Rheumatoid arthritis (RA) is a complex, multifactorial disease that affects approximately 1 percent of the United States population. Across all age groups, RA predominates in females over males in a ratio of 2–3:1, although, in reproductive years, the ratio may be as high as 5:1.1

Within joints, the autoimmune mediated course of RA is characterized by four stages: (1) inflammation of the synovial membrane and joint capsule; (2) formation of a pannus (granulation tissue) that first covers and then invades cartilage and bone; (3) fibrous invasion of the pannus; and (4) calcification of the fibrous tissue. It is important to view RA, however, not only as a disease process that affects the joints, but as a systemic disorder that may include vasculitis, rheumatoid nodules in the pleural space, and blood-clotting abnormalities. Moreover, some common comorbidities of RA include cardiovascular disease, infections, malignancies, gastrointestinal (GI) disease, and osteoporosis.2 In fact, a prospective study has indicated that the average life span for patients with RA is shortened by 7 years in men and 3 years in women.3

There are various factors that may precede the clinical manifestation of RA and/or exacerbate the clinical course of RA in a susceptible individual. Such a multifactorial disease process lends itself comfortably to a naturopathic plan of treatment that is also multifactorial and includes dietary modification, botanical support, counseling, and appropriate physical medicine.

The Complex Etiology and Pathogenesis of RA

This review focuses on several factors that may predispose a patient to the development of RA and/or intensify symptoms that are characteristic of the disease, specifically, gut microflora influences, hormonal alterations, impairment in regulation of T-cell subsets, chronic exposure to environmental toxins, genetic influences, and total levels of oxidative stress.

Gut Microflora Influences

As discussed by Kjeldsen-Kragh,4 there are several ways in which the ecology of the gut flora may make an impact on the course of RA. For example, the bacteria Proteus mirabilis, a normal intestinal species that can also give rise to urinary tract infections, contains in one of its surface membrane proteins a sequence of 6 amino acids that is only 2 amino acids different from a sequence found on several types of human leukocyte antigen (HLA-DR) associated with RA. Antibody activity against a synthetically prepared peptide containing the sequence from Proteus was increased in patients with rheumatoid arthritis compared to healthy controls or patients with ankylosing spondylitis.5,6 In addition, the sequence occurring on the HLA has been shown to be the target of elevated levels of autoantibodies in a study of Japanese patients with RA.7 Moreover, when patients with RA fasted for 1 week and then were placed on a vegetarian diet (see sections on treatment) there was a significant reduction in anti-Proteus immunoglobulin G activity among the subjects who responded most to the diet, which correlated with a decrease in the activity of the patients’ disease.8 No such changes were seen in the level of antibody activity against Escherichia coli.

P. mirabilis, however, may not be the only floral species with the potential to contribute to the pathogenesis of RA. There are several studies demonstrating that injection of cell-wall fragments of Eubacterium aerofaciens or Bifidobacterium breve in rats results in a form of arthritis that is similar to RA.9 In addition, an increase of Clostridium perfringens in the bowels of patients with RA has been shown, although this effect might also be attributed to the effects of treatment with anti-inflammatory drugs.10–12

It is perhaps not surprising that, among the numerous possible species of bowel microbes living along the thin epithelium separating outside world from gut-associated lymphatic tissue, there exists an antigenic potential to trigger an immune response that may become misdirected at the self. The presence and effect of mycoplasma on the pathogenesis of RA should also be considered within the confines of the clinical presentation.

Hormonal Alterations

Another lens through which to view the pathophysiologic of RA is to explore the significance of changes in glucocorticoid and sex hormones both before and during the course of RA. This area is exceedingly complex as researchers try to decipher which changes may actually be causes of RA and which changes may be secondary to the already established inflammatory process of RA. A review by Masi et al.,13 published in 1995, analyzed collective results of controlled trials measuring sex hormones in patients with RA who had not been previously treated with glucocor-
ticoids. The findings did indicate that dehydroepiandrosterone (DHEA) sulfate was significantly decreased in premenopausal and postmenopausal women with RA, although the magnitude of difference was more pronounced in the premenopausal subjects (a 39-percent decrease in premenopausal versus a 19-percent decrease in postmenopausal subjects). Among the men, the clearest finding was that serum testosterone levels were consistently decreased in the men with RA versus the controls.

Perhaps one of the most valuable hormonal studies of patients with RA is one in which serum was actually collected in subjects 4–20 years before any of the subjects had developed RA. For each subject that eventually developed RA, samples from 4 controls matched for race, age, and menopausal status at study entry were included. This study found significantly lower levels of DHEA-sulfate among the youngest group of premenopausal women who years later developed RA compared to controls who did not. This youngest group (mean age of 29 at study entry with a mean onset of RA at 41 years) also showed a significant dissociation between DHEA sulfate and cortisol levels, a dissociation that was not seen among the older subjects who also went on to develop RA. The interpretation of these results was that dysfunction of the adrenal cortex may be a long-term marker for RA in a minority of women or that such dysfunction may actually lead to RA onset in some younger women.

Other hormonal alterations may occur both at the onset and throughout the course of RA. For example, while research indicates that, in patients with recent onset of RA (less than 1 year), cortisol levels are actually elevated compared to controls, there is also evidence that “normal” cortisol levels seen in other studies of patients with RA are, in fact, inadequate considering the amount of chronic inflammation. In addition, it has long been observed that pregnancy, a time of increased estrogen and cortisol, is a time during which many women experience remission of RA symptoms. These hormone changes of pregnancy are associated with increased levels of anti-inflammatory cytokines interleukin (IL)-4 and IL-10 and a decrease in production of proinflammatory cytokines interferon-γ and IL-2, as reviewed by Østensen.

Regulation of T-cell subsets

An imbalance between subsets of T-cells, with a resulting loss of immunologic tolerance to self, is another perspective from which to view RA. In fact, RA may be considered a disease process in which an immune response based on the action of T1 cells predominates over T2 cells, characterized by an increase in levels of interferon-γ and a cellular immune response. There continues to be debate over the precise role and ultimate significance of this theory. In one recent study that may open new avenues of research in this area, researchers found a decrease of a regulatory subset, Tr1, which produces the anti-inflammatory cytokine IL-10, in the blood of patients with RA compared to controls. The reduced levels of Tr1 were inversely correlated with levels of Th1 cells in the synovial fluid, with C-reactive protein levels, and with a score of disease activity.

Environmental Toxins and Genetic Predisposition

While still controversial, there are several studies linking exposure to crystalline silica with RA. The most recent of these is a study by the Occupational Health and Safety Administration, examining a cohort of 4626 workers in the industrial-sand industry. By examining available death records of workers, which may have mentioned multiple diseases on a death certificate (RA is often listed as a contributory cause or other significant condition), a standard mortality ratio was calculated by comparing the cohort with the U.S. population. The standard mortality ratio (SMR) of arthritis in the cohort was 4.36 (95 percent; confidence interval (CI) 2.76–6.54). Also, this data demonstrated a positive correlation between cumulative silica exposure and the incidence of RA.

A final factor that may influence the severity of the clinical course of RA is that of genetics, specifically HLA-DRB1 alleles. It is interesting to note, however, that while twin studies do indicate a significant increased risk for one twin acquiring RA if the other twin is exhibiting symptoms, these studies also suggest that the maximum level of genetic contribution to the concordance rate of twins with RA is about 15 percent. Indeed, genetic contribution is one significant factor, but there are still other factors, such as those outlined above, which also deserve careful attention.
attention, and that, at this time, may be more amenable to therapeutic intervention.

**Oxidative Stress**

In a recent review by Darlington and Stone, an overview is provided of the pro-oxidative scene present in RA. Of key importance is the production of nitric oxide (NO), which can generate peroxynitrite and hydroxyl radicals. Hydroxyl radicals generated via this or other mechanisms can then break hyaluronic acid down, interfere with proteoglycans, and limit the functioning of proteinase inhibitors. In addition, the synovial fluid of patients with RA may contain iron, which is capable of catalyzing the production of hydroxyl radicals from superoxide and hydrogen peroxide. The activated macrophages and neutrophils present in the pannus are themselves a source of pro-oxidants that lead to joint damage.

An epidemiologic study involving a Finnish cohort of 18,709 subjects, of whom 122 developed RA, found that both low selenium and α-tocopherol could be risk markers for RA. The interesting findings showed that low selenium was probably a risk factor specifically for RF negative RA, while low α-tocopherol levels probably represented a risk factor that was independent of RF status. An additional report on 1400 people whose levels of the key antioxidants beta-carotene, vitamin E, and selenium were measured before any of the volunteers had symptoms of RA indicated a significantly reduced antioxidant status in the 14 patients who later developed RA.

**Overall Naturopathic Approach**

It is of fundamental importance when dealing with any autoimmune condition to address, as completely as possible, the underlying causes that allow sufficient disturbance to homeostasis to occur and result in a self-attack being triggered. Nevertheless, this limited review of factors contributing to the etiology and pathogenesis of RA partially demonstrates the complexity of the disease process. It may even be the case that, while one individual’s RA is based largely in adrenal cortex dysfunction, another patient’s RA may develop after an immune response to Proteus, and still another patient’s RA may result from prolonged exposure to silica. And, even when etiologic factors are identified, we still must consider the issue of susceptibility; after all, not everyone with some adrenal dysfunction, some exposure to Proteus, or some time working in the industrial-sand industry will develop RA. Thus, the overall aspect of health and human frame must be addressed and a naturopathic approach including clinical nutrition, botanical medicines, counseling, and appropriate physical medicine has a good deal to offer.

**Clinical Nutrition**

**Fasting**

There is some evidence that, for many patients, a week of fasting followed by a vegetarian diet will reduce the symptoms of RA over the course of a year. During the fasting period of the study cited, subjects were allowed to eat garlic, vegetable broth, a decoction of potatoes and parsley, herbal teas, and the juices of carrots, beets, and celery. (Note that, in addition to potentially suppressing the immune system because of hypocaloric intake, this...
fasting diet also provides an excellent source of phytochemicals that assist in detoxification and is itself rich in antioxidants.) Following the fasting, subjects introduced new foods one at a time, discontinuing them if any increase in pain, stiffness, or joint swelling was noticed. If, after a week of waiting, reintroduction resulted in a repeat exacerbation, then that item was removed for the rest of the study period. New food items being introduced excluded gluten, meat, fish, eggs, dairy foods, refined sugar, citrus, salt, strong spices, preservatives, alcohol, tea, and coffee for 3–5 months. After that time, dairy products and gluten were allowed to be introduced one at a time.

Over the course of the year, the group of 27 dieters noted statistically significant decreases in pain, duration of morning stiffness, number of tender and swollen joints, sedimentation rate, C-reactive protein (CRP), and white-blood-cell count, compared to the 26 controls. The magnitude of the difference between the two groups at the end of the study was appreciable. For example, the dieters reported an average duration of morning stiffness of approximately 1.5 hours compared to more than 2.5 hours reported in the control group. The average CRP at the end of the year was roughly 30 mg/L in the control group and less than 20 mg/L in the dieters.

A more recent study of fasting by patients with RA also has produced some interesting results. Specifically, after a week of vegetable-juice fasting, this study found significant decreases in sedimentation rate, CRP, and tender-joint count, as well as experiencing a 37-percent decrease in the proinflammatory cytokine IL-6. In addition, there was a significant increase in DHEA-sulfate levels, which was also seen in patients that were placed on a ketogenic diet.

One of the ways in which this dietary approach may have been beneficial to dieters was via the alteration of their gut flora. Stool samples from the 27 fasting/vegetarian subjects and 26 controls were analyzed for their content of various fatty acids, which are components of the cell walls of intestinal bacteria. Significant changes were found between the fatty-acid profiles of dieters who were “high-responders” to the diet and those who were “low-responders.”

Hence, addressing GI integrity and ecology is essential when autoimmune-modulated responsiveness to potential antigens can serve as triggers. From a nutritional perspective, the prudent clinician must scrutinize GI health closely, for the alimentary tract is the most crucial boundary between the external macro-world and the well-defined and well-ordered and sometimes precariously balanced internal micro-world.

With regard to the study, there were no significant changes seen within the control group throughout the year. Within the dieting group, changes in fatty-acid profile, and thus changes in gut flora, were apparent at each of the stages of the diet when major changes were made, i.e., the fasting period versus the period of food introduction versus the lactovegetarian period of study. Given the potential for fasting and strict diet to alter bowel flora in ways correlating with improvement in the course of RA, and the possibility that, in some cases, flora may play a causative role in RA, it makes sense to discuss this approach with patients who are considering clinical options.

**Hormonal Support**

Because adrenal dysfunction may play an underlying role in RA development, it seems logical, in some cases, to provide support with the androgen DHEA. The reasons for DHEA supplementation are based at this point in an idea that arose from viewing several sets of study results. First, as already reviewed, androgen hormones were commonly decreased in women and men patients with RA (DHEA in women and testosterone in men). Second, the results of recent research showing that patients with chronic RA experienced significantly increased levels of cortisol and epinephrine under the very acute mental stress of a presurgical setting and that these levels were significantly depressed under general anesthesia. Such a pattern was not seen in controls with osteoarthritis. This pattern suggests to us that, at least in some patients with RA, attempting to deal with stress creates an increased demand for glucocorticoids, which, even if successfully met, may be incompletely coordinated with the control of androgen secretion. As a result, a healthy relationship between these two groups of hormones is not maintained. Moreover, whether such events are pri-
mary or secondary to the development of RA, it would seem that such supplementation could have benefit being that DHEA-sulfate has been shown to decrease the expression of the gene coding for the proinflammatory IL-6, high levels of which predispose patients to a worsening course of RA.

Supplemental Antioxidant/ Anti-Inflammatory Support

There is certainly theoretical support in several ways for the use of omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in the treatment of patients with RA. Not only do omega-3 acids compete with omega-6 acids for metabolism by lipooxygenase and cyclo-oxygenase, the former can become included in phospholipid membranes at the expense of arachidonic acid. Several trials, some open and others controlled, have demonstrated benefit for patients with RA who consumed fish oils, with dosages of EPA in the range of anywhere from 2 to 20 g per day, for lengths of time from 6 to 24 weeks.

A reasonable therapeutic trial may be a dose of from 3 to 6 g per day of fish oils providing a natural mix of EPA and DHA, stabilized with vitamin E and/or the fat soluble form of vitamin C, ascorbyl palmitate. Other oils, such as olive oil, γ-linolenic acid (GLA), and Lyprinol® (Tyler Encapsulations, Wilsonville, Oregon) may also provide anti-inflammatory benefit for patients with RA. Particularly noteworthy and reflective of the potential benefits of essential fatty acids, GLA has been positively highlighted in research for its therapeutic benefit.

Not only may therapy with fatty acids be helpful in the treatment of RA, there is also evidence that regular consumption of fish reduces the risk of developing RA. Epidemiologic research suggests that baked or broiled fish consumption, at least 2 servings per week, was associated with a significant decrease in the risk of RA (odds ratio, 0.57; confidence interval, 0.35-0.93) compared to less than one serving per week.

Given the ongoing oxidative stress present in RA, there is certainly a rationale for supplementation with the common antioxidants, vitamins A, C, and E. In fact, levels of retinol and its binding protein have been shown to be lower in patients with RA than in matched controls. In addition to being an antioxidant, vitamin C is also required to hydroxylate proline and lysine in order to produce collagen. In one double-blind study of subjects given 600 international units of vitamin E, 2 times per day for 12 weeks, there was a small, but significant analgesic effect compared to controls. While the extent of the analgesic effect attributable to vitamin E is clearly not as great as that derived from nonsteroidal anti-inflammatory drug (NSAID) use, it should be remembered that one of the comorbidities of RA is cardiovascular disease. If vitamin E is included in treatment for this reason alone, its use would be justified and, if it also provides some pain relief without the side effects of NSAID use, so much the better. It would also seem that selenium, which is reduced in the serum of patients with RA, and is a required coenzyme for glutathione peroxidase, would be beneficial as a supplement. In this case, however, long-term (26 weeks) supplementation failed to increase the depressed activity of glutathione peroxidase found in patients with RA.

Botanical Medicines

One of the most supportive botanical medicines for the patient with RA may well be curcumin or turmeric (Curcuma longa). Notable for its ability to act as an antioxidant and anti-inflammatory, curcumin seems well suited for treating this condition. More recent research suggests that curcumin is a potent inhibitor of the signaling pathway utilized by a specific type of IL-6, called oncostatin M. If not inhibited via this pathway, oncostatin M signaling results in the transcription/translation of metalloproteinases and their inhibitors. An imbalance between metalloproteinases and their inhibitors may represent one of the mechanisms of joint damage in RA. To be able to slow metalloproteinase expression down may represent one of the many recently discovered mechanisms of efficacy of an ancient herb.

A second botanical option recently reported in the botanical literature is the Ayurvedic herbal combination Maharasnadh Quathar (MQR). In a 3-month study that involved 45 patients with this herbal combination and a second group treated with another traditional preparation, the patients in the MQR-treated group demon-
Oleoresin gum extracts of boswellia, with 37.5–65 percent boswellic acid, exert potent anti-inflammatory actions via inhibition of proinflammatory mediators such as leukotrienes.

strated significant increases in the activity of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase.\(^{56}\) Another finding of the study was that lipid peroxidation was reduced by 34 percent in the MQR-treated group. MQR is a combination of 26 herbs, with the bulk (70 percent) of its composition accounted for by alpinia galangal (*Alpinia calcarata*), but also including a variety of other plants, such as ginger (*Zingiber officinale*), tropical almond (*Terminalia chebula*), ashwagandha (*Withania somnifera*), and coriander also called Chinese parsley (*Coriandrum sativum*).

Oleoresin gum extracts of boswellia (*Boswellia serrata*), with 37.5–65 percent boswellic acid, exert potent anti-inflammatory actions via inhibition of proinflammatory mediators such as leukotrienes. The recommended boswellia dose is 150 mg 3 times per day.\(^ {57}\) Bromelain, a commonly used proteolytic enzyme, has direct clinical application for treating RA, as do other enzymes. Select results have yielded upward of 73-percent positive results, ranging from good to excellent.\(^ {58}\) Ginger extracts have demonstrated benefit as well, with good pain relief, with proposed mechanisms conjectured to include one or more of the following mechanisms of action: thromboxane synthetase inhibition and prostacyclin agonists and prostaglandin synthesis inhibition.\(^ {59}\) These herbs and numerous others show promise for alleviating symptoms and potentially modulation of pathophysiologic changes. Other select herbs that have been used in the treatment of RA include: cayenne (*Capsicum frutescens*), feverfew (*Tanacetum parthenium*), devil’s claw (*Harpagophytum procumbens*), stinging nettle (*Urtica dioica*), thunder god vine (*Tripterygium wilfordii*), and yucca (*Yucca glauca*).

Counseling

While many general practitioners will not have the same level of counseling skill as a trained psychologist or counselor, this is an area that deserves greater attention in the treatment of a patient with RA. In a preliminary, controlled study of group therapy sessions with patients of RA, in which the patients decided on their own topics of discussion in a series of 12 weekly sessions, the area of greatest concern was that of lost self-esteem.\(^ {60}\) Patients reported feeling unable to meet self-set expectations of productivity and rewards in their relationships with others, and reported difficulties in communicating adequately regarding the problems they faced with those around them, including their families and physicians. It is noteworthy that, within the group of patients participating in group counseling, there were significant improvements in scores of self-concept, specifically in the categories of self-satisfaction and family-self.

Developing and implementing quality communication skills, such as restating a patient’s concerns, asking if there is anything else that needs to be discussed, and expressing empathy appropriately will help to create an atmosphere in which both the patient and physician are understood and honored. In addition, assisting the patient in identifying stress triggers and teaching stress-reduction techniques, such as abdominal breathing, may help to reduce the load placed on a beleaguered hypothalamic-pituitary-adrenal axis.

Physical Medicine

A final therapy of benefit to patients with RA is hydrotherapy (defined here as the combination of water immersion and exercise). In a study of 139 patients with chronic RA, subjects were randomly divided into groups receiving hydrotherapy, seated immersion, land exercise, or progressive relaxation.\(^ {61}\) Subjects attended two 30-minute sessions per week for 4 weeks and were assessed using the Arthritis Impact Measurement Scales 2 questionnaire. The group showing the greatest improvement (although all the therapies were somewhat helpful) was the hydrotherapy-treated group, with subjects reporting significant reductions in joint tenderness and improved knee range of motion. Some patients may also find benefit from the application of alternating hot and cold compresses.

Conclusion

Patients with RA experience the symptoms of a disease process that is exceedingly complex. There are a number of possible etiologic factors, perhaps some as yet undiscovered, and the exact causes of the autoimmune-driven inflammation characteristic of the disease may vary from one susceptible individual to another. The presence and effect of mycoplasma on the pathogenesis of RA should also be considered within the confines of the clinical presentation. A comprehensive treatment
Effective treatment tools from clinical nutrition, botanical medicine, counseling, and physical medicine, should significantly help many patients with RA to live with less pain.

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