Fibromyalgia & Gulf War Illness

Treatment Using Laser Stimulation of the Autonomic Nervous System

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Goals

- Brief review of history & epidemiology of fibromyalgia
- Discuss similarities and differences between fibromyalgia and widespread myofascial pain (and fibromyalgia and Gulf War Illness)
- Review autonomic nervous system dysfunction in fibromyalgia → resulting potential unifying neuroendocrinologic model of fibromyalgia
- Brief review of acupuncture's autonomic effects
- Discuss how fibromyalgia and GWI can be treated via metal or laser needle stimulation of selected acupoints affecting autonomic nervous system

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Fibromyalgia "Fun Facts"

- Widespread body pain affects ~3.6% of the US adult population
- Fibromyalgia prevalence ≥2% of the US adult population (>5 million)
- Prevalence estimates range up to 5%
- Similar prevalence in other countries

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Fibromyalgia "Fun Facts"

- 1904 Gowers coined termed "fibrositis"
- 1945 Kelly describes local and distant referred-pain caused by "fibrositis" nodules
- History of fibromyalgia (aka fibrositis, tension myalgia, etc) closely intertwined

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Oldest Description of Fibromyalgia?

"The evils of whole body impediment stay in the blood vessels, moving up & down along the channels… The wind, cold, and dampness settle in the flesh and compress the flesh, making the fluids coagulate to become froth. The froth is affected by cold and condenses. The condensation extrudes the textures of the muscles to make them split. The splitting causes pain… *The evils can reach the Organs."*

Nei Jing, 200 BC

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What Is Fibromyalgia?

- A syndrome *(not a disease)*
- Widespread tenderness in the trunk and extremities both anteriorly & posteriorly
  (11/18 points for 3 months in 3 body regions- per ACR)
- r/o definable (measurable) conditions
  (↑ sedimentation rate ↔ polymyalgia rheumatica, ↑ RF ↔ rheumatoid arthritis, ↑ TSH ↔ hypothyroidism)

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No Clear Causation

↓

Frustrating For Clinicians To Treat !

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What Is The Difference Between Fibromyalgia and Diffuse Myofascial Pain?

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Similarities

- Widespread trigger points in the extremities and trunk
- Impairments in function related to same (up to 26.5% of those with fibromyalgia receiving disability)
- Sleep disturbances

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Differences (Big)!

- 7:1 female to male ratio fibromyalgia (some report 8-9:1 ratio)
- 1:1 female to male ratio in chronic myofascial pain
- *THE ASSOCIATED CONDITIONS*
- 4-25 times more prevalent in individuals with fibromyalgia than in those not diagnosed with that condition

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Clinical Condition	% Fibromyalgia Patients	% General Populaton
Chronic headache	50%	5%
Dysmenorrhea	60%	15%
Endometriosis	15%	2%
Interstitial cystitis	25%	<1%
Irritable bladder/ urethra	15%	<1%
Irritable bowel syndrome	60%	10%
Mitral valve prolapse	75%	15%
Multiple chemical sensitivities	40%	5%
Restless legs syndrome	30%	2%
TMJ syndrome	25%	5%

Green Shade= Discussed in Epidemiology of Gulf War Illness

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Similarities and Differences:

Fibromyalgia and Gulf War Illness

- Fatigue, memory issues, muscle pain, bowel issues, rashes, multiple chemical sensitivities described in both
- Many conditions associated with fibromyalgia are not associated with GWI
- Women only slightly more affected than men in GWI (? fewer women in combat theater)
- Development of GWI has apparent relationship to chemical exposure(s)

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Autonomic Nervous System (ANS) & Fibromyalgia

The missing link?

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SANS Effects	PANS Effects
"fight or flight"	"rest and digest"
↑ alertness/vigilance	↓ alertness/vigilance
↑ heart rate and contractility	↓ heart rate and contractility
↑ breathing rate & bronchodilitation	↓ breathing rate & bronchoconstriction
↑ cardiac/skeletal muscle blood flow	↓ cardiac/skeletal muscle blood flow
↓ gut blood flow	↑ gut blood flow
↓ cutaneous blood flow	↑ cutaneous blood flow
↑ blood sugar	↓ blood sugar
↑ temperature	↓ temperature
↓ gut contractility	↑ gut contractility
↓ bladder contractility	↑ bladder contractility
↓ salivation	↑ salivation
↓ lacrimation	↑ lacrimation
↓ digestion	↑ digestion

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ANS Physiologic Dysfunctions in Fibromyalgia

(as opposed to functions)

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Autonomic Nervous System Imbalance in Fibromyalgia *(relative degree of tonus)*

Clinical Condition	SANS	PANS
Migraine	↑ initial phase	↑ later phase
IBS (diarrhea predominant)	↓	↑
IBS (constipation predominant)	↑	↓
Interstitial Cystitis	↑	↑
Raynaud's-like phenomenon	↑	↓
Endometriosis	↑	↓
Aseptic Prostatitis	↑	↓
Idiopathic Urethritis	↑	↓
Skeletal Muscle Tone	↑	-

IBS= irritable bowel syndrome
SANS= sympathetic autonomic nervous system
PANS= parasympathetic autonomic nervous system

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Literature Support

- Migraine (Petrouka, 2004)
- Irritable Bowel Syndrome (Mazur, 2007)
- Interstitial Cystitis (Pacak, 2001 in cat)
- Endometriosis (Possover, 2005)
- Idiopathic Urethritis (Husmann, 2006)
- TMJ Syndrome (Rodrigues, 2006)

All described elevated SANS pathogenesis!

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Medications Demonstrating Efficacy for Fibromyalgia

Good Efficacy	Marginal Efficacy
Pregabalin	NSAID agents
Gabapentin	Opioids
Duloxitene	
Milnacipran	
Cyclobenzaprine	

NSAID= non-steroidal anti-inflammatory drugs

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No One Has All The Answers !

Neuroendocrine Model of Fibromyalgia

Brain

Hypothalamus = Controller

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Hypothalamus

- SANS and PANS responses of the organism are opposite in their effects
- Hypothalamus is the central nervous system site that controls the balance of these responses
- Circadian rhythms of sleep as well as appetite regulation, mood, and temperature also are regulated at the hypothalamic level

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Hypothalamus

- SANS output from its posterolateral nuclei → interomediolateral nuclei of spinal cord
- PANS output from its anteromedial nuclei → vagus nerve
- Controls cortisol + catecholamine release through the HPA axis *(SANS activation with slower onset and longer duration)*
- Controls descending inhibition of pain at the spinal cord dorsal horn through descending pathways from the rostroventral medulla, periaqueductal gray, and locus ceruleus

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Hypothalamic Dysfunction in Fibromyalgia

- Systemic catecholamine release via the HPA axis +
- ↑ Hypothalamic SANS output to the interomediolateral cells of the spinal cord +
- ↓ Descending pain inhibition at the spinal cord level =
- Sensitization of primary nociceptors (and wide dynamic range neurons)

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Clinical Research Support

- Plasma catecholamine concentrations are increased in patients with fibromyalgia

  Torpy et al. Arthritis Rheum 2000;43(4):872-880

- Elevated catecholamine levels are associated with hyperalgesia

  Khasar et al. J Neurophysiol 1999;81(3):1104-1112

- Persistent hyperactive sympathetic nervous system (SANS) activity occurs in fibromyalgia (most apparent at night)

  Martinez-Lavin et al. Arthritis Rheum 1998; 41(11):1966–71

  Cohen et al. J Rheumatol 2001;28(3):581–9

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Clinical Research Support

- Reduction in the stress response in those with fibromyalgia to a variety of stressors that predominantly affects corticotropin and epinephrine
- Blunted stress response and increased basal sympathetic hyperactivity may indicate an ***impaired ability to modulate the ANS***, in terms of turning on and turning off the system
- "Alterations in hypothalamic function likely contribute to this impaired stress response"

  Adler and Geenen, *Rheum Dis Clin N Am* 31 (2005) 187–202

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Synthesis of Findings

- Chronic absolute ↑ activity of SANS output centrally
- → ↑ serum catecholamine
- → ↓ responsiveness of catecholamine to stress in fibromyalgia
- → ↓ responsiveness of corticotropin in fibromyalgia (↑ CSF levels of sP in fibromyalgia → ↓ CRH release)

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Clinical Research Support

- ↓ release of the opioid β-endorphin, corticotropin, and cortisol (anti-inflammatory properties that may reduce pain)
- ↓ CRH neuron effect on hypothalamus and other central ANS sites' effect on descending pain inhibition, including medullary catecholaminergic groups and locus ceruleus norepinephrine

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Clinical Research Support

- Women have smaller increases in plasma catecholamines in response to exercise stress than men
- Women have smaller increases in corticotropin in response to a brief psychosocial stress
- ? Central reason for increased fibromyalgia in females

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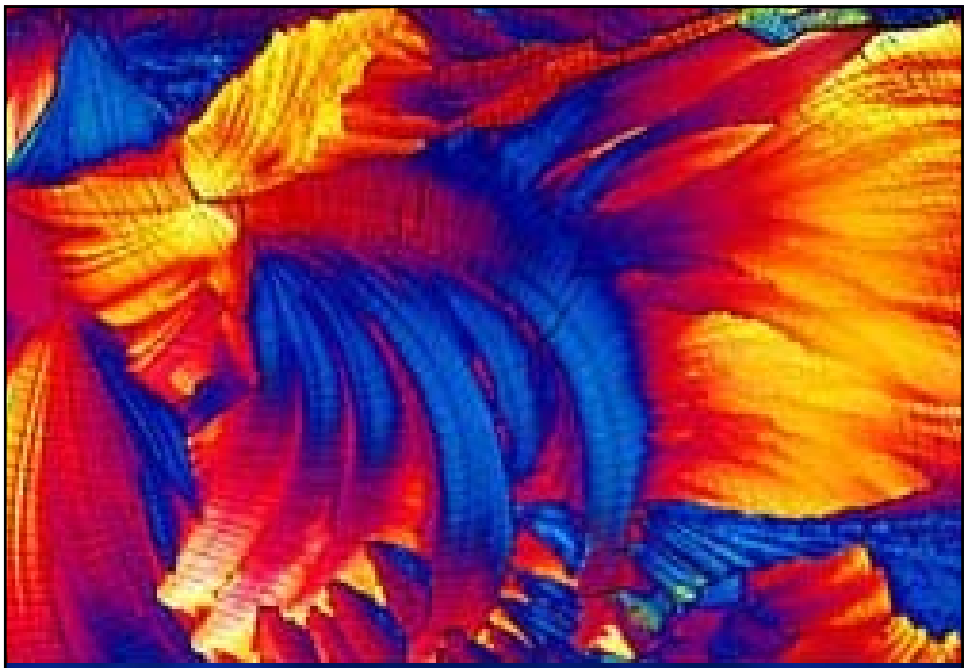

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B -endorphin

Paleocortex Input to Hypothalamus

- Right insular cortex → sympathetic outflow to the hypothalamus
- Left insular cortex → parasympathetic outflow
- Orbitofrontal + medial prefrontal cortex areas → hypothalamus allows emotions to directly influence autonomic balance
- Amygdala integrates behavioral and autonomic responses from the somatosensory cortex and limbic system structures (medial prefrontal cortex, orbitofrontal cortex, cingulate gyrus, hippocampus, anterior & medial thalamic nuclei
- Amygdala effect on hypothalamus inhibitory

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Clinical Research Support

- Abnormally high metabolic activity seen in the thalamus, amygdala, hippocampus, cingulate gyrus, and other limbic system structures in fibromyalgia patients

  Williams et al. Arthritis Res Ther 2006; 8(6): 224

- Psychological stress causes degranulation of mast cells (many estrogen receptor positive) → neurogenic inflammation

  Alexacos et al. Urology 1999; 53(5):1035-40

  Eutamene et al. J Physiol 2003; 553(3) 959-966

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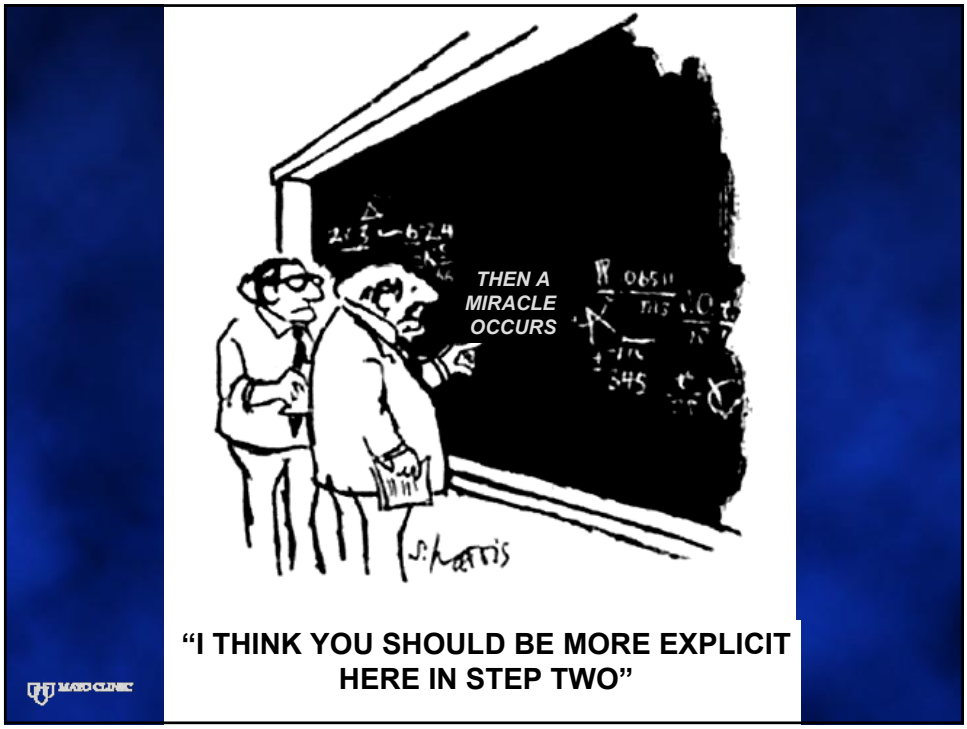

"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO"

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Peripheral Mechanisms

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Neurogenic Inflammation

- Physiologic phenomenon that occurs in vivo
- Efferent (antidromic) outflow from the spinal cord (dorsal root reflexes, or DRR) causes nociceptive C-fibers to release substance P (sP), calcitonin gene related peptide (cGRP), and somatostatin from their terminal axons
- → bradykinin, histamine, and serotonin release from local vasculature (plasma), platelets, & macrophages
- → further activate those nociceptive neurons
- = a local positive feedback loop results

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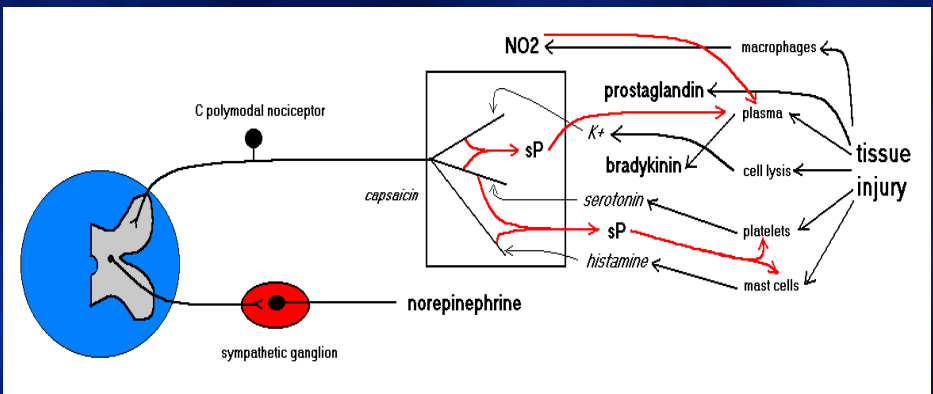
Peripheral Sensitization & Neurogenic Inflammation



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Neurogenic Inflammation Effects

- Local edema →fibromyalgia nodules?
- Widespread neurogenic inflammation → widespread myofascial tenderness (fibromyalgia tender points?) without overt presence of inflammatory cells
- Neurogenic inflammation via dorsal root reflexes and the propriospinal pathways → ascending and descending sensitization of nociceptors in adjacent spinal levels → spread of pain and tenderness to wider areas of the body
- Sensitization of primary nociceptors → sensitization of wide dynamic range neurons in the deeper spinal cord lamina, which have much wider cutaneous receptive fields as well as afferent sensory input from viscera (visceral hypersensitivity?)

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Research Evidence

- Active trigger points have markedly increased concentrations of inflammatory mediators
- Muscle sites (soleus) distant from those trigger points demonstrated lesser elevations of these inflammatory mediators (higher than normal)
- → central nervous system sensitization

Shah et al. Arch Phys Med Rehab 2008;89(1):16-23

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Ascending Pathways

- Primary nociceptors relay through the lateral spinothalamic tract to the lateral thalamus to the somatosensory cortex to localize painful stimuli *(neospinothalamic)*
- Wide dynamic range neurons send afferent signals through the paleospinothalamic tract to the anterior and medial thalamus relay to limbic system structures which subserve the emotional and behavioral reactions to the painful stimuli *(paleospinothalamic)*
- Completes positive feedback loop

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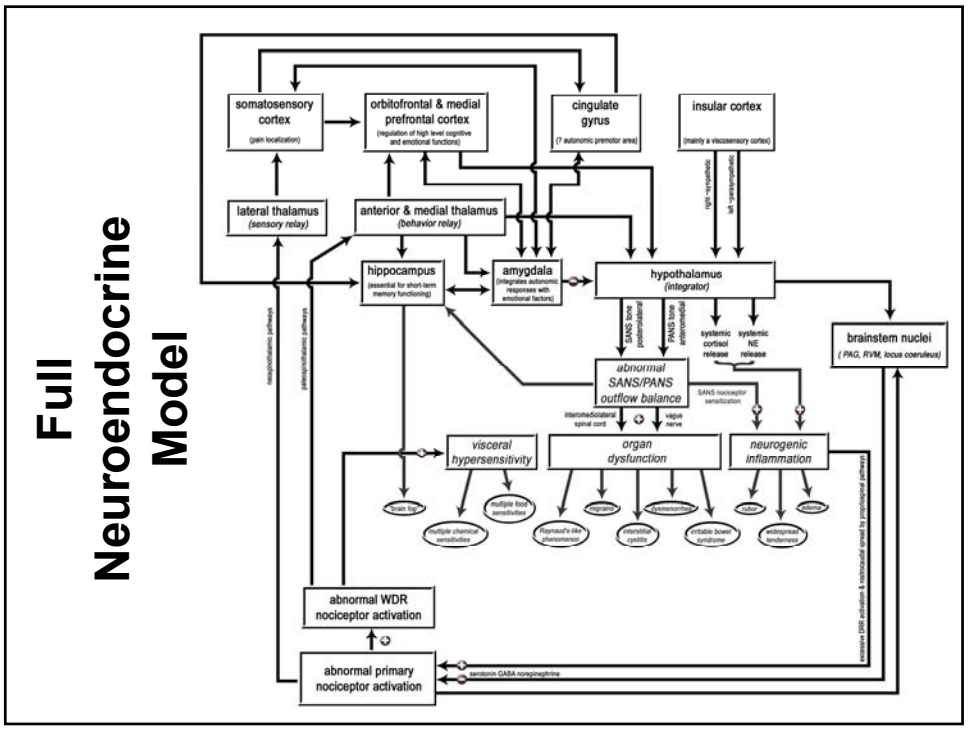

Too Much Information !?

Simplified Model

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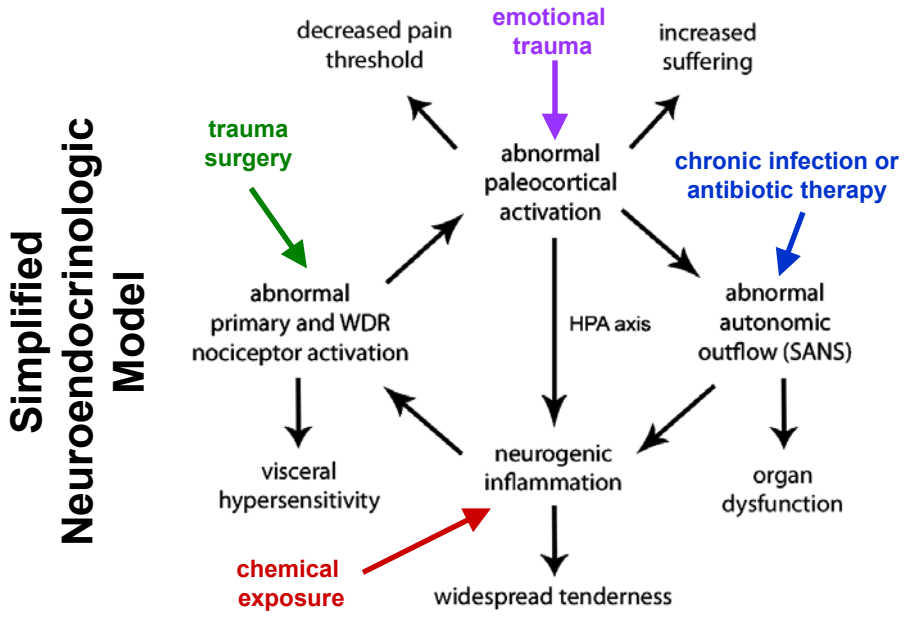
Simplified Neuroendocrinologic Model



A Variety of Insults Can Initiate Positive Feedback Loop!

Gulf War Illness

- Veterans with highest pyridostigmine and pesticide exposure have greater incidence of GWI
- Dose dependent risk noted, both in number of days used as well as amount used
- PB exposure of 22 doses (usual dose for a week) associated with greater risk of GWI

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Gulf War Illness

- Organophosphate pesticides → AChE inhibition
- Pyridostigmine bromide → AChE inhibition
- 33% DEET applicator and 75% lotion used in Gulf War (civilian 10-25%)- neurotoxic and works synergistically with organophosphate pesticides
- Permethrin has central & peripheral nervous system toxicity, enhances ACh release

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Gulf War Illness

- 100,000 troops may have been exposed to low level sarin and cyclosarin after Khamisiyan munitions explosion
- coalition bombing reportedly destroyed 20 metric tons of sarin at Al Muthanna and Muhammadiyat
- cancer and changes in brain structure and function in a dose response manner to nerve agent exposures
- possible long term effects of sarin exposure including fatigue, headache, and depression noted in Tokyo subway sarin attack survivors

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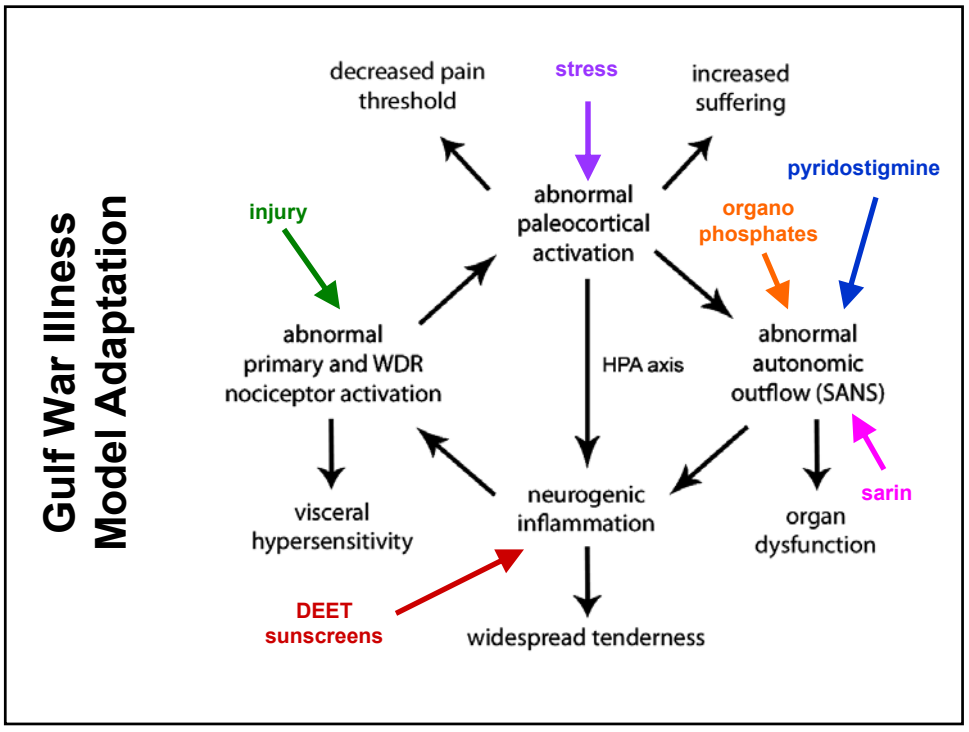

Gulf War Illness

- HPA axis abnormalities
- reduced pituitary ACTH
- increased ACTH & cortisol suppression to dexamethasone, though serum cortisol level normal
- autonomic dysfunction not well defined *(change in heart rate variability, pupillary reaction to medication, tilt table response)*

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Gulf War Illness

- neuropsychological changes attention and executive system including memory visuospatial skills, psychomotor skills, and mood/emotional functioning
- cortex and hippocampus aptosis
- reduced functioning in brainstem, basal ganglia, and hippocampus
- hippocampal and basal ganglia volumes reduced on MRI, reduced blood flow insula and frontal cortex on SPECT imaging

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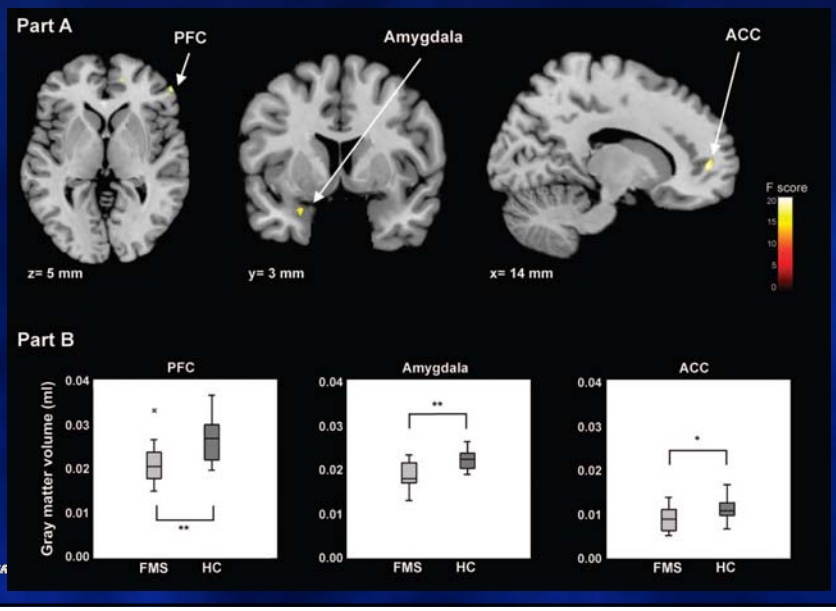
Gray Matter Loss in Fibromyalgia



Gray Matter Loss in Fibromyalgia

- individuals with fibromyalgia exhibit a 3.3 times greater age-associated decrease in gray matter volume when compared with healthy controls
- Each year of fibromyalgia ~ 9.5 times the normal loss of gray matter with aging
- functional significance of gray matter atrophy in fibromyalgia might include impaired endogenous pain inhibition and deficits in cognitive function
- altered brain morphology associated with cognitive impairment in fibromyalgia adjacent to and partially overlaps brain regions associated with pain modulation

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Using Ancient Knowledge To Treat Autonomic Dysfunction

Acupuncture Knowledge Base

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Human Embryonic Development

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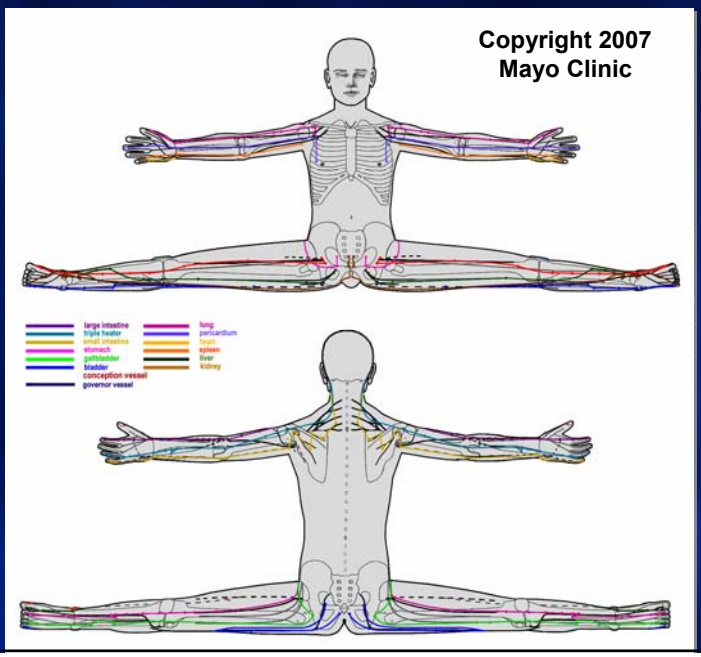
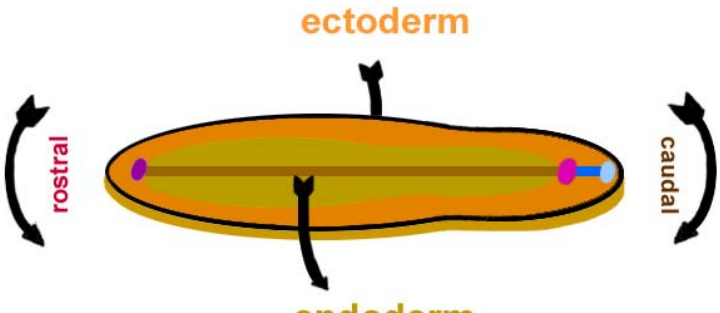
Principal Meridians Superimposed



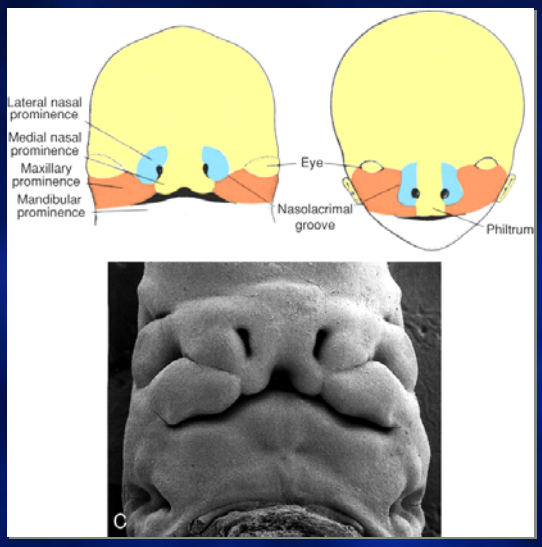
3 Week Embryo



- prochordal plate
- notochordal process
- neural fold
- primitive node
- primitive streak
- cloacal membrane

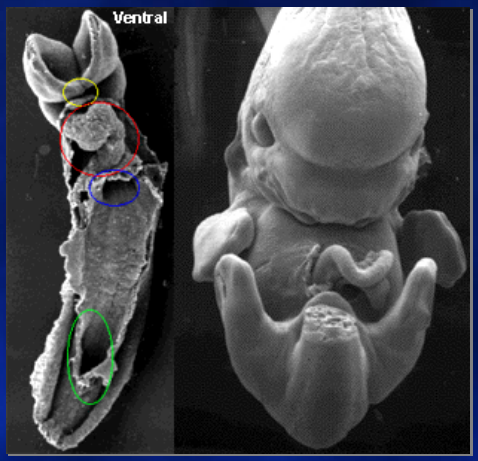
Governor Vessel Development

- Primitive knot
- Primitive streak
- Notochord
- Frontonasal prominence- differentiates to form the forehead, nose, philtrum, and adjacent gingival tissue (ending at stomatomedum)
- This occurs by 6 weeks post conception!

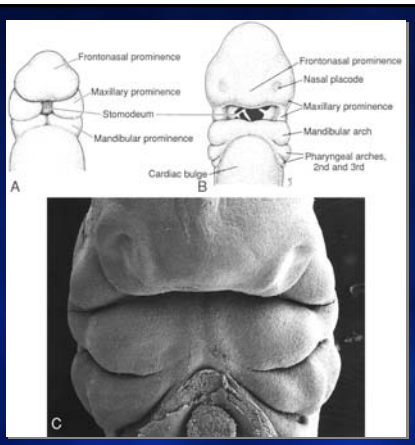


Ectoderm → Governor Vessel → Most Yang (SANS) Area of Body

Conception Vessel Meridian Development

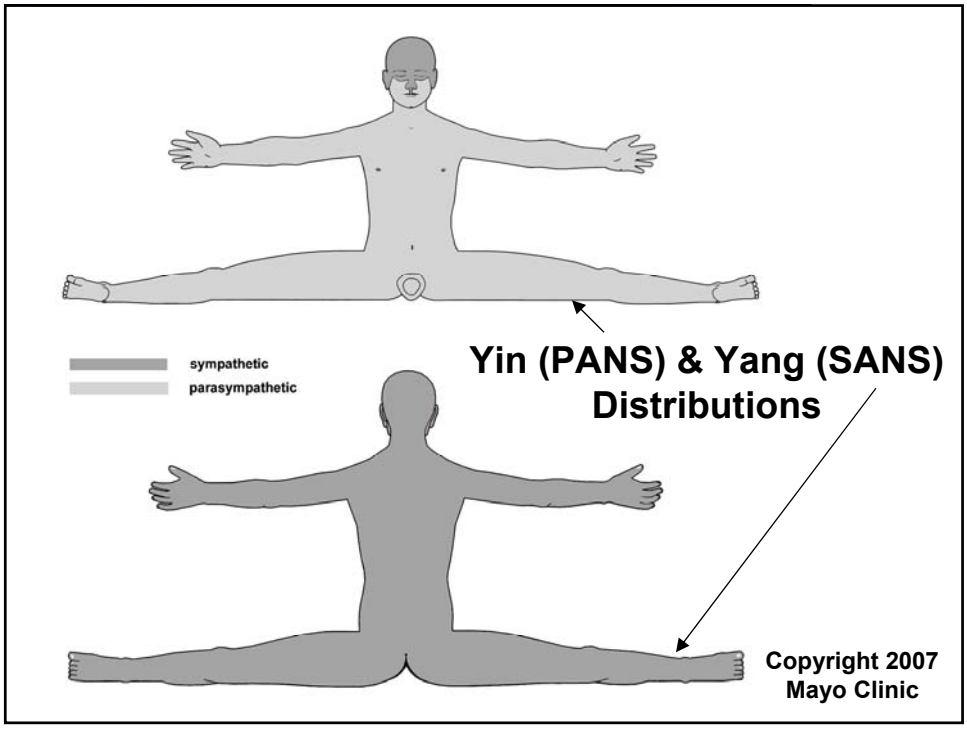


4 wk 6 wk



- Lateral embryonic fold ~3 weeks forms chest and abdominal cavities
- Branchial arches fuse at this time anteriorly to form neck and jaw

Endoderm → Conception Vessel → Most Yin (PANS) Area of Body


sympathetic
parasympathetic
Yin (PANS) & Yang (SANS)
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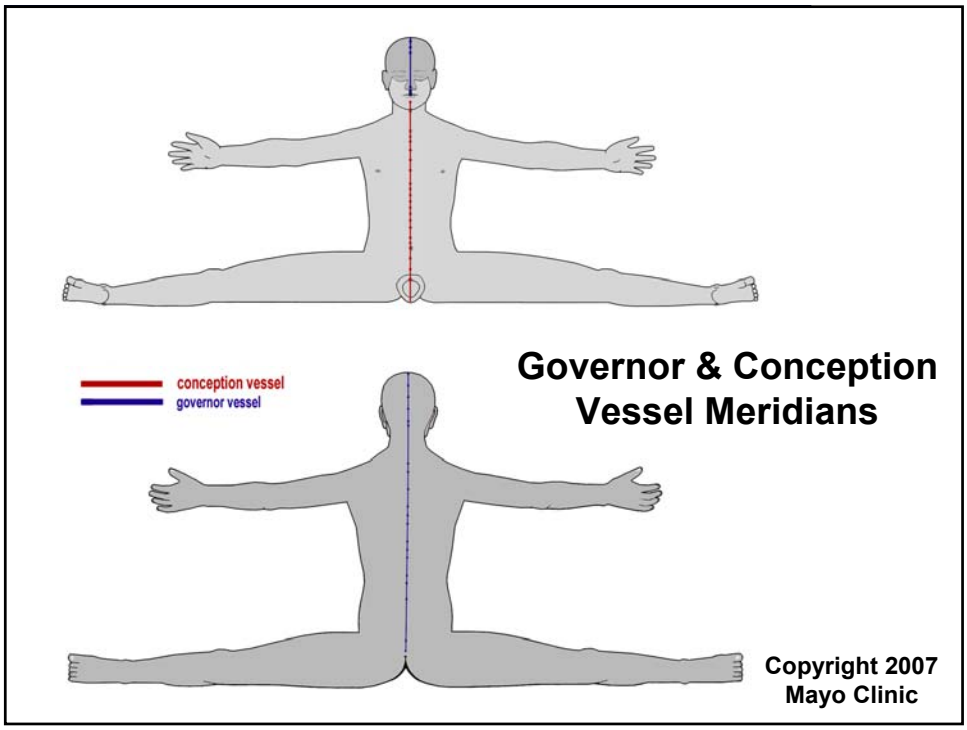
conception vessel
governor vessel
Governor & Conception
Vessel Meridians
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Shu Points, SANS, & Osteopathy

Organ	Shu Point	Spinal Level	Sympathetic Segmental Innervation	Osteopathic Level
Lung	BL-13	T3	T2-T5 (T2-T7)	T3-T9
Pericardium	BL-14	T4	T1-T4 (T1-T5)?	C8, T1-T8?
Heart	BL-15	T5	T1-T4 (T1-T5)	C8, T1-T8
Liver	BL-18	T9	T7-T9 (T5-T10)	T6-T11
Gallbladder	BL-19	T10	T7-T10 (T5-T10)	T6-T11
Spleen	BL-20	T11	T6-T10 (T5-T11)	T7-T10
Stomach	BL-21	T12	T6-T10 (T5-T11)	T7-T10
Triple Heater (?Adrenal)	BL-22	L1	Cortex T6-L2 Medulla T11-L1	
Kidney	BL-23	L2	T11-L1 (T10-L2)	T9-L2
Large Intestine	BL-25	L4	Proximal 2/3 T11-L1 (T6-L1) Distal 1/3 L1-L2 (T6-L2) (White- afferent S2-S4)	T9-L1
Small Intestine	BL-27	S1	T9-T11 (T6-T12)	T6-T11 duodenum & jejunum
Bladder	BL-28	S2	T11-L2 (White -afferent S2-S4) S2-S3 parasympathetic	

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Acupuncture & ANS Stimulation

- SANS
  - Governor Vessel most sympathetic
  - Sympathetic "switches" on posterior surface of extremities
- PANS
  - Conception Vessel most parasympathetic
  - Parasympathetic "switches" on anterior surface of extremities

Can selectively influence SANS or PANS deficiencies in fibromyalgia via acupuncture!

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Metal or Laser Stimulation of Acupoints

Restore Autonomic Balance

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Pilot Study Results

Metal Versus Laser Needles for Musculoskeletal Pain

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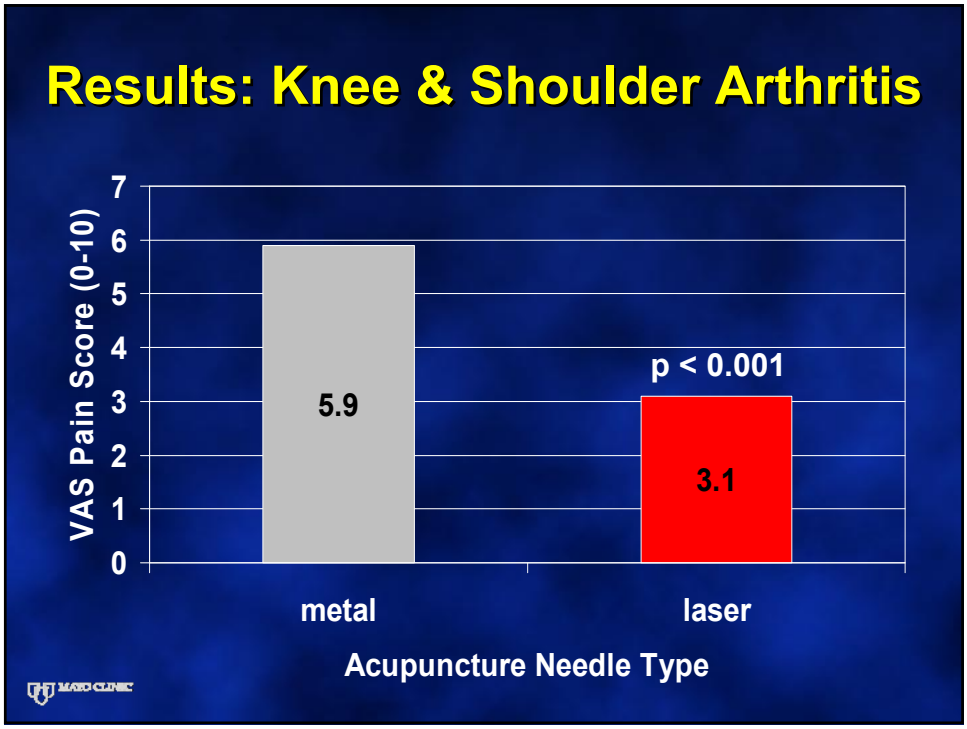
Results: Knee & Shoulder Arthritis
VAS Pain Score (0-10)
7
6
5
4
3
2
1
0
5.9
p < 0.001
3.1
metal
laser
Acupuncture Needle Type
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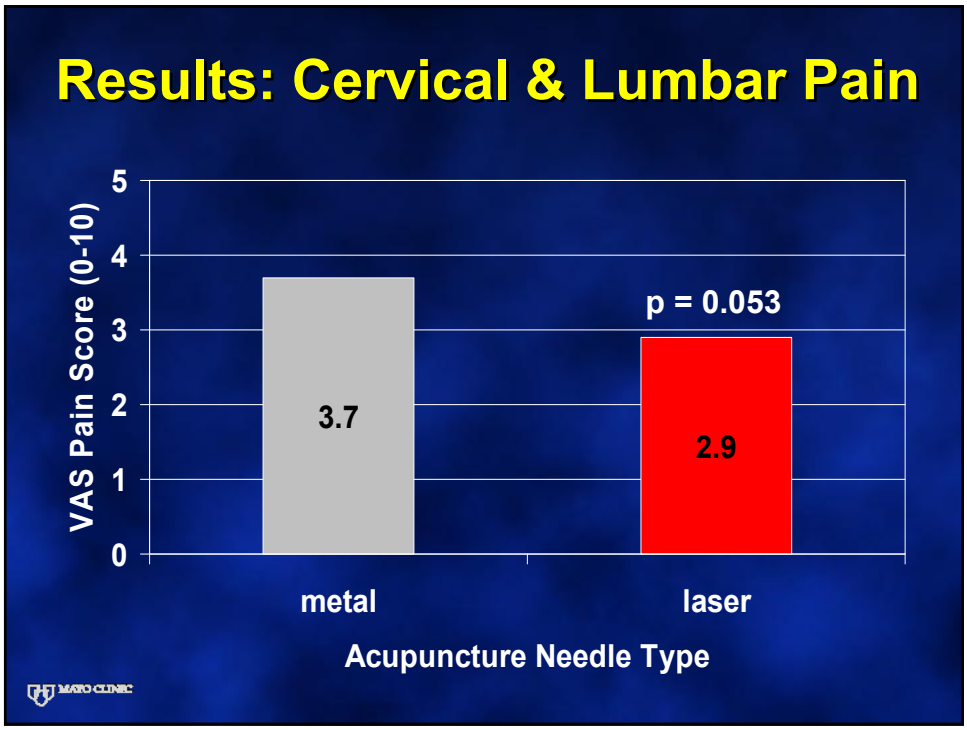
Results: Cervical & Lumbar Pain
VAS Pain Score (0-10)
5
4
3
2
1
0
3.7
p = 0.053
2.9
metal
laser
Acupuncture Needle Type
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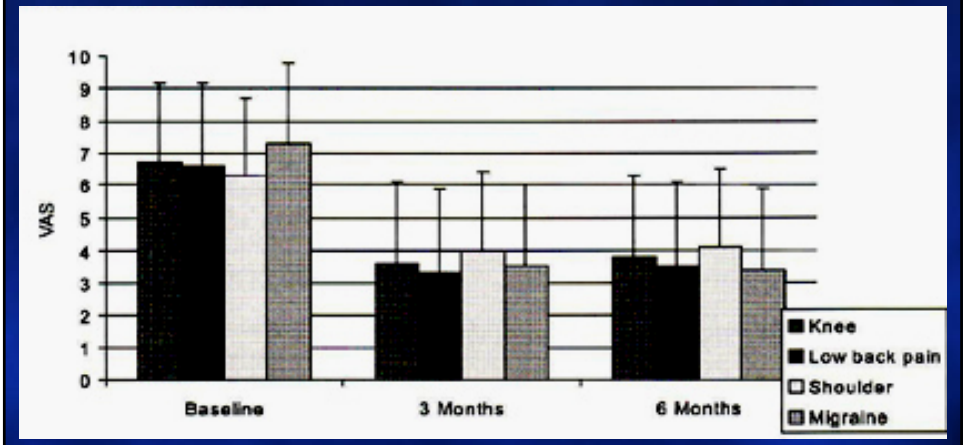
GERAC Laserneedle Arm



1,395 subjects studied!

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Evolution of Acupuncture Needles

Laserneedle
12 laser system

allows treatment with laser at multiple acupoints

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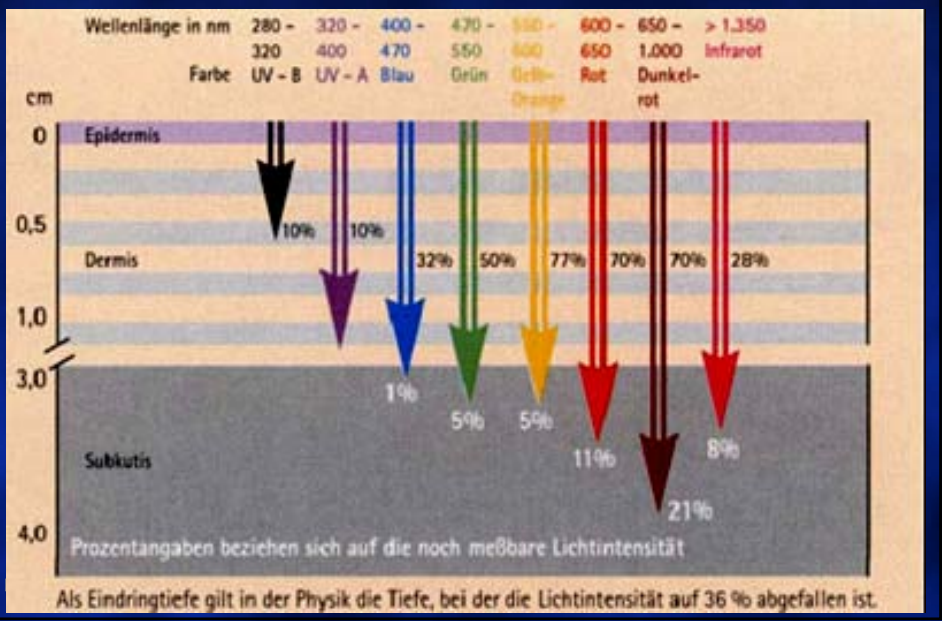
Depth of Laser Light Penetration



Laser Treatment Examples

Future Opportunities

IV Laser Stimulation

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Intravenous Blood Irradiation

- Intravenous laser blood irradiation was accomplished for the first time approximately 25 years ago in the former Soviet Union
- Laser light was brought directly into the flowing blood through a one-way-catheter
- In-vitro-tests soft laser irradiation of white blood cells produced beneficial effects in expression of interferons, interleukins, and immunoglobulins
- Strong mitochondrial energetic effects (ATP, giant mitochondria, cellular respiration)

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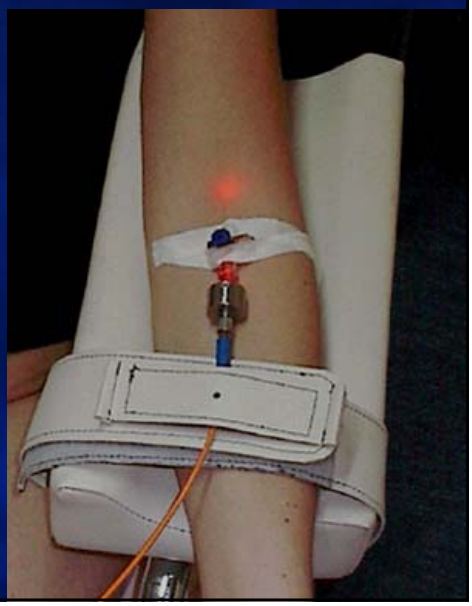
Intravenous Blood Irradiation

- performed with extremely low power (1-3 mw) laser
- exposure time of 20-60 minutes
- performed daily (up to 10 treatments) with a break on the weekend



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Laserneedle Study in Fibromyalgia

- In a private pain clinic in Germany
- 246 fibromyalgia patients received usual care including medication
- 82 received traditional acupuncture as well
- 72 received Laserneedle acupuncture 10 treatments plus intravenous laser treatment ("at least 3")
- 5 weeks of treatment

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VAS Pain Score Fibromyalgia

	Onset	End of study
MED	8.7	6.8
ACU	8.5	6.0
LAS	8.5	4.4
LAS+IV	8.9	2.9

MED = medications, ACU = needle acupuncture, LAS = laser acupuncture, LAS+IV = combination of laser acupuncture with intravenous laser irradiation

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Pain Disability Index Fibromyalgia

	Onset	End of study
MED	54	51
ACU	48	36
LAS	49	35
LAS+IV	52	22

MED = medications, ACU = needle acupuncture, LAS = laser acupuncture, LAS+IV = combination of laser acupuncture with intravenous laser irradiation

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Depression Index Fibromyalgia

	Onset	End of study
MED	34	23
ACU	37	24
LAS	42	12
LAS+IV	40	12

MED = medications, ACU = needle acupuncture, LAS = laser acupuncture, LAS+IV = combination of laser acupuncture with intravenous laser irradiation

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Fibromyalgia Treatment

Limited but Favorable Experience

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Fibromyalgia Treatment – Laser or Metal Needles

- Fibromyalgia, Chronic Fatigue Syndrome, (and Gulf War Illness) patients are energetically depleted in both PANS and SANS (Yin & Yang)
- Stimulation of sympathetic switches in arms and legs (Wong) to build Yang/SANS
- Mingmen treatment +/- parasympathetic switches to build Yin/PANS (all chronic conditions have Yin deficiency)
- Ongoing development- determining whether PANS or SANS is the most deficient in each person affected

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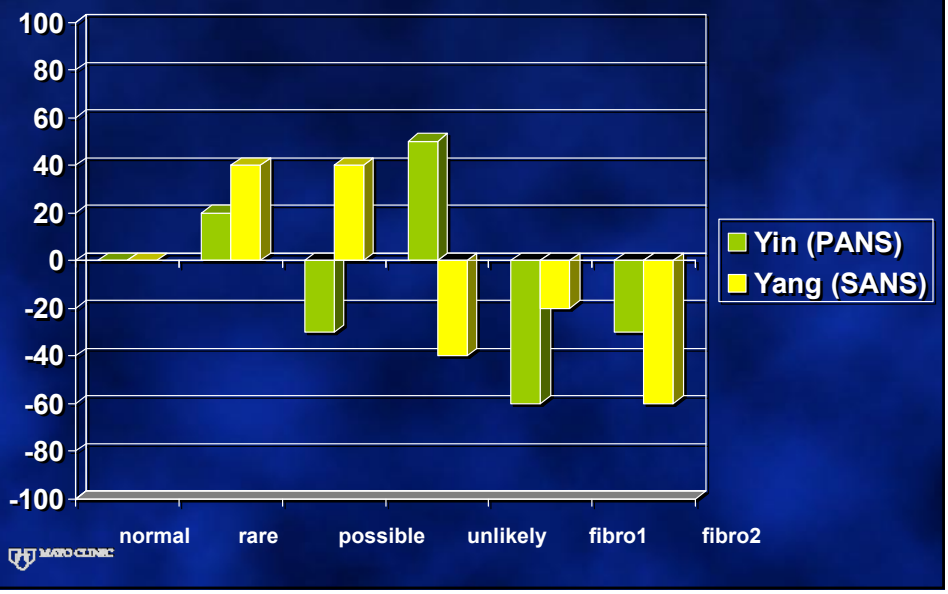
Autonomic Balance- The Challenge



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Measuring ANS Objectively

- Resting pulse rate
- Blood pressure
- Temperature- central/peripheral
- Sweat output
- Constipation versus diarrhea
- Urinary frequency versus hesitancy
- Meiosis versus mydriasis
- ? other

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Measuring ANS Objectively

- Heart rate variability
- Thermography or thermistor
- Sweat test
- Tilt table
- Pupillary reaction to sympathomimetic drugs
- Quantitative bowel sound activity?
- Blood assays for SANS and PANS metabolites

too expensive outside of research setting?

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Conclusions

- Satisfactory, well-tolerated treatments for fibromyalgia and chronic fatigue syndrome have been sparse to date
- In part, this is because an adequate model of their pathogenesis has been lacking
- GWI has significant overlap of its symptoms and laboratory findings with fibromyalgia
- Interventions to improve the health of veterans with GWI have had limited success

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Conclusions

- This neuroendocrine model (and preliminary clinical results) suggest acupuncture stimulation of ANS offers a potential avenue to reduce the symptoms and hence improve the quality of life of veterans with GWI
- Laser acupuncture offers a pain-free, essentially risk free method of treating pain and restoring autonomic nervous system homeostasis
- Further investigations of the potential benefits of laser stimulation of the autonomic nervous system to treat GWI, fibromyalgia, and CFS would prove beneficial

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