthopedic Surgery, Northwestern University Medical School, advocated this method of treatment for persistent backaches.[27]

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