Reducing Pain and Inflammation Naturally. Part 6: Nutritional and Botanical Treatments Against "Silent Infections" and Gastrointestinal Dysbiosis, Commonly Overlooked Causes of Neuromusculoskeletal Inflammation and Chronic Health Problems

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Abstract: AT LEAST 56-70% OF PATIENTS WITH CHRONIC INFLAMMATORY ARTHRITIS ARE CARRIERS OF "SILENT INFECTIONS." Non-infectious microbiological causes of musculoskeletal pain are commonly overlooked, and many doctors are unfamiliar with appropriate assessments and treatments for these conditions. Many patients have musculoskeletal pain and systemic inflammation as a result of "occult infections", "silent infections", or "dysbiosis"—including several subcategories of harmful relationships between the human host and his/her microbial guests or neighbors. This article reviews basic and advanced concepts so that clinicians can gain the practical insight necessary for effective clinical intervention.

INTRODUCTION

Approximately 70% of patients with chronic arthritis are carriers of "silent infections", according to a 1992 article published in the peer-reviewed medical journal *Annals of the Rheumatic Diseases*.[1] A 2001 article in this same journal which focused exclusively on five bacteria showed that 56% of patients with idiopathic inflammatory arthritis had gastrointestinal or genitourinary dysbiosis.[2] Indeed, research evidence strongly indicates that bacteria, yeast/fungi, amebas, protozoa, and other "parasites" (rarely including helminths/worms) are an underappreciated cause of neuromusculoskeletal inflammation. This article will explain the mechanisms by which "silent infections" and "dysbiosis" can cause and perpetuate numerous health problems, and I will also discuss basic assessment and treatment measures that can be used clinically to help patients with microbe-induced musculoskeletal inflammation.

One of the problems that plagues many healthcare providers of all professions is that most doctors are still under the spell of the "Pasteurian paradigm of infectious disease", namely that pathogenic microorganisms cause disease by causing *"infection."* Relatedly, Koch's Postulates first published in 1884 held that "the organism must be found in all animals suffering from the disease, but not in healthy animals" and "the cultured organism should cause disease when introduced into a healthy animal." The major problems with the models proposed by Pasteur and Koch are that both of these models fail to appreciate 1) adverse microbe-host interactions which may not result in nor result from a true "infection", and 2) the importance of the patient's biochemical individuality and genetic uniqueness which results in the observed phenomenon that not all patients exposed to a particular microbe will express the associated disease. Supported amply by the research reviewed herein, healthcare providers have an obligation to move beyond these primitive "pathogenic" and "infection-based" models of microorganism-induced disease to apprehend the more common "functional" disorders that can result from exposure to microbes.

PARADIGM SHIFT #1: MICROORGANISMS CAN CAUSE DISEASE EVEN WHEN NOT CAUSING "INFECTION"

We now recognize at least fourteen mechanisms by which microorganisms can cause immune dysfunction that promotes neuromusculoskeletal inflammation. Each of the following exemplifies a mechanism by which microbes can cause "disease" without causing an "infection." Mechanisms by which microorganisms can contribute to musculoskeletal inflammation without causing "infection" include but are not limited to the following:

1) Molecular mimicry: Several microbes have peptides and other structures that resemble or "mimic" the peptides and cell structures found in human tissues. Thus, when the immune system fights against the microbe, the antibodies and T-cells can "cross-react" with the tissues of the human host. In this way, the immune system begins attacking the human body, which is otherwise an innocent bystander—the victim of "friendly fire."[3]

2) Superantigens: Many viral, bacterial, and fungal microbes produce "superantigens", molecules which are capable of causing widespread, nonspecific, and unregulated pro-inflammatory immune activation. One of the hallmarks of superantigens is their ability to induce polyclonal T- and B-lymphocyte activation and the production of excessive levels of cytokines and other inflammatory effectors.[4] Obviously, when the body is in such a state of unregulated hyper-inflammation, inevitably some of this inflammation will affect the structures of the musculoskeletal system, especially since articular tissues are predisposed to immune attack. Several research groups have found evidence of superantigen involvement in the pathogenesis of rheumatoid arthritis.[5,6]

3) Peptidoglycans and exotoxins from gram-positive

bacteria: Peptidoglycans from gram-positive bacteria such as group-A streptococci can cause malaise, fever, dermatosis, tenosynovitis, cryoglobulinemia (immune complex disease), and arthritis.[7] Experimental arthritis can be induced in animals by exposing them to group-B streptococci isolated from the nasopharynx of human patients with rheumatoid arthritis.[8] *Staphylococcus aureus* is a gram-positive bacterium, certain strains of which produce the toxic shock syndrome toxin-1 (TSST-1) that causes scalded skin syndrome, toxic shock syndrome, and food poisoning; other strains of *Staph aureus* that do not produce TSST-1 are also capable of causing toxic shock syndrome from colonization of bone, vagina, wounds, or rectum.[9] Experimental evidence has shown that peptidoglycan-polysaccharide complexes from "good" and "normal" bacteria such as Bifidobacteria and *Lactobacillus casei* can also induce an inflammatory arthritis; this speaks against the "more is better" approach to probiotic supplementation and also demonstrates how bacterial overgrowth of the small bowel (detailed later) can induce joint pain even if the patient's stool test shows no pathogens.[10,11]

4) Endotoxins (lipopolysaccharide) from gram-negative bacteria: Many different species of gram-negative bacteria produce endotoxin, also known as bacterial lipopolysaccharide (LPS). Even in the absence of viable bacteria, the exposure of humans to endotoxin, say for example by intravenous administration for the purpose of experimentation, produces a wide range of adverse physiologic consequences, including 1) triggering an acute pro-inflammatory response resembling febrile illness or sepsis, 2) increasing intestinal permeability, causing "leaky gut"[12], 3) inhibiting hepatic detoxification[13], 4) disrupting the blood-brain barrier and promoting neurodegeneration via neuroinflammation.[14-16] Endotoxin/LPS often function similarly to superantigens, and their effects are synergistic, resulting in altered tissue function and widespread inflammation.

5) Enhanced processing of autoantigens: When the immune system perceives the presence of microbial molecules, processes are enhanced which facilitate the processing and presentation of preexistent antigens to the immune system, which then targets these antigens for destruction. Of course, this is beneficial when fighting a true infection; but there is mounting evidence that chronic silent infections can facilitate the processing and presentation of the body's own antigens (autoantigens) which are then attacked. Clinically, we see the immune system attacking the body, and we call this an "autoimmune disease" even though the original cause of the problem may have been an occult infection or exposure to specific microbial molecules.

6) Bystander activation: Evidence suggests that we all have immunocytes capable of attacking our body tissues, and thus we all have the potential to develop autoimmune disease. Normally, these autoreactive cells are kept anergic, dormant, quiescent, and otherwise inactive through various mechanisms that regulate the immune system; in this way, such autoreactive cells can be considered "bystanders" because they are not really doing anything and are basically "standing by." Bystander activation occurs when these cells are awakened by the cascade of inflammatory processes that occur as a result of superantigen exposure, molecular mimicry, immune complex deposition, or xenobiotic immunotoxicity. Bystander activation can contribute to the development of autoimmunity.

7) Immune complex formation and deposition due to the activation of B-lymphocytes/plasma cells: Chronic infection generally results in the increased production of immune complexes, which are polymeric antigen-antibody combinations. Antigen-antibody combinations are formed when the immune system is fighting against a virus, bacteria, yeast, or food allergen. Although essential for the destruction and clearance of pathogenic antigens, immune complexes pose a problem for the body due to 1) the difficulty in clearing them from the systemic circulation, and 2) their proclivity for deposition in the skin and joints.[17] Indeed, immune complexes are significant contributors to most "autoimmune" diseases; immune complex deposition is responsible for triggering joint inflammation in rheumatoid arthritis[18] and for the facial rash and other clinical manifestations which characterize systemic lupus erythematosus (SLE, lupus). Immune complex deposition directly contributes to the renal disease and vasculitis common in patients with autoimmune disease. Patients with autoimmune disease commonly have circulating IgM and IgA antibodies against bacteria from the gastrointestinal and genitourinary tracts[19] clearly indicating an active immune response against these bacteria and implying breaches in mucosal integrity. Research suggests that IgA immune complex diseases may be particularly amenable to treatment with physiotherapeutic treatments (colonics and enemas), nutritional supplementation (proteolytic enzymes), and botanical interventions ("liver herbs") as discussed later in this paper.

8) Haptenization: A nonantigenic microbial molecule may bind to a nonantigenic human molecule and result in the formation of a new hybridized or "haptenized" molecule which stimulates immunologic attack. Haptenization may be the underlying mechanism by which viruses induce autoimmunity[20] and appears to be a primary mechanism by which *Staphylococcus aureus* contributes to autoimmune vasculitis in Wegener's granulomatosis.[21] Indirectly, microbes—particularly bacteria—may induce xenobiotic-mediated haptenization by altering detoxification of pharmaceutical or pollutant chemicals, as discussed below.

Toxic metals and chemicals probably trigger autoimmunity via haptenization[22], and, in a recent animal study, exposure to bacterial endotoxin exacerbated metal-induced autoimmunity.[23] Thus, microbial exposure appears synergistic with toxic metal/chemical exposure for the incitement of autoimmunity.

9) Damage to the intestinal mucosa: One of the indirect ways by which gastrointestinal microbes can cause non-infectious disease is by damaging the intestinal mucosa, a situation which results in "leaky gut." The increased absorption of debris from the gut—"antigen overload" from otherwise benign yeast, bacteria, and foods—results in overstimulation of the immune system[24], resulting in enhanced autoantigen processing and bystander activation as discussed above. I have provided a detailed illustration of this complex phenomenon in *Integrative Orthopedics* and on-line at www.optimalhealthresearch.com/gastro. It is well-known that exacerbations and relapse of the autoimmune diseases ulcerative colitis and Crohn's disease are preceded by increases in intestinal permeability; this is direct evidence of "leaky gut" preceding clinical disease.[25] Evidence of "leaky gut" is seen in several systemic inflammatory disorders, including asthma[26], eczema[27], psoriasis[28], Behcet's disease[29], ankylosing spondylitis[30] and seronegative spondyloarthritis[31], and nearly all of the so-called "idiopathic" juvenile arthropathies" such as enteropathic spondyloarthropathy and oligoarticular juvenile idiopathic arthritis.[32] A "leaky gut" type of intestinal disease (protein-losing enteropathy) is also seen in some patients with lupus.[33]

10) Inhibition of detoxification: It is well-known that bioaccumulation of toxic chemicals can result in autoimmunity and systemic inflammation via immunodysregulation. Examples of this include 1) the increased autoimmunity seen in farmers exposed to pesticides[34], 2) the scleroderma-like disease that results from exposure to vinyl chloride[35], 3) the association of mercury and pesticide exposure with lupus[36], and 4) the well-recognized connection between drug and chemical exposure and various autoimmune syndromes such as drug-induced lupus.[37] Indeed, more than 40 pharmaceutical drugs are known to cause drug-induced lupus, and bystander activation appears to be one of the mechanisms involved.[38] Thus having established the general premise that "chemical exposure can promote autoimmune disease", it seems logical and probable that anything which would inhibit the body's ability to detoxify these chemicals would likewise increase the risk for autoimmunity. Stated differently, factors that inhibit detoxification and which therefore increase the body burden of immunotoxic xenobiotics would serve to indirectly contribute to immunodysfunction, including autoimmunity. Indeed, patients with lupus and systemic sclerosis show defects in detoxification[39], and it has been reported that patients who undergo a comprehensive detoxification protocol commonly experience a normalization of their immune function and alleviation of their autoimmune diseases.[40,41] Dysbiotic bacterial overgrowth of the gastrointestinal tract directly impairs detoxification via the following four mechanisms: 1) Bacterial lipopolysaccharide (endotoxin) has been shown to dramatically impair Phase 1 of chemical detoxification.[42] 2) Bacterial overgrowth can lead to excess production of methane which causes constipation[43] and thus increases the "toxic load" in the colon which then increases the load on the liver via the portal circulation. 3) Several species of bacteria produce deconjugating enzymes (such as beta-glucuronidase) that cleave previously "detoxified" toxins from their water-soluble moieties thus allowing the toxin to be reabsorbed in a mechanism termed "enterohepatic recycling"[44] or "enterohepatic recirculation."[45] 4) Damage to the intestinal mucosa increases absorption of intraluminal contents and thus increase the toxic load placed on the detoxification mechanisms, which are mostly located in the liver; eventually these pathways become depleted, rendering the host susceptible to the consequences of nutritional depletion and impaired detoxification.[46] Taken together these enterometabolic mechanisms are consistent with the observance of increased risk for xenobiotic-associated diseases such as breast cancer[47,48] and Parkinson's disease[49,50] in patients with chronic constipation. Furthermore, we would expect that patients with endotoxin-producing bacterial overgrowth of the small intestine would be more susceptible to the chemical accumulation that leads to multiple chemical sensitivity syndrome (MCS) and the xenobiotic-induced immune dysfunction that may result. In my own clinical practice, I have seen many patients with chemical sensitivity respond very favorably to the eradication of their intestinal bacterial overgrowth, and I consider this treatment essential for all patients with autoimmune disease.

11) Antimetabolites: Yeast and bacteria can produce certain molecules which "jam up", "monkey wrench", or otherwise interfere with normal human cellular metabolism. The best example is D-lactic acid, which impairs human metabolic pathways that are designed to work with the "human" form of this metabolite: L-lactic acid. Commonly resulting in headache, fatigue, depression, and sometimes death, D-lactic acidosis is extensively well documented in the medical research literature and commonly occurs in association with bacterial overgrowth of the intestine, particularly following intestinal bypass surgery.[51] Other antimetabolites produced from (intestinal) microbes which are associated with human disease and dysfunction include ammonia, tryptamine, tyramine, octopamine, mercaptates, aldehydes, alcohol, tartaric acid, indolepropionic acid, indoleacetic acid, skatole, indole, putrescine, and cadaverine. Many of these metabolites are seen in higher

amounts in patients with migraine, depression, weakness, confusion, schizophrenia, agitation, hepatic encephalopathy, chronic arthritis and rheumatoid arthritis. Gut-derived neurotoxins from bacteria and yeast may contribute to austistic symptomatology[52,53], and case reports have consistently demonstrated that excess absorption of bacterial metabolites can alter behavior in humans and result in acute neurocognitive decline and behavioral abnormalities in children.[54] Hydrogen sulfide, produced by intestinal bacteria such as *Citrobacter freundii*[55], is a mitochondrial poison[56] and is strongly associated with disease activity in ulcerative colitis.[57] Degradation of tryptophan by bacterial tryptophanase would predispose to a "functional tryptophan deficiency" with resultant insufficiency of serotonin which would contribute to hyperalgesia, depression, hypoadrenalism, and insomnia; indole and skatole, which are gut-derived bacterial degradation products of tryptophan, produce an inflammatory arthritis that is identical to rheumatoid arthritis in animal models.[58,59]

12) "Autointoxication", "hepatic encephalopathy" and "intestinal arthritis-dermatitis syndrome": The term "autointoxication" fell out of favor among American allopaths in the 1940s despite the recognition and objective documentation that systemically absorbed microbial metabolites from the colon could adversely affect systemic health, particularly neurocognitive function.[60] "Hepatic encephalopathy" seems to be one of the currently acceptable terms for this phenomenon, and it is probable that the condition exists among some outpatients to a milder degree than that which is classically seen in patients with fulminant liver failure. Recognition that excess or abnormal microbes in the gut could cause neuropsychiatric symptoms contributed to the rationale for the use of colonic irrigation in clinical practice which was fully endorsed by the American Medical Association in a position paper published in 1932.[61] Concurrently, an article published in the *New England Journal of Medicine*[62] in this same year documented the clinical benefits of colonic irrigation in patients with mental disease; the treatment was deemed effective against most cases of dementia, depression, neurosis and many cases of irritability, headaches, and hypertension. Enemas and colonics, which promote hepatobiliary detoxification[63] and cleanse the bowel of harmful microbes, were valued by clinicians as a cure or adjunctive treatment for numerous systemic diseases.[64] Although the term "autointoxication" has recently been eschewed as "unscientific", all medical professionals recognize that gastrointestinal dysbiosis can cause clinical condition characterized by inflammatory vasculitis, dermatitis, and arthritis; current terms for this condition include "bowel-associated dermatosis-**arthritis** syndrome"[65], "intestinal **arthritis**-dermatitis syndrome"[66], and "bypass disease"[67]—all of which are largely mediated by the intraintestinal formation, mucosal resorption, and systemic deposition of immune complexes in skin, joints, kidneys, and vascular endothelium.

13) Impairment of mucosal and systemic defenses: Microbial colonization of mucosal surfaces can result in impaired local immunity by causing loss of protective secretory IgA or by causing direct tissue damage that results in increased absorption of microbial, dietary, or environmental antigens. Several microorganisms such as *Entamoeba histolytica*[68], *Streptococcus sanguis*[69], and *Candida albicans*[70] externalize a protein-digesting enzyme (proteinase) that "digests" defensive immunoglobulins, including secretory IgA and humoral immunoglobulins. The proteinases produced by *Candida* are capable of lysing not only sIgA but also keratin and collagen[71], obviously providing for a breach of protection from other infections and antigens. In this way, mucosal microbial colonization with yeast/bacteria that secrete proteases/proteinases can "open the door" to exposure to other microbes or antigens that promote resultant infection or "allergy", respectively. Furthermore, because IgA is destroyed by the protease, the infection is allowed to fester, resulting in on-going immune stimulation and its consequences such as bystander activation. This may explain why women with chronic vaginal candidiasis, which always implies chronic yeast overgrowth of the intestine[72], have nearly double the incidence of allergic rhinitis compared to patients without chronic yeast overgrowth.[73] Further supporting the link between yeast and allergy is another recent study showing that allergy/atopy is more common in patients with chronic yeast infections.[74] *Candida* produces an immunotoxin called "gliotoxin", which suppresses human immune function.[75] The combination of mucosal damage, destruction of sIgA, immunosuppression, and microbial overgrowth synergize to sensitize the systemic immune system toward allergic and pro-inflammatory disease.[76]

14) Impairment of mucosal digestion by microbial proteases and inflammation: Similar to the degradation of human IgA by microbial proteases/proteinases is the degradation of mucosal digestive enzymes such as the disaccharidases (sucrase, maltase, lactase, and isomaltase) and dipeptidases. First, impaired digestion of carbohydrates skews the intestinal milieu toward one favorable to bacterial/yeast overgrowth by increasing the levels of carbohydrate substrate upon which microbes feed. Impaired peptide breakdown promotes immune sensitization, protein malnutrition, and putrefaction. Second, inflammation resultant from intestinal dysbiosis further impairs carbohydrate digestion via downregulation of sucrase-isomaltase gene expression by inflammatory cytokines.[77] Third, destruction of microvilli exacerbates loss of mucosal enzymes and leads to additional malab-

sorption, maldigestion, and increased macromolecular absorption, such as seen in patients with intestinal giardiasis.[78] Impairment/reduction of disaccharidases and dipeptidases is also seen in patients with inflammatory bowel disease.[79] Fourth and finally, bacterial proteases work synergistically with biofilm formation to nullify immunologic attack (via immunosuppression and cytokine inactivation) and are important for the establishment of chronic mucosal colonization.[80]

In sum, this survey of the literature supports the concept that intestinal dysbiosis can contribute to systemic pain, inflammation, and immune activation by numerous mechanisms, and that many of these "silent infections" are self-perpetuating by various mechanisms. Clinical experience has shown us again and again that eradicating dysbiosis helps normalize immune function, alleviate autoimmunity and allergy, reduce inflammation, improve detoxification, and to help "cure" people of their previously "incurable" multiple chemical sensitivity and environmental illness.

PARADIGM SHIFT #2: ERADICATING HARMFUL MICROBES FROM THE INTERNAL/EXTERNAL ENVIRONMENT CAN HELP CURE OTHERWISE "INCURABLE DISEASE"

In the previous section, I described the biochemical/physiologic mechanisms by which microorganisms can contribute to disease (without causing a classic "infection") and promote systemic inflammation and human disease. Thus having developed the precept that "microorganisms can cause inflammatory disease by non-infectious means", I will state here that the cure of human disease by eradication of harmful microbes is not a requirement to prove the validity of this thesis. Inflammation and autoimmunity are self-perpetuating phenomena that can persist despite the effective eradication of the principle cause, and research has demonstrated that microbial antigens can remain present in synovial fluid for several years after the eradication of the primary infection. With that said, we are fortunate to observe that many patients with autoimmunity are indeed benefited and occasionally "cured" by removal of instigating microbes. I have seen this on numerous occasions in my clinical practice, and this phenomenon has also been documented in the research literature. Examples published in the research include the amelioration of one patient's scleroderma with the eradication of intestinal bacterial overgrowth[81], the amelioration of Wegener's granulomatosis with antimicrobial therapy against *Staphylococcus aureus*[82,83], and the alleviation of inflammatory arthritis following the use of antibiotics against genitourinary *Chlamydia trachomatis* and gastrointestinal *Salmonella enteritidis, Yersinia enterocolitica, Shigella flexneri* or *Campylobacter jejuni*.[84]

THE SIX MAIN LOCI OF DYSBIOSIS—FOCUS ON GASTROINTESTINAL DYSBIOSIS

For a microorganism to induce a systemic pro-inflammatory immunodysregulatory response in a human, the microbe or its metabolic products must be exposed to a susceptible host. Non-infectious microbial overgrowth can occur inside the body (gastrointestinal, sinus, genitourinary, or dental), on the surface of the body (dermal), or outside of the body (environmental). The adverse physiologic and clinical effects can be similar regardless of the location of the microorganism. The term "dysbiosis" is classically applied to harmful, non-infectious relationships between the human host and yeast, bacteria, protozoans, amoebas, or other "parasites" located specifically in the gastrointestinal tract, and "dysbiosis" is now an accepted term in the medical literature.[85] However, we must also appreciate that harmful, noninfectious microbe-host interactions can also occur when microbes are localized in the sinuses, oral cavity, genitourinary tract, skin, and in the external environment. I prefer to use a broad definition of dysbiosis that implies "a relationship of non-infectious host-microorganism interaction that adversely affects the human host" and then to specify the subtype based on the location: gastrointestinal, oral, sinus, genitourinary, dermatologic, or environmental. Gastrointestinal dysbiosis is clearly the prototype for understanding other types of dysbiosis; this is because it seems to be the most common form of dysbiosis, perhaps due to the large numbers and types of microbes in the gut and the extensive surface area of the gastrointestinal tract. For the sake of brevity, I will only emphasize gastrointestinal dysbiosis here and will provide an introduction to sinus, genitourinary, dental, cutaneous, and environmental dysbiosis, each of which is discussed in greater detail in my textbook *Integrative Rheumatology*.

Gastrointestinal dysbiosis: We all have bacteria and occasionally small quantities of yeast in our intestines, and this is normal and healthy. However, problems arise when these yeast/bacteria become imbalanced or when *harmful* yeast, bacteria, parasites take up residence within the gut. Particularly in the European research literature, this condition has been more widely researched and is referred to as "dysbacteriosis" or "dysbacterosis." These latter terms imply that the problem has a *bacterial* origin, which is potentially misleading since dysbiosis commonly involves bacteria and *yeast* (including but not limited to *Candida albicans*) and commonly other harmful non-bacterial microbes such as *Giardia lamblia, Blastocystis hominis, Endolimax nana, Entamoeba histolytica* and a cast of other malcontents that adversely affect the overall health of their human host.[86] "Candidiasis" and yeast-related problems have been described in the research literature and general press.[87] Dysbiosis is probably a major aspect of the phenomenon that was previously referred to in the medical

literature as "autointoxication" and which was effectively treated with dietary modifications, nutritional supplementation, and colonic irrigation. Given that endotoxin/lipopolysaccharide is one of the major activators of nuclear factor Kappa-B (NF-kappaB)[88], and that NF-kappaB activation is a major rate-limiting step in the production of pro-inflammatory cytokines and in the induction of pro-inflammatory enzymes such as cyclooxygenase, lipoxygenase, and inducible nitric oxide synthase,[89] then the link between dysbiosis and systemic inflammation becomes clear: gastrointestinal bacterial overgrowth leads to excess production and absorption of endotoxin, which then initiates immune dysfunction and a systemic pro-inflammatory response. Thus, the sequelae of dysbiosis are mediated by alterations in human physiology rather than being directly caused by the microbe. Current research has linked several microbes with human autoimmune/inflammatory diseases, for example *Entamoeba histolytica* has been linked with Henoch Schonlein purpura[90], *Klebsiella pneumoniae* with ankylosing spondylitis[91], *Proteus mirabilis* with rheumatoid arthritis[92] and ankylosing spondylitis[93], *Pseudomonas aeruginosa* with multiple sclerosis[94], and *Helicobacter pylori* with reactive arthritis.[95] Building upon a previous system of categorization proposed by Galland[96], here I describe six different types of gastrointestinal dysbiosis:

1) Insufficiency dysbiosis: This results when there is an insufficient quantity of the "good bacteria." Absence of "good bacteria" such as *Bifidobacteria* and *Lactobacillus* leaves the gastrointestinal tract vulnerable to colonization with pathogens and is associated with increased risk for bacterial overgrowth and other intestinal diseases. Furthermore, good bacteria in the intestines normalize systemic immune response and promote proper digestion, elimination and nutrient absorption. Numerous scientific studies have documented the powerful benefits of supplementing with good bacteria (probiotics), supporting their growth with fermentable carbohydrates such as inulin and fructooligosaccharides (prebiotics), and by co-administering probiotics with prebiotics (synbiotics).

2) Bacterial overgrowth: This is a quantitative excess of yeast and bacteria in the gut. Bacterial overgrowth of the small bowel is a well-established medical problem that is particularly common in diabetics, the elderly, the immunosuppressed, and patients on "antacid" drugs.[97] This commonly results in gas, bloating, constipation and/or diarrhea as well as myalgias and systemic immune activation.[43] Animal studies have proven that it is possible to reactivate peripheral arthritis by inducing bacterial overgrowth of the small bowel; endotoxins and other microbial products stimulate a systemic pro-inflammatory state which re-activates inflammation of joints and periarticular structures.[98] Bacterial overgrowth of the small intestine is seen in 84% of patients with irritable bowel syndrome[43] and in 100% of patients with fibromyalgia.[99] Researchers recently demonstrated that endotoxins can lead to impairment of muscle function and a lowered lactate threshold[100], thereby explaining the link between intestinal dysbiosis and chronic musculoskeletal pain that is not responsive to drugs or manual therapies. In patients with lupus, gastrointestinal bacteria are abnormal (decreased colonization resistance[101]), and it is possible that gastrointestinal bacteria in these patients may translocate into the systemic circulation to induce formation of antibodies that cross-react with double-stranded DNA to produce the clinical manifestations of the disease.[101,102] Relatedly, Drs. Over and Bucknall[81] describe a patient with systemic sclerosis who achieved long-term remission of her disease following antibiotic treatment for intestinal bacterial overgrowth. Bacterial overgrowth generally leads to pathologically synergistic clinical effects mediated by fermentation, putrefaction, constipation, increased enterohepatic recycling, bile acid deconjugation, malabsorption (particularly fat-soluble nutrients and vitamin B-12), nutritional deficiencies, sugar cravings, increased intestinal permeability, immune complex formation, and induction of a systemic pro-inflammatory response which is particularly prone to manifest as vasculitis and arthritis.[43,103,104]

3) Immunosuppressive dysbiosis: Some microbes, particularly yeast, produce toxins that suppress immune function. The immunosuppressive mycotoxin produced by *Candia albicans* is called gliotoxin, and it is produced at the site of yeast overgrowth, thus suppressing local—and possibly, systemic—immune function.[105,106] Since secretory IgA is the first line of defense against allergens and infections in the gastrointestinal tract, its destruction by microbes such as *Candida albicans* and *Entamoeba histolytica* retards this immune barrier, and this can be considered a form of immunosuppression.

4) Hypersensitivity dysbiosis: Some people have an exaggerated immune response to otherwise "normal" yeast and bacteria. In this situation, we have to eradicate their "normal" yeast or bacteria in order to alleviate their hypersensitivity reaction. The best example of this is the severe intestinal inflammation that some patients develop in response to intestinal colonization with *Candida albicans,* which is generally considered "nonpathogenic" in small amounts. In susceptible patients *Candida* can induce a severe local inflammatory reaction, such as colitis, that only remits with antifungal treatment.[107] Gastrointestinal overgrowth of *Candida albicans* and *C. glabrata* caused near-fatal hypersensitivity alveolitis that remitted with eradication of gastrointestinal candidiasis.[108] It is clear that some women become "allergic" to their own vaginal *Can-*

dida albicans[109]; undoubtedly there are also men who are likewise allergic to their own intestinal yeast.

5) Inflammatory dysbiosis and "reactive arthritis": Some people with specific genotypes and HLA markers are susceptible to a pro-inflammatory "autoimmune" syndrome that occurs following a noninfectious exposure to specific microbial molecules that are structurally similar to human body tissues—a phenomenon previously described as molecular mimicry. The best-known example of systemic musculoskeletal inflammation caused by microbial exposure is "reactive arthritis" such as Reiter's syndrome, which is classically seen in patients with the genotype HLA-B27 following urogenital exposure to *Chlamydia trachomatis*.

6) Amoebas, cysts, protozoans, and other "parasites": In this case when we use the term "parasites'" we are not talking about worms, *per se,* although these are occasionally found with parasitology examinations. Certain microorganisms are not consistent with optimal health and should be eliminated even though the microbe is not classically identified as a "pathogen." Individual microorganisms are discussed later in this article.

Sinorespiratory dysbiosis: Patients with acute and chronic rhinosinusitis commonly display a rich mixture of bacteria and fungi in their sinuses. Regarding bacteria, both anaerobic and aerobic bacteria are seen, as are gram-positives such as *Staphylococcus aureus* and *Streptococcus* sp, and gram-negative (endotoxin-producing) species including *Klebsiella pneumoniae, Proteus mirabilis, Bacteroides, Haemophilus parainfluenzae, Haemophilus influenzae,* and Peptococcus/Peptostreptococcus.[110,111] In a landmark publication in *Mayo Clinic Proceedings*[112], the authors found that almost all patients with chronic sinus congestion had occult sinus infections, and they concluded, *"Fungal cultures of nasal secretions were positive in 202 (96%) of 210 consecutive chronic rhinosinusitis patients."* Perhaps the best current exemplification of the link between sinus infections and chronic inflammatory disease is seen in patients with Wegener's granulomatosis, who have a high incidence of sinus colonization with *Staphylococcus aureus*. Once considered "idiopathic", Wegener's granulomatosis is a systemic autoimmune disease characterized by vasculitis, respiratory complications, and renal failure; without treatment it is often fatal within 12 months of diagnosis. Recently, patients with Wegener's granulomatosis have been found to have subclinical sinus colonization with *Staphylococcus aureus*. In these patients, *Staphylococcus aureus* produces a superantigen as well as an antigenic acid phosphatase which induces autoimmune vasculitis, nephritis, the production of antineutrophil anticytoplasmic antibody (ANCA), and the formation of immune complexes. Antimicrobial treatment to eradicate *Staphylococcus aureus* results in clinical remission of the "autoimmune" disease[82], thus proving the microbe-rheumatic link. Interestingly, 97% of patients severely infected with the gastrointestinal "parasite" *Entamoeba histolytica* develop self-destructive ANCA, leading to the possibility that this microbe can induce or sustain autoimmunity.[83]

Dental dysbiosis: The human oral cavity is heavily populated by microbes, and these microbes and their products such as endotoxin can enter the bloodstream to induce a pro-inflammatory response via "metastatic infection" and "metastatic inflammation", respectively.[113] The systemic inflammatory response triggered by mild oral/dental "infections" is now believed to exacerbate conditions associated with inflammation, such as cardiovascular disease and diabetes.[114] Patients with recalcitrant inflammation might be referred to a "biologic dentist" for evaluation and treatment of occult dental and mandibular infections.

Genitourinary dysbiosis: It is well-known that genitourinary infection with *Chlamydia trachomatis* can produce systemic inflammation—"reactive arthritis"—and result in the condition previously known as Reiter's syndrome.[84] Often fatal, toxic shock syndrome results from the absorption of toxins and superantigens from *Staphylococcus aureus* directly through the genitourinary mucosa. In a study of 234 patients with inflammatory arthritis, 44% of patients had a silent genitourinary infection, mostly due to *Chlamydia, Mycoplasma,* or *Ureaplasma*.[115] It is therefore clear that microbial contamination of the genitourinary tract may lead to a systemic pro-inflammatory response in susceptible individuals.

Cutaneous dysbiosis: Microorganisms from dermal infections such as acne can incite systemic inflammation either by dermal absorption of bacterial[116] and fungal[4] (super)antigens and by serving as loci for metastatic infections which produce septic arthritis.[117] Patients with the autoimmune vasculitic syndrome known as Behcet's disease are more likely to develop arthritis if their skin lesions are infected.[118] Thus, topical and/or systemic antimicrobial treatment along with immunonutrition (detailed later) may be necessary for complete treatment of patients with inflammatory autoimmunity caused by dermal infections.

Environmental dysbiosis: "Toxic mold syndrome" describes patients with systemic health problems resultant from exposure to fungal bioaeresols, classically associated with mold-contaminated buildings following water damage. Such individuals may develop neuromuscular autoimmunity that resembles multiple sclerosis and idiopathic inflammatory polyneuropathy mediated in part by antibodies against endogenous neuronal structures.[119] Additional evidence makes it clear that mold exposure can

lead to pro-inflammatory immune activation and resultant multisystem autoimmunity.[120] This is yet another example of how microorganisms can cause human disease without causing "infection."

GASTROINTESTINAL DYSBIOSIS: IDENTIFICATION AND ERADICATION

Clinicians should suspect gastrointestinal dysbiosis in their patients with gas, bloating, alternating constipation/diarrhea, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity, severe allergies, and autoimmunity, especially Crohn's disease, ulcerative colitis, rheumatoid arthritis, and ankylosing spondylitis. Bacterial overgrowth of the small bowel can be objectively documented with measurement of post-carbohydrate hydrogen/methane, but I consider a history of postprandial gas and bloating to be sufficiently diagnostic. The single best test for the assessment of gastrointestinal dysbiosis is a comprehensive stool analysis and comprehensive parasitology examination performed by a specialty laboratory that provides bacterial culture, yeast culture, microscopic exam, and measurement of sIgA to assess mucosal immune response, along with markers of inflammation such as lactoferrin, calprotectin, and/or lysozyme. Additional markers can help put microbiological findings into the proper context.

CLINICAL AND LABORATORY ASSESSMENT OF GASTROINTESTINAL STATUS

Clinical assessment of gastrointestinal function begins with a thorough history. Frequent gas and bloating indicates excess gastrointestinal fermentation by yeast and/or overgrowth of aerobic bacteria. Abdominal pain, chronic constipation, and/or diarrhea are clear indications for stool testing; however clinicians must remember that some of the most heavily colonized patients will have no gastrointestinal symptoms. Thus, assessment and treatment for gastrointestinal dysbiosis is not unnecessary simply because the patient lacks gastrointestinal symptoms. The lactulose and mannitol assay evaluates paracellular (pathologic) and transcellular (physiologic) absorption, respectively; and an increased latulose:mannitol ratio is a non-specific finding that indicates gastrointestinal damage, generally due to 1) enterotoxin consumption such as with alcohol or NSAIDs, 2) malnutrition, 3) food allergy including celiac disease, 4) severe systemic illness, and/or 5) dysbiosis—excess/harmful yeast, bacteria, or parasites. Comprehensive stool analysis assesses digestion, absorption, inflammation, and comprehensive parasitology examinations (x3) assess for bacteria, yeast, and parasites. These tests should be performed by a specialty laboratory rather than a regular medical or hospital laboratory.

PROBLEMATIC BACTERIA, YEAST, AND PARASITES: A LISTING OF COMMONLY ENCOUNTERED MICROBES

With the single exception of *Dientamoeba fragilis,* all of the following yeast, bacteria, and "parasites" have been observed in various patients in my private practice of chiropractic and naturopathic medicine. Even though several of these are considered nonpathogenic by the outdated allopathic conceptualizations that are still hypnotized by Pasteur and Koch, their presence is generally inconsistent with optimal health and their eradication is rewarding for both doctor and patient. One of the benefits of specialized stool testing is that it allows the presence of microbes to be determined within a context that evaluates the patient's individualized response. For example, the finding of a mild degree of *Candida albicans* ("+1" on a 0-4 scale) might be considered insignificant; however if no other pathogens are identified, and the secretory IgA, lactoferrin, and lysozyme levels are highly elevated, then the clinician is justified in determining that the patient is having a hypersensitivity reaction to an otherwise "benign" yeast. Recently I worked with a patient with rheumatoid arthritis in whom we found mild *Citrobacter freundii* ("+1") which was barely enough to arouse my interest until I noted that he had an exaggerated mucosal inflammatory response; eradication of the bacteria lead to an immediate and profound reduction in his symptomatology and systemic inflammation (e.g., his C-reactive protein decreased from 124 to 7 mg/L within four weeks). Remember, we are not looking for classic "infection" here; we are looking to determine which underlying disruptions may be exacerbating inflammation and the patient's symptomatology.

Blastocystis hominis: Patients with *B. hominis* commonly have fatigue. Some patients will have abdominal pain, nausea, vomiting, diarrhea, weight loss as well as anorexia, flatus, and eosinophilia.[121-123] "Typical symptoms include diarrhea, crampy abdominal pain, nausea, vomiting, low-grade fever, gas, malaise, and chills. Fecal leukocytes are occasionally seen."[124] *B. hominis* can cause colitis.[125]

***Candida albicans* and other yeasts:** Although normal in small amounts ("+1"), excess *Candida* in the intestines is never a sign of optimal health. Patients may have mild general symptoms such as fatigue and dyscognition ("brain fog"); gas and intestinal bloating following consumption of carbohydrates are common. *Candida* produces an immunosuppressive myotoxin called gliotoxin as well as an IgA-destroying protease and can cause watery diarrhea, particularly in elderly, ill, and immunosuppressed patients. It is always present in the gastrointestinal tract of women with recurrent yeast vaginitis.[72] Some people have an inflammatory hypersensitivity to *Candida,* as it can cause

local allergic dermatitis/mucositis[109], colitis[107], and pulmonary inflammation (from gastrointestinal colonization).[108] Other yeasts such as *Candida parapsilosis* and *Geotrichum capitatum* are occasionally seen and should be eradicated.

Citrobacter freundii: Also known as Ci*trobacter rodentium, Citrobacter freundii* is described as a gram-negative aerobe and facultative anaerobe; it may cause gastroenteritis in humans. Animal studies have shown that this bacterium can induce an intense inflammatory response in the gastrointestinal tract that resembles inflammatory bowel disease. Like several other intestinal bacteria, most strains of *Citrobacter freundii* produce hydrogen sulfide which interferes with mitochondrial function and energy production and appears to contribute to ulcerative colitis.[57]

Endolimax nana: *Endolimax nana* is a protozoa with world-wide distribution and is commonly considered an harmless commensal of the intestine. However, intestinal infection with *Endolimax nana* can cause a peripheral arthropathy that is clinically similar to rheumatoid arthritis and which remits with effective parasite eradication.[126] In my own clinical practice, I have seen several cases of intestinal colonization with *Endolimax nana* in patients who presented with chronic fatigue, myalgia, eczema, and especially refractory chronic vaginitis.

***Entamoeba histolytica*:** *E histolytica* can induce tissue damage, amebic colitis, and liver abscess.[127] *E histolytica* was associated with Henoch Schonlein purpura in a single case report.[128] Amebic colitis may be misdiagnosed as ulcerative colitis.[86] Associated with induction of antineutrophil cytoplasmic antibodies, such as seen with the vasculitic disease Wegener's granulomatosis[83], *E histolytica* may produce manifestations similar to irritable bowel syndrome, rheumatoid arthritis, fibromyalgia, food allergy, or multiple chemical sensitivity and can exacerbate HIV infection.[86]

***Giardia lamblia*:** Giardia is causatively associated with abdominal pain, diarrhea, constipation, bloating, chronic fatigue, and food allergy/intolerance, and can exacerbate irritable bowel syndrome, rheumatoid arthritis, food allergy, or multiple chemical sensitivity.[86,129] Some infections are relatively asymptomatic.

***Klebsiella pneumoniae*:** Many cases of gastrointestinal colonization with this microorganism produce no acute gastrointestinal symptoms such as nausea, vomiting, constipation, or diarrhea. Patients may have mild general symptoms such as fatigue and dyscognition ("brain fog"). *Klebsiella* can cause diarrhea and acute gastroenteritis. It is associated with reactive arthritis such as ankylosing spondylitis.[91] Since it is a gram-negative bacteria, it produces an endotoxin that is capable of impairing cytochrome p-450 and reducing clearance and excretion of drugs.[130]

Proteus mirabilis: *Proteus* is a gram-negative bacteria that produces endotoxin. Gastrointestinal and urinary tract colonization with *Proteus* is associated with rheumatoid arthritis[92] and ankylosing spondylitis.[93] In one of my patients, his response to gastrointestinal *Proteus* caused an "idiopathic inflammatory polyneuropathy" that disappeared within one month of parasite eradication; this patient had previously been assessed by several neurologists with MRI, CT, CSF analysis, and neuroconductive tests, none of which lead to diagnosis or effective treatment.

Pseudomonas aeruginosa: Many cases of gastrointestinal colonization with this microorganism produce no acute gastrointestinal symptoms such as nausea, vomiting, constipation, or diarrhea. Patients may have mild general symptoms such as fatigue and dyscognition ("brain fog"). *Pseudomonas aeruginosa* is a gram-negative bacteria, produces endotoxin and can cause antibiotic-associated diarrhea. Patients with multiple sclerosis show evidence of a heightened immune response against *Pseudomonas aerugeniosa,* suggesting the possibility of immune cross-reactivity.[94]

Helicobacter pylori: *H. pylori* is a gram-negative endotoxin-producing rod that causes stomach ulcers and appears to cause reactive arthritis in some patients.[95]

Group A streptococci, Streptococcus pyogenes: Intestinal overgrowth of this bacterium, which produces peptidoglycans, can cause dermatosis, polyarthritis, tenosynovitis, malaise, fever, and cryoglobulinemia.[7] Non-infectious manifestations precipitated by infection with *S. pyogenes* include autoimmune neuropsychiatric disorders (including obsessive-compulsive disorder and Sydenham's chorea), dystonia, glomerulonephritis, and reactive arthritis.[131] Certain strains of *S. pyogenes* produce an exotoxin that can cause toxic shock syndrome.[132]

"Gamma strep" and Enterococcus: "Gamma strep", *Enterococcus faecalis,* and S*treptococcus faecalis* are somewhat interchangeable terms. These terms refer to gram-positive Enterococcus species such as *Enterococcus faecalis,* which cause urinary tract infections, bacteremia, intra-abdominal infections, and endocarditis. Enterococci produce lipoteichoic acid which is pro-inflammatory in a manner similar to endotoxin from gram-negative bacteria, and these gram-positive bacteria also appear to produce a superantigen.[133] "Gamma strep" is commonly identified in stool tests of patients with chronic unwellness and fatigue.

Staphylococcus aureus: Gastrointestinal colonization with *Staph aureus* should be eradicated immediately due to the well-known inflammatory consequences of the toxins

and superantigens this bacterium produces. *Staphylococcus aureus* is a gram-positive bacterium, certain strains of which produce the toxic shock syndrome toxin-1 (TSST-1) that produces scalded skin syndrome, toxic shock syndrome, and food poisoning; other strains of *Staph aureus* that do not produce TSST-1 are also capable of causing toxic shock syndrome from colonization of bone, vagina, wounds, or rectum.[134] Gastrointestinal colonization with *Staph aureus* is a known cause of acute colitis[135], and nasal carriage of this bacterium appears to trigger autoimmunity in patients with Wegener's granulomatosis.[82]

Aeromonas hydrophila: *Aeromonas hydrophila* can cause colitis and should be eradicated immediately upon detection.[136]

Dientamoeba fragilis: *Dientamoeba fragilis* is a flagellate protozoan that can cause diarrhea, abdominal pain, nausea, vomiting, fatigue, malaise, eosinophilia, urticaria, pruritus and/or weight loss. It is commonly associated with pinworm infection and may produce a clinical picture that mimics food allergy, colitis, or eosinophilic enteritis.[137]

NATURAL TREATMENTS FOR THE ERADICATION OF GI DYSBIOSIS AND RELATED IMMUNE-COMPLEX DISEASES

Although antimicrobial drugs may be used, these are not universally curative and are not necessarily "more powerful" or "more effective" than natural treatments. Even when treating dysbiosis caused by microorganisms, we must look "beyond the bugs" and ensure that treatment is comprehensive, as well as effective.

Diet modifications *("starve the microbes"):* The diet plan should ensure avoidance of sugar, grains, soluble fiber, gums, prebiotics, and dairy products since these contain fermentable carbohydrates that promote overgrowth of bacteria and other microorganisms in the gut. Short-term fasting starves intestinal microbes, temporarily eliminates dietary antigens, alleviates "autointoxication", and stimulates the humoral immune system in the gut to more effectively destroy local microbes.[138,139] Thus, implementation of the "specific carbohydrate diet" popularized by Gotschall[140] along with periodic fasting, which has obvious anti-inflammatory benefits[141], can be used therapeutically in patients with conditions associated with dysbiosis-induced inflammation. Plant-based low-carbohydrate diets can lead to favorable changes in the quality and quantity of intestinal microflora. Hypoallergenic diets are proven beneficial for the treatment of the immune complex disease mixed cryoglobulinemia.[142,143]

Antimicrobial treatments *("poison the microbes, not the patient"):* Anti-microbial herbs can be used which directly kill or strongly inhibit the intestinal microbes. The most commonly used and well-documented botanicals in this regard are listed in the section below. Antimicrobial treatment is frequently continued for 1-3 months, and co-administration of drugs can be utilized when appropriate. Sometimes antimicrobial drugs are necessary, especially for acute and severe infections; often nutritional and botanical interventions are safer and more effective. Although these herbs are generally taken orally, some of them can also be applied topically (in a cream or lotion), and nasally (in a water lavage). Botanical medicines are generally used in combination, and lower doses of each can be used when used in combination compared to the doses that are necessary when the herbs are used in isolation.

Oregano oil in an emulsified and time-released tablet: Botanical oils that are not emulsified do not attain maximal dispersion in the gastrointestinal tract; products that are not time-released may be absorbed before reaching the colon in sufficient concentrations. Emulsified oil of oregano in a time-released tablet is proven effective in the eradication of harmful gastrointestinal microbes, including *Blastocystis hominis, Entamoeba hartmanni,* and *Endolimax nana*.[144] An in vitro study[145] and clinical experience support the use of emulsified oregano against *Candida albicans*. The common dose is 600 mg per day in divided doses.

Berberine: Berberine is an alkaloid extracted from plant such as *Berberis vulgaris*, and *Hydrastis canadensis*, and it shows effectiveness against *Giardia*, *Candida*, and *Streptococcus* in addition to its direct anti-inflammatory and antidiarrheal actions. Oral dose of 400 mg per day is common for adults.[146]

***Artemisia* species:** 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.[147] In a recent study treating patients with malaria, "the adult artemisinin dose was 500 mg; children aged < 15 years received 10 mg/kg per dose" and thus the dose for an 80-lb child would be 363 mg per day by these criteria.[148] I commonly use artemisinin at 200 mg per day in divided doses for adults with dysbiosis. One of the main benefits of artemisinin is its systemic bioavailability.

St. John's Wort (*Hypericum perforatum*): Best known for its antidepressant action, hyperforin from *Hypericum perforatum* also shows impressive antibacterial action, particularly against gram-positive bacteria such as *Staphylococcus aureus, Streptococcus pyogenes* and *Streptococcus agalactiae*. According to in vitro studies, the lowest effective hyperforin concentration is 0.1 mcg/mL against *Corynebacterium diphtheriae* with increasing effectiveness against multiresistant *Staphylococcus aureus* at higher concentrations of 100 mcg/mL.[149] Since oral dos-

ing with hyperforin can result in serum levels of 500 nanogram /mL (equivalent to 0.5 microgram/mL) then it is possible that high-dose hyperforin will have systemic antibacterial action. Regardless of its possible systemic antibacterial effectiveness, hyperforin should clearly have antibacterial action when applied "topically" such as when it is taken orally against gastric and upper intestinal colonization. Extracts from St. John's Wort hold particular promise against multidrug-resistant *Staphylococcus aureus*[150], and there is also evidence for its effectiveness against *Helicobacter pylori*.[151]

Myrrh *(Commiphora molmol):* Myrrh is remarkably effective against parasitic infections.[152] A recent clinical trial against schistosomiasis 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."[153]

Bismuth: Bismuth is commonly used in the empiric treatment of diarrhea and is commonly combined with other antimicrobial agents to reduce drug resistance and increase antibiotic effectiveness.

Peppermint (*Mentha piperita*): Peppermint shows antimicrobial and antispasmodic actions and has demonstrated clinical effectiveness in patients with bacterial overgrowth of the small bowel.

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.[154] Components of uva ursi potentiate antibiotics. This herb has some ocular and neurologic toxicity and should be used with professional supervision for low-dose and/or short-term administration only.[155]

Cranberry: Cranberry is particularly effective for the prevention and adjunctive treatment of urinary tract infections, mostly by inhibiting adherence of *E. coli* to epithelial cells.[156]

Thyme *(Thymus vulgaris):* Thyme extracts have direct antimicrobial actions and also potentiate the effectiveness of tetracycline against drug-resistant *Staphylococcus aureus*.[157] Thyme also appears effective against *Aeromonas hydrophila*.[158]

Clove *(Syzygium species):* Clove's eugenol has been show in animal studies to have a potent antifungal effect.[159]

Anise: Although it has weak antibacterial action when used alone, anise does show in vitro activity against molds.[160]

Buchu/betulina: Buchu has a long history of use against urinary tract infections and systemic infections.[161]

Caprylic acid: Caprylic acid is a medium chain fatty acid that is commonly used in patients with dysbiosis, particularly that which has a fungal/yeast component. Beside empiric use, caprylic acid may be indicated by culture-sensitivity results provided with comprehensive parasitology.

Dill *(Anethum graveolens):* Dill shows activity against several types of mold and yeast.[162]

Brucea javanica: Extract from *Brucea javanica* fruit shows *in vitro* activity against *Babesia gibsoni, Plasmodium falciparum*[163], *Entamoeba histolytica,*[164] and *Blastocystis hominis*.[165,166]

Acacia catechu: *Acacia catechu* shows moderate in vitro activity against *Salmonella typhi*.[167]

Oral administration of proteolytic enzymes: The use of polyenzyme therapy in patients with dysbioic inflammation is justified for at least four reasons. First, orally administered proteolytic enzymes are efficiently absorbed by the gastrointestinal tract into the systemic circulation[168] to then provide a clinically significant anti-inflammatory benefit as I reviewed recently.[169] Second and more specifically, oral administration of proteolytic enzymes is generally believed to effect a reduction in immune complexes and their clinical consequences[170], and immune complexes are probably a major mechanism of dysbiosis-induced disease and are pathogenic in rheumatoid arthritis[171] and many other autoimmune diseases such as systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, and polyarteritis nodosa.[172] Third, proteolytic enzymes have been shown to stimulate immune function[173] and may thereby promote clearance of occult infections. Fourth, proteolytic enzymes degrade microbial biofilms and increase immune penetration and the effectiveness of antimicrobial therapeutics.[174]

Probiotic supplementation *("crowd out the bad with the good"):* Given that "healthy" intestinal bacteria can alleviate disease and promote normal immune function[175], then it is conversely true that a condition of harmful or suboptimal intestinal bacteria could promote disease and lead to immune dysfunction. For patients with gastrointestinal and genitourinary dysbiosis, supplementation with *Bifidobacteria, Lactobacillus,* and perhaps *Saccharomyces* and other beneficial strains is mandatory. The wide-ranging and well-documented benefits seen with probiotic supplementation provide direct and indirect support for the importance of microbial balance in health and disease. Supplementation with probiotics (live bacteria) is the best option, however prebiotics (such as fructooligosaccarides), and synbiotics (probiotics + prebiotics) may also be used. Synbiotic supplementation has been shown to reduce endotoxinemia and clinical symptoms in 50% of patients with

minimal hepatic encephalopathy[176], and probiotic supplementation safely ameliorated the adverse effects of bacterial overgrowth in a clinical study of patients with renal failure.[177]

Immunonutrition: Obviously the diet should be nutritious and free of sugars and other "junk foods" that promote inflammation and suppress immune function.[178] Especially in patients with gastrointestinal dysbiosis, vitamin and mineral supplementation should be used to counteract the effects of malabsorption, maldigestion, and hypermetabolism that accompany immune activation. Additionally, oral glutamine in doses of six grams three times daily can help normalize intestinal permeability, enhance immune function, and improve clinical outcomes in severely ill patients.[179] Zinc and vitamin A supplementation are each well-known to support immune function against infection. Selenium has anti-inflammatory, antioxidant, and antiviral actions.[180] Vitamin D supplementation reduces inflammation, protects against autoimmunity, and promotes immunity against viral and bacterial infections.[181] Supplementation with IgG from bovine colostrum can also provide benefit against chronic and acute infections.[182,183] Extracts from bovine thymus are safe for clinical use in humans and have shown anti-infective and anti-inflammatory benefits[184] as well as antirheumatic/anti-inflammatory benefits in patients with autoimmune diseases[185-187]; in an animal study of experimental dental disease, administration of thymus extract was shown to normalize immune function and reduce orodental dysbiosis.[188]

Hepatobiliary stimulation for IgA-complex removal: The binding of immunoglobuin A (IgA) with antigen creates IgA immune complexes that contribute to tissue destruction by complement activation (alternate pathway) and other pathomechanisms in IgA nephropathy[189], Henoch-Schonlein purpura[190], rheumatoid vasculitis[191], lupus[192], and Sjogren's syndrome.[193] Autoreactive IgA antibodies are a characteristic of lupus and Sjogren's syndrome[193] and correlate strongly with disease activity in rheumatoid arthritis.[194] Immune complexes containing secretory IgA that has been reabsorbed from mucosal surfaces mediate many of the clinical phenomenon of dysbiosis-related disease[17], and these same IgA-containing immune complexes are eliminated from the systemic circulation via the liver and biliary system[195,196], thus providing the rationale for the use of botanicals and physiotherapeutics that promote liver function and bile flow in the treatment of IgA-mediated inflammatory disorders. Numerous experimental studies in animals have shown that circulating IgA immune complexes are taken up by hepatocytes and then secreted into the bile for elimination.[197,198] The fact that bile duct obstruction retards systemic clearance of IgA immune complexes and that normalization/optimization of bile flow reduces serum IgA levels by enhancing biliary excretion in animals[199-200] and humans[201] proves the importance of ensuring optimal hepatobiliary function and supports the use of botanical and physiological therapeutics that facilitate bile flow. A 1929 clinical study with human patients published in *Archives of Internal Medicine* provided irrefutable radiographic documentation that therapeutic enemas safely and effectively stimulate bile flow for 45-60 minutes following administration[63], and this finding, along with the obvious quantitative reduction in intestinal microbes induced by such "cleansing", helps explain the reported benefits of colonics/enemas in patients with systemic illness[40,61,62,64] and other immune-complex associated diseases such as cancer.[202] Validation of this concept is demonstrated by the significant efficacy of immunoadsorption[203] and plasmapheresis[204,205] (techniques for removing immune complexes) in patients with lupus. Furthermore, this directly supports the naturopathic concept of "treating the liver" in patients with systemic disease by the use of dietary and botanical therapeutics that stimulate bile flow, such as beets, ginger[206], curcumin/turmeric[207], *Picrorhiza*[208], milk thistle[209], *Andrographis paniculata*[210], and *Boerhaavia diffusa*.[211]

Ensure generous bowel movements and consider therapeutic purgatives *(purge: to free from impurities):* Dysbiotic patients should consume a low-fermentation fiber-rich diet that allows for 1-2 very generous bowel movements per day. Constipation must absolutely be eliminated; there is no place for constipation in patients being treated for dysbiosis of any type. Patients with severe or recalcitrant dysbiosis can start the day with a laxative dose of ascorbic acid (e.g., 20 grams with 4 cups of water) and should expect liquid diarrhea within 30-60 minutes. The goal here is purgative physical removal of enteric microbes; in high concentrations, ascorbic acid has a direct antibacterial effect. Magnesium in elemental doses of 500-1,200 mg also helps soften stool and promote laxation.

SUMMARY AND CONCLUSIONS

Microbes contribute to noninfectious human diseases by numerous and complex direct and indirect mechanisms. Patients may have several types of dysbiosis at the same time, as we see in patients with Behcet's syndrome characterized by pulmonary infection with *Chlamydia pneumonia*[212], cutaneous infection with *Staphylococcus aureus*[213], and orodental infection with *Streptococcus sanguis*.[69] Add in a few genetic traits and some nutritional deficiencies, and it becomes easy to see why rheumatic diseases are generally still considered "idiopathic" when reviewed from a reductionistic medical paradigm that fails

to appreciate the interconnected and "holistic" web of influences that synergize to produce systemic inflammation. For the majority of patients in outpatient clinical practice, the location of their dysbiosis is the gut, which is easily assessed with specialized stool testing and parasitology examinations, and which is easily treated with oral botanical antimicrobials and dietary modification. In my own clinical practice, I consider stool testing extremely valuable and estimate that 80% of parasitology examinations return with at least one clinically-relevant abnormality. Testing for and treating dysbiosis is an absolutely essential consideration in patients with gas, bloating, alternating constipation/diarrhea, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity, severe allergies, arthritis, and autoimmunity. In addition to hundreds to thousands of years of traditional use, many botanical medicines have modern peer-reviewed clinical and experimental research supporting their role in the eradication of acute and chronic infections. Beyond the use of antimicrobial herbs, other treatments such as diet therapy, immunonutrition, hepatobiliary stimulation, probiotics, and proteolytic enzymes clearly have a role in the treatment of patients with musculoskeletal inflammation secondary to dysbiosis. With their superior knowledge of natural anti-inflammatory therapeutics including diet[214], balanced broad-spectrum fatty acid supplementation[215], botanical and nutritional antiinflammatories[216] (including high-dose vitamin D)[181], NF-kappaB inhibitors[217], and anti-allergy treatments[218], chiropractic and naturopathic physicians have the power to safely and effectively aid the vast majority of patients with degenerative and inflammatory musculoskeletal disorders. Additional details for testing and treatment of all major autoimmune disorders are provided in *Integrative Rheumatology*.[219]

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