The Case for Utilizing Prolotherapy as a Promising Stand-Alone or Adjunctive Treatment for Over-Manipulation Syndrome

[1]Karina Gordin

[2]Ross Hauser

1 Karina Gordin, BA, MS, is a medical journalist, and a member of the National Association of Science Writers (NASW) and American Medical Writers Association (AMWA)
May be contacted at write@healthwright.org

2 Ross Hauser received his M.D. from the University of Illinois, Chicago, and completed his residency at Loyola-Hines VA-Marianjoy Hospitals in Physical Medicine and Rehabilitation. He is now the medical director of Caring Medical, and co-founder of the physician-run, comprehensive Prolotherapy clinic, Caring Medical & Rehabilitation Services in Oak Park, Illinois. He coauthored the national best seller "Prolo Your Pain Away! Curing Chronic Pain with Prolotherapy," along with a four-book topical mini series of Prolotherapy books.
May be contacted at drhauser@caringmedical.com

KEY WORDS: Chiropractic; HVLA; Iatrogenic Disease; Ligament Laxity; Manipulation; Manual Therapy; Over-Manipulation Syndrome; Prolotherapy; Platelet-Rich Plasma; Range of Motion; Spine

ABSTRACT

Objective

The medical term 'manipulation' may refer to any passive movement. Primarily the term refers to a sudden thrust of small amplitude, performed at a rapid speed accompanied by an audible crack. This manual procedure, also known as 'Grade V Mobilization,' 'adjustment,' and 'spinal manipulation therapy (SMT)' is used extensively in the chiropractic and osteopathic professions, and is steadily gaining popularity with physiotherapists, medical practitioners, and podiatrists. With growing popularity comes the responsibility to analyze long-term therapeutic and physiologic effects of joint manipulation and the corollary risk Over-Manipulation Syndrome (OMS). As used in this text, OMS is defined as a musculoskeletal condition characterized by a constellation of symptoms ranging from chronic pain to muscle spasms due to ligament laxity and joint instability, induced by manipulation performed by practitioner, and/or self-manipulation.

Design

This literary synthesis critically analyzes long-term effects of high-velocity, low-amplitude thrust manipulation on connective tissue stability/mobility, and presents a basis for alternative approaches designed to minimize complications. Through a comprehensive cross-examination of research study results, this review investigates the long-term effects of spinal manipulation, and initiates a discussion about the research methodologies and relevant findings related to the therapy.

Method

The review process involved compiling scientific publications and searching indexed biomechanical and medical studies relating to SMT treatment techniques, measurements of mechanical and safety parameters, and manipulable lesions. Relevance to spinal manipulation was the primary criterion for selecting articles for inclusion in the review. Original reports, surveys, case studies, Meta

analyses, and relevant content in any of the subfields of spinal manipulation were selected, irrelevant of date of publication.

Conclusion

Currently there are numerous accepted manual procedures but no singular biomechanical parameter to predict which procedure type is most effective and safe, and which manual treatment offers the greatest likelihood of long-term recovery. While hypotheses and classification systems are continuously investigated, the current level of safety remains ambiguous; as such, alternative therapies like Prolotherapy, which may counteract potential risks, are useful.

INTRODUCTION

A growing collection of major studies and surveys report a trend toward chiropractic therapy, as dissatisfaction with traditional medicine mounts amongst conventional healthcare providers, payers and the general public. The Federal Agency for Health Policy and Research (AHCPR) observed that chiropractic is now the third largest group of doctoral-level providers in North America, with over 50,000 practicing practitioners today.[1] Polls released by Landmark Healthcare Inc. demonstrated that one in every five adults ages 55 to 64 uses the manual therapy to restore a properly functioning musculoskeletal system. Conversely, chiropractic treatment for children is growing in popularity as well, so with the changing population demographics, the demand for chiropractic is expected to grow 20 percent by 2018, much faster than the national average for most professions.[2]

Clearly the complementary approach to treating mechanical disorders emerges as a promising therapy, offering immediate relief of symptoms without the use of drugs or surgery. It is no wonder that in just a single year more than 250 million[3] adults sought the noninvasive service for pain reduction and functional impairments. Particularly, a Rand Corp. study[4] sites low-back pain, extremity weakness and numbness, vertebral subluxations, and migraines as primary reasons for seeking the service. Chiropractic philosophy recognizes such conditions as corollary of improper communication between the nervous system and skeletal trauma, and strives to manage them accordingly; as such, common therapies that guide bones and tissue to correct positions in order to restore vital brain/body pathways include cryotherapy, trigger point therapy, ergonomic/postural guidance, and most commonly, spinal manipulation therapy (SMT). The latter approach, comprising 73.5 percent of all chiropractic visits[5], is of greatest interest and controversy, playing a dominant role in conservative medicine for centuries.

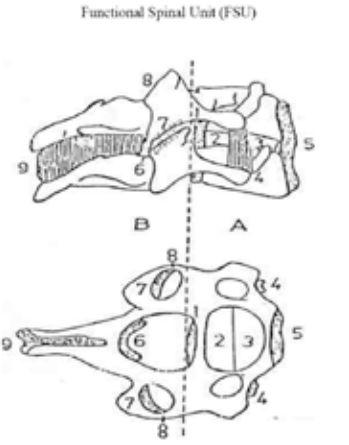
Indicated as early as 2700 b.c.e. in ancient Chinese texts, the art of restoring joint play through passive movement has been practiced in early societies spreading from Babylon and Tibet to South American groups of Mayan, Aztec and Zoltec Indians, as well as Native American tribes like the Sioux and Winnebago. Largely, manipulation traces its roots to the ancient Greek physician Hippocrates who advocated the procedure for the treatment of many diseases, which he warned are commonly related to the spine. To adjust displaced vertebrae and other distortions, a combination of spine-stretching contraptions were used, which one may say modeled medieval instruments of torture. Luckily adjustments have been perfected since the time of hauling patients upward via a windlass, as cables securely restrained legs to the base. Now practitioners typically use their own body weight to exert a controlled thrust on misaligned or subluxated spinal segments, rather than binding patients to frames suspended vertically from pulleys and violently jerked. Of course not all ancient techniques were crude. Like the drop tables used today as part of the Thompson Technique, Hippocrates recorded the use of supine spinal manipulation, during which time patients lay facedown and endured a less immobilizing joint mobilization procedure:

The physician or anyone else who is strong and not ignorant should place the thenar (fleshy palm) of the one hand upon the protuberance and the thenar of the other hand upon the former to force the vertebra, by a quick jerk, to slip back into its former place[6]. In other words, Hippocrates described a strong and not ignorant physician administering the high velocity/low amplitude (HVLA) technique, used widely today.

In theory, HVLA adjustments strive to repair pathological barriers† via a quick thrust (high velocity) over a short distance (low amplitude). As such, peak forces (PF) in excess of the clinician's body weight create vertebral movements in the paraphysiological zone†, reducing asymmetry[7] and hypertonicity[8], relieving whiplash[9], spastic muscle[10], back[11 12 13] and neck[14] pain, decreasing skeletal muscle inhibition[15 16], and to a lesser extent alleviating cervicogenic headaches[17] and migraines[18], distending fibrosed articulations, and other lesions of a mechanical nature. While the preponderance of studies on clinical efficacy support the use of manipulation for the management of such dysfunctions, the basic science is limited by a lack of solid data on the nature of the underlying symptoms and pathology.[19] For instance, pain of the cervical and sacral spine[20] (LBP) is a clinical entity with the greatest amount of research; even so, questions remain concerning how the pain is represented, viz., is back pain an observed sensation, a loss of function, an asymptomatic abnormality, or perhaps a change in biomechanical or biochemical morphology? What characteristics qualify an accurate prognosis based on response to treatment? Accordingly, how does one measure such mechanisms to confirm that manipulation is safe and effective? Well, health care interventions like SMT typically rely on a hierarchy of evidence[21] to draw conclusions; of greatest merit are randomized, controlled trials (RCT), followed by cohort and case control studies, which in the case of SMT may be too small to evaluate risk of complications[22]. In treating headaches for example, the hierarchy of evidence is less conclusive, with published series studies[23 24 25 26 27] and pilot studies[28] offering an abundance of anecdotal evidence with variable results. Considering over 38 million procedures are performed annually in the US[29] for neck pain and headaches, more studies are warranted to investigate the effect of PF on target tissues that are largely responsible for neck stability, and which incidentally are susceptible to dislocations, subluxation, tears, and laxity. Large-scale randomized clinical trials have yet to be conducted to draw stronger, more definitive conclusions; likewise, RCT designs investigating the nature of dysfunctions and manipulable lesions may use animal, treatment dummy, cadaver or conceptual models, thereby bringing into question the validity of the results in a clinical setting. Clinical outcome study designs on the other hand have the advantage of representing cases in real life clinical settings. But whereas clinical evidence on benefits is steadily accumulating, minimal quantitative data are available to demonstrate outcome and safety from a physiologic and biomechanics stand point[30]. Parenthetically, biomechanics is an important component of research as this science strives to discern external and internal forces acting on biological systems and the corresponding effects. Concerning HVLA in particular, one of the most intriguing questions in biomechanics pertains to the purported "distribution-problem,"[31] which aims at calculating (theoretically) or measuring (experimentally) external forces exerted by a chiropractor on internal structures of the biologic system, primarily the muscles, tendons, ligaments, bones, discs and articular cartilage. Experimentally, external forces have been measured using treatment simulators, force platforms and pressure sensitive mats. Despite the reproducibility of results under virtually identical conditions, the disadvantage of such treatment simulators relates to their inadequate representation of real clinical situations. Theoretically[32], forces exerted by chiropractors on patients have been determined, but on account of mathematically complex mechanical representations of spinal manipulative treatments,

accurate predications of contact forces are questionable[33]. With regards to internal forces, there are very few, if any studies of this kind that identify which structures absorb and transmit forces, to what degrees they are deformed and how close internal forces approach ultimate failure loads. As yet, the distribution-problem has not been determined theoretically, even in relatively straightforward systems where direct internal force can be conceivably measured[34 35 36] using cadavers. So from a strictly scientific standpoint, explaining the treatment effects as well as transmission of stresses and strains across soft tissues remains in question. Thus, while HVLA has been a long-standing remedy for musculoskeletal complaints, risks attributable to wide variations in mechanical parameters are necessary considerations.

Figure 1.



A: Anterior elements: 1- Posterior longitudinal ligament; 2- Intervertebral disk, posterior half; 3- Intervertebral disk, anterior half; 4- Intertransverse ligament; 5- Anterior longitudinal ligament. *B*, Posterior elements: 6- Yellow ligament; 7- Facet capsule; 8- Articular facet; 9- Interspinous and intertransverse ligament.
Reprinted with permission from CRANIO: The Journal of Craniomandibular Practice. April 1987, Vol. 5, NO. 2

BACKGROUND

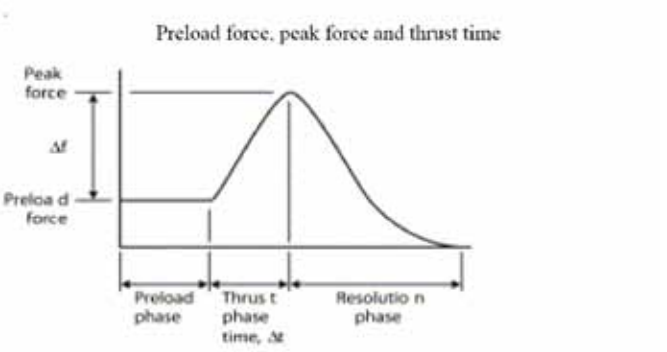
Manipulative therapy has evolved like most medical treatments, by trial and error. Not until the 1975 National Institute of Neurological Communicable Disease and Stroke sponsored conference has scientific effort been directed toward spinal manipulation research[37]. Since then substantial strides were made in fostering interest in this promising procedure, compelling further research efforts in understanding manipulation biomechanics and elements of the underlying lesions. Despite limitations of today's knowledge, what seems clear from the accumulated evidence, both empirically developed during the past century and more recent experiments, is that spinal lesions may have etiologies, disorders and therapies of a mechanical nature. As follows, many hypotheses focus on mechanical mechanisms of action, viz. resolving altered body segment kinematics as well as load distribution between joint tissue components[38 39 40]. Because opinions of authorities diverge widely, other hypotheses range from physiological[41] to purely psychological effects[42]; still, some anecdotal observations and systematic reviews demonstrated no affect other than time alleviating pain and functional disability[43 44]. A single mechanism that describes beneficial aspects of HVLA comprehensively does not exist, particularly one that is accepted by the majority of the scientific community. To date, the lack of a unifying scientific paradigm in chiropractic research has inhibited a general consensus regarding the most reliable approach to evaluating HVLA mechanics. In spite of efforts to standardize outcome measures[45 46], an absence of the "gold standard" results in a number of separate hypotheses, accounting only for a narrow sample of clinical observations. Consequentially, the basis for a manipulable lesion[47 48] is hinged on speculation from indirect evidence for probable mechanisms. Direct evidence remains equivocal. In the meantime, over 25 different manipulation procedures are nevertheless used[49], varying by unknown amounts in mechanical factors, including displacements generated by applied loads. This is clinically relevant because, for instance, the simple facet syndrome is thought to arise from inappropriate loading of the facet joints[50], which are often targeted during HVLA[51]. Without a systematic understanding or a set of standards by which procedures are performed, rational strategies for improving the delivery

of HVLA are hindered, and associated risks are largely not identifiable[52].

TREATMENT OUTLINE

The current level of our understanding of manipulation, coupled with the widely divergent views, is unacceptable in the context of permitting patients to make treatment decisions based on available data. Minimizing risks by maximizing efforts in understanding side effects, contraindications and idiosyncrasies will paint a more realistic picture of therapeutic (and physiologic) approaches, which may in turn facilitate the anticipation of positive and negative patient responses, as well as improve the future of manipulation treatment delivery. The challenge in achieving that level of understanding is subject to the physical nature of performing HVLA, which entails operating under widely varying conditions of load, as dictated by patient weight, bulk and position. While conceptual models and experimental data endeavor to define such conditions via the global reference system[53] for the body, questions remain. Specifically, what are the circumstances under which different loads are safe, and how do such loads act on the spine? Few studies have concentrated on the load sharing function[54 55 56 57], so data on load shifting strategies (i.e. from muscle to ligament) can be helpful in discerning the kind of tissues involved in injury. As it stands, current studies show soft tissue/connective tissue[58] sequelae; after all, the spinal column formed by the vertebrae is joined with two ribbonlike ligaments, the anterior longitudinal and the posterior longitudinal ligaments (SEE FIGURE 1), which are effected by PF, shear as well as excessive flexion, extension and rotational thrusts. Orthopedic textbooks show that excessive shear forces such as posterior shear of the superior vertebrae may induce ligamentous damage, while anterior shear of the superior vertebrae has been documented to cause facet fracture leading to spondylolisthesis[59]. Given the oblique fiber direction of the complex interspinous tissue, a likely scenario of ligament pathology may be the thrusting of the pelvis forward, generating a posterior shearing of the lumbar joints when the spine is fully flexed, ultimately leading to ligament laxity and acceleration of instability and degenerative changes. Apparently the specific type of injury appears to be modulated by loading rate; principally, anterior shear forces generated undefinable soft tissue injury at low load rates (100 N/s) while fractures of vertebral body and facet were observed at higher load rates (7000 N/s). Such wide ranging preload (SEE FIGURE 2) and uniaxial peak forces depend on a variety of factors, including the HVLA technique, targeted spinal regions, and most notably, the strength/gender/experience of manipulator[60]. For instance, studies[61] show that peak forces for sacroiliac joint adjustments in a side-lying position are approximately 400 N; even so, this load never exceeded 200 N for some chiropractors, while it never dipped below 800 N for other chiropractors manipulating a minimum of six different patients. This result implies that peak treatment forces may easily differ by a factor of 2 to 4 from one chiropractor to another. Loading to the thoracic spine region may also be significant, with some

Figure 2.



Reprinted from *Journal of Bodywork and Movement Therapies*, 14/3, Walter Herzog, The Biomechanics of Spinal Manipulation, 280-286, with permission from Elsevier.

authors[62 63 64] reporting single components of applied loads varying from 77 N to 870 N, and one reported case of 1800 N65. A study measuring peak forces demonstrated a range of 200N to 1600 N for the same segment, which is an eightfold difference [66]. These wide variations complicate delineating patient responses as well as injury thresholds, studied as a function of decreased stiffness as loads are administered. Compounded with potential pre-existing degenerative disorders, loads and energy absorbed by an intervertebral joint is significantly reduced, to one half and one third, respectively[67]. In fact, disc narrowing or facet arthrosis is likely to alter the geometry of the vertebral joints enough to affect the ligament's ability to restrain motion. In short, the expression concerning knee joints also applies to the spine: "ligament damage marks the beginning of the end [68]."

Soft tissue of the upper cervical spine (CS) is functionally more vulnerable to quick thrusts of high magnitude on account of the atlanto-axial joint anatomy. With little osseous stability, high functional demands are placed on the supporting ligamentous structures, rendering the region more susceptible to laxity, subluxation and particularly atlanto-axial dislocation (ADD)[69] following injury to transverse atlantar or alar ligaments. The upper C0-C2 region is mostly stabilized by ligaments, including the apical, anterior longitudinal and capsular, vertical band of the cruciate ligament, and ligamentum flavum[70], so even minor injuries largely affect stability of the spine. C4-C6 segments experience a higher rate of mechanical stress and degeneration, predisposing them to injury following physiologic motions like forceful axial rotation, extension combined with flexion, and axial rotation combined with lateral bending[71]. Because the bony structures facilitate mobility (as opposed to stability) the principal cervical ligaments are under greatest tension in rotation and flexion. Sudden or sustained rotation and extension[72 73] have been implicated in pathological events like cauda equina and disk herniation; specifically, techniques involving axial rotation coupled with compressive loadings were implicated as risk factors for tearing of intervertebral disk (IVD) annular fibers. A literature review74 found IVD herniation in 61 of 295 cases investigated for SMT complications. A five year retrospective study[75] concluded that cervical spinal manipulation therapy (CSMT) may aggravate preexisting cervical disc herniation or precipitate it, while a systematic review[76] identified case reports citing disc herniation following over-extension, rotational thrusts. One hundred eighty-five specific manipulation related complications were indicated in a literature review of articles published between 1925 and 1993[77]. Approximately 12 percent involved disk herniation, 8 percent pathologic fracture or dislocations, and 3 percent generalized increase in pain. Disc injuries of the lumbar spine have also been documented, including rupture of intervertebral disc, L4-L5 rupture with caudal ecuina Syndrome (CES)78, CES due to central L3-4 disc sequestration as well as L4-5 central disc prolapse respectively[79], and a number of related injuries involving the manipulation under anastehsia (MUA) technique[80 81 82]. Because the function of the IVD involves maintaining alterable space between two adjacent vertebral bodies, as well as aiding in flexibility of the spine and assisting in proper assimilation of compressive loads, pathologic changes of the IVD have a strong impact on ligament stability and ultimately spinal biomechanics. Indeed HVLA procedures are designed to safeguard against injury by reducing high risk motion and forces in susceptible patients; however, the success of these strategies is limited by certain factors, such as A) manipulator's ability to reliably control the load and manual delivery of quick thrusts beyond the normal range of motion B) manipulator's ability to accurately diagnose potential underlying conditions.

According to Shekelle et al.[83] as well as Powell et al.[84], complications that occur during chiropractic sessions may be to a large extent attributed to misdiagnosing (SEE FIGURE 3). Other studies have likewise

suggested a number of likely diagnostic-related reasons for adverse reactions, including diagnostic error, and limited diagnostic tools like clinical screening examinations, which can otherwise aid in discerning conditions vulnerable during delivery of therapeutic peak force. Kleynhans[85] outlined a collection of likely practitioner-related causes of adverse reactions, and proposed three major factors:

- Lack of rational clinical attitude in case management
- Lack of technique skill
- Lack of knowledge or diagnostic error.

Figure 3

SMT complications of the lower back

COMPLICATIONS FROM LOW BACK SMT REPORTED CAUSES 1911-1991	
Category	N
Disc pathology/injury	65
Diagnostic error	10
Vascular insult	5
Excessive SMT	1
Rib fracture	1
Abdominal and inguinal hernia	2
Neoplasm	1
Unknown cause	1
Total	86

Printed with permission from: Allan GJ Terrett and Andries M. Kleynhans: Complications from Manipulation of the Low Back. Chiropractic Journal of Australia 1992;22:129-39.

This is further affirmed in a RAND review,[86] which observed complications following HVLA in patients without any observed predisposing risk factors or positive pre-manipulativetesting. In the case of LBP for example, Moffroid et al[87] surveyed theeffectiveness of 114 separate diagnostic maneuvers; the individual orthopedic tests, suchas those distinguishing between healthy and unhealthy low-back pain patients, had a wide range of accuracy. With that caveat in mind, their continued use is considerable regardless of poor scientific performance. Examination procedures with a high yield of information about LBP are limited since only specific clinical entities like disc lesion, ankylosing spondylitis, or degenerative joint disease may be visualized, rendering radiographic and laboratory testing rather ineffectual in evaluating nonspecific low-back pain. Whereas the correlation between radiographic findings and clinical manifestations of spinal pain has been inconclusive, the use of imaging to assess SMT effects has not been further pursued. Physical indices, including range of motion (ROM), palpitation and orthopedic testing results have proved to be subject to substantial inter-examiner variability, which may put their reliability in question[88]. In general, manual examinations are used to varying degrees to determine the presence, location, and extent of the potential underlying disorder; more localized biomechanical examinations assess ROM, stiffness, local pain sensitivity, and tissue compliance. It appears that the soundness of such examination techniques are not as well established, and their reliability ranges widely (Kappa = -0.21 to r = 0.88)[89 90 91]. Positional tests emulate the stresses produced during manipulation on the osseous, muscular, ligamentous and vascular structures, but such testing procedures less accurately reproduce the stress of the thrust. Marked improvements in medical imaging have enabled higher sensitivities and negative predicative values, but when diagnosing areas like the CS using radiographic, CT and MR imaging, the anatomic and dynamically complex region is less accurately translated into digital images that may acceptably guide clinical practice[92]. So while the upper cervical spine's unique morphology is well-understood, unpredictable examination findings and symptoms cause forecasting of injury-related risks quite challenging[93]. For patients with cervical impairments, manipulation may be a more viable treatment option once pre-screening protocols demonstrate greater sensitivity to identify-

ing at-risk individuals and diagnostic results are correctly interpreted. A retrospective multicenter study by Davis et al94 found that misinterpreted and/or delayed radiograph diagnoses, as well as lack of appropriate cervical spine radiographs contributed to overlooked cervical spine injuries. Such study outcomes underscore the importance of definitive diagnoses and prognoses, particularly when determining a patient's candidacy for HVLA based on factors such as underlying symptoms, misalignments, co-morbidities, as well as spinal anomalies, which may readily preclude the treatment's usage on account of soft tissue susceptibility to injury. Spinal anomalies such as deviations of spinous processes from the midline complicate the determination of fractures, instabilities, dislocations and structural defects, which if misdiagnosed, may be aggravated by SMT95. Because the spinous process serves for the attachment of muscles and ligaments, which are susceptible to iatrogenic complications, the burden of proof for medical necessity rests with the treating doctor of chiropractic. Generally speaking, spinal anomalies are not uncommon; their individual radiographic patterns display considerable variations, and associated clinical symptoms are as yet not fully understood. Developmental anomalies with delayed symptoms presented beyond the third decade96 may be less readily diagnosed, so trauma such as sudden or sustained rotation combined with extension can aggravate adjacent structures, create progressive hypermobility in the capsular ligaments, and precipitate spinal instability. Corollary soft tissue trauma may be indirectly diagnosed via plain radiography and computerized tomography evidence of fractures, subluxations or dislocations; after all, in the cervical spine, fractures are commonly associated with concomitant ligamentous injury. Namely, one study[97] found that 42 percent of cervical spine injuries had evidence of dislocation, of which 66 percent had concurrent fractures. However, ligamentous impairments may occur in the absence of bony damage so it may not be detected on routine examinations like x-rays, which rely on vertebral body alignment or asymmetry to postulate soft tissue lesions.

An old adage in chiropractic affirms the importance of knowing when not to adjust rather than when to adjust. After all, IVD pathology and aggravation of preexisting lesions (particularly where mechanical instability, dislocations and fractures are present) may lead to more severe conditions such as compression of the spinal cord, and degenerative spondylosis, which can precipitate mechanical strain of the vertebral arteries. In a study on cadavers, Toole at al[98] concluded that flexion and axial rotation as low as 45 degrees, or lateral bending as little as 30 degrees was sufficient to interfere with arterial shape. Additional displacement between 5 and 10 degrees induced a complete blockage of the vertebral arteries; such motions spanned within the normal ROM. The possible mechanism of insult may be explained by the onset of clinical instability, which results in loss of the spine's ability, under physiologic loads, to maintain the normal functions between vertebrae, inducing damage and irritation of spinal cord or nerve roots, as well as structural deformity and/or incapacitating pain. Considering the vertebral artery's close proximity to neighboring ligaments at the atlanto-axial joint, progression of vertebrobasilar artery (VBA) accidents following head rotation-extension, accompanied by a forceful thrust, is observed most frequently at the upper cervical spine. Lower-back lumbar spine accidents and incidents are less life-threatening than VBA cases, which may explain why they are more often overlooked and under-reported. Three reasons are postulated for the disparity between lower-back and cervical spine injury rate of reporting:

- Lumbar disc lesions are not fatal
- Lumbar spine injuries rarely involve severe neurological sequelae
- Unlike VBA trauma, the practitioner may not necessarily cause the lumbar spine injury, but aggravates the preexisting lesion for which he is consulted.

As such, it appears that the more severe injuries are documented in published reports; although, even in such cases the reported incidence may not reflect the true incidence. In fact, one review assumes that only 10 percent of injuries are actually reported, while a recent survey demonstrated an underreporting rate of 100 percent[99], rendering many of the estimations inaccurate. This may be in part because the actual number of manipulations and caseloads of patients receiving, say, cervical spine manipulation, is unknown[100]; such lack in data has led to a wide variation of estimates. Although most reports point to a low rate of incidences, some authors[101 102 103 104 105 106] have speculated that relying on published cases may account for an underestimation of cervical spine injuries. Moreover, cases reported in newspapers and magazines have not been documented in medical or chiropractic literature[107]. Prospective and systematic studies detailing manipulative procedures and their side-effects are crucial in determining risks and addressing further issues; however, one issue facing prospective study designs concerns poor follow-up rates. In the 2 largest prospective studies[108] involving 1058 and 625 patients, respectively, loss at follow-up was a potentially serious problem since patients who experienced a severe adverse effect would simply not return for the subsequent consultation. Most evidence pertaining to risks arising from HVLA thrust maneuvers is based on case reports, surveys, literature reviews as well as insurance and legal claims records. As such, malpractice claims can offer testimony to relative harm caused by therapeutic procedures involving high-velocity, low amplitude thrusts. The National Chiropractic Mutual Insurance Company listed six most common claims as:

- Disc problems- 29%
- Failure to diagnose- 13%
- Fracture- 9%
- Soft tissue- 7%
- Cerebrovascular accidents- 6%
- Aggravation of prior condition- 4%

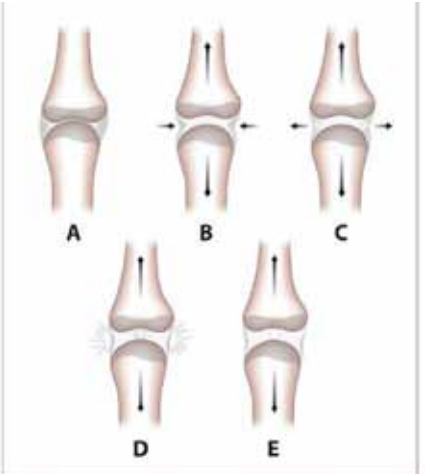
Less severe complications usually referred to as "normal reactions" and "adverse reactions" listed in claims reports[109] include muscular aches and pains, headaches, radiating discomfort, vertigo and limb weakness, and diffuse pain lasting less than 2 days. Stoddard[110] states that a painful reaction to SMT which lasts longer than two days suggests:

- Joint is inflamed or the soft tissues too irritable
- The patient resists and adhesions are merely stretched painfully
- Manipulation provokes a late reaction in a degenerated disc
- Joint is hypermobile already
- Manipulation is incorrectly applied
- Exact mechanical diagnosis is misconstrued and an improper technique is performed on a region unfit for SMT
- Manipulation is excessively forceful

Excessively forceful manipulation performed in a region unfit for high-velocity, lowamplitude treatments may be observed particularly in the upper cervical spine, where pain lasting longer than 2 days following hyperextension and rotation may be frequently observed. In fact, some practitioners cite cause for policy change, recommending that rotation techniques should not be the first treatment of choice; studies[111 112] parallel that notion, stating that almost by definition, events involving sudden or sustained rotation and extension of the neck, such as SMT and whiplash accidents, commonly result in local discomfort, pain, dizziness and other "normal reactions" as well as mild and moderate side-effects. Particularly, whiplash following motor vehicle accidents (MVA) entails forced flexion and reclination of the head at forces as low as 4G with a duration of acceleration from one hundred to two hundred milliseconds, which (for an average head's mass of 10 pounds) is equivalent to a force of 100 Newtons increasing rapidly for approximately one hundred to two hundred milliseconds, and may similarly result in pain, dizziness, IVD annular fiber tearing, VBA dissection, rotary

dislocations, instabilities, and other transient to severe adverse effects. Even if the motions of extension and flexion are not excessive, the neck may be forced to the extreme ends of normal range. In fact, MVA related whiplash and SMT whiplash-like reactions share comparable risks, in that the patients/vehicle occupants are typically unprepared for the sudden impact (such as peak forces in excess of the treating clinician's body weight or sudden acceleration and deceleration of motor vehicle), in which case the muscles are typically relaxed, allowing external and internal forces to largely affect soft tissue like discs, ligaments and zygopophysial (facet) joints. Of note, persistent neck pain can be traced to zygapophysial joints, one or more intervertebral discs, or both; a research study by Drs. Bogduk and Aprill[113] demonstrated zygopophysial joints were alone the cause of pain in 23 percent of patients, while in 20 percent of patients discs were the cause of pain, and in 41 percent, the zygopophysial joints and disc were both contributing factors; after all, small tears in intervertebral disc walls are implicated as residual "pain generators." In a separate study[114], the authors noted that painful joints were observed in 50 percent of whiplash victims, and in this population, cervical zygapophysial joint pain was the most common source of neck pain. Presently it is challenging to diagnose painful joints, considering the poor correlation between radiographic appearance of joints and their pain status. Joints which ostensibly appear in poor condition may be painless, and vice versa, joints that appear normal can be a source of pain; moreover, the area tender to the touch may be mistakenly attributed to muscle rather than facet pain. Thusly, when SMT is the treatment of choice for whiplash[115], proper diagnosing of potential underlying complications may be challenging but imperative, so that further injury may be prevented. Once the pain is properly identified, chiropractic care may provide a considerable degree of symptom relief, despite the fact that studies show that such benefits may be of a temporary nature, prompting frequent return visits. According to R.A. McKenzie, author of The Lumbar Spine; Mechanical Diagnosis and Therapy: "Most [manipulation] treatments appear to be directed at pain relief for the present[ed] episode. Episodic relief by therapy of any kind makes the patient dependent on that therapy and thereafter he will seek a quick answer for what is essentially a life long problem. Whenever his back pain recurs he must attend a physician, manipulative therapist, chiropractor or osteopath. I believe that treatment dependency is undesirable and should be avoided where possible." Typically, the prognosis after whiplash is quite favorable though for twenty five percent of the injured population, persistent neck pain may develop into a chronic, permanent fixture in day to day life. In such cases, careful determination must be made about the effect of a large number of repeat SMT treatments, which have been recommended for patients with such chronic conditions. Lance[116] recounts a case in which a thirty year-old female developed an L5 subluxation following 136 manipulations for LBP. Such mismanagement of SMT may be traced to current confusion surrounding the ambiguity of treatment procedures themselves. Few published reports offer an explicit, objective description of HVLA techniques used, the identity of practitioners administering the procedure, or a means of determining their skill levels[117]; moreover, because there is little, often no scientific basis for the manner in which treatments should be performed, the dosage of treatment, as well as the length of the treatment's continued use[118], risk of soft tissue injury progression is not unlikely. Aside from the more immediate risk of aggravating or contributing to mechanical lesions, there exists the less recognized risk of inadvertently creating a dependency for care that may or may not be indicated, as seen in the L5 subluxation case, or more commonly amongst self-manipulators, aka knuckle crackers. Specifically, the behavior of knuckle cracking (KC) is a form of finger joint manipulation, typically performed habitually due to immediate relief of joint tension and increased joint

Figure 4



Changes in Joint Structures During Manipulation. A. Normal Synovial Joint. **B.** Joint is distracted during manipulation (arrows show forces) and joint capsule is stretched. To maintain same volume inside the joint, the capsular ligaments invaginate. **C.** Once the tension reaches a certain threshold, the capsular ligament initiates an elastic recoil on the joint. **D.** As the manipulative forces continue to the anatomical limits of the capsule, the stress on the capsular ligaments suddenly increases, triggering high threshold receptors in the ligament to snap the joint back. **E.** The gases within the joint have coalesced into one area of the joint, as the joint has been distracted a significant distance with the manipulation.

Adapted from: Brodeur R. The Audible Release Associated with Joint Manipulation. *Journal of Manipulative and Physiological Therapeutics*. 18(3):1995:155-164.

range of motion[119]. This palliative effect may be explained by the cavitation mechanism, or "pop," which accompanies KC following axial distraction, hyperflexion, hyperextension or lateral deviation of the knuckle joint. This physiologic event lengthens part or all of the joint space and in turn greatly decreases intra-articular pressure, causing gas-bound synovial fluid to form coalesced, microscopic bubbles. Once joint space reaches maximum distraction, joint fluid permeates areas of negative pressure, and larger bubbles suddenly collapse into numerous microscopic bubbles, leading to the characteristic cracking sound. The stretching of joint ligaments during articular release additionally increases gapping of the joint[120] and broadens the distribution of synovial fluid, ultimately enabling temporary restoration of joint motion[121]. While this maneuver certainly brings a sense of relief, the poorly understood mechanical sequelae of long-term, repetitive KC on joint ligaments casts doubt on actual self-manipulation benefits.

Wives tales and urban legends claim that KC leads to arthritis of hand joints, and while such adverse effects are cited but not well supported in medical literature, various investigations demonstrate other soft tissue complications like ligament sprain and tendon tears, following forceful self-manipulation, accompanied by the audible pop[122]. One study[123] described a case of chondrocalcinosis in the first and fourth metacarpophalangeal (MCP) joint as well as ligamentous ossification in third MCP joint, caused presumably by chronic KC. Castellanos and Axelrod[124] examined the relation between habitual knuckle cracking and hand function in 300 patients aged 45 years or older without known neuromuscular, inflammatory, or malignant disease. While there was no significant preponderance of arthritis of the hand, hand swelling and lower grip strength was more likely present in habitual KC cases (18 to 60 years). Duration and frequency is a relevant consideration since the more times this maneuver is performed, the greater the risk of ongoing mechanical wear of affected surfaces, and the potential to aggravate underlying musculoskeletal conditions (SEE FIGURE 4). Although temporary yet immediate relief and release of tension and stiffness is tempting, such excessive use of joint manipulation may cause laxity of ligaments supporting the joint, leading to hypermobility or generating additional stress that may eventually accelerate dysfunction[125].

Similar to mechanisms involved in self-manipulation, professionally performed HVLA stretches the spine, paravertebral† tissues and other joints so as to alleviate underlying pain and improve locomotor function. In other words, the individual structures like discs, facets, ligaments, nerves and muscles may experience a concentration of local stresses and production of symptoms specific to the affected tissue, leading to dysfunction and biomechanical changes[126]. Spinal manipulation therapy in turn applies controlled and inertial forces to the spine,

generated by acceleration of the body segment mass in question, and unbuckles the motion segments, thereby reducing stresses within the functional spinal unit (FSU)† [127]. While literature is sparse concerning this mechanism's lasting palliative effects, evidence from reviews and studies supports the conclusion that it provides at least short-term enhancement of ROM and pain relief. In the former case, a randomized, controlled trial studied whether a 3-wk series of SMT had any lasting effect on passive cervical ROM. Thirty-nine headache sufferers demonstrated an increase in passive cervical ROM; though, there was no statistically significant difference with the control group, and the changes were of a "temporary nature." Expressly, one week following the last of a series of manipulations, the improvement in ROM noted earlier had abated. In the latter case regarding short-term pain relief, the Quebec Task Force, the Manga and Angus report, and the Agency for Health Care Policy and Research published large-scale literature reviews, which reached the consensus that there is moderate evidence of short-term efficacy in the treatment of LBP. This view is shared by literature reviews examining short-term improvement in pain associated with head and neck disorders[128]. Evidence for long-term benefits is much less conclusive. Several randomized clinical trials not only evaluated SMT for its lasting efficacy, but compared it to a number of other treatments. The meta-analysis by Gross et al. demonstrated that combining SMT with other treatments reduces pain more effectively than as a singular treatment. A possible explanation for this may relate to the fact that high magnitude external forces applied at a very high rate to spinal joint capsules transmit a rush of proprioceptive messages that segmentally modulate the spine's neuromuscular tone, prompt the release of trapped meniscoids, shift toxic disc fluid that irritates nerves, and thusly temporarily relieve pain, improve mobility, correct alignment and other nervous and mechanical system functions. However, what this mechanism may not address is the root problem of musculoskeletal disabilities, including underlying poor tissue repair and instability, which other rational treatment options may correct. One such co-intervention, which systematic reviews[129] suggest effectively improves SMT's performance in relieving pain and disability, is Prolotherapy.

Spinal manipulation in conjunction with Prolotherapy

Like SMT, the principle behind Prolotherapy dates back thousands of years to Hippocrates, who historians recorded using red-hot needles to stabilize dislocated shoulder joints of soldiers on the battlefield. More recently, from approximately 1835 to 1945, important contributions to the injection therapy involved the use of sclerosing type agents for hernias to proliferate new fibrous tissue. Dr. McDonald, a prominent physician at the time, reported an outstanding 97 percent cure rate in over 10,000 hernia cases. More modern day Prolotherapy techniques were pioneered in the 1930's by Dr. George S. Hackett, a general surgeon, who observed that "Injections made at the junction of ligament and bone resulted in profuse proliferation of new tissue at this union." Thereafter, Dr. Hackett spent many years tenaciously evolving and refining the injection therapy, which he defined as "the rehabilitation of an incompetent structure by the generation of new cellular tissue." In other words, Prolotherapy (short for "proliferation" therapy) is an orthopedic procedure that consists of injecting a mild irritant solution into soft tissue, jump-starting the production of new tissue at the fibrous (ligament and tendon) junction with the bone, and in such way harnesses the body's own capacity to heal. It follows that both of the CAM therapies, Prolotherapy and spinal manipulation therapy, share the common philosophy that the body boasts an innate ability to heal itself, and all that is required to stimulate a stagnant repair process is a nudge, be it a high-velocity, low-amplitude thrust, or an injection. But whereas SMT manually restores musculoskeletal/nerve pressure

Figure 5.

Reproduced with permission from eStroke Australia and the National Stroke Foundation

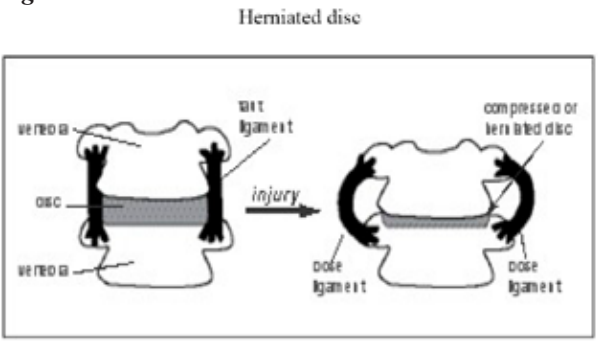
function by acting on lesions, conformable to forces and moments, Prolotherapy acts on lesions by eliciting a temporary, low grade inflammation at the site of weakness, in turn encouraging the body to initiate the new healing cascade. The first step in this process involves an injection of a proliferant solution, typically either 15 percent dextrose, polidocanol, or sodium morrhuate mixed with an anesthetic, delivered directly into the fibro-osseous junction. The first stage of the wound-healing cascade is thus initiated, prompting vital inflammatory responses like fibroblast and platelet activation (SEE FIGURE 5), which repair and reinforce injured connective tissue. In relatively severe cases of musculoskeletal injury, such as in whiplash related acute labrum tears, marked by referred pain from the cervical spine, a more potent concentration of platelets may be required for enhanced connective tissue regeneration. In this case, the proliferant solution, platelet-rich plasma (PRP), may be injected into the shoulder. Much like dextrose or sodium morrhuate, PRP leads to an inflammatory reaction that stimulates a prematurely aborted repair process and enhances the recruitment, proliferation and differentiation of cells involved in tissue regeneration. The rationale for PRP arises from the concentration of platelets releasing varied bioactive proteins responsible for attracting macrophages, mesenchymal stem cells, as well as osteoblasts, which promote necrotic tissue removal, collagen synthesis and healing. Based on this principle, platelets are injected into the damaged connective tissue to stimulate a supra-physiologic release of growth factors. Specifically, 30-60 ml of venous blood is drawn from the anticubital vein, then placed in an FDA approved centrifuge and separated into platelet poor plasma (PPP), red blood cells (RBC) and platelet-rich plasma. While the PPP is discarded, approximately 3 to 6 cc of PRP is available to be injected into the injured site.

Therapeutic efficacy may be expected with a minimum increase of 4 x the platelet concentration baseline, raising the count from approximately 200,000platelets/ul to nearly 1,000,000platelets/ul. Upon injection, growth factors are released and act locally to recruit undifferentiated cells to the site of injury and trigger mitosis. One such growth factor is transforming growth factor beta (TFG- b), which is particularly active during inflammation, influencing the regulation of cellular migration and proliferation, as well as stimulating cell replication and fibronectic binding interactions130. Vascular endothelial growth factors (VEGF) are potent stimulators of angiogensis and are most abundant post the inflammatory stage, much like other growth factors that play roles in tissue remodeling, stimulation of type I collagen synthesis, osteoid production, endothelial cell replication, and other necessary stages of repair[131]. With such a potent cocktail of bioactive proteins hastening the rate of healing, a typical treatment regimen may involve a series of just two to three sessions, at four to six week intervals; dextrose based Prolotherapy injections for adults with longstanding pain may require from four to eight treatments, similarly spaced. The long stretch of time between every consultation enables the healing to naturally take its course in three stages: inflammatory, proliferative and remodeling. One of the primary goals during the first

stage involves synthesis of collagen- the major component of most connective tissue that the physical behavior of ligaments and tendons depends on. Because new collagen shrinks as it matures, the injected ligaments tighten and grow stronger. While the initial stage occurs primarily in the first week following injury, the proliferative phase occurs during the first four to six weeks, in which time immune cells secrete polypeptide growth factors, stimulating the wide array of regenerative cellular processes. Given that fibroblasts are the primarily deficient cells with chronic injury, the proliferative phase is vital for musculoskeletal renewal; notably, during this period, collagen is laid down by fibroblasts, significantly increasing tendon and ligament strength. While the rapid increase in wound strength is most evident in the five weeks following injury, the rate declines significantly during the final remodeling stage, which can last up to one-and-ahalf years. In this time of decreased cellular and synthetic activity, type III collagen is replaced by type I, reorganization occurs, and blood neovessels disappear. On account of new collagen tissue synthesis and subsequent fortification of weakened connective tissue, Prolotherapy results are in many instances permanent, and significantly improve quality of life. In fact, studies[132] have demonstrated the formation of fibrous connective tissue that is thicker and stronger than prior to injury, testifying to the ongoing creation of new tissue. Over the years, such positive biological responses have been documented by case reports[133], pilot[134], retrospective[135], open face prospective and double-blind placebo controlled studies[136], particularly in the treatment of a wide range of conditions including chronic sprains and/or strains, cartilage and whiplash injuries, migraines, joint pain, chronic tendonitis/tendonosis†, degenerative disc disease, arthritis, and of course chronic musculoskeletal pain. In one such RCT[137] study evaluating the use of PRP for patients with chronic epicondylar pain that failed conservative treatments, a 60 percent improvement in visual analog pain scores was reported eight weeks following Prolotherapy; at 6 months and 12-38 months, an 81 percent and 93 percent improvement was observed, respectively. Of note, there were no adverse reactions or complications reported. Considering such compelling results, it is no wonder more patients are now considering Prolotherapy for chronic pain conditions that either defy common conventional treatments, or are accelerated by them. The April 2005 issue of the Mayo Clinic Health Letter reported that "In the case of chronic ligament and tendon pain that hasn't responded to more conservative treatments such as prescribed exercise and physical therapy, Prolotherapy may be helpful." This is especially true for chronic nonhealing tendon injuries, which are particularly recalcitrant to common treatments like mobilization and manipulation[138], and may require the additional boost of growth factors to regenerate capillaries and improve vascularity, accelerate tendon cell proliferation, and stimulate type 1 collagen and protein synthesis. One study examining the crucial role of PRP in tendon healing found that locally injected PRP is instrumental as an activator of circulation-derived cells for enhancing initial tendon healing processes[139]. Cell culture studies examining in vivo use of PRP in tendon injuries found that the active releasate demonstrates a positive effect on cell proliferation, accelerates the catabolic demarcation of traumatically injured tendon matrices, and promotes angiogenesis[140]. Current literature reveals similar benefits in the use of PRP for osteoarthritis (OA), a degenerative joint disorder for which manual treatments like SMT are "relatively contraindicated"[141]. In fact, there are only a few therapeutic options for patients with mild to moderate arthritis, most of which are palliative and address symptoms rather than transform the biochemical environment of the joint. Considering there are >27 million Americans aged 25 and older who suffer from OA[142], natural rehabilitative treatments that recover articular function and cartilage repair via stimulation of chondrocyte proliferation, are

important to systematically examine as potential treatment options. A concise report by Anitua et al[143] endeavored to identify key biochemical pathways that may be targeted therapeutically through biological interventions like PRP. A natural preparation of biologically active molecules in a fibrin matrix delivered within the joint compartment targeted synovial fibroblasts and induced hyaluronic acid secretion, thus reversing destruction of cartilage and other OA pathogeneses of the major articular micro-environment, like synovial membranes, subchondral bone, ligaments and tendons. Clinical effects of intra-articular platelet-rich plasma injections for osteoarthritis were further evaluated in a prospective, preliminary pilot study[144], using a group of patients with primary and secondary knee OA. Following three platelet rich plasma injections in the affected knee at approximately four week intervals, a significant and almost linear improvement in Knee Injury and Osteoarthritis Outcome Scores (including pain and symptom relief) was demonstrated. In a double-blind, placebo-controlled study[145] also evaluating the effects of Prolotherapy (using a 10 percent dextrose solution) for OA of the knee, participants showed significant improvements in pain at rest and while walking, reduction in swelling, episodes of "buckling," and range of flexion. The same research group performed a similar doubleblind trial of 27 people with OA of the hands. The results at 6-month follow-up demonstrated that ROM and pain with movement improved significantly in the treated group, as compared to placebo. In cases of intervertebral disc degeneration, a painful disease of the spine for which SMT is also "relatively-contraindicated," the role of PRP Prolotherapy has been extensively examined. A study by Chen et al.[146] demonstrated that PRP can act as a growth factor cocktail that not only promotes mRNA expression and chondrogenic gene upregulation, but fosters tissue-engineered nucleus formation regeneration via the Smad pathway. These results are relevant because, as the study commentated, the onset age for disc degeneration is around 30 to 50 years, so PRP may be a therapeutic substrate with great potential for preventing further disc destruction. It must also be noted that no adverse reactions or complications were reported. In fact, Prolotherapy is considered a very safe, low-risk procedure, with the most common reaction being soreness immediately following treatment. But Prolotherapy is after all a minimally invasive medical procedure and, as such, carries some risks. As with spinal manipulation therapy, which greatly depends on the chiropractor's proper technique application, a rare but feasible Prolotherapy risk relates to poor technique, in which case the Prolotherapist may puncture a lung while performing the procedure in the thoracic vertebrae region, or puncture the spinal canal while treating any area of the spine, resulting in a cerebrospinal fluid leak. Because Prolotherapy induces inflammation, obvious associated reactions include pain, stiffness, swelling as well as bruising, typically lasting 1 to 7 days. For both SMT and Prolotherapy, pathological and structural contraindications include active infections, psychological intolerance characterized by unwillingness to experience possible after-treatment discomfort, and active rheumatoid arthritis. Otherwise, some musculoskeletal conditions contraindicated for SMT may in fact be indicated for Prolotherapy, like in the case of osteoarthritis, degenerative disc disease, and even non-severe spondylolisthesis/multi-level spondylolysis. Whether SMT precipitates/aggravates these articular derangements or is deemed comparatively unsafe in their treatment, Prolotherapy may be a viable treatment option considering their underlying ligament, tendon and joint etiologies. This is especially true in cases involving aggravation of preexisting lesions such as weak spinal ligaments and deteriorating intervertebral discs. In particular, such underlying pathologies may precipitate disc herniation[147] when maximum compression and high velocity thrusts, performed at the limit of range, target naturally aging discs

Figure 6



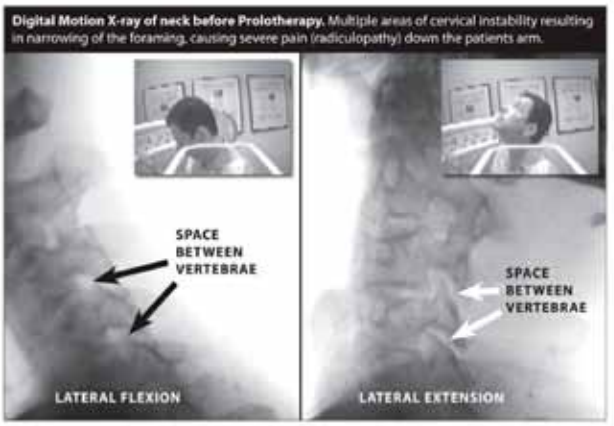
As a natural consequence, flattening of a disc due to compression or herniation results in laxity of ligaments attached to the adjacent vertebrae

that are often less pliable and have a limited ability to withstand normal pressures. After all, during the natural progression of aging, disc edges are more prone to cracking and tearing[148], so if the pressure increases sufficiently, disc fluid may leak through such fissures and potentially lead to additional degeneration such as decreased disc height. Simultaneously, ligaments that support discs may become more lax and weakened, resulting in the joint's progressive instability, potentiality to herniate[149] (SEE FIGURE 6) and subsequent ongoing back and neck pain[150]. Interestingly, when treating conditions such as LBP and herniation, both Prolotherapy and SMT literature reviews advocate that non-steroidal anti-inflammatory drugs (NSAIDs) are generally either "relatively-contraindicated" or "greatly discouraged." One report[151], assessing Prolotherapy as a primer for pain management and its indications for use asserts that systematic use of corticosteroids or NSAIDS is relatively contraindicated due to their counterproductive action on the inflammatory process. After all, tissue regeneration through angiogenesis, extracellular matrix production, and collagen synthesis via autocrine and paracrine effects of growth factors, is originally orchestrated by the immune system's inflammatory response. While SMT's mechanism of action is intrinsically different, in that the manual adjustments aim to normalize the relationship between structure and function and restore maximal, pain-free movement of the musculoskeletal system, the therapy nevertheless discourages the use of NSAIDS, as they do not allow the body to heal as it was designed. Ultimately, both Prolotherapy and spinal manipulation therapy capitalize on the body's innate capacity to heal, with particular success in the treatment of cervical, thoracic and lumbar musculoskeletal syndromes. With Prolotherapy growing in popularity as more people search for alternatives to short-term palliative or invasive surgical procedures, and spinal manipulation therapy steadily becomes a more mainstream therapeutic approach with immediate results, it is expected that both chiropractors and Prolotherapists continue to explore not only the value of their method of treatment, but the side-effects and risks as well. After all, moderate risk of injury is considered acceptable on a population basis, but to the patient, even a small risk is undoubtedly unacceptable, if at all preventable.

DISCUSSION

SMT's objective is well established: to provide loads and displacements along predetermined lines of action using predetermined total load. While systematic studies must be undertaken to examine how well these aims are actually achieved in practice, in theory they are better understood: the total load includes external forces and moments transmitted through the body, as well as inertial loads generated by movement of individual body segments. In accordance with Newton's second law, inertial forces arise from the acceleration of body segment mass in any direction; inertial moments are generated by the mass sustaining rotational accelerations[152]. Ideally, these loads must be balanced at every successive joint, as they induce varying degrees of stress and deformation in the constituents which form the FSU. If one of the constituents sustains excess stress, the biological phenomenon

Figure 7

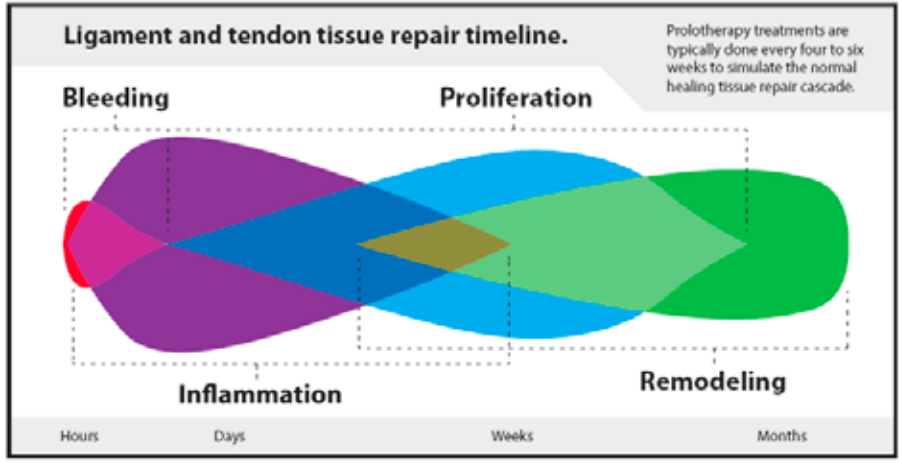


responsible for injury may be provoked. Namely, clinical experience shows that shunting of loads to tissues not normally recruited to withstand excess stress can result in microscopic tearing of ligaments and microscopic scarring around the joints. Such micro-structural damage following low forces and strains may also contribute to spinal deformation, degenerative disk disease, clinical hypermobility[153], and a condition now identified as Over-Manipulation syndrome[154]. Parenthetically, one of the authors (RH) observed in his clinical practice that OMS may be induced by just a single overly forceful manipulation, or by a series of low-level manipulations that eventually lead to ligament injury or laxity, prompting the development of joint subluxations in the segment where the ligament fails its function of holding the two bones in place. In a case series carried out by RH, consecutive patients diagnosed with cervical instability (cervical ligament laxity) were questioned about their experience with SMT or neck self-manipulation, and the treatment's potential causative effect on their condition[155]. In total, 166 (43%) patients received some SMT, 15 of whom performed self-manipulation on their necks. Additionally, there were 12 patients that performed self-manipulation on their necks but did not receive prior SMT. Thus, 178 of 387 (46%) of chronic neck pain patients diagnosed with cervical instability had some type of prior spinal manipulation. In total, 60 of the 166 (36%) patients that received SMT felt it made the original neck pain condition worse, while 20 of 27 patients (74%), who performed self-manipulation, felt they were making their condition worse. A follow-up study is being conducted to further delineate what role SMT or self-manipulation plays in the cause of OMS, ligament laxity, and its perpetuation of chronic neck pain, and associated symptoms.[156] Literature and clinical experience indicates that the most common therapeutic procedure in chiropractic practice that most likely induces such complications is the adjustment, or high-velocity, low amplitude manipulative thrust. Local compressive tensile or shearing forces are the likely agents responsible for acute injury, compounded by repetitive use damage, which may arise from excessive prolonged or recurrent tissue loads. One of the most likely structures to be injured by such mechanically mediated forces is the capsular ligaments of the cervical spine, as they are least protected and vulnerable to rotational thrusts. Evidence supporting current theories on cervical manipulation injury mechanics is based on anatomical relations of soft tissues in the neck and how motions (SEE FIGURE 7) of the head may influence them[157]. For instance, because of vertebral artery proximity to the lateral cervical articulations, stroke may be induced as a result of mechanical compression or excessive stretching of arterial walls. While the pathogenesis of ischemia is unknown, the vascular injury may occur as a natural consequence of some underlying medical condition, such as unstable adjacent articulations and lax ligaments. Clinical screenings that may detect such conditions are advocated as a means to prevent injury, with central features of examination tools involving patient history and symptom provocation testing;

however, the sensitivity and specificity of "warning signs" collected from such screenings have not been established. In fact, patients who exhibit none of the "warning signs", which can otherwise alert clinicians to some assumed contraindication to SMT, may still experience injury following both extreme and combined motions of the head. Ladermann[158] recognized the limitations of screening patients to prevent cervical SMT-induced injury, and even proposed that some of the provocation testing may expose patients to additional risks. This is further examined by Grant[159], who suggested that the rapid thrust component of cervical spine manipulation is poorly simulated during testing, a limitation which may contribute to the lack of test sensitivity. In Kleynhans outline of likely practitioner related causes of adverse reactions, it is unsurprising that lack of knowledge or diagnostic error is a major cause that accounts for a high number of iatrogenic injuries reported in literature, including pathological fractures, dislocations in the upper cervical spine following rupture of transverse atlantal or alar ligaments, disc herniation/protrusion, and vertebrobasilar insufficiency. Albeit the rate of such severe neurological and segmental lesions seemingly appear rarely, their frequency can only be approximated since the actual number of manipulations and caseload of patients receiving the adjustments is unknown. The majority of accidents reported in case series or surveys have been previously overlooked, indicating that under-reporting frequently is high, with two surveys[160 161] suggesting that under-reporting may be close to 100 percent.

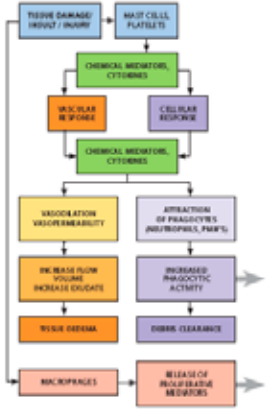
Unlike more severe accidents, mild to moderate incidents are nonfatal and occur in a large proportion of the population, as demonstrated by two case series that corroborated results from several decisive investigations[162 163]. Risk-benefit assessments of SMT must therefore account not just for serious complications but also for the more transient "normal reactions," including dizziness, nausea, local/radiating discomfort, headache, and other symptomatology associated with events involving sudden or sustained rotation and extension of the neck, and whiplash-like loads of combined shear, bending and compression forces[164]. Considering there are approximately 250 million chiropractor visits every year with nearly one third of them ending up in some form of spinal manipulation, it is apparent that this manual therapy is increasingly accepted and used; therefore, it is critical to examine every aspect of the involved risks and determine its appropriateness in various clinical scenarios. In the case of whiplash, characterized by hyper-flexion induced ligamentous sprains, zygapophyseal joint dislocations with concomitant vertebral fractures, herniation and other patterns of soft tissue complications, a rational treatment option with minimal adverse reaction and lasting effects is particularly imperative. After all, what starts as a localized injury, may readily progress into a more severe condition, which if improperly diagnosed and treated, may provoke the onset of symptoms like body-wide pain, consistent with fibromyalgia. For instance, patients with cervical segmental hypermobility or recurrent somatic dysfunction at C2-C3 and above may complain of headaches and pain at the skull base. Mid-cervical dysfunction is often associated with primary neck discomfort, while lower cervical involvement at C5-C6 may generate lower neck and posterior shoulder pain. Customary therapies oftentimes treat the expression of such injuries (pain), in thus way offering a considerable degree of symptom relief. Because such palliative care tends to be of a temporary nature, frequently prompting return visits, a more rational treatment approach aims to address the pain by treating its fundamental cause: ligament/tendon laxity and joint instability. After all, the brunt of injury is sustained by nerve ending-rich connective-tissue, which soft-tissue structures like joint capsules, IVD walls, ligaments and tendons are composed of. So when the connective-tissue's tensile capacity is exceeded, laxity and dysfunction of intervertebral segments may follow, during which time excess motion may generate irritation of nerve endings (hence pain).

The Biology of Prolotherapy



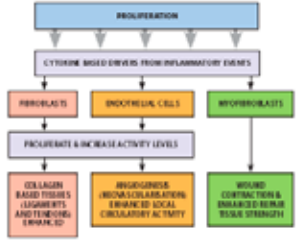
Inflammatory Cascade.

After tissue damage by injury, the body attempts to heal the area by mediating this cascade. When the body is unable to heal itself, which is often the case when avascular (no or little blood supply) tissues such as ligaments, tendons, cartilage and fibrocartilage (meniscus and labrum) are injured, Prolotherapy is utilized to stimulate healing.



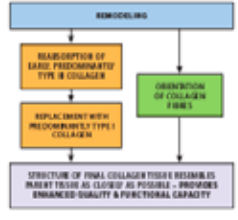
Proliferation Cascade.

Prolotherapy stimulates healing via inflammation. After Prolotherapy solutions are injected into the injury site, a cellular reaction takes place in which various cells including fibroblasts, endothelial cells and myofibroblasts form new blood vessels and ultimately lay down collagen which enhances tissue repair and strength.



Tissue Remodeling Cascade.

The final phase of healing is tissue remodeling. For many months after an injury or Prolotherapy, tissue continues to remodel. The new tissue that results looks and functions very closely to the original tissue before the injury. Once the tissue strength approaches that of the normal parent tissue, pain resolves.



As such, treating connective tissue in turn treats pain. But because of poor vascular supply, connective tissue tends to be very stubborn to heal, so a treatment modality designed to boost the tissue's natural repair processes is an integral factor in eliminating pain. Otherwise, incomplete recovery and even subsequent minor injuries may provoke scar tissue formation, ROM limitations, and strength deficits. In fact, one study[165] estimated that the best expected outcome of completed connective tissue repair is the return to normal length, but only 50 percent to 60 percent of pre-injury tensile strength. Such tissue insufficiency coupled with interfering factors such as stress, smoking and poor treatment choices, may prove to be sufficient stimuli that initiate laxity and chronic pain. Prolotherapy is based on the premise that chronic musculoskeletal pain is the result of incomplete repair of fibrous connective tissue, ultimately contributing to ligament and tendon weakness or relaxation (laxity). Thereafter, any load-bearing may stimulate pain mechanoreceptors, which will keep firing with use as long as connective tissue remains functionally insufficient. In the case that compromised tensile strength or tightness is not corrected adequately to arrest pain mechanoreceptor activation, chronic sprain or strain may ensue. This is the vicious cycle that Prolotherapy addresses: reinitiating the inflammatory process that resumes and/or jump-starts the connective tissue repair sequence, in turn healing and strengthening lax ligaments and tendons, and ultimately permanently eliminating musculoskeletal pain.

CONCLUSION

Recent reports estimate that up to 8.3 percent of the US population uses some form of complementary or alternative[166 167] medicine, of which approximately 30 percent to 40 percent likely receives Grade V chiropractic adjustments[168]. Such figures are unsurprising, considering the frequency of manipulable conditions in the United States. In fact, frequency is such that each year 1 in 20 people are unable to work on account of back pain[169], a condition that the chiropractic philosophy most commonly addresses[170 171]. Likewise, sixty three percent of back pain related absences in manual workers may be responsible for the loss of more than fifteen million man days per annum.[172] In industrial societies, LBP in particular is the most common cause of occupation disability. Along with headaches, it accounts for the most frequent category of pain that practitioners commonly contend with. It is therefore quite clear why, in spite of the few large-scale studies concerning biomechanical responses to manipulation, millions of treatments are nevertheless performed annually. With such great numbers comes a greater responsibility to assay mechanisms of action and in turn the mechanisms of injury.

The study of manipulable lesion expression remains an applied science, with the interplay of related clinical observations converging to likely hypothetical mechanisms of action. Consensus within literature relates to root causes of lesions, which stem from altered biomechanical behavior, with local and/or remote effects manifesting as clinical signs and symptoms. A singular core hypothesis, which may otherwise explain variations in clinical presentation observed in practice, is still lacking. As such, a systematic review of normal and abnormal mechanics may be useful in determining a single, plausible mechanism. Some postulations include changes in joint kinematics, an increase in joint movement, pain threshold and muscle strength, as well as attenuation of alpha motoneuron activity, enhanced proprioceptive behavior, and release of beta-endorphins; such interactions between biomechanics, biochemistry and neurophysiology of the spinal and paraspinal tissue responses accounts for the complexity encountered while studying treatment efficacy, outcome and management. While scientific and clinical studies advertising treatment efficacy are widely available, the number of studies investigating the mechanical, physiological or neurological effects is small, so a direct link between treatment forces, effects generated by forces and subsequent restor-

ative effects are almost entirely absent. Studies have suggested that manipulative therapy techniques are more heterogenous than other medical therapies, comparing the modality with multiple control treatments[173], which further complicate delineating conclusions regarding treatment efficacy and outcome. Therefore, one of the goals of HVLA related research is to identify a paradigm, which may ultimately expand the scope of interpreting currently available study findings.

With surveys showing average number of chiropractic treatments per practitioner in the order of 4000/annum, SMT has logically become the subject of numerous trials investigating its increasingly popular role in treating musculoskeletal conditions. Currently, many trials are conducted in areas of comparative efficacy, but as the service gains popularity in the mainstream of manual medicine, more efforts should be directed toward studying total treatment forces, repeat treatment effects, complications, contraindications and idiosyncrasies, so that positive and negative patient responses can be anticipated and the relative risks of the various methods and techniques may be recognized. Indeed a theoretical framework exists from which hypotheses about biomechanical effects of spinal manipulation can be developed, but in the meantime, an experimental body of evidence indicates that rotation combined with extension and traction may be responsible for aggravating lesions of the FSU; after all, a functionally isolated connection is unprotected and can only withstand a small load. In the interest of clinical considerations, when certain neck or body techniques direct force on an individual connection by separating it from adjacent stabilizers, injury to "isolated" tissue may arise even at a low total loading range. As such, when the head is rotated to one side and simultaneously extended in the sagittal plane, a compression injury of a cervical articular pillar may readily occur; similarly, sprain injury is possible when ligaments are isolated by head and neck position. Such pathological changes may dispose the spine to progressive hypermobility of capsular ligaments and degeneration at various anatomic regions. On account of the fundamental interdependence between various spinal motion segment components, patients are in turn predisposed to neuropathy if the spine is sufficiently hyper-flexed, hyper-extended or compressed, such as during axial loading[174]. Despite a purported low-incidence rate of neuropathy related accidents, one review article[175] assessing one hundred seventy-seven published cases of injury, noted that arterial dissection or spasm, and lesions of the brain stem were the most frequently reported. A comprehensive search[176] of online and bibliographical databases identifying relevant case reports, surveys, and review articles, determined that of the 295 SMT complications derived from the literature, 165 cases were related to VBAs; 61 cases to disc herniation or progression to cauda equine syndrome; 13 cerebral complications other than VBAs; and 56 other complications. Such pathological changes are clear manifestations of degenerative vertebral changes with corollary neuropathic accidents, since in the case of the 61 disc herniation complications for instance, progressive disc degeneration and interspace thinning may lead to the development of spondylosis, which may induce compression of the spinal cord following neck flexion. Hyper-flexion may result in buckling and infolding of the ligamentum flavum against the spinal cord[177]. Clinical screening examinations like patient history and symptom provocation are widely advocated for the detection and prevention of such conditions; however, the poorly established sensitivity and specificity of "warning signs" combined with the HVLA adjustment has the potential to provoke complications due to diagnostic error. As yet there is minimal compelling evidence supporting the use of symptom provocation testing, Doppler ultrasound, brain imaging, or arteriograpy as accurate clinical screening tools to identify patients at risk of injury from SMT, particularly of the cervical spine[178]. Diagnostic tools like x-rays, CT, MRI and EMG may exhibit

normal results, providing limited insight into regions responsible for the ongoing pain. This may not only prove quite challenging in determining a diagnosis, but may also contribute to treatment related complications due to inappropriate treatment choices, and other instances in which coexisting and unrecognized conditions are not managed with correct techniques, thus delaying more rational treatment options. Within this landscape, Prolotherapy is becoming a promising standalone or adjunctive treatment that not only functions as a "first line of therapy" for treating chronic musculoskeletal disorders, but may effectively repair, manage and even reduce risk of manual therapy induced accidents or injuries. As our population ages and remains active, the rate of orthopedic related injuries will rise dramatically, and the expectation for faster recovery using less invasive and safer alternatives can be anticipated. The concept of using platelet-rich plasma Prolotherapy addresses such trends in healthcare by providing fast, long-term results in a safe and minimally invasive manner. Other biological modalities that meet such criteria include stem cells, gene therapy and autologous or bioengineered cytokines; but as yet they're strictly experimental and not available in clinical practice. Manual medicine is simple, non-invasive and fast, but despite the clinical evidence and apparent wide usage, SMT's safety is undermined by the unknown biological mechanisms underlying its effects. While this discrepancy may not negate beneficial effects observed in clinical practice, the treatment is less readily accepted by the wider scientific and healthcare community, and more importantly, rational strategies for augmenting the delivery of HVLA is limited. Research continues to reveal mechanisms responsible for the effective relief of pain as well as neurological and biomedical changes in the spine following adjustments to correct vertebral subluxation. Even so, the same studies conclude that such changes are "shortlived" [179] and little quantitative data are available with respect to pathognomonic diagnostic presentation and the effect of local stress on individual structural elements (disc, facet, ligament, tendon, muscle), which complicates delineating long-term therapeutic effects as well as potential risks associated with long-term, cumulative treatment protocols. Whether the relative harm elicited by chiropractic therapeutic procedures involves rare cerebrovascular accidents, herniation, laxity, subluxation, or aggravation of prior condition following misdiagnosis or improper technique application, employing Platelet-Rich Plasma Prolotherapy to augment iatrogenesis is advocated to immediately initiate cellular and tissue healing via the wound-healing cascade. This inflammatory response is particularly useful for ligament and tendon tissues, which inherently receive a poor blood supply, so the duration of healing is considerably longer than for other tissues; therefore, a therapy that not only relieves pain associated with the musculoskeletal trauma but also completely heals the underlying dysfunction will successfully arrest further injury to the local and adjacent structures. Following a series of injections that cause temporary, low-grade inflammation and thus "trick" the body into initializing a new healing cascade, fibroblasts are activated and synthesize precursors to mature collagen, thereby reinforcing soft tissue. Specifically, studies[180] show that the inflammatory stimulus increases the level of growth factors that either resume or initiate a new connective tissue repair sequence to accomplish one prematurely aborted or perhaps never even started. Whether Prolotherapy is used in conjunction with spinal manipulation, as a preventative first line of therapy or in some cases as an auxiliary measure to reverse inadvertent adverse reactions, it has shown to not only treat symptoms associated with post-traumatic degenerative, overuse, and painful conditions of the musculoskeletal system, but safely "welds" lax, hypermobile and subluxated pathologies of connective tissue, guaranteeing permanent healing. Ultimately, exciting new developments are being

considered in the quest for optimizing soft tissue repair, both in sphere of manual and orthomolecular medicine. In the meantime, safety issues require regular and rigorous attention, and regardless of transient or severe adverse reactions, the tolerable level of risk associated with any therapeutic interventions must be weighed against evidence of therapeutic efficacy.

DEFINITIONS †

- Pathological barriers: permanent motion limitation generated by pathologic tissue transformation
- Paraphysiological zone: articular surfaces suddenly separated by high-velocity thrust during joint play, subduing an elastic barrier of resistance while producing an audible release (cavitations)[181]
- Paravertebral: Located alongside the spinal column or adjacent to vertebra
- Functional Spinal Unit (FSU): spinal unit composed of two adjacent vertebrae and related soft tissue, including ligaments and capsule, facet joints, and intervertebral disk
- Tendinosis: degeneration of the tendon's fibrous material known as collagen
- Tendonitis: inflammation of tendon

KEY POINTS

- The use of flexion-extension radiographs, provocation testing and similar diagnostic tools like xrays for the initial evaluation of non-traumatic patient presenting with spinal complaints is not well established.
- Soft tissue of the upper cervical spine (CS) is functionally more vulnerable to quick thrusts of high magnitude on account of the atlanto-axial joint anatomy.
- There are few studies investigating which structures absorb or transmit internal forces, to what degree they are deformed, and how close such forces approach ultimate failure loads. Treatment effects and transmission of stresses and strains across soft tissue in turn remains in question.
- Until HVLA techniques are more explicitly defined, as well as the dosage and duration of treatment's continued use is objectively examined, safety concerns remain, regarding dependency on care and aggravating mechanical lesions.
- Prolotherapy is an orthopedic procedure, consisting of injecting mild irritant solutions into soft tissue to jump-start the production of new tissue at the fibrous (ligament and tendon) junction with the bone, thus harnessing the body's own capacity to heal.
- Platelet Rich Plasma therapeutic efficacy may be expected with a minimum increase of 4 x the platelet concentration baseline, raising the count from approximately 200,000 platelets/ul to nearly 1,000,000 platelets/ul.

REQUEST

The authors shall be grateful to receive case data related to complications arising from SMT of the spine.

CONFLICT OF INTEREST

Ross Hauser authored the book "Prolo Your Sports Injuries Away" and currently performs Prolotherapy at his clinic in Oak Park, Illinois.

There are no competing financial interests

REFERENCES

1 Coulter I, et al. Patients using chiropractors in North America: Who are they and why are they in chiropractic care? *Spine*. 2002;7(3):291-297.

2 Bureau of Labor Statistics, U.S. Department of Labor, Occupational Outlook Handbook, 2010-11 Edition, Chiropractors, on the Internet at www.bls.gov/oco/ocos071.htm (visited January 01, 2012).

3 Licht PB, et al. Is cervical spinal manipulation dangerous? *J. Manipulative Physiol. Ther.* 2003;26:48-52.

4 Hurwitz E, et al. RAND. The appropriateness of manipulation and mobilization of the cervical spine. 1996. Available at http://www.rand.org/pubs/monograph_reports/2007/MR781.pdf. (Visisted on January 01, 2012).

5 Haldeman S, et al. Clinical perceptions of the risk of vertebral artery dissection after cervical manipulation: the effect of referral bias. *The Spine Journal*. 2002;2:334-342.

6 Ligeros K. How Ancient Healing Governs Modern Therapeutics. New York, NY:G.P. Putnam's and Sons;1937.

7 Surkitt D, et al. High velocity low amplitude manipulation of the atlanto axial joint: effect on atlanto axial and cervical spine rotation asymmetry in asymptomatic subjects. *J Osteopathic Med*. 2000;3:13-9.

8 Herzog W, et al. Electromyographic responses of back and limb muscles associated with spinal manipulative therapy. *Spine.*1999; 24 (2):146-152.

9 Woodward M, et al. Chiropractic treatment of chronic whiplash. *Injury*.1996;27:643-645.

10 Gillette R. A speculative argument for the coactivation of diverse somatic receptor populations by forceful chiropractic adjustments. *Manual Med.*1987;3:1-14.

11 Haldeman S. Spinal manipulative therapy in sports medicine. *Clin. Sports Med*. 1986;5:277-293.

12 Ratis K, et al. Spinal manipulation for back pain. *Hosp Pract*.1989;15:89-90,95,108.

13 Wyke B.D. Aspects of Manipulative Therapy. Philadelphia: Churchill Livingstone; 1985, 72-77.

14 Kjellman G, et al. A critical analysis of randomized clinical trials on neck pain and treatment efficacy. *Scand J. Rehabil. Med.*1999; 31:139-152.

15 Gillette R. A speculative argument for the coactivation of diverse somatic receptor populations by forceful chiropractic adjustments. *Manual Med.* 1987;3:1-14.

16 Haldeman S. Spinal manipulative therapy in sports medicine. *Clin. Sports Med.* 1986;5:277-293.

17 Nilsson N. A randomized controlled trial of the effect of spinal manipulation in the treatment of cervicogenic headache. *J Manipulative Physiol Ther.*1995;18(7):435-40.

18 Tuchin P, et al. A randomized controlled trial of chiropractic spinal manipulative therapy for migraine. *J Manipulative Physiol. Ther*.2000; 23:91-95.

19 Haldeman S. Presidential address, North American Spine Society: Failure of the pathology model to predict back pain. *Spine*.1990;15:718-24.

20 Bigos S, et al. Acute lwo back problems in adults. Clinical practice guideline No. 14. AHCPR Publication No. 95-0642. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services; December 1994.

21 Sackett, DL, et al. Clinical Epidemiology: A Basic Science for Clinical Medicine. Boston/Toronto: Little, Brown and Company; 1985.

22 Cassidy DJ, et al. Risk of vertebrobasilar stroke and chiropractic care. *Spine*.2008;33:176-183.

23 Koes BW, et al. Spinal manipulation and mobilization for back and neck pain: a blinded review. *Br. Med. J*.1991; 303:1298-1303.

24 Koes BW, et al. Randomized clinical trial of manipulative therapy and physiotherapy for persistent back and neck pain complaints: results of a one year follow-up. *Br. Med. J*.1992;304:601-605.

25 Koes BW, et al. The effectiveness of manual therapy, physiotherapy and treatment by the general practitioner for nonspecific back and neck complaints: a randomized clinical trial. *Spine*.1992;17:28-35.

26 Koes BW, et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. *J. Manipulative Physiol. Ther.*1992;15:16-23.

27 Koes BW, et al. The effectiveness of manual therapy, physiotherapy and continued treatment by the general practitioner for chronic nonspecific back and neck complaints: design of a randomized clinical trial. *J. Manipulative Physiol. Ther.*1991;14:498-502.

28 Whittingham W, et al. The effect of manipulation (toggle recoil technique) for headaches with upper cervical joint dysfunction: a pilot study. *J Manipulative Thysiol. Ther*.1994;17:369-375.

29 Shekelle PG, et al. Cervical spine manipulation: summary report of a systematic review of the literature and a multidisciplinary expert panel. *J Spinal Disord*.1997;10:223-228.

30 Triano JJ, et al. Biomechanics of spinal manipulative therapy. The Spine Journal. 2001;1(2): 121-130.

31 Crowninshield RD, et al. The prediction of forces in joint structures: distribution of intersegmental resultants. *Exerc Sport Sci Rev.*1981;9:159-181.

32 Haas M. The physics of spinal manipulation. Part IV. A theoretical consideration of the physician impact force and energy requirements needed to produce synovial joint cavitation. *J Manipulative Physiol Ther.*1990;13:378-383.

33 Herzog, W. The physics of spinal manipulation. *J Manipulative Physiol Ther.*1992;15:405-5.

34 Walmsley B, et al. Forces produced by medial gastrocnemius and soleus muscles during locomotion in freely moving cats. *J Neurophysiol*.1978;41:1203-1215.

35 Dul J, et al. Muscular synergism. I. On criteria for load sharing between synergistic muscles. *J Biomech.*1984;17:663-673.

36 Herzog W, et al. Validation of optimization models that estimate the forces exerted by synergistic muscles. *J Biomech*. 1991;24:31-39.

37 Goldstein M. The research status of spinal manipulative therapy, NINCDS. US Government Print Office;1975.

38 Bergmann T, et al. Chiropractic technique. New York: Churchill Livingstone; 1993:51-122.

39 Koes BW, et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. *J Manip Physiol Ther.* 1991;14:498-502.

40 Nansel D, et al. Effect of unilateral spinal adjustments on goniometrically assessed cervical lateral flexion end range asymmetries in otherwise asymptomatic subjects. *J Manip Physiol Ther.*1989;12:419-27.

41 Pickar JG. Neurophysiological effects of spinal manipulation. *Spine*. 2002;2(5):357-71.

42 Williams NH, et al. Psychological response in spinal manipulation: a systematic review of psychological outcomes in randomized controlled trials. *Comple-*

ment Ther Med. 15(4):271-83.

43 Ernst E, et al. A systematic review of systematic reviews of spinal manipulation. *J R Soc Med*. 2006; 99(4):192-196.

44 Ernst E, et al. Chiropractic for low back pain: We don't know whether it does more good than harm. *Bmj*. 1998;317:160.

45 Bigos S. Perils, pitfalls, and accomplishments of guidelines for treatment of back problems. *Neurol. Clin.*1999;17:179-192.

46 Devo, R, et al. Outcome measures for low back pain research. A proposal for standardized use. *Spine*. 1998;20:2003-2012.

47 Lee R, et al. Load displacement time characteristics of the spine under posteroanterior mobilization. *Aust J Physioltherap.*1992;38:115-123.

48 Conway PJW, et al. Forces required to cause cavitation during spinal manipulation of the thoracic spine. *Clin Biomech*.1993;8:210-214.

49 Triano J, et al. Motions of the head and thorax during neck manipulation. *Journal of manipulative and physiol ther.*1994;17(9).

50 Jones TR, et al. Lumbar zygapophyseal joint meniscoids: evidence of their role in chronic intersegmental hypomobility. *J Manipulative Physiol Ther.* 1989;12 (5):374-385.

51 Herzog W. The biomechanics of spinal manipulation. *Journal of Bodywork & Movement Therapies* 2010;14:280-286.

52 E. Ernst. Chiropractic spinal manipulation for back pain. *Br J Sports Med*. 2003;37:195–196.

53 Goodvin C, et al. Development of a real-time three-dimensional spinal motion measurement system for clinical practice. *Med Bio Eng Comput*. 2006;44:1061–1075.

54 Panjabi MM, et al. Physiologic strains in the lumbar spinal ligaments: an in vitro biomechanical study. *Spine*. 1982;7(3):192-203.

55 Goel VK, et al. The Role of lumbar spinal elements in flexion. *Spine*. 1985;10(6):516-523.

56 Hedtmann A, et al. Measurement of human lumbar spine ligaments during loaded and unloaded motion. *Spine*.1989;14(2):175-185.

57 Myklebust JB, et al. Tensile strength of spinal ligaments. *Spine*.1988;13(5):526-531.

58 Ernst E. Deaths after chiropractic: a review of published cases. *Int J Clin Pract.* 2010;64(8):1162-5.

59 Herzog, W. Clinical Biomechanics of Spinal Manipulation. Philadelphia: Harcourt Brace & Company, 2000.

60 Forand D, et al. The forces applied by female and male chiropractors during thoracic spinal manipulation. *J Manipulative Physiol Ther.* 2004;27(1):49-56.

61Herzog W, et al. The biomechanics of spinal manipulation. *Phys and Rehab Med.* 2001;12(2&3):191-216.

62 Hessel B, et al. Experimental measurement of the force exerted during spinal manipulation using the Thompson technique. *J Manipulative Physiol. Ther*.1990;8:448-453.

63 Brennan PC, et al. Enhanced phagocytic cell respiratory burst induced by spinal manipulation: potential role of substance. *J Manipulative Physiol Ther.* 1991;14(7):399-408.

64 Lee R, et al. Load displacement-time characteristics of the spine under posteroanterior mobilization. *Aust J Physiother.* 1992;38(2):115-123.

65 Yoganandan N, et al. Stiffness and strain energy criteria to evaluate the threshold of injury to an intervertebral joint. *J Biomech*.1989;32(2):135-142.

66 Herzog W. Biomechanics of spinal manipulation. *Journal of bodywork and movement therapies*. 2010; 14:280-286.

67 Herzog W, et al. The biomechanics of spinal manipulation. *Critical Reviews in Physical and Rehab. Med*.2001;13(2&3):191-216.

68 Pompe van Meerdervoort. Knee ligament injuries. *S Afr Med J.* 1979;55(23):942-6.

69 Blaine ES. Manipulation (chiropractic) dislocation of the atlas. *JAMA*. 1925; 85:1356.

70 Dvorak J, et al. Functional anatomy of the alar ligaments. *Spine.*1987;12:183-9.

71 Herzog, W. Clinical Biomechanics of Spinal Manipulation. Philadelphia: Harcourt Brace & Company, 2000.

72 Haldeman S, et al. Risk factors and precipitating neck movements causing vertebrobasilar artery dissection after cervical trauma and spinal manipulation. *Spine*. 1999;24:785-94.

73 J Dvorak, et al. How dangerous is manipulation to the cervical spine? *Manual medicine.* 1985;2:1-4.

74 Assendelft, et al. Complications of spinal manipulation: a comprehensive review of the literature. *J Family Pract.* 1996;42(5):475-480.

75 Malone D, et al. Complications of cervical spine manipulation therapy: 5 year retrospective study in a single group practice. *Neursurg Focus.* 2002;13(6).

76 Stevinson B, et al. Neurological complications of cervical spine manipulation. *J Roy Soc Med*. 2001;94:107-10.

77 Vick DA, et al. The safety of manipulative treatment: Review of the literature from 1925 to 1993. *J Am Osteopath Assoc*. 1996;96(2):113–115.

78 Richard J. Disc rupture with cauda equine syndrome after chiropractic adjustment. *J Med*. 1967;67(2):2496-8.

79 Lehmann OJ, et al. Beware the prolapsed disc. *Br J Hosp Med*. 1991;46-52.

80 Mutschler HH. Die Ischias-Skoliose und ihre Behandlung. Z Ortho und ihre Grenzgebiete. 1938;67:105- 116.

81 Eyre-Brook Al. A study of late results from disk operations. *BrJ Surg*. 1952;39(156):289-96.

82 Weiss J et al. Die Behandlung lumbaler discushernien im ventralen durchbhang. Archiv fur orthopadische and unfall chirurgie 1955;48:612-30.

83 Haldeman S, et al. Guidelines for chiropractic quality assurance and practice parameters: proceedings of the Mercy Center Consensus Conference. Gaithersburg, MD: Aspen Publishing; 1993.

84 Powell FC, et al. A risk/benefit analysis of spinal manipulation therapy for relief of lumbar or cervical pain.*Neurosurgery*.1993 ;33:73–79.

85 Kleynhans AM. Complications and contraindications to spinal manipulative therapy. Modern Developments in the Principle and Practice of Chiropractic. New York: Apple-Century-Crofts; 1980.

86 Hurwitz El, et al. Manipulation and mobilization of the cervical spine: a systematic review of the literature. *Spine*. 1996;21:1746-1759.

87 Moffroid MT, et al. Sensitivity and specificity of the NIOSH low back: Final report. Burlington VT: University of Vermont; may 31, 1992.

88 Samo, DG, et al. Validity of three lumbar sagittal motion measurement methods: surface inclinometers compared with radiographs. *J. Occup. Environ. Med.* 1997;39:209-216.

89 Leach RA. The chiropractic theories: a synopsis of scientific research. Baltimore: Williams & Wilkins;1986.

90 Triano JJ, et al. The use of instrumentation and laboratory examination procedure by the chiropractor. Principles and practice of chiropractic. New York: Appleton & Lange;1980.

91 Liang MH, et al. Clinical evaluation of patients with a suspected spine problem. The adult spine: principles and practice. New York: Raven Press; 1991.

92 Brandenstein D, et al. Unstable subaxial cervical spine injury with normal computed tomography and magnetic resonance initial imaging studies: report of four cases and review of the literature. *Spine*. 2009;34(20):743-50.

93 McGregor M, et al. Vertebrobasilar compromise associated with cervical manipulation. *Top Clin Chiro*. 1995;2(3):63-73.

94 Davis JW, et al. The etiology of missed cervical spine injuries. *J Trauma*. 1993;34:342-346.

95 Williams PL, et al. Gray's anatomy. Edinburgh: Churchill Livingstone;1989.

96 Chopra JS, et al. Craniovertebral anomalies: a study of 82 cases. *Br J Neurosurg*. 1988;2:455-464.

97 Chiu W, et al. Ligamentous injuries of the cervical spine in unreliable blunt trauma patients: Incidence, evaluation, and outcome. *J. Trauma.* 2001;50:457-464.

98 Toole J, et al. Influence of head position upon cerebral circulation. *Arch Neurol*.1960;2:616-623.

99 Ernst E. Chiropractic spinal manipulation for back pain. *Br J Sports Med*. 2003;37:195–19.

100 Fabio R. Manipulation of the cervical spine: Risks and benefits. *Physical Therapy*.1999;79(1):50-65.

101 Frisoni GB, et al. Vertebrobasilar ischemia after neck motion.*Stroke.*1991;22:1452–1460.

102 Rivett DA, et al. A prospective study of complications of cervical spine manipulation. *Journal of Manual Manipulative Therapy*.1996 ;4:166–170.

103 Patijn J. Complications in manual medicine: a review of literature. *Journal of Manual Medicine*. 1991;6:89–92.

104 Powell FC, et al. A risk/benefit analysis of spinal manipulation therapy for relief of lumbar or cervical pain. *Neurosurgery.*1993;33:73–79.

105 Robertson JT. Author's rebuttal [letter]. *Stroke.*1982;13:260–261.

106 Lee KP, et al. Neurologic complications following chiropractic manipulation: a survey of California neurologists. *Neurology.*1995;45:1213–1215.

107 Terrett AGJ. Misuse of the literature by medical authors in discussing spinal manipulative therapy injury. *J Manipulative Physiol Ther*.1995;18:203–210.

108 Ernst E. Spinal manipulation: Its safety is uncertain. *JAMC*. 2002;166(1).

109 Senstad O, et al. Frequency and characteristics of side effects of spinal manipulative therapy. *Spine*.1997;22(4):435-441.

110 Stoddard A. Manual of Osteopathic Practice. London: Hutchinson; 1969.

111 Leboeuf Yde, et al. Side effects of chiropractic treatments: a prospective study. *J Manipulative Physiol. Ther*.1997 Oct;20(8):511-5.

112 Endo K, et al. Cervical vertigo and dizziness after whiplash injury. *European Spine Journal.*2006;15(6):886-890.

113 Bogduk N, et al. On the nature of neck pain, discography and cervical zygapophysial joint blocks. *Pain.* 1993;54(2):213-217.

114 Lord S, et al. Chronic cervical zygopophysial joint pain after whiplash: A placebo controlled prevalence study. *Spine.*1996;21(15):1737-1744.

115 Woodward, et al. Chiropractic treatment of chronic whiplash. *Injury.* 1996;27:643-645.

116 Lance P. Traitements orthopedique et chirurgical des algies rachidiennes. *Rev Practicien*.1964;11:3637- 3643.

117 Van Tulder MW, et al. Conservative treatment of acute and chronic nonspecific low back pain: a systematic review of randomized controlled trials of the most common interventions. *Spine.* 1997;22(18):2128–56.

118 Herzog W, et al. The biomechanics of spinal manipulation. *Critical Reviews in Physical and Rehab. Med.*2001;13(2&3):191-216.

119 Protopapas MG, et al. Joint cracking and popping: understanding noises that accompany articular release. *J Am Osteopath Assoc*.2002;102:283-7.

120 Heilig D. The thrust technique. *J Am Osteopath Assoc.* 1981;81:244-248.

121 Meal GM, et al. Analysis of the joint crack by simultaneous recording of sound and tension. *J Manipulative Physiol Ther.* 1986;9(3):189-195.

122 Chan PS, et al. Consequences of knuckle cracking: a report of two acute injuries. *Am J Orthop*. 1999 Feb;28(2):113-4.

123 Watson P, et al. Habitual joint cracking and radiological damage. *BMJ.*1989;299:1566.

124 Castellanos J, et al. Effect of habitual knuckle cracking on hand function. *Ann Rheum Dis*. 1990;49:308- 30.

125 Protopapas MG, et al. Joint cracking and popping: understanding noises that accompany articular release. *J Am Osteopath Assoc*.2002;102:283-7.

126Triano JJ. Biomechanics of spinal manipulative therapy. *The Spine Journal.* 2001;1:121–130.

127 Triano JJ, et al. Motions of the head and thorax during neck manipulations. *J Manipulative Physiol Ther.* 1994;17(9):573–83.

128 Fabio R. Manipulation of the cervical spine: Risks and benefits. *Physical Therapy*.1999;79(1):50-65.

129 Yelland MJ, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. *Spine*. 2004;29:9-16.

130 Muschler G, et al. Spine fusion using cell matrix composites enriched in bone marrow derived cells. *Clin Orthop Relat Res.*2003;(407):102-118.

131 Sclafani A, et al. Modulation of wound response and soft tissue ingrowth in synthetic and allogeneic implants with platelet concentrate. *Arch Facial Plast Surg.*2005;7:163-169.

132 Reeves KD. Prolotherapy: Present and future applications in soft-tissue pain and disability. Injection Techniques: Principles and practice. *Physical Medicine and Rehabilitation Clinics of North America.* 1995;(6)4:917-923.

133 Hooper A, et al. Case report of whiplash related chronic neck pain treated with intraarticular prolotherapy. *Journal of Whiplash and Related Disorders*.2005;4(2):23-27.

134 Scarpone M, et al. The efficacy of Prolotherapy for lateral epicondylosis: a pilot study. *Clin J Sport Med.* 2008;18(3): 248–254.

135 Schwartz R. Prolotherapy: A literature review and retrospective study. *Journal of Neurology*, *Orthopedic Medicine, and Surgery.* 1991;12:220-223.

136 Dechow E et al. A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. *Rheumatology*.1999;38(12):1255-9.

137 Mishra A, et al. Treatment of chronic elbow tendinosis with buffered Platelet-Rich Plasma. *Am J Sports Med.* 2006;34(11):1774-1778.

138 Cooper SR, et al. Chiropractic management of tendinopathy: a literature synthesis. *J Manipulative Physiol Ther.* 2009;32(1):41-52.

139 Kajikawa Y, et al. Platelet rich plasma enhances the initial mobilization of circulation derived cells for tendon healing. *J Cell Physiol*. 2008;215(3):837-45.

140 Jahr H, et al. Can platelet rich plasma enhance tendon repair? A cell culture study. *Am J Sports Med.* 2008;36(6):1171-8.

141 Kleynhans AM. The prevention of complications from spinal manipulative therapy. Aspects of manipulative therapy. Melbourne: Lincoln Institute of Health Sciences - Conference Proceedings; 1980.

142 Sampson S, et al. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis. *Am J. Phys. Med. Rehabil*. 2010;89(12):961-969.

143 Anitua E, et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. *Rheumatology*. 2007;46(12):1769-1772.

144 Sampson S, et al. Injection of platelet rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. *American Journal of Physical Medicine and Rehab.*2010;89(12):961-969.

145 Reeves K, et al. Randomized, prospective double-blind, placebo-controlled study of dextrose Prolotherapy for knee osteoarthritis with or without ACL laxity. *Alternative Therapies.*2000;6(2):68-80.

146 Chen WH, et al. Tissue-engineered intervertebral disc and chondrogenesis using human nucleus pulposus regulated through TGF-b1 in platelet-rich plasma. *Journal of Cellular Physiology*. 2006;209:744- 754.

147 Alpers BJ. The problem of sciatica. *Medical Clinics of North America*. 1953; 37:503.

148 Acarpglu ER, et al. Degeneration and aging affect the tensile behavior of human lumbar annulus fibrosus. *Spine*. 1995; 20:2690-2701.

149 Krag MH et al. Thoracic and lumbar internal disc displacement distribution from in vitro loading of human spinal motion segments: experimental results and theoretical predictions. *Spine*. 1987; 12:1001- 1007.

150 Borenstein DG. Chronic low back pain. *Rheumatological Disease Clinics of North America*. 1996; 22:439-456.

151 Stovitz, SD, et al. NSAIDs and musculoskeletal treatment - what is the clinical evidence? *The Physician and Sports Medicine*. 2003;31:1.

152 Triano et al. Biomechanics of spinal manipulative therapy. *The Spine Journal*. 2001;1:121–130.

153 Campbell SE, et al. The value of CT in determining potential instability of simple wedge-compression fractures of the lumbar spine. *AJNR*.1995;16(7):1385-1392.

154 Hauser, A. 2011. Prolotherapy: An alternative therapy for lower back pain in athletes. Chicago Sports Medicine. Retrieved June 11th, 2012, from http://chicagosportsmedicine.com/low_back_pain.html

155 Review of charts from Caring Medical and Rehabilitation Services in Oak Park, Illinois, from October 2009 through June 2012.

156 Hauser, R. The role of SMT and self-manipulation in the cause and perpetuation of cervical instability. A case series. Ongoing research.

157 Bergmann T, et al. Joint assessment principles and procedures. Chiropractic Technique. New York: Churchill Livingstone; 1993:51-122.

158 Ladermann JP. Cerebrovascular accidents related to chiropractic care: further considerations. European Journal of Chiropractic.1990;38:63–68.

159 Grant R. Vertebral artery concerns: premanipulative testing of the cervical spine. P*hysical Therapy of the Cervical and Thoracic Spine*. New York, NY: Churchill Livingstone Inc;1994 :145–165.

160 Egizii G, et al. Spinal manipulation: survey of French medical physicians who graduated with the national diploma of osteopathy from Strasbourg University. *Ann Readapt Med Phys*. 2005;48:623 -31.

161 Dupeyron A, et al. Complications following vertebral manipulation—a survey of a French region physicians. *Ann Readapt Med Phys*.2002;46:33 -40.

162 Cagnie B, et al. How common are side effects of spinal manipulation and can these side effects be

predicted? *Man Ther*.2004;9:151-6.

163 Hurwitz EL, et al. Adverse reactions to chiropractic treatment and their effects on satisfaction and clinical outcomes among patients enrolled in the UCLA neck pain study. *J Manipulative Physiol Ther.*2004;27:16 -25.

164 Siegmund GP, et al. Mechanical evidence of cervical facet capsule injury during whiplash: a cadaveric study using combined shear, compression, and extension loading. *Spine.* 2001;26(19):2095-101.

165 Andriacchi T, et al. Ligament: injury and repair. *Acta Rheum Scand*. 1956;2:109-116.

166 Altman B, et al. Use of alternative care providers by the adult population: utilization patterns and expenditures. Workshop presentation. National Center for CAM and Alternative Medicine, June 14, 2000.

167 Eisenberg DM, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survery. *JAMA*. 2002;280:1569–75.

168 Druss BG, et al. Association between use of unconventional therapies and conventional medical services. *JAMA*. 1999;282:651–6.

169 undefined. AAOS. Aching backs impact cost, disability. January 2009. Available at http://www.aaos.org/news/aaosnow/jan09/research6.asp. Accessed March 2, 2012.

170 Breen AC. Chiropractors and the treatment of back pain. *Rheumatol Rehabil*. 1977;16:207-217.

171 Haldeman S. Spinal manipulative therapy: A status report. *Clin Orthop*.1983;179:62-70.

172 Anderson JAD. Back pain in industry. The lumbar spine and back pain. London: Sector Publishing; 1976.

173 Rubinstein S, et al. Spinal manipulative therapy for chronic low-back pain. 16 Feb 2011 DOI: 10.1002/14651858.CD008112.pub2 The Cochrane Library.

174 Ladd AL, et al. Congenital cervical stenosis presenting as transient quadriparesis in athletes: report of two cases.*J Bone Joint Surg Am*. 1986;68:1371-1374.

175 Lee KP, et al. Neurologic complications following chiropractic manipulation: a survey of California neurologists.*Neurology.*1995;45:1213–1215.

176 Assendelft WJ, et al. Complications of spinal manipulation: a comprehensive review of the literature. *The Journal of Family Practice*. 1996; 42(5):475-80.

177 Breig A. Biomechanics of the centra nervous system: some basic normal and pathological phenomena. Stockholm: Almquist & Wiksell;1960.

178 McGregor M, et al. Vertebrobasilar compromise associated with cervical manipulation. *Topics in Clinical Chiropractic*.1995;2:63–73.

179 Maigne JY, et al. Mechanism of action of spinal manipulative therapy. *Joint Bone Spine*. 2003

Sep;70(5):336-41.

180 Reeves KD. Prolotherapy: Basic Science, Clinical Studies, and Technique. Pain Procedures in Clinical Practice. Philadelphia: Hanley and Belfus; 2000. pp 172-190.

181 Leach RA. The Chiropractic Theories: A Textbook of Scientific Research. Baltimore, MD: Lippincott Williams & Wilkins;2004.