

SOUTH BAYLO UNIVERSITY

**INFLUENCE OF ACUPUNCTURE ON THE INFLAMMATORY
PROCESSES AND IMMUNITY**

by

Mehrdad Joukar

**A RESEARCH PROJECT SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE**

Doctor of Acupuncture and Oriental Medicine

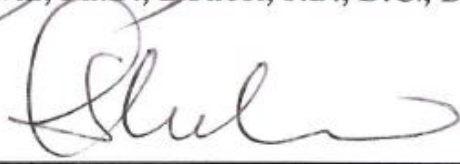
ANAHEIM, CALIFORNIA

JUNE 2016

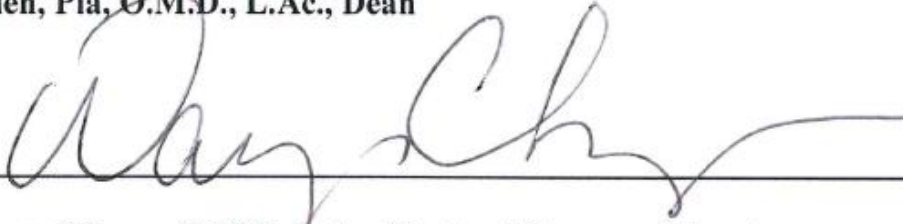
**THE DISSERTATION OF MEHRDAD JOUKAR
APPROVED BY RESEARCH PROJECT COMMITTEE**



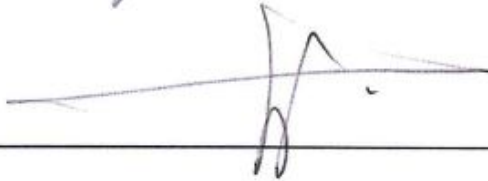
Follick, Edwin, Ph.D., DTheol, J.D., D.C., Director of Libraries and ADA Officer



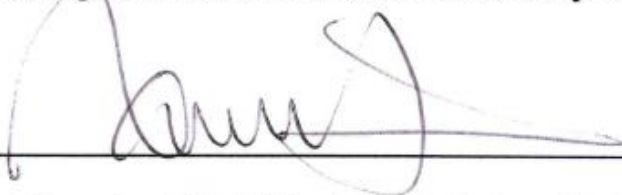
Melen, Pia, O.M.D., L.Ac., Dean



Cheng, Wayne, O.M.D, L.Ac., Doctoral Program Director



Li, Sheng, O.M.D., L.Ac., DAOM Clerkship Coordinator



Sun, Xuemin, M.D.(China), Ph.D., L.Ac., DAOM Research Coordinator

SOUTH BAYLO UNIVERSITY

ANAHEIM, CALIFORNIA

JUNE 30, 2016

Copyright
by
Mehrdad Joukar

2016

Influence of Acupuncture on the Inflammatory Processes and Immunity

A Literature Review Study

Mehrdad Joukar

SOUTH BAYLO UNIVERSITY AT ANAHEIM, 2016

Research Advisor: Sandjaya Trikadibusana, M.D. (Indonesia), M.S., DAOM, L.Ac.

ABSTRACT

Acupuncture can be used in treating many inflammatory diseases and painful conditions, and therefore is thought may be useful as an alternative therapy for generally accepted pharmacological interventions. The associate effect of acupuncture has been investigated in inflammatory diseases, including asthma, allergic rhinitis, ulcerative colitis, and rheumatoid arthritis. Since acupuncture can modulate the immune system it could be a useful treatment for different immune disorders.

Searches were implemented on the Pubmed databases for clinical trial and review studies in full text evaluating effectiveness of acupuncture in inflammatory disorders in humans and other animals. The experimental animal and clinical human studies in timeframe between 1994 and 2014 with limitation of language to English were included. The articles that did not have those criteria were excluded.

Mechanisms underlying the immunosuppressive actions of acupuncture and the acupuncture-controlled release of neuropeptides from nerve endings and subsequent vasodilative and anti-inflammatory effects through calcitonine gene related peptide (CGRP) are reviewed in this study. The complex interactions with substance P, the analgesic contribution of beta-endorphin and the balance between cell-specific pro-inflammatory and anti-inflammatory cytokines and interleukins are discussed. In addition, the role of T helpers, mast cells and macrophages and also relationship between glutathione and malondialdehyde levels with myeloperoxidase activity and lipid peroxidation are analyzed.

Anti-inflammatory effects of acupuncture include an antihistamine action and downregulation of proinflammatory cytokines such as TNF (Tumor Necrosis Factor)- α , IL (Interleukin)-1 β , IL (Interleukin)-6, and IL(Interleukin)-10 and proinflammatory neuropeptides such as SP (Substance P), CGRP (Calcitonin Gene Related Peptide), and VIP (Vaso-active intestinal peptide) which can enhance and prolong inflammatory response. Acupuncture seems to regulate various processes simultaneously, and is potentially very important method modulating immunity and inflammatory response of the body. However, more research is needed to elucidate specifically how immune mechanisms might be modulated by acupuncture in inflammatory disorders.

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	MATERIALS & METHODS	4
III.	RESULTS	5
IV.	DISCUSSION	18
V.	CONCLUSION	21
VI.	REFERENCES	22
	APPENDIX A	25
	APPENDIX B	26

I. INTRODUCTION

During excessive research scientists have described the influence of acupuncture on the inflammatory processes and immunity. Modern medicine understands inflammation as very complex reaction involving different networks of processes and immunity as multithreaded process happening constantly on different levels of functioning of the body. Acupuncture seems to regulate various processes simultaneously, and is potentially very important method modulating immunity and inflammatory response of the body. ⁽¹⁾

Acupuncture activates the defense systems. It influences specific and nonspecific cellular and humoral immunities; activates cell proliferation, including blood, reticuloendothelial, and traumatized cells; and activates leucocytosis, microbicidal activity, antibodies, globulin, complement, and interferon. It modulates hypothalamic-pituitary control of the autonomic and neuroendocrine systems, especially microcirculation, response of smooth and striated muscle, and local and general thermoregulation. ⁽²⁾

Immuno-stimulant points include LI-4, LI-11, ST-36, GB-39, SP-6, GV-14, BL-11, BL-20, BL-23, BL-24, BL-25, BL-26, BL-27, BL-28, and CV-12. Some, such as BL-47, are immunosuppressive. Antifebrile points include GV-14 and ST-36. Reactive reflex SHU points, MU points, and auricular points are useful in organic diseases. In immuno-mediated diseases, some or all of these points can be used with other points, especially local points and points of the major symptoms or points of the affected body part, area, function, or organ. ⁽²⁾

How can we prove that acupuncture does control inflammation? The immune response and inflammation is a complex multi-level process. It relies heavily on chemical messengers called

cytokines that help control things like blood vessel permeability (leakiness) and vasoconstriction/dilation at the injury site. Some of these cytokines promote inflammation such as interleukin IL-6 while others help decrease inflammation such as IL-10. Several studies reveal that both manual and electro acupuncture can have a dramatic effect on both leukocytes and their associated cytokines. Specifically, acupuncture was shown to decrease IL-6 and increase IL-10. (1, 2)

There are many articles and findings from different studies describing various elements of general acupuncture influence on immunity. In inflammation process, neutrophils and other materials slip through the cell walls and migrate to the injury site. In those studies levels of cytokines were directly measured and the level of capillary permeability was determined. The results showed that acupuncture resulted in a dramatic decrease in blood vessel permeability and a significant decrease in inflammation. Blood analysis showed a large increase in the anti-inflammatory cytokine Interleukin IL-10 in comparison to the non-acupuncture group. (1, 2, 12)

Acupuncture has been shown to have a significant influence experimentally on the regeneration and the reconstruction functions of nerves and muscles. Current studies show that the initial inflammatory response leads to an influx of neutrophils and macrophages, which play a crucial role in supplying cytokines of the growth factor and nitric acid, thus determining the migration of keratinocytes to the afflicted epithelium. Acupuncture reduces the inflammatory grade of the inflammatory phase; the fibrous proliferative grade is enhanced; the dynamics of epidermal changes in suggest that the thicknesses recorded in all stages are enhanced; Acupuncture facilitates a low mechanical stress in tissue and has a positive effect on the healing of muscular defects and wound. Acupuncture influences specific and non-specific cellular influx, activation

of cell proliferation and regulation of subsequently involved cells that will result in a complex mechanism of transport, further breakdown and clearance of all bioactive mediators. ^(3, 8)

As some observations highlight the stimulating effects of acupuncture to muscle afferents and blood flow through autonomic reflexes, the attributive effect of nitric oxide (NO) through local release and/or induction after acupuncture should also be considered. Significant and persistent increases in the arteriolar diameter were observed after acupuncture. NO levels were increased in rat striatum after cerebral artery occlusion, ischemia and reperfusion. Acupuncture antagonized the ischemia-elicited release of NO. ⁽⁸⁾

II. MATERIALS & METHODS

Electronic searches were implemented on the PubMed databases using the key words “acupuncture” and “Inflammation”. The inclusion criteria of selecting the research studies were as follow: the article types were clinical trial and review, the text availability was full text, the species in the studies were humans and other animals.

The experimental animal studies were conducted by the institutions that their preparations and research protocols were reviewed and approved by animal care and use committee for animal studies. The clinical human studies were conducted by reliable medical institutions .The timeframe of articles publication was set between 1994 and 2014.The language of publication was restricted to English only. The articles that did not have those criteria were excluded.

III. RESULTS

The insertion of the acupuncture's needle induces marked changes close to the needle in all the different tissues that are penetrated. These peripheral events might improve tissue function through vasodilatation in the skin due to axon reflexes, which cause an immediate flare reaction. This vasodilative effect could be caused by the release of calcitonin gene related peptide (CGRP) upon stimulation of Ad or C fibers. The local release of b-endorphin could be responsible for the short-term analgesic effect, whereas the neuropeptide- induced release of anti-inflammatory cytokines could be derived from lymphocytes and secondary activating cells, such as macrophages. In the periphery, the real level of CGRP is of crucial importance. Usually CGRP has been shown to be pro-inflammatory, but in low doses it has a potent anti-inflammatory action. In this respect the release of another neuropeptide, substance P, is not likely to attribute to this phenomenon, but could regulate CGRP release from nerve endings. The promotion of blood circulation by acupuncture could positively affect the enrolment of the whole cascade of inflammatory mediators that are undoubtedly involved in the subsequent processes during chronic inflammation. ^(3, 8, 12, 13)

In general, inflammation is associated with increasing temperature, oedema, redness, pain and loss of function. Furthermore, the direct and indirect effects of individual neuropeptides, cytokines and vasoactive mediators could be considered to play an intermediate role during and after acupuncture has been assessed. Assuming local blood flow is indeed stimulated by acupuncture, the neurogenic formation of vasoactive mediators could regulate blood flow and blood distribution to affected organs and tissue after inflammation has been initiated. ⁽⁸⁾

CGRP is a potent vasodilator that has been shown to have a physiological and pathological role in neurogenic inflammation, migraine, thermal injury, circulatory shock, pregnancy and menopause, hypertension and heart failure. Both substance P and CGRP have important roles in oedema formation and inflammation. Intra-neural substance P contributes to the severity of inflammation. ⁽⁸⁾

In musculocutaneous flaps in the rat, increased blood flow affected by acupuncture was comparable with the effects observed after injection of substance P and CGRP. In rats, acupuncture induced the release of substance P from peripheral terminals of primary sensory neurons. After repeated acupuncture, significantly higher concentrations of substance P and other neuropeptides such as neurokinin A and Neuropeptide Y were found in the rat brain. Needling of acupuncture points could result in activation of afferent fibres of peripheral nerves, which induces the release of endogenous opiate peptides from nerve cells. Beta-endorphins are believed to play an important intermediate role in the regulation of the analgesic effects obtained through acupuncture. ^(5, 8)

Very recently, the existence of regulatory IL-10-dependent T-cell populations was documented in allergic diseases. In asthma IL-2 and IL-6 plasma levels were decreased, whereas interferon (IFN)- γ , IL-4 and tumor necrosis factor (TNF)- α were increased. After acupuncture IFN- γ , IL-2, IL-4 and IL-6 were elevated and TNF- α was reduced. In allergic rhinitis in the acupuncture group IL-10 was reduced. In rheumatoid arthritis after acupuncture, the reduced IL-2 production was elevated. In ulcerative colitis, acupuncture inhibited the expression of pro-inflammatory cytokines IL-1 β and IL-6. In conclusion, the balance between T helper 1 cell-derived and T helper 2 cell-derived pro-inflammatory and anti-inflammatory cytokines was reset by acupuncture. ^(8, 10, 12)

Acupuncture induces peripheral events that might improve tissue function and induce local pain relief, based on mechanisms that include axon reflexes, release of neuropeptides such as CGRP, anti-inflammatory actions of neuropeptides like substance P, and local release of b-endorphin. After antidromic stimulation of the nociceptor, CGRP, substance P and b-endorphin are all released. Initially, substance P will activate mast cells and in a later phase also macrophages to secrete inflammatory mediators. As a consequence, the mast cell will not only secrete serotonin and histamine, but also cytokines such as TNF- α . In turn, TNF- α could prime sensory nerve endings. The activation of mast cells and mast cell-mediated inflammation is regulated by NO. (8, 10)

Macrophages will produce a number of cytokines and eicosanoids. In the blood vessel, CGRP will directly or indirectly affect vasodilation and extravasation via the stimulation of NO, VIP and bradykinin. Delayed dilatation to bradykinin is cyclooxygenase-2 dependent, whereas prostaglandin E2 potentiates bradykinin and induces pain. Substance P regulates the vasodilator activity of CGRP through the action of proteases from mast cells. (8, 11)

In the study which was conducted by Federal University of Ceara (UFC), Brazil they discovered the stimulation of ST-36 and SP-6 with electroacupuncture promoted a significant increase in systemic (plasma) and local (ovary) GSH (glutathione) levels compared with control group rates levels. The use of electroacupuncture has promoted an increase in GSH levels in the liver and kidneys and in random skin flaps of rats. Lipid peroxidation was more intense in rats treated with electroacupuncture as there was a significant raise in MDA (malondialdehyde) levels in electroacupuncture group rats. Furthermore, increased levels of MDA in rats treated with electroacupuncture shows that electroacupuncture may have a pro-peroxidative effect. Both acupuncture and electroacupuncture reduced MPO (myeloperoxidase) activity in ovarian tissue,

possibly by inhibiting neutrophil infiltration, suggesting that these methods of treatment may have a protective role in the estradiol -induced oxidative injury. ^(4, 12)

In the early phase of inflammation neutrophilic chemokines direct opioid-containing neutrophils in the inflamed tissue and stimulate opioid peptide release and antinociception. Acupuncture leads to a down-regulation of pro-inflammatory cytokines such as tumor necrosis factor (TNF-alpha) and interleukin (IL)-1beta at the site of inflammation. This anti-inflammatory as well as antinociceptive effect involved activation of the cannabinoid receptor 2 (CB2). They activate opioid receptors both at the level of the spinal cord as well as on peripheral sensory neurons at the site of inflammation. Acupuncture triggers END (beta-endorphin) transcription and translational in the inflamed tissue and this was attenuated by a CB2 antagonists. Opioid-containing leukocytes migrate into the inflamed tissue, release opioid peptides such as END (beta-endorphin), Met-enkephalin (ENK) and dynorphin A (DYN) and induce antinociception by binding to opioid receptors (μ , MOR; δ , DOR and κ , KOR) on peripheral nociceptive neurons. ^(5, 6)

In the study which was conducted by Department of Anesthesiology, University Hospital of Würzburg in Würzburg, Germany they discovered EA suppressed selected pro- and enhanced anti-inflammatory cytokines in a model of inflammatory pain in rats. In contrast to this pattern, electroacupuncture increased the production of the cytokine IFN (Interferon)-gamma and the chemokine CXCL (chemokine ligand) 10 at the site of inflammation leading to an increase in opioid-containing CXCR 3⁺ (chemokine receptor) macrophages. Macrophage-derived opioid peptides could activate opioid receptors on peripheral sensory neurons and suppressed inflammatory pain. ⁽⁶⁾

In the study which was conducted by Rutgers University New Jersey Medical School, Newark and reported in Nature Medicine they discovered Stimulating of ST36 with electroacupuncture activated two nerve tracts in mice that led to the production of a biochemical that quieted a sepsis-like inflammatory reaction that had been induced in mice. ^(7,9)

Table 1: Researches' results summary

№	Name of institute	Subject of study	Date of study	Type of study	Number of samples	Acupuncture points	Method of Acupuncture	Result
3	UVMC	Acupuncture and soft tissue healing	2014	Animal (Rabbit)	10	Non specific	Electro-Acupuncture	Ad/C fibers stimulation → CGRP release → Vasodilative effects
5	CVM	Anti-inflammatory effects of Electro-Acupuncture	2006	Animal (Mice)	1	Non specific	Electro-Acupuncture	Peripheral nerves activation → Neuropeptides release → Endogenous opiate peptides release → Anti-inflammatory & analgesic effects
8	EMC	Anti-inflammatory actions of Acupuncture	2003	Human	90	Non specific	Manual Acupuncture	Reset the balance between TH 1 & TH 2 cytokines: AR: IL-10 reduction RA: IL-2 elevation UC: IL-1b, IL-6 inhibition
11	GHI	Anti-inflammatory effects of Acupuncture	2013	Human	45	Non specific	Manual Acupuncture	Nociceptor antidromic stimulation → CGRP, substance P & b-endorphin release → Mast cell activation → Serotonin, histamine & cytokines secretion → Sensory nerve endings Mast cell activation → Proteases from mast cells → CGRP → Vasodilator activity Macrophage activation → Produce cytokines & eicosanoids → NO, VIP & Bradykinin stimulation → Delayed dilatation & induces pain
4	FUC	Acupuncture	2013	Animal	24	ST-36, SP-6	Electro-	GSH increase in plasma, ovary & other organs

		effects on estradiol-induced inflammation		(Rat)			<i>Acupuncture</i>	→ MDA increase→ Peroxidative effect Neutrophil infiltration inhibition→ MPO reduction in ovary →Protective role in oxidative injury
6	<i>UHW</i>	Electro-acupuncture effects on inflammatory pain	2014	<i>Animal (Rat)</i>	10	<i>GB-30</i>	<i>Electro-Acupuncture</i>	Cytokines down-regulation in inflamed tissue →END transcription & translational → CB2 activation → Opioid receptors activation → Antinociceptive effect Leukocytes migration into inflamed tissue → Opioid peptides release →Binding to opioid receptors on nociceptive neurons →Induce antinociception Cytokine & chemokine production increase in inflamed tissue → Increase in macrophages →Opioid peptides → Activate opioid receptors on sensory neurons →Suppressed inflammatory pain
7	<i>RNJMS</i>	Electro-acupuncture effects on immune system vagal modulation	2014	<i>Animal (Mice)</i>	20	<i>ST-36</i>	<i>Electro-Acupuncture</i>	Nerve tracts activation → Biochemical production →Sepsis-like inflammatory reaction

IV. DISCUSSION

Acupuncture developed from the traditional Chinese Medicine techniques that can trace recorded origins back to the 2nd century BC. Acupuncture involves the stimulation of acupoints that are located at lines of meridians that correspond to the flow of energy through the body. It is designed to balance the flow of energy within the body, involves piercing the skin with thin needles to stimulate strategic points on the body. Modern acupuncture has evolved other methods of stimulating acupoints including the use of an electrical current (electro stimulation) and by applying pressure (acupressure). Complementary and alternative medicine (CAM) treatments are becoming increasingly popular in the USA. It is estimated Americans spends an average of \$ 33.9 billion per year on CAM treatments with acupuncture is one of the most common type of them. ^(16, 17, 18)

If it was proven to be effective, acupuncture would be an attractive alternative to conventional treatments for many patients. Previous studies have shown that side effects are rare in acupuncture and generally only minor. Furthermore the cost of acupuncture sessions is likely to be comparable to that of symptomatic medication. In addition many patients dislike daily medication use, and a drug-free, safe treatment option therefore has considerable attractions. ^(16, 17, 18)

Acupuncture is a therapeutic modality for the treatment or prevention of several inflammatory diseases, including asthma, rhinitis, inflammatory bowel disease and rheumatoid arthritis.

Experimental and clinical trials have shown that acupuncture and electroacupuncture have

beneficial effects in different painful inflammatory conditions. Other applications of acupuncture include treatment of inflammation, trauma, infections, autoimmune diseases, allergies, and also stimulation of tissue healing in burns, ulcers, wounds, ischemia and necrosis.^(2, 12, 16, 17, 18)

Inflammation is a key part of the body's defense system; it is the innate immune system response to an attack on the body. This can occur through a blunt-force or penetrating tissue injury or in response to an infection caused by a pathogen. Exposure to chemical irritants or toxins will cause inflammation, as will burns, frostbite, or other injuries. The inflammation process protects the body by isolating the damaged area, attracting immune cells and molecules to the site and, in later stages, promoting the healing of affected tissues.^(19, 20)

Acute inflammation is short-lived, lasting only a few days. If it lasts longer, it is referred to as chronic inflammation. Chronic inflammation may last weeks, months, or beyond. Paradoxically, the inflammatory process itself may cause tissue damage while it is engaged in healing and repair. Thus, inflammation may play a role in such diverse disorders as Alzheimer disease, Asthma, inflammatory bowel disease (IBD) and psoriasis.^(19, 20)

Immunity is a state in which the body is protected from infectious disease. It is conferred by the immune system, a complex network of cells, tissues and chemicals that fight infection and kill organisms when they invade the body. There are three categories of immune protection, all of which help protect the body from infectious diseases. It can be innate or acquired, active or passive, and natural or artificial.^(14, 15)

The category of innate or acquired protection refers to the type of immune response that is mounted by the immune system. An innate immune response is not specific to the pathogen to

which the system is responding, and it happens almost immediately when an infectious organism invades the body. In contrast, an acquired immune response is specific to the pathogen and can take several days to build up. The acquired immune response also involves the development of immunological memory, a state in which the immune system can quickly mount a response to an infectious organism that it has previously encountered. ^(14, 15)

In the second category, passive or active, passive immunity is an impermanent form of acquired immunity in which antibodies against a disease are acquired naturally (as through the placenta to an unborn child) or artificially (as by injection of antiserum). On the other hand, active immunity is the process through which a human being builds up a specific resistance to a harmful substance. There are usually two ways this can happen; natural exposure, like when a person catches a cold or encounters a certain bacteria in the environment or vaccination which can also cause an active immune response through artificial means. The third category, natural or artificial immunity, refers to whether the protection has developed with or without intervention; for example, trans-placental antibody and vaccination. ^(14, 15)

V. CONCLUSION

Acupuncture has a dramatic effect on both leukocytes and their associated cytokines which can control blood vessel permeability and vasoconstriction/dilation at the injury site. It influences cellular influx, activation of cell proliferation and regeneration/reconstruction functions of nerves and muscles which can have a positive effect on the healing of muscular defects and wound.

Acupuncture stimulates local blood flow and muscle afferents through neurogenic formation of vasoactive mediators and autonomic reflexes. It modulates hypothalamic-pituitary control of the autonomic and neuroendocrine systems, especially microcirculation, response of smooth and striated muscle, and local and general thermoregulation.

Since acupuncture can modulate the immune system and inflammatory response of the body, it could be a useful treatment for different immune disorders and inflammatory diseases, including asthma, allergic rhinitis, ulcerative colitis, and rheumatoid arthritis.

There are many articles and findings from different studies describing various elements of general acupuncture influence on immunity. However, more research is needed to elucidate specifically how immune mechanisms might be modulated by acupuncture in inflammatory disorders.

VI. REFERENCES

1. Craig Amrine .Acupuncture for Reduce Inflammation article
<http://www.HiddenRhythmAcupuncture.com>
2. Rogers PA, Schoen AM, Limehouse J . Acupuncture for immune-mediated disorders. Europe
Pubmed central <http://www.europepmc.org>.PMID:1581655 abstract/MED/1581655
3. Valentin Parmen. Influence of Electroacupuncture on the Soft Tissue Healing Process. Jams
October 2014Volume 7, Issue 5, Pages 243–249
4. Elba Lucia Wanderley Santos' Effects of acupuncture and electroacupuncture on estradiol-
induced inflammation and oxidative stress in health rodents. NCBI Pubmed 2013 Aug;
28(8):582-8
5. Kim HW. The anti-inflammatory effects of low- and high-frequency electroacupuncture are
mediated by peripheral opioids in a mouse air pouch inflammation model. J Altern Complement
Med. 2006 Jan-Feb; 12(1):39-44
6. Ying Wang. CXCL10 Controls Inflammatory Pain via Opioid Peptide-Containing
Macrophages in Electroacupuncture. PLoS One. 2014 August 8; 9(8): e105841
7. Rafael Torres-Rosas. Dopamine mediates vagal modulation of the immune system by
electroacupuncture. Nature Medicine20, 291–295(2014) doi:10.1038/nm.3479
8. Freek J. Zijlstra. Anti-inflammatory actions of Acupuncture. Taylor&Francis Healthsciences
Mediators of Inflammation, 12(2), 59_/69 (April 2003)

9. Yun-Kyoung Yim. Electro-acupuncture at acupoint ST36 reduces inflammation and regulates immune activity in Collagen-Induced Arthritic Mice. Advance Access Publication 18 August 2006; eCAM 2007; 4(1)51–57 doi:10.1093/ecam/nel054
10. Claude Libert. Inflammation: A nervous connection. <http://www.nature.com> *Nature* 421, 328-329 (23 January 2003) / doi: 10.1038/421328a
11. John L. McDonald. The Anti-Inflammatory Effects of Acupuncture and Their Relevance to Allergic Rhinitis. *Evid. Based Complement Alternat. Med.* 2013 Feb 14. doi: 10.1155/2013/591796
12. Morgana Duarte da Silva. Involvement of Interleukin-10 in the Anti-Inflammatory Effect of Sanyinjiao (SP6) Acupuncture in a Mouse Model of Peritonitis. *Evid. Based Complement Alternat. Med.* 2011 Jun 5 / doi: 10.1093/ecam/neq036
13. Tian-Feng He. Electroacupuncture Inhibits Inflammation Reaction by Upregulating Vasoactive Intestinal Peptide in Rats with Adjuvant-Induced Arthritis. *Evid. Based Complement Alternat. Med.* 2010 Sep 14 / doi: 10.1155/2011/290489
14. Microbiology and Immunology Mobile Online
<http://www.microbiologybook.org/mobile/m.index.htm>
15. Types of immunity. <http://www.wisegeek.org>
16. National Institutes of Health. The cost of alternative medicine analysis
<http://www.nih.gov/news/health/jul2009/nccam-30.htm>

17. Roberts J, Huissoon A, Dretzke J, Wang D, Hyde C. A systematic review of the clinical effectiveness of acupuncture for allergic rhinitis. *BMC Complementary and Alternative Medicine* 2008; 8:13
18. My well being presented by Humana. The most popular complementary and alternative medicine therapies <http://www.mywell-being.com/health/think/most-popular-complementary-and-alternative-medicine-therapies>
19. Novimmune scientific advisory board. Inflammation and inflammatory mediators <http://www.novimmune.com/science/inflammation.html>
20. Torrey Pines Institute for Molecular Studies. Inflammatory disorders <http://www.tpims.org/disease-research/inflammatory-disorders>

VII. APPENDIX A

Inflammatory mediators include molecules inside and outside your body that play a role in inflammation.

CATEGORIES OF INFLAMMATORY MEDIATORS:

Cytokines: TNF- α , IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, Interferons (IFN- α , IFN- β , IFN- γ),

Chemokines

Neuropeptides: Substance P, CGRP (Calcitonin Gene Related peptide), VIP (Vaso-active intestinal peptide), Bradykinin , Neurokinin A, NeuropeptideY, Endogenous opiate peptides (Beta-endorphins)

Other Vaso-active substances: Eicosanoid, Serotonin, Histamine, NO (Nitric Oxide) ^(8, 14, 15)

VIII. APPENDIX B

Cytokines are a diverse group of non-antibody proteins that act as mediators between cells. The term cytokine is a general term used but there are other terms that are commonly used:

Monokines: cytokines produced by mononuclear phagocytic cells

Lymphokines: cytokines produced by activated lymphocytes, especially Th (T helper) cells

Interleukins: cytokines that act as mediators between leukocytes

Chemokines: chemotactic cytokines produced by many kinds of leukocytes and other cell types

CATEGORIES OF CYTOKINES:

A. Mediators of innate immunity:

Cytokines that play a major role in the innate immune system include: TNF (Tumor necrosis factor)- α , IL(Interleukin)-1, IL(Interleukin)-10, IL(Interleukin)-12, type I interferon (IFN- α , IFN- β), IFN(Interferon)- γ , and chemokine.

1. TNF (Tumor necrosis factor)- α

Tumor necrosis factor mediates the recruitment of neutrophils and macrophages to sites of infection. TNF (Tumor necrosis factor) - α also acts on the hypothalamus to produce fever and it promotes the production of acute phase proteins.

2. IL (Interleukin)-1

Interleukin 1 effects are similar to that of TNF (Tumor necrosis factor)- α and it also helps to

activate T cells.

3. IL (Interleukin)-10

Interleukin 10 is predominantly an inhibitory cytokine. It inhibits production of IFN (interferon)- γ by Th (T helper) 1 cells. It also inhibits cytokine production, resulting in a dampening of immune responses.

4. IL (Interleukin)-12

Interleukin 12 stimulates the production of IFN- γ and induces the differentiation of Th (T helper) cells to become Th (T helper) 1 cells. In addition, it enhances the cytolytic functions of Tc (T cytotoxic) and NK (Natural Killer) cells.

5. Type I interferons

Type I interferons (IFN- α , IFN- β) inhibit viral replication in cells. They also activate NK (Natural Killer) cells.

6. INF (Interferon)- γ

Interferon gamma is an important cytokine has numerous functions in both the innate and acquired immune systems.

7. Chemokines

Chemokines are chemotactic cytokines which recruit leukocytes to sites of infection and play a role in lymphocyte trafficking.

B. Mediators of acquired immunity:

Cytokines that play a major role in the acquired immune system include: IL (Interleukin)-2, IL (Interleukin)-4, IL (Interleukin)-5, TGF (Transforming growth factor)- β , IL (Interleukin)-10 and IFN (Interferon)- γ .

1. IL (Interleukin)-2

Interleukin 2 is the major growth factor for T cells. It also promotes the growth of B cells and can activate NK (Natural Killer) cells and monocytes.

2. IL (Interleukin)-4

Interleukin 4 stimulates the development of Th (T helper) 2 cells from native Th (T helper) cells and it promotes the growth of differentiated Th (T helper) 2.

3. IL (Interleukin)-5

Interleukin 5 is produced by Th (T helper) 2 cells and it functions to promote the growth and differentiation of B cells and eosinophiles. It also activates mature eosinophiles.

4. TGF (Transforming growth factor)- β

Transforming growth factor beta is primarily an inhibitory cytokine. It inhibits the proliferation of T cells and the activation of macrophages. It also acts on PMNs (Polymorphonuclear Neutrophils) and endothelial cells to block the effects of pro-inflammatory cytokines.

C. Stimulators of hematopoiesis:

Some cytokines stimulate the differentiation of hematopoietic cells. These include GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor) which promotes the differentiation of bone marrow progenitors, M-CSF (Macrophage Colony-Stimulating Factor), which promotes growth and differentiation of progenitors into monocytes and macrophages and G-CSF

(Granulocyte-Colony-Stimulating Factor), which promotes production of PMNs
(Polymorphonuclear Neutrophils).

(14, 15)