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

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ABSTRACT. Recent research suggests that Chronic Fatigue Syndrome (CFS), Fibromyalgia Syndrome (FMS), and Persian Gulf Syndrome (PGS) may represent the effects of dysfunctions involving the central and/or peripheral nervous system, neuroendocrine system, neuromuscular system, immune system, metabolism, or sleep patterns. Each systemic dysfunction is accepted here as being central to these syndromes but not causal. This two-part review introduces the theory that the syndromes listed above represent finitely variable combinations of multiple systemic dysfunctions which all share a common underlying etiology at the subcellular level: magnesium deficiency plus concomitant fluoride excess (MDFE). The theory is introduced in Part I; detailed evidence which supports the theory is presented in Part II. Treatment suggestions are listed at the end of Part II through a call for clinical trials to test this theory. *[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

THEORY INTRODUCTION

It is theorized here that the chronic Pain-Fatigue Syndromes (P-FSs) currently known as Chronic Fatigue Syndrome (CFS), Fibromyalgia Syndrome

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(FMS), and Persian Gulf Syndrome (PGS) represent finitely variable combinations of multiple systemic dysfunctions which all share a common underlying etiology at the subcellular level. This common etiology involves a particular nutrient/toxin interaction and imbalance: magnesium deficiency plus concomitant fluoride excess (MDFE). In this review the terms "deficiency" and "excess" denote relative but not absolute states because it is the *interaction* of two fundamental elements which is central to the theory of illness causation proposed here. Substantial evidence points to MDFE as being the underlying and treatable biochemical cause of complex, multi-systemic dysfunctions leading to devastating chronic illness.

Because fluorine is the *most* electronegative of all the elements–electronegativity indicates the inherent ability of an atom to attract electrons from other atoms with which it forms molecules–it is never found naturally in its elemental state as F_2 except in trace amounts in radioactive materials, but exists in the ionic fluoride form (F^-) or as a component of a variety of organic and inorganic fluorides (1). Thus, the word "fluoride" is common nomenclature used to refer to both fluorine and fluoride; the shortened form (F^-) is used here to denote both ionic fluoride and simple bioavailable fluorides unless clarity necessitates otherwise.

Regardless of the source of exposure (air, food, water, industrial chemicals, etc.) and the method of exposure (inhalation, ingestion, or absorption), fluoride tightly binds *in vivo* many cations which are required for homeostasis, including the essential macromineral magnesium (2). Magnesium is normally the second most abundant intracellular cation, subordinate only to potassium. Cation binding occurs in both acute and chronic fluoride exposure; the extent of cation binding–which can be immediately life threatening in high acute exposures–directly depends on the amount of bioavailable fluoride to which an individual is exposed (many fluorides are moderately to extremely toxic, others are quite inert and thus non-bioavailable). Fluoride's strong affinity to macrominerals enables it to combine with them at normal temperatures to form relatively insoluble compounds such as magnesium fluoride (MgF_2) and calcium fluoride (CaF_2).

This specific electronegative effect is central to the theory of illness causation proposed here: fluoride's predictable and consistently unfavorable effect on Mg status and function via the formation of biochemically impotent or deviant MgF_2 complexes, and/or direct competition for Mg binding sites. Both of these conditions cause the disruption of hundreds of Mg-dependent enzymes crucial to normal cellular and organ system activity. In essence, these effects of F^- on Mg *functionally decrease to a much lower level* the amount of bioactive Mg available for critical cellular processes. Thus, the higher the level of bioavailable F^- in the body, and the lower the level of bioavailable Mg, the greater this primary pathological effect will be.

Although beyond the scope of this paper, essential microminerals as well as some nonmetals are also bound by F^-. These trace elements are vital for normal immune system function, as well as the production and function of critical enzyme systems (3,4). Microminerals such as iron, zinc, manganese, and copper function as metalloenzymes, coenzymes, and enzyme activators, or as components of biologically active macromolecules. It is proposed here that at least some of the baffling symptoms in CFS, FMS, and PGS (identified herein as Pain-Fatigue Syndromes–P-FSs) may be due, or partially due, to the unfavorable effects of F^- on essential micromineral bioavailability and function, especially when their dietary intake is inadequate or when substantial losses due to stress or illness occur. "It is now clear that essential metal deficiencies do influence health effects from toxic metal exposures and that adequate dietary essential metals are necessary for prevention and intervention of metal toxicities" (5).

In addition to the negative effect of F^- on the bioavailability and function of Mg and other minerals, ionic fluoride may also produce multiple pathologies by disrupting key amino acids which form the basic structure of proteins (6); this disruption may be particularly apparent in collagen, gelatin, and elastin in connective tissues which exhibit widespread symptomatic pathologies in P-FSs. Other principal proteins which may be subject to disruption by F^- are myosin and actin in striated muscle tissue, thyroglobulin in thyroid, thymus histones in thymus, keratin in the epidermis, fibrinogen in blood, serum globulin in serum, hemoglobin in red blood cells, lecithoprotein in blood, brain, and bile, and chondroprotein in tendons and cartilage.

In brief, the macromolecular structure of all proteins is maintained by interpeptide hydrogen bonds. These bonds occur between the Nitrogen-Hydrogen (N-H) group of one amide fragment and the carbonyl group of another fragment on a parallel chain. Ionic fluoride is bioisosteric with the hydrogen (H) atom as well as the hydroxyl (OH^-) group, and it has been suggested that the F^- ion can compete successfully for the N-H bond in amide systems (the amide-fluoride hydrogen bond is the second strongest hydrogen bond known) and possibly other systems involving N-H bonding (6). "Considering the prevalence of hydrogen bonding involving N-H in biological systems, including DNA, it may well be important to avoid undue exposure in high concentrations of fluoride ion, which may be able to disrupt them. We believe that we have found, in its strong hydrogen bonding potential toward the NH group of amides and related biomolecules, an explanation of how this reputedly inert ion [F^-] could disrupt key sites in biological systems" (6). In addition, fluoride also readily replaces hydroxyl (OH^-) groups (7); this occurs, for example, in hydroxyapatite, with the F^- replacement of OH^- groups forming fluorapatite in bone and teeth which has a crystal lattice structure very different from, and structurally and metabolically inferior to,

hydroxyapatite. Thus, it is these other biochemical effects of fluoride, in addition to its direct effect on Mg status and function, which, though not described in great detail here, are also important to this theory of illness causation.

It is hypothesized here that, when considered together, the results of chronic fluoride exposure plus chronic magnesium deficiency (both briefly reviewed next) comprise the devastating constellation of multi-systemic symptoms in Pain-Fatigue Syndromes.

First, the following symptoms of "hydrofluorosis" (also known as endemic fluorosis) in humans reflect the widespread, systemic effects of chronic, low-level fluoride exposure (8) which is most common in tropical and subtropical areas of the world having variable levels of naturally-occurring waterborne fluoride:

"1. The disease is initiated by dull pain in the lower spine, by paresthesias and muscular pains in the distal portion of arms and legs. The pains are fleeting, worse on awakening; they tend to improve with increased muscular activity; they are associated with cutaneous hyperesthesia and hypoesthesia.
2. The patient loses muscular control of arms and legs. At first, he drops such items as cups and books from his hands. While walking or standing, loss of control of the lower extremeties causes him to fall down. As the disease progresses, akinesia and mask-like face reminiscent of Parkinson's Disease develop. Later, complete paraplegia ensues [in severe cases].
3. Nausea, anorexia and vomiting, abdominal distension, spastic pain in various parts of the abdomen occur early in the disease in approximately 40% of the cases. X-rays of the stomach are either negative or suggestive of chronic gastritis. There is achlorhydria and achylia.
4. The gastrointestinal symptoms may assume the features of chronic gastritis, ileitis, colitis, associated with episodes of ulcers in the buccal cavity. In the bowels there is increased spasticity, leading to either constipation or diarrhea.
5. General malaise, fatigue, loss of mental acuity and hypokinesia gradually turn into extreme exhaustion and a state of cachexia. Headaches range from dull to extremely severe migraine type. Increasing pain and stiffness of the lumbar and cervical spine lead to typical "poker back" before skeletal changes are demonstrable by x-ray.
6. Even in its early stages, urinary tract pathology, namely pyelitis, cystitis and urethritis occur accompanied by polyuria and polydipsia, dryness in mouth, conjunctivae and in nasal passages. This may lead to blepharitis and secondary pyogenic lesions in the anterior nares and in eyelids.

7. Visual disturbances, due to degenerative changes in the retina and allergic manifestations such as urticaria, dermatitis, and allergic nasal disease occur."

Individuals who have been diagnosed with CFS, FMS, or PGS are all too familiar with the symptoms listed above. Thus, it is proposed here that endemic fluorosis is just one of many serious illnesses on a limited three-dimensional spectrum of systemic dysfunctions caused by fluoride excess and its *in vivo* effects on, primarily, the essential macromineral Mg and various critical proteins.

Second, symptoms of Tetany syndrome (9), caused by chronic Mg deficit, will also be very familiar to patients diagnosed with a Pain-Fatigue Syndrome (hereafter P-FS):

"1. central manifestations of emotional lability, breathlessness and hyperventilation, tremor, headache, dizziness, insomnia and asthenia;
2. peripheral manifestations of paresthesia, formication, fasciculation, cramps, radicular pain and poor exercise tolerance;
3. organ-specific functional disorders producing palpitation, chest pain, pallor, diaphoresis, Raynaud's phenomenon, biliary dyskinesia or spastic colon;
4. 'trophic' phenomena with fragility of nails, hair and teeth;
5. [when Mg deficiency is severe] acute crises characterized by hyperventilation, syncope, convulsion, carpal-pedal spasm."

Individuals with latent tetany who are normocalcemic (adequate Ca, low Mg) are prone to chronic candidiasis and candida allergy, and often experience associated clinical syndromes such as dysmenorrhea, migraine headaches, and irritable bowel (10). These additional pathologies are extremely common in patients with P-FSs.

Although Mg deficiency has been logically suspected in the etiology of PF-Ss (11) and clinical trials utilizing Mg therapy have been conducted with CFS and FMS patients (12-14) with modest to moderate success, the levels of Mg that were employed as well as the length of time that they were employed are proposed here to have been insufficient. It is hypothesized here that when a significant level of bioavailable F^- is present *in vivo* the daily requirement of Mg will be much greater, perhaps several times greater, than the current U.S. recommended dietary allowance (RDA) of 4.5 mg/kg of Mg per day for adults, and 6 mg/kg of Mg per day for children ages 1-15 (15,16). (These values are approximately equal to 285 mg of Mg per day for a 140 pound adult woman, and 218 mg of Mg per day for an 80 pound child.). Long-term balance studies have indicated much greater needs for Mg than the current U.S. RDA; more than 1000 mg per day is often necessary to maintain a

positive balance when a person is under stress (17,18). [This hypothesis will likely hold true for trace elements as well; organisms under stress are at much higher risk from consequences of trace element deficiencies; tissues under anabolic stress are especially sensitive to trace element deficiencies (19).]

In short, it is hypothesized here that even individuals who ingest amounts of Mg currently believed to be nutritionally adequate will experience symptoms of hypomagnesemia in the presence of substantial *in vivo* levels of bioavailable F^- (this would hold true for pets, livestock, and all other animals as well as humans). In essence, a "mild" Mg deficiency as determined by laboratory tests may, in physiological reality, be a *moderate to severe* Mg deficiency due to the presence of significant bioavailable F^-. In addition, a "low normal" reading may in fact reflect a *mild to moderate* deficiency of Mg. "In general, suboptimal intakes of the essential nutrient [Mg] exacerbate the adverse effects of the toxic element [F^-], whereas intakes of the nutrient greater than requirement protect against the toxic element" (20). It is hypothesized here that ingesting a consistently high level of Mg will not only protect against symptoms of Mg deficiency, but may also "bind" excess ionic fluoride and render it incapable of producing many additional pathologies via direct effects on protein systems, for example.

During the past 50+ years, however, humans have experienced chronically deficient intakes of Mg (according to U.S. RDA guidelines) as well as chronically-increasing exposure to F^- from many different sources (21,22). It is theorized here that this fundamental nutrient/toxin interaction and imbalance, which has increased in severity over time and continues to do so, has produced profound systemic pathologies. The result is baffling and devastating chronic illnesses (various Pain-Fatigue Syndromes) which have not been attributed to other known causes. These illnesses have become increasingly common in the past twenty years, and are becoming strikingly apparent in ever-younger patient populations. "Chronic pain syndromes such as fibromyalgia and reflex sympathetic dystrophy constitute an increasing percentage of new patient referrals to pediatric rheumatology clinics" (23).

It is proposed here that the chronic illness caused by MDFE presents with persistent, identical or nearly identical constellations of symptoms of varying severity that typically wax and wane. Spontaneous, permanent remissions are very rare (24,25). These symptoms include but are not limited to profound fatigue and weakness, musculoskeletal pain, headaches of variable intensity and form, gastrointestinal disturbances, significant cognitive difficulties, altered emotional states, profound sleep disturbances, and significantly altered immune system function. All symptoms invariably worsen when the affected individual experiences additional psychological or physical stress.

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. It is suggested here that human physiology is only partially able to effectively and adaptively deal with the myriad fundamental effects of MDFE which impact every cell and organ system; chronic illness of varying severity is the unfortunate but inevitable result.

This illness syndrome is not new but is increasing in prevalence in modern societies (23,26), posing an alarming threat to public health. Known today primarily as FMS, CFS, or PGS in the U.S., this grave illness has gone by many other names throughout human history. A partial list probably includes: Iceland (Akureyri) disease, Royal Free disease, Punta Gorda fever, Newcastle's disease, war syndromes, neurocirculatory asthenia, psychogenic rheumatism, cardiac neurosis, post-traumatic stress disorder, chronic Epstein-Barr virus, fibrositis, postviral fatigue syndrome, hysteria or mass hysteria, atypical poliomyelitis, anxiety neurosis, epidemic vegetative neuritis, epidemic neuromyasthenia, neurasthenia, and myalgic encephalomyelitis (ME, a term still used in Great Britain, Canada, and Europe) (27-37). Somatization disorder and hypochondria may also be included in this list, and are hypothesized here to share the same biochemical etiology.

It is proposed here that FMS, CFS, and PGS (among closely-related others) are, in reality, the same illness which manifests itself in slightly different ways depending upon multiple factors which are addressed here in Parts I and II. When one looks carefully at modern clinical test results and chronic symptomatology, the former distinctions between patients with differing diagnoses disappear. ". . . few differences exist in the domains of symptoms, examination findings, laboratory tests, functional status, psychosocial features, and psychiatric disorders" in patients with CFS and FMS (32). "CFS in children and PJFS (primary juvenile fibromyalgia syndrome) appear to be overlapping clinical entities and may be indistinguishable by current diagnostic criteria" (33).

Therefore, both historical and current differential diagnoses do not reflect the real existence of separate and distinct illnesses having significantly different etiologies, signs, symptoms, and clinical courses. Rather, differential diagnoses are proposed here to reflect one or more of the following:

1. the patient's most bothersome symptom(s) reported at the time of diagnosis;

2. identifiable clinical signs at the time of diagnosis;
3. the diagnosing physician's area of expertise or bias (34);
4. the patient's individual physiologic responses to MDFE;
5. the patient's current or recent levels of bioactive Mg and bioactive F^-.

Factor 1 alone, for example, easily produces the following: If a patient presents with fatigue as the most bothersome of the entire constellation of symptoms, she will likely be diagnosed with CFS. If a patient presents with pain being primary, she will likely be diagnosed with FMS. Should the patient be a veteran of the Gulf War, she will likely be diagnosed as having PGS. At present, the values of factors 4 and 5 will be unknown both to the patient and physician, but will theoretically determine the values of factors 1 and 2.

The potentially varying biochemical profiles of patients variously diagnosed with CFS, FMS, and PGS (among others), based on available laboratory and clinical tests, are hypothesized here to primarily reflect the interaction effects of varying intra- and intercellular levels of F^- and Mg. These interaction effects may, as the biochemistry is investigated and defined, eventually be predictable. Differing test results may also reflect a particular "stage" of the illness which undoubtedly mirrors not only the direct effects of underlying pathology, but also the indirect effects of variable compensatory mechanisms which are engaged at critical times and to varying degrees in response to significant subcellular, cellular, organ, and system dysfunctions. Further compounding the research problem is that these illness "stages" probably do not reflect a progressive linear function, but most probably reflect a multitude of potential interaction effects involving nutrients, toxins, specific dysfunctions, specific compensatory mechanisms, and perhaps many unknown factors as well. These interaction effects are hypothesized here to underlie the baffling variability in patient profiles regarding symptoms, clinical signs, and functional capacities.

This comprehensive theory of magnesium deficiency plus concomitant fluoride excess (MDFE) easily explains the etiology and pathogenesis of the P-FSs currently known as CFS, FMS, and PGS. In addition, the myriad biochemical effects of MDFE completely account for observations 1-10 which were developed for CFS (35) (here [the syndromes] replaces the term "CFS"):

"1. It causes fatigue, exhaustion, and the other symptoms of [the syndromes];
2. If 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 specific causal relationship of MDFE to observations 1-10 will be presented in Part II.

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. Overviews of these two interacting elements are presented next to form the necessary foundation for subsequent detailed arguments in Part II regarding the etiology and pathogenesis of PF-Ss.

OVERVIEW OF MAGNESIUM

Approximately 90% of all magnesium in healthy individuals is found in bone and muscle tissue; the remainder is distributed throughout the body, including the central nervous system. The total body load of magnesium is regulated primarily by the small intestine and kidney, which in healthy individuals moderate, respectively, absorption and excretion of Mg in response to fluctuating Mg requirements. The excretion of Mg and Ca is interdependent; excess Ca intake promotes the excretion of both Ca and Mg. Thus, in addition to low dietary intake of Mg, significant dietary and supplemental Ca intake (widely promoted by the news media and via specific product advertising to prevent osteoporosis) may also substantially contribute to Mg deficiency, particularly in women.

A normal skeleton contains approximately half of total body Mg, serving as a storehouse of Mg and Ca as well as many trace elements; Mg incorporation into hard tissue increases elasticity and protects against fractures. During acute periods of low Mg intake, impaired absorption, or excess excretion, the existing surface Mg content of normal bone can decrease. However, this adaptive skeletal mobilization of Mg may not be sufficient to protect the extracellular Mg pool and critical organs (e.g., heart, kidney, brain) from the consequences of Mg deficiency (36).

Intracellular Mg is an essential cofactor for hundreds of enzyme systems, particularly those that catalyze intracellular metabolism. Perhaps most impor-

tantly in this review are those enzymes that hydrolyze and transfer phosphate groups, such as enzymes participating in reactions involving adenosine triphosphate (ATP) which is present in all cells, but especially in muscle cells–muscle energy is stored in ATP (37). Cellular mitochondria contain the Mg-dependent enzymes necessary for the aerobic stages of cell respiration, and synthesize most ATP.

As the major constituent of the active transport mechanism of sodium and potassium across cell membranes, ATP is necessary for the utilization of glucose, the metabolism of lipids, proteins, nucleic acids, and coenzymes, muscle contraction, methyl group transfer, and many other normal reactions; a deficiency of bioavailable Mg will significantly affect those functions. Indeed, Mg is a fundamental and absolute requirement for all enzyme reactions that are catalyzed by ATP (38). Under conditions of substantial Mg deficiency (hypomagnesemia), mitochondrial function is greatly impaired. This impairment increases the relative amount of anaerobic glycolysis occurring system-wide, creating a metabolic acidosis. As explained in the next section, alkalotic animals tolerate significantly higher fluoride doses for longer periods of time than do acidotic animals (39).

Under stressful conditions of any kind, Mg deficiency increases susceptibility to physiologic damage (40,41). In addition, stress causes a shift of Mg from the intracellular space to the extracellular space via adrenergic effects. This initial, short-term protective effect is thought to buffer the physiologic response to stress by increasing the circulating serum level of Mg (Mg is actively transported across the blood-brain barrier–a process which also requires adequate ATP). However, this intracellular-extracellular shift also increases urinary excretion of Mg, depleting body stores which, if not quickly and adequately replenished, leads to significant pathologies. Therefore, Mg deficiency and chronic stress affect each other in a pathogenic vicious cycle (9), and stress of any kind, whether short- or long-term, significantly increases the body's need for Mg. It is vital to emphasize here that serum Mg values can easily be in the normal range even when intracellular Mg is depleted (42,43).

Therefore, the higher the bioavailable level of F^-, the less Mg will need to be lost in order to produce significant pathology. The converse is also true; the lower the bioavailable level of F^-, the more Mg will need to be lost to produce pathology. (More about the interaction of Mg and F under "Overview of Fluoride" below.) Again, it is the *interaction* of two elements which is central to the theory of illness causation presented here. The issues of age and gender and how they relate to MDFE will be dealt with in Part II.

To continue, a critical level of Mg concentration in the central nervous system (CNS) is required for normal function; when the CNS Mg concentration drops below this level, neurologic dysfunction invariably occurs. This

dysfunction may be mild to severe, depending upon the amount of bioavailable Mg which can be utilized for critical functions. Under conditions of severe peripheral Mg deficiency, depressed serum levels of Mg can be partially replaced by cerebrospinal fluid Mg. However, if large amounts of Mg are lost from the CNS via bulk flow and/or diffusion, profound CNS disturbances occur (44,45). Symptoms of reactive CNS Mg deficiency and central pontine myelinolysis are very similar and both occur more often in women.

Subacute magnesium deficiency is now common in industrialized societies because of Mg-depleted agricultural soils, changing dietary patterns, alcohol use, Mg-depleting processing of foodstuffs, Mg-depleting pharmaceutical use [e.g., aminoglycosides (46,47)], and use of surface water with low Mg content (48,49). It has been estimated that at least 15-20% of the population in developed countries experiences a marginal primary magnesium deficit which reflects a typical intake of less than 4 mg/kg per day (50). "A reasonable estimate of this decrease is that magnesium intake decreased by almost 20% during the period 1910-1965, but may now be 29-38% lower than it was in 1910" (21).

In addition to greatly reduced dietary intake of Mg, many widely-used prescription drugs, including penicillamine, decrease bioavailable Mg levels. Penicillamine is hypothesized to reduce Mg levels by chelating Mg and inactivating pyridoxine hydrochloride (vitamin B_6) which is required for the cellular uptake of Mg. Experimental vitamin B_6 deficiency causes cellular losses of both magnesium and zinc; both of these minerals are necessary for pyridoxine-dependent enzymes. This loss of Mg and Zn has been hypothesized to lead to aberrations of lymphoid tissue (51). Other drugs which can cause excessive losses of Mg are some diuretics, cisplatin, digoxin, and cyclosporin (45). Ethyl alcohol use, though, may represent the most important drug-induced cause of Mg deficiency in adults (52).

"... note that the toxic effect of fluoride is a direct function of the severity of the magnesium deficiency. Thus, very low levels of dietary fluoride are toxic at ultra-low levels of dietary magnesium, whereas much higher levels of fluoride are innocuous when dietary magnesium is increased" (21). Higher levels of fluoride are probably not innocuous in the long term even in the presence of moderate to high levels of Mg, but may be considerably less likely to cause severe pathologies in the short term provided toxicity-reducing levels of Mg are present

OVERVIEW OF FLUORIDE

Fluorine, an element in the halogen group (with chlorine, iodine, and bromine), is widely distributed in nature. It is approximately the 13th most common element in the earth's crust, the most electronegative of all elements

(easily oxidizing many elements to their highest oxidation state), and one of the most violently reactive substances known. As noted earlier, it is never found naturally in its elemental state as F_2 except in trace amounts in radioactive materials, but exists in the ionic form (F^-) or as a component of a variety of organic and inorganic fluorides. These fluorides demonstrate a wide diversity of chemical and physiologic activity (1). Elemental fluorine combines with hydrogen to form hydrogen fluoride which easily dissolves in water to form hydrofluoric acid (HF).

Acute fluoride poisoning produces profound hypocalcemia (cation-binding process) with resultant inhibition of normal blood coagulation. As a metabolic poison, it stimulates some enzymes, such as adenylate cyclase, but severely inhibits others, such as Na^+-K^+-ATPase and the enzymes of carbohydrate metabolism such as succinate and isocitrate dehydrogenase. Fluoride can affect enzymes of active transport mechanisms (alkaline phosphatase), lysosomal enzymes (acid phosphatase), enzymes involved in the anaerobic metabolic pathway (lactate dehydrogenase and alpha-glycerophosphate dehydrogenase), and enzymes of the pentose shunt (6-phosphogluconate and glucose-6-phosphate dehydrogenases) (53). In acute fluoride toxicity, death can result from these processes and also from a delayed, explosive hyperkalaemia which essentially shuts down cardiac muscle activity (54).

Although acute fluoride exposure is relatively uncommon, chronic human exposure to fluorides from multiple sources has increased significantly in the past 100 years. The two most common routes of human fluoride exposure are inhalation and ingestion. Fluorides can also be easily absorbed through the skin (as in accidental occupational poisoning) and to a lesser extent through the oral mucosa (from fluoride-containing dentifrices). Plasma fluoride levels increase in proportion to the chronic level of fluoride exposure regardless of the method or source, rather than being homeostatically controlled as was once believed (55).

The use of fluorinated compounds in medicine has greatly increased since the 1950s; four unique properties of elemental fluorine have promoted its use in biologically active compounds (2):

"1. fluorine most closely resembles bioactive hydrogen analogues with respect to steric requirements at the receptor sites;
2. fluorine alters electronic effects, owing to its high electronegativity;
3. fluorine imparts improved oxidative and thermal stability to the parent molecule;
4. fluorine imparts lipid solubility, thereby increasing the *in vivo* absorption and transport rates in membranes."

The Carbon-Fluorine bond's size similarity to the Carbon-Hydrogen bond analogue allows a fluorinated compound to readily enter into a binding site,

which subsequently produces a biological effect which is longer-term with much slower metabolism and excretion of the active compound (2). The extent to which any fluorine-containing pharmaceutical can be metabolized to release organic and inorganic fluorides is of concern. General categories of drugs which contain bioactive fluorinated compounds include analgesics (e.g., flufenamic acid), antibacterial agents (e.g., ciprofloxacin, floxacillin), appetite depressants (e.g., fenfluramine), tranquilizers (e.g., triflupromazine, haloperidol), antidepressants (e.g., fluoxetine), diuretics (e.g. flumethiazide), muscle relaxers (e.g., flumetramide), anti-inflammatories (e.g., flazalone), and inhalation anesthetics (e.g., isoflurane). In addition, nuclear magnetic resonance imaging (NMR) techniques employ perfluoro crown ethers which are of particular use when administered to the cerebrospinal fluid compartment for brain and spinal cord diagnostics.

Many herbicides, insecticides, and fungicides are also fluorinated organic compounds (2). For example, sodium fluoroacetate is an effective rodenticide and is highly toxic to all animals, including humans. This compound mimics acetate and is incorporated into the tricarboxylic acid cycle of cellular respiration. Here it is converted to fluorocitric acid which inhibits aconitate hydratase, the enzyme which normally catalyzes the dehydration of citric acid. Thus, the energy-producing cycle is interrupted and citric acid accumulates in the organism.

Fluorides are widely used in other industries, for example: manufacturing aluminum; producing fertilizers; smelting nickel, copper, gold, and silver; catalyzing organic reactions; preserving wood; inhibiting fermentation; creating steel, iron, glass, ceramics, pottery, and enamel products; coating welding rods; and cleaning graphite, windows, metals, and glassware. High industrial exposures can occur in aluminum production, fertilizer production, and manufacture of glass; variable exposures are widespread in the remaining industries noted above and others (56). Occupational fluorosis, which is similar to endemic fluorosis described below, was first described in 1932 involving cryolite (fluorine-containing ore, Na_3AlF_6) workers, and can occur with any long-term occupational exposure to common fluorides. A decade or two earlier, reports described the chronic fluorine intoxication of livestock (a disease called gaddur, long known in Iceland) near aluminum and superphosphate factories in Europe (57).

Local airborne concentrations of fluorides depend primarily on the level of industrial gaseous and particulate fluoride emissions, coal-burning activity (industrial energy production or individual home heating and cooking activities), and/or the presence of active fluoride-emitting volcanoes and fumaroles. All major sources of airborne fluoride substantially contaminate plants, soil, and water locally and downwind of the origin (58).

Hekla volcano in Iceland, for example, is one of many volcanoes world-

wide which are consistently high fluoride emitters. It has erupted 20 times since Iceland was settled, and exploded in 1947 after a hundred year period of quiet; this massive eruption lasted from March 1947 until April 1948, sending fluoride-containing aerosols and ash as far away as Finland. In the autumn of 1948 the first cases of "epidemic neuromyasthenia" were identified in Iceland; later this came to be known as Akureyri disease or Iceland disease (27). There is also a high unexplained incidence of thyroid cancer in Iceland (59). Damage to the thyroid gland's structure and function has been observed in rats with both iodine deficiency and excessive fluoride intake (60). It has been shown that NaF is clastogenic in human and great ape cells (but not in rodent cells), although clastogenicity does not always imply carcinogenicity (61).

Fluorinated general anesthestics are also a common source of inhaled fluorides, exhibiting varying levels of toxicity (e.g., hepatic and renal dysfunction) primarily depending upon the particular chemical formulation of anesthetic used, duration of anesthesia, and hepatic and renal status of the patient. The extent to which an anesthetic can be metabolized to release inorganic fluoride (which is then stored and excreted to variable extents) is generally of greatest concern. Early fluorinated anesthetics (e.g., methoxyflurane) were metabolized to a much greater extent than are anesthetics in current use (this may be significant for older P-FSs patients who underwent one or more surgeries many years ago). However, modern compounds such as isoflurane, desflurane, and sevoflurane still undergo some degree of fluoride-releasing biotransformation and can cause hepatotoxicity and nephrotoxicity in any surgical patient (62-64).

The level of fluoride in foods and water varies widely in normal, "free choice" human diets; tiny amounts (at the level of micrograms) of fluoride are ubiquitous in foods, and it is impossible to develop a nutritious diet completely free of fluoride. Water supplies may be naturally or artificially fluoridated; the natural/artificial distinction is irrelevant here, however, since common water-borne fluorides such as CaF_2 are soluble in gastric acid (HCl) even if relatively insoluble in water, and are then readily absorbed.

Ingested fluoride is absorbed primarily from the gastric lumen as the undissociated molecule HF [all F^-–releasing compounds form HF when mixed with HCl in the stomach (65)]; the rate and magnitude of absorption is pH-dependent. Note that HF also permeates renal tubules, urinary bladder, and lipid bilayer membranes (66). Persons with higher than normal gastric acidity (e.g., stress-induced) will absorb F^- to a faster and greater extent than usual. There is some evidence to suggest that higher peak levels of plasma F^- are more toxic than are lower levels. If fluoride is absorbed faster and to a greater extent than normal, these peak levels will also be higher and potentially produce more severe symptomatology. This scenario is predictable given fluoride's ability to bind cations as well as disrupt proteins.

After gastric absorption of the undissociated molecule HF, upon reaching regions of higher pH the molecule dissociates to release ionic fluoride and protons. Fluoride migrates passively and predictably *in vivo* from areas of lower pH (acidic) to areas of higher pH (alkaline). "Fluoride can be forced to migrate from cells" (and can thus be excreted, or re-deposited in hard tissues or lipids) "by alkalinization of the extracellular fluid, a process which expands the transmembrane pH gradient" (39); as previously noted, alkalotic animals tolerate significantly higher fluoride doses for longer periods of time than do acidotic animals. After ingestion or inhalation by adults, under normal circumstances approximately 50% of F^- is excreted by the kidney within 24 hours–also a pH-dependent process (67)–and about 50% is deposited in bone and other calcified tissues. A portion can also be easily stored in lipids, as F^- can permeate lipid bilayer membranes; note that the CNS contains a high proportion of lipids.

It is important to note that upon exposure children excrete significantly less and store significantly more F^- in bone; children have much lower renal clearance rates of F^- (68). In addition, fluorides exert a toxic effect on the carbohydrate metabolism of the kidney, creating severe metabolic distress in the tissue that is actively involved in excreting fluoride. For example, high levels of lysosomal enzymes found in the distal convoluted tubules of squirrel monkeys who were provided water containing 1 or 5 ppm fluoride were hypothesized to indicate an increased catabolism of the epithelial cells lining the nephron (53). Thus, individuals with underlying kidney disease are at much higher risk of fluoride toxicity, and individuals who have no prior kidney dysfunction may develop chronic renal disease when fluoride excretion levels are significant over long periods of time (69,70).

"The precise dietary concentration at which fluoride ingestion becomes harmful is difficult to define. No single value is appropriate because low-level toxicosis depends upon duration of ingestion, solubility of the fluoride source, general nutritional status, species of animal, age when ingested, and toxicity-modifying components of the diet" (71). The average human intake of fluoride, however, has increased from 0.2-0.8 mg/day in the 1940s and 1950s to the 2-5 mg/day levels found in more recent years (21). The prevalence of dental fluorosis in North America has also increased since the 1930s-1940s (22). "It is no longer feasible to estimate with reasonable accuracy the level of fluoride exposure simply on the basis of concentration in drinking water supply" (43).

With an average intake of 4 mg of F^- per day, at least half (or 2 mg) would be normally retained; "a retention of 2 mg/day would mean that after 40 years the bone of an average individual would have fluoride levels of approximately 10,000 ppm, i.e., similar to those associated with skeletal fluorosis" (72). The phenomenon of fluoride storage in bone (and other

tissues) is critical here: substantial stored fluoride plus ongoing fluoride intake constitutes greater *in vivo* bioavailability of fluoride than intake alone would create. (It is important to note that individuals are commonly diagnosed as having CFS or FMS around age 40; many symptoms, however, are likely to have been present and disturbing for some years prior to diagnosis at middle age.) This phenomenon (further explained below) becomes critical in women near and at menopause, when the loss of estrogen contributes to greater bone resorption, and thus creates higher systemic exposure to fluoride previously stored in bone.

As mentioned earlier, endemic fluorosis (dental and skeletal fluorosis, also called chronic fluorine poisoning or hydrofluorosis) occurs in many areas of the world having variable but usually significant levels of natural fluoride in the drinking water, especially in tropical and subtropical countries of the African and Asian continents, and in many areas in the Indian subcontinent. Fluorosis also occurs in regions (as in China) where water levels of F^- are not significant but where coal burning is primarily used for home cooking and heating. When burned or heated to high temperatures, nonsoluble F^- contained in coal and hearth/oven bricks is converted into water-soluble F^- which is then chronically inhaled, especially by women and children (73).

Fluorosis is characterized by increased metabolic turnover of bone, impaired bone collagen synthesis, and increased avidity for calcium, and is associated with a generalized inflammatory reaction (74,75). Symptoms of endemic fluorosis are common in both humans and livestock in affected areas; the disorder is known as darmous in North Africa. The severity of endemic fluorosis is usually related to the level of fluoride in drinking water, length of time of exposure, average regional temperature, economic and nutritional status of the population, and patterns of physical activity (76). "Patterns of physical activity" may be of particular interest here, as many (most?) P-FS patients report being at least moderately and often extremely physically active prior to symptom development. At least three factors may be at work; (a) physical exercise is a stressor which may significantly contribute to Mg depletion; (b) people who are physically active, especially in hot weather, must drink more fluids–the level of fluoride (parts per million, or ppm) in highly-consumed fluids will be a factor; and (c) physical exercise may promote the incorporation of F^- into bone and other hard tissues (especially in regularly-exercised muscle-bone connections), and some of the stored F^- may be subsequently released into extracellular fluids and soft tissues during normal bone resorption processes.

The term "fluorosis" was originally applied in the early 1900's to the more obvious clinical signs and symptoms of high fluoride deposition in bone and tooth enamel (for example, skeletal exostoses and mottled teeth). More recent studies have confirmed, however, that fluorosis involves widespread, systemic effects as well. Among the soft-tissue pathologies reported are skeletal muscle degeneration, red blood cell abnormalities, adrenal gland dysfunction, and widespread connective tissue abnormalities (77). It is of considerable interest here to note that orthopedic surgeons in industrialized countries are encountering disorders in young, sometimes very young, athletes that were formerly seen only in adults, such as stress fractures, dislocations, subluxations, and epicondylitis (78).

With continuing exposure to F^- at any level, incorporation into bone normally proceeds in a linear fashion, and always produces bone which is abnormal (79). With regard to the use of fluorides in caries prevention efforts, "the dental successes may have occurred at the expense of the skeleton" (80). Osteosclerosis is predominant in patients with fluorosis who also have adequate Ca intake; osteomalacia or osteoporosis occurs in patients who have marginal or suboptimal Ca intake. "We must consider the very real possibility that fluoride (even at levels felt to be safe and optimal for the prevention of dental caries) may, in fact, aggravate the risk of developing osteoporosis" (79). The nutritional status of Ca in individuals with fluorosis appears to greatly influence hormonal profiles and modifies the type of bone changes (74).

Fortunately, with continuous modeling (in children) and remodeling (in adults) of bone *in the absence of continued fluoride exposure from external sources*, fluorosis is slowly reversible. The "excess" fluoride is excreted in the urine and normal bone is formed if the essential ingredients are present. On the other hand, "continued release of accumulated fluoride could prevent blood fluoride concentrations from returning to normal and could cause a continued exposure of other body tissues to fluoride. The reversibility of skeletal fluorosis and skeletal storage of fluoride could then, theoretically, lead to chronic effects" (81). It is hypothesized here that these chronic effects may be prevented or successfully treated with substantial intake of Mg (most particularly) and other nutrients such as Ca and trace minerals.

Thus, the degree of continuing soft-tissue toxicity may well depend on the stored levels of F^- in the body, the rate of F^- turnover and excretion (in the absence of continued F^- intake), plus the fluctuating levels of bioavailable Mg; it has been suggested that about half of accumulated F^- in the body would be excreted in about eight or nine years under normal, "no treatment" circumstances (81).

It is interesting to note here that in a follow-up study of osteoporotic patients previously given sodium fluoride (NaF) to increase bone mass, at 1.5 years after the NaF was discontinued these patients actually lost spinal bone mass at a rate *faster* than that usually seen during the phase of rapid bone loss immediately after menopause–despite ongoing therapy with estrogen (estrogen normally inhibits bone resorption) and calcium (82). This occurrence may reflect the body's attempt to rid itself of the toxic levels of F^- stored in

bone. In addition, it is hypothesized here that the "normal" rapid bone loss seen after menopause may reflect a complex adaptive process whereby significant levels of F^- are finally released from female bone during a time when pregnancy (and fetal exposure to higher, more toxic levels of F^-) cannot occur. Further evidence regarding gender and MDFE is presented in Part II.

Fluoride's impact on acetylcholinesterase (AChE), the ubiquitous critical enzyme which hydrolyzes acetylcholine (ACh) at a high rate of activity (turnover time of 150 microseconds), is particularly relevant to this argument since (a) magnesium is a potent activator of AChE, and (b) various fluoride compounds (e.g., sulfonyl fluorides) irreversibly bind to the active sites of AChE action *in vivo*, completely inhibiting AChE action at those bound sites. Acetylcholine is widespread throughout the body and functions in various classes of neurons in both the central and peripheral nervous systems by, for example, conveying sensory information to the brain and controlling muscular tension. These neurons include preganglionic fibers of both the sympathetic and parasympathetic nervous systems, motor neurons to skeletal muscle, and neurons within the central nervous system.

Acetylcholine release can be either excitatory (e.g., skeletal muscle cell) or inhibitory (e.g., cardiac muscle cell), depending on the nature of the receptor and tissue type with which it interacts. ACh is critically involved with, for example, motor behavior, sleep, memory, vasodilation, gastrointestinal peristalsis, and cardiac inhibition. In the central nervous system (CNS), muscarinic rather than nicotinic responses predominate, but many central cholinoceptive neurons exhibit either mixed responses (e.g., Renshaw cells, small cells with short axons that connect motor nerve axons with each other) or predominately nicotinic responses which are excitatory with fast onset and short duration (e.g., neurons in the thalamus, the region of the brain which receives all sensory stimuli as the site of initial recognition and integration of pain, touch, and temperature, and which also plays an important role in the generation of signals that regulate the hypothalamic-pituitary-adrenal (HPA) axis) (83). Dysfunction of the HPA axis has been demonstrated in patients with FMS (84) and CFS (85).

As noted above, ACh normally has an exceptionally short life span as its action is terminated within microseconds by enzymatic degradation. Acetylcholine is hydrolyzed to acetate and choline by AChE, which is located in the synaptic cleft between neurons, or between the neuron and the muscle cell membrane. (Interestingly, cholinesterases are also found in non-neuronal tissues–a fact which may be highly relevant to this argument, but specific effects are unknown.) When the action of AChE is blocked (as by a fluoride compound), ACh accumulates in the synaptic cleft and persists in regions close to the neuronal membrane for at least several seconds because removal

by diffusion alone is very slow. The ACh molecule which diffuses off a receptor and is not immediately degraded by AChE "may attach to another receptor and open its ionophore, thus repeatedly depolarizing the membrane" (86).

The excess ACh which accumulates can also spill over onto adjacent neurons (87) producing as yet undefined and potentially devastating neurochemical effects in the peripheral as well as the central nervous system; one very possible CNS result could be the disturbance of serotoninergic systems (88) found in FMS and CFS patients. In addition, it appears that spontaneous release of ACh is increased by F^- which stimulates adenylate cyclase, an enzyme necessary for the production of cyclic AMP (89). Furthermore, AChE is inhibited by excess substrate; that is, AChE is most active against low concentrations of ACh, but is inhibited by higher concentrations (90).

Anticholinesterase agents (including many fluorinated compounds, such as DFP and Sarin) cause ACh to accumulate at cholinergic receptor sites. This inhibition of AChE function is capable of producing effects that are equivalent to excessive stimulation of cholinergic receptors throughout the central and peripheral nervous systems (91). Anti-ChE agents are responsible, at variable dosages, for stimulation of muscarinic receptor responses at autonomic effector organs, stimulation (followed by–with high enough doses–depression or paralysis) of autonomic ganglia and skeletal muscle, and stimulation (with occasional subsequent depression) of cholinergic receptor sites in the CNS.

Anti-ChE agents, especially organophosphorous types, also exert a number of "direct" postsynaptic actions on the receptor-channel macromolecule and/or its channel component; they cause morphological, pathological (muscle myopathies and neurotoxicity followed by demyelination), and teratological changes (83). Nicotinic actions of anti-ChE agents at the neuromuscular junctions of skeletal muscle cause muscle fatigue and generalized weakness, involuntary twitchings, scattered fasiculations, and eventually severe weakness and paralysis (91). "When inhibition of the enzyme [AChE] is great, synaptic function can be so completely disrupted that the nervous system cannot operate and the organism dies; it is for this reason that inhibitors of AChE are the major products used throughout the world as insecticides and as potential war 'nerve' gases" (86).

Thus, F^- excites skeletal muscle possibly by activating adenylate cyclase in the nerve ending, inhibiting cholinesterase, and/or increasing sensitivity of the endplate to ACh–mechanisms unrelated to decalcification at the site of the neuromuscular junction. One precise mechanism investigated in experiments using sodium fluoride (NaF) is hypothesized as follows: "NaF activates adenylate cyclase, thus raising the cAMP level in the nerve ending; cAMP improves spontaneous or evoked release of the transmitter; the

m.e.p.p. frequency is raised, ChE is inhibited, and the ACh sensitivity of the endplate is increased; depolarization of the endplate region by ACh is made so intensive that the action potential is generated; finally fibrillation occurs or the twitch is augmented as a result of recruitment of the muscle fibers" (92).

Decreased degradation of ACh may also result in increased quantities of ACh reaching smooth muscles, which activates excitatory muscarinic receptors. Cholinesterase inhibition can, therefore, also increase sympathetic tone by eliciting spontaneous discharge of ganglionic neurons and activating central sympathoadrenal pathways, which when chronic can result in a sustained, exhausting, system-wide "fight or flight" response. For example, intravenous administration of physostigmine (a "reversible" AChE inhibitor) in the absence of stimulation results in a gradual increase in muscle tension. When muscle tension returns to baseline, parasympathetic stimulation then results in a large, abrupt contraction. Thus, following AChE inhibition parasympathetic activation elicits muscle contraction by stimulation of sympathetic nerve terminals. Over-activity of sympathetic neurons may be produced within various body systems as a consequence of AChE inhibition (93).

Part II of this review describes in greater detail the theorized primary role of MDFE in the etiology and pathogenesis of P-FSs.

REFERENCES

1. Knight AL. Fluorides. In: Zenz C, Dickerson OB, Horvath EP, eds. *Occupational Medicine.* 3rd ed. St. Louis: Mosby; 1994:496-500.
2. Howe-Grant M, ed. *Fluorine Chemistry: A Comprehensive Treatment.* New York: John Wiley & Sons; 1995.
3. Underwood EJ. *Trace Elements in Human and Animal Nutrition.* New York: Academic Press; 1971.
4. Navia JM, Aponte-Merced L, Punyasingh K. Fluoride Metabolism in Humans. In: Prasad AS, ed. *Essential and Toxic Trace Elements in Human Health and Disease.* New York: Alan R. Liss, Inc.; 1988:229-250.
5. Goyer RA. Toxic and Essential Metal Interactions. *Annu Rev Nutr.* 1997; 17:37-50.
6. Emsley J, Jones DJ, Miller JM, et al. An Unexpectedly Strong Hydrogen Bond: Ab Initio Calculations and Spectroscopic Studies of Amide-Fluoride Systems. *J Am Chem Soc.* 1981;103:24-28.
7. Messer HH. Fluorine. In: Frieden E, ed. *Biochemistry of the Essential Ultratrace Elements.* New York: Plenum Press;1984:55-87.
8. Waldbott GL. Fluoride in Clinical Medicine. *Int Arch Allergy Appl Immunol.* 1962;20(suppl 1):1-60.
9. Galland L. Magnesium, Stress and Neuropsychiatric Disorders. *Magnes Trace Elem.* 1991-92;10(2-4):287-301.
10. Galland L. Normocalcemic Tetany and Candidiasis. *Magnesium.* 1985;4: 339-344.

11. Durlach J, Bac P, Durlach V, et al. Neurotic, Neuromuscular and Autonomic Nervous Form of Magnesium Imbalance. *Magnes Res.* June 1997;10(2):169-195.
12. Cox IM, Campbell MJ, Dowson D. Red Blood Cell Magnesium and Chronic Fatigue Syndrome. *Lancet.* 1991;337:757-760.
13. Abraham GE, Flechas JD. Management of Fibromyalgia: Rationale for the Use of Magnesium and Malic Acid. *J Nutr Med.* 1992;3:49-59.
14. Russell IJ, Michalek JE, Fletchas JK, Abraham GE. Treatment of Fibromyalgia Syndrome with Super Malic®: A Randomized, Double Blind, Placebo Controlled, Crossover Pilot Study. *J Rheumatol.* 1995;22(5):953-958.
15. Durlach J. Recommended Dietary Amounts of Magnesium: Mg RDA. *Magnes Res.* September 1989;2(3):195-203.
16. National Research Council Subcommittee on the Tenth Edition of the RDAs. *Recommended Dietary Allowances.* 10th ed. Washington, DC: National Academy Press; 1989:187-194.
17. 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.* May 1990;35(5):503-507.
18. Seelig MS. Magnesium Requirements in Human Nutrition. *Magnes Bull.* 1981;1a:26.
19. Dreosti IE. Trace Elements in Nutrition. *Med J Aust.* August 9 1980;2:117-123.
20. Fox MRS. Effects of Dietary Mineral Levels on Metabolism and Requirements. *Neurotoxicology.* 1983;4(3):113-120.
21. Marier JR. Comments on Magnesium Intake and Fluoride Intake in the Modern-Day World. *Proc Finn Dent Soc.* 1980;76:82-92.
22. Burt BA. The Changing Patterns of Systemic Fluoride Intake. *J Dent Res.* May 1992;71(5):1228-1237.
23. Cassidy JT. Progress in Diagnosing and Understanding Chronic Pain Syndromes in Children. *Curr Opin Rheumatol.* 1994;6(5):544-546.
24. Vercoulen JH, Swanink CM, Fennis JF, et al. Prognosis in Chronic Fatigue Syndrome: A Prospective Study on the Natural Course. *J Neurol Neurosurg Psychiatry.* May 1996;60(5):489-494.
25. Norregaard J, Bulow PM, Prescott E, et al. A Four-Year Follow-Up Study in Fibromyalgia. Relationship to Chronic Fatigue Syndrome. *Scand J Rheumatol.* 1993;22(1):35-38.
26. White KP, Speechly M, Harth M, et al. Fibromyalgia in Rheumatology Practice: A Survey of Canadian Rheumatologists. *J Rheumatol.* April 1995;22(4): 722-726.
27. Ramsay AM. *Myalgic Encephalomyelitis and Postviral Fatigue States: The Saga of Royal Free Disease.* 2nd Ed. London: Gower Medical Publishing; 1988.
28. Johnson H. *Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic.* New York: Penguin Books; 1996:196-216.
29. Briggs NC, Levine PH. A Comparative Review of Systemic and Neurological Symptomatology in 12 Outbreaks Collectively Described as Chronic Fatigue Syndrome, Epidemic Neuromyasthenia, and Myalgic Encephalomyelitis. *Clin Infect Dis.* 1994;18(suppl 1):S32-S42.

30. Hyams KC, Wignall FS, Roswell R. War Syndromes and Their Evaluation: From the U. S. Civil War to the Persian Gulf War. *Ann Intern Med.* September 1 1996;125(5):398-405.

31. Clauw DJ, Chrousos GP. Chronic Pain and Fatigue Syndromes: Overlapping Clinical and Neuroendocrine Features and Potential Pathogenic Mechanisms. *Neuroimmunomodulation.* May 1997;4(3):134-153.

32. Buchwald D. Fibromyalgia and Chronic Fatigue Syndrome: Similarities and Differences. *Rheum Dis Clin North Am.* May 1996:22(2):219-243.

33. Bell DS, Bell KM, Cheney PR. Primary Juvenile Fibromyalgia Syndrome and Chronic Fatigue Syndrome in Adolescents. *Clin Infect Dis.* January 1994;18(suppl 1): S21-S23.

34. Levine PH. Epidemic Neuromyasthenia and Chronic Fatigue Syndrome: Epidemiological Importance of a Cluster Definition. *Clin Infect Dis.* 1994;18(suppl 1): S16-S20.

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

36. Wallach S. Availability of Body Magnesium During Magnesium Deficiency. *Magnesium.* 1988;7(5-6):262-270.

37. Aikawa JK. The Role of Magnesium in Cellular Processes. In: *Magnesium: Its Biologic Significance.* Florida: CRC Press; 1981:21-29.

38. Aikawa JK. A General Hypothesis Concerning the Biochemical and Cellular Functions of Magnesium. In: *The Relationship of Magnesium to Disease in Domestic Animals and in Humans.* Springfield, IL: Charles C. Thomas; 1971:3-43.

39. Whitford GM. The Physiological and Toxicological Characteristics of Fluoride. *J Dent Res.* February 1990;69:539-549.

40. Kusniec F, Fisher G, Sela BA, et al. Magnesium Protects Against Anaphylactic Shock and Cardiac Myolysis in Guinea-Pigs. *J Basic Clin Physiol Pharmacol.* Jan 1994;5(1):45-58.

41. Seelig MS. Consequences of Magnesium Deficiency on the Enhancement of Stress Reactions: Preventive and Therapeutic Implications (a review). *J Am Coll Nutr.* October 1994;13(5):429-446.

42. Aikawa JK. Magnesium Deficiency in Man. In: *Magnesium: Its Biologic Significance.* Florida: CRC Press; 1981:57-68.

43. Al Ghamdi SM, Cameron EC, Sutton RA. Magnesium Deficiency: Pathophysiologic and Clinical Overview. *Am J Kidney Dis.* November 1994;24(5):737-752.

44. Langley WF, Mann D. Central Nervous System Magnesium Deficiency. *Arch Intern Med.* March 1991;151(3):593-596.

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

46. Zaloga GP, Chernow B, Pock A, et al. Hypomagnesemia is a Common Complication of Aminoglycoside Therapy. *Surg Gynecol Obstet.* June 1984;158(6): 561-565.

47. Kaloyanides GJ. Antibiotic-Related Nephrotoxicity. *Nephrol Dial Transplant.* 1994;9(suppl 4):130-134.

48. Rylander R. Environmental Magnesium Deficiency as a Cardiovascular Risk Factor. *J Cardiovasc Risk.* February 1996;3(1):4-10.

49. Marier JR. Magnesium Content of the Food Supply in the Modern-Day World. *Magnesium.* 1986;5(1):1-8.

50. Durlach J, Durlach V, Bac P, et al. Magnesium and Ageing. II. Clinical Data: Aetiological Mechanisms and Pathophysiological Consequences of Magnesium Deficit in the Elderly. *Magnes Res.* December 1993;6(4):379-394.

51. Seelig MS. Auto-Immune Complications of D-Penicillamine–A Possible Result of Zinc and Magnesium Depletion and of Pyridoxine Inactivation. *J Am Coll Nutr.* 1982;1:207-214.

52. Rivlin RS. Magnesium Deficiency and Alcohol Intake: Mechanisms, Clinical Significance and Possible Relation to Cancer Development (a review). *J Am Coll Nutr.* 1994;13(5):416-423.

53. 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.

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

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

56. Grandjean P. Classical Syndromes in Occupational Medicine. Occupational Fluorosis Through 50 Years: Clinical and Epidemiological Experiences. *Am J Ind Med.* 1982;3:227-236.

57. Roholm K. Fluorine Intoxication. *A Clinical-Hygienic Study with a Review of the Literature and Some Experimental Investigations.* London: H. K. Lewis & Co., Ltd.; 1937.

58. Shupe JL, Peterson HB, Leone NC, eds. *Fluorides: Effects on Vegetation, Animals and Humans.* Salt Lake City, UT: Paragon Press; 1983.

59. Arnbjornsson E, Arnbjornsson A, Olafsson A. Thyroid Cancer Incidence in Relation to Volcanic Activity. *Arch Environ Health.* January 1986;41(1):36-40.

60. Guan Z-Z, Zhuang Z, Yang P-S, et al. Synergistic Action of Iodine-Deficiency and Fluorine-Intoxication on Rat Thyroid. *Chin Med J.* 1988;101(9):679-684.

61. Kishi K, Ishida T. Clastogenic Activity of Sodium Fluoride in Great Ape Cells. *Mutat Res.* 1993;301:183-188.

62. Kharasch ED. Metabolism and Toxicity of the New Anesthetic Agents. *Acta Anaesthesiol Belg.* 1996;47(1):7-14.

63. Lochhead KM, Kharasch ED, Zager RA. Spectrum and Subcellular Determinants of Fluorinated Anesthetic-Mediated Proximal Tubular Injury. *Am J Pathol.* June 1997;150(6):2209-2221.

64. Martin JL, Plevak DJ, Flannery KD, et al. Hepatotoxicity After Desflurane Anesthesia. *Anesthesiology.* 1995;83:1125-1129.

65. National Research Council Committee on Toxicology. *Health Effects of Ingested Fluoride.* Washington: National Academy Press; 1993.

66. Whitford GM, Pashley DH. Fluoride Absorption: The Influence of Gastric Acidity. *Calcif Tissue Int.* 1984;36:302-307.

67. Whitford GM. The Metabolism and Toxicity of Fluoride. In: Myers HM ed. *Monographs in Oral Science.* Vol 13. Basel: Karger; 1989.

68. Spak CJ, Berg U, Ekstrand J. Renal Clearance of Fluoride in Children and Adolescents. *Pediatrics.* 1985;75(3):575-579.

69. Lantz O, Jouvin MH, de Vernejoul MC, et al. Fluoride-Induced Chronic Renal Failure. *Am J Kidney Dis.* 1987;10(2):136-139.

70. Bond AM, Murray MM. Kidney Function and Structure in Chronic Fluorosis. *Br J Exp Pathol.* 1952;33(2):168-176.

71. National Research Council Committee on Animal Nutrition. *Mineral Tolerance of Domestic Animals.* Washington, DC: National Academy Press; 1980:189.

72. Taves DR. Is Fluoride Intake in the United States Changing? In: Johansen E, Taves DR, Olsen TO, eds. *Continuing Evaluation of the Use of Fluorides.* Boulder, CO: Westview Press;1979:149-157.

73. Chen Y, Lin M, He Z, et al. Air Pollution-Type Fluorosis in the Region of Pingxiang, Jiangxi, Peoples' Republic of China. *Arch Environ Health.* July/August 1993;48(4):246-249.

74. 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.

75. Susheela AK, Jethanandani P. Serum Haptoglobin and C-Reactive Protein in Human Skeletal Fluorosis. *Clin Biochem.* 1994;27(6):463-468.

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

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

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

79. Kleerekoper M. Fluoride and the Skeleton. *Crit Rev Clin Lab Sci.* 1996; 33(2):139-161.

80. Kleerekoper M. Fluoride and the Skeleton. In: Bilezikian JP, Raisz LG, Rodan GA, eds. *Principles of Bone Biology.* New York: Academic Press;1996:1053-1062.

81. Grandjean P, Thomsen G. Reversibility of Skeletal Fluorosis. *Br J Ind Med.* 1983;40:456-461.

82. Talbot JR, Fischer MM, Farley SM, et al. Gains Made in Spinal Bone Density in Response to Fluoride Therapy for Osteoporosis Are Not Maintained After Fluoride Therapy is Discontinued. *J Bone Miner Res.* 1991;7(suppl 1):118 (abstract).

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

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

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

86. Standaert FG. Pharmacology of the Neuromuscular Junction. In: Brumback RA, Gerst JW, eds. *The Neuromuscular Junction.* Mount Kisco, NY: Futura Publishing Co.;1984:121-294.

87. Callister RJ, Sah P. The Removal of Acetylcholine by Diffusion at Nicotinic Synapses in the Rat Otic Ganglion. *J Physiol.* 1997;505(1):165-175.

88. 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.* May 1996;22(2):267-284.

89. Dryden WF, Singh YN, Gordon T, et al. Pharmacological Elevation of Cyclic AMP and Transmitter Release at the Mouse Neuromuscular Junction. *Can J Physiol Pharmacol.* March 1988;66(3):207-212.

90. Silver A. Some Enzymological Aspects of Acetylcholinesterase. In: *The Biology of Cholinesterases.* Amsterdam: North Holland Publishing Co.; 1974:10. Neuberger A, Tatum EL. eds. *Frontiers of Biology;* vol. 36.

91. Taylor P. Anticholinesterase Agents. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* New York: McGraw-Hill; 1996:161.

92. Hattori T, Maehashi H. Excitation of Skeletal Muscle by Fluoride. In: Tsunoda H, Yu M-H eds. *Fluoride Research 1985.* Amsterdam: Elsevier; 1986:277-284. *Studies in Environmental Science;* vol. 27.

93. Beauregard CL, Smith PG. Parasympathetic Excitation of Sympathetic Innervation After Cholinesterase Inhibition. *Br J Pharmacol.* 1996;117:51-54.

94. Martin AE. Fluorides and General Health: Introduction. In: *Fluorides and Human Health.* Geneva: World Health Organization; 1970:273.

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

96. National Research Council Committee on Biologic Effects of Atmospheric Pollutants. *Fluorides.* Washington, DC: National Academy of Sciences; 1971:4.

97. 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.

98. 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.* November 1994;39(11):991-994.