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THE USE OF GUAIFNESIN IN FIBROMYALGIA

This technical supplement is intended primarily for medical personnel who are familiar with *fibromyalgia*. Herein we offer our description of the disease, our theory as to the cause, and our treatment for its reversal. We extend the following to support our perceptions of the disturbed physiology and biochemistry that produce the illness.

The syndromes of fibromyalgia, chronic fatigue, myofascial pain, and chronic candidiasis are variants in a disease spectrum that should be merged under one name. Differing pain thresholds and affected areas alter clinical presentations and lead to disparate nomenclature. The name Fibromyalgia infers pain in muscles and fibers. *Energopenia* would be more descriptive since that term would identify a lack of energy as the underlying cause.

When visiting physicians, patients focus on their currently worst and omit less-dominant symptoms. The following is a compilation of potential presenting complaints. **Musculoskeletal** pain (any muscle, tendon, ligament, joint, leg or foot cramps, numb or tingling limbs-digits-face); **brain** (fatigue, irritability, depression, apathy, nervousness, anxiety, insomnia, suicidal ideation, impaired memory and concentration); **irritable bowel** (nausea, gas, bloating, cramps, pain, constipation, diarrhea); **genitourinary** (dysuria, urgency, pungent urine, bacterial or interstitial cystitis, vulvodynia); **dermatologic** (rashes: hives, eczema, vesicles, acne, rosacea, seborrheic or neurodermatitis, red or clear maculopapules; brittle nails, dry hair with premature loss, paresthesias, allodynia, itching, purpura); **head, eye, ear, nose and throat** (variably-located headaches, dizziness or imbalance, vertigo, dry-irritated eyes, conjunctivitis, blepharitis, dark-circled lower eyelids, crusty discharges or morning grit, blurred vision, nasal congestion and excess mucus, post-nasal drip, abnormal tastes, painful tongue, scalded mouth, tinnitus or low-pitched sounds); **miscellaneous** (weight gain, low-grade fever, water retention, restless legs, heightened sensitivity to light, sounds and odors sufficient to cause nausea or headaches; **allergies** (late-onset hayfever or asthma).

Symptoms usually begin spontaneously, but patients often attribute the onset to stress, infection, surgery or trauma. Yet with a careful history we can often jog memories into recalling symptoms such as the misnomer of ‘growing pains’ in childhood. Symptoms are cyclic and initially interspersed with good and bad days. Progressively, serious incapacity prevails without significant respite. My fifty-year observations strongly suggest that unresolved fibromyalgia deteriorates into osteoarthritis. Older family members relate many past symptoms, but eventually, joint pains dominate. When examined they display the same physical lesions as their affected relatives.

Fibromyalgia is multi-genetic with aberrant genes scattered on a few chromosomes. We currently participate in a genetic study that has thus far revealed three abnormal genes in forty percent of our study patients. Tissue susceptibilities and variable symptoms reflect the interplay of dominant and recessive genes. We have diagnosed patients aged two and others with late onset in their seventies. There is equal frequency in pre-pubertal boys and girls, but a strong female preponderance (85%) in adulthood. Obviously, males remain carriers so either parent may transmit mutant genes.

Fifty years ago we began treating fibromyalgia (then nameless) with uricosuric agents. Seventeen years ago we found the therapeutic value of the barely-uricosuric **guaifenesin** that we have now used for over ten thousand patients¹. Cyclic clearing reproduces prior symptoms reminiscent of purging gout. With medication, lesions reverse using various dosages according to patient responses. The required, cumulative dosages of **long-acting** drug are as follows: 300 mg. twice daily favorably affects 20% of patients; 600 mg. bid, 80%; 1800 mg. per day 90%. We add **short-acting** tablets (400 mg.) in whatever increments are needed for the remaining 10% and to bypass the cytochrome system. Particularly impeding is CYP-450 3A4 that partially destroys many long-acting medications during their transit-delayed absorption. Over one-hundred drugs may raise its level and thereby force dosage adjustments. Short-acting guaifenesin circumvents some of that assault due to rapid absorption. By combining long with short acting drug, we bypass some cytochrome exposure and yet maintain near twenty-four hour protection.

Individual genetic responsiveness determines the time needed for recovery. Even the slowest responders clear a minimum of one year of accumulated lesions for every two months of treatment. Lower-dosage patients greatly accelerate the process. Improvement is initially expressed in hours, later in days and eventually in weeks.

Like uricosurics, renal effects of guaifenesin are totally blocked by salicylates. Such agents are readily absorbed through the skin, oral or intestinal mucosa and a portion concentrates in the proximal renal tubules. Plants use salicylates to heal wounds, signal other plants, repel pests, or kill soil organisms. Their sap readily adheres to skin so vinyl gloves should be worn when gardening and closed shoes when walking on grass. Lotions containing botanicals such as aloe, ginseng, castor or camphor oils, mint family members found in muscle balms, mouthwashes, lozenges or candies, deliver salicylates systemically within seconds. Many razor strips, deodorants, and lip balms contain blockers. Most tooth pastes contain unlisted mint and/or salicylates. Conjugating liver capacity that renders food sources harmless is limited and is readily overwhelmed by plant concentrates so often included in supplements.

Our physical examination is more thorough than the limited search for *eleven-out-of-eighteen-tender-points* recommended by the American College of Rheumatology. We search for swollen tissues and sketch our findings on a body caricature. An image results that depicts the shapes, sizes and locations of lesions (see *illustration*). Our **maps** are objective because we ignore subjective expressions of pain and so avoid the pitfall of variable pain thresholds. We re-map patients on all subsequent visits and are able to document sequential reversal of the illness. Certain tissues are preferentially affected: the earliest lesions appear near the elbows, followed by the sternomastoid and trapezial areas. **Spastic muscle bundles of the left thigh (vastus lateralis and rectus femoris) are present in 100% of adults and reliably validate the diagnosis. Those same lesions dependably clear within one month in compliant patients on an adequate dosage of medication** (see below).

The steadily-contracted muscles, tendons and ligaments we uncover are working tissues. Only a fundamental biochemical aberration could force fibromyalgic cells into such unrelenting overdrive. Theories seeking to explain the illness should neither ignore the plethora of symptoms arising from excitable and non-excitable tissues, nor the palpable abnormalities.

Since plasma uric acid levels were consistently normal, my success using uricosuric agents to treat this new entity forced me to implicate an anion other than urate. Cumulative data strongly point to a faulty metabolism of inorganic phosphate (P_i). Tissue excesses would evoke no inflammatory response, but would induce system-wide, biochemical misadventures. Using probenecid or guaifenesin, our limited urinary studies showed a steep increase in twenty-four hour excretion of phosphate. Uricosuric agents and guaifenesin equally promote lysis of dental calculus and cyclically normalize defective fingernails, both structures that are mineralized by calcium phosphate.

Several studies support our theory. Exercise fatigue is usually attributed to lactic acid and cell acidification. However, muscles recycle lactate for energy production and low pH heightens fiber sensitivity to calcium – two actions that increase endurance. In a study of maximal wrist-flexion exercises, pH froze at 6.2 but exhaustion only prevailed after a **nine-fold increase in diprotonated phosphate** ($H_2PO_4^-$).² Thus two anions are required to buffer the H^+ assault on pH and thereby avoid myocyte apoptosis. The unrelenting sinew contractions of fibromyalgia are akin to a twenty-four hour, continuous exercise that produces excess H^+ and P_i retention in mitochondria. Since ATP production is reduced by P_i accumulations, fatigue must follow as per the following formula

$$\Delta G = \frac{ATP}{ADP + P_i} \quad (\Delta G = \text{energy change}) \quad (P_i = \text{inorganic phosphate})$$

Many papers have addressed the energy deprivation of fibromyalgia; we refer to only a few. Bengtsson and Henricksson biopsied swollen and tender areas in trapezii and found a 20% reduction in ATP as well as the phosphocreatine reservoir of high-energy phosphates. The situation was actually worse because normal tissue was included and tested from the cored specimens.³ Adjacent and unaffected muscle tissues were barely altered. This was confirmed by Lindman.⁴ Strobel found increased P_i , decreased phosphocreatine and low pH in contracted spinal erector muscles of fibromyalgics using ^{31}P magnetic resonance spectroscopy⁵. Other studies support this including one that tested patients at rest.⁶ Low erythrocyte ATP has also been reported. Newer studies have revealed low ATP in platelets (Bazzichi⁷). A similar state exists in neutrophils from chronic fatigue patients (to us fibromyalgia) as determined by Myhill who coined the term “ATP profile”⁸.

The P_i to PCr ratio is an accepted measure of available cellular energy and is clearly altered by the decreased PCr cited above. High intracellular AMP and ADP found in some studies strongly signals energy deprivation. Reported increases in plasma pyruvate and low or normal lactate suggest intact anaerobic metabolism. High pyruvate suggests a fully-operative Krebs' cycle that for whatever reason does not segue properly into the more effective, aerobic sequences.

PATIENT: _____ DATE: _____

Fatigue	Hunger/Tremors	Eye Irritation	Bloating	Itching
Irritability	Palpitations	Nasal Congestion	Constipation	Rashes
Nervousness	Panic Attacks	Abnormal Tastes	Diarrhea	Sensitivities
Depression	Frontal Headaches	a) Bad	Dysuria	a) Chemical
Insomnia	Occipital Headaches	b) Metallic	Frequent Urine	b) Light
Impaired Concentration	General Headaches	Ringing Ears	Bladder Infections	c) Odor
Impaired Memory	Dizziness	Numbness	Vaginitis	d) Sounds
Anxiety	a) Vertigo	Swollen Legs	Weight Changes	Allergies
Salt Craving	b) Imbalance	Leg Cramps	Brittle Nails	Growing Pain
Sugar Craving	c) Faintness	Nausea	Burning	Pain
Sweating	Blurred Vision	Gas	Skin Sensations	

Though non-diagnostic and difficult to reproduce, other aberrations have been reported: **decreased** growth hormone, IGF-1, serotonin, free ionic Ca^{2+} , calcitonin, free urinary cortisol and a weak cortisol response to ACTH, certain amino acids, neuropeptide Y, defective T cell activation, poor TSH response to TRH; **increased** serum prolactin, mast cell recruitment to the epidermis that release their contents such as histamine, heparin, and multiple other cytokines; elevated homocysteine and substance P in cerebrospinal fluid, and plasma angiotensin converting enzymes. A report by Zhang and others including us have recently reported several elevated cytokines and exciting changes induced by guaifenesin.⁹ A report of genetic mutations is in preparation. These collective findings underscore the likelihood of a fundamental, metabolic error that is *erratically* and *variably* imposed upon selected tissues. Our earlier suggestion for a more descriptive nomenclature seems apropos in view of such multiple-organ involvement.

Ingested P_i is 80-90% absorbed via dedicated receptors in the small intestine. The proximal renal tubules respond to bodily requirements either by reabsorbing it from glomerular filtrates or by measured excretion of surpluses. We postulate a basic tubular defect as well as other, chromosome-scattered, genetic aberrations that alter tissue rapport. Such disharmony could certainly arise from pathologic retention of inorganic phosphate when it accumulates beyond buffering requirements and then imposes near-hibernation on intracellular organelles.

As described above, we implicate excess H_2PO_4 as prime suspect for the body-wide dearth of ATP and the exhaustion of fibromyalgia. Phosphate is heavily concentrated and energized in mitochondria by triple-bonding with adenosine to form ATP. Though phosphate successfully binds matrix hydrogen, it also leads to cellular fatigue by blocking egress of H^+ to the outer chamber and thus creates a proton deficit in that space. Such trapping obstructs the mandatory to-and-fro transport of H^+ via the inner membrane rotor that is essential for ATP production. The accumulated matrix H^+ lowers pH, which attracts more phosphate and increased formation of diprotonated P_i .

ATP can be exported from muscles and platelets to currently higher expenditure sites. This support must falter in fibromyalgics since it barely meets energy demands and too often, not at all. Tiny energy surpluses do occasionally arise and permit bursts of effort. Such free spending soon results in erratic deficits that account for rapidly shifting symptoms. Other high-energy phosphate suppliers (ITP^3 , GTP^3) may likewise stumble when saddled with the *accelerated metabolism* of fibromyalgia. High energy demands from the stresses of healing infections, accident or surgical damage, and emotional upsets can be final insults that initiate attacks.

The ultimate messenger, calcium, drives cells to perform their specialized functions. Nanomolar blishes reflect the intensity of incoming signals and are distributed to various organelles. Tiered impulses permit graded efforts carried to the extreme as rigor mortis. Calcium enters cells to buffer the negatively-charged P_i^{2-} . ATP-driven pumps must then extrude calcium from cells or force storage into mitochondria and endoplasmic reticula to halt cellular activity. ATP-depleted fibromyalgics insufficiently man the pumps and fail to restore a mandatory calcium-free cytosol. Continuous goading by such residual calcium induces unrelenting tissue work and further exhausts an ever-dwindling energy supply. That is the only logical explanation for the steadfast tissue spasms of fibromyalgia. **Sustained cytosol calcium levels permit neither brain-muscle-tendon-ligament relaxation** nor full rest for non-excitables tissues. Since physiologic dilutions must be maintained water is internalized through co-entry of sodium and chloride. Palpable lesions are mainly due to intracellular water retention. Swelling presses on nerves to elicit pain, paresthesias, and allodynia.

As patients become progressively more sedentary the body responds by destroying up to 80% of what it interprets as surplus mitochondria. Carbohydrate craving follows in a futile attempt to generate energy. Its metabolites have difficulty connecting into the fewer remaining, dysfunctional mitochondria. Residual glucose releases insulin that abets its conversion to fat, subsequent storage and weight gain. Insulin wreaks further havoc by strongly promoting renal re-absorption of phosphate and its cellular absorption that in turn traps glucose for local consumption.

Body wide secretions try to eject the offending ions as phosphoric acid. Tears may burn and desiccate leaving crystals, the morning “sand.” Salivary outflows produce a scalded oral mucosa, bad or metallic tastes, lingual irritation, and finally precipitate out as dental calculus (calcium phosphate). Amorphous urinary sediments are composed of calcium phosphate, oxalate, or carbonate. They precipitate in the bladder and, upon urination, abrade the trigone and urethral mucosa to cause dysuria. That added to frequency, urgency and lower abdominal pain lead to the diagnosis of “interstitial cystitis.” The denuded surfaces also facilitate bacterial invasion and repeated bladder infections. The vaginal mucosa and muscles are likewise irritated as reflected by vulvitis, vestibulitis, bacterial or fungal infections, and dyspareunia.

Other mucosal surfaces in the eye, lids or mouth may also suffer acidic burns. The integument is often affected causing paresthesias, allodynia, defective nails (chipping or peeling), poor hair texture and growth. Mast cells malfunction and add to systemic discomfort by releasing cytokines (eotaxin, MCP-1, TNF alpha, IL-6 etc.) into the epidermis, bronchial, intestinal, vaginal, and bladder mucosas¹⁰. Among those secretions are histamine that induces itching, various rashes, and heparin that accounts for the easy bruising seen in 80% of fibromyalgic women.

HYPOGLYCEMIA

Steady fuel consumption of overworked tissues demands energy replenishment frequently reflected as sugar craving. Carbohydrates generate very little however since ATP production is impaired downstream. Especially patients from families with diabetes mellitus or dysregulated beta-cell function evoke exaggerated insulin responses. They suffer episodes of **hypoglycemia** or **glucopenia**, the preferred term for tissue glucose deprivation especially brain. Genter and Ipp studied twenty young, healthy subjects during glucose tolerance testing. They sampled blood every ten minutes and measured counter-regulatory hormone releases. Nine suffered acute epinephrine effects despite what seemed acceptably-normal glucose levels.¹¹ Individual thresholds vary for instigating corrective neuro-endocrine responses. Recurrent bouts alter set points and initiate counter measures only at lower glucose levels.^{12,13} Restriction of high-glycemic-index foods restores normal signaling within two weeks.

The **acute symptoms** are flagrant: tremors; clamminess; pounding, fluttering or rapid heart; headaches; weakness; irritability; anxiety; intense hunger; faintness; even panic attacks --all induced by counter-regulatory surges of epinephrine. They last about twenty minutes and typically strike a few hours postprandially or nocturnally. Were such complaints made by insulin-dependent diabetics, physicians would unhesitatingly diagnose hypoglycemia without the challenge of an unreliable glucose tolerance test. They are collectively diagnostic of glucopenia and should not be attributed to fibromyalgia. The **chronic** symptoms cannot be separated from fibromyalgia. They include: fatigue, irritability, nervousness, depression, insomnia, impaired memory and concentration, irritable bowel syndrome, water retention and aching. All facets of hypoglycemia, acute or chronic, totally regress by closely adhering to a low-carbohydrate diet.

Many fibromyalgics gain weight, some possibly due to lassitude, but perhaps more from the loss of mitochondria as mentioned above. The body does not feed unused, expendable structures. Additionally, the surviving organelles are inefficient and they struggle to produce basic survival requirements for ATP. The energy-starved brain and various hormones encourage carbohydrate gorging. Thus, insulin surges and glucagon releases are suppressed: a perfect milieu for weight gain. Malonyl CoA is enhanced to promote the conversion of glucose to fatty acids and insulin triggers storage of triglyceride.

Aerobic exercises as simple as walking restore mitochondria in red muscle fibers (type I), those most affected in fibromyalgia. Such resurrected structures increase energy production, burn calories and initiate weight reduction. Anaerobic workouts benefit primarily the less-affected white fibers (type II) that contain far fewer mitochondria.

TREATMENT SUMMARY

In summary, this paper is long in theory but based on many facts, some that we have not discussed. Guaifenesin is highly successful for treating fibromyalgia, but is totally ineffective if salicylates gain entry from whatever portal. Even relatively tiny

amounts found in cosmetics, toothpastes and botanicals lodge in the proximal renal tubule and negate drug benefits.^{14,15,16,17,18} Genetic makeup determines dosage, susceptibility to blocking and cytochrome recruitment. Hypoglycemia and carbohydrate intolerance cause confusion if not properly addressed and wrongly suggest inadequate control of fibromyalgia. During improvement, patients should begin aerobic exercising and thereby restore mitochondria. **Adherence to our protocol must be meticulous or there will be no benefits.** Physicians who deviate from this design do disservice to their patients and condemn them to failure.

It is our mission to disseminate information gleaned by a single physician and a fifty-two year experience. Our protocol uses a non-toxic, over-the-counter drug that works to mitigate an innate metabolic error. Most research focuses on obtunding symptoms and ignores the root cause of the illness. We offer the only currently successful protocol for reversing fibromyalgia. We hope to wean physicians and patients away from symptomatic '**threatments**' that promote polypharmacy with the use of habituating or addicting drugs.

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