The clinical applications of mesotherapy outside the realm of nonsurgical cosmetic medicine are almost entirely unheard of in the United States. However, in France, the birthplace of mesotherapy, it is first and foremost a pain and sports medicine modality. Mesotherapy is of particular interest to clinicians due to its safety, tolerability, cost effectiveness and seeming efficacy when compared to conventional treatment protocols. This discussion is intended to provide an overview of mesotherapy as it is practiced in France for the treatment of chronic pain and acute injury.

History of Mesotherapy

In 1952, Dr. Michel Pistor, a generalist practicing in rural France, administered 10 mL of procaine intravenously in an attempt to abort an acute asthma attack in a patient. While the treatment did not ameliorate the patient’s respiratory status, upon follow-up, the patient reported a significant improvement in his impaired hearing. Soon thereafter, Dr. Pistor began experimenting with superficial injections of procaine around the ears of hearing-impaired patients and experienced some success. Soon his practice was full of hearing-impaired patients seeking treatment. His results were mixed. However, many of these patients saw improvement in seemingly unrelated conditions such as eczema of the auditory canal and temporomandibular joint (TMJ) pain. In addition, patients reported improvement in tinnitus, which can be related to hearing impairment.¹

Dr. Pistor continued experimenting with superficial injections of procaine for the treatment of a variety of disorders. On June 4, 1958, he published an article describing his clinical success with this novel procedure in which he stated, “the action on the tissues originating from the mesoderm is so extensive that these treatments should be called mesotherapy” (author’s translation). This was the first time the term “mesotherapy” appeared in print. Dr. Pistor described mesotherapy as “smallest dose, infrequently, in the correct location.”²

The mesoderm is one of the three embryologic, histological classifications—endoderm, mesoderm and ectoderm. The cells of the endoderm develop primarily into the internal organs while the cells of the mesoderm level develop into dermis and hypodermis, fatty tissues and the musculoskeletal system. The ectoderm becomes, among other tissues, the brain and epidermis. The term “mesotherapy” therefore refers to injections into the dermis and hypodermis, which originate from the mesoderm. As will be discussed later, one mesotherapy technique developed after Dr. Pistor’s 1958 paper involves injecting the epidermis, which originates from the ectoderm. However, it is important to note that the mesoderm exists only in embryos; there is no mesoderm layer of the human skin—a statement commonly made in error by English language mesotherapists. One is not “injecting into the mesoderm.” Rather, one is injecting into those structures that have arisen from mesoderm.

The first international conference on mesotherapy took place in 1976—also the year in which mesotherapy was first used in inpatient settings in France. In 1981, Dr. Jacques Le Coz introduced mesotherapy into the orthopedic clinic at the Institute Nationale du Sports (National Institute of Sports) in Paris. In 1987, the French Academy of Medicine officially recognized mesotherapy as a legitimate treatment modality within conventional medicine.³

Currently in France, although still viewed as experimental and unproven, mesotherapy is recognized as a legitimate treatment modality by the French Academy of Medicine and is reimbursable by that country’s national social security medical coverage. It has been integrated into France’s largest sports medicine facility⁴ and is practiced in a number of pain management centers in France⁵ as well as in North Africa⁶. Apart from the French Society of Mesotherapy, some of the more established national mesotherapy associations or societies can be found in Algeria, Argentina, Belgium, Brazil, Colombia, Great Britain, Germany, Greece, Israel, Italy, Mexico, Portugal, Russia, Switzerland, Spain, Tunisia, Turkey and Venezuela. The popularity of cosmetic mesotherapy is currently exploding in Asia, with new national associations and societies being formed every year.

Basic tenants of mesotherapy

Mesotherapy is characterized by its unique styles of injection—various superficial injections using specialized short needles and specific techniques directly over the sites of the affected structures.⁷ The proposed mechanism of action of mesotherapy is that solutions that are injected intracutaneously remain in the area longer than they would if delivered via deeper injection because they are cleared more slowly by the general circulation. In addition, it is felt that these superficially injected solutions continue to penetrate into the deeper tissues. Kaplan and Raincourt injected radioisotope-marked calci-
tonin and found, upon serial scans, that the more superficial the injections, the longer the solution remained in the area.\textsuperscript{8} Le Coz and DuPont conducted an experiment on patients scheduled to undergo arthroscopic surgery of the knee. The subjects were divided into three groups. The first group received intraepidermic papules of a diluted NSAID, the second group received subcutaneous injections of the same solution using 4-mm needles, and the third received deep intramuscular injections of the same solution. At 1 and 3 hours post injection, venous blood draws were performed to determine serum levels of the NSAID. It was found that uniformly, the shallower the injection, the lower the level of the substance present in venous circulation at both 1 and 3 hours post injection. During arthroscopy, synovial biopsies were performed and all groups were found to have NSAID present, though tissue concentration levels were not determined.\textsuperscript{9} Mesotherapy therefore appears to be a novel technique for administering medicines locally to the area of the pathology with the skin acting as a natural time-release system.

There are currently three principal mesotherapy injecting techniques—point by point, nappage (French for “covering”) and epidermic. Point by point was first described in the context of mesotherapy by Dr. Pistor. It is very simply the injection of 0.02 cc to 0.05 cc of solution after perpendicularly inserting a 4-mm, generally a 4-mm needle is used and is not fully inserted, perhaps only 0.5 mm to 2 mm deep, and only a drop of solution is introduced at each site at approximately 0.25-cm to 0.5-cm intervals. In this way, one is able to infuse a large area of skin with the solution while achieving a profound cutaneous stimulation that mimics certain ancient acupuncture practices. When done correctly, the practitioner performs a “sweep” of nappage. Pinpoint bleeding occurs 5 to 10 seconds later. Nappage is without a doubt the least comfortable technique for the patient. The third technique is epidermic, first described by Perrin.\textsuperscript{11} As the name implies, this is the most superficial of the techniques. When performed correctly, the basal layer is not penetrated. Dr. Perrin developed this technique in 1989 so that he could perform mesotherapy on children without pain, after a minor mishap treating his daughter for a sinus infection. A 13-mm (or \(\frac{1}{2}\)-inch) 27- to 31-gauge needle is positioned at a very steep angle to the surface of the skin, then, with the bevel oriented away from the skin, it is dragged along the skin while light, positive pressure is applied to the syringe’s plunger. The needle will bend slightly from the angle and the pressure. When treating certain anatomical contours such as the cervical spine and the occipital ridge, the practitioner may bend the needle before treating in order to maintain a correct needle position. Most practitioners will use a slight bouncing action described as “Parkinsonian.” The epidermic technique is intended to produce a shallow groove in the uppermost layers of keratinized epithelial cells which in turn is covered with a bead of solution. When performed correctly, there is no bleeding or scratching but one is able to see the solution quickly absorb into the skin. Epidermic technique is done in a grid pattern at 1-cm intervals over the entire affected area. When either nappage or epidermic technique is performed, the patient must be advised to avoid “spray-on tanning” for a minimum of 24 hours post treatment.

Local anesthetics are used in the vast majority of mesotherapy protocols—either lidocaine 1% or procaine 1%—always without epinephrine. Local anesthetics are used for their anesthetic properties that are believed to be longer acting when injected mesotherapeutically. As is taught by the French Society of Mesotherapy, lidocaine is generally indicated for the treatment of acute conditions, while procaine is indicated for chronic conditions because of its additional vasodilatory properties.\textsuperscript{12}

In France, mesotherapists commonly use the vasodilatory medication Fonzylane (buflomédil) when treating pain. Trental\textsuperscript{®} (pentoxifylline), also commonly used in France, is an FDA-approved medication that is not a true vasodilator but may be used in the place of buflomédil in the United States. The approved use for pentoxifylline is for the treatment of intermittent claudication. The drug improves microcirculation by decreasing the blood’s viscosity and by improving erythrocyte flexibility. Pentoxifylline has been shown to increase leukocyte deformability and inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to significantly increase with therapeutic doses of pentoxifylline in patients with peripheral arterial disease.\textsuperscript{13} Mesotherapists believe that by increasing microcirculation of localized tissue beds, the elimination of metabolic waste is facilitated. Injecting pentoxifylline mesotherapeutically is believed to exercise the drug’s therapeutic effect for a longer period of time compared to other routes of administration.\textsuperscript{14}

Pentoxifylline has been shown in animal studies to demonstrate antinociceptive activity. It is a tumor necrosis factor-alpha and interleukin-1 beta antagonist.\textsuperscript{15} It has been shown to be an interleukin-1 alpha receptor agonist which therefore limits inflammatory hyperalgesia.\textsuperscript{16} Local administration of pentoxifylline causes inhibition of proinflammatory cytokine synthesis and antagonizes hyperalgesia in formalin-injected rats.\textsuperscript{17}

Of particular interest is French mesotherapists’ liberal use of salmon calcitonin (sCT) for the treatment of a broad range of chronic pain disorders. Salmon calcitonin is best known as an antostereoporotic agent administered as a nasal spray, but its analgesic effects in the treatment of acute osteoporotic fracture have been well documented.\textsuperscript{18-21} Researchers have examined the anti-nociceptive properties of sCT for a range of disorders including advanced metastatic malignancy\textsuperscript{22-24}, reflex sympathetic dystrophy\textsuperscript{25}, phantom limb pain\textsuperscript{26-28} and diffuse sclerosing osteomyelitis of the humerus\textsuperscript{29}. One animal study demonstrated sCT’s ability to potentiate the analgesic effect of amitriptyline and paroxetine\textsuperscript{30}.\textsuperscript{26-28}
The mechanisms of analgesic action of sCT are believed to be multifactorial. An anti-inflammatory action has been suggested. Studies in animals and in humans demonstrate that, in some but not all cases, calcitonin increases plasma beta-endorphin levels. It is possible that specific binding sites for salmon calcitonin exist in the brain. It’s worth mentioning that while the clinical use of sCT appears safe, it is not without risk of side effects or adverse reactions. Nausea without vomiting and mild local inflammatory reactions at the site of injection are encountered in approximately 10% of patients receiving sCT and transient severe nausea and vomiting occurs in approximately 1 in 300 patients. Flushing of the face or hands, skin rashes, nocturia, pruritus of the ear lobes, feverish sensation, pain in the eyes, poor appetite, abdominal pain, edema of the feet and salty taste have been reported in patients treated with salmon calcitonin. Administration of sCT has been reported in isolated cases to cause hypersensitivity reaction.

The majority of scientific data on mesotherapy in sports medicine and for the treatment of pain are currently written in French and consist of clinical case studies. These papers are published in the journal of the French Society of Mesotherapy, which is not Medline indexed but which has been published for 30 years. One such clinical case study showed mesotherapy to be beneficial in the treatment of 65 patients suffering from chronic thoracic back pain due to arthritis, spinal stenosis and sprain/strain that was inadequately controlled using conventional methods, namely, NSAIDs, narcotic analgesics, muscle relaxants and physiotherapy. Another clinician describes his results after treating 267 cases of degenerative articular pain and suggests that mesotherapy appears to be an effective and reasonable treatment option, especially in light of the complete absence of adverse events or reactions in the treatment group. One paper describes the mesotherapeutic treatment of 210 patients with soft tissue musculoskeletal pain not satisfactorily controlled with conventional methods. These patients were treated mesotherapeutically with local anesthetics, NSAIDs, sCT and a nonsedating, centrally acting muscle relaxant (thiocolchicoside). The results suggest mesotherapy to be a reasonably effective treatment option, especially in light of poor patient tolerance of the commonly used interventional--injection of corticosteroids. Another paper which describes the use of mesotherapy in 132 cases of patients with back and neck pain that had not been ameliorated by at least 3 months of conventional treatment also shows mesotherapy to be a promising treatment option in terms of safety and efficacy. Mesotherapy has been shown to be helpful in a variety of commonly seen sports medicine conditions such as Achilles tendinitis. Lambert describes his success in treating 48 cases of Osgood-Schlatter.

A systematic review and descriptive analysis of the current data and better constructed, large scale trials are needed. However, mesotherapy appears to be a promising modality in the treatment of a variety of painful disorders. It is of particular interest because of its excellent safety profile, tolerability to the patient, cost effectiveness and seeming efficacy.