Reducing Pain and Inflammation Naturally. Part 7: Rheumatoid Arthritis as a Prototypic Pattern of Inflammation

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In light of recent developments and advances in scientific knowledge and integrative physiology, the view that rheumatoid arthritis (RA) and most other "autoimmune diseases" are "idiopathic" is no longer intellectually defensible, scientifically tenable, or ethically responsible. Readers of the previous six parts of this *"Reducing Pain and Inflammation Naturally"*[1-6] series should already be adept at the implementation of each of the foundational components of the "Five-Part Nutritional Wellness Protocol"[7] and should now be ready to add more advanced assessments and interventions in the treatment of disorders of systemic inflammation.

The following abbreviated excerpt from *Integrative Rheumatology*[8] provides a summary of some of the most important clinical and therapeutic considerations in the integrative management of systemic inflammation. As the prototype for systemic musculoskeletal inflammation, RA will serve as an exemplary "pattern of inflammation" while readers should appreciate the applicability and limitations of this model to other inflammatory diseases and disorders. (See Figure 1.)

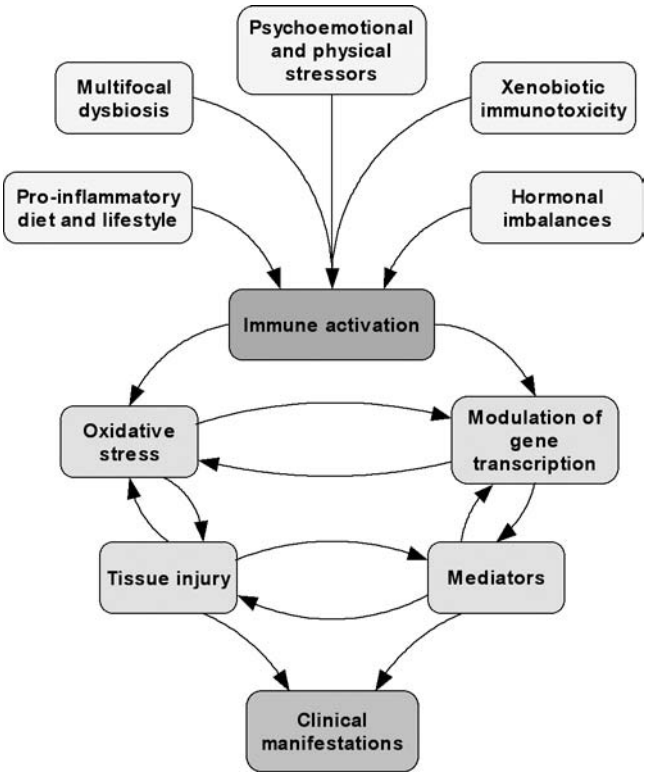


Figure 1. Contributors to the immune activation that underlies chronic inflammation: Note that "immune activation" necessarily precedes the pathophysiologic processes that result in clinical manifestations. Immune activation itself is preceded by dietary, nutritional, microbial, psychoemotional, hormonal, and xenobiotic imbalances. When therapeutics (e.g., steroids and immunosuppressive drugs) are employed exclusively to suppress harmful immune activation, the patient is condemned to life-long illness because the fundamental causes and factors which lead to and perpetuate the immune dysfunction are not addressed. Only when the causes of immune dysfunction have been successfully ameliorated can the patient hope to experience authentic long-term relief; only then has true health-care (rather than disease-care) been delivered. Image from *Integrative Rheumatology.*

PATHOPHYSIOLOGY, CLINICAL CHARACTERISTICS, DIAGNOSIS, COMPLICATIONS:

RA is a persistent, symmetric, destructive, inflammatory peripheral arthritis that affects up to 1% of all populations and is considered the second most common rheumatic diagnosis after osteoarthritis. From the allopathic perspective, RA is seen as a chronic "idiopathic" inflammatory disorder primarily affecting the peripheral joints but also affecting the axial skeleton and internal organs; it is generally treated with NSAIDs and other anti-inflammatory and immunosuppressive drugs, which are palliative and have no chance of providing cure. Conversely, from the perspective of integrative medicine, the condition is considered highly amenable to multicomponent treatment plans that address the allergic, dysbiotic, nutritional, and hormonal components of this multifaceted phenomenon.

A pathogenic hallmark of the disease is immune complex formation and intra-articular deposition with resultant release of cytokines and other pro-inflammatory mediators. Immune complexes are important instigators of rheumatoid arthritis and vasculitis, and rheumatoid factor (RF) antibodies are important contributors to these immune complexes.[9] The chronic inflammation leads to synovial thickening, villous hypertrophy (pannus formation), and intraarticular colonization with activated lymphocytes and plasma cells. The localized immunocytes cause inflammation and tissue destruction via elaboration of matrix metalloproteinases (including collagenases), prostaglandins, and cytokines such as IL-1.

Etiologic considerations include genetic predisposition (especially HLA-DR4, which is positive in 70% of RA patients, compared to 28% of control patients), urbanization and the "Western lifestyle,"[10, 11] tobacco cigarette smoking, female gender (including predisposition to

chronic urinary tract infections/colonization, especially due to *Proteus mirabilis*[12, 13]), hyperestrogenism/dysestrogenism, hypoandrogenemia, vitamin D deficiency, psychoemotional stress, food allergies, and orodental and gastrointestinal dysbiosis (especially hypersensitivity dysbiosis against *Eubacterium aerofaciens*[14]; see January 2006 issue of *Nutritional Perspectives* for review of dysbiosis).

Clinical presentations are somewhat variable given the systemic and inflammatory nature of the disease; however, the stereotypic presentation is that of localized hand/wrist pain and inflammation along with nonspecific systemic manifestations such as fatigue, malaise, low-grade fever, and anorexia. RA can affect any age, either gender; however, it is 2-3x more common in women, and the typical onset is between 25-50 years of age. "Peripheral symmetric polyarthritis" is a classic description for RA; but this same description can be applied to many cases of hemochromatosis[15] and SLE as well. Generally, clinicians note palpable joint swelling with synovitis and effusion, and patients describe morning stiffness that lasts up to about an hour. The joints most commonly affected are the wrists, MCP, PIP, MTP (metatarsophalangeal) joints, and knees (Baker's cyst is common). In severe or advanced disease, essentially any joint in the body—including the TMJ and upper cervical spine—can be involved. Upper cervical spine involvement can lead to atlantoaxial instability; thus, upper cervical spine manipulation is contraindicated until atlantoaxial instability has been excluded clinically or radiographically. Generalized osteoporosis is common due to inflammation, disuse/deconditioning, hypogonadism, and drug effects (especially corticosteroid-induced osteoporosis). Advanced complications include radial deviation of the wrists and ulnar deviation of the fingers, swan neck deformity (PIP hyperextension with DIP hyperflexion), and boutonniere deformity (PIP hyperflexion with DIP hyperextension). In the skin, rheumatoid nodules (subcutaneous inflammatory granulomas) are seen in up to 30% of patients; these are occasionally seen in patients with hemochromatoic arthropathy mimicking RA. Rheumatoid vasculitis leads to impaired tissue perfusion, causing necrosis of affected tissues: fingers, skin, internal organs, and nerves (peripheral neuropathy). Lung involvement can cause dyspnea, pulmonary nodules, and fibrosis. Ocular complications are seen in 1% of patients but can lead to rapid blindness. Up to 20% of patients with RA develop Sjogren's syndrome or other autoimmune syndromes such as SLE, MS, Hashimoto's thyroiditis; "mixed connective tissue disease" can easily co-exist beside a primary clinical presentation of RA.

Major differential diagnoses include hemochromatosis and iron overload, osteoarthritis, SLE, septic arthritis, reactive arthritis, gout, calcium pyrophosphate dihydrate deposition disease, arthritis related to viral infection (such as parvovirus and hepatitis C), psoriatic arthritis (rarely, the joint inflammation of psoriatic arthritis precedes the dermatologic lesions), adult Still's disease, and osteosarcoma and Ewing's sarcoma, especially in young adults presenting with lower extremity periarticular inflammation. RA patients have an increased frequency of septic arthritis, and clinicians must be aware that an "RA flare" could be an infectious complication; erythematous febrile monoarthritis with leukocytosis is the classic presentation, diagnosed definitively with joint aspiration.

Following the history and appropriate physical exam, laboratory assessments are necessary. Goals of laboratory testing are 1) exclude serious life-threatening conditions (e.g., septic arthritis), 2) quantitatively and qualitatively assess patient's health status, 3) determine nature and severity of underlying diseases and disorders for which correction can contribute to an overall improvement in immune function and reduction in total inflammatory load (TIL). Beyond the basic CBC, UA, and metabolic/chemistry panel, the most laboratory important tests include the following; for completeness, imaging techniques are mentioned at the end of this section on laboratory tests:

1. Cyclic citrullinated protein antibody; anti-CCP antibodies: anti-cyclic citrullinated peptide antibody: Anti-CCP antibodies have 95-98% specificity for RA[16]; this test is likely to become the future laboratory standard in the diagnosis and prognosis of RA.[17]

2. C-reactive protein: CRP is a nonspecific marker of systemic inflammation. CRP can be used to support the diagnosis (as it indicates inflammation) and can be used to monitor the disease and the response to treatment.[18]

3. Ferritin: All patients with polyarthritis must be tested for iron overload with the lab tests serum ferritin and transferrin saturation.[19] As an acute phase reactant, serum ferritin is elevated by inflammation; as a marker for iron status, serum ferritin is elevated by iron overload and lowered by iron deficiency. Transferrin saturation and serum iron should be low in RA due to inflammation, whereas they are commonly elevated in patients with iron overload. In order to determine the acute phase contribution to an elevated ferritin level, an independent marker of inflammation such as CRP or ESR should be tested simultaneously. Since the diagnosis of iron overload cannot be excluded based on history and physical exam, patients with laboratory evidence of iron overload should undergo diagnostic phlebotomy, liver MRI, or liver biopsy; liver biopsy is not a prerequisite to phlebotomy therapy and must

never delay treatment.[20]

4. Rheumatoid factor: RF is positive in 70-80% of patients with RA but is not specific and is not necessary for the diagnosis of RA. RF provides "supportive evidence" for the diagnosis of RA only in the presence of corresponding clinical manifestations. Diseases (other than RA) associated with RF positivity include iron overload, chronic infections, viral hepatitis, sarcoidosis, and bacterial endocarditis.
5. Thyroid assessment: Hypothyroidism can mimic systemic rheumatic disease by causing an inflammatory oligoarthropathy and myopathy, complete with elevations of CRP and ESR.[21]
6. Complete hormone assessment: Patients with RA commonly show elevations of prolactin and estradiol along with insufficiencies of testosterone, cortisol, and DHEA. Hormonal imbalances can be corrected by nutritional, pharmacologic, and botanical treatments; additional details are provided in Chapter 4 on *"Orthoendocrinology"* in *Integrative Rheumatology*.[8]
7. Lactulose-mannitol assay for "leaky gut": An elevated lactulose:mannitol ratio (also called the intestinal permeability (IP) test) is *sensitive* but not *specific* for the presence of intestinal mucosal disorders. An elevated lactulose:mannitol ratio correlates with 1) malnutrition, 2) inflammatory bowel disease, 3) NSAID or ethanol enterotoxicity, 4) food allergies including celiac disease, and/or 5) gastrointestinal dysbiosis/parasitosis, the latter of which then needs to be characterized with comprehensive stool testing and comprehensive parasitology. Astute clinicians can generally exclude items 1-3 with appropriate history, physical examination, and routine laboratory assessments, thus leaving an abnormal IP test to be attributed to food allergies or GI dysbiosis, the former of which is assessed serologically or with elimination-challenge protocol while the latter is assessed with comprehensive stool testing (including fecal sIgA and inflammatory markers such as lactoferrin and lysozyme) and comprehensive parasitology, which includes microscopic, culture, and antigen/toxin detection techniques.
8. Comprehensive stool analysis and comprehensive parasitology with bacterial and fungal culture and sensitivity: A three-sample comprehensive parasitology examination performed by a specialty laboratory is strongly recommended as a minimal component of basic care. All patients with RA should be presumed to have gastrointestinal dysbiosis until proven otherwise by both laboratory and clinical means.[22] Comprehensive parasitology testing is necessary but not sufficient for the comprehensive assessment of gastrointestinal dysbiosis, since a significant portion of patients will have falsely normal results. Many arthritogenic gastrointestinal infections, such as with *Eubacterium* species[23] are not detectible by current laboratory methods—again, see *Nutritional Perspectives* (Jan 2006) and *Integrative Rheumatology*[8] for additional details. If stool parasitology results reveal the identity of specific dysbiotic microbe(s), these should be aggressively targeted with specific treatments; otherwise, patients are treated empirically with a combination of dietary, botanical, and appropriate pharmacologic antimicrobials for a minimum of 4-8 weeks.
9. Mucosal swab and culture: Dysbiotic microbes can be detected in the mouth, nasopharynx, and genitourinary tracts of patients with persistent systemic inflammation. Mucosal swab for culture, sensitivity, and DNA identification can be performed by any clinician. The best single review article on this topic was published by Patricia Noah PhD in *Seminars in Dermatology* in 1990.[24]
10. Imaging: Radiographs only have utility for clarifying diagnostic uncertainty later in the disease, for screening for complications such as atlantoaxial instability, or for pre-operative assessment in patients who are candidates for joint repair or replacement. Radiographic findings when clustered are relatively specific in developed disease: soft tissue swelling, periarticular osteoporosis, joint space narrowing due to loss of cartilage, marginal erosions, ulnar deviation of the fingers, and subluxation and dislocation may occur. CT and MRI are not routinely used except to assess for concomitant disease or complications.

The diagnosis of RA is established by pattern recognition of the typical clinical manifestations and laboratory abnormalities and reasonable exclusion of protean diseases such as hepatitis C, SLE, and iron overload. Traditional criteria are listed here; however, "Failure to meet these criteria does not exclude the diagnosis."[25] In 2008, Liao et al[26] showed that CCP antibodies could replace rheumatoid nodules in the criteria for diagnosing RA and that this modification lead to increased diagnostic sensitivity, especially for early RA with symptom duration less than 6 months; as they note and as the current author agrees, early diagnosis helps improve long-term outcomes and treatment efficacy.

Criteria for diagnosing rheumatoid arthritis (must have 4 of the following 7 manifestations):

- ☐ Morning stiffness > 1 hour
- ☐ Non-traumatic polyarthritis of at least 3 joints for > 6 weeks
- ☐ Arthritis of the wrists/hands/knuckles/fingers
- ☐ Symmetric arthritis (may not be applicable in patients with peripheral neuropathy, stroke, or hemiplegia)
- ☐ Rheumatoid nodules (this criteria may soon be officially replaced by CCP antibodies)
- ☐ Positive RF (this criteria was developed before the use of CCP antibodies)
- ☐ Radiographic manifestations: must include marginal erosions or periarticular osteoporosis

Disease complications are common and range from the inconveniences of pain and inflammation for patients with mild disease to the major complications of joint deformity, occupational and social disability, serious cardiovascular/renal/pulmonary/cerebral complications (due mostly to inflammation, fibrosis, vasculitis, and accelerated atherosclerosis), and infections (especially septic arthritis), depression, and suicide.

Clinical visits should include surveillance for subjective and objective indicators of disease progression/remission, treatment compliance (including overcompliance with its risk of adverse toxic effects or unnecessary expense, or undercompliance with attendant hazards of inefficacy and disease exacerbation), and overall health status. Questions are answered, and problems addressed. Necessary consultations are scheduled as needed; the referring provider sends a narrative letter and ensures that the patient has a scheduled appointment. Anticipatory scheduling of laboratory tests and follow-up visits is performed. Access to treatments should be verified. Appropriate documentation is mandatory.

Standard medical treatments include discouraging "food and diet quackery"[27] and the use of NSAIDS as first-line treatment; these interventions contrast with the biomedical research literature showing that nutritional interventions are efficacious and science-based and that NSAIDs can promote intestinal hyperpermeability, hepatic and renal failure (dose-dependent toxicity), gastrointestinal hemorrhage, and accelerated joint destruction (especially indomethacin). Various drugs for anti-inflammation and immunosuppression are used in the medical management of RA; these drugs offer practically no hope of ever curing the patient of his/her disease, but they do have a very valuable role in preventing major complications from disease exacerbations, especially when inflammation or vasculitic ischemia threatens the heart, kidneys, or nervous system. A common sequence of medicalization used by rheumatologists is 1) begin treatment with daily/PRN low-dose prednisone (5-7.5 mg/day) and weekly methotrexate (7.5-15 mg/week, with daily folic acid to improve efficacy and reduce toxicity), then add 2) hydroxychloroquine and/or sulfasalazine as disease progresses, and finally, when the patient becomes "resistant to treatment", 3) add either an oral immunosuppressant or one of the "biologics" such as the parenterally-administered TNF/cytokine blockers: etanercept, infliximab, adalimumab. Surgery is used for deformities and other orthopedic complications, including atlantoaxial instability and articular destruction. Although RA, like other autoimmune conditions, waxes and wanes within somewhat predictable parameters, clinicians must be alert to potential for severe exacerbations which necessitate hospitalization and pharmacologic immunosuppression; for this reason the current author has published guidelines (freely available on-line[28]) which include the caveat of co-management with a hospital-privileged rheumatologist or internist for urgent and emergency situations.

NUTRITIONAL AND INTEGRATIVE TREATMENTS FOR RA AND OTHER APPLICABLE PATTERNS OF INFLAMMATION:

Integrative clinicians have a wide range of safe and efficacious therapeutics which produce collateral and synergistic benefits in the treatment of systemic inflammation and the promotion of wellness. Concisely reviewed below are some of the more pertinent considerations in the management of multifaceted systemic inflammation such as noted in RA.

- Avoidance of pro-inflammatory foods: Pro-inflammatory foods act *directly* and *indirectly* to promote and exacerbate systemic inflammation. Direct mechanisms include the activation of Toll-like receptors and NF-kappaB, while *indirect* mechanisms include depleting the body of anti-inflammatory nutrients and dietary displacement of more nutrient-dense anti-inflammatory foods. Arachidonic acid (found in cow's milk, beef, liver, pork, and lamb) is the direct precursor to pro-inflammatory prostaglandins and leukotrienes and pain-promoting isoprostanes.[29] Saturated fats promote inflammation by activating/enabling pro-inflammatory Toll-like receptors, which are otherwise "specific" for inducing pro-inflammatory

responses to microorganisms.[30] Consumption of saturated fat in the form of cream creates marked oxidative stress and lipid peroxidation that lasts for at least 3 hours postprandially.[31] Corn oil rapidly activates NF-kappaB (in hepatic Kupffer cells) for a pro-inflammatory effect[32]; similarly, consumption of PUFA and linoleic acid promotes antioxidant depletion and may thus promote oxidation-mediated inflammation via activation of NF-kappaB. Linoleic acid causes intracellular oxidative stress and calcium influx and results in increased NF-kappaB-stimulated transcription of pro-inflammatory genes.[33] High glycemic foods cause oxidative stress[34, 35] and inflammation via activation of NF-kappaB and other mechanisms—e.g., *white bread causes inflammation*[36] as does *a high-fat high-carbohydrate fast-food-style breakfast.*[37] High glycemic foods suppress immune function[38, 39] and thus promote the perpetuation of microbial colonization and dysbiosis. Delivery of a high carbohydrate load to the gastrointestinal lumen promotes bacterial overgrowth[40, 41], which is inherently pro-inflammatory[42, 43] and which appears to be myalgenic in humans[44] at least in part due to the ability of endotoxin to impair muscle function.[45] Overconsumption of high-carbohydrate low-phytonutrient grains, potatoes, and manufactured foods displaces phytonutrient-dense foods such as fruits, vegetables, nuts, seeds, and berries which contain more than 8,000 phytonutrients, many of which have antioxidant and thus anti-inflammatory actions.[46]

- Supplemented Paleo-Mediterranean diet: The health-promoting diet of choice for the majority of people is a diet based on abundant consumption of fruits, vegetables, seeds, nuts, omega-3 and monounsaturated fatty acids, and lean sources of protein such as lean meats, fatty cold-water fish, soy and whey proteins. This diet obviates overconsumption of chemical preservatives, artificial sweeteners, and carbohydrate-dominant foods such as candies, pastries, breads, potatoes, grains, and other foods with a high glycemic load and high glycemic index. Described first by Vasquez[47], this "Paleo-Mediterranean Diet" is a combination of the "Paleolithic" or "Paleo diet" and the well-known "Mediterranean diet", both of which are well described in peer-reviewed journals and the lay press. The *specific carbohydrate diet* (SCD) detailed by Gottschall[48] is an anti-microbial diet plan specifically designed to eliminate bacterial overgrowth of the bowel and the associated hypersensitivity dysbiosis; the stipulations of this diet are generally met by the Supplemented Paleo-Mediterranean Diet. This diet is the most nutrient-dense diet available, and its benefits are further enhanced by supplementation with vitamins, minerals, and the health-promoting fatty acids: ALA, GLA, EPA, DHA, and oleic acid.

- Avoidance of allergenic foods: Any patient may be allergic to any food, even if the food is generally considered a health-promoting food. Generally speaking, the most notorious allergens are wheat, citrus (especially citrus *juice* due to the industrial use of fungal hemicellulases), cow's milk, eggs, peanuts, chocolate, and yeast-containing foods. According to a study in patients with migraine, some patients will have to avoid as many as 10 specific foods in order to become symptom-free.[49] Celiac disease can present with inflammatory oligoarthritis that resembles rheumatoid arthritis and which remits with avoidance of wheat/gluten. Clinicians must explain to their patients that celiac disease and wheat allergy are two different clinical entities and that exclusion of one does not exclude the other, and in neither case does mutual exclusion obviate the promotion of intestinal bacterial overgrowth (i.e., pro-inflammatory dysbiosis) by indigestible wheat oligosaccharides. Readers should appreciate that RA may be a disease that begins in the intestine via the interplay of dietary and microbial antigens and that, early in the disease, dietary interventions can be as powerful as pharmacologic immunosuppression/anti-inflammation with prednisolone; the authors of a recent clinical trial concluded, "This study supports the concept that rheumatoid arthritis may be a reaction to a food antigen(s) and that the disease process starts within the intestine."[50]

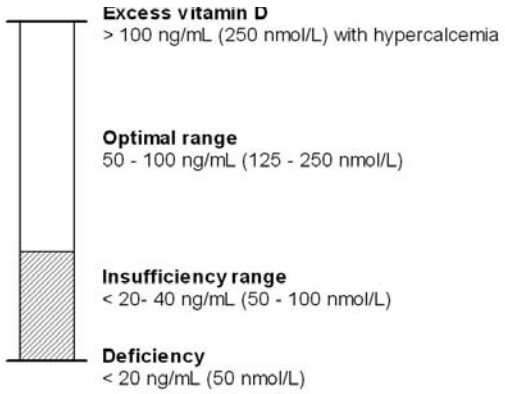
- Gluten-free vegetarian/vegan diet: Gluten-free vegetarian diets benefit patients with RA.[51] Vegetarian/vegan diets have a place in the treatment plan of all patients with autoimmune/inflammatory disorders[52, 53, 54]; this is also true for patients for whom long-term exclusive reliance on a meat-free vegetarian diet is either not appropriate or not appealing. The benefits of gluten-free vegetarian diets are well documented, and the mechanisms of action are well elucidated, including the reduced intake of pro-inflammatory arachidonic acid, iron[55], common food antigens, gluten and gliadin[56, 57], pro-inflammatory sugars[58] and the increased intake of omega-3 fatty acids, micronutrients[59], and anti-inflammatory and antioxidant phytonutrients.[60] Vegetarian diets also effect subtle yet biologically and clinically important changes—both *qualitative*

and *quantitative*—in intestinal flora[61, 62] that correlate with clinical improvement.[63] Patients who rely on the Paleo-Mediterranean diet (which is inherently omnivorous) can use vegetarian *meals* on a daily basis or for days at a time—for example, by having a daily vegetarian meal, or one week per month of vegetarianism. Some (not all) patients can use a purely vegetarian diet long-term provided that nutritional needs (especially protein and cobalamin) are consistently met.

- Short-term fasting: Fasting deprives intestinal microbes of substrate,[64] stimulates intestinal B-cell immunity,[65] improves the bactericidal action of neutrophils,[66] reduces lysozyme release and leukotriene formation,[67] and ameliorates intestinal hyperpermeability.[68] In case reports and clinical trials, short-term fasting (or protein-sparing fasting) has been documented as safe and effective treatment for SLE,[69] RA,[70] and non-rheumatic diseases such as chronic severe hypertension,[71] moderate hypertensionlxxii, obesity,[72, 73, 74] type-2 diabetes,[75] and epilepsy.[76]

- Broad-spectrum fatty acid therapy with ALA, EPA, DHA, GLA and oleic acid: Fatty acid biochemistry and supplementation was reviewed in detail in the first two sections of this series published in *Nutritional Perspectives*.[1,2] Fatty acid supplementation should be delivered in the form of combination therapy with ALA, GLA, DHA, and EPA. Given at doses of 3,000 – 9,000 mg per day, ALA from flaxseed oil has impressive anti-inflammatory benefits demonstrated by its ability to halve prostaglandin production in humans.[77] Numerous studies have demonstrated the benefit of GLA in the treatment of rheumatoid arthritis when used at doses between 500 mg – 4,000 mg per day.[78, 79] Fish oil provides EPA and DHA which have well-proven anti-inflammatory benefits in rheumatoid arthritis[80, 81, 82] and lupus.[83, 84] ALA, EPA, DHA, and GLA need to be provided in the form of supplements; when using high doses of therapeutic oils, *liquid* supplements that can be mixed in juice or a smoothie are generally more convenient and palatable than are *capsules*. For example, at the upper end of oral fatty acid administration, the patient may be consuming as much as one-quarter cup per day of fatty acid supplementation; this same dose administered in the form of pills would require as many as 72 capsules to attain the equivalent doses of ALA, EPA, DHA, and GLA. Therapeutic amounts of oleic acid can be obtained from generous use of olive oil, preferably on fresh vegetables. Supplementation with polyunsaturated fatty acids warrants increased intake of antioxidants from diet, fruit and vegetable juices, and from properly formulated supplements. Since patients with systemic inflammation are generally in a pro-oxidative state, consideration must be given to the timing and starting dose of fatty acid supplementation and the need for antioxidant protection; some patients should start with a low dose of fatty acid supplementation until inflammation and the hyperoxidative state have been reduced. Clinicians must realize that fatty acids are not clinically or biochemically interchangeable and that one fatty acid does not substitute for another; each of the health-promoting fatty acids—ALA, GLA, EPA, DHA, and oleic acid—must be supplied in order for its benefits to be obtained; imbalanced supplementation causes or exacerbates biochemical imbalances and produces suboptimal results.

- Vitamin D3 supplementation with physiologic doses and/or tailored to serum 25(OH)D levels: Correction of vitamin D deficiency supports normal immune function against infection and provides a clinically significant anti-inflammatory[85] and analgesic benefit in patients with back pain[86] and limb pain.[87] A reasonable dose of vitamin D3 for adults is and 4,000 IU per day; however many adult patients achieve better clinical response with doses of 10,000 IU per day.[88] Deficiency and response to treatment are monitored with serum 25(OH)vitamin D while safety is monitored with serum calcium; inflammatory granulomatous diseases and certain drugs such as hydrochlorothiazide increase the propensity for hypercalcemia and warrant increment dosing and frequent monitoring of serum calcium. Vitamin D2 (ergocalciferol) is not a human nutrient, is less efficacious and potentially more toxic than vitamin D3, and should not be used in clinical practice. Emulsification of vitamin D3 improves efficacy and dependability of oral supplementation, as demonstrated in a recent clinical trial published in *Journal of Clinical Endocrinology and Metabolism*[89] contrasting 2,000 IU dry-form vitamin D2 daily against 50,000 IU dry-form vitamin D2 weekly against 2,000 IU emulsified vitamin D3 (Bio-D-Mulsion Forte™, Biotics Research Corporation) daily. Emulsified vitamin D3 produced a better dose-response relationship than the other forms of vitamin D administration.



Interpretation of serum 25(OH)D levels. Modified from Vasquez et al, *Alternative Therapies in Health and Medicine* 2004 and Vasquez A. *Musculoskeletal Pain: Expanded Clinical Strategies* (Institute for Functional Medicine) 2008. (Copyright © 2009 by Alex Vasquez. OptimalHealthResearch.com)

- Assessment for dysbiosis in various locations: Dysbiosis is state of adverse interaction between subclinical microbial colonization and the human host.[8] Dysbiosis can be triggered by different microbes of different domains and subspecies, and dysbiotic foci can occur in a variety of locations such as the gut, nasopharynx, and genitourinary tract. Clinicians should approach all RA patients with the presumption that one or more dysbiotic foci exist, and then implement appropriate clinical assessments and interventions. Yeast, bacteria, and other "parasites" are treated as indicated based on identification and sensitivity results from comprehensive parasitology assessments, including culture, microscopy, and DNA amplification.
    - Orodental dysbiosis: Patients with RA have heightened antibody levels against common oral bacteria. IgG levels against *Porphyromonas gingivalis, Prevotella melaninogenica, Bacteroides forsythus,* and *Prevotella intermedia* were found to be significantly higher in RA patients when compared with those of controls.[90] In the first human clinical trial to test the hypothesis that treatment of orodental dysbiosis would provide subjective and objective clinical benefits for patients with RA, Al-Katma et al[91] showed that periodontal treatment consisting of scaling, root planing, and oral hygiene instruction reduced symptom scores and ESR levels in patients with RA. This remarkable research proves that orodental dysbiosis is a contributor to the systemic inflammation seen in RA; by extension, this research also supports the model that inflammation in RA is multifaceted, rather than singular in origin.
    - Genitourinary dysbiosis: Microbial contamination of the genitourinary tract can cause a systemic pro-inflammatory arthritogenic response in susceptible individuals. In a study of 234 patients with inflammatory arthritis, 44% of patients had asymptomatic genitourinary colonization, mostly due to *Chlamydia, Mycoplasma,* or *Ureaplasma,* leading the authors to conclude, "urogenital swab culture is the only useful diagnostic method for the detection of the arthritogenic infection in extra-articularly asymptomatic patients with undifferentiated oligoarthritis."[92]
    - Gastrointestinal (GI) dysbiosis: Gastrointestinal parasite infections, such as with *Endolimax nana*,[93] can induce a systemic inflammatory response that mimics rheumatoid arthritis and is cured with parasite eradication. Patients with RA should be presumed to have GI dysbiosis until proven otherwise by the combination of 1) comprehensive parasitology testing performed by a specialty laboratory, and 2) empiric broad-spectrum antimicrobial treatment including the use of dietary, botanical, and pharmacologic antimicrobials for at least four weeks of treatment. Generally, probiotics (without prebiotics or synbiotics) and antifungal treatment such as oregano or nystatin should be used alongside antibacterial treatments. Commonly used antibacterial/antifungal drugs include metronidazole, erythromycin, tetracycline, ciprofloxacin, penicillin, cephalexin, minocycline, and nystatin. Botanical treatments are described separately in the following section.
- Botanical treatments for dysbiosis: Various botanical medicines have been used for thousands of years for the eradication of infectious diseases. Commonly employed botanical medicines include the following:
    - Oregano oil: Emulsified oil of oregano in a time-released tablet (ADP®, patented by Biotics Research Corporation) has demonstrated effectiveness in the eradication of harmful gastrointestinal microbes, including *Blastocystis hominis, Entamoeba hartmanni,* and *Endolimax nana* according to a human clinical trial.[94] An *in vitro* study[95] and clinical experience support the use of emulsified oregano against *Candida albicans* and various bacteria. The common dose is 600 mg per day in divided doses for 6 weeks.

- Berberine: Berberine is an alkaloid extracted from plants such as *Berberis vulgaris,* and *Hydrastis canadensis,* and it shows effectiveness against *Giardia, Candida,* and *Streptococcus* in addition to some direct anti-inflammatory and antidiarrheal actions. Oral dose of 400 mg per day has been traditionally common for adults;[96] newer clinical research using human patients has shown short-term safety and efficacy of berberine used at much higher doses: 1,000 mg per day showed very impressive cholesterol-lowering benefits in hypercholesterolemic patients,[97] and 1,500 mg per day showed hypoglycemic benefits for patients with type-2 diabetes mellitus.[98]
- Artemisia annua: Artemisinin has been safely used for centuries in Asia for the treatment of malaria, and it also has effectiveness against anaerobic bacteria due to the pro-oxidative sesquiterpene endoperoxide.[99, 100] This author has commonly used artemisinin at 200 mg per day in divided doses for adults with dysbiosis. Given its pro-oxidative mechanism, treatment should probably be of limited duration, i.e., 1-2 months; concomitant neuroprotection with CoQ-10 would be reasonable. Antioxidants should not be administered at the same time as artemisinin, but rather several hours apart.
- St. John's Wort *(Hypericum perforatum)*: Hyperforin from *Hypericum perforatum* shows impressive antibacterial action in vitro, particularly against gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae*[101] and perhaps gram-negative Helicobacter pylori.[102] Doses of 300-600 mg three times per day of a 3% hyperforin standardized extract are customary in the treatment of depression.
- Peppermint *(Mentha piperita)*: Peppermint shows antimicrobial and antispasmodic actions and has demonstrated clinical effectiveness in patients with bacterial overgrowth of the small bowel.
- Myrrh *(Commiphora molmol)*: Myrrh is remarkably effective against parasitic infections.[103] A recent clinical trial against schistosomiasis[104] showed "The parasitological cure rate after three months was 97.4% and 96.2% for *S. haematobium* and *S. mansoni* cases with the marvelous clinical cure without any side-effects."[105]
- Uva Ursi: Uva ursi can be used against gastrointestinal pathogens on a limited basis per culture and sensitivity findings; its primary historical and modern use is as a urinary antiseptic which is effective only when the urine pH is alkaline.[106] Components of uva ursi potentiate antibiotics.[107] This herb has some ocular and neurologic toxicity and should be used with professional supervision for low-dose and/or short-term administration only.[108]
- Additional antimicrobial botanical medicines: Although several of these have a history of human consumption, modern clinical trials are needed to establish and document their proper clinical use. Thyme extracts have direct antimicrobial actions and also potentiate the effectiveness of tetracycline against drug-resistant *Staphylococcus aureus*;[109] thyme also appears effective against *Aeromonas hydrophila.*[110] Clove (*Syzygium* species) contains eugenol, which has been shown in animal studies to have a potent antifungal effect.[111] Anise shows weak antibacterial action when used alone, yet has in vitro activity against molds.[112] Buchu (betulina) has a long history of use against urinary tract infections and systemic infections.[113] Dill *(Anethum graveolens)* shows activity against several types of mold and yeast.[114] Extract from *Brucea javanica* fruit shows in vitro activity against *Babesia gibsoni, Plasmodium falciparum*,[115] *Entamoeba histolytica*[116] and *Blastocystis hominis.*[117, 118] *Acacia catechu* shows moderate *in vitro* activity against S*almonella typhi*.[119]

- Correction of hormonal imbalances ("orthoendocrinology"): The phrase "orthoendocrinology" was first coined by Vasquez in *Integrative Rheumatology*[8] as a specific therapeutic protocol to reestablish hormonal balance in patients with systemic inflammation. Patients with systemic inflammation commonly show elevations of prolactin and estradiol along with insufficiencies of testosterone, cortisol, and DHEA (sulfate). As part of the comprehensive management of autoimmunity, physicians should test serum levels of prolactin, cortisol (preferably with ACTH challenge), DHEA-sulfate, free and total testosterone, estradiol, and thyroid hormones; abnormalities should be corrected. Patients with RA and SLE have higher basal and stress-induced levels of prolactin compared with normal controls; prolactin is proinflammatory and can be lowered by use of thyroid hormone, *Vitex astus-cagnus,* and the drugs

bromocriptine,[120] and cabergoline.[121] Estradiol is proinflammatory and is elevated in men with RA;[122] serum estradiol levels can be lowered by weight reduction, alcohol avoidance, varicocele repair, an "anti-estrogen diet" including licorice and crucifers, and the drugs anastrozole and letrozole. Testosterone has anti-inflammatory benefits and low levels should be corrected either by treating the underlying problem (e.g., rapid conversion to estrogen by adipose tissue) or using transdermal testosterone or anastrozole/letrozole. DHEA is an anti-inflammatory and immunoregulatory hormone that is commonly deficient in patients with autoimmunity and inflammatory arthritis; deficiencies should be corrected with doses ranging from 50-200 mg per day with preference for lower doses used in a broad therapeutic context.

- Oral enzyme therapy with proteolytic/pancreatic enzymes: Polyenzyme supplementation can be used to ameliorate the pathophysiology induced by immune complexes, as seen in rheumatoid arthritis.[123]
- Anti-inflammatory and analgesic botanicals: Botanical medicines with anti-inflammatory benefit can be used as part of a comprehensive program. The best-researched botanical medicines for the treatment of pain and inflammation are *Uncaria tomentosa* and *U. guianensis,*[124, 125] *Harpagophytum procumbens*,[126, 127, 128, 129, 130] willow bark,[131, 132] *Boswellia serrata*.[133] See previous publication in this journal (*Nutritional Perspectives* 2005 April) for review.[3]
- Phytonutritional modulation of NF-kappaB: As a stimulator of pro-inflammatory gene transcription, NF-kappaB plays a central role in the pathogenesis of synovitis and joint destruction seen in RA.[134] Nutrients and botanicals which either directly or indirectly inhibit NF-kappaB for an anti-inflammatory benefit include vitamin D, curcumin (requires piperine for absorption), lipoic acid, green tea, rosemary, grape seed extract, propolis, zinc, high-dose selenium, N-acetyl-L-cysteine, resveratrol, GLA via PPAR-gamma and EPA via PPAR-alpha. See previous publication in this journal (*Nutritional Perspectives* 2005 July) for review,[4] several phytonutritional products targeting NF-kappaB are available.
- Glucosamine sulfate and chondroitin sulfate: Glucosamine and chondroitin sulfates are well tolerated and well documented for effective treatment of osteoarthritis. Symptomatic benefit in RA has been demonstrated.[135] Clinicians should appreciate that glucosamine sulfate is more effective than glucosamine hydrochloride, and that several months and years of treatment are necessary to appreciate full benefit of treatment. An additional benefit to the use of chondroitin sulfates is their cardioprotective role, which is particularly important for RA patients given their increased risk of cardiovascular death; see *Nutritional Perspectives* 2005 July for review.
- Creative self-expression and therapeutic writing: Limited evidence indicates that self-expressive writing can significantly reduce symptomatology in patients with RA.[136] Acute and chronic psychoemotional stress causes the pattern of hormonal imbalances previously described and weakens mucosal defenses thereby promoting the establishment and perpetuation of dysbiosis-induced systemic inflammation.
- Xenobiotic avoidance and detoxification: Exposure to and bodily accumulation of immunotoxic chemicals and heavy metals contributes to many chronic diseases. Specifically, exposure to polychlorinated biphenyls (PCB), nondioxin-like PCBs, and organochlorine pesticides appears to increase the risk for developing RA.[137] Avoidance, patient-centered identification, and "detoxification" of these immunotoxins should be pursued in appropriately selected patients.[8]

CONCLUSION:

Rheumatoid arthritis (RA) is a multicomponent "pattern of systemic inflammation" that can be effectively ameliorated when each of the causative contributors is effectively addressed; many of these contributors have already been identified and are readily assessable and treatable. Labeling the disease as "idiopathic" reveals ignorance of the accumulative advances in scientific and clinical research that are progressively deciphering this previously enigmatic disease; failure to appreciate and act upon this research abets life-long pharmacologic dependency (with its attendant costs, toxicity, and side effects) and denies suffering patients the opportunity for authentic improvements in health status. The integrative treatment of RA and other chronic diseases with evidence-based multicomponent protocols including dietary, nutritional, botanical, orthoendocrinologic, psychoemotional, antimicrobial, antixenobiotic, and pharmacologic treatments should become the standard of care. As the only doctorate-level clinicians with profession-wide training in dietary, nutritional, botanical, orthoendocrinologic, psychoemotional, antimicrobial, antixenobiotic, and pharmacologic treatments, chiropractic and naturopathic physicians are core

team members in the interdisciplinary management of complex chronic illnesses.

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