

# Case for Prolotherapy

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**H**R3962 guarantees quality, affordable healthcare with expanded access to “reasonable and customary” treatments, which aim to ultimately reduce the growth in health care spending. But questions remain: are the affordable, “reasonable and customary” treatments indeed of quality and will therefore reduce health care spending, or should the health care reform be reformed to include reasonable and non-customary treatments as well?

To answer these questions we needn’t look further than a costly, growing epidemic like musculoskeletal disease, which affects 1 in 4 Americans today, and amounts to \$849 billion in direct and indirect expenditures.<sup>1</sup> In fact, joint, muscle, tendon, and ligament impairments are the leading cause of disability in the United States, and are projected to increase in the next 25 years if our current medical care approach is not thoroughly reviewed and updated. According to the World Health Organization (WHO), musculoskeletal disorders are a leading cause of morbidity, and substantially influence health and quality of life, inflicting an enormous burden of cost on health care systems.<sup>2</sup> Even so, comprehensive research overwhelmingly points to poor results<sup>3</sup> exhibited by insured customary procedures, which in turn will put a greater financial strain on health care organizations in the forthcoming years.

## CORTISONE

Currently, health insurers manage the scope of musculoskeletal disorders by covering customary treatments ranging from steroid injections and arthroscopic surgeries to spinal fusions, which not only cost Americans extra billions in preventable expenses, but are not well supported in double-blind studies. Dr. Richard Wrenn’s experimental study investigating the effect of cortisone on the restoration of injured tendon strength and elasticity, demonstrated suppressed fibroblastic reactions (connective tissue formation) to injury following intramuscular injections of cortisone.<sup>4</sup> In a comparable study by Chandler et al., an intra-muscular hydrocortisone injection was

shown to accelerate degenerative osteoarthritic changes of the hip joint, following 18 treatments.<sup>5</sup> A similar case was reported by Sweetnam et al., although only 3 injections were administered in the study. Steinberg et al. observed a Charcot-like arthropathy (joint dislocation) in a rheumatoid knee after 22 hydrocortisone injections over a 2-year period; identical changes were reported in both knees of a patient who had received a total of 52 intra-articular injections of corticosteroid over a period of 14 months. Essentially, the aforementioned variety of tissue pain and inflammation is suppressed by palliative corticosteroid injections, at the cost of decreased collagenase, and compromised prostaglandin and granulation tissue formation. Simply put, the latter collagen rich tissue must be formed by fibroblasts to heal injured sites, so suppression accounts for poor circulation and jeopardized immune cell repair processes. Because the corticosteroids block glucose uptake in the tissues, thus enhancing protein breakdown and inhibiting new protein synthesis, formation of collagen (protein) and collagen dependent cartilage is arrested.<sup>6</sup> A study carried out at University Central Hospital in Helsinki confirmed that even after a single steroid injection into the knee, cartilage digestion of the joint occurred, while cartilage elasticity was simultaneously reduced.<sup>7</sup> In a parallel study examining articular cartilage in joints, it was found that 16 weeks following a single joint injection, cartilage remained biochemically and metabolically impaired.<sup>8</sup> Undoubtedly cortisol and synthetic analogs may prevent or suppress the development of local heat, redness, swelling and tenderness, by which inflammation is recognized,<sup>9</sup> but on the microscopic level, vital processes are also prevented or suppressed, such as inflammatory cascade, capillary and fibroblast proliferation, deposition of collagen and granulation tissue (scar) formation.<sup>10</sup>

## NSAIDS

While cortisone injections are still considered the standard of care, non-steroidal anti-inflammatory drugs (NSAIDs) are the second line of attack, typically recommended for the first three to five days following acute connective tissue injury, or ongoing administration for chronic musculoskeletal conditions. Unlike corticosteroids, this treatment is non-steroidal as the name implies, yet the main function likewise aims to reduce inflammation. By blocking the production of prostaglandins and leukotrienes,

both treatment forms mediate the inflammatory process, inhibiting blood flow to injured area, reducing protein synthesis, compromising new blood cell formation, fibroblast proliferation and ultimately collagen formation. Rashad et al. cited a study, examining the effects of NSAIDs on the course of osteoarthritis (OA), stating that synthesis of cartilage matrix component was inhibited by anti-inflammatory drugs such as sodium salicylate and indomethacin, and thus accelerating arthritic changes.<sup>11</sup> A retrospective study surveying patients with osteoarthritic hips suggests that NSAIDs contributed to destruction of the hip joint, confirmed by x-ray studies.<sup>12</sup> In another study examining the use of perhaps the most popular anti-inflammatory drug used in sports medicine, ibuprofen, in the treatment of tendon injuries, it was found that ibuprofen decreased flexor tendon strength by 300% at four weeks.<sup>13</sup> Unquestionably anti-inflammatory medications, like steroid injections, immediately reduce pain, offering athletes and employees quick relief and prompt return to sport or work, but such short term benefits are likely outweighed by ensuing tissue damage, including chondrocyte necrosis (cartilage cell damage) and reduction of fibroblast growth and collagen synthesis in the joint. Given that 99% of tendon by dry weight is collagen,<sup>14</sup> and fibroblastic growth is crucial to mechanical stability and strength of tendons and ligaments, it is unfounded to treat injured collagen with fibroblast inhibiting anti-inflammatories. Is it any wonder that adverse drug reaction (ADRs) statistics link NSAIDs to a class of drugs with the highest frequency of side-effects and deaths,<sup>15</sup> with incidences of adverse events accounting for an estimated 7,600 deaths and 76,000 hospitalizations in the United States?<sup>16</sup> Side-effect lists for NSAIDs occupy 50% of space for each drug in the *Physician's Desk Reference*,<sup>17</sup> with one side-effect being increased healthcare expenditures.

High costs of unsupported NSAID treatments compound the long-term economic burden of musculoskeletal disease. Between 1996-1998 and 2002-2004, the use of prescriptions rose substantially, with more than 2.3 billion prescription medications<sup>18</sup> filled for persons with musculoskeletal disease. The widespread use of coxibs for inflammatory conditions partly accounts for the mean annual prescription costs, which were computed in 2004 to be \$653 to \$1,196 per person.<sup>19</sup> In brief, prescription

costs, along with costs associated with treating prescription side-effects comprise a substantial sum of avoidable healthcare expenditures.

#### ARTHROSCOPIC SURGERY

Following an arsenal of NSAIDs, the classic next step to tackling non-healing injury involves a scalpel or arthroscope. The latter method, also known as arthroscopic surgery, is a therapeutic modality that serves as both a diagnostic and surgical tool. Less conservative when compared to NSAIDs and corticosteroids, surgical procedures treat pain via removal of tissue rather than removal of inflammation; all the same, cartilage repair may be stifled.<sup>20</sup> Common sites for such procedures include arm (and shoulder), foot and knee regions, which are frequently subject to repetitive strain, high impact fractures, over exertion, and repetitive workplace and sport related trauma. The former region accounts for 53%–59% of total fractures treated, while lower limb fractures account for 42%–48% throughout the years. In sports trauma, which accounted for 9% of impairments in 2004, the lower extremity is most commonly injured; fractures of the ankle, foot or toes accounted for more than one-half of treated lower-limb fractures. Dislocated knee joint episodes represent 63% of the 5.1 million injuries treated in 2004, with shoulder dislocations representing 6%.<sup>21</sup> In the event of such injuries, surgical reconstruction and arthroscopic shaving is recommended, especially when knee meniscal tearing is involved, rotator cuff strains occur, or anterior cruciate ligaments become lax.

#### TRADITIONAL TREATMENT OF MENISCUS & ACL INJURIES

In terms of meniscal tears, partial or full meniscectomy is commonly performed, since it is widely believed that the inner two-thirds of meniscus tissue (white zone) heal poorly otherwise.<sup>22</sup> However, because the meniscus

functions as a shock absorber and indirectly provides nutrition to the articular cartilage, removal may interfere with nutritional support, triggering cartilage deterioration, subsequently placing excessive contact stress pressure on the bone, lessening shock absorption and potentially inducing arthritis. Numerous studies demonstrate that contact stress

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pressure on articular cartilage significantly increases, following meniscal removal.<sup>23</sup> One such study exhibited a 110% increase in contact stress pressure following partial meniscectomy, and 200% increase following total removal. The study concluded that “the contact stresses increased in proportion to the amount of meniscus removed.”<sup>24</sup> In an animal study, it was shown that meniscal repair may largely cause further spreading of the injury to non-injured meniscal tissue.<sup>25</sup> To add insult to injury, early arthroscopic complications may also be attributed to side-effects, including bleeding into the joint, infections, which account for 12.1% of complications, and thromboembolic disease (blood clots), accounting for 6.9%.<sup>26</sup> One study reported 30 saphenous (femoral) nerve injuries, 6 peroneal (fibular) nerve injuries, 22 infections, 3 vascular injuries, and 4 cases of thrombophlebitis (irritation or infection of blood vessels).<sup>27</sup> Anterior cruciate ligament reconstruction exhibits distinct side-effects following arthroscopic procedures, such as sepsis (infection), skin necrosis, arthrofibrosis (excessive scar tissue), tourniquet paralysis, amongst other complications.<sup>28</sup> The most common side-effect following ACL reconstruction; however, is arthrofibrosis, engendering loss of flexion, extension, or both—an incidence shown to be as high as 3.7%.<sup>29</sup> This complication may be attributed to factors such as infection and bleeding into the joint, followed by immobilization (stress deprivation); further arthroscopic manipulation may be required for scar resection.<sup>30</sup> Supplementary complications may arise from ACL reconstruction surgery techniques involving replacement of injured ligament with prosthesis or tendon to stabilize the knee. In one five year study examining arthroscopic ACL reconstruction with patellar tendon graft, ruptures occurred in 5% of patients.<sup>31</sup> More over, grafts have been found to be three to four times stiffer than actual ACL’s, while artificial graft particles were implicated in stimulating proliferative arthritis when injected into the knees.<sup>32</sup>

#### TRADITIONAL TREATMENTS FOR SHOULDER INJURIES

Shoulder arthroscopy is also fraught with complications including nerve injury, rotator cuff tears, as well as the hemarthrosis (bleeding into joint) and infections.<sup>33</sup> A possible explanation for such risks may be related to the instrumentation. Joints, which normally hold approximately 5 milliliters of fluid, are forcefully pumped with upwards of 120 milliliters of fluid to distend the joint, increase visibility and clear debris, after which large probes, shavers and pumps are inserted to trim and

suture.<sup>34</sup> Clearly the incision site is vulnerable to infection, and considering the size of area operated on, stretching, swelling and increased sensitivity is reported.<sup>35</sup> Though rarer, risks like blood clots and strokes are attributed to use of anesthesia in surgery.<sup>36</sup>

#### COST BURDEN OF TRADITIONAL TREATMENTS

The high cost of customary treatment related side-effects imposes an increasing financial burden on government, our nation’s fiscal future, state economy, and of course our households; after all, poor patient outcomes require follow-up treatments, postpone time off work, and increase direct/indirect expenditures, which raise growth in health care spending, and ultimately render the affordable, customary treatments costly. Particularly, in 2004 the sum of direct expenditures in health care costs and indirect expenditures in lost wages was estimated to be 7.7% of the national gross domestic product. One facet of the latter statistic relates to ambulatory care visits to physicians (direct expenditure), which accounts for a large and growing share of healthcare utilization. In any given year, at least 85% of persons with musculoskeletal disorders use this resource, averaging around six such visits per year. Between 1996-1998 and 2002-2004, ambulatory physician visits increased from 435.5 million to 507.9 million.<sup>37</sup> That is one example of direct expenditures of the musculoskeletal disorders burden; others include hospital inpatient and outpatient services, physician and other practitioner services, home health care, prescription drugs, and administration as well as non-health sector costs. Taking arthroscopic knee surgery into consideration, the national average price is \$11,900,<sup>38</sup> with additional costs for rehabilitation; ambulatory surgery mean charge for arthroscopy was \$8,970 in 2007,<sup>39</sup> while the mean charge per visit/stay in a community hospital for inpatient knee surgery was computed to be \$38,674.<sup>40</sup> It appears that price range hinges on location and type of facility, insurance and co-pay, patient age, et cetera.

Indirect expenditures relate to mortality and morbidity, including the value of productivity losses, and value of lifetime earnings.<sup>41</sup> For instance, improperly treated musculoskeletal conditions present tremendous morbidity costs due to lost work days and lifelong pain that requires ongoing management. In 2005, the National Center for Health Statistics reported in its National Health Interview Survey that 1 in 6 persons (16%) employed in the previous 12 months in the US accounted for lost work

totaling nearly 437.6 million days.<sup>42</sup> On average, workers lost 12 days in a 12 month period, while more than 1 in 5 persons (21%) reported at least 1 bed day in the previous 12 months all due to musculoskeletal disorders, with total bed days reported at more than 810.3 million. Wage losses for persons aged 18 to 64, added in 2004 another \$339 billion, or 3.1% of the GDP<sup>43</sup> to the total cost. Parenthetically, comparing cost of musculoskeletal disease to the GDP provides a firm perspective on the rising, preventable costs that profoundly impact our nation's economy; thus, emphasizing the need for new, quality, cost-effective treatments that will consume a less substantial portion of our healthcare resources. Since the 1996-1998 period, expenditures have grown by at least 0.4% of GDP, and are likely to continue growing more severe as a result of a graying boomer population, costly treatment approaches, lost work days, extended bed days and lost earnings. Accordingly, health care services worldwide will be facing severe financial pressures in the next 10 to 20 years due to the escalation in the numbers of people affected by musculoskeletal disease.<sup>44</sup>

#### INITIATIVES TO IMPROVE BONE AND JOINT HEALTH

To prevent this model, President George W. Bush launched a global, multi-disciplinary initiative in 2002, which primarily focuses on improving bone and joint health, reversing physical, emotional and financial demands of musculoskeletal disorders, and forestalling the projected statistics. The organization aims to accomplish its mission by developing new treatment approaches through research and educating policy makers, professionals and public, as well as increasing investment in health policy research, and finally delineating the underlying mechanisms of musculoskeletal disorders, and their response to treatments. Unquestionably, delineating underlying mechanisms is the best place to start. Connective tissue physiology as well as the etiology and pathophysiology of musculoskeletal diseases must be revisited. Better appreciation of mechanisms relating to connective tissue healing and recovery, inflammation as well as the precipitating causes of strains, sprains, tendinopathy, and lax ligaments, may compel a reassessment and subsequent overhaul of our treatment approach and thereby reduce direct/indirect expenditures, growth in health care spending, and preclude risk of adverse reactions and risk of re-injury.

To regress momentarily, studies presented earlier confirm that our current treatments effectively take for granted

the body's innate response to injury by suppressing a series of actions, starting with the inflammatory cascade, which in fact play a variety of restorative roles. Hence, inflammation is closely interwoven with the process of repair.<sup>45</sup> The key issue is, though inflammation and proliferation equates repair, the process is slow, and that is unacceptable for a medical system that strives for immediate results. On account of poor vascularization,<sup>46</sup> low oxygen consumption, and anaerobic energy generation, the resulting metabolic rate of connective tissue is gradual, and healing capacity is limited<sup>47</sup> leading to fibrosis (formation of scar tissue), and suboptimal tissue integrity and functionality.<sup>48</sup> Even so, it must be noted that despite poor blood supply, *unsuppressed* fibroblasts and chondrocytes can undergo rapid division in response to a variety of stimuli, including trauma, and are therefore able to regenerate the tissue of origin, such as cartilage.<sup>49</sup> Connective tissue cells, like chondrocytes, fibroblasts and osteocytes, which secrete connective tissue matrix, are dormant in adult mammals; yet, they proliferate in response to injury with fibroblasts expressly proliferating widely and constituting the connective tissue growth once stimulated by inflammation. By recognizing the conflicting medical perspectives and corollary practices, a compromise is warranted, which embraces the body's fundamental regenerative capacity; yet, hastens the repair process through improved customary treatment approaches to ensure that connective tissue injuries are less debilitating, and the burden of musculoskeletal disease in America reversed.

#### THE ROLE OF PROLOTHERAPY

One such compromise is Prolotherapy. Non-steroidal, non-surgical, and pro-inflammatory, this "proliferative injection therapy" is founded on the fundamental understanding of connective tissue injury and healing mechanisms; in spite of the intervention's less profitable nature, when compared to current customary treatments, it seamlessly culminates the "Bone and Joint Decade" efforts to offer a cost-effective, novel, preventative and therapeutic approach to mitigating societal and personal musculoskeletal burdens. With a Western medical treatment like Prolotherapy widely available, physical and economic burdens are avoidable even if tendon, ligament and joint injuries are not, occurring unexpectedly at the workplace, on the field, at home or in collision accidents. Too often what may start off as a trivial sprain, can progress into a disabling chronic pain condition. Such as, ankle sprains are exceptionally common in the general

and athletic populations; approximately 25,000 people sprain their ankles daily.<sup>50</sup> If improperly handled, the sprained tissue may become scarred over, stiff and a source of ongoing pain. While the scenario in which ankle injuries occur is not uncommon, injury progression could be; in brief, total relief of such structures begins with understanding of the structures.

Ligaments and tendons are a complex of interdependent collagen, elastin, glycoproteins, protein polysaccharides, glycolipids, water and cells.<sup>51</sup> Collagen is the major component of the extracellular matrix, or “connective tissue,” constituting approximately 25% of the protein in mammals.<sup>52</sup> Therefore the physical behavior of ligaments and tendons, and their healing potential depends greatly on their main component, collagen, and the ground substance of collagen fibers, water and proteoglycans. Fibroblasts synthesize the collagen and proteoglycans in muscles, ligaments, tendons and fascia; chondrocytes, which are connective tissue cells much like fibroblasts, are involved in the formation of cartilage. As noted earlier, fibroblasts and chondrocytes normally demonstrate a low level of replication; however, in response to stimuli, such as trauma, these cells undergo rapid division capable of regenerating native tissue.<sup>53</sup> More specifically, the connective tissue cells (including osteocytes from bone) constitute tissue growth in response to inflammation.<sup>54</sup> In other words, when the body sustains an injury, it is the first stage of healing—inflammation, which compels structure repair through fibroblast and chondrocyte proliferation. Extinguishing inflammation is like suppressing a fever; rather, it is best to just monitor this natural response to microbes by creating an inhospitable environment. Likewise, inflammation is best monitored and permitted to carry out its roles, including increasing circulation, and attracting the same cells that might fight bacteria or virus during a fever.

The inflammatory process is the first phase of healing, followed by proliferative and remodeling phases; if the first phase is compromised, the subsequent reactions are undermined, decreasing chances of complete tissue healing. Specifically, following injury, platelets and numerous immune cells release a potent vasodilator, histamine. This effect is prolonged by mediators such as serotonin, bradykinins and prostaglandins, which in turn encourage circulation, increase capillary permeability, allow subsequent passing of protein rich fluid to injured intercellular spaces, and attract inflammatory cells. Such

complex processes lend the classic redness and warmth, swelling and pain, which characterize soft tissue injury. Often trainers and physicians are disapproving of such accompanying signals, containing them with treatments like corticosteroids and NSAIDs, but pain and swelling simply indicate properly functioning repair mechanisms. In fact, NSAIDs and corticosteroids are at best mere palliative treatments that reduce inflammation and subsequent symptoms by respectively inhibiting the enzyme cyclooxygenase, which in turn inhibits the formation of prostaglandins, or the enzyme phospholipase A2, which blocks the production of prostaglandins and leukotrienes. Already the underlying cause of disease is neglected. Leukotrienes are hormone-like, potent chemotactic and chemokinetic agents,<sup>55</sup> so inhibiting these mediators jeopardizes their role of attracting immune cells to the specific area. Cortisone reduces the quantity of macrophage, or clean-up cells, inhibits fibroblast proliferation responsible for collagen production, and of course thwarts leukocytes, which stimulate the inflammatory process in the injured tissue.

Conversely, it must be noted that inflammation is unconstructive and must be subdued when it becomes systemic. This latter condition however gives inflammation an undeserved reputation. Unlike the acute state, systemic and chronic inflammation underlies the genesis of rheumatoid arthritis, life-threatening allergic reactions, cancer, and even some forms of fatal kidney disease; this notion of unmanageable inflammation has disgraced the biological response, compelling medical practitioners to stifle it in every situation. But in the case of connective tissue injuries, inflammation has chronic tendencies only if improperly handled, while the initial swelling performs an adaptive function, jumpstarting the healing process. Yes, customary treatments have their time and place, such as in complete tears, but otherwise in common tendon and ligament restoration, stimulating inflammation for faster repair is justified. And that’s just what Prolotherapy does.

An alternative/complementary injection therapy firmly anchored in clinical and scientific methodology, Prolotherapy has garnered quite a following of practitioners and recipients in its 50 plus years of practice. This success is largely owed to repeated favorable outcomes in local clinical settings, as opposed to organized funding and industry sponsored research. Logically the United States Bone and Joint Decade, which strives to improve quality

of care by encouraging nonexclusive collaborative efforts, should recognize a treatment such as Prolotherapy, which meets its objective of providing low-risk, low-cost, high-quality care that could reduce direct/indirect expenditures, help speed recovery and challenge the projected statistics of impending personal and societal financial pressures. Since the initiative's launch, many advances have been made; even so, musculoskeletal conditions remain costly, chronic, and all too common to an aging population with high expectations of the health system. Accordingly, it is imperative to review and update agendas of the industry, government, hospitals and universities, which generate the majority of scientific research; that is, overcoming hurdles set up by pharmaceutically driven interests will framework the ultimate success of the Bone and Joint Decade. This involves re-educating, or rather "advancing the understanding" of government and health agencies, a very notion the Decade stresses; as a matter of course funding and research may be merited to underfunded, under-recognized unconventional treatments like Prolotherapy, which are currently criticized for unsatisfactory study designs, lack of placebo controls, and blindness. Without the fair amount of studies backing up anecdotal success, seemingly Prolotherapy is unlikely to become a mainstream Western medical therapy, after all, medical schools, which rightly adhere to grounding their education in evidence-based science, are naturally disinclined to expose students to minimally studied allopathic medical injection therapies, albeit erected on replicable and predictable clinical results, empirical data collection and of course official scientific experimentation.

#### THE FINANCIAL COMPONENT

As a whole, Western medicine's poor track record in treating underlying mechanical dysfunction warrants funding interventions like Prolotherapy, which if studied with blindness and controls, *ideally* may become the quality, affordable "reasonable and customary" treatments covered by health insurers today. *Realistically*, healthcare is a business not insulated from profit driven interests. According to a concept review published in *The Journal of Bone and Joint Surgery*, medicine is now an industry partly due to business principles drawn upon by government regulators; this shapes medicine, inadvertently increases overhead, encourages competitiveness and promotes struggle for market share.<sup>56</sup> That is quite evident when considering profit margins of customary treatments; NSAIDs are fast approaching the three billion dollar mark in annual sales,<sup>57</sup>

with 70 to 75 million NSAID prescriptions written annually in the United States alone, with additional expenditures to treat adverse effects.<sup>58</sup> A retrospective cohort study examining side-effect treatment costs following NSAID administration for arthritis extrapolated that 3.9 billion was spent on treating arthritis, thus adding 45.5% to the cost of arthritis treatment.<sup>59</sup> As for arthroscopy, surgeons readily perform these "highly reimbursable procedures,"<sup>60</sup> with costs ranging in the thousands, mounted by MRI and x-ray, ancillary and rehabilitation charges.<sup>61</sup> Low corticosteroid costs and short treatment duration is off set by side-effect generated revenue, which as remarked upon by the *Denver Business Journal*, boosts the lucrative health care crisis<sup>62</sup> and the swollen bottom lines of the pharmaceutical industry,<sup>63</sup> which incidentally contributed more to the public record of steroid research than any other industry before.<sup>64</sup> A non-pharmacologic treatment like Prolotherapy on the other hand is a relatively simple procedure that uses readily available proliferant solutions like dextrose, glycerin, minerals, sodium morrhuate, autologous growth factors, and other pro-inflammatory compounds<sup>65</sup> that naturally offer long-term relief through stimulation of collagen formation, fibroblast production and the strengthening as well as tightening of injured connective tissue structures.

Time and again Prolotherapy delivers such results, and the basic healing mechanism is quite straightforward. A proliferant is injected, leading to local inflammation, which in turn triggers a wound-healing cascade, resulting in new collagen deposition. The naturally occurring protein shrinks as it matures, tightening and strengthening the injected ligament, tendon, meniscus, muscle, cartilage or joint of the back, ankle, wrist, hip, knee, and other such areas typically bearing the brunt of force. Because the rate of healing is rapid, and minimal injections required, Prolotherapy fell out of favor during the 1980's considering its "unprofitable" nature. After all, with Prolotherapy fewer people would require pain medication and expensive surgery, thus eclipsing the drug company foothold. Funding and advancements necessary to propel the unprofitable venture into the spotlight were thus arrested; as follows, the current volume and strength of available data is insufficient for the Medicare Board, which covers well-supported, double-blind studied therapies. But this is no longer a viable excuse for Prolotherapy's delayed success, for the societal and economic cost of musculoskeletal disease presents a compelling argument for expanding research to new fronts. Solutions lie not

in drug company sponsored research, for Prolotherapy is inherently unprofitable; after all, short treatment duration and efficient recovery targets the injury's root cause, preventing future wear and tear of supporting structures, permanently welding disabled ligaments and tendons to bone, and rendering adverse reactions near obsolete. In 1993, a survey was published, reviewing Prolotherapy injections performed by 95 physicians on a total of 494,845 patients.<sup>66</sup> Of these, 343,897 sought treatment for low back pain, while 98,430 for other spinal areas and 27% received non-spine peripheral joint injections. Of all the patients, only 66 reported minor complications, including 24 reports of allergic reactions and 29 cases of pneumothorax, all of which were swiftly resolved. Fourteen reports accounted major complications, which required hospitalization or ongoing care. In summary, there were only 80 complications for a total of 494,845 patients, yielding only a 0.00016% chance of complications. Literally, risks associated with Prolotherapy are continual pain relief, or rather continual pain relief following a sharp pinch when skin is punctured. In that case, patients sensitive to injections may receive local anesthesia, tranquilizers and pain medications.

Of course like any other invasive medical procedure, Prolotherapy too has potential side-effects, including risk of infection, stiffness, increased pain, bruising, bleeding, and other rarer risks. But what's more at risk is chronic pain associated with improper preliminary treatment, and at a time when joint disease accounts for half of all chronic conditions in the elderly,<sup>67</sup> alternative solutions are now more critical than ever. But they do not hinge on agendas of well-funded research institutes or government and health agency re-education programs; rather, solutions lie in the empowerment of the people, and their "participation in decisions about their care and treatment,"<sup>68</sup> as noted by the Bone and Joint Decade initiative. Forty percent of all women over the age of 50 years are expected to endure at least one osteoporotic fracture in their lifetime.<sup>69</sup> That is to say, 1 out of 3 women over the age of 50 are collectively encouraged to review all their treatment options and make informed decisions before settling on any therapy; with new patient expectations, physicians may be compelled to update their practices to meet demands. More than 130 million annual visits to healthcare providers rank

One Prolotherapy study showed that for a total of 494,845 patients, only 80 experienced complications, yielding only a 0.00016% chance of complications.

musculoskeletal conditions as the number one reason for physician calls.<sup>70</sup> In other words, nearly 1 in 2 Americans over the age of 18 may be empowered to demand that research of reasonable treatments like Prolotherapy be funded, and ultimately covered by health insurers once an adequate volume of methodically conducted studies are available.

By the year 2020, elderly will account for 25% of the population in countries with developed market economies.<sup>71</sup> This otherwise neutral statistic alas presages an increased rate of musculoskeletal disorders that represent half of all chronic conditions in individuals 65 years and older.<sup>72</sup> The aging population steadily approaching the 25% demographic should take heart in the fact that Prolotherapy is available, insured or not (though hopefully so by at least 2020). Unrestricted access to this low-tech, low-risk injection procedure, at

a fraction of the cost, offers a refuge for the young and elderly alike, in developed and emerging market economies, by reinforcing potential complications with tissue welding techniques, guaranteeing lasting pain relief and recovery. Prolotherapy is the solution, demonstrating in virtually every case growth of normal, stronger ligament and tendon tissue following stimulation of the body's natural healing mechanisms; and there are a

sufficient amount of sound studies, including case reports, pilot, retrospective, open face prospective and double-blind placebo controlled, which confirm these facts. Dr. Y. King Liu used the knee ligament in rabbits to quantify the strength of tissue formed by Prolotherapy.<sup>73</sup> In his study, a 5% cold liver oil extract solution was injected 5 times into the femoral and tibial attachments of the medial collateral ligament, and then compared to non-injected ligaments. Results demonstrated significantly increased ligamentous mass, thickness, and strength. Particularly, within a 6 week period, ligament mass increased by 44%, thickness by 27% and the ligament-bone junction strength by 28%. To confirm Dr. Y King Liu's results by illustrating the tissue proliferating process, while testing how the procedure applies to tendons, Dr. J.A. Maynard and associates treated rabbit tendons with the same solution.<sup>74</sup> Following proliferant injections, the actual tendon circumferences increased an average of 20 to 25% after 6 weeks. The researchers observed, "The increase in

circumference appeared to be due to an increase in cell population (immune cells), water content, and ground substance (glue that holds the collagen together...) Consequently, not only is there an increase in the number of cells, but also a wider variety of cell types, fibroblasts, neutrophils, lymphocytes, plasma cells, and unidentifiable cells in the injected tissues.<sup>77</sup> These findings are not unlike what biologically occurs when injured tissue self-repairs, so the source of pain and injury is mended rather than covered up, and essentially turns a chronic injury into one that is acute<sup>75</sup> by activating the immune system. On these grounds it is fitting to say that Prolotherapy is the solution, as it induces the natural healing mechanisms of the body by increasing circulation, in turn transferring not only nutrients but immune cells that stimulate tissue restoration through growth of collagen.

#### FAR REACHING EFFECTS OF PROLOTHERAPY

Prolotherapy injections are not limited to ligaments and tendons of the knee and spine, but produce similarly successful results when administered into the neck, shoulder, groin, wrists, hips, etc. Efficacy of Prolotherapy for groin functional impairments was studied in 2005 by Reeves, et al.<sup>76</sup> Career-altering groin/abdominal pain, non-responsive to conservative treatment trials, jeopardized top athletic performance of professional rugby and soccer players. Following monthly injections of 12.5% dextrose in 0.5% lidocaine in abdominal and adductor attachments on the pubis, 66 of 75 elite athletes returned to full elite-level, unrestricted performance in an average of 3 months. While that is impressive, osteoarthritis pain has also been studied, with successful results. In a recent double-blind placebo controlled study, knee osteoarthritis symptoms demonstrated statistically and clinically significant improvements at 1 and 3 years follow-up after injections. When present, ACL laxity improved as well.<sup>77</sup> In another study, finger and thumb osteoarthritis showed improvement after 6 months following Prolotherapy injections, with 42% improvement in pain and 8 degree improvement in flexibility.<sup>78</sup> Such findings attest to Prolotherapy effectiveness, with a healing rate averaging between 75–90%,<sup>79</sup> and fast recovery. The latter point is critical when considering the indirect expenditure impact on the total GDP, with prolonged recovery time comprising a major facet of productivity losses. In

fact, Prolotherapy is one of the only treatments that actually encourage movement post-treatment to aid the healing process, and that itself could be considered rehabilitation. Repair and regeneration begins within the first few days and does not involve the prolonged period of residual pain and disability that, say, surgery recovery involves with the rehabilitation course potentially lasting weeks, months or even years. More over, unlike inpatient operative procedures, Prolotherapy does not require general anesthesia/epidural and the execution lasts mere minutes as opposed to hours, costing hundreds as opposed to tens of thousands, thus mitigating direct expenditures associated with customary treatments.

#### COST ADVANTAGES OF PROLOTHERAPY

Societal and personal financial burdens are further mitigated by the fact that Prolotherapy sidesteps expensive MRI and x-ray tests, and rejects the prolonged and costly pain medication approach, which may ultimately wear off. To put the differential costs into perspective, 2 to 3 proliferative injections for young patients and 4 to 8 for adults at approximately \$250-600 per session is comparatively an inexpensive out-of-pocket medical investment; for a patient without insurance, Prolotherapy is a cost-effective, viable alternative to customary treatments like prescription pain medications that cost several hundred dollars per month, doctor recommended EMG/NCV or MRI, which may cost approximately \$1,200 and \$2,500 respectively, as well as pricey operative procedures, and their follow-up rehabilitation fees ranging in the hundreds per visit. Such preventable costs, which profoundly impact our nation's economy, may be arrested by redirecting focus to treatments with low administrative costs, short treatment duration and minimal risks.

As it stands, the social impact of musculoskeletal pathologies entails high costs, in terms of treatment and loss of income; a reform that aims to address such healthcare pitfalls must target costly treatments, which fail to deliver results and contribute to unnecessary spending. As such, reviewing the economic impact of past health spending is one of the keys to our long-term fiscal future. Total national health spending steadily increased from approximately 6% of GDP in 1965 to more than 16% in 2007,<sup>80</sup> and this rising health care trend, which is a major share of the economy, is expected to continue in the future.

It is projected that by 2018, national health spending is anticipated to comprise just over one-fifth, or 20.3%, of GDP.

In fact, between 2008 and 2018, average annual health spending growth is expected to surpass average annual growth in the overall economy by 2.1 percentage points per year.<sup>81</sup> It is thus projected that by 2018, national health spending is anticipated to comprise just over one-fifth, or 20.3%, of GDP.<sup>82</sup> This grave course our nation is bound for may be redirected by increasing investment in health policy research and spurring the Bone and Joint Decade initiative to revolutionize treatment approaches. That includes weeding out conventional therapies that treat distinct conditions uniformly, as well as overhauling the prevailing model of chronic pain management, which hinges on anti-inflammatory medication and injections. No matter who pays for such care, it does not offer patients better quality of life, and thereby drives up health care costs without yielding corresponding long-term benefits. Perhaps Prolotherapy doesn't after all fit in an industry whose financial incentives and insurance payment policies encourage physicians to order more tests and costly procedures, then its time to fit the industry to Prolotherapy. Besides limiting costs, this will help, not hinder physicians to fulfill their Hippocratic Oath as their tool kits are broadened to tackle complex conditions in a personalized program. Proactive physicians translates into medicine that is more participatory with a preventive focus that moves beyond adequate into optimal.

(See Table 1.)

Returning to the initial question examining whether the “reasonable and customary” treatments should be reformed to also include reasonable and *non*-customary treatments, well, that's for the patients to answer. Once patients recognize that musculoskeletal conditions, including osteoarthritis, cost nearly 128 billion per year in direct medical expenses,<sup>83</sup> and that Prolotherapy heals connective tissue, regardless of injury severity and location, then the answer is clear. Indeed the reform driven research trend should favor cost-effective interventions that reflect the patient's own innate regenerative capacity. National spending trends and poor results exhibited by customary treatments present compelling evidence for better coverage of therapies that may ultimately save the health industry billions of dollars per year, but more importantly save the increasing human toll by delivering care patients deserve. ■

BIBLIOGRAPHY

References for this article are available online at [www.journalofprolotherapy.com](http://www.journalofprolotherapy.com).

The benefits of Prolotherapy versus traditional methods, including surgery:

- cost effective
- safe form of long-term pain relief
- swift recovery
- general anesthesia/epidural is not required
- MRI is not required
- limits long-term medication use
- prompt return to activity encouraged/mobility not restricted
- exceptional safety track record
- minimal side-effects
- treatment is minimally invasive and quick (minutes versus hours)

**Table 1. The benefits of Prolotherapy versus traditional methods.**