



The International
Chiropractors Association

Immune Function
and
Chiropractic

What Does the
Evidence
Provide?

28 March 2020

Second Edition



1926 - 2020

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

105
YEARS OF
CHIROPRACTIC



A Message from the President of the International Chiropractors Association

March 28, 2020

One week ago, the ICA released its initial report “*Immune Function and Chiropractic What Does the Evidence Provide?*” and announced the creation of a comprehensive collection of resources and information regarding the current coronavirus (COVID-19) at <http://www.chiropractic.org/covid/>.

As we release the second edition of the International Chiropractors Association’s report, with 7 additional references, misinformation continues to circulate on social media and various websites regarding the available scientific evidence related to the immune system and how much of that evidence may be clinically relevant. Medical personnel around the world are grappling with providing sufficient care for individuals who have taken ill with upper respiratory illnesses such as the flu and Coronavirus-19 (COVID). Researchers and scientists are fast tracking clinical trials in search of a ‘magic bullet’. Government officials, operating with little evidence, are scrambling to enact public policies to mitigate the threats to our communities world-wide. The FDA is expediting the approval for the use of promising treatments prior to the completion of the usually required clinical trials. The “rules of the game” are rapidly changing right before our eyes as regulators begin to recognize that too much “red tape” can do more harm than good.

The current focus on COVID-19 necessitates an ongoing evaluation of the essential services provided by chiropractors who support the non-infectious, urgent and acute neuromusculoskeletal conditions. The chiropractic community, most of whom are small business owners dispersed in large cities and small towns all around the United States and the world, continues to provide essential healthcare services to support their patients during this time of extreme stress.

Many chiropractors have the capacity to provide spinal x-rays in their offices thus reducing the burden on emergency rooms; and reducing the exposure of these patients to others who are potentially infectious. Social distancing requirements combined with strict safety protocols are stressing all health care facilities both large and small. Recent federal legislation seeks to provide much needed resources to all members of the healthcare community as we all unite to do our part. The ICA will continue to develop this resource and provide access to the latest available information in order to enable all chiropractors world-wide to make their decisions based upon an evaluation of the best and most current evidence available.

ICA urges its members to listen to the local directives, to follow the Centers for Disease Control and Prevention’s guidance on measures to take to stop the spread of COVID-19. We have provided a link to the CDC’s page from our COVID page (<http://chiropractic.org/covid>). Rumors abound on social media that some in the chiropractic profession may ignore their local directives or challenge their authority in



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court. We ask that no chiropractor make this his or her “I am Spartacus” moment. The ICA is confident that as more pandemic modeling data becomes available each day, new short term public policies will be adopted.

ICA also affirms that our doctors should retain the rights to use their best judgement, in conjunction with the local directives, and conditions in their own communities to determine if and how they will be open during these challenging times. We appreciate those who are providing chiropractic to first responders and hospital personnel. As essential healthcare service providers, our members are needed more than ever to serve those under extreme stress.

Recognizing the desire of our members to help their current patients and community, the ICA has since COVID-19 was declared a global pandemic given clear guidance to our members that **no claims may be asserted that chiropractic is a prophylactic or cure for COVID-19.** The virus is so new, that no studies have been conducted evaluating the immune response of COVID-19 patients to chiropractic adjustments.

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, 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.

In publishing this report, the ICA provides to our membership, at their request, a summary of existing research; and calls for expanded research resources. This second edition of this report makes minor edits and adds additional studies.

Yours in health,

A handwritten signature in black ink, reading "Stephen P. Welsh, DC, FICA".

Stephen P. Welsh, DC, FICA
President

The contents of this report are not intended to be a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding COVID-19, infectious diseases or any symptom or condition.



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 caregivers. 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.

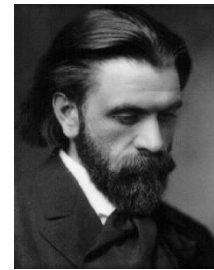


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In 2020, the chiropractic profession celebrates the 125th anniversary of the founding of the profession by D.D. Palmer. He is quoted as saying, *“One question was always uppermost in my mind in my search for the cause of disease. I desired to know why one person was ailing and his associate, eating at the same table working in the same shop, at the same bench, was not. Why? What difference was there in the two persons that caused one to have pneumonia, catarrh, typhoid or rheumatism, while his partner, similarly situated, escaped? Why?”*^[3]

The questions raised by the founder of chiropractic relate to the immune system and are questions still in need of further research 125 years later.

“Medicine is the study of disease and what causes man to die. Chiropractic is the study of health and what causes man to live.”¹



Attributed to
BJ Palmer, DC, PhC
Founder of the International
Chiropractors Association

¹ One of our sage members provided that this quote was actually from Clarence S. Gonstead, DC, who made significant contributions to the field. The quote is widely attributed to Dr. Palmer, however; we wish to note that it may have originally been a statement from Dr. Gonstead.



COVID-19 and the Need for Research

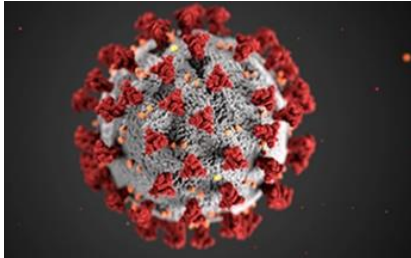
Stanford researcher, John P.A. Ioannidis stated, “The current coronavirus disease, Covid-19, has been called a once-in-a-century pandemic. But it may also be a once-in-a-century evidence fiasco. At a time when everyone needs better information, from disease modelers and governments to people quarantined or just social distancing, we lack reliable evidence... “. [4]

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.[5] 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 and partnering entities.
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 peer reviewed research is not proof of a lack of benefit.
5. One should not discount the important of clinical observation and patient reports, they are the foundation from which the evidence-base is built.



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'. In the first edition of this report, we noted there were 44 clinical trials registered with clinicaltrials.gov for COVID-19. Not even one was for any non-drug, non-biologic approach. As of March 28, 2020, there are now 202 registered clinical trials. Among these are IV vitamin C, numerous other drugs including thalidomide: dietary supplements, Traditional Chinese Medicine, and observational studies about additional adverse outcomes such as myocardial damage. There are no studies that addressing the relationship between the nervous system and the immune system and the effects of chiropractic care. Answers for scientific questions never asked through research will never be answered to the satisfaction of the scientific community.

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

The conversation about immune function is bigger than COVID-19 infection alone. The ICA has been clear that no claims can be made about COVID-19 and chiropractic. We make this statement on every document we issue in regard to this pandemic.

A healthy functioning immune system is critical to overall health and wellness. It is vital to the body's innate ability to seek balance in health sometimes referred to as homeostasis, as Cannon referred to as the 'Wisdom of the Body'[6]. The conversation that all 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



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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'.[7] "Psychological conditions, such as stress or depression, are known to compromise immune defenses and increase the likelihood of infections."[8]

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."[9]

Chiropractic supports the whole person. Vitalistic chiropractors 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



We Cannot Ignore the Affects that Weeks or Months of Fear, Stress and Anxiety Created by the COVID-19 Global Pandemic Response May have on Health Status

Renowned endocrinologist and expert in integrative health care Professor Leonard Wisneski, MD, FACP provided a history of scientific knowledge around the effects on human health related to exposure to stress, stress syndrome, and stress response in his textbook, "The Scientific Basis for Integrative Health". The chapter summarizing the literature on the effects on stress and health, noting that a 1991 study published in the *New England Journal of Medicine* building on historical anecdotal data found that 'psychological stress was associated in a dose response manner with an increased risk of acute infectious respiratory illness.'[10, 11]

The science literature is significant supporting the likelihood that the effects of the worry, stress, fear and anxiety that people around the world are feeling every day for weeks on end will have detrimental effects on their health; at a time when a simple visit to any health care provider is limited.

A recently published report summarized what the extensive body of peer reviewed science supports, "Emerging from this large body of research is substantial evidence that exposure to life stress and adversity can negatively affect human functioning, disease risk, and longevity." And "...human brain and immune system are principally designed to keep the body biologically safe, which they do by continually monitoring and responding to social, physical, and microbial threats in the environment. ... When sustained, however, this multilevel biological threat response can increase individuals' risk for several inflammation-related disease conditions that dominate present-day morbidity and mortality."[12]

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.”[13]

Two Pillars of the Immune System The Immune system is built upon two pillars – the innate immunity and adaptive immunity (sometimes referred to as acquired immunity).[14-17]

Innate Immunity is the nonspecific first line of defense in our immune system. Innate has not been sensitized by external actions such as previous infections or vaccinations. It is not stimulated by specific antigens.

Adaptive Immunity, sometimes referred to as acquired or specific immunity is a subset of the immune system that develops very specialized responses as a result of exposure to pathogens. The system creates immunological memory to create an enhanced response to protect if the same pathogen exposure happens at a subsequent time. The adaptive immune system sometimes has challenges distinguishing between harmful and harmless foreign molecules, which is associated with conditions such as hay fever or seasonal allergies.

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 issues 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.”[18, 19]
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.”[20]

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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.[21] Recent research findings point to the role of “neuropeptide in immune functions”[8]
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.[22]
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.[23]
6. CD4 T lymphocytes counts are the essential measure of progression of disease in HIV patients.[24, 25]

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.[26]

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.**[27]

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** [28]

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. 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.**”[29]

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 a single spinal manipulation “enhanced polymorphonuclear cell activity that was associated with a slight,



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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.[28]

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.”[30]

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.”[31]

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, luteinizing 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.[32]

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 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.[33]

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. [34]

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.[23]

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.[35]

7. **CD4 Count response to Upper Cervical Adjustment.** A 1994 Randomized Clinical Trial found that the CD4 counts in HIV positive patients in the control group experienced a 7.96% decrease while those who received an upper cervical adjustment experienced a 48% increase in CD4 cell levels. While the study was limited by small subject groups, the outcomes are compelling.[36]

8. **Spinal Manipulation and Immune Response Literature Review.** A lay language summary of the existing research posted online provides the following summary, “The studies described above demonstrate an accumulation of evidence that indicates spinal manipulation may influence the immune system's response to various stimuli. Three of the studies suggest that manipulation consistently reduced the production of pro-inflammatory mediators associated with tissue damage and pain from articular structures. Two studies provide evidence that manipulation consistently reduced the production of pro-inflammatory mediators associated with tissue damage and pain from articular structures. Two studies provide evidence that manipulation may induce and enhance production of the immunoregulatory cytokine IL-2 and the production of immunoglobulins as well.”[37]

9. **A literature review of tumor necrosis factor (TNF),** well-known inflammatory cytokine in the pathological development of various human diseases, its physiological roles and the molecular mechanisms underlying spinal manipulation therapy (SMT) and a we propose a novel mechanism by which SMT may achieve clinical benefits by using certain beneficial features of TNF.[38]

10. **Cervicogenic headache (CHA) response to adjustment.** A small study, out of Hungary, two patients with whiplash injury and disk herniation developed CHA associated with very high TNF-alpha levels. After manipulative therapy, these patients became symptom-free, and their TNF-alpha levels decreased substantially.[39]

11. **Neurol Response to Vertebral Subluxation.** A literature review was conducted concerning human or animal studies of neural responses to vertebral subluxation, vertebral displacement or movement, or both.[40]

12. **Autonomic Nervous System Response.** To review recent findings from basic physiologic research about the effects of somatic stimulation of spinal structures on autonomic nervous system activity and the function of dependent organs. The collective experience of the chiropractic profession is that aberrant stimulation at a particular level of the spine may elicit a segmentally organized response, which may manifest itself in dysfunction within organs receiving autonomic innervation at that level. The authors



observation is that this experience is at odds with classic views of neuroscientists about the potential for somatic stimulation of spinal structures to affect visceral function. The authors concluded that, “Recent neuroscience research supports a neurophysiologic rationale for the concept that aberrant stimulation of spinal or paraspinal structures may lead to segmentally organized reflex responses of the autonomic nervous system, which in turn may alter visceral function.”[41]

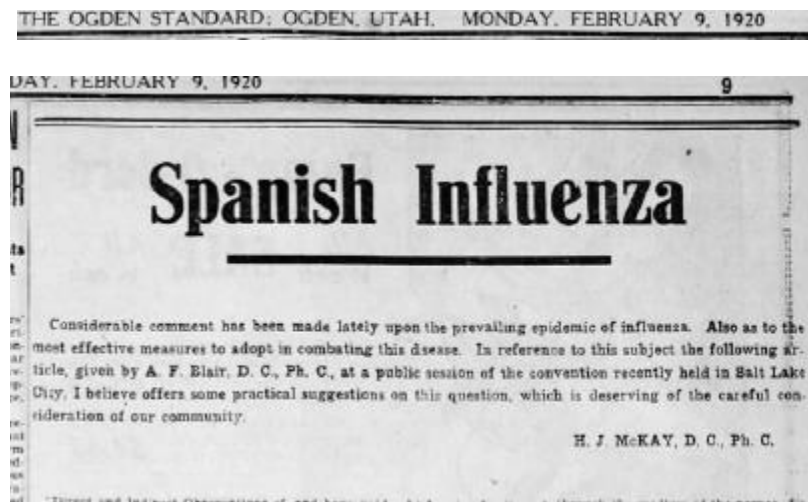
13. **Spinal Manipulation to reduce adverse effects of somatosympathetic.** “There is an increasing body of evidence that the nervous system is capable of modulating the immune response. Receptors for neuromodulators and neurohormones have been found on human T lymphocytes. Activation of these receptors 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.”[31]

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 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.

After the publication of the first edition of this report, the ICA was contacted by academic researchers who suggest that chiropractic colleges do not have the capacity in their research departments to conduct such research. The ICA shares this statement without a qualifier on its merit and notes, that if chiropractic colleges have not yet had the ability to develop this research capacity, then we as a community need to work to grow this capacity and to develop positive affiliations with other academic institutions to achieve the capacity to have well designed clinical and basic science research conducted.

The 1918 Influenza History



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.

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. It is provided for information purposes.

“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. While the below data were gathered by the Osteopathic Association, the data were not prepared in a scientific article and subjected to the peer review process of journals. The information was gathered in Davenport, Iowa, home of Palmer College and reported across the country in meetings and even in newspapers.[42, 43]



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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 10,0000	950	For every 10,000	25
New York City Pneumonia	For every 10,000	6400	For every 10,000	100

In addition to the above data from the United States, Chiropractic is known to have been used during the 1918 Influenza outbreak 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. [44]

There are chiropractors today, who earnestly seek to have this studied during this COVID-19 pandemic and are willing to participate at their local hospitals, or to provide care in their own clinics to hospital personnel, first responders, and others who are at high risk for COVID-19 in a research project if asked.

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.



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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 our colleagues within the profession to join with us in seeking greater research resources for our academic institutions and their research partners. 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 through a healthy, balanced 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.

The contents of this report are not intended to be a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your physician or other qualified health provider with any questions you may have regarding COVID-19, infectious diseases or any symptom or condition.

Bibliography

1. Begley CG, Ioannidis JP. Reproducibility in science: improving the standard for basic and preclinical research. *Circ Res*. 2015;116(1):116-26.
2. Al-Almaie SM, Al-Baghli NA. Evidence based medicine: an overview. *J Family Community Med*, 2003;10(2):17-24.
3. Palmer DD. Text-book of the science, art and philosophy of chiropractic for students and practitioners. 1910, Portland Oregon, Portland Printing House Co. 1007 p.
4. Ioannidis JPA. A fiasco in the making? As the coronavirus pandemic takes hold, we are making decisions without reliable data, in COVID-19. 2020: STATNews.
5. Rand Corporation, Department of Defense, Final Report to Congressional Defense Committees - Chiropractic Clinical Trials, US Department of Defense, Editor. 2019, US Government: Washington, DC. p. 12.

6. Ramsay DS, Woods SC. Clarifying the roles of homeostasis and allostasis in physiological regulation. *Psychol Rev.* 2014;121(2):225-47.
7. Centers for Disease Control and Prevention. Manage Anxiety & Stress. 2020 March 14, 2020 [cited 2020 March 18, 2020]; A plain language discussion of managing stress with links to other information. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prepare/managing-stressanxiety.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fabout%2F coping.html.
8. Whewey J, Mackay CR, Newton RA, et al. A fundamental bimodal role for neuropeptide Y1 receptor in the immune system. *J Exp Med.* 2005;202(11):1527-38.
9. Jonas WB. How healing works: get well and stay well using your hidden power to heal. First edition. ed. 2018, California: Lorena Jones Books, Ten Speed Press. ix, 326 pages.
10. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med.* 1991;325(9):606-12.
11. Wisneski LA. The scientific basis of integrative health. 3rd ed. 2017, Boca Raton, FL. CRS Press. p. 688.
12. Slavich GM. Social Safety Theory: a biologically based evolutionary perspective on life stress, health, and behavior. *Annu Rev Clin Psychol*, 2020. Mar 6. doi: 10.1146/annurev-clinpsy-032816-045159
13. National Institute of Allergy and Infectious Diseases, National Institutes of Health. Immune System Research - Overview of the immune system. Immune System Research 2013 December 30, 2013 [cited 2020 March 18]; Available from: <https://www.niaid.nih.gov/research/immune-system-research>
<https://www.niaid.nih.gov/research/immune-system-overview>
<https://www.niaid.nih.gov/research/immune-response-features>
<https://www.niaid.nih.gov/research/immune-cells>
<https://www.niaid.nih.gov/research/immune-tolerance>
<https://www.niaid.nih.gov/research/immune-system-disorders>
<https://www.niaid.nih.gov/research/research-frontiers-immune-system>
14. Turvey SE, Broide DH. Innate immunity. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S24-32.
15. Li G, Yaohua Fan Y, Lai Y, et al. Coronavirus infections and immune responses. *J Med Virol.* 2020; 92(4):424-32.

16. Margulies DH, Jiang J, Natarajan K. Structure and function of molecular chaperones that govern immune peptide loading. *Subcell Biochem.* 2019;93:321-37.
17. Lee HS, Belkhadir Y. Damage control: cellular logic in the root immune response. *Cell Host Microbe.* 2020;27(3):308-10.
18. Schwart M. Protective autoimmunity as a T-cell response to central nervous system trauma: prospects for therapeutic vaccines. *Prog Neurobiol.* 2001;65(5):489-96.
19. Teodorczyk-Injeyan JA, Sparkes BG, Mills GB, et al. Impairment of T cell activation in burn patients: a possible mechanism of thermal injury-induced immunosuppression. *Clin Exp Immunol.* 1986;65(3):570-81.
20. Sokol CL, Luster AD. The chemokine system in innate immunity. *Perspect Biol.* 2015;7(5): a016303. doi: [10.1101/cshperspect.a016303](https://doi.org/10.1101/cshperspect.a016303)
21. Li, C. and K. Kim, Neuropeptides. *WormBook*. 2008 Sep 25:1-36. doi: 10.1895/wormbook.1.142.1.
22. Li FX, Xu F, Lin X, et al. The role of substance P in the regulation of bone and cartilage metabolic activity. *Front Endocrinol.* 2020;11:77. doi: [10.3389/fendo.2020.00077](https://doi.org/10.3389/fendo.2020.00077)
23. Teodorczyk-Injeyan JA, Injeyan HS, McGregor M, Harris GM, Ruegg R. Enhancement of in vitro interleukin-2 production in normal subjects following a single spinal manipulative treatment. *Chiropr Osteopat.* 2008;16:5. doi: 10.1186/1746-1340-16-5.
24. Grant MD, Smail FM, Rosenthal KL. Cytotoxic T-lymphocytes that kill autologous CD4+ lymphocytes are associated with CD4+ lymphocyte depletion in HIV-1 infection. *J Acquir Immune Defic Syndr.* 1994;7(6):571-9.
25. Gnatienco, N, Lioznov D, Raj A, et al. Design of a randomized controlled trial to link infectious and Narcology Care (LINC-II) in St. Petersburg, Russia. *Addict Sci Clin Pract.* 2020;15(1):1. doi: [10.1186/s13722-020-0179-8](https://doi.org/10.1186/s13722-020-0179-8)
26. Wirth B, Gassner A, de Bruin ED, et al. Neurophysiological effects of high velocity and low amplitude spinal manipulation in symptomatic and asymptomatic humans: a systematic literature review. *Spine.* 2019;44(15):E914-E926.
27. Inami A, Ogura T, Watanuki S, et al. Glucose metabolic changes in the brain and muscles of patients with nonspecific neck pain treated by spinal manipulation therapy: a [(18)F]FDG PET study. *Evid Based Complement Alternat Med.* 2017:4345703.



28. Cramer G, Budgell B, Henderson C, Khalsa P, Pickar J. Basic science research related to chiropractic spinal adjusting: the state of the art and recommendations revisited. *J Manipulative Physiol Ther*. 2006;29(9):726-61.
29. Brogden KA, Guthmiller JM, Salzet M, Zasloff M. The nervous system and innate immunity: the neuropeptide connection. *Nat Immunol*. 2005;6(6):558-64.
30. Galaasen Bakken A, Axén I, Eklund A, O'Neill S. The effect of spinal manipulative therapy on heart rate variability and pain in patients with chronic neck pain: a randomized controlled trial. *Trials*. 2019;20(1):590.
31. Fidelibus JC. An overview of neuroimmunomodulation and a possible correlation with musculoskeletal system function. *J Manipulative Physiol Ther*. 1989;12(4):289-92.
32. Kovanur-Sampath K, Mani R, Cotter J, Gisselman AS, Tumilty S. Changes in biochemical markers following spinal manipulation-a systematic review and meta-analysis. *Musculoskelet Sci Pract*. 2017;29:120-31.
33. Teodorczyk-Injeyan JA, McGregor M, Triano JJ, Injeyan SH. Elevated production of nociceptive CC Chemokines and sE-Selectin in patients with low back pain and the effects of spinal manipulation: a nonrandomized clinical trial. *Clin J Pain*. 2018;34(1):68-75.
34. Lohman EB, Pacheco GR. The immediate effects of cervical spine manipulation on pain and biochemical markers in females with acute non-specific mechanical neck pain: a randomized clinical trial. *J Man Manip Ther*. 2019;27(4):186-96.
35. Teodorczyk-Injeyan JA, Injeyan HS, Ruegg R. Spinal manipulative therapy reduces inflammatory cytokines but not substance P production in normal subjects. *J Manipulative Physiol Ther*. 2006;29(1):14-21.
36. Selano JL, Hightower BC, Pflieger B, Collins KF, Grostic JD. The effects of specific upper cervical adjustments on the CD4 counts of HIV positive patients. *Chiropr Res J*. 1994;3(1):32-39.
37. Slosberg M. Immune responses to spinal manipulation. In *Dynamic Chiropractic*. 2011;29(10).
<https://www.dynamicchiropractic.com/mpacms/dc/article.php?id=55320>
38. Zhang L, Yao CH. The physiological role of tumor necrosis factor in human immunity and its potential implications in spinal manipulative therapy: a narrative literature review. *J Chiropr Med*. 2016;15(3):190-6.



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39. Ormos G, Mehrishi JN, Bakacs T. Reduction in high blood tumor necrosis factor-alpha levels after manipulative therapy in 2 cervicogenic headache patients. *J Manipulative Physiol Ther.* 2009;32(7):586-91.
40. Bolton PS. Reflex effects of vertebral subluxations: the peripheral nervous system. An update. *J Manipulative Physiol Ther.* 2000;23(7):512-3.
41. Budgell BS. Reflex effects of subluxation: the autonomic nervous system. *J Manipulative Physiol Ther.* 2000;23(2):104-6.
42. Advertisement, What Chiropractic Really Does, in The News Democrat. 1919: Paducah, KY. p. 5.
43. McKay HJ. Spanish Influenza, in The Ogden Standard. 1920: Ogden, Utah. p. 9.
44. Rhodes WR. The official history of chiropractic in Texas. 1978, Austin: Texas Chiropractic Association. 188 p.

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15 DAYS TO SLOW THE SPREAD

Listen to and follow the directions of your **STATE AND LOCAL AUTHORITIES**.

IF YOU FEEL SICK, stay home. Do not go to work. Contact your medical provider.

IF YOUR CHILDREN ARE SICK, keep them at home. Do not send them to school. Contact your medical provider.

IF SOMEONE IN YOUR HOUSEHOLD HAS TESTED POSITIVE for the coronavirus, keep the entire household at home. Do not go to work. Do not go to school. Contact your medical provider.

IF YOU ARE AN OLDER PERSON, stay home and away from other people.

IF YOU ARE A PERSON WITH A SERIOUS UNDERLYING HEALTH CONDITION that can put you at increased risk (for example, a condition that impairs your lung or heart function or weakens your immune system), stay home and away from other people.



For more information, please visit
CORONAVIRUS.GOV

DO YOUR PART TO SLOW THE SPREAD OF THE CORONAVIRUS

Even if you are young, or otherwise healthy, you are at risk and your activities can increase the risk for others. It is critical that you do your part to slow the spread of the coronavirus.

Work or engage in schooling **FROM HOME** whenever possible.

IF YOU WORK IN A CRITICAL INFRASTRUCTURE INDUSTRY, as defined by the Department of Homeland Security, such as healthcare services and pharmaceutical and food supply, you have a special responsibility to maintain your normal work schedule. You and your employers should follow CDC guidance to protect your health at work.

AVOID SOCIAL GATHERINGS in groups of more than 10 people.

Avoid eating or drinking at bars, restaurants, and food courts — **USE DRIVE-THRU, PICKUP, OR DELIVERY OPTIONS.**

AVOID DISCRETIONARY TRAVEL, shopping trips, and social visits.

DO NOT VISIT nursing homes or retirement or long-term care facilities unless to provide critical assistance.

PRACTICE GOOD HYGIENE:

- *Wash your hands, especially after touching any frequently used item or surface.*
- *Avoid touching your face.*
- *Sneeze or cough into a tissue, or the inside of your elbow.*
- *Disinfect frequently used items and surfaces as much as possible.*

CORONAVIRUS.GOV

School operations can accelerate the spread of the coronavirus. Governors of states with evidence of community transmission should close schools in affected and surrounding areas. Governors should close schools in communities that are near areas of community transmission, even if those areas are in neighboring states. In addition, state and local officials should close schools where coronavirus has been identified in the population associated with the school. States and localities that close schools need to address childcare needs of critical responders, as well as the nutritional needs of children.

Older people are particularly at risk from the coronavirus. All states should follow Federal guidance and halt social visits to nursing homes and retirement and long-term care facilities.

In states with evidence of community transmission, bars, restaurants, food courts, gyms, and other indoor and outdoor venues where groups of people congregate should be closed.