

## Fibromyalgia

## ABSTRACTS

- Aaron LA., 2000. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder.
- Barkhuizen A., 2001. Pharmacologic treatment of fibromyalgia.
- Clauw DJ., 1997. The relationship between fibromyalgia and interstitial cystitis.
- Crofford LJ, 2001. Complementary and alternative therapies for fibromyalgia.
- Dauvilliers Y., 2001. [Sleep in fibromyalgia: review of clinical and polysomnographic data]
- Diehl HW., 1994. Cetyl myristoleate isolated from Swiss albino mice: an apparent protective agent against adjuvant arthritis in rats.
- Dykman KD., 1998. The effects of nutritional supplements on the symptoms of fibromyalgia and chronic fatigue syndrome.
- Gagnier JJ., 2001. The therapeutic potential of melatonin in migraines and other headache types.
- Glass JM., 2001. Cognitive dysfunction in fibromyalgia.
- Guler M., 1992. Clinical characteristics of patients with fibromyalgia.
- Harbige LS., 1998. Dietary n-6 and n-3 fatty acids in immunity and autoimmune disease.
- Herschler RJ., 1990. U.S. Patent 4,973,605: Use of Methylsulfonylmethane to Relieve Pain and Relieve Pain and Nocturnal Cramps and to Reduce Stress-Induced Deaths in Animals.
- Jacob SW., 1999. The Miracle of MSM: The Natural Solution for Pain
- Jacobsen S., 1991. Oral S-adenosylmethionine in primary Fibromyalgia. Double-blind clinical evaluation.
- Jeong JH., 2000. Effects of extremely low frequency magnetic fields on pain thresholds in mice: roles of melatonin and opioids.
- Kaartinen K, 2000. Vegan diet alleviates Fibromyalgia symptoms.
- Kipper-Galperin M., 1999. Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interleukin-6] in astrocytes.
- Leventhal LJ., 1991. Fibromyalgia and parvovirus infection.
- Lubrano E., 2001. Fibromyalgia in patients with irritable bowel syndrome. An association with the severity of the intestinal disorder.
- McCain GA., 1989. Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis.
- Miller CS., 1999. Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abidction.
- Nasralla M., 1999. Multiple mycoplasmal infections detected in blood of patients with chronic fatigue syndrome and/or fibromyalgia syndrome.
- Neeck G., 1992. Thyroid function in patients with fibromyalgia syndrome.
- Palm O., 2001. Fibromyalgia and chronic widespread pain in patients with inflammatory bowel disease: a cross sectional population survey.
- Pekarkova I., 2001. Does exogenous melatonin influence the free radicals metabolism and pain sensation in rat?
- Regland B., 1997. Increased concentrations of homocysteine in the cerebrospinal fluid in patients with Fibromyalgia and chronic fatigue syndrome.
- Russell IJ., 1995. Treatment of Fibromyalgia syndrome with Super Malic: a randomized, double blind, placebo controlled, crossover pilot study.
- Schorr M., 2001. Mild sleep deprivation alters hormonal activity.
- Shochat T., 1998. Melatonin--the key to the gate of sleep.
- Stevens A., 2000. Both pain and EEG response to cold pressor stimulation occurs faster in fibromyalgia patients than in control subjects.
- Straub RH., 1998. Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence.
- Sugiyama T., 2001. Inhibition of glutamate transporter by theanine enhances the therapeutic efficacy of

doxorubicin.

Thomas AW., 2001. A comparison of rheumatoid arthritis and fibromyalgia patients and healthy controls exposed to a pulsed (200 microT) magnetic field: effects on normal standing balance.

Thomason P., 2002. Discussion of "The Effects of Candida and Aspergillus"

Wallace DJ., 2001. Cytokines play an aetiopathogenetic role in Fibromyalgia: a hypothesis and pilot study.

Wilke WS., 1981. Hypothyroidism with presenting symptoms of fibrositis.

Wilson RB., 1999. Antipolymer antibody reactivity in a subset of patients with fibromyalgia correlates with severity.

Wise CM., 1992. Musculoskeletal chest wall syndromes in patients with noncardiac chest pain: a study of 100 patients.

Yu CX., 2000. [Melatonin influences the release of endogenous opioid peptides in rat periaqueductal gray]

Yunus MB., 1999. Genetic linkage analysis of multicase families with Fibromyalgia syndrome.

Vgontzas AN., 2001. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications.

Vgontzas AN., 1999. Circadian interleukin-6 secretion and quantity and depth of sleep.

**Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder.**

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Arch Intern Med 2000 Jan 24;160(2):221-7

**BACKGROUND:** Patients with chronic fatigue syndrome (CFS), fibromyalgia (FM), and temporomandibular disorder (TMD) share many clinical illness features such as myalgia, fatigue, sleep disturbances, and impairment in ability to perform activities of daily living as a consequence of these symptoms. A growing literature suggests that a variety of comorbid illnesses also may commonly coexist in these patients, including irritable bowel syndrome, chronic tension-type headache, and interstitial cystitis. **OBJECTIVE:** To describe the frequency of 10 clinical conditions among patients with CFS, FM, and TMD compared with healthy controls with respect to past diagnoses, degree to which they manifested symptoms for each condition as determined by expert-based criteria, and published diagnostic criteria. **METHODS:** Patients diagnosed as having CFS, FM, and TMD by their physicians were recruited from hospital-based clinics. Healthy control subjects from a dermatology clinic were enrolled as a comparison group. All subjects completed a 138-item symptom checklist and underwent a brief physical examination performed by the project physicians. **RESULTS:** With little exception, patients reported few past diagnoses of the 10 clinical conditions beyond their referring diagnosis of CFS, FM, or TMD. In contrast, patients were more likely than controls to meet lifetime symptom and diagnostic criteria for many of the conditions, including CFS, FM, irritable bowel syndrome, multiple chemical sensitivities, and headache. Lifetime rates of irritable bowel syndrome were particularly striking in the patient groups (CFS, 92%; FM, 77%; TMD, 64%) compared with controls (18%) ( $P < .001$ ). Individual symptom analysis revealed that patients with CFS, FM, and TMD share common symptoms, including generalized pain sensitivity, sleep and concentration difficulties, bowel complaints, and headache. However, several symptoms also distinguished the patient groups. **CONCLUSIONS:** This study provides preliminary evidence that patients with CFS, FM, and TMD share key symptoms. It also is apparent that other localized and systemic conditions may frequently co-occur with CFS, FM, and TMD. Future research that seeks to identify the temporal relationships and other pathophysiologic mechanism(s) linking CFS, FM, and TMD will likely advance our understanding and treatment of these chronic, recurrent conditions.

### **Pharmacologic treatment of fibromyalgia.**

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Curr Pain Headache Rep 2001 Aug;5(4):351-8

Fibromyalgia is a chronic syndrome characterized by widespread pain, unrefreshed sleep, disturbed mood, and fatigue. Until such time as we have a clearer understanding of the trigger and/or pathophysiologic mechanisms producing these symptoms, pharmacologic treatment should be aimed at individual symptoms. Such treatment should ideally be offered as part of a multidisciplinary treatment program using both pharmacologic and nonpharmacologic treatment modalities. Critical components of any successful fibromyalgia treatment program include addressing physical fitness, work and other functional activities, and mental health, in addition to symptom-specific therapies. The main symptoms that should be addressed include pain, sleep disturbances including restless leg syndrome, mood disturbances, and fatigue. Pharmacologic therapy should also be considered for syndromes commonly associated with fibromyalgia including irritable bowel syndrome, interstitial cystitis, migraine headaches, temporomandibular joint dysfunction, dysequilibrium including neurally mediated hypotension, sicca syndrome, and growth hormone deficiency. This article provides general guidelines in initiating a successful pharmacologic treatment program for fibromyalgia.

### **The relationship between fibromyalgia and interstitial cystitis.**

J Psychiatr Res 1997 Jan-Feb;31(1):125-31

Interstitial cystitis (IC) is a relatively uncommon and enigmatic disorder characterized by pain in the bladder and pelvic region, typically accompanied by urinary urgency and frequency. Fibromyalgia is a more common disorder, with the prominent symptoms being diffuse musculoskeletal pain and fatigue, and it has been well established that there is substantial clinical overlap between fibromyalgia and chronic fatigue syndrome (CFS). Although genitourinary and musculoskeletal symptoms predominate in IC and fibromyalgia respectively, both disorders share a number of features, including similar demographics, "allied conditions" (e.g. irritable bowel syndrome, headaches, etc.), natural history, aggravating factors, and efficacious therapy. We hypothesized that there was substantial clinical overlap between fibromyalgia and IC, and examined cohorts of individuals with these two disorders in parallel, to compare the spectrum of symptomatology. Sixty fibromyalgia patients, 30 IC patients, and 30 age-matched healthy controls were questioned regarding current symptomatology. A dolorimeter examination was also performed in the three groups to assess peripheral nociception. We found that the frequency of current symptoms was very similar for the fibromyalgia and IC groups. Both the fibromyalgia and IC patients displayed increased pain sensitivity when compared to healthy individuals, at both tender and control points. These data suggest that IC and fibromyalgia have significant overlap in symptomatology, and that IC patients display diffusely increased peripheral nociception, as is seen in fibromyalgia. Although central mechanisms have been suspected to contribute to the pathogenesis of fibromyalgia for some time, we speculate that these same types of mechanisms may be operative in IC, which has traditionally been felt to be a bladder disorder.

### **Complementary and alternative therapies for fibromyalgia.**

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Curr Rheumatol Rep 2001 Apr;3(2):147-56

Fibromyalgia (FM) is a syndrome of chronic widespread musculoskeletal pain that is accompanied by sleep disturbance and fatigue. Clinical treatment usually includes lifestyle modifications and pharmacologic interventions meant to relieve pain, improve sleep quality, and treat mood disorders. These therapies are often ineffective or have been shown in clinical studies to have only short-term effectiveness. Pharmacologic treatments have considerable side effects. Patients may have difficulty complying with exercise-based treatments. Thus, patients seek alternative therapeutic approaches and physicians are routinely asked for advice about these treatments. This article reviews nontraditional treatment alternatives, from use of nutritional and herbal supplements to acupuncture and mind-body therapy. Little is known about efficacy and tolerance of complementary and alternative therapies in FM and other chronic musculoskeletal pain syndromes. Most studies on these treatments have been performed for osteoarthritis, rheumatoid arthritis, or focal musculoskeletal conditions. Clinical trials are scarce; the quality of these trials is often criticized because of small study population size, lack of appropriate control interventions, poor compliance, or short duration of follow-up. However, because of widespread and growing use of alternative medicine, especially by persons with chronic illnesses, it is essential to review efficacy and adverse effects of complementary and alternative therapies.

### **[Sleep in fibromyalgia: review of clinical and polysomnographic data] [Article in French]**

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Neurophysiol Clin 2001 Feb;31(1):18-33

Fibromyalgia syndrome is a common chronic pain syndrome that is often associated with sleep disturbances characterized by subjective experience of non-restorative sleep. The complaints of sleep disturbances are correlated with polysomnographic features showing clear abnormalities in the continuity of sleep as well as in the sleep architecture. Sleep-recording abnormalities are characterized by a reduced sleep efficiency with increased number of awakenings, a reduced amount of slow wave sleep and an abnormal alpha wave intrusion in non rapid eye movement, termed alpha-delta sleep. These data were confirmed by spectral analysis of sleep showing an increased EEG power density in the higher frequency band and a reduced EEG power density in the lower frequency bands. Moreover, other microstructural aspects of sleep were modified with high frequency of arousals and alpha-K complex reported, both indicators of fragmented sleep. The fibromyalgia symptoms may relate to a non-restorative sleep disorder associated with the alpha-EEG sleep anomalies. However, alpha-EEG sleep anomaly is non-specific for fibrositis, also seen in normal controls during stage 4 sleep deprivation. Moreover, fibromyalgia patients may also experience primary sleep disorder such as sleep apnea or periodic leg movements. The etiology of this common condition is incompletely understood and the existence of a specific entity of fibromyalgia is still a matter of debate. However, several studies have found abnormal brain metabolism of substances such as serotonin implicated in sleep arousal and pain mechanisms and administration of tricyclic antidepressants and selective serotonin reuptake inhibitors may be useful in fibromyalgia. Pain, poor sleep quality and anxiety may contribute to the

clinical picture. Several factors such as psychological, environmental, genetic factor, altered serotonin metabolism and altered sleep physiology are involved in the pathogenesis of fibromyalgia.

### **Cetyl myristoleate isolated from Swiss albino mice: an apparent protective agent against adjuvant arthritis in rats.**

Diehl HW, May EL. Department of Pharmacology, Medical College of Virginia, Richmond 23298.

J Pharm Sci 1994 Mar;83(3):296-9

Cetyl myristoleate was isolated from National Institutes of Health, general purpose, Swiss albino mice that were immune to the polyarthritis induced in rats with Freund's adjuvant. This substance, or material synthesized from cetyl alcohol and myristoleic acid, afforded good protection against adjuvant-induced arthritic states in rats. In limited comparisons, cetyl oleate, also found in Swiss albino mice, gave lesser protection, whereas cetyl myristate and cetyl elaidate, the trans-isomer of cetyl oleate, appeared to be virtually ineffective. Dosage of the protective compound as well as the site of injection of Freund's adjuvant was important.

### **The effects of nutritional supplements on the symptoms of fibromyalgia and chronic fatigue syndrome.**

Dykman KD, Tone C, Ford C, Dykman RA. Mannatech Inc., Coppell Texas 75019, USA.

Integr Physiol Behav Sci 1998 Jan-Mar;33(1):61-71

This article reports the results of a within-subject design. Fifty subjects with a physician diagnosis of fibromyalgia (FM) and/or chronic fatigue syndrome (CFS) were interviewed using a structured interview form. Each subject was interviewed initially, and again nine months later (follow-up). Subjects had, on their own, consumed nutritional supplements including freeze-dried aloe vera gel extract; a combination of freeze-dried aloe vera gel extract and additional plant-derived saccharides; freeze-dried fruits and vegetables in combination with the saccharides; and a formulation of dioscorea complex containing the saccharides and a vitamin/mineral complex. With medical treatments, approximately 25 percent of FM patients improve, but the beneficial effects of medical treatment rarely persist more than a few months. All subjects in this study had received some form of medical treatment prior to taking the nutritional supplements, but none with enduring success. Nutritional supplements resulted in a remarkable reduction in initial symptom severity, with continued improvement in the period between initial assessment and the follow-up. Further research is needed to verify these results, specifically crossover designs in well-defined populations.

### **The therapeutic potential of melatonin in migraines and other headache types.**

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Altern Med Rev 2001 Aug;6(4):383-9

A large number of individuals suffer from migraine headaches. Several theories attempt to explain migraine etiology. One such theory holds that since environmental stimuli are well known to trigger migraine headaches, the pineal gland may be involved in migraine etiology. Specifically, a pineal gland irregularity may be the physical origin of migraine headaches, with subsequent physiological changes being secondary. Research has found the pineal hormone melatonin is low in migraine patients. Additionally, several studies found administering melatonin to migraine sufferers relieved pain and decreased headache recurrence in some cases. It has been suggested melatonin may play an important therapeutic role in the treatment of migraines and other types of headaches, particularly those related to delayed sleep phase syndrome. Current research supports the hypothesis that migraines are a response to a pineal circadian irregularity in which the administration of melatonin normalizes this circadian cycle; i.e., melatonin may play a role in resynchronizing biological rhythms to lifestyle and subsequently relieve migraines and other forms of headaches. In addition, research testing the administration of melatonin found it safe in migraine sufferers, with few or no side effects. However, a larger, randomized control trial is needed to definitively determine if administration of melatonin to migraine patients is effective.

### **Cognitive dysfunction in fibromyalgia.**

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Curr Rheumatol Rep 2001 Apr;3(2):123-7

Fibromyalgia is a puzzling syndrome of widespread musculoskeletal pain. In addition to pain, patients with fibromyalgia frequently report that cognitive function, memory, and mental alertness have declined. A small body of literature suggests that there is cognitive dysfunction in fibromyalgia. This article addresses several questions that physicians may have regarding cognitive function

in their patients. These questions concern the types of cognitive tasks that are problematic for patients with fibromyalgia, the role of psychological factors such as depression and anxiety, the role of physical factors such as pain and fatigue, the nature of patients' perceptions of their cognitive abilities, and whether patients can be tested for cognitive dysfunction. Critical areas for further investigation are highlighted.

### **Clinical characteristics of patients with fibromyalgia.**

Guler M, Kirnap M, Bekaroglu M, Uremek G, Onder C. Department of Physical Medicine and Rehabilitation, Black Sea Technical University, Trabzon, Turkey.

Isr J Med Sci 1992 Jan;28(1):20-3

Fibromyalgia, also known as fibrositis and muscle rheumatism, is a common, noninflammatory, painful musculoskeletal disorder. It is common between the ages of 30 and 60 years and has a female to male ratio of 5 to 1. Essential symptoms of fibrositis are pain, fatigue, disturbed sleep, morning stiffness and local tenderness. Subjective swelling, paresthesia and numbness sometimes occur. Multiple host and environmental factors seem to contribute to the onset and course of fibromyalgia. Modest improvement follows treatment by antidepressive agents, physical measures and reduction in stress. In this study 60 patients with fibromyalgia were investigated and the clinical characteristics of these patients are described and compared with those in other studies.

### **Dietary n-6 and n-3 fatty acids in immunity and autoimmune disease.**

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Proc Nutr Soc 1998 Nov;57(4):555-62

Clearly there is much evidence to show that under well-controlled laboratory and dietary conditions fatty acid intake can have profound effects on animal models of autoimmune disease. Studies in human autoimmune disease have been less dramatic; however, human trials have been subject to uncontrolled dietary and genetic backgrounds, infection and other environmental influences, and basic trial designs have been inadequate. The impact of dietary fatty acids on animal autoimmune disease models appears to depend on the animal model and the type and amount of fatty acids fed. Diets low in fat, essential fatty acid-deficient, or high in n-3 fatty acids from fish oils increase the survival and reduce disease severity in spontaneous autoantibody-mediated disease, whilst linoleic acid-rich diets appear to increase disease severity. In experimentally-induced T-cell-mediated autoimmune disease, essential fatty acid-deficient diets or diets supplemented with n-3 fatty acids appear to augment disease, whereas n-6 fatty acids prevent or reduce the severity. In contrast, in both T-cell and antibody-mediated auto-immune disease the desaturated and elongated metabolites of linoleic acid are protective. Suppression of autoantibody and T lymphocyte proliferation, apoptosis of autoreactive lymphocytes, and reduced pro-inflammatory cytokine production by high-dose fish oils are all likely mechanisms by which n-3 fatty acids ameliorate autoimmune disease. However, these could be undesirable long-term effects of high-dose fish oil which may compromise host immunity. The protective mechanism(s) of n-6 fatty acids in T-cell-mediated autoimmune disease are less clear, but may include dihomo-gamma-linolenic acid- and arachidonic acid-sensitive immunoregulatory circuits such as Th1 responses, TGF beta 1-mediated effects and Th3-like responses. It is often claimed that n-6 fatty acids promote autoimmune and inflammatory disease based on results obtained with linoleic acid only. It should be appreciated that linoleic acid does not reflect the functions of dihomo-gamma-linolenic and arachidonic acid, and that the endogenous rate of conversion of linoleic to arachidonic acid is slow (Hassam et al. 1975, 1977; Phylactos et al. 1994; Harbige et al. 1995). In addition to effects of dietary fatty acids on immunoregulation, inflammation as a consequence of immune activation in autoimmune disease may also be an important mechanism of action whereby dietary fatty acids modulate disease activity. In conclusion, regulation of gene expression, signal transduction pathways, production of eicosanoids and cytokines, and the action of antioxidant enzymes are all mechanisms by which dietary n-6 and n-3 fatty acids may exert effects on the immune system and autoimmune disease. Probably the most significant of these mechanisms in relation to our current understanding of immunoregulation and inflammation would appear to be via fatty acid effects on cytokines. The amount, type and balance of dietary fatty acids and associated antioxidant nutrients appear to impact on the immune system to produce immune-deviation or immunosuppressive effects, and to reduce immune-mediated inflammation which will in turn affect the susceptibility to, or severity of, autoimmune disease.

### **U.S. Patent 4,973,605: Use of Methylsulfonylmethane to Relieve Pain and Relieve Pain and Nocturnal Cramps and to Reduce Stress-Induced Deaths in Animals,**

Herschler, R.J.

November 27, 1990.

### **The Miracle of MSM: The Natural Solution for Pain 1999.**

Jacob, S.W., Lawrence, R.M., Zucker, M.

New York: G.P. Putnam's Sons/Berkeley Group.

### **Oral S-adenosylmethionine in primary Fibromyalgia. Double-blind clinical evaluation.**

Jacobsen S, Danneskiold-Samsøe B, Andersen RB. Department of Rheumatology, Frederiksberg Hospital, Copenhagen, Denmark.

Scand J Rheumatol 1991;20(4):294-302

S-adenosylmethionine is a relatively new anti-inflammatory drug with analgesic and anti-depressant effects. Efficacy of 800 mg orally administered s-adenosylmethionine daily versus placebo for six weeks was investigated in 44 patients with primary Fibromyalgia in double-blind settings. Tender point score, isokinetic muscle strength, disease activity, subjective symptoms (visual analog scale), mood parameters and side effects were evaluated. Improvements were seen for clinical disease activity ( $P = 0.04$ ), pain experienced during the last week ( $P = 0.002$ ), fatigue ( $P = 0.02$ ), morning stiffness ( $P = 0.03$ ) and mood evaluated by Face Scale ( $P = 0.006$ ) in the actively treated group compared to placebo. The tender point score, isokinetic muscle strength, mood evaluated by Beck Depression Inventory and side effects did not differ in the two treatment groups. S-adenosylmethionine has some beneficial effects on primary Fibromyalgia and could be an important option in the treatment hereof.

### **Effects of extremely low frequency magnetic fields on pain thresholds in mice: roles of melatonin and opioids.**

Jeong JH, Choi KB, Yi BC, Chun CH, Sung KY, Sung JY, Gimm YM, Huh IH, Sohn UD. Department of Pharmacology, College of Pharmacy, Chung Ang University, Seoul, Republic of Korea.

J Auton Pharmacol 2000 Aug;20(4):259-64

1. We studied the effects of extremely low frequency (ELF, 60 Hz) magnetic fields (MFs) on pain thresholds using the hot plate test. The implication of opioid and benzodiazepine system in the MFs-induced alteration of pain thresholds was also studied. 2. There was an increase at night time and a decrease at daytime of pain thresholds in normal mice. Exposure of MFs (24 h, 20 gauss (G)) inhibited the increase of pain thresholds at night time and even produced hyperalgesia at daytime. 3. The increase of pain thresholds induced by melatonin at daytime was inhibited by exposure to MFs (24 h, 20 G) or opioid antagonist naloxone. The MFs and naloxone synergically inhibited hypoalgesia produced by melatonin. The hyperalgesia at daytime after MFs exposure was potentiated by the benzodiazepine agonist, diazepam, and inhibited by the benzodiazepine antagonist, flumazenil. There was no significant difference in all rotarod performance we tested. 4. From these results, it is suggested that exposure to MFs inhibits the increase of pain thresholds at night time and produces hyperalgesia at daytime with the involvement of opioid and benzodiazepine systems.

### **Vegan diet alleviates Fibromyalgia symptoms.**

Kaartinen K, Lammi K, Hyöyry M, Nenonen M, Hanninen O, Rauma AL. Department of Physiology, University of Kuopio, Finland. hietanen.kaartinen@pp.inet.fi

Scand J Rheumatol 2000;29(5):308-13

The effect of a strict, low-salt, uncooked vegan diet rich in lactobacteria on symptoms in 18 Fibromyalgia patients during and after a 3-month intervention period in an open, non-randomized controlled study was evaluated. As control 15 patients continued their omnivorous diet. The groups did not differ significantly from each other in the beginning of the study in any other parameters except in pain and urine sodium. The results revealed significant improvements in Visual analogue scale of pain (VAS) ( $p=0.005$ ), joint stiffness ( $p=0.001$ ), quality of sleep ( $p=0.0001$ ), Health assessment questionnaire (HAQ) ( $p=0.031$ ), General health questionnaire (GHQ) ( $p=0.021$ ), and a rheumatologist's own questionnaire ( $p=0.038$ ). The majority of patients were overweight to some extent at the beginning of the study and shifting to a vegan food caused a significant reduction in body mass index (BMI) ( $p=0.0001$ ). Total serum cholesterol showed a statistically significant lowering ( $p=0.003$ ). Urine sodium dropped to 1/3 of the beginning values ( $p=0.0001$ ) indicating good diet compliance. It can be concluded that vegan diet had beneficial effects on Fibromyalgia symptoms at least in the short run.

### **Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interleukin-6] in astrocytes.**

Kipper-Galperin M, Galilly R, Danenberg HD, Brenner T. Laboratory of Neuroimmunology, Hadassah University Hospital, Jerusalem, Israel.

Dihydroepiandrosterone (DHEA) is a native neurosteroid with immunomodulating activity. DHEA effectively protects animals from several viral, bacterial and parasitic infections and it was suggested that its age-associated decline is related with immunosenescence. In the present study we examined the ability of DHEA to inhibit the production of inflammatory mediators by mycoplasma-stimulated glial cells and to change the course of acute central nervous system (CNS) inflammatory disease in vivo. Addition of DHEA (10 microg/ml) markedly inhibited tumor necrosis factor alpha (TNFalpha) and interleukin-6 (IL-6) production (98 and 95%, respectively), whereas nitric oxide (NO) and prostaglandin E2 (PGE2) production was not affected. However, daily administration of 0.5 mg DHEA to mice or 5 mg to rats did not change the clinical outcome of experimental autoimmune encephalomyelitis (EAE).

### **Fibromyalgia and parvovirus infection.**

Leventhal LJ, Naides SJ, Freundlich B. Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia.

Arthritis Rheum 1991 Oct;34(10):1319-24

An infectious cause of fibromyalgia (FM) has been hypothesized based upon the observed similarity of this entity and chronic fatigue syndrome. Three patients developed symptoms of FM after documented episodes of acute parvovirus B19 infections. B19 antibody determinations were obtained approximately 1 month after the symptoms began; both IgM and IgG titers were positive at that time. All 3 patients met criteria for FM. Polysomnography performed on 2 of the patients revealed profound alpha-wave intrusion throughout nonrapid eye movement sleep. A more careful search for viral infections in FM patients whose symptoms appear following a "flu-like" illness appears warranted.

### **Fibromyalgia in patients with irritable bowel syndrome. An association with the severity of the intestinal disorder.**

Lubrano E, Iovino P, Tremolaterra F, Parsons WJ, Ciacci C, Mazzacca G. Physical Medicine and Rehabilitation Department, University Federico II, Naples, Italy.

Int J Colorectal Dis 2001 Aug;16(4):211-5

Fibromyalgia (FM) syndrome and irritable bowel syndrome (IBS) are functional disorders in which altered somatic and or visceral perception thresholds have been found. The aim of this study was to evaluate the prevalence of FM in a group of patients with IBS and the possible association of FM with patterns and severity of the intestinal disorder. One hundred thirty consecutive IBS patients were studied. The IBS was divided into four different patterns according to the predominant bowel symptom and into three levels of severity using a functional severity index. All patients underwent rheumatological evaluation for number of positive tender points, number of tender and swollen joints, markers of inflammation, and presence of headache and weakness. Moreover, patients' assessments of diffuse pain, mood and sleep disturbance, anxiety, and fatigue were also measured on a visual analogue scale. The diagnosis of FM was made based on American College of Rheumatology classification criteria. Nonparametric tests were used for statistical analysis. Fibromyalgia was found in 20% of IBS patients. No statistical association was found between the presence of FM and the type of IBS but a significant association was found between the presence of FM and severity of the intestinal disorder. The presence of FM in IBS patients seems to be associated only with the severity of IBS. This result confirms previous studies on the association between the two syndromes.

### **Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis.**

McCain GA, Tilbe KS. Department of Medicine, University of Western Ontario, London, Canada.

J Rheumatol Suppl 1989 Nov;19:154-7

Twenty patients with fibromyalgia syndrome and 20 patients with rheumatoid arthritis (RA) were assessed as outpatients over a 3 day period with respect to peak and trough levels of plasma cortisol, growth hormone, prolactin, ACTH and thyroid stimulating hormone. Patients with fibromyalgia syndrome had loss of diurnal variation in plasma cortisol (trough levels 347.3 +/- 254.7 vs 232.8 +/- 70.0 nmol/l, p less than 0.001) compared with RA patients. Thirty-five percent (7/20) of patients with fibromyalgia syndrome and only 5 percent (1/20) of those with RA exhibited abnormal dexamethasone suppression tests (p less than 0.001). No differences were noted in the diurnal variation of other hormones tested. Beck Depression Inventory scores were similar in both groups and no patient exhibited clinical evidence of depression. These data suggest alteration in the pituitary hypothalamic axis with respect to cortisol secretion in fibromyalgia syndrome, perhaps as a consequence of chronic pain.

### **Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abidction.**

Toxicol Ind Health 1999 Apr-Jun;15(3-4):284-94

'Toxicant-induced loss of tolerance' (or TILT) describes a two-step disease process in which (1) certain chemical exposures, e.g., indoor air contaminants, chemical spills, or pesticide applications, cause certain susceptible persons to lose their prior natural tolerance for common chemicals, foods, and drugs (initiation); (2) subsequently, previously tolerated exposures trigger symptoms. Responses may manifest as addictive or abdictive (avoidant) behaviors. In some affected individuals, overlapping responses to common chemical, food, and drug exposures, as well as habituation to recurrent exposures, may hide (mask) responses to particular triggers. Accumulating evidence suggests that this disease process might underlie a broad array of medical illnesses including chronic fatigue, fibromyalgia, migraine headaches, depression, asthma, the unexplained illnesses of Gulf War veterans, multiple chemical sensitivity, and attention deficit disorder.

### **Multiple mycoplasmal infections detected in blood of patients with chronic fatigue syndrome and/or fibromyalgia syndrome.**

Nasralla M, Haier J, Nicolson GL. The Institute for Molecular Medicine, Huntington Beach, CA 92649-1041, USA.

Eur J Clin Microbiol Infect Dis 1999 Dec;18(12):859-65

The aim of this study was to investigate the presence of different mycoplasmal species in blood samples from patients with chronic fatigue syndrome and/or fibromyalgia syndrome. Previously, more than 60% of patients with chronic fatigue syndrome/fibromyalgia syndrome were found to have mycoplasmal blood infections, such as *Mycoplasma fermentans* infection. In this study, patients with chronic fatigue syndrome/fibromyalgia syndrome were examined for multiple mycoplasmal infections in their blood. A total of 91 patients diagnosed with chronic fatigue syndrome/fibromyalgia syndrome and with a positive test for any mycoplasmal infection were investigated for the presence of *Mycoplasma fermentans*, *Mycoplasma pneumoniae*, *Mycoplasma hominis* and *Mycoplasma penetrans* in blood using forensic polymerase chain reaction. Among these mycoplasma-positive patients, infections were detected with *Mycoplasma pneumoniae* (54/91), *Mycoplasma fermentans* (44/91), *Mycoplasma hominis* (28/91) and *Mycoplasma penetrans* (18/91). Multiple mycoplasmal infections were found in 48 of 91 patients, with double infections being detected in 30.8% and triple infections in 22%, but only when one of the species was *Mycoplasma pneumoniae* or *Mycoplasma fermentans*. Patients infected with more than one mycoplasmal species generally had a longer history of illness, suggesting that they may have contracted additional mycoplasmal infections with time.

### **Thyroid function in patients with fibromyalgia syndrome.**

Neeck G, Riedel W. Department of Rheumatology and Physical Medicine, University of Giessen, Bad Nauheim, Germany.

J Rheumatol 1992 Jul;19(7):1120-2

Thyroid function was tested in 13 female patients with primary fibromyalgia syndrome (FS) and 10 healthy age matched controls by intravenous injection of 400 micrograms thyrotropin-releasing hormone (TRH). Basal thyroid hormone levels of both groups were in the normal range. However, patients with primary FS responded with a significantly lower secretion of thyrotropin and thyroid hormones to TRH, within an observation period of 2 h, and reacted with a significantly higher increase of prolactin. Total and free serum calcium and calcitonin levels were significantly lower in patients with primary FS, while both groups exhibited parathyroid hormone levels in the normal range.

### **Fibromyalgia and chronic widespread pain in patients with inflammatory bowel disease: a cross sectional population survey.**

Palm O, Moum B, Jahnsen J, Gran JT. Department of Rheumatology, Ostfold Central Hospital, Sarpsborg, Norway.

J Rheumatol 2001 Mar;28(3):590-4

**OBJECTIVE:** To assess the prevalence of fibromyalgia (FM) and chronic widespread pain (CWP) in a population based cohort of patients with inflammatory bowel disease (IBD). **METHODS:** Patients in a prospective survey on newly diagnosed IBD were, 5 years after study entry, invited to a clinical examination including the investigation of musculoskeletal manifestations. A total of 521 patients were examined, corresponding to 80% of surviving cases with definite diagnoses of ulcerative colitis (UC) and Crohn's disease (CD). The diagnoses of FM and CWP strictly followed the American College of Rheumatology classification criteria of 1990. **RESULTS:** At clinical examination, FM was diagnosed in 18 patients (3.5%), 3.7% with UC and 3.0% with CD. The prevalence was 6.4% in females and 0.4% in males. Thirty-eight patients (7.3%) had CWP (8.5% with UC; 4.8% with CD). The female:male ratio

was 27:3 in the UC group and 8:0 in CD. In 19 patients (50%), CWP occurred after onset of IBD. No correlation with the extent of intestinal inflammation and the occurrence of FM and CWP was found. **CONCLUSION:** The prevalences of FM and CWP in patients with IBD were similar to those of the general population. There were no differences in prevalence of FM and CWP between UC and CD. Chronic idiopathic inflammation of the intestine does not appear to predispose to chronic widespread pain.

### **Does exogenous melatonin influence the free radicals metabolism and pain sensation in rat?**

Pekarkova I, Parara S, Holecek V, Stopka P, Trefil L, Racek J, Rokyta R. Department of Normal, Pathological and Clinical Physiology, Third Faculty of Medicine, Charles University, Prague, Czech Republic. ivanapekarkova@seznam.cz

Physiol Res 2001;50(6):595-602

Melatonin has been shown to play a role in antioxidative defence. We therefore studied its effect on oxidative damage to the rat cerebral cortex evoked by painful stimulation and immobilization-induced stress. Moreover, the effect of melatonin on chronic pain perception was examined. Rats were injected with either a high dose of melatonin (100 mg/kg i.p.) or a vehicle for five days and were subjected to painful stimulation or immobilization stress 30 min after the treatment. To determine the degree of oxidative stress, the levels of free radicals, thiobarbituric acid reactive substances (TBARS) as indicators of lipid peroxidation and glutathione peroxidase (GSHPx) were estimated in somatosensory cortex. Pain perception was measured by the tail-flick and plantar test. Melatonin reduced the level of TBARS previously increased by painful stimulation. Melatonin also exhibited a slight analgesic effect in those animals exposed to painful stimulation but its role in free radical scavenging did not contribute to this effect.

### **Increased concentrations of homocysteine in the cerebrospinal fluid in patients with Fibromyalgia and chronic fatigue syndrome.**

Regland B, Andersson M, Abrahamsson L, Bagby J, Dyrehag LE, Gottfries CG. Institute of Clinical Neuroscience, Goteborg University, Sweden.

Scand J Rheumatol 1997;26(4):301-7

Twelve outpatients, all women, who fulfilled the criteria for both Fibromyalgia and chronic fatigue syndrome were rated on 15 items of the Comprehensive Psychopathological Rating Scale (CPRS-15). These items were chosen to constitute a proper neurasthenic subscale. Blood laboratory levels were generally normal. The most obvious finding was that, in all the patients, the homocysteine (HCY) levels were increased in the cerebrospinal fluid (CSF). There was a significant positive correlation between CSF-HCY levels and fatiguability, and the levels of CSF-B12 correlated significantly with the item of fatiguability and with CPRS-15. The correlations between vitamin B12 and clinical variables of the CPRS-scale in this study indicate that low CSF-B12 values are of clinical importance. Vitamin B12 deficiency causes a deficient remethylation of HCY and is therefore probably contributing to the increased homocysteine levels found in our patient group. We conclude that increased homocysteine levels in the central nervous system characterize patients fulfilling the criteria for both Fibromyalgia and chronic fatigue syndrome.

### **Treatment of Fibromyalgia syndrome with Super Malic: a randomized, double blind, placebo controlled, crossover pilot study.**

Russell IJ, Michalek JE, Flechas JD, Abraham GE. Department of Medicine, University of Texas Health Science Center, San Antonio 78284-7874, USA.

J Rheumatol 1995 May;22(5):953-8

**OBJECTIVE.** To study the efficacy and safety of Super Malic, a proprietary tablet containing malic acid (200 mg) and magnesium (50 mg), in treatment of primary Fibromyalgia syndrome (FM). **METHODS.** Twenty-four sequential patients with primary FM were randomized to a fixed dose (3 tablets bid), placebo controlled, 4-week/course, pilot trial followed by a 6-month, open label, dose escalation (up to 6 tablets bid) trial. A 2-week, medication free, washout period was required before receiving treatment, between blinded courses, and again before starting open label treatment. The 3 primary outcome variables were measures of pain and tenderness but functional and psychological measures were also assessed. **RESULTS.** No clear treatment effect attributable to Super Malic was seen in the blinded, fixed low dose trial. With dose escalation and a longer duration of treatment in the open label trial, significant reductions in the severity of all 3 primary pain/tenderness measures were obtained without limiting risks. **CONCLUSIONS.** These data suggest that Super Malic is safe and may be beneficial in the treatment of patients with FM. Future placebo-controlled studies should utilize up to 6 tablets of Super Malic bid and continue therapy for at least 2 months.

### **Mild sleep deprivation alters hormonal activity.**

Schorr, M.

### **Melatonin--the key to the gate of sleep.**

Shochat T, Haimov I, Lavie P. Sleep Laboratory, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa.

Ann Med 1998 Feb;30(1):109-14

This article reviews the evidence that melatonin, a hormone produced by the pineal gland during the dark hours, plays a major role in the regulation of the sleep-wake cycle. In recent years, our laboratory has been involved in a large-scale project aimed at investigating the role of endogenous melatonin in sleep-wake regulation and the effects of nonpharmacological levels of melatonin on sleep. Based on our finding on the precise coupling between the endogenous nocturnal increase in melatonin secretion and the opening of the nocturnal sleep gate, we propose that the role of melatonin in the induction of sleep does not involve the active induction of sleep, but is rather mediated by an inhibition of a wakefulness-producing mechanism in the central nervous system. Our studies also suggest that exogenously administered melatonin may be beneficial in certain types of insomnia that are related to disturbances in the normal secretion of the hormone.

### **Both pain and EEG response to cold pressor stimulation occurs faster in fibromyalgia patients than in control subjects.**

Stevens A, Batra A, Kotter I, Bartels M, Schwarz J. Department of Psychiatry, University of Tübingen, Universitätsklinik für Psychiatrie und Psychotherapie, Osianderstr. 24, 72076, Tübingen, Germany. andreas.stevens@med.uni-tuebingen.de

Psychiatry Res 2000 Dec 27;97(2-3):237-47

Pain-evoked brain potentials elicited by laser stimulation have been repeatedly shown to be abnormal in fibromyalgia syndrome. However, to our knowledge this is the first study assessing enduring (cold pressor) pain and correlated EEG changes in fibromyalgia. EEG power and subjective pain ratings during the cold pressor test were analyzed and contrasted with tasks not involving sensory stimulation (rest, mental arithmetic and pain imagery) in 20 patients with fibromyalgia and 21 healthy control subjects. Fibromyalgia patients both perceived pain and judged pain as intolerable earlier than control subjects, while pain intensity ratings and EEG power changes during subjective awareness of pain were similar in both groups. In patients and control subjects, pain was correlated with a rise in delta, theta and beta power. EEG power spectra during pain imagery and mental arithmetic were significantly different from those observed during the cold pressor test. In conclusion, fibromyalgia patients seem to process painful stimuli abnormally in a quantitative sense, thus producing both the sensation of pain, as well as the associated EEG patterns, much earlier than control subjects. However, the quality of the pain-associated EEG changes seems similar.

### **Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence.**

Straub RH, Konecna L, Hrach S, Rothe G, Kreutz M, Scholmerich J, Falk W, Lang B. Department of Internal Medicine I, University Medical Center, Regensburg, Germany. rainer.straub@klinik.uni-regensburg.de

J Clin Endocrinol Metab 1998 Jun;83(6):2012-7

Interleukin-6 (IL-6) is one of the pathogenetic elements in inflammatory and age-related diseases such as rheumatoid arthritis, osteoporosis, atherosclerosis, and late-onset B cell neoplasia. In these diseases or during aging, the decrease in production of sex hormones such as dehydroepiandrosterone (DHEA) is thought to play an important role in IL-6-mediated pathogenetic effects in mice. In humans, we investigated the correlation of serum levels of DHEA, DHEA sulfate (DHEAS), or androstenedione (ASD) and IL-6, tumor necrosis factor-alpha, or IL-2 with age in 120 female and male healthy subjects (15-75 yr of age). Serum DHEA, DHEAS, and ASD levels significantly decreased with age (all  $P < 0.001$ ), whereas serum IL-6 levels significantly increased with age ( $P < 0.001$ ). DHEA/DHEAS and IL-6 (but not tumor necrosis factor-alpha or IL-2) were inversely correlated (all patients:  $r = -0.242/-0.312$ ;  $P = 0.010/0.001$ ). In female and male subjects, DHEA and ASD concentration dependently inhibited IL-6 production from peripheral blood mononuclear cells ( $P = 0.001$ ). The concentration-response curve for DHEA was U shaped (maximal effective concentration,  $1.5 \times 10^{-8}$  mol/L), which may be the optimal range for immunomodulation. In summary, the data indicate a functional link between DHEA or ASD and IL-6. It is concluded that the increase in IL-6 production during the process of aging might be due to diminished DHEA and ASD secretion. Immunosenescence may be directly related to endocrinosenescence, which, in turn, may be a significant cofactor for the manifestation of inflammatory and age-related diseases.

### **Inhibition of glutamate transporter by theanine enhances the therapeutic efficacy of doxorubicin.**

Sugiyama T, Sadzuka Y, Tanaka K, Sonobe T. School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, 422-8526,

Theanine, a major amino acid existing in green tea, enhanced the antitumor activity of doxorubicin (DOX) due to inhibition of DOX efflux from tumor cells. In order to clarify the mechanism, we have investigated the contribution of glutamate transporters to the action of theanine, because theanine is a glutamate analogue. In M5076 ovarian sarcoma cells, glutamate transport inhibitors reduced the efflux of DOX, as well as theanine. Incidentally, theanine significantly inhibited the glutamate uptake by M5076 cells in a concentration-dependent manner similar to specific inhibitors. These results suggested that the inhibition of DOX efflux was induced by the inhibition of glutamate transport by theanine. In addition, RT-PCR and Western blot analysis revealed the expression of GLAST and GLT-1, astrocytic high-affinity glutamate transporters, in M5076 cells. Thus, theanine was shown to competitively inhibit the glutamate uptake by acting on these glutamate transporters. This action suggested the contribution of glutamate transporters to the inhibition of DOX efflux by theanine. We revealed the novel mechanism of enhancement of the antitumor efficacy of DOX via the inhibition of glutamate transporters by theanine.

### **A comparison of rheumatoid arthritis and fibromyalgia patients and healthy controls exposed to a pulsed (200 microT) magnetic field: effects on normal standing balance.**

Thomas AW, White KP, Drost DJ, Cook CM, Prato FS. The Lawson Health Research Institute, Department of Nuclear Medicine & MR, St. Joseph's Health Care, 268 Grosvenor Street, London, N6A 4V2, Ontario, Canada. athomas@lri.sjhc.london.on.ca

Specific weak time varying pulsed magnetic fields (MF) have been shown to alter animal and human behaviors, including pain perception and postural sway. Here we demonstrate an objective assessment of exposure to pulsed MF's on Rheumatoid Arthritis (RA) and Fibromyalgia (FM) patients and healthy controls using standing balance. 15 RA and 15 FM patients were recruited from a university hospital outpatient Rheumatology Clinic and 15 healthy controls from university students and personnel. Each subject stood on the center of a 3-D forceplate to record postural sway within three square orthogonal coil pairs (2 m, 1.75 m, 1.5 m) which generated a spatially uniform MF centered at head level. Four 2-min exposure conditions (eyes open/eyes closed, sham/MF) were applied in a random order. With eyes open and during sham exposure, FM patients and controls appeared to have similar standing balance, with RA patients worse. With eyes closed, postural sway worsened for all three groups, but more for RA and FM patients than controls. The Romberg Quotient (eyes closed/eyes open) was highest among FM patients. Mixed design analysis of variance on the center of pressure (COP) movements showed a significant interaction of eyes open/closed and sham/MF conditions [ $F=8.78$  (1,42),  $P<0.006$ ]. Romberg Quotients of COP movements improved significantly with MF exposure [ $F=9.5$ (1,42),  $P<0.005$ ] and COP path length showed an interaction approaching significance with clinical diagnosis [ $F=3.2$ (1,28),  $P<0.09$ ]. Therefore RA and FM patients, and healthy controls, have significantly different postural sway in response to a specific pulsed MF.

### **Discussion of "The Effects of Candida and Aspergillus"**

Thomason, P. (Herbal Research, inventor of Fibrex).

2002 May 11 and 12. Oceanside, CA: The International Holistic Healing Circle and Society.

### **Cytokines play an aetiopathogenetic role in Fibromyalgia: a hypothesis and pilot study.**

Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH. Department of Medicine/Division of Rheumatology, Cedars-Sinai Medical Center/UCLA School of Medicine, Los Angeles, CA, USA.

**OBJECTIVE:** To measure soluble factors having a possible role in Fibromyalgia (FM) and compare the profiles of patients with recent onset of the syndrome with patients with chronic FM. **METHODS:** The production of cytokines, cytokine-related molecules, and a CXC chemokine, interleukin (IL)-8, was examined. Fifty-six patients with FM (23 with <2 yr and 33 with >2 yr of symptoms) were compared with age- and sex-matched healthy controls. Cytokines and cytokine-related molecules were measured in sera and in supernatants of peripheral blood mononuclear cells (PBMC) that were incubated with and without lectins and phorbol myristate acetate (PMA). **RESULTS:** No differences between FMS and controls were found by measuring IL-1 $\beta$ , IL-2, IL-10, serum IL-2 receptor (sIL-2R), interferon gamma (IFN- $\gamma$ ), and tumour necrosis factor alpha (TNF- $\alpha$ ). Levels of IL-1R antibody (IL-1Ra) and IL-8 were significantly higher in sera, and IL-1Ra and IL-6 were significantly higher in stimulated and unstimulated FM PBMC compared with controls. Serum IL-6 levels were comparable to those in controls, but were elevated in supernatants of in vitro-activated PBMC derived from patients with >2 yr of symptoms. In the presence of PMA, there were additional increases in IL-1Ra, IL-8 and IL-6 over control values. **CONCLUSIONS:** In patients with FM we found increases over time in serum levels and/or PBMC-

stimulated activity of soluble factors whose release is stimulated by substance P. Because IL-8 promotes sympathetic pain and IL-6 induces hyperalgesia, fatigue and depression, it is hypothesized that they may play a role in modulating FM symptoms.

### **Hypothyroidism with presenting symptoms of fibrositis.**

Wilke WS, Sheeler LR, Makarowski WS.

J Rheumatol 1981 Jul-Aug;8(4):626-31

Eight patients who initially presented with signs and symptoms of the fibrositis syndrome, without overt hypothyroid disease, were found to have chemical evidence of hypothyroidism. Myalgic symptoms resolved in 6 of 8 patients treated with low dose thyroid replacement. In addition, another hypothesis of pathophysiology of the myalgic symptoms observed in patients with hypothyroidism related to sleep disturbance is offered.

### **Antipolymer antibody reactivity in a subset of patients with fibromyalgia correlates with severity.**

Wilson RB, Gluck OS, Tesser JR, Rice JC, Meyer A, Bridges AJ. Autoimmune Technologies, L.L.C., New Orleans, Louisiana 70112, USA. rwilson@communique.net

J Rheumatol 1999 Feb;26(2):402-7

**OBJECTIVE:** To determine the prevalence of antipolymer antibodies (APA) in patients with fibromyalgia (FM) and autoimmune disease control groups and to determine if the presence of these antibodies correlates with severity in patients with FM. **METHODS:** Sera from patients with FM (n = 47), osteoarthritis (OA) (n = 16), and rheumatoid arthritis (RA) (n = 13) were analyzed. Patients with implants of any kind and patients with concurrent autoimmune conditions were excluded from study. Banked sera from autoimmune disease controls including poly/dermatomyositis (n = 15), RA (n = 30), systemic lupus erythematosus (SLE) (n = 30), and systemic sclerosis (SSc) (n = 30) were also analyzed. To determine if seroreactivity correlates with severity, banked sera from patients with FM assessed as severe (n = 28) or mild (n = 37) and from controls (n = 21) were assayed. **RESULTS:** Following analysis, the prevalence of seroreactivity was found to be higher in patients with FM (22/47, 47%) compared to patients with OA (3/16, 19%; p<0.1) or RA (1/13, 8%; p<0.05) and the autoimmune disease control sera from poly/dermatomyositis (2/15, 13%; p<0.05), and patients with RA (3/30, 10%; p<0.01), SLE (1/30, 3%; p<0.01), and SSc (1/30, 3%; p<0.01). The prevalence of APA seroreactivity was also significantly higher in patients with severe FM (17/28, 61%) compared to patients with mild FM (11/37, 30%; p<0.05) and controls (4/21, 19%; p<0.01). In addition, both mean threshold and mean tolerance dolorimetry scores were significantly lower in the seropositive patients with mild FM (1.33+/-0.21, 1.95+/-0.25, respectively) compared to the seronegative patients (1.83+/-0.08, 2.53+/-0.11; p<0.05 for both comparisons, respectively). **CONCLUSION:** These results reveal that an immunological response, production of anti-polymer antibodies, is associated with a subset of patients with FM. The results also suggest that the APA assay may be an objective marker in the diagnosis and assessment of FM and may provide additional avenues of investigation into the pathophysiological processes involved in FM.

### **Musculoskeletal chest wall syndromes in patients with noncardiac chest pain: a study of 100 patients.**

Wise CM, Semble EL, Dalton CB. Department of Medicine, Bowman Gray School of Medicine, Winston-Salem, NC 27103.

Arch Phys Med Rehabil 1992 Feb;73(2):147-9

One hundred patients with chest pain and negative coronary arteriography were evaluated for musculoskeletal chest wall findings. Sixty-nine patients had chest wall tenderness. Typical chest pain was evoked by palpation in 16 patients. Tender areas were not found in a control group of patients without chest pain. A diagnosis of fibrositis could be made in five patients, including two in whom chest palpation reproduced typical chest pain. The sternal and xiphoid area, left costosternal junctions, and left anterior chest wall were the areas where tenderness was most common, but no significant differences were found comparing locations of tenderness in those with reproduction of typical pain. There was no significant difference in location, exacerbating factors, or other musculoskeletal symptoms among different groups of patients. Thus, most patients with noncardiac chest pain have chest wall tenderness that is not found in a control group without chest pain. However, reproduction of pain by palpation, a more specific diagnostic finding, is found in a minority of these patients.

### **[Melatonin influences the release of endogenous opioid peptides in rat periaqueductal gray] [Article in Chinese]**

Yu CX, Wu GC, Xu SF, Chen CH. State Key Laboratory of Medical Neurobiology, Department of Neurobiology, Shanghai Medical University, Shanghai 200032, China.

Sheng Li Xue Bao 2000 Jun;52(3):207-10

The present study was undertaken to explore central mechanisms underlying the analgesic effect of melatonin. Push-pull perfusion technique and radioimmunoassay were used to observe the changes in the contents of beta-endorphin (beta-Ep) and leucine-enkephalin (L-EK) in the perfusate from the rat periaqueductal gray (PAG) after administration of melatonin. 30-50 min after an intraperitoneal injection of melatonin (110 mg/kg), the beta-Ep content in the perfusate was increased significantly, while the L-EK content was not changed. Pain threshold was measured using the warm water tail-flick test during the push-pull perfusion of the PAG. It was found that the rat pain threshold was increased significantly 40 min after the intraperitoneal injection of melatonin (110 mg/kg). The results suggest that melatonin may promote the release of beta-Ep in the PAG, which may be one of the mechanisms of the analgesic effect of melatonin.

### **Genetic linkage analysis of multicase families with Fibromyalgia syndrome.**

Yunus MB, Khan MA, Rawlings KK, Green JR, Olson JM, Shah S. Division of Rheumatology, University of Illinois College of Medicine at Peoria, 61656, USA. Yunus@uic.edu

J Rheumatol 1999 Feb;26(2):408-12

**OBJECTIVE:** Based on the reports of familial aggregation of Fibromyalgia (FM) syndrome, we investigated its possible genetic linkage to HLA by studying multicase families. **METHODS:** Forty Caucasian multicase families with a diagnosis of FM (American College of Rheumatology criteria) in 2 or more first degree relatives were investigated. Eighty-five affected and 21 unaffected members of 41 sibships were studied. Depression symptomatology was assessed by Zung Self-rating Depression Scale (SDS). HLA typing was performed for A, B, and DRB 1 alleles, and haplotypes were determined with no knowledge of the subject's diagnosis. We investigated genetic linkage to the HLA region by evaluating sibships in multicase families. **RESULTS:** Sibship analysis showed significant genetic linkage of FM to the HLA region ( $p = 0.028$ ). Subgroup analysis was also performed for 17 families where the proband was also noted to have depression (with an SDS index value  $\geq 60$ ). We found that the presence of depression did not influence the observed results ( $p = 0.22$ ). **CONCLUSION:** Our study of 40 multicase families confirms existence of a possible gene for FM that is linked with the HLA region. Our results should be regarded as preliminary and their independent confirmation by other studies is warranted.

### **Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications.**

Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. Sleep Research and Treatment Center, Department of Psychiatry, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033, USA. avx3@psu.edu.

J Clin Endocrinol Metab 2001 Aug;86(8):3787-94

Although insomnia is, by far, the most commonly encountered sleep disorder in medical practice, our knowledge in regard to its neurobiology and medical significance is limited. Activation of the hypothalamic-pituitary-adrenal axis leads to arousal and sleeplessness in animals and humans; however, there is a paucity of data regarding the activity of the hypothalamic-pituitary-adrenal axis in insomniacs. We hypothesized that chronic insomnia is associated with increased plasma levels of ACTH and cortisol. Eleven young insomniacs (6 men and 5 women) and 13 healthy controls (9 men and 4 women) without sleep disturbances, matched for age and body mass index, were monitored in the sleep laboratory for 4 consecutive nights, whereas serial 24-h plasma measures of ACTH and cortisol were obtained during the fourth day. Insomniacs, compared with controls, slept poorly (significantly higher sleep latency and wake during baseline nights). The 24-h ACTH and cortisol secretions were significantly higher in insomniacs, compared with normal controls ( $4.2 \pm 0.3$  vs.  $3.3 \pm 0.3$  pM,  $P = 0.04$ ; and  $218.0 \pm 11.0$  vs.  $190.4 \pm 8.3$  nM,  $P = 0.07$ ). Within the 24-h period, the greatest elevations were observed in the evening and first half of the night. Also, insomniacs with a high degree of objective sleep disturbance (% sleep time  $< 70$ ), compared with those with a low degree of sleep disturbance, secreted a higher amount of cortisol. Pulsatile analysis revealed a significantly higher number of peaks per 24 h in insomniacs than in controls ( $P < 0.05$ ), whereas cosinor analysis showed no differences in the temporal pattern of ACTH or cortisol secretion between insomniacs and controls. We conclude that insomnia is associated with an overall increase of ACTH and cortisol secretion, which, however, retains a normal circadian pattern. These findings are consistent with a disorder of central nervous system hyperarousal rather than one of sleep loss, which is usually associated with no change or decrease in cortisol secretion or a circadian disturbance. Chronic activation of the hypothalamic-pituitary-adrenal axis in insomnia suggests that insomniacs are at risk not only for mental disorders, i.e. chronic anxiety and depression, but also for significant medical morbidity associated with such activation. The therapeutic goal in insomnia should be to decrease the overall level of physiologic and emotional arousal, and not just to improve the nighttime sleep.

### **Circadian interleukin-6 secretion and quantity and depth of sleep.**

Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, Kales A, Prolo P, Wong ML, Licinio J, Gold PW, Hermida RC,

Patients with pathologically increased daytime sleepiness and fatigue have elevated levels of circulating interleukin-6 (IL-6). The latter is an inflammatory cytokine, which causes sickness manifestations, including somnolence and fatigue, and activation of the hypothalamic-pituitary-adrenal axis. In this study, we examined: 1) the relation between serial measurements of plasma IL-6 and quantity and depth of sleep, evaluated by polysomnography; and 2) the effects of sleep deprivation on the nyctohemeral pattern of IL-6 secretion. Eight healthy young male volunteers were sampled for 24 h twice, at the baseline state, after a normal night's sleep and after total overnight sleep deprivation. At the baseline state, IL-6 was secreted in a biphasic circadian pattern with two nadirs at 0800 and 2100 and two zeniths at 1900 and 0500 ( $P < 0.01$ ). The baseline amount of sleep correlated negatively with the overall daytime secretion of the cytokine ( $P < 0.05$ ). Also, depth of sleep at baseline correlated negatively with the postdeprivation increase of daytime secretion of IL-6 ( $P < 0.05$ ). Sleep deprivation changed the temporal pattern of circadian IL-6 secretion but not the overall amount. Indeed, during the post-deprivation period, the mean daytime (0800-2200 h) levels of IL-6 were significantly higher ( $P < 0.05$ ), whereas the nighttime (2200-0600 h) levels were lower than the predeprivation values. Thus, sleep-deprived subjects had daytime oversecretion and nighttime under-secretion of IL-6; the former might be responsible for their daylong somnolence and fatigue, the latter for the better quality (depth) of their sleep. These data suggest that a good night's sleep is associated with decreased daytime secretion of IL-6 and a good sense of well-being and that good sleep is associated with decreased exposure of tissues to the proinflammatory and potentially detrimental actions of IL-6. Sleep deprivation increases daytime IL-6 and causes somnolence and fatigue during the next day, whereas postdeprivation decreases nighttime IL-6 and is associated with deeper sleep.

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