

## THE USE OF GUAIFENESIN IN FIBROMYALGIA

This technical supplement is intended primarily for medical personnel who are familiar with *fibromyalgia*. Herein we describe the disease, our theory as to the cause, and our treatment protocol for its reversal. The following paragraphs are offered in support for our current perceptions of the disturbed physiology and biochemistry that produce the illness.

The syndromes of fibromyalgia, chronic fatigue, and myofascial pain are variants of a complex spectrum that should be merged under one name. Dominantly affected areas and differing pain thresholds greatly alter clinical presentations and lead to such disparate nomenclature. The name Fibromyalgia infers pain in muscles and fibers. *Energopenia* (dearth of energy) would be a more unifying term to describe the underlying pathology.

When visiting physicians, patients usually focus on their currently worst and omit less-disturbing symptoms. The following is a compilation of potential presenting complaints. **Musculoskeletal** pain (any muscle, tendon, ligament, joint), leg or foot cramps, restless legs, numb or tingling limbs-digits-face); **brain** (fatigue, irritability, depression, apathy, nervousness, anxiety, insomnia, suicidal ideation, impaired memory and concentration, heightened sensitivity to light, sounds and odors sufficient to induce nausea or headaches); **irritable bowel** (nausea, gas, bloating, cramps, pain, constipation, diarrhea); **genitourinary** (dysuria, urgency, pungent urine, bacterial or interstitial cystitis, vulvodynia); **dermatologic** (rashes: hives, eczema, pruritic 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 and irritated eyes, conjunctivitis, blepharitis, dark-circles in the lower eyelids, crusty discharges and 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, and **allergies** including late-onset hayfever or asthma).

PATIENT: \_\_\_\_\_ DATE: \_\_\_\_\_

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

Symptoms usually begin spontaneously, but patients sometimes attribute onset to stress, infection, surgery or trauma. Yet, with a careful history we often jostle memories into recalling symptoms such as “growing pains” in childhood. Symptoms are cyclic and initially intersperse with good and bad days. Progressively, serious incapacity prevails without much respite. My fifty-five year observations suggest that unresolved fibromyalgia segues into osteoarthritis. Older family members describe years of symptoms that are currently dominated by joint pains. They display the same physical lesions as their affected relatives.

We contend that fibromyalgia is an illness induced by an interplay of mutant genes that further alter recessive and dominant traits. We have diagnosed patients aged two and others with late onset in their seventies. We can now offer supporting data for the existence of a multigenetic disorder. Feng and our research group have reported corroborating evidence<sup>(1,2)</sup>. Three errant genes on scattered chromosomes have surfaced in up to 40% of our study patients. These polymorphisms seem to share closely related, biochemical pathways since their interweaving effects produce the combined syndromes we recognize as fibromyalgia. The search is ongoing; two other genetic suspects are under investigation.

Serial findings in children reveal a pecking order of musculoskeletal susceptibilities that succumb sequentially to the genetic misadventure. The incidence of juvenile fibromyalgia is equal in boys and girls, but consistent improvement

occurs at puberty. The differing metabolic needs between the sexes later skews statistics and 85% of adult patients are women. Nevertheless, asymptomatic males remain genetic carriers and either parent can transmit the disease. We expect a variety of symptoms from patients at presentation. Descriptions of pain dependably point to the locations of lesions we will find on palpation.

Fifty-five years ago we began treating fibromyalgia (then nameless) with uricosuric agents. Twenty-two years ago we found a potent, therapeutic value from the barely uricosuric **guaifenesin** that we have now used for over ten thousand patients<sup>(3)</sup>. Cyclic clearing reproduces prior symptoms reminiscent of purging gout. With this medication, lesions reverse using various dosages determined according to patient responses. The required, cumulative dosages of **longer-acting** drug are as follows: 300 mg, twice daily favorably affects 20% of patients; 600 mg, twice daily, 80%; 1800 mg, daily, 90%. We add **short-acting** tablets (400 mg.) in whatever increments are needed for the remaining 10% to bypass deleterious cytochrome effects. Particularly destructive is CYP-450 3A4, which especially attacks extended-release medications owing to their long transit down the gut and their delayed absorption. Over one hundred drugs and supplements may raise its level and thereby force dosage adjustments. Short-acting guaifenesin circumvents some of that assault. It is rapidly absorbed, but its 4-5 hour effect is too brief for it to be used alone. So we combine it with longer-acting medication and thus gain tandem proficiency.

Individual genetic responsiveness determines dosages and time needed for recovery. Even the slowest responders clear a minimum of one year of accumulated 'debris' 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 the uricosuric agents, renal effects of guaifenesin are totally blocked by salicylates. That compound is readily absorbed through the skin, the oral and intestinal mucosa. A portion concentrates in the proximal renal tubules<sup>(4,5)</sup>. Plants use salicylates to heal their wounds, signal other plants, repel pests, or kill soil organisms<sup>(6)</sup>. 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, camphor, or jojoba oils; mint family members found in muscle balms, mouthwashes, lozenges, or candies deliver salicylates systemically within a few seconds<sup>(7)</sup>. Many razor strips, deodorants, and lip balms contain blockers as do tooth pastes that regularly harbor listed or unlisted mint. Conjugating liver capacity that renders food sources harmless, is limited and is readily overwhelmed by plant concentrates so often included in supplements<sup>(8)</sup>.

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. We produce an image that depicts the shape, size and location of lesions (see *illustration*). Our **maps** are objective: we ignore subjective expressions of pain during the examination and so avoid the pitfall of variable pain thresholds. We re-map patients on all subsequent visits and are thereby able to document sequential reversal of the illness. Certain tissues are preferentially affected. The earliest lesions appear at elbow entheses, followed by the left sternomastoid and trapezial structures. **Spastic muscle bundles of the thighs (vastus lateralis and rectus femoris especially left) are present in 100% of adults and reliably validate the diagnosis. Those same lesions dependably clear within one month in compliant patients taking an adequate dosage of medication** (see adjacent page).

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 ubiquitous, 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, despite a strong cytokine response, evoke no inflammation, but do 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 are mineralized with calcium phosphate.

Studies other than our own support our theory. Exercise fatigue has been attributed to lactic acid accumulation and consequent cellular acidification. Muscles actually recycle or export lactate for energy production and thereby reduce acid entrapment. In fact lower pH actually augments fiber sensitivity to calcium and promotes contraction. In a study, during maximal wrist-flexion exercises, pH froze at 6.2 but exhaustion prevailed only after a **nine-fold increase in**

**intracellular diprotonated** phosphate ( $\text{H}_2\text{PO}_4^{-2}$ )<sup>(9)</sup>. Thus, inorganic phosphate buffers two  $\text{H}^+$  and stops further assault on pH and avoids myocyte apoptosis. The unrelenting sinew contractions of fibromyalgia are akin to a twenty-four hour, continuous exercise that produces even more  $\text{H}^+$  necessitating further  $\text{P}_i$  intervention into mitochondria. Patients spiral downward as a consequence. Since ATP production is reduced by  $\text{P}_i$  accumulations, progressive 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 formidable 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 for high-energy phosphates. The situation was actually worse because normal tissue was included and tested from the cored specimens<sup>(10)</sup>. Unaffected muscle in adjacent tissues was barely altered. This was confirmed by Lindman<sup>(11)</sup>. Strobel found increased  $\text{P}_i$ , decreased phosphocreatine and low pH in contracted spinal erector muscles of fibromyalgics using  $^{31}\text{P}$  magnetic resonance spectroscopy<sup>(12)</sup>. Other studies support this including one that tested patients at rest<sup>(13)</sup>. Low ATP in platelets and erythrocytes has also been reported by Bazzichi<sup>(14)</sup>. A similar state exists in neutrophils from chronic fatigue patients (that we consider fibromyalgia) was discovered by Myhill who proposed the term *ATP profile*<sup>(15)</sup>.

Physiologists accept the  $\text{P}_i$  to PCr ratio as a measure of fatigue and cellular energy availability. The depressed PCr cited above and high intracellular AMP and ADP reported in some studies, attest to metabolic fatigue. Increases in plasma pyruvate, but low or normal lactate status have been shown reflecting an intact anaerobic metabolism. High pyruvate suggests a fully-operative glycolytic pathway that, for whatever reason, does not properly segue into an effective, aerobic sequence anticipated from the Krebs' cycle.

Ingested  $\text{P}_i$  is 80-90% absorbed via dedicated receptors in the small intestine. The proximal renal tubules and intestinal cells respond to bodily requirements either by reabsorbing or eliminating surpluses. We postulate a basic tubular defect as well as other, chromosome-scattered, genetic aberrations that alter tissue rapport. Genetically altered intestinal cells may also prove to be participants. The disharmony of fibromyalgia could certainly arise from pathologic retention of inorganic phosphate when it accumulates sufficiently to impose near-hibernation function on intracellular organelles.

As described above, we implicate excess  $\text{H}_2\text{PO}_4$  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  $\text{H}^+$  to the outer chamber and creates a proton deficit in that space. Such matrix trapping obstructs the mandatory to-and-fro  $\text{H}^+$  migration through the inner membrane the chemical cascade that is essential for ATP production. Accumulated matrix  $\text{H}^+$  lowers pH, which attracts more phosphate and increases formation of diprotonated  $\text{P}_i$ .

ATP can be exported from muscles and platelets to sites that momentarily require higher energy expenditure. Recipient tissues must falter somewhat in fibromyalgia since they barely meet resting energy demands and certainly not those required for exercise. Tiny energy surpluses do occasionally arise and permit restricted bursts of activity. Such free spending soon results in erratic deficits that account for rapidly shifting symptoms. Other high-energy phosphate suppliers ( $\text{ITP}^3$ ,  $\text{GTP}^3$ ) may likewise stumble when saddled with the *accelerated metabolism* of fibromyalgia. Energy thefts from the stresses of healing infections, accidents, surgical damage, and emotional upsets can reliably trigger attacks.

The ultimate intracellular messenger, calcium, drives cells to perform their specialized functions. The intensity of cytosolic and organelle blushes or flushes reflect the demand of incoming signals. Tiered impulses permit graded efforts as exemplified to the extreme by rigor mortis. Calcium enters cells to buffer the negatively-charged  $\text{P}_i^{-2}$ . ATP-driven pumps must then extrude calcium from cells or restore 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 calcium lurking promotes unrelenting work from affected tissues and exhausts already-dwindled energy stores. That seems the only logical explanation for the unrelenting tissue spasms of fibromyalgia. **Sustained cytosolic calcium levels do not allow complete brain-muscle-tendon-ligament relaxation**; possibly a lesser effect in non-excitabile tissues. Physiologic dilutions must be maintained. Water is internalized under high pressure by the

co-entry of sodium and chloride. The resultant swelling produces palpable lesions. Pressure on nerves is expressed by a host of sensations such as pain, paresthesias, and allodynia.

Though non-diagnostic and difficult to reproduce, other aberrations have been reported: **decreased** growth hormone, IGF-1, serotonin, free ionic  $\text{Ca}^{2+}$ , calcitonin, free urinary or salivary 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 cytokines; elevated homocysteine and substance P in cerebrospinal fluid, and plasma angiotensin converting enzymes. These findings have often proven evanescent, fluctuating, or erroneous.

Research results published by Zhang and our group revealed several abnormal, pro-inflammatory cytokines. Twenty-three out of the tested twenty-five were elevated in our untreated patients. On guaifenesin, ten were reduced or normalized, five stayed the same, and eight were raised <sup>(16)</sup>. Such mixtures apparently neutralize each other and successfully avoid systemic inflammation. That may well explain the absence of laboratory abnormalities in fibromyalgia. Genetic mutations now surfacing should greatly add to these findings and help clarify the metabolic errors that constitute fibromyalgia.

As patients become forcibly 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 with the remaining, dysfunctional mitochondria. Residual glucose releases insulin, which abets its conversion to fat, subsequent storage and weight gain. Insulin wreaks further havoc by strongly promoting renal re-absorption of phosphate. It is driven into myocytes and adipocytes along with water and therein combines with glucose trapping it for local consumption.

Body-wide secretions eject some of the offending ions in the form of phosphoric acid. Tears may burn and desiccate leaving crystals, morning “sand.” Salivary outflows may scald the oral mucosa, produce bad or metallic tastes, lingual irritation, and finally the precipitates of dental calculus ( 75% 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, bladder spasms, 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 and lids 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 mucosa <sup>(17)</sup>. Among those secretions is histamine, which induces itching, various rashes, and heparin that accounts for the easy bruising seen in 80% of 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. Patients from families with diabetes mellitus or dysfunctional beta cells are more likely to evoke exaggerated insulin responses. They suffer episodes of **hypoglycemia** or dramatic **glucopenia** in the 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 <sup>(18)</sup>. Individual thresholds vary for instigating corrective neuro-endocrine responses. Recurrent bouts alter set points and initiate counter measures only at lower glucose levels <sup>(19,20)</sup>. 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 one to four hours postprandially, nocturnally, by provocative meals or delayed eating. Were such complaints described by insulin-dependent diabetics, physicians would unhesitatingly diagnose hypoglycemia without challenging them with an unreliable and punitive glucose tolerance test.

Collectively, symptoms are sufficiently diagnostic of glucopenia and should not be confused with 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 close adherence to a low-carbohydrate diet.

Many fibromyalgics gain weight, some possibly owing 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 of ATP. The energy-starved brain and various hormones encourage carbohydrate gorging. That evokes insulin surges and also suppression of glucagon: a perfect milieu for weight gain. Malonyl CoA is enhanced to promote the conversion of glucose to fatty acids and insulin then 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 organelles increase energy production, burn calories and facilitate weight reduction. Anaerobic workouts benefit primarily the less-affected white fibers (type II) which contain far fewer mitochondria. Combining both types is ideal for recovering full metabolic prowess.

## **TREATMENT SUMMARY**

In summary, this paper is long in theory, but it is based on accumulating evidence some that we have not discussed. Guaifenesin is highly effective for treating fibromyalgia, but proves worthless 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. 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 reversal of the disease.** 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-five 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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