A Nutrient/Toxin Interaction Theory of the Etiology and Pathogenesis of Chronic Pain-Fatigue Syndromes: Part II

Julia A. Laylander

ABSTRACT. This second part of the review paper covers the evidence in favor of the theory which proposes that Chronic Fatigue Syndrome, Fibromyalgia Syndrome, and Persian Gulf Syndrome represent finitely variable combinations of multiple systemic dysfunctions which share a common underlying etiology at the subcellular level: magnesium deficiency plus concomitant fluoride excess (MDFE). Treatment suggestions are listed at the end of the manuscript through a call for clinical trials to test the theory presented. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: getinfo@haworthpressinc.com]*

KEYWORDS. Chronic fatigue syndrome, fibromyalgia syndrome, Persian Gulf syndrome, magnesium, fluoride, etiology

INTRODUCTION

The nutrient/toxin interaction theory that magnesium deficiency plus concomitant fluoride excess (MDFE) is the underlying biochemical cause of chronic Pain-Fatigue Syndromes (P-FSs) such as Chronic Fatigue Syndrome (CFS), Fibromyalgia Syndrome (FMS), and Persian Gulf Syndrome (PGS) was introduced in Part I. Now Part II presents substantive, detailed evidence

Julia A. Laylander is a student at University of New Mexico, 29 Anne Pickard Loop, Tijeras, NM 87059.

This research was partially funded by MacArthur Fellowship to Eric L. Charnov.

that supports this theory of the fundamental and treatable biochemical cause of CFS, FMS, and PGS.

Any theory which attempts to explain the etiology and pathogenesis of chronic Pain-Fatigue Syndromes (P-FSs) must completely account for observations 1-10 which were developed for CFS (1) (here [the syndromes] replaces the term "CFS"):

1. It causes fatigue, exhaustion, and the other symptoms of [the syndromes];.
2. It affects children as well as adults, but rarely affects children under the age of five;
3. It affects women more than men;
4. It causes both epidemics and sporadic cases;
5. It is rarely, if ever, fatal;
6. It causes immune system dysfunction;
7. Onset of its symptoms may be either sudden or gradual;
8. There is a spectrum of illness severity;
9. [The syndromes] occur more commonly in patients with a history of allergy and/or asthma;
10. There is an increased incidence of [the syndromes] within families.

The cumulative pathological effects of chronic low-level fluoride exposure (*regardless of source*), and/or periodic acute but relatively high-level, sub-lethal fluoride exposure (*also regardless of source*), when temporally paired with low levels of bioavailable magnesium, elegantly account for observations 1-10 noted above and easily explain each profound systemic dysfunction as described in the literature.

OBSERVATION #1: IT CAUSES FATIGUE, EXHAUSTION, AND THE OTHER SYMPTOMS OF [THE SYNDROMES]

The proposed causal relationship of magnesium deficiency plus concomitant fluoride excess (MDFE) to each major symptom of P-FSs (noted where appropriate as pertaining to CFS, FMS, and/or PGS in particular) will be described in turn: fatigue and weakness, musculoskeletal pain, headaches, gastrointestinal disturbances, cognitive difficulties, altered emotional states, sleep disturbances, and altered immune system function. Additional commonly-associated signs and symptoms will also be examined: mitral valve prolapse, interstitial cystitis, unusual reactions to medications, light sensitivity/vision problems, shortness of breath, hypoglycemia, and restless legs.

To review, all symptoms listed above, and others not specifically mentioned, are theorized here to be either direct results of MDFE or indirect results of compensatory physiological mechanisms which follow from specific subcellular, cellular, organ, and system dysfunctions caused by MDFE. Depending on the individual, these compensatory mechanisms may or may not be significantly successful in regaining a degree of homeostasis, and may often work against each other to cause even more distressing symptomatology. A "cascade" of dysfunction (widely described in the literature on CFS and FMS) follows from MDFE, and results in an extremely complex and ultimately baffling web of pathology containing many "vicious cycle" elements.

Fatigue and Weakness

At least three major effects of MDFE can cause extreme fatigue and muscle weakness: disturbed energy production, AChE inhibition, and potassium efflux from cells.

The pathological effect of MDFE on mitochondrial energy production was reviewed in Part I; this effect alone, when systemic and chronic, can cause serious muscle fatigue and weakness. In addition, the chronic elevations of ACh observed with organophosphorous poisoning or chronic use of reversible cholinesterase inhibitors has been shown to eventually result in down-regulation of ACh receptors (2). Fluoride also induces a potassium efflux from cells (hyperkalaemia), especially from muscle cells. One hypothesis of potassium efflux is that "the agent [F^-] poisons Na^+-K^+-ATPase on the cell surface, so that potassium leaks out of the intracellular space and sodium leaks in, raising intracellular sodium and triggering Na^+-Ca^{2+} exchange. The subsequent rise in intracellular calcium opens Ca^{2+}-dependent potassium channels, and an explosive [in acute toxicity] potassium efflux ensues (especially from muscle cells) with potentially lethal effects on the heart" (3). Although this scenario was developed to explain the fatal potassium efflux in acute inorganic fluoride toxicity, this same mechanism will be at work, although to a lesser extent, in chronic fluoride toxicity, contributing to extreme weakness and fatigue.

Psychomotor problems (e.g., dizziness/vertigo, lack of balance, inability to correctly judge and control distance and speed of one's own movements, uncoordinated small- and large-muscle motions) are also common and seemingly related to muscle fatigue and weakness in P-FSs. The mechanisms involved likely reflect serious disruptions in *both* the central and peripheral nervous systems caused by MDFE. Note that mortality rates are higher among veterans of the Persian Gulf War than among veterans deployed elsewhere, with most of this increase caused by unintentional fatal injuries (particularly motor vehicle accidents but including other types of accidents), and that these accidental death rates were slightly more pronounced in women (4).

Musculoskeletal Pain

Endemic fluorosis, described in Part I, is characterized by painful ossifications of ligaments, muscle insertions, and joint capsules (5). In early stages of fluorosis, there is slight edema as well as globular and crystalline material impregnation in periosteal collagenous fibers. The fibers of the muscular attachments and the tendon insertions are mineralized in early stages of fluorosis; symptoms and radiological changes occur *first* in areas of greater muscular activity (6). Fluoride also stimulates new but abnormal bone formation at the sites of muscular insertions on bones; therefore, bones which have strong, frequently-used muscles attached to them will show early and obvious changes (7).

The site-based, soft-tissue ossification process of fluorosis produces pain which generates axon reflexes. Neuropeptides (such as substance P) are released, stimulating responses such as degranulation of mast cells and release of plasmakinines (resulting in local edema), arousing nociceptors which activate, in turn, the release of proinflammatory cytokines, resulting in the remodeling of the extracellular matrix by collagen. In developing fluorosis, this process can be chronic, resulting in a vicious cycle of pathology: collagen disruption produces pain, pain produces more collagen disruption, more collagen disruption causes more pain, and so on. It has been hypothesized that alterations in collagen metabolism are systemic in FMS tender points, with the development of concentric layers of collagen around preterminal sensitive nerve fibers (8). In addition, sodium fluoride has been shown to interfere with the maturation and normal metabolism of tissue collagen (9).

The "tender point" pain in FMS patients, which is often excruciating and intractable, is localized in areas of insertion of muscle in tendon and in tendon on bone. Total tender point sites are consistent and predictable in FMS, and are located in specific sites most directly and frequently involved with maintaining an upright posture and supporting the head, and those sites most frequently exercised during normal daily activities. (The most bothersome sites, then, can vary from person to person.) The fact that patients with P-FSs cannot physically do what they used to routinely and pleasurably do (without experiencing significant and often extreme pain, soreness, and stiffness) is hypothesized here to be a direct reflection of this specific pathophysiological process of fluorosis which targets most-often-used connection sites of muscle, tendon, and bone.

Painful tetany can be caused by hypocalcemia and/or hypomagnesemia. As fluoride is taken up into bone or calcified soft tissues, fluorapatite [$3(Ca_3(PO_4)_2 . CaF_2)$] formation may strongly catalyze the uptake of calcium and magnesium, resulting in hypocalcemia and hypomagnesemia. A reduction in extracellular magnesium and calcium concentrations enhance both central and peripheral neuronal excitability by "decreasing membrane surface charge screening, facilitating the activation of inward currents" (10). Fluorides are sometimes used in the experimental treatment of osteoporosis, and in some patients a calcium deficiency with secondary hyperparathyroidism occurs even when the patients ingest 1500 mg/day of supplemental Ca (11). The Ca and Mg in fluorotic bone and pathologically calcified soft tissues, after deposition and integration into matrix, are also thought to be more strongly bound than they would be in normal bone and calcified tissues, and thus become less available for adaptive mobilization (release from bone) under conditions of soft tissue deficiencies. This fact may be important in the gender differences in P-FSs discussed later.

As mentioned in Part I, fluorotic bone is abnormal and highly susceptible to stress fractures. It is also possible, then, that at least some of the pain experienced, especially "deep level" pain in the legs, may actually originate in bone from stress-induced microfractures. In two controlled trials in the U. S. using sodium fluoride (NaF) for treating postmenopausal osteoporosis there was an increased occurrence of the "painful lower extremity syndrome" (sudden onset of intense, disabling pain over the affected portion of the skeleton) which is believed by many to be caused by fluoride-induced stress fractures. Others believe that this pain is caused by an "intense osteoblastic response to NaF" which is the desired therapeutic response (12,13). Certainly both processes may be at work in the genesis of fluoride-stimulated bone pain.

Regarding postmenopausal osteoporosis, it has been proposed that the most cost-effective approach to treatment would be to raise the RDA of Mg to 1000 mg, and lower the RDA of Ca to 500 mg (14). In view of the theorized critical role of Mg in P-FSs presented here, the first part of this approach is likely to produce significant benefits beyond the treatment of osteoporosis, although increased intake of Ca may be necessary as well in patients who have osteoporosis and a P-FS.

Aortic and other soft tissue calcifications also occur in fluorosis and can produce pain. Fluoride leads to cellular toxicity, disrupting membranes of smooth muscle cells and mitochondrial structure. This causes the accumulation of Ca^{2+} in the mitochondria which is later released and binds to the plasma membrane, forming matrix vesicles which are finally extruded into the extracellular matrix. The calcium deposited in the aorta and other soft tissues may be in the form of hydroxyapatite, fluorapatite, or amorphous calcium phosphate (15).

In addition, accumulation of ACh at the neuromuscular junction can lead to involuntarily sustained muscle contraction, which leads to increased excitability of nociceptors in muscle, which leads to more muscle tension and more pain. "The ensuing neuronal hyperexcitability and trophic changes induced by a disturbed axonal transport system may be major factors of pain

in fibromyalgia" (16). The muscles of FMS patients show an inability to relax in between repetitive voluntary contractions (17). As mentioned in Part I, AChE inhibition can increase sympathetic tone by eliciting spontaneous discharge of ganglionic neurons and activating central sympathoadrenal pathways; defective sympathetic control can also result in disturbed microcirculation and nociceptor excitation, causing more pain (16).

Secretion of growth hormone (GH) is greatest during stage-4 sleep, and it has been proposed that sleep disturbances (see below) are responsible for disruption of the normal growth hormone axis in FMS. This growth hormone-IgF-1 axis functions as an important anabolic stimulus for musculoskeletal tissues; low levels of IgF-1 have been suggested to be a result of HPA axis dysfunction (18). A deficit of stage-4 sleep-dependent release of GH, with subsequent depressed levels of somatomedin C, prevents the proper repair of myoskeletal structures (19). Therefore, disrupted growth hormone production and function are likely also related to the diffuse muscle pain which is characteristic of P-FSs (20).

Widespread degeneration and disintegration of myofibrils and myofilaments, plus structurally abnormal mitochondria, are found in the muscles of individuals with endemic fluorosis (21). Furthermore, a number of studies have found muscle abnormalities in persons with CFS and FMS. Some pertinent clinical findings have included abnormal mitochondria, "moth-eaten" type I fibers, ragged red fibers, low ATP at tender points, low oxidative enzymes, low tissue pO_2, low pH, metachromatic substance in intrafibrillar tissue, spontaneous EMG activity at tender points, lower capillary density, mucoid substance and giant myofilaments, and type II fiber atrophy (22). Each finding can be caused by the pathological effects of MDFE.

The strong probability that any peripherally-generated pain impulses, no matter what the cause, may also be "amplified" by CNS dysfunction cannot be ignored. (See "Cognitive Difficulties" below.) This sensory amplification process no doubt can affect all senses: sight, hearing, taste, touch, smell–resulting in variable sensory system dysfunctions characterized by chronic hypersensitivities (or perhaps hyposensitivities or variable hyper- and hyposensitivities in some cases) to nearly all external and internal stimuli.

Headaches

Headaches in P-FSs may, of course, be caused by the same factors which produce musculoskeletal pain. Areas with distinct mineralization of collagenous fibers inserting into the skull surface bone have been found in patients with industrial fluorosis (5). The head and neck exhibit a highly developed system of muscles, tendons, and ligaments which are all extremely vulnerable to the pathological effects of MDFE.

In addition, a large number of clinical and experimental studies has established the role of Mg in the pathogenesis of migraine headaches. The concentration of Mg in the CNS affects serotonin receptors, nitric oxide synthesis and release, NMDA receptors, and other migraine related receptors as well as neurotransmitters. Mg deficiency may also contribute to the cerebral vasospasm of some patients with migraine headache. One study found a significantly greater deficit of erythrocyte Mg in migraine patients than in controls (23). "The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionized magnesium" (24). In 1974, a double-blind test found that some individuals developed migraine-like headaches, visual disturbances, and depression with a daily intake of only 1 mg F^- (25); although it was not measured, it is likely that these particular individuals also had very low levels of bioavailable Mg.

Severe eye-area pain is a common feature of headaches in P-FSs. "Extraocular muscles differ from other skeletal muscle and are especially affected by [cholinergic] agonists. Mixed among the ordinary striated muscle cells are bands of unique muscle cells, tonic fibers, that have several neuromuscular junctions per cell and a total sarcolemmal surface that is chemically sensitive. They are driven to prolonged slow but strong contractures that shorten the muscle and compress the eye" (26). These contractures can produce intense pain.

Gastrointestinal Disturbances

Persons with endemic fluorosis commonly experience gastrointestinal symptoms, most frequently abdominal pain. Histological findings of the gastroduodenal mucosa have included loss of microvilli, a cracked-clay appearance, and the presence of surface abrasions on the mucosal cells (27). A randomized double blind study investigated the response of gastric mucosa to 7 days exposure to sodium fluoride (NaF) and sodium monofluorophosphate (MFP) tablets in healthy male volunteers. No severe gastric lesions were observed in the MFP group, but 70% of the NaF group exhibited significant gastric mucosal lesions. These included acute hemorrhages and free blood in the gastric lumen (28).

Primary irritable bowel syndrome (IBS) and fibromyalgia frequently coexist; patients with fibromyalgia have a high prevalence of gastrointestinal complaints, and "there may be a common pathogenic mechanism for both conditions" (29). The effects of dysregulated ACh on peristalsis is one likely contributing factor to gastrointestinal disturbances. Fluoride's toxic effect on the epithelium and endothelium may also result in leaky gut syndrome and chronic malabsorption conditions which may unfortunately contribute to a patient's impaired nutritional status. Esophageal reflux, an additional common gastrointestinal problem, is hypothesized here to have the same underlying

cause as mitral valve prolapse: MDFE's pathophysiological effect on connective tissues which can cause functional as well as morphological changes.

Cognitive Difficulties

When trying to describe their memory problems, many individuals diagnosed with CFS, FMS, and PGS remark that they feel as if they are developing Alzheimer's disease (AD). This self-appraisal may, in fact, be quite insightful since it is generally accepted that one early and consistent feature of Alzheimer's disease is degeneration of cholinergic projections from the basal forebrain to the neocortex and hippocampus. "Compelling evidence indicates that oxidative stress, mitochondrial dysfunction and perturbed subcellular calcium homeostasis play pivotal roles in the neuronal death process in AD" (30). The three factors just mentioned are counted among the many toxic effects of fluoride, although fluoride's possible role in the pathogenesis of AD seems not to have been investigated.

Magnesium appears to play an important regulatory role in the gating of excitatory amino acid neurotransmitter channels within the brain; a reduction of brain Mg may decrease the Mg blockade of the N-methyl-D-aspartate (NMDA) receptor, increasing neuronal excitability and cell permeability for calcium ions (which can induce seizures) that, in turn, plays a crucial role in the pathogenesis of brain damage (31). Alterations in intracellular Mg could produce secondary brain injury through such possible mechanisms as alterations in calcium influx or edema formation, impairment of glucose utilization and energy metabolism, or alterations in DNA and protein synthesis (10).

Therefore, the striking similarity of memory deficits in people with early AD and those with P-FSs is intriguing and bears further study. The active neuronal uptake of choline, present in blood from the diet and in the synaptic cleft following the *normal* hydrolysis of released ACh, is considered a limiting step for the synthesis of new ACh. The brain phospholipid metabolism for the generation of choline may be very important, "because under certain stress circumstances, the maintenance of choline levels may require "autocannibalism" of cholinergic neurons" (32). Since fluoride disrupts the enzymatic degradation of ACh, and also inhibits phospholipid metabolism, it would be interesting to investigate whether this proposed autocannibalism process also contributes to significant neuronal losses and subsequent memory deficits exhibited by *both* AD and P-FSs patients.

It is also interesting that chronic P-FS patients often report more severe cognitive and emotional problems the day or two after they engage in significant physical activity. Since significant physical activity is a stressor which contributes to the loss of Mg which may not be quickly or adequately replenished, reports of increased cognitive and emotional problems occurring after physical exercise are not surprising. In addition, particularly in patients for whom muscle pain is a primary symptom, physical exercise leads to increased pain and distress during the few days after the exercise. Again, increased Mg loss from exercise stress plus increased F^- bioavailability is hypothesized here to be the cause of both post-exercise exacerbations.

Fluoride has the ability to enter the brain under normal circumstances and affect its function; the blood-brain barrier is unable to exclude the fluoride ion from entering nerve tissue and fluoride accumulates in brain tissues (33). In a literature review exploring the possibility that fluoride causes cerebral impairment (34), the author summarizes: "The difficulties with concentration and memory described in relation to exposure to fluoride did not occur in isolation but were accompanied by other symptoms of which general malaise and fatigue were central. Other symptoms included those involving joints, the gastrointestinal system, the urinary tract, peripheral nerves and muscles." The author concludes by saying, "There would appear to be some evidence that chronic exposure to fluoride may be associated with cerebral impairment affecting particularly concentration and memory in some individuals. These symptoms are reminiscent of those seen in the chronic fatigue syndrome."

In addition, cholinergic agonists and antagonists affect the levels and turnover of other neurotransmitters as well, including catecholamines, indole amines, and amino acids (32). Important central cholinergic pathways emanate from the medial forebrain cholinergic systems and radiate to the limbic system, cortex, and the hypothalamus. Serotonin dysregulation, for example, has been proposed to play a role in the abnormal HPA axis profiles seen in patients with CFS (35). Low rates of turnover of three neurotransmitters–serotonin, norepinephrine, and dopamine–based on measurements of cerebrospinal fluid (CSF) metabolite levels, have been found in persons with FMS (36). As previously mentioned, the serious disruption in ACh and AChE functions induced by MDFE likely has a significant negative impact on the normal functioning of many additional neurotransmitter systems and cognitive functions, although the precise mechanisms involved have yet to be delineated.

Furthermore, stress makes the blood-brain barrier more permeable to substances such as toxins, drugs, peripheral neurotransmitters, and viruses that are ordinarily excluded. Stress-induced breakdown of the blood-brain barrier may allow high levels of F^- to enter the CNS. For example, stress intensifies AChE inhibition by pyridostigmine bromide (PD) because of increased brain penetration of PD (a "reversible" anti-ChE drug provided to Gulf War soldiers as a prophylactic against nerve gas exposure); soldiers taking the drug experienced a three-fold increase in symptoms related to CNS functions relative to documented symptoms produced in young, healthy volunteers during peacetime. These acute symptoms included headaches, insomnia, drowsi-

ness, nervousness, difficulties in focusing attention, and impaired circulation capacities (37).

In brief, the access of any anti-ChE compound (including fluoride) to the brain of a stressed individual adds even more "stress like" symptoms, resulting in a vicious cycle of ever-increasing stress and ever-increasing brain penetration of aversive substances which affect cognitive performance to varying degrees. The hippocampal formation, for example, contains high levels of adrenal steroid receptors and is especially sensitive and vulnerable to the effects of stress (38).

Altered Emotional States

". . . it is now abundantly clear that any reasonable understanding of chronic fatigue syndrome must grapple directly with the issue of illness comorbidity, particularly with respect to psychiatric disease, and the role of stress in its onset and course" (35). Increased ACh levels in the central nervous system cause depressive symptoms, and are consistently associated with exaggerated effects of ACh on parasympathetic ganglionic affector sites (pupil constriction, alimentary canal smooth muscle contraction, bronchiole constriction, heart rate, increased glandular secretion except sweat glands) in persons with affective disorders (39). Cholinergic agonists and anticholinesterase agents also induce psychomotor retardation; this can include fatigue, lack of thoughts, and lethargy. Centrally acting cholinomimetic agents release the corticotrophin releasing factor and elevate serum ACTH and cortisol levels, reflecting transient increases in HPA axis activity. Indeed, most of the systemic manifestations of stress in general (behavioral, cardiovascular, and neuroendocrine) are replicated by central cholinergic activation. It is important to remember here that chronic hyperactivation of ACh receptors both in the peripheral and central nervous systems can eventually result in receptor down-regulation.

"Mild Mg deficiency appears to be common among patients with disorders considered functional or neurotic and appears to contribute to a symptom complex that includes asthenia, sleep disorders, irritability, hyperarousal, spasm of striated and smooth muscle and hyperventilation" (40). It is posited here that "primary" affective disorders such as anxiety and depression, particularly when associated with somatic complaints, may be early, or perhaps not-so-early, warning signals of MDFE–indeed, affective disorders which are not attributable to another known cause may well be among the very first symptoms of MDFE. Because the CNS is particularly vulnerable to the effects of MDFE, and females are particularly vulnerable to the effects of MDFE (further discussed later); these two simple facts may account for the observation that women are over-represented not only in P-FSs, but also as seekers and utilizers of mental health services. The incidence of depression is

on the rise in the U.S., as is the incidence of chronic P-FSs–this parallel increase may reflect a common underlying etiology.

Sleep Disturbances

"Disturbances in the sleeping-waking brain with accompanying alterations in the chronobiology of neuroendocrine, immune and thermal regulatory systems may be involved in the pathogenesis of fibromyalgia and CFS" (41). Pathological "alpha-delta" sleep patterns, accompanied by superficial and fragmented sleep with increased awakenings and reduced REM and slow wave sleep, are found in patients with FMS (42).

In rats subjected to a Mg-deficient diet, the animals exhibited skin vasodilation, red conjunctiva, erected hair, hyperexcitability, and aggressiveness. Their sleep-wakefulness cycle was disrupted, and consisted of an increase in wakefulness at the expense of both SWS (slow-wave sleep) and PS (paradoxical sleep). After 6-7 weeks of the Mg-deficient diet, the sleep effects were even more profound, with an average 50% increase in wakefulness and a significant decrease in SWS of about 25%; this effect was attributed to excessive activation of excitatory amino acids caused by Mg-deficiency. Eventually, PS stabilized, and was surprisingly less affected compared to SWS. The rats also showed important oscillations in SWS state with frequent periods of wakefulness. All these disordered sleep-wake phenomena disappeared about 2-4 weeks after a return to a normal, Mg-sufficient diet (31).

The brainstem sends cholinergic fibers to the midbrain and thalamus, and this system is related to sleep-wake rhythms. Slow-wave sleep requires low ACh concentrations in the brain, and rapid-eye-movement sleep (REM) is associated with high levels of ACh. Phases of sleep are also differentially sensitive to a number of endogenous neuropeptides and cytokines (43). Cholinergic neurons, by interacting with other cell groups, including monoaminergic and GABAergic neurons, and by differential modes of firing, "may shape the responsiveness and activity of the reticular core and thalamo-cortical systems across the sleep-waking cycle" (44). Corticostatin, a neuropeptide which regulates cortical activity, when administered into rat brain ventricles specifically enhances slow-wave sleep, apparently by antagonizing the effects of ACh on cortical excitability (45). Extracellular ACh concentrations in the rat thalamus are high during both wakefulness and REM sleep, but are significantly lower during slow-wave sleep (46).

The fundamental rhythmicity of central cholinergic neuron bursting activity is perhaps at least partially responsible for the maintenance of normal circadian rhythms and normal sleep patterns; this rhythmicity may be disrupted by AChE inhibition and subsequent ACh accumulation in the synapse.

As with nearly all the other major symptoms of P-FSs, sleep disorders reflect a "circular causality" or "vicious cycle" model of pathology. That is,

MDFE is theorized here to cause severe sleep disturbances and disordered circadian rhythms, and these disturbances in turn cause further neurochemical disruptions which directly and indirectly contribute to the overall high level of illness-related stress and system-wide pathologies. These pathologies lead to greater deficits of Mg, which enhances the toxicity of F^-, which increases sleep disturbances and disordered circadian rhythms. Normal, refreshing sleep is believed to be vital for the maintenance of health; sleep disorders in P-FSs no doubt contribute significantly to the extreme ill-health of affected individuals.

Altered Immune System Function

It has been suggested that immune activation could precipitate and/or perpetuate the neuroendocrine abnormalities in patients with CFS and FMS (35). When plasma Mg is markedly reduced in rats, one of the earliest molecular markers of the pathophysiological process is elevation of plasma substance P (SP), calcitonin gene related peptide and prostaglandin E2, followed by histamine and the inflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor-α). [Note that CSF levels of substance P are three times normal in FMS patients (48).] Leucocyte subpopulation pools increase progressively. Mg-deficiency induced SP also affects T lymphocyte regulation and influences their secretion of immunoregulatory cytokines. These changes in cytokine production and release have been hypothesized to have a progressive effect on different components of the immune system (47).

Thus, Mg deficiency induces an acute-phase inflammatory response that is followed by a chronic-phase inflammation. "The major components of an inflammatory process are a rise in circulating polymorphonuclear leucocytes, intravascular stimulation of platelets and endothelial cells, and a cascade of adhesive events involving several adhesion molecules. These pathophysiological events, which are mediated by substance P, modulate the vasodilatory response, and the leakage of plasma into the surrounding tissue" (49).

Therefore, SP elevation is believed to be the initial trigger which stimulates a number of host defense systems: macrophages which produce inflammatory cytokines, mast cells which release histamine, and free radical production in many different types of cells such as endothelial cells and circulating white blood cells, including cells in the CNS, from pathologically-increased protein oxidation and lipid peroxidation, for example (50). "Protein peroxidations are probably implicated in fibromyalgia physiopathological events" (51).

Although mammalian tissues contain numerous defenses against oxidative stress, some of these have been shown to be compromised during Mg deficiency (52). Glutathione, for example, detoxifies free radicals and lipid peroxides; the level of glutathione in red blood cells (RBCs) of rats is significantly reduced after 2-3 weeks on a Mg-deficient diet. Decreased levels of ascorbate in the liver, brain, and other tissues has also been found in Mg deficiency; since ascorbate regenerates reduced vitamin E from oxidized vitamin E, its loss would lead to vitamin E deficiency as well. Protein oxidation and lipid peroxidation products accumulate in Mg deficiency; protein-carbonyls, for example, accumulate in the kidney and brain (52). Thus, chronic free radical damage to cells and organ systems may be profound in persons with MDFE; the brain is especially sensitive to oxygen radicals.

Frequent infections often plague patients with P-FSs. Among Mg-dependent functions of immune cells are binding of IgM to lymphocyte cell membranes, aggregation of macrophages by lymphokines, antigen-induced adherence of helper T cells to B cells, and binding of antigen to macrophage RNA. All four of these functions are important in immune regulation, and the last two are particularly important for the processing of immunologic information (53). In addition, "intracellular synthesis, transport and subsequent membrane insertion or release of receptors important for immunoregulation require high energy phosphate compounds and are sensitive to disturbances in intracellular energy levels" (54).

It is possible that persons with P-FSs caused by MDFE may experience frequent and possibly severe infections caused by fluoride-resistant pathogens, or pathogens which do not require significant levels of Mg. Conversely, fluoride-sensitive or high-Mg requiring pathogens may be less likely to cause infection; however, some pathogens (especially viruses) may develop a certain immunity to fluoride in human hosts having high levels of bioavailable fluoride. An intriguing theory about the generation of variant viruses suggests that "debilitated cellular and humoral immune responses due to trace element deficiencies may impair virus clearance in infected organisms, which favors the generation of virus variants with altered biological properties" (55). Increased mutagenesis triggered by oxidative stress, especially in RNA viruses with genetic plasticity, could be a major force in the emergence of new viral pathogens, some of which may well develop considerable fluoride resistance.

Mitral Valve Prolapse

Mg-deficiency has been proposed as a significant (perhaps the most important) cause of primary mitral valve prolapse (MVP) (56). Many patients with heavily symptomatic MVP have low serum Mg, and Mg supplementation leads to symptom improvement (decreased weakness, chest pain, dyspnea, palpitations, and anxiety) and decreased catecholamine excretion.

The pathological effects of MDFE can lead to morphological and functional changes of the mitral valve, only one of many collagen and connective tissue aberrations which are widespread in P-FSs.

Interstitial Cystitis (IC)

Since fluoride is eliminated through the kidneys and will accumulate in the bladder before voiding, it is likely that the toxic effects of MDFE on bladder cells account for all related IC symptoms such as urinary frequency, nocturia, and suprapubic pain on bladder filling. Substance P has been implicated in the pathogenesis of IC, since it triggers mast cell secretion (57). Histological findings in IC include increased mast cell infiltration of the bladder wall, and urothelium that is thin, easily detached, and almost absent in many areas. Also observed is a generalized pancystitis with infiltration of the lamina propria by mononuclear and chronic inflammatory cells. This defective bladder epithelium causes loss of the "blood-urine" barrier, resulting in a leaky membrane permeable to small (and often toxic) molecules. Acute stress causes flare-ups of IC symptoms.

This inflammatory bladder disease, when diagnosed as primary, is most commonly seen in women 30 to 70 years of age; IC has a female-male ratio of about 9:1. "[Primary] IC and fibromyalgia have significant overlap in symptomatology, and IC patients display diffusely increased peripheral nociception, as is seen in fibromyalgia" (58).

Unusual Reactions to Medications

Dysfunction of or a significant decrease in Mg-dependent and microelement-dependent enzymes responsible for the normal breakdown and elimination of foreign chemical compounds such as drugs and toxins could easily account for at least a portion of many abnormal responses to medications in persons with P-FSs. Mg-deficient rats have been shown to have markedly lower in vivo and in vitro rates of hepatic drug metabolism (59). "It is possible that impaired porphyrin metabolism reduces the amount of heme available for cytochrome P450, part of the liver's major detoxification system for foreign chemicals, which could result in intensified symptoms for a wide range of exposures" (60). It has also been found that "many people who exhibit environmental intolerances or chronic disease have impaired sulfation of phenolic xenobiotics" (61).

FMS and CFS often involve multiple chemical sensitivities (MCS); it is now thought by some researchers that MCS may be the same disorder (62), since people with chemical sensitivities often also report headaches, chronic fatigue, musculoskeletal aching, chronic respiratory inflammation, attention deficit, and hyperactivity (in younger children). They may also have tremors, seizures, and mitral valve prolapse (60). "In general, demographic and clinical factors and health locus of control do not clearly distinguish patients with CFS, FMS, and MCS. Symptoms typical of each disorder are prevalent in the other two conditions" (62).

Patients with MCS demonstrate many physiological and biochemical abnormalities and are usually sicker than control groups of allergic patients. MCS is often associated with mitral valve prolapse, hypothyroidism, autoimmune thyroiditis, and specific abnormalities of amino acid and essential fatty acid metabolism. MCS patients and controls (allergic patients) demonstrate an equal prevalence of magnesium and vitamin B_6 deficiencies. "It is possible that these various abnormalities are caused by some unidentified fundamental metabolic or neuroendocrine disturbance that is common to states of hypersensitivity. Anti-oxidant deficiencies may certainly contribute to hypersensitivity to environmental pollutants and toxic chemicals" (63). Clinicians report increasing numbers of patients with multiorgan symptoms which allegedly result from exposure to environmental chemicals; these symptoms include profound fatigue, mental confusion, myalgia, depression, anxiety, dizziness, headache, insomnia, loss of appetite, and numbness of the extremities. Objective findings are almost always absent or inconclusive (64).

The enzyme dysfunctions, free radical damage, and cellular and organ system damage caused by MDFE can easily magnify responses to chemical exposures which usually do not immediately affect others adversely. Impaired detoxification and elimination of myriad natural and manufactured toxins as well as pathogens constitute yet another vicious cycle element in P-FSs; increasing body loads of foreign substances become another stressor which increases the loss of Mg, and increased Mg loss further compromises the body's ability to effectively deal with all toxic or pathogenic substances.

Light Sensitivity/Vision Problems

The human retina is capable of synthesizing and releasing ACh (65); thus there is evidence for cholinergic neurotransmission. Again, AChE inhibition leads to the accumulation of ACh which, in the retina, may directly affect vision. As mentioned, CNS "amplification" of sensory signals could easily cause light sensitivity. Signal processing may also be fundamentally disrupted by MDFE in the CNS.

Note that senile and pre-senile macular degeneration (age-related cellular degeneration of unknown cause in the macular region of the retina) is also more common in women than in men (66). Macular degeneration is the leading cause of visual impairment in persons over age 50.

Shortness of Breath

The pathophysiological effects of MDFE can increase bronchial secretions, affect muscle contractions (including those of the diaphragm), cause sympathetic stimulation of smooth muscle, and induce metabolic acidosis. Each of these toxic effects either alone or in combination may produce sensations of shortness of breath.

In addition, magnesium deficiency has been implicated in the etiology of asthma. Oral and intravenous Mg therapy has been used with some success in both the prevention and treatment of asthma (67-69).

Hypoglycemia

As discussed in Part I, fluoride exerts an inhibitory effect on a number of enzymes, including esterases, asymmetrical hydrolases, and phosphatases. Fluoride has also been shown to inhibit the tyrosine kinase activity of insulin receptors; tyrosine kinase activity is essential for certain normal cellular responses to insulin, and the tyrosine kinase activity of insulin receptors shows a strict requirement for Mg^{2+} ions. Impaired glucose tolerance is a common finding in patients with endemic fluorosis, which is reversible upon removal of exposure to fluoride (70).

The tyrosine phosphotransferase function of the insulin receptor is an absolute requirement for the hormone to activate the receptor signalling function in cells. Fluoride inhibits the phosphotransferase catalysis by interacting directly with the insulin receptor as a Mg^{2+}-F^- complex, behaving as a slow-binding inhibitor of the insulin-receptor kinase activity. The insulin receptor becomes sensitive to fluoride action only when it has bound to Mg; binding of Mg to a saturable site of the insulin receptor is required for inhibition, but the precise mechanism by which fluoride inhibits the Mg-insulin receptor complex remains unknown (71,72).

The body may compensate for this inhibitory effect on insulin receptors (which may functionally mimic a diabetic state) by hyper-producing insulin, subsequently causing hypoglycemia. Hypoglycemia alone can cause weakness, tremors, muscle twitching, nausea, vomiting, facial pallor, palpitations, and an increased respiratory rate.

Restless Legs

This phenomenon is characterized by severe but difficult to describe dysesthesias felt deep within the lower extremities, often associated with jerking and twitching muscles. These sensations are accompanied by an irresistable urge to move the legs. Symptoms frequently occur at night, or after the limbs have been at rest for a period of time; restless legs can interfere greatly with sleep (73).

One study of a female patient found electromyographic (EMG) and muscle biopsy abnormalities, and a strikingly high level of both Ca and Mg in the CSF; although no explanation was given for these high levels, it is possible that CNS stores of Ca and Mg were being mobilized and transported to the Ca/Mg-deficient periphery. Interestingly, this patient demonstrated a complete absence of leg muscle twitches during delta (slow wave) sleep (73).

Another study of ten patients with "restless legs syndrome" demonstrated neuromuscular hyperexcitability and some signs of neuropathy. Sleep was disordered, with agitated sleep with frequent periods of awakening though the night and a concomitant decrease in the duration and percentage of deep slow wave sleep. Magnesium deficiency was hypothesized to be the cause (74).

OBSERVATION #2: IT AFFECTS CHILDREN AS WELL AS ADULTS, BUT RARELY AFFECTS CHILDREN UNDER THE AGE OF FIVE

MDFE can occur at any age, but may *appear* to be rare in very young children. There are two possible explanations for this phenomenon: (a) Fluoride accumulates in both hard and soft tissues over time; young children have not lived long enough for marginally-toxic levels to accumulate. Exceptions to this generalization would be children who have been exposed to relatively high levels of fluoride via, for example, general anesthetics, fluorinated pharmaceuticals, environmental contamination, or ingested fluoridated toothpaste. It should be noted that neonates are very sensitive to the effects of toxic elements, since the neonatal period is characterized by higher absorption rates and enhanced interactions between toxic and essential elements (75). Fluorides can be passed to nursing babies through breast milk. (b) Very young children simply lack the vocabulary and cognitive ability to describe distressing symptoms, and also lack the personal experience which would help them distinguish between good health and ill health. Since adults are diagnosed with a P-FS primarily on the basis of verbally-reported subjective symptoms, young children may lack the capacity to describe in sufficient detail their distressing and baffling physical and emotional feelings.

"Growing pains" is a dismissive term long used to describe children's uncomfortable and painful sensations in the legs and arms; note that these sensations are often associated with headaches, stomach aches, sleep disturbances, and chronic illnesses of varying types. "Idiopathic musculoskeletal pain is a common cause of referral to a pediatric rheumatology clinic and is often associated with significant morbidity" (76). One study found a prevalence rate of 11.4% in a sample of 1807 normal children, as reported by their parents via questionnaire (77). The pain reported in this sample was usually in the lower limbs; more specifically, pain was usually bilateral and reported as being in the calf, knee, thigh, ankle, foot, arm, groin, and hand. The children variously described the pain as being throbbing (19%), dull (16%), sharp (14%), burning (5%), or tingling (3%). Over half of the children also complained of feeling restless, fatigued, weak, and stiff. Twenty-five percent of the children reported that the pain woke them up at night, and in 22% the pain seemed to begin after exercise. Over half the affected children experienced pain during the day as well as at night. Teachers reported that children with growing pains were more anxious and fearful than other children.

It appears that girls report growing pains more than boys, and there seems to be a bimodal age distribution of symptoms which peak from three to nine years of age, and again in early adolescence. (These peaks may well correspond to periods of rapid bone growth, hence rapid uptake of F^- by bone–forming fluorapatite–with resultant hypomagnesemia and hypocalcemia.) Growing pains are often intense, and folklore suggests that they occur most frequently at night (bone remodeling is active at night). Parents notice periods of irritability during the day and crying at night which correspond to the times their children experience growing pains (78).

It is proposed here that growing pains may well be an early manifestation of MDFE; if so, prompt intervention to prevent chronic problems is required. "The presence of growing pains might be a marker for more widespread dysfunction and might provide health professionals with an opportunity for timely and effective intervention for children in their family context" (77).

OBSERVATION #3: IT AFFECTS WOMEN MORE THAN MEN

Wide gender differences in the apparent prevalence rates of P-FSs have baffled patients and researchers alike. It has been estimated that FMS and CFS are 3-9 times more prevalent in women than men (the gender prevalence rates are sometimes more equal in epidemic or "cluster" cases of acute onset); even the prevalence rate of PGS is higher in women than men (79). Population-based studies of FMS suggest prevalence rates that fall between 0.7% and 13% in adult women, and between 0.2% and 3.9% in adult men (80).

It has been demonstrated in more than one species (rats, birds, and humans) that females store more F^- in bone and other calcified tissues than do males under identical environmental circumstances (81-84). It is hypothesized here that the increased rate and level of F^- sequestration in female bone may reflect an adaptive mechanism to protect a developing fetus from toxic levels of F^-. "Limitations on the supply of fluoride to the fetus probably reflect the ability of the maternal skeleton and kidneys to remove the bulk of an administered fluoride dose very rapidly, rather than suggesting the presence of an active placental barrier to fluoride transfer" (85).

In addition, F^- is also readily stored in lipids in both sexes; as previously mentioned, the central nervous system contains an unusually high proportion of lipids and is seriously affected in P-FSs, resulting in, for example, significant cognitive and emotional dysfunctions. Not only do human females often have a greater proportion of body-wide lipids than do males per any given body weight and mass, but these lipids are also more widely and evenly distributed throughout the female anatomy (86).

Thus, the reasons for the wide gender differences in P-FSs may be quite

simple: the two factors of faster and higher levels of bone and lipid storage of F^- provide human females with significantly more bioavailable fluoride throughout their entire systems at any given time; this difference may become even more pronounced around menopause, when estrogen levels drop and more F^- is released into the bloodstream during increased bone resorption processes. Estrogen is a Mg-sparing hormone; thus it is not surprising that the onset of FMS, or more severe symptomatology of existing FMS, often correlates with the onset of menopause (87), and that symptom exacerbations in younger women are frequently correlated with periods of lower estrogen levels which occur at certain predictable times during the menstrual cycle. Estrogen also inhibits bone resorption; less inhibited bone resorption may release a greater amount of F^- into the bloodstream. Many female patients (and some clinicians) have long suspected a "hormone connection" in FMS and CFS; at least part of this connection may simply be estrogen's ability to conserve bioavailable Mg in various ways.

In addition, a study of the neurobehavioral effects of NaF in rats found that hippocampal fluoride levels significantly increased and behavior was significantly affected in adult females; adult males receiving identical fluoride exposure did not have significantly elevated fluoride levels in the hippocampus, nor did they exhibit significant behavioral disturbances (33). Broader findings of this study, with perhaps additional significant implications for humans, indicated that male rats were most sensitive to prenatal fluoride exposure, whereas females were more sensitive to weanling and adult fluoride exposures.

Furthermore, significant gender differences in the stress response are apparent in both laboratory animals and humans, with females showing consistently greater responses. These responses include higher corticosterone and ACTH levels, greater functional activity of the HPA axis, higher plasma vasopressin levels, and greater release of posterior pituitary hormone, oxytocin, and prolactin (88). Again, centrally acting cholinomimetic agents release the corticotrophin releasing factor and elevate serum ACTH and cortisol levels, reflecting transient increases in HPA axis activity. It is possible that the greater bioavailability of F^- in females contributes to a greater stress response than is seen in males. Furthermore, a greater physiological response to stress in females certainly contributes to greater losses of Mg. More research is needed to fully elucidate the underlying cause(s) and effects of significant gender differences in the neuroendocrine response during stress in humans.

OBSERVATION #4: IT CAUSES BOTH EPIDEMICS AND SPORADIC CASES

It is hypothesized here that an epidemic of P-FSs can follow an outbreak of a communicable illness, volcanic eruption, new F^- emitting industrial

activity, or any other situation which exposes people within a certain geographic boundary to significant levels of F^- and/or lowers bioavailable levels of Mg. Many "outbreaks" of P-FSs have occurred in clusters of people living or working fairly closely together, such as in a boarding school, hospital, or convent (89). Such populations could be (or could have been) exposed, for example, to locally-used fluoride-containing pesticides, rodenticides, or antiseptics, or fluoride-containing coal smoke from heating and cooking activities. In addition, such close-living groups (or communities) often experience outbreaks of communicable illnesses; Mg loss during illness has long been recognized. Should groups of affected individuals living or working together also share similar or identical meals, a diet deficient in Mg will contribute to symptomatology. Community access (or lack of access) to Mg-containing foods may be a major contributory factor. "When a disease outbreak of unknown etiology occurs, tissue element levels may be useful in determining whether a deficiency or toxicity of some element may be involved" (75).

A "mini-epidemic" of a P-FS within one family is not uncommon; geographically-close family members may share common dietary patterns, culinary water, air, levels of physical activity, communicable illnesses, and are significantly affected by each other's "life stresses." Each of these factors can contribute either to lowered bioavailable Mg and raised bioavailable F^-, or both.

Sporadic cases (isolated individual cases) are obviously equally likely with MDFE.

OBSERVATION #5: IT IS RARELY, IF EVER, FATAL

While it is true that the pain, fatigue, disrupted sleep, altered emotional states, and other unpleasant and even seriously disabling symptoms of MDFE are rarely fatal in and of themselves (the tragic exception being suicide), many of the deleterious long-term systemic effects can eventually prove fatal; therefore, cautious exception is taken to this observation. Any P-FS theoretically caused by MDFE is posited here to be much more serious than is commonly believed, and should be treated as a potentially life-threatening illness.

For example, if a patient who has been diagnosed with FMS, CFS, or PGS dies of a heart attack or stroke, infection, kidney failure, bleeding ulcer, or fall down a flight of stairs, the victim's P-FS will not be blamed. Rather, the specific cause of death might read "cardiovascular accident," "pneumonia," "renal failure," "duodenal hemorrhage," or "head trauma due to accidental fall." The proximate cause of death will appear on paper, although a specific

pathology due to chronic MDFE was very possibly the ultimate underlying cause of each fatality: MDFE causes cardiovascular system damage (aortic calcification (15), valvular disease, cardiomyopathy, thrombosis (high Ca/low Mg), cardiac lesions (47), fluctuating blood pressure), immune dysfunction as well as susceptibility to fluoride-resistant pathogens, kidney toxicity (90), erosion of gastrointestinal endothelium, and serious sensory, balance, and coordination problems which can lead to accidental death.

OBSERVATION #6: IT CAUSES IMMUNE SYSTEM DYSFUNCTION

See "Altered Immune System Function" above.

OBSERVATION #7: ONSET OF ITS SYMPTOMS MAY BE EITHER SUDDEN OR GRADUAL

A P-FS can have an acute onset, with patients experiencing noticeable symptoms occurring, for example, within a variable period of time after an illness, surgery, emotionally or physically stressful experience, fluoride-emitting volcanic activity, or trauma such as an automobile accident, e.g., increased rates of FMS have been found after cervical spine injury (91). For example, a study which analyzed findings in 18,495 Persian Gulf veterans found that in persons suspecting with PGS, symptom onset was often delayed "with two-thirds of symptoms not developing until after individuals returned from the Gulf War and 40% of symptoms having a latency period exceeding one year" (92). This finding led the researchers to conclude that toxic exposures were *less likely* to be responsible for symptom development; however, since toxic exposures are a chemical stressor which can certainly lower bioavailable Mg, and fluoride-containing toxins predictably raise bioavailable F^-, the theory of MDFE leads to the opposite conclusion. Any circumstance which acutely lowers bioavailable Mg and raises bioavailable F^- leads to systemic pathologies which in turn cause the further depletion of Mg and the eventual development of symptoms.

The ratio of Mg to F^- can drop precipitously over a very short time, from a few hours to a few days or weeks, producing a sudden onset of symptoms. Surgery is of particular significance, since the use of fluorinated general anesthetics increases exposure to F^- and the physical and emotional trauma of surgery decreases Mg. For example, a syndrome called "postcardiac injury rheumatism" (93), common after lengthy cardiac surgery, is proposed here to be yet another example of a P-FS caused by MDFE. Additionally, breast

augmentation/implantation surgery has been associated with the subsequent development of autoimmune and/or connective tissue disease (also known as "human adjuvant disease") with features strikingly similar or identical to those of CFS and FMS. However, breast surgery of any kind *per se* has been shown to be associated with an apparent increase in "muscular rheumatism" (94). Fluoride-emitting volcanic eruptions are also important in that significant amounts of F^- become available for inhalation, ingestion, and possibly absorption through the skin, and the emotional and physical stress of dealing with an eruption can reduce bioavailable Mg.

Patients often report the development of a P-FS after an illness such as the 'flu.' Acute febrile infections cause significant losses of body nutrients (including Mg) via the actions of proinflammatory cytokines; the multiple endocrine responses seen during acute infections are similar to, and actually typify, the endocrine responses seen during other forms of stress (95). Other circumstances which increase the body's requirements for essential nutrients include anxiety, pain, and physical trauma–therefore, it naturally follows that a person with a P-FS will have a significantly elevated (but unfortunately most often unmet) need for essential nutrients, including Mg. Any decrease in body nutrients during infection or stress is followed by an increase in the physiologic requirement for nutrients during the recovery phase; if the nutrients are not adequately and speedily replaced, chronic specific nutrient deficiencies, of Mg and microelements for example, may ensue. Therefore, a deficiency of Mg first initiated by, for example, an acute illness, psychological stressor, or injury can easily be sustained in a "vicious cycle" of pathology, resulting in serious chronic illness–particularly when a significant amount of bioavailable F^- is present.

Does stress "cause" P-FSs? To the extent that any kind of physical, emotional, or mental stress leads to the depletion of Mg, the belief that stress causes P-FSs may well be true for a particular individual–as far as it goes. This could account for anecdotal reports that some persons who are abused in childhood, who survive natural disasters, or who serve in wartime, for example, develop P-FSs. However, not all persons who are stressed, even those who are severely stressed over substantial periods of time, become chronically ill. Why? To produce a P-FS, the level of bioavailable Mg must drop to the point where significant dysfunction occurs; it is proposed here that *the bioavailable level of F^- will be the critical contributing factor* (second only to Mg intake) which determines this point.

When a P-FS develops gradually over time, it is hypothesized here that the Mg to F^- ratio slips ever lower over months or years which produces a slow onset of symptoms. These "non-specific" symptoms (such as headaches, muscle aches, sleep disorders, and gastrointestinal problems) are often dismissed as unimportant, or when the patient is older as natural consequences

of the aging process. Chronic stress, poor diet, psychological problems, and chronic illness or disability can all contribute to the relatively slow development of illness theoretically caused by MDFE. This development of an ever-decreasing ratio of Mg to F^- easily explains why a P-FS can develop *any time* after *any type* of physical, mental, or emotional stress, and also why a P-FS is a common "secondary" illness in persons with underlying chronic physical or emotional illnesses of varying types.

In brief, each scenario–sudden or gradual onset–appears to be equally likely, based on historical reports (see Observation #4). It has been suggested that those who have an acute onset (of CFS) may have a better prognosis than those with gradual onset.[96] This may reflect the fundamental difference between some acute and normally reversible episodes which only temporarily increase F^- and decrease Mg, and long-term circumstances which contribute to chronically increased F^- and decreased Mg. Since it has been proposed here that males excrete higher levels of F^- than females, and that females may lose more Mg because of greater stress responses, gender differences in acute/resolving vs. chronic P-FSs should be investigated.

OBSERVATION #8: THERE IS A SPECTRUM OF ILLNESS SEVERITY

There is a spectrum of illness severity which is apparent not only between individuals, but within the same individual over time. Variability in specific symptomatology or clinical signs is proposed here to primarily be a reflection of the particular levels of bioavailable Mg and F^- at any given time (and the complex interactions which may occur with changing ratios), as well as the effects of shifting compensatory mechanisms, both of which produce the fluctuating types and levels of symptoms and signs which have frustrated patients and researchers alike. Further complicating the picture, additional contributing factors will likely include the patient's gender, age, overall nutritional status, general level of health and physical fitness, pre-existing health conditions, and unavoidable lifestyle demands on specific physical and mental resources.

Although P-FSs are not considered by many clinicians to be "progressive" (implying non-reversible) illnesses, many patients report that various symptoms–particularly pain and cognitive problems–do increase in amount and severity over time, that new symptoms appear with the passage of time, and that overall disability worsens even with current treatment protocols. Indeed, it is common for patients to experience a progression in the severity of existing symptoms and the addition of many new symptoms over several months or years, until they reach a plateau of illness and disability which absolutely precludes most normal activities. This scenario is entirely predictable if one assumes ever-decreasing bioavailable levels of Mg and ever-in-

creasing bioavailable levels of F^-. With the eventual development of a "full-blown" constellation of severe symptoms due to chronic MDFE, many patients become unable to care for their families and homes, cannot engage in income-producing work, and cannot participate in even the mildest recreational activities. Depending upon the individual's circumstances, the development of a "full blown" state of illness may take only weeks or months, or may take several years.

It is important here to emphasize that the enormous, Mg-depleting stress caused by not only the symptoms of the P-FS itself but also the severe restriction of normal activities contributes significantly to the maintenance and exacerbation of both physical and emotional aspects of the illness, resulting in a true vicious cycle of pathology which, unless the underlying cause is treated or eliminated, becomes a lifelong situation.

OBSERVATION #9: [THE SYNDROMES] OCCUR MORE COMMONLY IN PATIENTS WITH A HISTORY OF ALLERGY AND/OR ASTHMA

Magnesium deficiency has been implicated in the etiology of asthma. In addition to the increased prevalence of P-FSs, asthma morbidity and mortality are on the rise (97). Oral and intravenous Mg therapy has been used with some success in both the prevention and treatment of asthma (67-69).

Note that "seventy-five percent of all adult hospital admissions for asthma are women" (98). There appears to be a relationship between menstrual cycle phases and asthma exacerbations in adult females; "asthma presentations are least frequent when serum estradiol levels are at a sustained peak. We observed a four-fold variation in asthma presentations during the perimenstrual interval, when serum estradiol levels decrease sharply after that prolonged peak" (98). Again, the influence of estrogens on both Mg status and F^- release from bone is hypothesized here to be a significant factor.

Therefore, two mechanisms may be at work regarding the observation that P-FS patients often have a history of allergy or asthma: (a) Allergy/asthma symptoms are a chronic physiological stressor which contributes to the increased excretion of Mg; (b) Allergy/asthma symptoms may be an early indicator of MDFE; dysregulatory effects on the immune system caused by Mg deficiency can result in allergic/asthmatic manifestations.

OBSERVATION #10: THERE IS AN INCREASED INCIDENCE OF [THE SYNDROMES] WITHIN FAMILIES

At least two explanations are possible: (a) Genetically-related family members may share underlying physiologic patterns of handling Mg and F^-;

(b) Family members (whether genetically related or not) share common dietary and physical activity patterns, "life stresses," and when geographically close share common levels of F^- exposure via, for example, water and air. Again, both probably work together.

In addition, ethnic differences have been found in the frequency distribution of serum cholinesterase activity (99); it is not unlikely that other ethnic, familial, and population differences will be found for the activity of other enzyme systems which may moderate some specific effects of MDFE.

SUGGESTED TREATMENT PROTOCOL AND PREVENTION STRATEGY

"The final assessment of the effects of any substance on man can be determined only by observations on man himself, and in making such observations, full consideration has to be given to the variations in the reactions of individuals and to the diverse effects of different environments" (100). Clinical trials can easily test the validity of this theory of MDFE by utilizing relatively long-term (at least several months' duration), carefully controlled, randomized, double-blind tests of the suggested treatment elements listed below with patients who have been diagnosed as having FMS, CFS, PGS, and other P-FSs.

Expensive, time-consuming, and (most particularly) invasive tests which attempt to determine patients' levels of bioavailable Mg and/or F^- at any given time are neither necessary nor advisable, since absolute values of each element can fluctuate significantly over even relatively short periods of time (creating baffling symptom fluctuations) and provide little useful information. However, regular urinalysis to detect the level of F^- may be of some clinical value in the absence of more effective, noninvasive strategies (101) to determine levels of fluoride accumulation and excretion in body fluids and tissues.

If the theory of MDFE is correct, any effective treatment protocol will necessarily include individually-tailored variations of the following components, all of which must probably be followed for the remainder of each patient's life after diagnosis:

(1) *Substantially increase bioavailable Mg.* Increasing daily intake of Mg to a level well above the recommended RDA may be accomplished via significant dietary changes and Mg supplementation. Intake between 500 mg and 1000 mg per day (or more) may be necessary. Use of alcoholic beverages may need to be significantly decreased or curtailed altogether to prevent excess excretion of Mg. Efforts to achieve optimal acid-base balance may be helpful.

(2) *Avoid exposure to all identifiable sources of fluoride.* These include

foods and beverages containing relatively high levels of fluoride (e.g. green/black teas; some mineral waters; several types of seafood, especially fish with bones and shrimp; gelatin; poultry skin; pesticide-contaminated produce; some beers and wines); water that is naturally or artificially fluoridated to any detectable level, *regardless of ppm*–1 ppm equals 1 mg/liter of water, and 1 mg/kg in food (102) (ingestion of distilled water, essentially fluoride-free, is advised); dentifrices containing fluoride (toothpastes, mouthwashes); fluorinated pharmaceuticals; fluorinated general anesthetics; contaminated air; fluoride-containing pesticides/rodenticides; and occupational exposure.

(3) *Optimize elimination of body stores of fluoride*. This may include maintaining a neutral or slightly alkaline urine and significantly increasing fluoride-free fluid intake. Prudent weight loss to reduce excess lipid stores may also be critical.

(4) *Counteract toxic effects of fluoride with easily-assimilated dietary supplements*. In addition to Mg, these include Ca, vitamin D, B-vitamins, trace minerals, and especially antioxidants such as vitamins A, C, and E. Lipoic acid, a water- and fat-soluble antioxidant long used in Europe, may be of significant value. Since estrogen is a Mg-sparing hormone, estrogen replacement therapy for peri- and post-menopausal patients might be considered as a possible therapeutic adjunct.

(5) *Manage pain aggressively to reduce stress*. Very strong prescription analgesics may temporarily be necessary, as OTC analgesics are most often completely ineffective against the severe bone and muscle pain of P-FSs. A comprehensive lifestyle stress-lowering or stress-management program may be of significant value.

(6) *Discontinue use of any medications which do not produce significant positive effects*. Unnecessary and marginally-effective medications will impede recovery and put additional strain on kidneys and liver.

(7) *Begin and maintain a regular exercise program, but only when symptoms of pain and fatigue significantly subside, to avoid further injury*. Regular aerobic and weight-bearing exercise is crucial to improving general physical and mental health, but more specifically to rebuilding and maintaining healthy muscle and bone previously damaged by MDFE. Any program of physical activity, however, must be very slowly and gradually introduced and must be accompanied by sufficient intakes of essential nutrients.

Components 1 and 2 are absolutely necessary according to the proposed theory, but any treatment protocol which includes *all* the above components will theoretically be much more effective than one which ignores one or more of components 3-7. Again, while clinical trials utilizing Mg therapy have been conducted previously with CFS and FMS patients (103-105), the levels of Mg that were employed are proposed here to have been insufficient (and fluoride was not considered as a factor), thus producing less than completely

successful results. The theory of illness causality proposed here, describing magnesium deficiency *plus* concomitant fluoride excess, indicates that a consistent and much higher intake of Mg as well as complete avoidance of F^- will be necessary to produce significant, perhaps complete, symptom relief, and must probably be maintained indefinitely.

The optimal levels or dosages of all elements involved in each treatment component, based on carefully-constructed patient profiles, will need to be determined. Identifiable general profiles of use to clinicians may include patients of similar age and gender, who share similar durations of disability, severity of symptoms, and specific pronounced organ system pathologies. Since, in general, body stores of F^- are greater with increasing age, it is hypothesized that comprehensive treatment will provide faster and significantly greater relief of symptoms in younger patients. The converse will likely be true; older patients may respond more slowly and modestly, even when strictly complying with treatment regimens.

It remains to be discovered which pathological effects of MDFE are completely reversible, and which, if any, may be irreversible; the vulnerable central nervous system is of particular concern. Again, the probabilities of reversible/irreversible effects are likely to primarily depend on each patient's past relative bioavailable levels of Mg and F^-, and the length of time over which pathology-producing levels were present.

If this theory of MDFE is correct, complete relief of all reversible symptoms will occur only when the patient's Mg levels are raised to and maintained in an optimal range, and fluoride stores decrease to the level where bioavailable fluoride levels are insufficient to produce any noticeable toxic effects (any level of fluoride is probably toxic to cells in its immediate environment, but extremely low levels may not produce symptoms). A complete recovery, if it is possible, may take years to achieve since F^- stored in hard tissues will be excreted relatively slowly during normal bone turnover processes; approximately 5-10% of adult bone is remodeled each year.

Fortunately, prevention of a chronic illness theoretically caused by MDFE is straightforward and achievable. Lifelong (from conception) optimal intake of Mg, and avoidance of F^- from all identifiable sources as much as possible [also from conception, since F^- passes through the placenta (106,107)] is theorized to prevent the development of a P-FS caused by MDFE.

CONCLUSION

It has been proposed here that many chronic Pain-Fatigue Syndromes (including CFS, FMS, and PGS) are caused by magnesium deficiency plus concomitant fluoride excess (MDFE), and that these chronic illnesses present a major and growing worldwide public health problem due to decreasing

intake of Mg and ever-increasing levels of exposure to fluoride compounds used in industry, agriculture, medicine, and household and personal hygiene products. It has been proposed that bioavailable F^- is the most critical factor, second only to Mg intake, which directly influences the bioavailability and function of Mg. It has also been proposed that the level of intake of Mg, by virtue of Mg's ability to "bind" excess fluoride into less soluble compounds, will directly influence many toxic effects of fluoride such as the disruption of key amino acids in protein systems.

Particularly (but not necessarily) under the conditions of feminine gender, physical and/or emotional stress, and low Ca and trace mineral intake, even very low levels of fluoride exposure when temporally paired with marginal to severe Mg deficiency, if unrecognized and untreated, are theorized here to cause gravely debilitating and ultimately life-threatening pathologies which involve every organ system. Evidence has been presented which strongly suggests that humans, particularly women and children, are much more susceptible to the toxic systemic effects of low levels of fluoride exposure (regardless of the source and method) than was previously believed, especially when significant Mg deficiency is present.

REFERENCES

1. Bell DS. *The Doctor's Guide to Chronic Fatigue Syndrome: Understanding, Treating, and Living with CFIDS.* New York: Addison-Wesley; 1995:201-202.

2. Martyn JA, White DA, Gronert GA, et al. Up- and Down-Regulation of Skeletal Muscle Acetylcholine Receptors. Effects on Neuromuscular Blockers. *Anesthesiology.* May 1992;76(5):822-843.

3. McIvor ME. Acute Fluoride Toxicity: Pathophysiology and Management. *Drug Saf.* 1990;5(2):79-85.

4. Kang HK, Bullman TA. Mortality Among U.S. Veterans of the Persian Gulf War. *N Engl J Med.* 1996;335:1498-1504.

5. Franke J. Ossifications and Calcifications of Muscle and Tendon Insertions in Human Industrial Fluorosis. In: Tsunoda H, Yu M-H eds. *Fluoride Research 1985.* Amsterdam: Elsevier; 1986:335-339. *Studies in Environmental Science*; vol. 27.

6. Anand JK, Roberts JT. Chronic Fluoride Poisoning in Man: A Review of the Literature in English (1946-1989) and Indications for Research. *Biomed Pharmacother.* 1990;44:417-420.

7. Krishnamachari, KAVR. Skeletal Fluorosis in Humans: A Review of Recent Progress in the Understanding of the Disease. *Prog Food Nutr Sci.* 1986;10:279-314.

8. Sprott H, Muller A, Heine H. Collagen Crosslinks in Fibromyalgia. *Arthritis Rheum.* August 1997;40(8):1450-1454.

9. Sharma YD. Effect of Sodium Fluoride on Collagen Cross-Link Precursors. *Toxicol Lett.* 1982:10(1):97-100.

10. Morris ME. Brain and CSF Magnesium Concentrations During Magnesium Deficit in Animals and Humans: Neurological Symptoms. *Magnes Res.* 1992;5(4): 303-313.

11. Dure-Smith BA, Farley SM, Linkhart SG, et al. Calcium Deficiency in Fluoride-Treated Osteoporotic Patients Despite Calcium Supplementation. *J Clin Endocrinol Metab.* January 1996;81(1):269-275.

12. Kleerekoper M, Peterson E, Nelson DA. A Randomized Trial of Sodium Fluoride as a Treatment for Postmenopausal Osteoporosis. *Osteoporos Int.* 1991;1:155-162.

13. Riggs BL, Hodgson SF, O'Fallon WM. Effect of Fluoride Treatment on the Fracture Rate in Postmenopausal Women with Osteoporosis. *N Engl J Med.* 1990; 322:802-809.

14. Abraham GE, Grewal H. A Total Dietary Program Emphasizing Magnesium Instead of Calcium. Effect on the Mineral Density of Calcaneous Bone in Postmenopausal Women on Hormonal Therapy. *J Reprod Med.* 1990;35(5):503-507.

15. Susheela AK, Kharb P. Aortic Calcification in Chronic Fluoride Poisoning: Biochemical and Electronmicroscopic Evidence. *Exp Mol Pathol.* 1990;53:72-80.

16. Zimmerman M. Pathophysiological Mechanisms of Fibromyalgia. *Clin J Pain.* 1991;7(suppl 1):S8-S15.

17. Elert JE, Rantapaa-Dahlqvist SB, Henriksson-Larsen K, et al. Muscle Performance, Electromyography and Fibre Type Composition in Fibromyalgia and Work-Related Myalgia. *Scand J Rheumatol.* 1992;21(1):28-34.

18. Bennett RM, Cook DM, Clark SR, et al. Hypothalamic-Pituitary-Insulin-Like Growth Factor-1 Axis Dysfunction in Patients with Fibromyalgia. *J Rheumatol.* 1997;24(7):1384-1389.

19. Neeck G, Riedel W. Neuromediator and Hormonal Perturbations in Fibromyalgia Syndrome: Results of Chronic Stress? *Baillieres Clin Rheumatol.* November 1994;8(4):763-775.

20. Crofford LJ, Demitrack MA. Evidence that Abnormalities of Central Neurohormonal Systems Are Key to Understanding Fibromyalgia and Chronic Fatigue Syndrome. *Rheum Dis Clin North Am.* 1996;22(2):267-284.

21. Kaul RD, Susheela AK. The Muscle. In: The Symposium on the Non-Skeletal Phase of Chronic Fluorosis. *Fluoride.* 1976;9(1):9-18.

22. Simms RW. Is There Muscle Pathology in Fibromyalgia Syndrome? *Rheum Dis Clin North Am.* May 1996;22(2):245-266.

23. Thomas J, Thomas E, Tomb E. Serum and Erythrocyte Magnesium Concentrations and Migraine. *Magnes Res.* June 1992:5(2):127-130.

24. Mauskop A, Altura BM. Role of Magnesium in the Pathogenesis and Treatment of Migraines. *Clin Neurosci.* 1998;5(1):24-27.

25. Grimbergen GW. A Double-Blind Test for Determination of Intolerance to Fluoridated Water (preliminary report). *Fluoride.* 1974;7:146-152.

26. Standaert FG. Pharmacology of the Neuromuscular Junction. In: Brumback RA, Gerst JW eds. *The Neuromuscular Junction.* New York: Futura Publishing Co.;1984:121-294.

27. Dasarathy S, Das TK, Gupta IP, et al. Gastroduodenal Manifestations in Patients with Skeletal Fluorosis. *J Gastroenterol.* June 1996;31(3):333-337.

28. Muller P, Schmid K, Warnecke G., et al. Sodium Fluoride-Induced Gastric Mucosal Lesions: Comparison with Sodium Monofluorophosphate. *Z Gastroenterol.* April 1992;30(4):252-254.

29. Sivri A, Cindas A, Dincer F, et al. Bowel Dysfunction and Irritable Bowel Syndrome in Fibromyalgia Patients. *Clin Rheumatol.* May 1996;15(3):283-286.

30. Mattson MP. Advances Fuel Alzheimer's Conundrum. *Nat Genet.* November 1997;17:254-256.

31. Depoortere H, Francon D, Llopis J. Effects of a Magnesium-Deficient Diet on Sleep Organization in Rats. *Neuropsychobiology.* 1993;27(4):237-245.

32. Karczmar AG. Brief Presentation of the Story and Present Status of Studies of the Vertebrate Cholinergic System. *Neuropsychopharmacology.* 1993;9(3):181-199.

33. Mullenix PJ, Denbesten PK, Schunior A., et al. Neurotoxicity of Sodium Fluoride in Rats. *Neurotoxicol Teratol,* 1995;17(2):169-177.

34. Spittle B. Psychopharmacology of Fluoride: A Review. *Int Clin Psychopharmacol.* 1994;9:79-82.

35. Demitrack MA. Neuroendocrine Correlates of Chronic Fatigue Syndrome: A Brief Review. *J Psychiatr Res.* 1997;31(1):69-82.

36. Russell IJ, Vaeroy H, Javors M, et al. Cerebrospinal Fluid Biogenic Amine Metabolites in Fibromyalgia/Fibrositis Syndrome and Rheumatoid Arthritis. *Arthritis Rheum.* May 1992;35(5):550-556.

37. Friedman A, Kaufer D, Shemer J, et al. Pyridostigmine Brain Penetration Under Stress Enhances Neuronal Excitability and Induces Early Immediate Transcriptional Response. *Nat Med.* December 1996;2(12):1382-1385.

38. McEwen BS, Magarinos AM. Stress Effects on Morphology and Function of the Hippocampus. *Ann N Y Acad Sci.* June 21 1997;821:271-284.

39. Janowsky DS, Overstreet DH, Nurnberger JI Jr. Is Cholinergic Sensitivity a Genetic Marker for the Affective Disorders? *Am J Med Genet.* 1994;54:335-344.

40. Galland L. Magnesium, Stress and Neuropsychiatric Disorders. *Magnes Trace Elem.* 1991;10(2-4):287-301.

41. Moldofsky H. Sleep, Neuroimmune and Neuroendocrine Functions in Fibromyalgia and Chronic Fatigue Syndrome. *Adv Neuroimmunol.* 1995;5:39-56.

42. Branco J, Atalaia A, Paiva T. Sleep Cycles and Alpha-Delta Sleep in Fibromyalgia Syndrome. *J Rheumatol.* June 1994;21(6):1113-1117.

43. de Lecea L, Criado JR, Prospero-Garcia O, et al. A Cortical Neuropeptide with Neuronal Depressant and Sleep-Modulating Properties. *Nature.* May 16 1996; 381:242-245.

44. Jones BE. The Organization of Central Cholinergic Systems and Their Functional Importance in Sleep-Waking States. *Prog Brain Res.* 1993;98:61-71.

45. de Lecea L, del Rio JA, Criado JR, et al. Cortistatin Is Expressed in a Distinct Subset of Cortical Interneurons. *J Neurosci.* August 1 1997;17(15):5868-5880.

46. Williams JA, Comisarow J, Day J, et al. State-Dependent Release of Acetylcholine in Rat Thalamus Measured by *in vivo* Microdialysis. *J Neurosci.* September 1994;14(9):5236-5242.

47. Weglicki WB, Dickens BF, Wagner TL, et al. Immunoregulation by Neuropeptides in Magnesium Deficiency: *Ex vivo* Effect of Enhanced Substance P Production on Circulating T Lymphocytes from Magnesium-Deficient Mice. *Magnes Res.* 1996;9:3-11.

48. Russell IJ, Orr MD, Littman B, et al. Elevated Cerebrospinal Fluid Levels of Substance P in Patients with the Fibromyalgia Syndrome. *Arthritis Rheum.* November 1994;37(11):1593-1601.

49. Kurantsin-Mills J, Cassidy MM, Stafford RE, et al. Marked Alterations in Circulating Inflammatory Cells During Cardiomyopathy Development in a Magnesium-Deficient Rat Model. *Br J Nutr.* November 1997;78(5):845-855.

50. Weglicki WB, Phillips TM. Pathobiology of Magnesium Deficiency: A Cytokine/Neurogenic Inflammation Hypothesis. *Am J Physiol.* September 1992;263(3 pt 2): R734-R737.

51. Eisinger J, Zakarian H, Pouly E, et al. Protein Peroxidation, Magnesium Deficiency and Fibromyalgia. *Magnes Res.* 1996;9(4):313-316.

52. Weglicki WB, Mak IT, Kramer JH, et al. Role of Free Radicals and Substance P in Magnesium Deficiency. *Cardiovasc Res.* 1996;31:677-682.

53. Galland L. Magnesium and Immune Function: An Overview. *Magnesium.* 1988;7:290-299.

54. Karlsson H, Nassberger L. *In vitro* Metabolic Inhibition of the Human Lymphocyte: Influence on the Expression of Interleukin-2 Receptors. *Immunol Cell Biol.* October 1992;70(5):309-313.

55. Domingo E. RNA Virus Evolution, Population Dynamics, and Nutritional Status. *Biol Trace Elem Res.* January 1997;56(1):23-30.

56. Lichodziejewska B, Klos J, Rezler J, et al. Clinical Symptoms of Mitral Valve Prolapse Are Related to Hypomagnesemia and Attenuated by Magnesium Supplementation. *Am J Cardiol.* March 15 1997;79(6):768-772.

57. Pang X, Marchand J, Sant GR, et al. Increased Number of Substance P Positive Nerve Fibers in Interstitial Cystitis. *Br J Urol.* June 1995;75(6):744-750.

58. Clauw DJ, Schmidt M, Radulovic D, et al. The Relationship Between Fibromyalgia and Interstitial Cystitis. *J Psychiatr Res.* January-February 1997;31(1):125-131.

59. Becking GC. Hepatic Drug Metabolism in Iron-, Magnesium-, and Potassium-Deficient Rats. *Fed Proc.* November 1976;35(13):2480-2485.

60. Ziem G, McTamney J. Profile of Patients with Chemical Injury and Sensitivity. *Environ Health Perspect.* March 1997;105(suppl 2):417-436.

61. McFadden SA. Phenotypic Variation on Xenobiotic Metabolism and Adverse Environmental Response: Focus on Sulfur-Dependent Detoxification Pathways. *Toxicology.* July 1996;111(1-3):43-65.

62. Buchwald D, Garrity D. Comparison of Patients with Chronic Fatigue Syndrome, Fibromyalgia, and Multiple Chemical Sensitivities. *Arch Intern Med.* September 26 1994;154(18):2049-2053.

63. Galland L. Biochemical Abnormalities in Patients with Multiple Chemical Sensitivities. *Occup Med.* October 1987;2(4):713-720.

64. Salvaggio JE, Terr AI. Multiple Chemical Sensitivity Multiorgan Dyesthesia, Multiple Symptom Complex, and Multiple Confusion: Problems in Diagnosing the Patient Presenting with Unexplained Multisystemic Symptoms. *Crit Rev Toxicol.* November 1996;26(6):617-631.

65. Hutchins JB, Hollyfield JG. Human Retinas Synthesize and Release Acetylcholine. *J Neurochem.* July 1986;47(1):81-87.

66. Knave B, Tengroth B, Voss M. Age and Sex Distribution of Some Retinal Macular Diseases: Senile and Presenile Macular Degeneration and Central Serous Retinitis. *Acta Ophthalmol Suppl.* 1984;161:95-103.

67. Ciarallo L, Sauer AH, Shannon MW. Intravenous Magnesium Therapy for Moderate to Severe Pediatric Asthma: Results of a Randomized, Placebo-Controlled Trial. *J Pediatr.* December 1996;129(6):809-814.

68. Ziment I. Alternative Therapies for Asthma. *Curr Opin Pulm Med.* January 1997;3(1):61-71.

69. Hill J, Micklewright A, Lewis S, et al. Investigation of the Effect of Short-Term Change in Dietary Magnesium Intake in Asthma. *Eur Respir J.* October 1997;10(10):2225-2229.

70. Trivedi N, Mithal A, Gupta SK, et al. Reversible Impairment of Glucose Tolerance in Patients with Endemic Fluorosis. *Diabetologia.* 1993;36:826-828.

71. Vinals F, Testar X, Palacin M, et al. Inhibitory Effect of Fluoride on Insulin Receptor Autophosphorylation and Tyrosine Kinase Activity. *Biochem J.* 1993;291: 615-622.

72. Vinals F, Camps M, Testar X, et al. Effect of Cations on the Tyrosin Kinase Activity of the Insulin Receptor: Inhibition by Fluoride is Magnesium Dependent. *Mol Cell Biochem.* 1997;171:69-73.

73. Frankel BL, Patten BM, Gillin JC. Restless Legs Syndrome. Sleep-Electroencephalographic and Neurologic Findings. *JAMA.* December 2 1974;230(9):1302-1303.

74. Popoviciu L, Asgian B, Delast-Popoviciu D, et al. Clinical, EEG, Electromyographic and Polysomnographic Studies in Restless Legs Syndrome Caused by Magnesium Deficiency. *Rom J Neurol Psychiatry.* January 1993;31(1):55-61.

75. Fox MRS. Effects of Dietary Mineral Levels on Metabolism and Requirements. *Neurotoxicology.* 1983;4(3):113-120.

76. Malleson PN, al Matar M, Petty RE. Idiopathic Musculoskeletal Pain Syndromes in Children. *J Rheumatol.* November 1992;19(11):1786-1789.

77. Oberklaid F, Amos D, Liu C, et al. "Growing Pains": Clinical and Behavioral Correlates in a Community Sample. *J Dev Behav Pediatr.* April 1997;18(2):102-106.

78. Weiner SR. Growing Pains. *Am Fam Physician.* 1983;27(1):189-191.

79. Natelson BH. *NJ Center for Environmental Hazards Research.* FEDRIP Database, National Technical Information Service (NTIS); 1996.

80. Bradley LA, Alarcon GS. Fibromyalgia. In: Koopman WJ ed. *Arthritis and Allied Conditions: A Textbook of Rheumatology.* New York: Williams and Wilkins; 1997.

81. Michel JN, Suttie JW, Sunde ML. Fluorine Deposition in Bone as Related to Physiological State. *Poult Sci.* 1984;63(7):1407-1411.

82. Vikoren T, Stuve G. Fluoride Exposure and Selected Characteristics of Eggs and Bones of the Herring Gull (*Larus argentatus*) and the Common Gull (*Larus canus*). *J Wildl Dis.* April 1996;32(2):190-198.

83. Smith FA, Gardner DE, Hodge HC. Age Increase in Fluoride Content in Human Bone. *Fed Proc.* 1953;12:368.

84. Bixler D, Muhler JC, Shafer WG. Experimental Dental Caries. V. The Effects of Desalivation and Castration on Caries and Fluorine Storage in the Rat. *J Nutr.* 1954;52:345-353.

85. Messer HH. Fluorine. In: Frieden E ed. *Biochemistry of the Essential Ultratrace Elements.* New York: Plenum Press; 1984:55-87.

86. Vogel JA, Friedl, KE. Body Fat Assessment in Women. Special Considerations. *Sports Med.* April 1992;13(4):245-269.

87. Russell IJ. Neurohormonal Aspects of Fibromyalgia Syndrome. *Rheum Dis Clin North Am.* 1989;15:149-168.

88. Jezova D, Jurankova E, Mosnarova A, et al. Neuroendocrine Reponse During Stress with Relation to Gender Differences. *Acta Neurobiol Exp.* 1996;56:779-785.

89. Ramsay AM. Myalgic Encephalomyelitis and Postviral Fatigue States: The Saga of Royal Free Disease. 2nd Ed. London: Gower Medical Publishing; 1988.

90. Manocha SL, Warner H, Olkowski, ZL. Cytochemical Response of Kidney, Liver and Nervous System to Fluoride Ions in Drinking Water. *Histochem J.* 1975;7:343-355.

91. Buskila D, Neumann L, Vaisberg G, et al. Increased Rates of Fibromyalgia Following Cervical Spine Injury. *Arthritis Rheum.* March 1997;40(3):446-452.

92. Kroenke K, Koslowe P, Roy M. Symptoms in 18,495 Persian Gulf War Veterans. Latency of Onset and Lack of Association with Self-Reported Exposures. *J Occup Environ Med.* June 1998;40(6):520-528.

93. Mukhopadhyay P, Chakraborty S, Mukherjee S. Postcardiac Injury Rheumatism. *J Assoc Physicians India.* June 1995;43(6):388-390.

94. Friis S, Mellemkjaer L, McLaughlin JK, et al. Connective Tissue Disease and Other Rheumatic Conditions Following Breast Implants in Denmark. *Ann Plast Surg.* July 1997;39(1):1-8.

95. Beisel WR. Herman Award Lecture, 1995: Infection-Induced Malnutrition–From Cholera to Cytokines. *Am J Clin Nutr.* October 1995;62(4):813-819.

96. Levine PH. Epidemiologic Advances in Chronic Fatigue Syndrome. *J Psychiatr Res.* January-February 1997;31(1):7-18.

97. Corbridge TC, Hall JB. The Assessment and Management of Adults with Status Asthmaticus. *Am J Respir Crit Care Med.* May 1995;151(5):1296-1316.

98. Skobeloff EM, Spivey WH, Silverman R, et al. The Effect of the Menstrual Cycle on Asthma Presentations in the Emergency Department. *Arch Intern Med.* September 9 1996;156(16):1837-1840.

99. Hosseini J, Firuzian F, Feely J. Ethnic Differences in the Frequency Distribution of Serum Cholinesterase Activity. *Ir J Med Sci.* January 1997;166(1):10-12.

100. Leone NC, Martin AE, Minoguchi G, et al. Fluorides and General Health. In: *Fluorides and Human Health.* Geneva: World Health Organization; 1970:273-321.

101. Selwitz RH. Strategies for Improving Methods of Assessing Fluoride Accumulation in Body Fluids and Tissues. *Adv Dent Res.* 1994;8(1):111-112.

102. National Research Council Committee on Biologic Effects of Atmospheric Pollutants. *Fluorides.* Washington, DC: National Academy of Sciences; 1971.

103. Cox IM, Campbell MJ, Dowson D. Red Blood Cell Magnesium and Chronic Fatigue Syndrome. *Lancet.* 1991;337:757-760.

104. Abraham GE, Flechas JD. Management of Fibromyalgia: Rationale for the Use of Magnesium and Malic Acid. *J Nutr Med.* 1992;3:49-59.

105. Russell IJ, Michalek JE, Flechas JD, et al. Treatment of Fibromyalgia Syndrome with Super Malic: A Randomized, Double-Blind, Placebo Controlled, Crossover Pilot Study. *J Rheumatol.* 1995;22(5):953-958.

106. Shimonovitz S, Patz D, Ever-Hadani P, et al. Umbilical Cord Fluoride Serum Levels May Not Reflect Fetal Fluoride Status. *J Perinat Med.* 1995;23(4):279-282.

107. Brambilla E, Belluomo G, Malerba A, et al. Oral Administration of Fluoride in Pregnant Women, and the Relation Between Concentration in Maternal Plasma and in Amniotic Fluid. *Arch Oral Biol.* 1994;39(11):991-994.