

## ME/CFS and FMS Research Abstracts

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Emphasis Added

### 1997

*Authors* Ziem G. McTamney J.

*Title* **Profile of patients with chemical injury and sensitivity.**

*Source* Environmental Health Perspectives. 105 suppl. 2: 417-36, 1997 Mar.

*Abstract* Patients reporting sensitivity to multiple chemicals at levels usually tolerated by the healthy population were administered standardized questionnaires to evaluate their symptoms and the exposures that aggravated these symptoms. Many patients were referred for medical tests. It is thought that patients with chemical sensitivity have organ abnormalities involving the liver, nervous system (brain, including limbic, peripheral, autonomic), immune system, and porphyrin metabolism, probably reflecting chemical injury to these systems. Laboratory results are not consistent with a psychologic origin of chemical sensitivity. Substantial overlap between chemical sensitivity, fibromyalgia, and chronic fatigue syndrome exists: the latter two conditions often involve chemical sensitivity and may even be the same disorder. Other disorders commonly seen in chemical sensitivity patients include headache (often migraine), chronic fatigue, musculoskeletal aching, chronic respiratory inflammation (rhinitis, sinusitis, laryngitis, asthma), attention deficit, and hyperactivity (affected younger children). Less common disorders include tremor, seizures, and mitral valve prolapse. Patients with these overlapping disorders should be evaluated for chemical sensitivity and excluded from control groups in future research. Agents whose exposures are associated with symptoms and suspected of causing onset of chemical sensitivity with chronic illness include gasoline, kerosene, natural gas, pesticides (especially chlordane and chlorpyrifos), solvents new carpet and other renovation materials, adhesives/glues, fiberglass, carbonless copy paper, fabric softener, formaldehyde and glutaraldehyde, carpet shampoos (lauryl sulfate) and other cleaning agents, isocyanates, combustion products (poorly vented gas heaters, overheated batteries), and medications (dinitrochlorobenzene for warts, intranasally packed neosynephrine, prolonged antibiotics, and general anesthesia with petrochemicals). **Multiple mechanisms of chemical injury that magnify response to exposures in chemically sensitive patients can include neurogenic inflammation (respiratory, gastrointestinal, genitourinary), kindling and time-dependent sensitization (neurologic), impaired porphyrin metabolism (multiple organs), and immune activation.**

### 1996

*Authors* Aarflot I Bruusgaard D.

*Title* **Association between chronic widespread musculoskeletal complaints and thyroid autoimmunity. Results for a community survey.**

*Source* Scandinavian Journal of Primary Health Care. 14(2):111-5. 1996 Jun.

*Abstract* **OBJECTIVE:** To test a hypothesis derived from observations in general practice that thyroid antibodies were associated with chronic widespread musculoskeletal complaints. **DESIGN:** Cross-sectional study of 4042 year old men and women based on a self-administered questionnaire and on results of blood tests. **SETTING:** Sarpsborg municipality Norway. **PARTICIPANTS:** 737 men and 771 women who attended the National Health Screening Service's mobile unit in 1989 and answered the questionnaire. **MAIN OUTCOME MEASURES:** Prevalence of detectable microsomal thyroid antibodies in persons with and without chronic widespread musculoskeletal complaints. **RESULTS:** The prevalence of thyroid microsomal antibodies was

significantly higher in persons with than without chronic widespread musculoskeletal complaints (16% versus 7.3%,  $p < 0.01$ ) The increase was restricted to women (20.4% versus 11.6%.  $p = 0.02$ ). Thyroid function tests did not differ significantly between the two groups. **CONCLUSION: The association between chronic widespread musculoskeletal pain complaints and thyroid antibodies in women may reflect a subgroup of patients in which thyroid autoimmunity, rather than thyroid dysfunction, is important. A possible relationship of fibromyalgia is discussed as well as a hypothetical role for thyrotropin releasing hormone.**

*Authors* Alvarez Lario B, Alonso Valdivielso IL, Aletgre Uopez I. Martel Soteres C. Viejo Banuelos IL. Maranon Cabello A.

*Title* **Fibromyalgia syndrome: overnight falls in arterial oxygen saturation.**

*Source* American Journal of Medicine. 101(1):54-60, 1996 Jul.

*Abstract* **PURPOSE:** Sleep alterations and muscular changes suggesting hypoxia have been reported in fibromyalgia syndrome (FS) pathophysiology. We tested the hypothesis that patients with FS pathophysiology. We tested the hypothesis that patients with FS show falls in the oxygen saturation of hemoglobin in arterial blood (SaO<sub>2</sub>%) during sleep. **PATIENTS AND METHODS:** Overnight SaO<sub>2</sub>% measured by digital pulse oximetry in 28 randomly selected women who met 1990 American College of Rheumatology criteria for the diagnosis of FS and 15 similar controls. Considering the results of pulse oximetry and in order to evaluate the possible presence of a sleep apnea syndrome (SAS) as the reason for the nocturnal desaturations, the Epworth Sleepiness Scale (ESS) was mailed to the patients and controls. Patients and controls who had a score higher than 10 on the ESS underwent a polysomnographic study. **RESULTS:** Patients with FS showed lower overnight minimum SaO<sub>2</sub>% (86.8  $\pm$  1.3 versus 90.7  $\pm$  0.9 in controls,  $P < 0.05$ ), greater number of desaturations (8.3  $\pm$  1.8 versus 2.7  $\pm$  0.8 in controls,  $P < 0.05$ ) and more desaturations/hour (1.3  $\pm$  versus 0.4  $\pm$  0.1 in controls,  $P < 0.05$ ), more night minutes in SaO<sub>2</sub>%  $<$  92% (56.3  $\pm$  12.9 versus 9.1  $\pm$  3.8 in controls,  $P < 0.01$ ) and more minutes in SaO<sub>2</sub>%  $<$  90% (14.7  $\pm$  3.7 versus 2.4  $\pm$  1.0 in controls,  $P < 0.05$ ). There were no differences between patients with FS and controls in ESS scores. Five patients (19.2%) in the FS group and 2 patient and 1 control subject showed on apnea-plus-hypopnea index higher than 5 (13 and 9, respectively) in polysomnographic study. **CONCLUSIONS: Patients with FS showed small overnight falls in SaO<sub>2</sub>% and spent more time during the night in SaO<sub>2</sub>% below 90% and 92% than did the control group. These alterations that, as a whole, are not due to the presence of an associated SAS could be important in FS pathophysiology.**

*Authors* Buchwald D. Pearlman I. Umali J. Schmalting K. Katon W..

*Title* **Functional Status in patients with chronic fatigue syndrome, other fatiguing illnesses, and healthy individuals.**

*Source* American Journal of Medicine. 101(4):364-70, 1996 Oct.

*Abstract* **BACKGROUND:** Chronic fatigue syndrome (CFS) is a condition that may be associated with substantial disability. The Medical Outcomes Study Short-Form General Health Survey (SF-35) is an instrument that has been widely used in outpatient populations to determine functional status. Our objectives were to describe if the usefulness of the SF-36 in CFS patients and to determine if the subscale scores could distinguish patients with CFS from subjects with unexplained chronic fatigue (CF), major depression (MD), or acute infectious mononucleosis (AIM), and from healthy control subjects (HC). An additional goal was to ascertain if subscales correlated with the signs and symptoms of CFS or the presence of psychiatric disorders and fibromyalgia. **DESIGN:** Prospectively collected case series. **SETTING:** Patients with CFS and CF were seen in university-based referral clinic and had undergone a complete medical and psychiatric evaluation. Other study subjects were recruited from the community to participate in research studies. **PARTICIPANTS:** The study included 185 patients with CRS, 246 with CF, 111 with AIM, and 25 with MD. There were 99 HC subjects. **MEASURES:** The SF-36 and a structured

psychiatric interview were used. The SF-36 contains 8 subscales: physical, emotional, social, and role functioning, body pain, mental health, vitality and general health -and a structured psychiatric interview. RESULTS: Performance characteristics (internal reliability coefficients, convergent validity) of the SF-36 were excellent. A strikingly consistent pattern was found for the physical functioning, role functioning, social functioning, general health, and body pain subscales, with the lowest scores in CFS, intermediate scores in AIM patients, and the highest scores in the HC subjects. The CFS patients had significantly lower scores than patients with CF alone on the physical functioning ( $P \leq 0.01$ ), role functioning ( $P \leq 0.01$ ) and body pain ( $P < 0.0001$ ) subscales. Their emotional functioning and mental health scores were worst among those with MD. The presence of fibromyalgia, being unemployed, and increasing fatigue severity all were associated with additional functional limitations across multiple functional domains, with increasing fatigue appearing to have the greatest effect. CONCLUSIONS : The SF-36 is useful in assessing **functional status in patients with fatiguing illnesses. Patients with CFS and CF have marked impairment of their functional status. The severity and pattern of impairment as documented by the SF-36 distinguishes patients with CFS and CF from those with MD and AIM, and from HC, but does not discriminate between CF and CFS.**

*Authors* Galbraith DN. Nairn C. Clements GB.

*Title* **Evidence of enteroviral persistence in humans.**

*Source* Journal of General Virology. 78 (Pt 2):307-12, 1997 Feb.

*Abstract* We have sought evidence of enteroviral persistence in humans. Eight individuals with chronic fatigue syndrome (CFS) were positive for enteroviral sequences, detected by PCR in two serum samples taken at least 5 months apart. The nucleotide sequence of the 5' non-translated region (bases 174-423) was determined for each amplicon. Four individuals had virtually identical nucleotide sequences ( $> 97\%$ ) in both samples. The sequence pairs also each had a unique staired pattern indicating that the virus had persisted. In one individual (HO), it was clear that there had been infection with two different enteroviruses. In the remaining three individuals, the lack of occurred, rather than persistence. **With the exception of HO, the sequences fell into a subgroup that is related to Coxsackie B-like viruses.**

*Authors* Konstantinov K. von Mikecz A. Buchwald D. Jones J. Gerance U. Tan EM.

*Title* **Autoantibodies to nuclear envelope antigens in chronic fatigue syndrome.**

*Source* Journal of Clinical Investigation. 98(8):1888-96, 1996 Oct. 15.

*Abstract* We have identified and partially characterized the autoantibodies in sera of 60 patients with chronic fatigue syndrome. Approximately 52% of the sera were found to react with nuclear envelope antigens. The combination of nuclear rim staining observed in immunofluorescence microscopy and immunoblot analysis of highly purified nuclear envelope proteins provided initial characterization of these autoantibodies. Further characterization showed that some sera immuno-precipitated the in vitro transcription and translation product of a human cDNA clone encoding the nuclear envelope protein lamin B 1. The autoantibodies were of the IgG isotype. **The occurrence of autoantibodies to a conserved intracellular protein like lamin B1 provides new laboratory evidence for an autoimmune component in chronic fatigue syndrome.**

*Authors* Kosek E. Ekholm J. Hansson P.

*Title* **Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms.**

*Source* Pain. 68 (2-3): 375-83, 1996 Dec.

*Abstract* This study, addressing etiologic and pathogenic aspects of fibromyalgia (FM), aimed at examining whether sensory abnormalities in FM patients are generalized or confined to areas with

spontaneous pain. Ten female FM patients and 10 healthy, age-matched females participated. The patients were asked to rate the intensity of ongoing pain using a visual analogue scale (VAS) at the site of maximal pain, the homologous contralateral site and two homologous sites with not or minimal pain. Quantitative sensory testing was performed for assessment of perception thresholds in these four sites. Von Frey filaments were used to test low-threshold mechanoreceptive function. Pressure pain sensitivity was assessed with a pressure algometer and thermal sensitivity with a ThermoTest. In addition the stimulus-response curve of pain intensity as a function of graded nociceptive heat stimulation was studied at the site of maximal pain and at the homologous contralateral site. FM patients had increased sensitivity to non-painful warmth ( $P < 0.01$ ) over painful sites and a tendency to increased sensitivity to non-painful cold ( $P < 0.06$  at all sites compared to controls, but there was no difference between groups regarding tactile perception thresholds. Compared to controls, **patients demonstrated increased sensitivity to pressure pain, ( $P < 0.001$ ), cold pain ( $P < 0.001$ ) and heat pain ( $P < 0.02$ ) over all tested sites. The stimulus-response curve was parallelly shifted to the left of the curve obtained from controls ( $P < 0.003$ ). Intragroup comparisons showed that patients had increased sensitivity to pressure pain ( $P < 0.01$ ) and light touch ( $P < 0.05$ ) in the site of maximal pain compared to the homologous contralateral site. These findings could be explained in terms of sensitization of primary afferent pathways or as a dysfunction of endogenous systems modulating afferent activity. However, the generalized increase in sensitivity found in FM patients was unrelated to spontaneous dysfunction. The additional hyperphenomena related to spontaneous pain are probably dependent on disinhibition/facilitation of nociceptive afferent input from normal (or ischemic) muscles.**

*Authors* MacFarlane JG. Shahal B. Mously C. Moldofsky H.

*Title* **Periodic K-alpha sleep EEG activity and periodic limb movements during sleep: comparisons of clinical features and sleep parameters.**

*Source* Sleep. 19(3):200-4, 1996 Apr.

*Abstract* The K-alpha sleep electroencephalographic (EEG) phenomenon is characterized by periodic (approximately 20-40 seconds) K-complexes, immediately followed by alpha-EEG activity (7.5-11 Hz) of 0.5- to 5.0- second duration. A group of 14 subjects with the periodic K-alpha anomaly was found to have a similar distribution pattern of interevent intervals as compared with previously published data for sleep-related periodic limb movement during sleep (PUMS). Sleep parameters and somatic symptoms of 30 patients with K-alpha were compared with 30 patients with PUMS. The periodic **K-alpha group was predominantly female, younger**, exhibiting more slow-wave sleep gastrointestinal symptoms **and muscular complaints and fewer movement arousals on overnight polysomnography. The K-alpha group presented uniformly with complaints of unrefreshing sleep, of ten associated with fibromyalgia and chronic fatigue syndrome. The PLMS group was predominantly male, showed greater sleep disruption and presented with a variety of sleep-related symptoms.**

*Authors* McGregor NR. Dunstan RH. Zerbes M. Butt HIL. Roberts TK. Klineberg U.

*Title* **Preliminary determination of the association between symptom expression and urinary metabolites in subjects with chronic fatigue syndrome.**

*Source* Biochemical & Molecular Medicine. 57(2):73-80, 1996 Apr.

*Abstract* Chronic fatigue syndrome (CFS/ME) is a debilitating fatigue illness that has an unknown etiology. We studied 20 chronic fatigue syndrome (CFS) patients, who complied with the Oxford and American CDC definitions, and 45 non-CFS subjects. Participants completed questionnaires, were clinically examined, and had first morning urine specimens collected, which were screened by gas chromatography-mass spectrometry for changes in metabolite excretion. Multivariate analysis of the urinary metabolite profiles differed significantly in the CFS patients

compared to the non-CFS patients ( $P < 0.004$ ). The CFS patients had increases in **aminohydroxy-N-methylpyrrolidine** ( $P < 0.00003$ , referred to as a chronic fatigue **symptom urinary marker 1, or CFSUM1**), **tyrosine** ( $P < 0.02$ ), **beta-alanine** ( $P < 0.02$ ), **aconitic acid** ( $P < 0.005$ ), and **glutamic acid** ( $P < 0.02$ ). **CFSUM1, beta-alanine, and CFSUM2 were found by discriminant function analysis to be the first, second and third most important metabolites, respectively for discriminating between CFS and non-CFS subjects. The abundances of CFSUM1 and beta-alanine were positively correlated with symptom incidence ( $P < 0.01$  and  $P < 0.001$ , respectively), symptom severity, core CFS symptoms, and SCL-90-R somatization ( $P < 0.00001$ ), suggesting a molecular basis for CFS.**

*Authors* Samborske W. Lacki JK. Wiktorowicz KE.

*Title* **The lymphocyte phenotype in patients with primary fibromyalgia.**

*Source* Upsala Journal of Medical Sciences. 101 (3): 251-6, 1996.

*Abstract* The aim of this study was to examine the lymphocyte phenotype in fibromyalgia (FM) patients. Nineteen patients [18 females, 1 male] who met the ACR classification criteria for FM were recruited into the study. The fluorescence of leukocytes was measured using Ortho Cytotron Absolute flow cytometer. Ortho-mune monoclonal antibodies [OK-Combo-Tests] were used for the determination of the following antigens: CD3/CD45RA cells as compared to healthy controls. We found a negative correlation between CD4 and CD8, CD3DR and IgE, CD3DR, CD3DR and CD8 was observed. **The inhibitory effect of CD8+ cells subpopulation of B-cells and thereby on IgE production in patients afflicting for allergy has been found in about 50% of our patients. Taken together the data thus far obtained present a coexistence of symptoms of allergy and FM.**

*Authors* Torpy DJ. Chrousos GP.

*Title* **The three-way interactions between the hypothalamic-pituitary-adrenal and gonadal axes and the immune system. [Review] [102 references]**

*Source* Baillieres Clinical Rheumatology. 10 (2):181-98, 1996 May.

*Abstract* The stress system is controlled by brain nuclei at the hypothalamus and brainstem. These nuclei interact with each other and control the HPA axis and sympathetic nervous systems respectively. Major inputs to the stress system arise from the cerebral cortex and subcortical systems, the sensory organs and nerves, and the endocrine and immune systems. The major peripheral effectors of the stress system are glucocorticoids and the catecholamines. Pathological hypoactivity of the stress system has been associated with atypical depression, the chronic fatigue/fibromyalgia syndromes and autoimmune inflammatory diseases; hyperactivity with melancholic depression and anxiety disorders. The stress system responds in a quantitatively and qualitatively specific fashion to different stressors. A major role of the HPA axis is to restrain the immune system and prevent tissue damage. Reciprocal interactions between the HPA axis and immune system constitutes a new endocrine feedback loop that has given rise to the field of neuroendocrine immunology. Gonadal axis hormones directly, and indirectly via the HPA axis of the inflammatory responses. Effects of the HPA axis on the gonadal axis are consistent with conservation and redirection of valuable resources towards homeostasis during times of stress. These complex interactions between the HPA axis, immune and the gonadal systems may prove to be fundamental in the genesis and perpetuation of autoimmune disease.

*Authors* Weibel RE. Benor DE.

*Title* **Chronic arthropathy and musculoskeletal symptoms associated with rubella vaccines. A review of 124 claims submitted to the National Vaccine Injury Compensation Program.**

*Source* Arthritis & Rheumatism. 39(9):1529-34, 1996 Sept.

*Abstract* **OBJECTIVE:** To report the outcome of 124 claims of chronic arthropath associated with rubella vaccine submitted to the National Vaccine Injury Compensation Program. **METHODS:** Medical records and testimony were reviewed separately by physicians and Special Masters to determine the clinical diagnosis and eligibility for compensation under the Program. **RESULTS:** Among the 124 subjects with chronic arthropathy, the onset occurred between 1 week and 6 weeks after the vaccination in 72, and <1 or > 6 weeks after the vaccination in 52. Various conditions developed in the 2 onset groups (1-6 weeks postvaccination, < 1 week or > 6 weeks postvaccination), including, respectively, unspecified arthritis (n = 29, n = 1), specified arthritis (n = 11, n = 19), arthralgia (n = 24, n = 7), fibromyalgia (n = 4, n = 14). Concordance of medical recommendations by Program physicians and Special Masters' decisions in 56 completed claims was 91%, with award mainly to patients with chronic unspecified arthritis and arthralgia. **CONCLUSION: The Program and the US Court of Federal Claims have accepted a causal relationship between currently used rubella vaccine in the US and some chronic arthropathy with an onset between 1 week and 6 weeks after vaccine administration.**

## 1995

*Authors* Costa DC. Tannock C. Brostoff J.

*Title* **Brainstem perfusion is impaired in chronic fatigue syndrome.**

*Source* QJM. 88(11):767-73, 1995, Nov.

*Abstract* We looked for brain perfusion abnormalities in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). An initial pilot study revealed widespread reduction of regional brain perfusion in 24 ME/CFS patients, compared with 24 normal volunteers. Hypoperfusion of the brainstem ( $0.72 \pm 0.05$  v.  $0.80 \pm 0.014$ ,  $p < 0.0001$ ) was marked and constant. We then tested whether perfusion to the brainstem in ME/CFS patients differs from that in normals, patients with major depression and others with epilepsy. Data from a total of 146 subjects were included in the present study: 40 normal volunteers, 67 patients with ME/CFS (24 in the pilot study. 16 with no psychiatric disorders, 13 with ME/CFS and depression, 14 with ME/CFS and other psychiatric disorders), 10 epileptics, 20 young depressed patients and 9 elderly depressed individuals. Brain perfusion ratios were calculated using  $^{99m}\text{Tc}$ -hexamethylpropylene amine oxime ( $^{99m}\text{Tc}$ -HMPAO) and single-photon emission tomography (SPET) with a dedicated three-detector gamma camera computer/system (GE Neurocam). Brain-stem hypoperfusion ( $0.71 \pm 0.03$ ) than did depressed patients ( $0.77 \pm 0.03$ ; ANOVA,  $p < 0.0001$ ). **Patients with ME/CFS have a generalized reduction of brain perfusion, with a particular pattern of hypoperfusion of the brainstem.**

*Authors* Drewes AM. Nielsen KD. Taagholt SJ. Bjerregard K. Svendsen L. Gade J.

*Title* **Sleep intensity in fibromyalgia: focus on the microstructure of the sleep process.**

*Source* British Journal of Rheumatology 34(7):629-35, 1995 Jul.

*Abstract* Alpha electroencephalography (EEG) predominance has been described during sleep in patients suffering from the fibromyalgia syndrome (FMS). However, EEG power density in the lower frequency bands probably better reflects the restorative functions of sleep. This study was conducted to describe the energy in all frequency bands in the sleep EEG. Ambulatory sleep recordings were performed on 12 women with FMS and 14 control women. Epochs were classified according to standard criteria. Moreover, all 2-s segments ( $n = 287,355$ ) of the EEG in non-rapid-eye-movement (NREM) 2-4 sleep were subjected to frequency analysis using autoregressive modeling. Frequency bands were: delta (0.5 - 3.5 Hz), theta (3.5 - 8 Hz), alpha (8 - 12 Hz), sigma (12 - 14.5 Hz) and beta (14.5 - 25 Hz). **In patients with FMS, there was a predominance of EEG power in the higher frequency bands (two-way analysis of variance (ANOVA), alpha:  $P = 0.043$ , sigma:  $P 0.0041$  at the expense of the lower frequencies**

(NAOVA, delta:  $P = 0.005$ ; theta:  $P 0.008$ ). The same trends were obtained for the individual sleep cycles. The calculations of total delta power in the time domain showed an exponentially declining curve in healthy subjects, but a flatter decline in FMS. The decreased power in low-frequency range might reflect a disorder in homeostatic and circadian mechanisms during sleep and may contribute to daytime symptoms in patients with fibromyalgia.

*Author* Drewes AM. Gade K. Nielsen KD. Bjerregard K. Taagholt SJ. Svendsen L.

*Title* **Cluster of sleep electroencephalographic patterns in patients with the fibromyalgia syndrome.**

*Source* British Journal of Rheumatology 34(12):1151-6, 1995 Dec.

*Abstract* Several electroencephalographic (EEG) abnormalities have been observed during sleep in patients suffering from the fibromyalgia syndrome (FMS). In this study, 12 patients with fibromyalgia and 14 control subjects had two polysomnographic recordings obtained at home. Data from the second night were subjected to blinded manual scoring as well as signal processing using linked or step-wise clustering for pattern recognition. In this procedure, a common learning set was generated using the spectral information in three 2 mm EEG samples from each of the sleep stages selected from five patients with FMS and five controls. In this way, 17 characteristic EEG classes were defined. All 2 s EEG segments from the whole night from all subjects were then assigned to one of these classes. Five of the classes (dominated by 0.5 -4.5 Hz activity) were more frequent in the control group, whereas three other classes (dominated by 8 - 11 Hz activity) were prevalent in the patient group. This trend was consistent in all sleep stages, although most striking in non-rapid eye movement (NREM) sleep. The predominance of these classes in the patient group may correspond to the alpha EEG sleep anomaly previously reported in subjects with FMS. More importantly, as the EEG power in the lowest frequency range (prevalent in controls) probably is a marker for restorative sleep, the subjects suffering from FMS, thereby contributing to some of the daytime symptoms of these patients.

*Author* Johansson O. Risberg J. Rosenhall U. Orndahl G. Svennerholm L. Nystrom S.

*Title* **Cerebral dysfunction in fibromyalgia: evidence from regional cerebral blood flow measurements, otoneurological tests and cerebrospinal fluid analysis.**

*Source* Acta Psychiatrica Scandinavica. 91(2):86-94, 1995 Feb.

*Abstract* Measurements of regional cerebral blood flow (rCBF), analysis of cerebrospinal fluid, auditory brain stem responses (ABR) and oculomotor tests were performed in 19 patients with fibromyalgia. The results from the rCBF measurements showed a normal flow level with a slight but significant focal flow decreases in dorsolateral frontal cortical areas of both hemispheres. The ABR results showed signs of dysfunction at least at the brain stem level and the oculomotor tests showed discrete changes in the cell differential count. Possible explanations for the involvement of the central nervous system in fibromyalgia are discussed.

*Author* Moldofsky H.

*Title* **Sleep, neuroimmune and neuroendocrine functions in fibromyalgia and chronic fatigue syndrome. I[Review] [177 references]**

*Source* Advances in Neuroimmunology. 5(1):39-56, 1995

*Abstract* The justification for disordered chronobiology for fibromyalgia and chronic fatigue syndrome (CFS) is based on the following evidence: The studies on disordered sleep physiology and symptoms of fibromyalgia and CFS; the experimental studies that draw a link between interleudin-1 (IL-1), immune-neuroendocrine-thermal systems and the sleep-wake cycle; studies

and preliminary data of the inter-relationships of sleep-wakefulness, IL-1, and aspects of peripheral immune and neuroendocrine functions in healthy men and in women during differing phases of the menstrual cycle; and the observations of alterations in the immune-neuroendocrine functions of patients with fibromyalgia and CFS (Moldofsky. 1993b, d). Time series analyses of measures of the circadian pattern of the sleep-wake behavioural system, immune, neuroendocrine and temperature functions in patients fibromyalgia and CFS should determine whether alterations of aspects of the neuro-immune-endocrine systems that accompany disordered sleep physiology result in nonrestorative sleep, pain, fatigue, cognitive and mood symptoms in patients with fibromyalgia and CFS.

*Author* Mountz TM. Bradley LA. Modell JG. Alexander RW. Triana-Alexander M. Aaron LA. Stewart KE. Alarcon GS. Mountz ID.

*Title* **Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels.**

*Source* Arthritis & Rheumatism. 38(7):926-38, 1995 Jul.

*Abstract* OBJECTIVE: To determine if regional cerebral blood flow (rCBF) in the left and right hemithalami or the left and right heads of the caudate nucleus is abnormal in women with fibromyalgia (FM). METHODS. Resting-state rCBF in the hemithalami and left and right heads of the caudate nucleus of 10 untreated women with FM and 7 normal control women was measured by single-photon-emission computed tomography. Pain threshold levels at tender and control points also were assessed in both the women with FM and the controls. RESULTS. The rCBF in the left and right hemithalami and the left and right heads of the caudate nucleus was significantly lower in women with FM than in normal controls ( $P = 0.01$ ,  $P = 0.003$ ,  $P = 0.01$ , and  $0.02$ , respectively). Compared with controls, the women with FM also were characterized by significantly lower cortical rCBF ( $P = 0.001$ ) and lower pain threshold levels at both tender points ( $P = 0.0001$ ) and control points ( $P = 0.0001$ ). **CONCLUSION. The findings of low rCBF and generalized low pain perception in women with FM may result from a functional abnormality within the central nervous system.**

## 1994

*Authors* Crofford U. Pillemer SR. Kalogeras KT. Cash J. Michelson D. Kling MA. et al.

*Title* **Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia.**

*Source* Arthritis & Rheumatism. 37(11): 1583-92, 1994 Nov.

*Abstract* OBJECTIVE. To examine basal and stimulated hypothalamic-pituitary-adrenal (H-P-A) axis and related hormone levels, including adrenocorticotropin (ACTH), cortisol levels, arginine vasopressin (AVP), and neuropeptide Y (NPY), in patients with fibromyalgia (FM). METHODS. Basal and ovine corticotropin-releasing hormone (oCRH)-stimulated HPA axis function were assessed in 12 patients with FM and in age and sex-matched normal subjects. Basal plasma AVP levels and AVP release after postural change were assessed and plasma NPY levels were measured in the same samples. RESULTS. Patients with FM had low 24 hour urinary free cortisol, but normal peak and elevated trough plasma cortisol levels, compared with normal subjects. The net integrated ACTH response to oCRH in FM was not significantly different from that in normal subjects, but tended toward an exaggerated response. There was a significant decrease in net integrated cortisol response to oCRH in FM patients, indicating adrenal hyporesponsiveness. AVP levels were not significantly different between FM patients and control subjects, but variability was greater among the FM patients. Plasma NPY levels were significantly lower in FM patients than in normal subjects. **CONCLUSION. These data support the view that HPA axis function is perturbed in patients with FM.** Further study is required to ascertain the

cause of HPA axis perturbations and their relationship to symptoms in patients with EM.

*Authors* Eisinger J. Plantamura A. Ayavou T.

*Title* **Glycolysis abnormalities in fibromyalgia.**

*Source* Journal of American College of Nutrition. 13 (2): 144-8, 1994 Apr.

*Abstract* **OBJECTIVE:** Primary fibromyalgia (EM) is a painful condition, generally treated by analgesic drugs and antidepressants, which has been associated with hyperpyruvicemia and reduced high energy phosphate in muscle. Biological investigations were performed in patients with EM to determine whether this syndrome was related to carbohydrate metabolism impairment. **METHOD:** Glycolysis was studied in 25 patients with FM, 10 patients with hypothyroidism (HO), 15 patients with osteoarticular chronic pain (OACP), and 36 healthy controls. Laboratory studies were performed on whole blood (pyruvate), erythrocytes (pyruvate kinase, 2-3 diphosphoglycerate, glyceraldehyde phosphodeshydrogenase, adenosine triphosphate), plasma and serum (lactate at rest and after forearm ischemic exercise, lactico deshydrogenase isoenzymes). **RESULTS.** Comparisons between study groups and controls demonstrated increased pyruvate and decreased lactate production in FM and HO; adenosine triphosphate and muscular isoenzymes of lacticodeshydrogenase were decreased in FM only; glycolysis was not significantly impaired in OACP. **CONCLUSIONS: These findings provide support that FM is associated with biochemical abnormalities which require appropriate metabolic therapy.**

*Authors* Gibson SJ. Littlejohn GO. Gorman MM. Helme RD. Granges G.

*Title* **Altered heat pain thresholds and cerebral event-related potentials following painful CO<sub>2</sub> laser stimulation in subjects with fibromyalgia syndrome.**

*Source* Pain. 58 (2):185-93, 1994 Aug.

*Abstract* A decrease in mechanical pressure pain thresholds, particularly over pre-designated tender points, is one of the defining characteristics of fibromyalgia syndrome (FS); however, changes in thermal pain sensitivity have not been investigated. The present study examined heat pain thresholds and cerebral event-related potentials following CO<sub>2</sub> laser stimulation in 10 subjects with FS and 10 age-matched control volunteers. The results indicate that patients with FS exhibit a significant reduction in heat pain threshold when tested on the dorsal surface of the hand. In accordance with previous research, we also found a decrease in mechanical pain threshold over pre-designated tender points and at control sites as well as a significantly larger mechanically induced neurogenic flare response. These measures were highly correlated with thermal pain threshold even though different anatomical sites were stimulated. Hence, it seems **likely that FS patients display a multimodal change in pain sensitivity which is generalized rather than anatomically restricted. patients with FS also displayed a significant increase in the peak-to-peak amplitude of the cerebral potential evoked by CO<sub>2</sub> laser stimulation at pain threshold intensity and 1.5 times pain threshold intensity. These findings suggest a greater activation of central nervous system (CNS) pathways following noxious input. Putative explanations for the increased CNS response are discussed, including mechanisms of peripheral nociceptor sensitization, altered CNS function and the role of psychological factors.**

*Authors* Grassi W. Core P. Carlino G. Salaffi F. Cervini C.

*Title* **Capillary permeability in fibromyalgia.**

*Source* Journal of Rheumatology. 21(7): 1328-31, 1994 Jul.

*Abstract* **OBJECTIVE.** To examine capillary permeability in fibromyalgia (FMS) we studied the nailfold capillaries of 13 unselected patients with EMS and 9 healthy controls using dynamic fluorescence video-microscopy. **METHODS.** The transcapillary permeability of a 20% solution of sodium fluorescein injected into an antecubital vein was assessed by videodensitometric analysis.

Their pericapillary and interstitial fluorescent light intensities (FUI) were calculated at different sites on a transverse axis crossing the selected capillary. **RESULTS.** Fluorescence videomicroscopy revealed no abnormalities in the pattern of dye distribution around the nailfold capillaries in the patient group. Videodensitometric analysis showed a trend to an increased early transcapillary diffusion in patients with EMS, but the difference was only significant at 3 s from the first appearance of the dye ( $p < 0.05$ ). From 10 s to 1 mm after the dye's appearance the mean FLI in the patients equaled that of the controls. The patients with FMS showed an earlier but lower FLI peak. Moreover, the FLI were significantly lower in the patients than in the controls from 5 to 30 mm after the dye appearance in all of the sites of the densitometric analysis ( $p < 0.05$ ). Thirty mm after the first appearance of the dye, the FLI was reduced by more than 50% in the patient group compared to the controls. **CONCLUSION. Our results indicate that transcapillary permeability and the interstitial persistence of the tracer in FMS are significantly reduced compared to controls. This difference may be caused by the abnormal microvascular dynamics induced by low capillary flow and by capillary bed hypotension.**

*Authors* Griep EN. Boersma JW. deKloet ER.

*Title* **Pituitary release of growth hormone and prolactin in the primary fibromyalgia syndrome**

*Source* Journal of Rheumatology. 21(11): 2125-30, 1994 Nov.

*Abstract* **OBJECTIVE.** Previously, we demonstrated hyperreactive adrenocorticotrophic hormone (ACTH) release in patients with primary fibromyalgia syndrome (primary EMS). We investigated the pituitary release of growth hormone (GH) and prolactin (PRL) in search of further disturbances in neuroendocrine reactivity possibly associated with the pathophysiology of reactivity possibly associated with the pathophysiology of primary FMS. **METHODS.** Ten female patients with primary FMS fulfilling the 1981 Yunus criteria and 10 matched, healthy and sedentary controls were subjected to an insulin induced hypoglycemia test; samples for measurement of glucose, GH and PRL were taken at intervals. **RESULTS.** Compared to controls, the patients with primary EMS displayed significantly lower basal GH levels, whereas their basal PRL levels were slightly, though significantly higher (respectively  $p = 0.021$  and  $p = 0.041$ ). Following hypoglycemia, there was a marked, statistically highly significant ( $p = 0.001$ ), hyperreactivity of the GH response in patients with primary EMS. The PRL response showed wide interindividual variation and did not differ between patients and controls. **CONCLUSION. Our findings indicate that fibromyalgia, along with ACTH hyperreactivity, also exhibits a distinct disturbance in the GH-somatomedin C axis. With regard to PRL, the variation in individual responses limits conclusion. The hyperreactive response patterns of GH and ACTH previously suggest a common origin, which might be related to a subtle glucocorticoid deficiency.**

*Authors* Neeck G. Riedel W.

*Title* **Neuromediator and hormonal perturbations in fibromyalgia syndrome: results of chronic stress?**

*Source* Baillieres Clinical Rheumatology. 8(4):763-75. 1994 Nov.

*Abstract* Since the first comprehensive description of the symptoms of FMS by Yunus et al (1981), numerous investigations have confirmed that EMS is a clinical entity. However, the aetiology of the syndrome is still not fully elucidated. It seems, however, logical to place the origin of the disordering the muscle. Muscle pain, especially at the muscle-tendon junctions, fatigue and stiffness are the first symptoms. A malfunction of energy metabolism has been detected in part of the muscle fibers. However, it has to be considered that the muscle is not an isolated entity. Its activity is controlled by segmentally arranged motor units of the ventral horn of the spinal cord in response to proprioceptive afferent signals arising in the muscle spindles or in other sensory elements including nociceptors. Together with supraspinal descending inputs, the spinal motor neuron pool is the common final pathway for segmental and suprasegmental inputs, making the

motor system extremely powerful for adaptive adjustments but also vulnerable if deficits occur in either of these input levels. A second, recently discovered abnormality seen in EMS is **a lowered serotonin level in peripheral and most likely also central structures**. The underlying mechanism seems to be defective absorption of the precursor amino acid typtophan from the gut. Serotonin is involved centrally in the regulation of sleep pattern, and at the spinal level it acts as a 'gain setter' of motorneuron excitability and suppresses signal transmission of noxious stimuli in dorsal horn neurons. Either of these **two disturbances, muscle energy depletion or serotonin deficiency, could by itself evoke many of the symptoms of FMS, and their combined appearance will perpetuate the disease**. Depressed levels of somatomedin C caused by a deficit of stage 4 sleep-dependent release of growth hormone (GH), might represent an additional factor in preventing proper development or repair of myoskeletal structures. Malabsorption of certain amino acids, possibly due to a genetic disorder of gut transport mechanisms may constitute an additional deleterious factor. The abnormalities found in the HPA and HPT axis may be seen as an attempt of the organism to restore homeostasis. The stimulus eliciting this counter-regulatory reaction may be pain or other afferent signals which normally do not reach the central nervous system. It is doubtful whether the unspecified activation of the HPA axis in a non-inflammatory disease is beneficial. Rather, on the contrary, **elevated glucocorticoid levels, via their mostly inhibitory action on various enzymes, may suppress repair of myoskeletal structures and alter feedback circuits, as shown paradigmatically in the regulation of thyroid hormones, with consequences on thyroid hormone-dependent mechanisms like parathyroid hormone secretion and calcium homeostasis. Whereas such peripheral deficits are easily discovered, their effects on central nervous system activities, especially as feedback signals on hypothalamic-releasing hormone neurons and their specific interaction, need further investigation to provide a rationale for a specific therapy of FMS.**

*Authors* Russell IJ. Orr MD. Littman B. Vipraio GA. Alboukrek D. Machalek JE. Lopez Y. MacKillip F.

*Title* **Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome.**

*Source* Arthritis & Rheumatism. 37(II):1593-601. 1994 Nov.

*Abstract* OBJECTIVE. To measure, and seek clinical correlates with, levels of substance P (SP) in the cerebrospinal fluid (CSF) of fibromyalgia syndrome (EMS) patients. METHOD. CSF from 32 EMS patients and 30 normal control subjects were tested for SP by radioimmunoassay. Clinical measures included tender point examination and standardized questionnaires. RESULTS. CSF SP levels were 3-fold higher in EMS patients than in normal controls ( $P < 0.001$ ), but they correlated only weakly with tenderness found on examination. CONCLUSION. **SP is significantly elevated in FMS CSF, but other abnormalities must exist in FMS to more fully explain their symptoms.**

*Authors* Waylonis GW. Perkins RH.

*Title* **Post-traumatic fibromyalgia. A long-term follow-up.**

*Source* American Journal of Physical Medicine & Rehabilitation. 73(6):403-12. 1994 Nov-Dec.

*Abstract* This report describes a follow-up study of 176 individuals seen between 1980 and 1990, in whom a diagnosis of post-traumatic fibromyalgia was made. Sixty-seven people completed a lengthy questionnaire and underwent a confirmatory physical examination using the American College of Rheumatology Criteria to confirm or deny the presence of fibromyalgia at the time of follow-up. A total of 60.7% noted the onset of symptoms after a motor vehicle accident, 12.5% after a work injury, 7.1% after surgery, 5.4% after a sports-related injury and 14.3% after other various traumatic events. Fifty-six of 67 individuals had 11 or more tender points (average, 13.5), 3 had 10 tender points and 7 had fewer than 10 or no tender points. Study subjects were asked to

compare the use of the following for the first 2 years after onset as well as the year preceding the current evaluation: biofeedback, medications, physical therapy, manipulation, massage therapy and tender point injections. In addition, we asked detailed questions regarding symptoms commonly seen in association with fibromyalgia (fatigue, sleep disturbance, etc.). Symptoms of traumatically induced fibromyalgia are quite similar to spontaneous fibromyalgia. There was a dramatic reduction in the use of all forms of physical treatments. Fifty-four % continued to use antidepressants. Eighty-five percent of the patients continued to have **significant symptoms and clinical evidence of fibromyalgia.**

## 1993

*Author* Arroyo JF, Cohen MI.

*Title* **Abnormal responses to electrocutaneous stimulation in fibromyalgia.**

*Source* Journal of Rheumatology 20(11):1925-31, 1993 Nov.

*Abstract* OBJECTIVE: As disturbed nociception may be relevant to the pathogenesis of fibromyalgia, nonnoxious electrocutaneous stimulation was used as a tool to investigate nonnoxious status. METHODS: Perception threshold and pain tolerance were studied in the upper limbs of 10 patients with fibromyalgia and 10 healthy volunteers. RESULTS: Perception threshold did not differ between the groups but the marked reduction in pain tolerance found in patients with fibromyalgia was accompanied by spread and persistence of dysesthesiae. CONCLUSION: The upper limbs of patients with fibromyalgia resembled regions of secondary hyperalgesia which may imply that perturbation of central nociceptive mechanisms is involved in the pathogenesis of this syndrome.

*Author* Bennett RM.

*Title* **Fibromyalgia and the facts. Sense or nonsense. (Review)**

*Source* Rheumatic Disease Clinics of North America. 19(1):45-59. 1993 Feb.

*Abstract* A recent flurry of important studies has provided critical new information that is relevant to the contemporary understanding of the fibromyalgia syndrome. The concept that these patients represent solely a form of masked depression or a distinctive syndrome of somatization is not supported by the current facts. **Rather it would appear that a characteristic peripheral nociceptive component is modulated by an interplay of complex central factors. A disruption of the neuroendocrine axis controlling growth hormone production may be the link between disturbed sleep and muscle pain, as growth hormone is produced predominantly during stage four sleep. A paradigm to link some of these newer findings is presented.**

*Author* Lieberman J, Bell DS.

*Title* **Serum angiotensin-converting enzyme as a marker for the chronic fatigue-immune dysfunction syndrome: a comparison to serum angiotensin-converting enzyme in sarcoidosis.**

*Source* American Journal of Medicine. 95(4):407-12, 1993 Oct.

*Abstract* PURPOSE: To study the reliability of a serum angiotensin-converting enzyme (ACE) assay as a marker for the chronic fatigue-immune dysfunction syndrome (CFIDS), and to compare some enzyme characteristics of ACE in CFIDS with that in sarcoidosis. PATIENTS AND METHODS: Forty-nine patients with CFIDS and 56 endemic control subjects from Lyndonville, New York, and Charlotte, North Carolina; plus 23 untreated patients with active sarcoidosis, 24 with sarcoidosis receiving corticosteroid therapy, and 32 patient controls without sarcoidosis from California. Serum ACE levels were determined with a spectrophotometric

method. The effect of freezing and thawing and the effect of storage at 4 degrees C were compared between CFIDS and sarcoidosis samples. RESULTS: Serum ACE levels were elevated in 80% of patients with CFIDS and 30% of endemic control subjects as compared with 9.4% of nonendemic California control subjects. The ACE activity in CFIDS differed from that in sarcoidosis because of its lability with storage at 4 degrees C in CFIDS and its partial activation with freezing and thawing. Thus, ACE activity was elevated in the majority of CFIDS patients either upon initial assay or upon a subsequent assay after refreezing. ACE activity was elevated in 87% of patients with active sarcoidosis and was not affected by storage or freezing and thawing. **CONCLUSIONS: Serum ACE elevations may be a useful marker for CFIDS, especially if a method can be developed to distinguish ACE in CFIDS from that in sarcoidosis. The sensitivity for CFIDS was 80%, with 68% specificity in an endemic area. The increased prevalence of serum ACE elevation in endemic controls as compared with nonendemic controls suggests that an ACE increase may be an early manifestation of CFIDS and supports the concept that CFIDS is a definite disease state.**

*Author* Moldolsky H.

*Title* **Fibromyalgia, sleep disorder and chronic fatigue syndrome. (Review)**

*Source* Ciba Foundation Symposium 173:262-79, 1993

*Abstract* Various research studies show that the amalgam of disordered sleep physiology, chronic fatigue, diffuse myalgia, and cognitive and behavioural symptoms constitutes a non-restorative sleep syndrome that may follow a febrile illness, as in the chronic fatigue syndrome. Where rheumatic complaints are prominent, such as a constellation of disturbed sleep physiology and symptoms also characterizes the fibromyalgia disorder. In contrast to chronic fatigue syndrome, fibromyalgia is associated with a variety of initiating or perpetuating factors such as psychologically distressing events, primary sleep disorders (e.g. sleep apnoea, periodic limb movement disorder) and inflammatory rheumatic disease, as well as an acute febrile illness. The chronic fatigue syndrome and fibromyalgia have similar disordered sleep physiology, namely an alpha rhythm disturbance (7.5-11 Hz) in the electroencephalogram (EEG) within non-rapid eye movement (NREM) sleep that accompanies increase nocturnal vigilance and light, unrefreshing sleep. Aspects of cytokine and cellular immune functions are shown to be related to the sleep-wake system. **The evidence suggests a reciprocal relationship of the immune and sleep-wake systems. Interference either with the immune system (e.g., by a viral agent or by cytokines such as alpha-interferon or interleukin 2) or with the sleeping-waking brain system (e.g., by sleep deprivation) has effects on the other system and will be accompanied by the symptoms of the chronic fatigue syndrome.**

*Authors* Moldolsky H. Wong MT. Lue FA.

*Title* **Litigation, sleep, symptoms and disabilities in postaccident pain [fibromyalgia].**

*Source* Journal of Rheumatology. 20(II):1935-40, 1993 Nov.

*Abstract* Twenty-four patients with chronic postaccident pain were studied with self-rating symptom checklists, polysomnography and disability questionnaires. All except one had fibromyalgia. Eight had litigation resolved (RO) while 16 had medicolegal claims still unresolved (UR). Patients from the R group were older, with a longer duration of symptoms and more occupation handicap compared to those from the UR group. There were no significant differences **between the 2 groups in polysomnographic findings and disability. Medicolegal claim status in these patients did not differentiate the outcome of their symptoms. Implications for litigation, treatment and further studies are discussed.**

*Authors* Buchwald D. Cheney PR. Peterson DL. Henry B. Wormsley SB. Geiger A, et al.

*Title* **A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection.**

*Source* Annals of Internal Medicine. 116(2):013-13, 1992 Jan 15.

*Abstract* **OBJECTIVE:** To conduct neurologic, immunologic, and virologic studies in patients with a chronic debilitating illness of acute onset. **DESIGN:** Cohort study with comparison to matched, healthy control subjects. **PATIENTS:** We studied 259 patients who sought care in one medical practice; 29% of the patients were regularly bedridden or shut-in. **MAIN OUTCOME MEASURES:** Patients had a higher mean ( $+1$ -SD) CD4/CD8 T-cell ratio than matched healthy controls (3.16 $\pm$ 1.5 compared with 2.3  $\pm$ 1.0, respectively;  $P$  less than 0.003). Magnetic resonance scans of the brain showed punctuate subcortical areas of high signal intensity consistent with edema or demyelination in 78% of patients (95% CI, 72% to 86%) and in 21% of controls (CI, 11% to 36%) ( $P$  less than 10<sup>-9</sup>). Primary cell culture of lymphocytes showed active replication of HHV-6 in 79 of 113 patients (70%; CI, 61% to 78%) and in 8 of 40 controls (20%; CI, 9% to 36%) ( $P$  less than 10<sup>-8</sup>), a finding confirmed by assays using monoclonal antibodies specific for HHV-6 DNA. **CONCLUSIONS: Neurologic symptoms, MRI findings, and lymphocyte phenotyping studies suggest that the patients may have been experiencing a chronic immunologically mediated inflammatory process of the central nervous system. The active replication of HHV-6 most likely represents reactivation of latent infection, perhaps due to immunologic dysfunction.** Our study did not directly address whether HHV-6, a lymphotropic and gliotropic virus, plays a role in producing the symptoms or the immunologic and neurologic dysfunction seen in this illness. Whether the findings in our patients, who came from a relatively small geographic area, will be generalizable to other patients with a similar syndrome remains to be seen.

*Authors* Greenfield S. Fitzcharies MA. Esdaile TM.

*Title* **Reactive fibromyalgia syndrome.**

*Source* Arthritis and Rheumatism. 35(6):678-81, 1992 Jun.

*Abstract* **OBJECTIVE.** To determine the frequency of a precipitating event occurring prior to the onset of fibromyalgia syndrome, in a consecutive series of patients. Outcome in patients in whom there was a causative factor was compared with the ten patients with primary fibromyalgia. **METHODS.** Records of patients presenting over a 4 year period who fulfilled criteria for fibromyalgia were reviewed, and patients were classified as having reactive fibromyalgia if the specific event prior to the onset of illness could be identified. Outcome features, including employment status and disability compensation, were compared in patients with reactive fibromyalgia versus those with primary fibromyalgia. **RESULTS.** Twenty-nine of 127 patients (23%) with a primary rheumatologic diagnosis of fibromyalgia reported having trauma, surgery, or a medical illness before the onset of fibromyalgia, and were classified as having reactive fibromyalgia. Patients in this group were more disabled than those with primary fibromyalgia, resulting in loss of employment in 70%, disability compensation in 34%, and reduced physical activity in 45%. **CONCLUSION. The development of fibromyalgia after a precipitating event may represent the onset of a prolonged and disabling pain syndrome with considerable social and economic implications.**

*Authors* Ichise M. Salit IE. Abbey SE. Chung DO. Gray B. Kirsh JC. Freedman M.

*Title* **Assessment of regional cerebral perfusion by 99Tcm-HMPAO SPECT in chronic fatigue syndrome.**

*Source* Nuclear Medicine Communication. 13(10):767-72, 1992, Oct.

*Abstract* Chronic fatigue syndrome (CFS) is a severely disabling illness of uncertain aetiology. It is characterized by a chronic sustained or fluctuating sense of debilitating fatigue without any other known underlying medical conditions. It is also associated with both somatic and neuropsychological symptoms. Both physical and laboratory findings are usually unremarkable.

Regional cerebral blood flow (rCBF) was assessed in 50 clinically defined CFS patients and 14 normal control (NC) subjects using 99Tcm-hexamethylpropyleneamine oxime (99Tcm-HMPAO) single photon emission computed tomography (SPECT). Compared with the NC group, **the CFS group showed significantly lower cortical/cerebellar rCBF ratios, throughout multiple brain regions ( $P < 0.05$ ). Forty-eight CFS subjects (80%) showed at least one or more rCBF ratios significantly less than normal values. The major cerebral regions involved were frontal (38 cases, 63%), temporal (21 cases, 35%) parietal (32 cases, 53%), and occipital lobes (23 cases, 38%). The rCBF ratios of basal ganglia (24 cases, 40%) were also reduced. 99Tcm-HMPAO brain SPECT provided objective evidence for functional impairment of the brain in the majority of the CFS subjects. The findings may not be diagnostic of CFS but 99Tcm-HMPAO SPECT may play an important role in clarifying the pathoetiology of CFS. Further studies are warranted.**

*Authors* Leventhal U. Naides ST. Freundlich B.

*Title* **Fibromyalgia and parvovirus infection.**

*Source* Arthritis & Rheumatism. 34(10):1319-24, 1991 Oct.

*Abstract* 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 B 19 infections. B 19 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 EM. 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.**

*Authors* Neeck O. Riedel W.

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

*Source* Journal of Rheumatology. 19(7):1120-2, 1992 Jul.

*Abstract* Thyroid function was tested in 13 female patients with primary fibromyalgia syndrome (FS) and 10 healthy age matched controls by intravenous injection of 100 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.**

*Authors* Romano TJ.

*Title* **Clinical experiences with post-traumatic fibromyalgia syndrome.**

*Source* West Virginia Medical Journal. 86(5);198-202, 1990 May.

*Abstract* Fibromyalgia syndrome (FS) is a musculoskeletal problem that has become more and more widely recognized. There are three types: primary (PFS idiopathic), secondary (associated with another disorder), and post-traumatic (PTFS). The latter condition, PTFS, is especially intriguing since quite often litigation is involved, and doubt is cast as to whether the patient is actually suffering. Accusations of malingering have been made. A retrospective chart review of 14 PTFS patients was made in an effort to ascertain the likelihood of malingering. Over the past two years, 14 patients (three male, 11 female) were treated for PTFS. The mean age was 37 years for both men and women. All had classic PTFS with a chronic musculoskeletal problem that started immediately after a traumatic event, classic myofascial tender points, poor sleep and normal standard laboratory tests. Twenty-three per cent went to trial, 77 settled out of court. All were

given a monetary award. **The vast majority (77 per cent) returned to a rheumatologist for continued treatment, suggesting that patients who meet strict FS criteria are not malingering and are indeed in need of medical help.**

*Authors* van Dendersen IC. Boersma 1W. Zeinstra P. Hollander AP. van Neerbos BR.

*Title* **Physiological effects of exhaustive physical exercise in primary fibromyalgia syndrome (PFS): is PFS a disorder of neuroendocrine reactivity?**

*Source* Scandinavian Journal of Rheumatology. 21(1): 35-7, 1992.

*Abstract* The influence of maximum exercise has been studied in 10 patients with primary fibromyalgia syndrome (PFS) and 10 healthy sedentary control persons. The exercise consisted of a bicycle ergometer test and a step test, both till exhaustion. In both tests, the mean maximum work load of the PFS patients was lower than that of the controls. Significantly lower values of serum **creatinekinase, myoglobin, cortisol, epinephrine and norepinephrine were found in PFS patients. A striking finding was a lower heart rate in PFS patients compared to the controls under the same work-load. The lower (nor)epinephrine concentration together with the lower heart rate suggests a disturbance of the sympathetic activity in PFS patients. The preliminary conclusion is that there is a disturbed reactivity of the sympathetic system as well as of the HPA axis in PFS.**

*Authors* Wolfe F. Smythe HA. Yunus MB. Bennett RM. Bombardier C. Goldenberg. DL. Tugwell, et al.

*Title* **The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee.**

*Source* Arthritis & Rheumatism. 33(2): 160-72, 1990 Feb.

*Abstract* To develop criteria for the classification of fibromyalgia, we studied 558 consecutive patients; 293 patients with fibromyalgia and 265 control patients. Interviews and examinations were performed by trained, blinded assessors. Control patients for the group with primary fibromyalgia were matched for age and sex, and limited to patients with disorders that could confused with primary fibromyalgia. Control patients for the group with secondary-concomitant fibromyalgia were matched for age, sex and concomitant rheumatic disorders. Widespread pain (axial plus upper and lower segment plus left- and right-sided pain) was found in 97.6% of all patients with fibromyalgia and 69.1% of all control patients. The combination of widespread pain and mild or greater tenderness in greater than or equal to 11 of 18 point sites yielded a sensitivity of 88.4% and a specificity of 81.1%. Primary fibromyalgia patients and secondary-concomitant patients did not differ statistically in any major study variable, and the criteria performed equally well in patients with and those without concomitant rheumatic conditions. **The newly proposed criteria for the classification of fibromyalgia are 1) widespread pain in combination with 2) tenderness at 11 or more of the 18 specific tender point sites. No exclusions are made for the presence of concomitant radiographic or laboratory abnormalities. At the diagnostic or classification level, the distinction between primary fibromyalgia and secondary-concomitant fibromyalgia (as defined in the text) is abandoned.**

*Authors* Yunus MB. Dailey 1W. Aldag IC. Masi AT. Iobe PC.

*Title* **Plasma tryptophan and other amino acids in primary fibromyalgia: a controlled study.**

*Source* Journal of Rheumatology. 19 (1):90-4. 1992 Jan.

*Abstract* To test the hypothesis that plasma tryptophan and/or its transport ratio is decreased in primary fibromyalgia (PF), we measured plasma tryptophan and its transport ratio in 29 patients with PF and 30 healthy controls without significant pain, in a blinded manner. Twenty-one other amino acids were also similarly analyzed among these study subjects. Transport ratio of

tryptophan was found to be significantly ( $p$  less than 0.01) decreased in PF compared with the control group ( $0.09 \pm 0.02$  vs  $0.10 \pm 0.02$ ). Plasma tryptophan level was lower in PF ( $45 \pm 10$  nmol/ml) than in healthy controls ( $51 \pm 15$  nmol/ml), showing a trend towards significance ( $p$  less than 0.09). Additionally, plasma histidine and serine levels were found to be significantly ( $p < 0.01$ ) lower in patients with PF than in controls. **Our results suggest that a decreased brain serotonin level, as possibility reflected by a decreased transport ratio of plasma tryptophan, may play a pathophysiologic role in PF.**