

The International
Chiropractors Association

Immune Function
and
Chiropractic

What Does the
Evidence
Provide?

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*Celebrating 94 Years of
Service to the Chiropractic
Profession and the Public*

105
YEARS OF
CHIROPRACTIC



Immune Function and Chiropractic – What Does the Evidence Provide?

Introduction

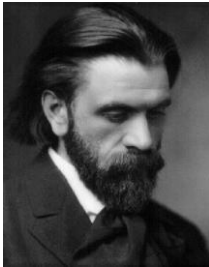
“Scientific advances are predicated on new knowledge that is robust and reliable and that serves as a solid foundation on which further advances can be built.” [1]

Evidence and observation have since the inception of caregiving driven the decision making of care givers. As caregiving became medicine, and now has evolved into health care, experts in health research have established a methodology known as evidence-based medicine or evidence-based health care to describe the ideal process of clinical decision making by health care professionals. Almost simultaneous to this was the promotion of meta-analysis and systematic reviews as methods of gathering the evidence on a topic and drawing quality conclusions. One of the great challenges with the promotion of systematic review has been the almost singular focus on examining randomized controlled trials and eliminating all other peer reviewed published studies from the pool of papers to be evaluated. In fact, one paper cited in this report started with a body of evidence of more than 1,300 articles and eliminated all but 8 to use in their systematic review.

David L. Sackett, the modern founder of Evidence-Based Health provided clarity to the intention. An evidence-based practice, “...aims at integrating individual clinical expertise with the best available external clinical evidence from systemic research and patient values.[2]

Every day, a million times a day, chiropractors make evidence-informed decisions with their patients. As a result, about a million times a day, safe, effective chiropractic care is provided world-wide.





Dr. B.J. Palmer
Founder of the International
Chiropractors Association

“Medicine is the study of disease and what causes man to die.

Chiropractic is the study of health and what causes man to live.”

COVID-19 and the Need for Research

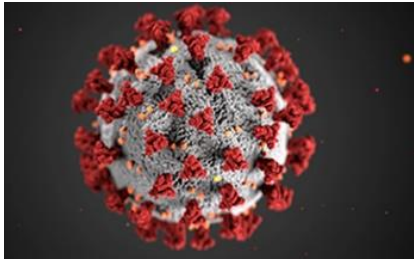
Stanford researcher, John P.A. Ioannidis stated, “The current coronavirus disease, Covid-19, has been called a once-in-a-century pandemic. But it may also be a once-in-a-century evidence fiasco. At a time when everyone needs better information, from disease modelers and governments to people quarantined or just social distancing, we lack reliable evidence... “. [3]

The Coronavirus-19 Global Pandemic, the need for fact-based, peer reviewed information, and the International Chiropractors Association (ICA) affirmation to the global chiropractic community that subluxation-based chiropractic practice is scientific and evidence-based, brings together several key points:

1. Research is essential to improving access to chiropractic as displayed in the recently completed 10 year chiropractic study by the US Department of Defense which confirmed that chiropractic to improve key fitness characteristics among active duty service personnel with low back pain and could lead to improve military readiness in such individuals.[4] As a result TRICARE is looking to expand access to chiropractic.
2. There is an urgent need to expand significantly the level of research funding available to US chiropractic institutions for basic and clinical research.
3. Many chiropractic peer reviewed publications are not PubMed Indexed and need to be for ease of information gathering both inside and outside the chiropractic community.
4. A lack of research evidence is not proof of a lack of benefit.



Coronavirus 19 (COVID-19) is so New there is No Credible Scientific Evidence to Support any Type of Treatment



As of March 2020, there are no cures for COVID-19 accepted in the scientific community. There are no recognized cures in conventional medicine or alternative health approaches for COVID-19. There are no vaccines, no drugs, no natural remedies, no alternative therapies that have been tested and the outcomes peer reviewed to meet any credible evidence-based standard in science. This includes chiropractic.

The ICA has previously provided clear reminders to its members of the importance of not advertising in any form the suggestion that chiropractic can cure, treat, prevent, or mitigate COVID-19 because the evidence to substantiate such a claim does not exist.

The evidence does not exist because the research on COVID-19 and chiropractic has not been conducted, just as it has not been conducted on most other treatment options that might be considered as potentially helpful or for potential 'off label use'. At present there are 44 clinical trials registered with clinicaltrials.gov for COVID-19. Not a single one is for any non-drug, non-biologic approach. Answers for scientific questions never asked through research will never be answered with any credibility.

If Chiropractic Cannot Cure or Prevent, COVID-19, Then Why Talk Immune Function?

The conversation about immune function is bigger than just COVID-19 infection alone. The ICA has been clear that no claims can be made about COVID and chiropractic.

The conversation that all of the experts in public health have been promoting is to use every means available to support one's immune system during the pandemic. (Adequate sleep, good nutrition, frequent hand washing with soap, etc.) There are other factors to consider as well. For example, the stress every member of the public, first responders, and health care professionals are feeling as a result of the changes in our everyday lives from the global pandemic. This stress is creating unprecedented levels of anxiety, and fear in some. Scientific evidence has validated that long-term exposure to stress negatively effects the immune system.

The issue of anxiety and stress has become so prevalent that the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) have begun promoting information to the public. From the CDC's website "Stress during an infectious disease outbreak can include:



- Fear and worry about your own health and the health of your loved ones
- Changes in sleep or eating patterns
- Difficulty sleeping or concentrating
- Worsening of chronic health problems
- Increased use of alcohol, tobacco, or other drugs

Among the recommendations to support oneself through the stress includes, ‘take care of your body’.[5] “Psychological conditions, such as stress or depression, are known to compromise immune defenses and increase the likelihood of infections.”[6]

Wayne Jonas, MD in his book, *How Healing Works*, wrote about the principles of healing, “In condition after condition, system after system, and person after person, I found three common factors that induced healing:

- (1) the rituals that helped a person have a meaningful experience,
- (2) the support of the whole person, and
- (3) the regular stimulation of a biological response.

The specific treatments and agents used varied by person, culture, theory, and place, but the processes were the same. Whole systems science showed us that a person is an ecosystem – more like a garden to be cultivated than a car to be fixed.”[7]

Chiropractic supports the whole person. Vitalistic chiropractors in particular address more than just the mechanics of the spine.

“While other professions are concerned with changing the environment to suit the weakened body, chiropractic is concerned with strengthening the body to suit the environment.”

Dr. B.J. Palmer

Immune Function

“The overall function of the immune system is to prevent or limit infection...The immune system can distinguish between normal, healthy cells and unhealthy cells by recognizing a variety of "danger" cues called danger-associated molecular patterns (DAMPs). Cells may be unhealthy because of infection or because of cellular damage caused by non-infectious agents like sunburn or cancer. Infectious microbes such as viruses and bacteria release another set of signals recognized by the immune system called pathogen-associated molecular patterns (PAMPs)... When the immune system first recognizes these signals, it responds to address the problem. If an immune response cannot be activated when there is sufficient need, problems arise, like infection. On the other hand, when an immune



response is activated without a real threat or is not turned off once the danger passes, different problems arise, such as allergic reactions and autoimmune disease.

The immune system is complex and pervasive...All immune cells come from precursors in the bone marrow and develop into mature cells through a series of changes that can occur in different parts of the body.”[8]

What is measured to study immune function? Researchers conducting scientific investigation start with a theory or hypothesis and determine what can be measured to gather valid information to answer whether the theory or hypothesis has merit. In looking at immune function, the below are a snapshot of measurements that are used in research to measure related to immunity.

1. T-lymphocytes (T-cells) are often used in studies to evaluate the immune response.[5] T-Cells are “important players in the adaptive arm of the immune system.” Because the central nervous system (CNS) is an immune-privileged site, immune response in the CNS are relatively restricted. The unique nature of the communication between the CNS and the immune system can be observed, for example, in the dialog between the CNS and T-cells.”[9]

2. “Chemokines are chemotactic cytokines that control cell migration and cell positioning throughout development, homeostasis, and inflammation. The immune system, which is dependent on the coordinated migration of cells, is particularly dependent on chemokines for its function. Not only do chemokines guide immune effector cells to sites of infection or inflammation, but they also coordinate interactions between immune cells. By doing so, chemokines promote interactions between the innate and adaptive immune systems, thus shaping and providing the necessary context for the development of optimal adaptive immune responses.”[10]

3. Neuropeptides expression has been studied extensively. More than 10,000 papers have been published as a result. Neuropeptides are short sequences of amino acids that function either directly or indirectly to modulate synaptic activity. In addition, neuropeptides may also function as primary neurotransmitters.[11] Recent research findings point to the role of “neuropeptide in immune functions”[6]

4. Substance P (SP) is a neuropeptide that is released from sensory nerve endings and is widely present in nerve fibers. SP acts on bones and related tissues by binding to receptors, thereby regulating bone metabolism, cartilage metabolism, and fracture healing. SP, a signaling substance, is recognized by both the immune system and the nervous system.[12]

5. Cytokine interleukin 2 (IL 2) is pivotal in T-cell dependent immune responses. There are well established protocols to utilize IL 2 assessment to study ability of T-cell to become activated.[13]



Chiropractic and the Nervous System

A professional librarian conducted a systematic literature of seven databases. Only 18 controlled studies were evaluated based on the *a priori* criteria. The effects of high velocity, low amplitude spinal manipulation were evaluated. An association between the spinal manipulation and the autonomic nervous system was confirmed through multiple measurers. The authors noted a need for high-quality studies that include patients, well characterized for pain duration and outcome measure baseline values and address the relation between changes in neurophysiology and pain.[14]

In a study of 21 young men with cervical pain and shoulder stiffness but without abnormalities in neck-to-shoulder MR images and without history of any prior treatments were evaluated. An MRI examination of the neck to shoulder area was conducted on all patients. The MR images were used as a reference for the anatomical locations of cervical muscles in the PET imaging. After spinal manipulation, PET imaging was conducted, cervical muscle tension was measured bilaterally at the superior part of the trapezius muscle using a tissue hardness meter and the mean value of three measurements were recorded. Salivary amylase levels were also measured for each subject using an amylase monitor to evaluate changes in autonomic nervous system (ANS) function.

The researchers “observed metabolic changes in the brain and skeletal muscles, as well as reductions in subjective pain, muscle tension, and salivary amylase, after spinal manipulation intervention. These results may be associated with reduced sympathetic nerve activity, suggesting that spinal manipulation induces a kind of relaxation similar to that achieved by biofeedback. The brain response to spinal manipulation may reflect the psychophysiological relaxation that accompanies reduced sympathetic nerve activity.[15]

A 2005 basic science review of chiropractic summarized the state of the science in several areas including the nervous system response to chiropractic spinal manipulation. The review confirmed that between 1997 and 2005 the basic science body of evidence confirming a relationship between chiropractic spinal manipulation and the central nervous system. They concluded, basic science studies support chiropractic theory that spinal subluxation and spinal manipulation impact neurologic function. In addition, the interdependence of nervous, endocrine, and immune systems has been discussed here. These studies suggest mechanisms by which spinal influences may mediate a clinically significant impact on immune function [16]

The Nervous System and the Immune System

The Nervous System and the Immune System Cross-Talk “Considerable evidence has mounted to support active communication between the nervous system and the immune system. The nervous system, including the brain and the peripheral divisions can either stimulate or inhibit various activities of both the innate and adaptive immune systems.



Page 7 of 14 - Immune Function and Chiropractic

Conversely, the immune system, through the release of cytokines, can influence the activity of the nervous system. Several excellent reviews have addressed the subjects of nervous and immune system “cross-talk” in great detail. Very recently, however, several peptides, recognized initially for their neural or neuroendocrine signaling functions have been shown to exhibit potent antimicrobial activity. This discovery signals the possibility that the nervous system, through utilization of these peptides, has the capacity to deliver anti-infective agents directly to innervated sites localized with great spatial specificity and delivered rapidly. The nervous and neuroendocrine systems, in principle, have the potential to serve a direct immune function.”[17]

The aforementioned Cramer, et. Al, 2005 review notes, “The central nervous system and immune system share modulator and receptor mechanisms by which the two systems communicate. Their interaction maintains both basal and stress-related homeostasis through two major pathways: the systemic sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis... The immune system is now thought to be ‘tuned’ by contrasting neural influences...When internal or external influences disturb homeostasis, both the SNS and HPA axis are activated, thereby increasing the peripheral levels of catecholamines and glucocorticoids to restore the steady state of the internal milieu. The review notes the most extensive body of science regarding chiropractic and the immune system at the time was by Brennan. Two noted findings were that that a single spinal manipulation “enhanced polymorphonuclear cell activity that was associated with a slight, but statistically significant, rise in plasma substance P.” In another study they found patients presenting with neuromusculoskeletal complaints had reduced numbers of circulating natural killer cells; but these cells were not functionally impaired.[16]

A 2018 article reporting on the study design of clinical trial designed to provide knowledge regarding the underlying mechanisms of the effects of Spinal manipulation provided the following analysis of the evidence: “Chiropractic care including spinal manipulative therapy (SMT) has been found to be a safe, effective and cost-effective non-invasive treatment for some types of spinal pain. SMT has both local and regional pain reducing effects as well as central nervous system effects such as a general reduction of pain sensitivity. SMT is thought to decrease pain by mechanically affecting muscular and joint function (i.e. normalizing muscle tone and improving joint mobility). However, recent experimental research has suggested that SMT may also be influencing the incoming /ascending pain signals (local nociceptive input affecting dorsal horn excitability or temporal summation) and/or the excitability of the central pain regulating mechanisms. A systematic review concluded that short-term sympathetic upregulation can be found with SMT, regardless of the spinal area being treated. This raises the question of whether the pain reducing effect of SMT is associated with a modulation of autonomic nervous system (ANS) activity.”[18]



Scientific Evidence

Chiropractic, Spinal Manipulation, and Adjustment

ICA is issuing this report and will continue adding to this list of studies that may be of interest to our members and the greater chiropractic community at large. The following studies include a review of the literature on the effects of spinal adjustment (manipulation) on immune function. The list also includes those studies in which biomarkers which also play a role in immune function are studied.

1. **Neuroimmunomodulation and a Possible Correlation with Musculoskeletal System Function** From 1989 – “There is an increasing body of evidence that the nervous system is capable of modulating the immune response. Receptors for neuromodulators and neurohormones have been found on human T lymphocytes. Activation of these receptors can be stimulatory or inhibitory depending on the neuroactive substance. The immune system may be able to communicate with the nervous system using neuromodulators and neurohormones secreted by lymphocytes. Sympathetic innervation of lymphoid tissues is not restricted to blood vessels and smooth muscle, but directly supplies lymphocytes and blood precursor cells. It is theorized that spinal fixations may adversely affect the immune response through somatosympathetic reflexes. Spinal manipulation can correct the spinal fixations and may eliminate the adverse effects of somatosympathetic reflexes.”[19]

2. **A Literature Review sought to determine the effects of spinal manipulation on biochemical markers** in humans and establish the level of evidence for changes in biochemical biomarkers. Spinal Manipulation (SM), defined as a high-velocity, low-amplitude thrust technique. Among the outcome measured sought were neuropeptides (neurotensin, oxytocin, SP) (2) inflammatory (TNF, IL) and (3) endocrine (cortisol, epinephrine, nor-epinephrine, leutinizing hormone) biomarkers from any body fluids (blood/urine/saliva). After removal of duplications, 1217 citations were screened. That was culled down to 96 abstracts screened, 45 full-text articles were assessed for eligibility. And a total of 8 trials included in the review.

The review found the studies varied in study design, quality, and outcomes. The conclusion after the review was that a moderate level of evidence existed in the eight studies which found that spinal manipulation influences various biomarkers typically identified as ones not only involved in pain perception/modulation but also play an important role in inflammation, tissue healing and immune response. Studies in the review found that Spinal Manipulation influences various biochemical markers. Spinal Manipulation can increase Substance P, neurotensin, oxytocin and interleukin levels and may influence cortisol levels post-intervention.[20]

3. **Low Back Pain and the production of Chemokines.** In a study evaluating the role of inflammation in nonspecific low back pain, an assessment of the production of migratory nociceptive chemokines, and sE-selectin (which activates endothelial cell

production) in patients with acute and chronic low back pain before and after spinal manipulation with a single high velocity low amplitude manipulative thrust to the involved segment in the lumbosacral region was conducted. Six adjustments were provided over a span of two weeks with the single thrust and no other additional treatment modalities. The 3-armed study was completed by 19 patients with acute low back pain; 23 with chronic low back pain; and 21 asymptomatic volunteers.

There were differences in mediators both within their own start and finish measures as well as between groups. Researchers documented significant differences existing in the levels of the studied chemokines between low back pain patients and the asymptomatic controls. Several of the chemokines studied were significantly augmented in acute low back pain patients when compared to the control patients. The production of one of the measured chemokines, CCL4, was significantly higher in the acute low back pain patients than the chronic low back pain patients at baseline; while the other measurements were not significantly different. Conversely, while the plasma content of sE-selectin varied somewhat between groups, compared with controls, the levels were not significantly different in the acute low back pain group but were significantly elevated in the chronic low back pain group. The outcomes after the two-week intervention period found that the mean chemokine production declined across the board in both groups of low back pain patients while remaining essentially unchanged in the asymptomatic group. The spinal manipulation protocol had no statistically significant effect on the sE-selectin production which remained significantly elevated in chronic low back pain patients and unchanged in the acute patients. This is the first step in evaluating the effect of chiropractic on chemokines and sE-selectin and what the changes may or may not mean in relation to both the inflammatory markers and immune system function. One of the still unanswered questions is whether or not the decline in certain chemokines production after spinal manipulation produces an immune response that provides a statistically significant level of protection against any or all bacterial or viral infection presentations to the body. Another unanswered question is whether or not a full adjustment, not just one thrust, provides a different response in the chemokine and sE-selectin responses.[21]

4. **Measuring Biomarkers for Pain before and after chiropractic care in female patients with acute non-specific mechanical neck pain.** Twenty-eight female patients aged 20 to 45 years with acute non-specific mechanical neck pain (NS-MNP) participated in the study. Of these, 13 subjects were randomly assigned to the experiment arm, and 15 to the control group which received a sham manipulation. The objective of the study was to determine if a consistent biochemical response or change in neuropeptide or cortisol serum concentrations occurred after cervical spinal manipulation. While the cortisol levels did not change significantly in either group after the cervical spinal manipulation; there was a significant increase in three of the neuropeptides of interest (oxytocin, neurotensin, and orexin). It is postulated that spinal manipulation may be capable of modulating these biomarkers. [22]



5. Spinal Manipulation effect on interleukin-2 production. The study measured the effect of spinal manipulation on selected parameters of the immune response. The study had three arms – the control group, a group that received spinal manipulation with cavitation (the audible release); and spinal manipulation without cavitation. The goal was to gather knowledge not only on the immune response, but also to determine if cavitation provides a measurable difference in outcomes. The outcomes of the study included a statistically significant increase in the production of IL-2 in both of the arms of the study in which patients received spinal manipulation relative to baseline and to the control group at 20 minutes post adjustment. An increase in IL-2 was also found 2 hours later. There were no differences between the two adjustments arms, meaning that cavitation did not appear to change the outcomes. In this study as with many others, the authors state, “the biological mechanisms associated with spinal manipulation are poorly understood.” The authors also stated that earlier studies have demonstrated increased activity of the innate immune response components following a single spinal manipulation. The authors concluded that a single high velocity, low amplitude thrust to the thoracic spine of asymptomatic subjects causes a significant enhancement in IL-2 secretion in vitro.[13]

6. Spinal Manipulative Thrust Reduces Inflammatory Cytokines. In a study of 64 asymptomatic subjects, were separated into three arms of the study, one to receive a single adjustment of the thoracic spine. The second group was a sham manipulation and the third was a venipuncture control. The authors stated, “the present study supports the hypothesis that the spinovisceral reflex effect can encompass functional activity of the immune system. We believe this to be the first report to demonstrate that a single manipulative thrust to an aberrant vertebral motion segment in the upper thoracic spine of asymptomatic subjects results in downregulation of the capacity of human leukocytes for the production of proinflammatory cytokines induced by lipopolysaccharide (LPS)-induced inflammatory response in invitro, in control subjects submitted to multiple venipunctures, became augmented.” The authors concluded there is a time dependent attenuation of LPS-induced production of the inflammatory cytokines unrelated to systemic levels of Substance P after spinal manipulative thrust. The central mechanism of action was not known.[23]

Anecdotal Evidence is Still Evidence

It is important to remember that the first forms of evidence, the precursor to formal research, is observation and anecdotal evidence. The observation that those who use chiropractic regularly and do not become ill with colds, flu, and other community shared illnesses is frequent within the profession and should not be ignored. It should instead lay the groundwork for a multi-site research study conducted within ICA Affiliated Chiropractic Colleges to study the whole person, all systems within the body and the health outcomes over time with regular chiropractic care. In this type of study, qualitative and quantitative analysis can take place, including the effects on the immune system. We cannot leave the study of immune function to small, well intentioned studies looking at a



Page 11 of 14 - Immune Function and Chiropractic

single spinal manipulation. We need a replication of what happens in chiropractic routinely. A secondary opportunity is practice-based research networks that can gather credible data for the development of peer-reviewed journal reports.

No discussion of immune function and chiropractic can be complete without including the history of chiropractic during the 1918 influenza outbreak known commonly as the Spanish Flu.

The 1918 Influenza History

Chiropractors are all taught the history of chiropractic including the account prepared by Wayne R. Rhodes, DC in writing about the history of chiropractic in the state of Texas. While this is not a scientific paper, it was published by Dr. Rhodes' peers in the Texas Chiropractic Association.

“The 1917 - 1918 influenza epidemic swept silently across the world bringing death and fear to homes in every land. Disease and pestilence, especially the epidemics, are little understood even now and many of the factors that spread them are still mysterious shadows, but in 1917-1918 almost nothing was known about prevention, protection, treatment or cure of influenza. The whole world stood at its mercy, or lack of it.”

He continues, “Chiropractors got fantastic results from influenza patients...” The statistics speak for themselves: In 1918, a time when there were no validated treatments for flu, the epidemic killed millions world-wide.

Data Provided from the 1918 Spanish Flu Comparing Treatment/Death Numbers				
Location	Patients Treated by Medical Doctors (MDs)	Deaths in Medical Patients	Number of Patients Treated by Doctors of Chiropractic (DCs)	Deaths in Chiropractic Patients
Davenport, Iowa	4,953	274	1,635	1
State of Iowa	93,590	6,116 (1 in 15 deaths)	(Excluding Davenport)– 4,735	6
State of Oklahoma			3,490	7
	In Oklahoma, after medical doctors gave up 233 patients as lost, chiropractors were called in with 208 survivors and 25 deaths			
Nationally			46394	54
New York City Influenza	For every 10,000	950	For every 10,000	25
New York City Pneumonia	For every 10,000	6400	For every 10,000	100



Page 12 of 14 - Immune Function and Chiropractic

Chiropractic was also used in France. Dr. S.T. McMurrain (DC) provided care in the influenza ward of Base Hospital No. 84 in Perigau. The medical officer in charge during the outbreak sent all influenza patients for chiropractic adjustments. The outcomes were so impressive that Dr. McMurrain would be commissioned in the Sanitary Corps. [24]

Conclusion

Chiropractic is a health care discipline which emphasizes the inherent recuperative power of the body to heal itself without the use of drugs or surgery. The practice of chiropractic focuses on the relationship between structure (primarily the spine) and function (as coordinated by the nervous system) and how that relationship affects the preservation and restoration of health. It is founded upon the principle that the body's innate recuperative power is affected by and integrated through the nervous system.

The current global health crisis surrounding the COVID-19 Pandemic has resulted in changes in our everyday lives and has created increased levels of stress and anxiety, and fear. Scientific evidence has validated that long-term exposure to stress negatively effects the immune system.

As an essential health care provider, the chiropractor is in a unique position to assist their patients during this time of heightened stress. Although there are no clinical trials to substantiate a direct causal relationship between the chiropractic adjustment and increased protection from the COVID-19 virus, there is a growing body of evidence that there is a relationship between the nervous system and the immune system. As a service to chiropractors around the world, and their patients, the ICA has committed to developing and maintaining this library of relevant scientific evidence.

The Way Forward

The International Chiropractors Association calls upon all of our colleagues within the profession to join with us in seeking greater research resources for our academic institutions. An increase in funding allotted through the current emergency pandemic appropriation and in future years will lead to the necessary clinical research-required to validate the role of doctors of chiropractic in promoting health and vitality by stimulating a healthy immune response.

We call upon our policy makers and legislators world-wide to support these efforts.

The Mission of the International Chiropractors Association is to protect and promote chiropractic throughout the world as a distinct health care profession predicated upon its unique philosophy, science, and art of subluxation detection and correction. We will continue to work each day to fulfill this mission.



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Page 14 of 14 - Immune Function and Chiropractic

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Please address any questions and provide any additional research studies to

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