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The Use of Uricosuric Agents in Fibromyalgia

This technical supplement is intended for medical personnel who are already familiar with ***fibromyalgia***. We herein extend the description of the disease, our perception of its cause, and the treatment for its reversal. We offer the following in support of our theory concerning the physiologic and biochemical basis for the illness.

The syndromes fibromyalgia, chronic fatigue, myofascial pain, and chronic Candidiasis are but variants in a disease spectrum that should be merged under one name. Differing pain thresholds and areas of involvement alter clinical presentations and unfortunately lead to disparate nomenclature. "Fibromyalgia" only infers pain in muscles and fibers. A better term, '***energopenia'*** would be more defining since it designates shortage of energy as the underlying cause.

Fibromyalgia is multi-genetic explaining variable susceptibilities from the interplay of dominant and recessive genes. We have met patients aged two and some with onset late 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 that either parent may transmit the illness. Our experience casts strong suspicion on aberrant phosphate metabolism that is normally controlled by several genes scattered on different chromosomes.

Symptoms usually begin spontaneously, but some patients attribute onset to stress, infection, surgery or trauma. Even so, we can often nudge their memories into recalling symptoms from a more remote past. The cycling nature of fibromyalgia initially intersperses good and bad days. Gradually and progressively, incapacity prevails without full respite. My fifty-year observations strongly suggest that unresolved fibromyalgia deteriorates into osteoarthritis. Older family members relate many past symptoms, but joint pains are currently dominant. Physical examination exposes the same lesions as found in their affected offspring and relatives.

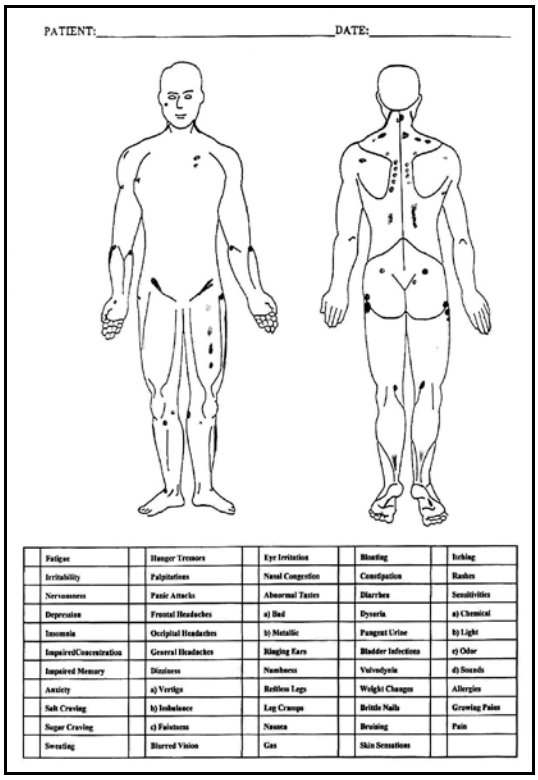
The following is a compilation of potential, presenting complaints. Patients often focus on their worst and omit momentarily less-dominant symptoms. M**usculoskeletal** pain (any muscle, tendon, ligament, joint; leg or foot cramps); **brain** (fatigue, irritability, depression, apathy, nervousness, anxiety, insomnia, suicidal ideation, impaired memory and concentration); **irritable bowel** (nausea, gas, bloating, cramps, pain, constipation, diarrhea); **genitourinary** (dysuria, pungent urine, bacterial or interstitial cystitis, vulvodynia); **dermatologic** (rashes: hives, eczema, pruritic vesicles, acne, rosacea, seborrheic or neurodermatitis, scattered red or colorless maculopapules; brittle nails, defective hair, paresthesias, itching); **head, eye, ear, nose and throat** (varieties of headaches, dizziness, vertigo, imbalance, dry eyes, blepharitis, conjunctivitis, crusty discharge or morning grit, blurred vision, nasal congestion, post-nasal drip, abnormal tastes, painful tongue, scalded mouth, tinnitus or lower-pitched sounds); **miscellaneous** (numb-tingling limbs, digits or face, weight gain, low-grade fever, water retention, sensitivity to light, sounds and odors -- nausea or headache-inducing--, restless leg syndrome**).**

Our physical examination is more thorough than the limited search for ***"eleven-out-of-eighteen-tender-points"*** recommended by the American Academy of Rheumatology. We palpate seeking the swollen tissues of fibromyalgia and sketch findings on a body caricature. We create an image that depicts the shapes, sizes and locations of lesions (see *illustration).*Our **'map'** is objective, ignores subjective expressions of pain, and thus avoids the pitfall of variable pain thresholds. We remap patients on all subsequent visits and thereby substantiate serial reversal of the illness. Tissues are preferentially affected: the earliest lesions appear on 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 if the dosage is adequate and patients are compliant.

Forty-eight years ago we began treating the then-nameless fibromyalgia with uricosuric agents. Fifteen years ago we realized the therapeutic value of **guaifenesin** and have now used it in over ten thousand patients. It is devoid of side effects. Cyclic clearing reproduces prior symptoms similar to the effects of purging gout. Using longer-acting medication, lesions reverse cumulatively at 300 mg. twice daily--effective for 20% of patients; 600 mg. bid, for 80%; 1800 mg. per day for 90%; obviously, more is needed for 10%. For those patients we add short acting tablets (400 mg) twice daily using whatever amount proves necessary.

Recent reports have described destruction of many medications by the cytochrome system. Over one-hundred drugs have been shown to increase such levels and can ultimately force guaifenesin dosage adjustments. Particularly offensive is CYP-450 3A4 that is present in the liver and distributed over most of the small intestine. Longer-acting drugs are attacked throughout their transit-delayed absorption. We circumvented some of that assault by adding short-acting guaifenesin to the longer-acting preparation. Rapid absorption bypasses some of the cytochrome exposure and yet some twenty-four hour protection continues with the combination.



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.

Renal effects of guaifenesin are totally blocked by salicylates. That agent is readily absorbed through the skin, oral or intestinal mucosa and some of it concentrates in the proximal renal tubules. Plants use salicylates to repel pests, soil organisms and for wound healing. Plant or grass saps readily adhere to skin so Vinyl gloves should be worn gardening and closed shoes when walking on grass. Lotions containing botanicals such as aloe, ginseng, castor or camphor oils, mint family members in muscle balms, mouthwashes, lozenges, or candies deliver salicylates systemically within seconds. Many razor strips, deodorants, lip and chap sticks contain blockers; most toothpastes have unlisted mint and/or salicylates. Conjugating liver capacity that renders food sources harmless is limited and readily overwhelmed by plant concentrates so often included in supplements.

Contracted muscles, tendons and ligaments are working tissues. Only a fundamental biochemical aberration could force fibromyalgic cells into such unrelenting overdrive. Theories seeking to explain the disease must also address the cause of these palpable abnormalities, the plethora of symptoms that arise from the central nervous system and from a host of non-excitable tissues. Our hypothesis is as follows:

Since plasma uric acid levels were consistently normal, my success using uricosuric agents led me to deduce that another anion was likely implicated. Accumulating data point to faulty metabolism of inorganic phosphate **(P_i)**. Excess retention would evoke no inflammatory response, but would induce system-wide biochemical misadventures. Our limited urinary studies using probenecid or guaifenesin demonstrated a steep increase in twenty-four hour phosphate excretion. Uricosuric agents and guaifenesin promote lysis of dental calculus and cyclically normalize defective fingernails, structures that are both mineralized by calcium phosphate.

Several biochemical studies support our theory. Exercise fatigue is erroneously attributed to lactic acid and falling pH. Muscles actually recycle lactate for energy production and acid 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 prevailed only after a **nine-fold increase in diprotonated** phosphate **(**$H_2PO_4^-$**)**.[3] Thus two anions are needed to halt further assault on pH and thereby avoid apoptosis. The unrelenting contractions of sinews in fibromyalgia are akin to twenty-four hour, continuous exercise and would likewise produce excess P_i and H^+. Fatigue must follow since ATP production is blocked by excess P_i according to the following formula:

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

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 phosphocreatine, the reservoir for high-energy phosphates. The situation was actually worse because normal tissue was included and tested in the cored specimens.[4] Adjacent and unaffected muscle tissues were barely altered. This was confirmed by Lindman.[5] Strobel found increased P_i, decreased phosphocreatine and low pH in contracted spinal erector muscles of fibromyalgia using ^{31}P magnetic resonance spectroscopy[6]. Other studies support this including one on patients at rest.[7] Low erythrocyte ATP has also been documented. Widespread cellular fatigue easily explains **all** of the symptoms of fibromyalgia.

More evidence exists for thwarted ATP production in the illness. Patients often complain of spontaneous flushing and sweating even at rest suggestive of uncoupling activity with heat rather than energy production. The P_i to PCr ratio is an accepted measure of cellular energy and is clearly altered by the decrease PCR cited above. AMP and ADP were also elevated in those studies, both strong signals of energy deprivation. Reported increases in plasma pyruvate and low or normal lactate suggest intact anaerobic metabolism.[11] An increased pyruvate also points to a Krebs' cycle that is working at full capacity or braking in response to erroneous signals regarding energy reserves.

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 (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 with a release of their contents such as histamine, heparin, and multiple other cytokines; elevated homocysteine and substance P in cerebrospinal fluid, and plasma angiotensin converting enzymes. Exciting research is now recording certain mutations and altered biochemistry in fibromyalgia. These collective reports underscore the very fundamental metabolic error *erratically* and *variably* imposed upon selected tissue and glandular function. Our earlier suggestion for a more descriptive nomenclature seems apropos in view of this documented, 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 this tissue rapport. The result of such disharmony would be excess systemic buffering of inorganic phosphate in susceptible cells with apportionment to the detriment of certain organelles.

Phosphate is heavily concentrated and energized in mitochondria by triple-bonding with adenosine to form ATP. However, matrix (inner chamber) excesses can lead to cellular fatigue by binding to hydrogen ions,

blocking its egress to the outer chamber, and thus creating a proton deficit in that space. Such trapping of H^+ obstructs mandatory to-and-fro transport through the inner membrane that is essential for ATP production. Accumulating matrix H^+ further lowers pH and increases formation of diprotonated P_i. We implicate excess H_2PO_4 trapping as prime suspect for the body-wide dearth of ATP and the exhaustion of fibromyalgia.

ATP can be exported from muscles and platelets to high expenditure sites. This support must falter in fibromyalgics since they barely meet energy demands and too often, not at all. Tiny energy surpluses do occasionally arise to permit bursts of effort. Such free spending soon results in erratic deficits to 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, surgery or accident damage, and emotional upsets can be final insults that to initiate attacks.

Calcium is the final messenger that drives cells to perform specialized functions. Nanomolar blushes or flushes reflect the intensity of signals from first-messengers. Tiered impulses permit graded efforts, in the extreme as rigor mortis. Calcium enters cells to buffer the negative-charged Pi^{2-}. ATP-driven pumps must then extrude calcium from cells or force storage into mitochondria and endoplasmic reticula or cellular activity cannot cease. 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 perpetual tissue spasms of fibromyalgia. ***Sustained sarcoplasmic calcium levels permit neither brain-muscle-tendon-ligament relaxation*** nor full rest for non-excitable tissues. Dilutions must be maintained so water is internalized by the obligatory co-entry of sodium and chloride; tissues swell, press on nerve fibers and produce pain.

As the illness worsens, patients become progressively more sedentary and 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. Excess glucose has difficulty connecting with the fewer remaining, dysfunctional mitochondria; it instead abets its own conversion to fat for storage. Obviously, Insulin is released and, since the body does not waste food, weight gain follows. Insulin strongly promotes renal re-absorption of phosphate wreaking further havoc since it drives more into cells to trap glucose for local consumption.

Body wide secretions try to eject the offending ions as phosphoric acid. Tears may burn and desiccate to form 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. Upon urination they abrade the trigone and urethral mucosa to cause dysuria. That added to frequency, urgency and lower abdominal pain suggests "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 are affected and add to systemic discomfort by releasing cytokines into the epidermis, bronchial, intestinal, vaginal, and bladder mucosas[8]. Among those secretions are histamine that provokes various rashes that are sometimes pruritic, and heparin that accounts for the easy bruising seen in 75% of fibromyalgic women.

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 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 acceptably-normal glucose levels.[9] Individual thresholds vary for instigating corrective neuro-endocrine responses. Recurrent bouts alter set points and initiate counter measures only at lower glucose levels.[10] Restriction of high-glycemic-index foods restores normal signaling within two weeks.

The a**cute 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 arguably due to inactivity imposed by fatigue. More important may be a loss of up to 80% of mitochondria induced by becoming sedentary. Additionally, surviving organelles are not totally efficient and struggle to produce enough ATP for full tissue function. The energy-starved brain and multiple hormones stimulate carbohydrate gorging. Insulin surges and glucagon suppression are the perfect combination for weight gain. Malonyl CoA is recruited by various signals, promotes the conversion of glucose to fatty acids, and insulin implements triglyceride storage. Walking and other aerobic exercises stimulate the primarily-affected red muscle fibers (type I) to regenerate mitochondria. Those resurrected structures help burn calories, abet weight reduction, and increase energy production. Anaerobic workouts such as resistance training benefit primarily the less-affected white fibers (type II), those far less endowed with mitochondria.

In summary, this paper is long in theory but based on many facts, some we have not discussed due to space limitations. Guaifenesin is highly therapeutic for fibromyalgia, but is 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.[12,13,14,15,16] Genetic makeup determines dosage, susceptibility to blocking and cytochrome recruitment. Hypoglycemia and carbohydrate intolerance cause confusion by wrongly suggesting inadequate control of fibromyalgia. During improvement, patients should begin aerobic exercising to restore mitochondria. ***Adherence to our protocol must be meticulous or there will be no improvement.*** Physicians who deviate from this design expose their patients to undeserved failures.

It is our mission to disseminate information gleaned by a single physician and his fifty-one year experiences.. Our protocol uses a non-toxic, over-the-counter drug that works to mitigate an innate metabolic error. Most current research focuses on obtunding symptoms and ignores the root cause, the energy deprivation that forces the widespread tissue malfunction. We offer the only successful treatment for reversing the lesions of fibromyalgia. We hope to wean physicians and patients from symptomatic '**threatments'** and polypharmacy with habituating and addicting drugs

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