

REVIEW OF THE LITERATURE

THE DIET-INDUCED PROINFLAMMATORY STATE: A CAUSE OF CHRONIC PAIN AND OTHER DEGENERATIVE DISEASES?

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ABSTRACT

Background: It is the rare physician who includes diet therapy and nutritional supplements in patient care. Perhaps this is because chiropractic and medical schools devote very few classroom hours to nutrition. It is also possible that physicians are under the misconception that a detailed biochemical understanding of each individual disease is required before nutritional interventions can be used.

Objective: The purpose of this article is two-fold: (1) to demonstrate that chronic pain and other degenerative conditions encountered in clinical practice have similar biochemical etiologies, such as a diet-induced proinflammatory state, and (2) to outline a basic nutritional program that can be used by all practitioners.

Data Sources: The data were accumulated over a period of years by reviewing contemporary articles and books and subsequently by retrieving relevant articles. Articles were also selected through MEDLINE and manual library searches.

Results: The typical American diet is deficient in fruits and vegetables and contains excessive amounts of meat, refined grain products, and dessert foods. Such a diet can have numerous adverse biochemical effects, all of which create a proinflammatory state and predispose the body to degenerative diseases. It appears that an inadequate intake of fruits and vegetables can result in a suboptimal intake of antioxidants and phytochemicals and an imbalanced intake of essential fatty acids. Through different mechanisms, each nutritional alteration can promote inflammation and disease.

Conclusion: We can no longer view different diseases as distinct biochemical entities. Nearly all degenerative diseases have the same underlying biochemical etiology, that is, a diet-induced proinflammatory state. Although specific diseases may require specific treatments, such as adjustments for hypomobile joints, β -blockers for hypertension, and chemotherapy for cancer, the treatment program must also include nutritional protocols to reduce the proinflammatory state. (*J Manipulative Physiol Ther* 2002; 25:168-79)

Key Indexing Terms: *Degenerative Disease; Inflammation; Pain; Antioxidants; Diet; Prostaglandins*

INTRODUCTION

Celsus (30 BC-38 AD) was the first to describe the characteristics of inflammation. His 4 cardinal signs of inflammation included rubor (redness), tumor (swelling), calor (heat), and dolor (pain). To these, loss of function was added by

Galen (130-200 AD) and later John Hunter (1728-1793). In the 18th and 19th centuries, scientists such as Boerhaave, Waller, and Addison showed that both the microcirculation and its contents were involved in initiating inflammation.¹

It was Hunter who proposed that inflammation is essentially a response to injury, rather than a disease entity itself. Hunter suggested that the inflammatory response is the same for all types of injury.¹ Many types of cell injury can cause inflammation, including hypoxia, physical agents such as trauma and burns, chemical agents and drugs, infectious agents, immunologic reactions, genetic derangements, and nutritional imbalances involving both deficiencies and excesses of various nutrients.²

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Hunter also suggested that the purpose of inflammation is to restore normal tissue function.¹ Modern authors agree that inflammation should lead to tissue repair and remodeling, which allow for the restoration of function.³ However, when acute inflammation becomes chronic, tissue healing cannot occur.¹ In this situation, the inflammatory process should be viewed as a disease process. Many diseases are, in fact, a manifestation of chronic inflammation. For example, rheumatoid arthritis, which is characterized by chronic inflammation of the synovial membrane, is classified as a disease and not as a transitional phase in the healing process.⁴ Research also suggests that chronic inflammation promotes the development of Alzheimer's disease.⁵ Today, asthma is viewed as a disease characterized by chronic airway inflammation.⁶ A recent review article states that acute respiratory distress syndrome, sarcoidosis, glomerulonephritis, psoriasis, inflammatory bowel diseases, rheumatoid arthritis, osteoarthritis, and atherosclerosis are all inflammatory diseases.⁶ Regarding gastrointestinal disease, "ulcerative colitis and Crohn's disease are characterized by chronic inflammation with superimposed acute inflammatory exacerbations."⁷

In fact, chronic inflammation has been viewed as a disease for many years. In the first edition of *Pathologic Basis of Disease*,⁸ published in 1974, Robbins clearly stated that numerous degenerative diseases are inflammatory in nature, such as gastritis, Crohn's disease, diverticulitis, ulcerative colitis, appendicitis, heart disease, cancer, cirrhosis, diabetes mellitus, and vascular disease. The description of gastritis in a recent edition of *Pathologic Basis of Disease*² provides an excellent example that illustrates how inflammation promotes disease.

Acute gastritis is an acute mucosal inflammatory process, usually transient in nature Chronic gastritis is defined as the presence of chronic mucosal inflammatory changes leading to mucosal atrophy and epithelial metaplasia, usually in the absence of erosions. The epithelial changes may become dysplastic and constitute a background for the development of carcinoma.²

In this description of gastritis, it can be seen that inflammation leads to the development of cancer; that is, cancer is an undesirable inflammatory response. This view of inflammation is clearly outlined in a recent text designed to prepare medical students for licensing examinations.⁹ The text is divided into 3 sections. Part 1 describes the normal inflammatory response to injury, Part 2 describes normal inflammatory responses to microorganisms, and Part 3 discusses undesirable inflammatory responses. Several diseases are mentioned in the section devoted to undesirable inflammatory responses, such as cirrhosis, cancer, osteoarthritis, and rheumatoid arthritis.⁹

On the basis of the information presented thus far, it is clearly inappropriate to view inflammation as merely a component of the healing process; rather, inflammation should be viewed as a key promoter of degenerative diseases, which kills millions of Americans each year. Indeed,

6 of the 10 leading causes of death in Americans are coronary heart disease, cancer, stroke, diabetes mellitus, atherosclerosis, and chronic liver disease and cirrhosis,^{10,11} all of which have been previously described as inflammatory in nature.

Because we are plagued by proinflammatory degenerative diseases, it is reasonable to conclude that the lifestyle of the American people is somehow "proinflammatory" in nature. I propose that a variety of dietary factors play a significant role in creating a "diet-induced proinflammatory state." This is a reasonable contention because it is known that the previously mentioned degenerative inflammatory diseases are promoted by dietary imbalances.¹⁰ This article outlines the manner in which a diet that is deficient in vegetables and fruits, antioxidants and phytochemicals, and omega-3 fatty acids can promote the development of the proinflammatory state.

DISCUSSION

Terminology and Conceptual Issues

Although the term "diet-induced proinflammatory state" is new, the concept that a diet rich in vegetables, fruits, and the proper fats can prevent a host of proinflammatory degenerative diseases is now well accepted.

Today, we have overwhelming evidence that diets rich in vegetables and fruit but moderate in meat and fat are associated with a reduced risk of various forms of cancer, cardiovascular disease as well as other diseases such as arthritis, diabetes or cataract. Even the aging process appears to be favorably reduced by high fruit and vegetable intake.¹²

If eating sufficient vegetables, fruits, and the proper fats can help to prevent inflammatory diseases, it is then reasonable to suggest that an inadequate intake of these foods would promote inflammation and disease and that such a diet should therefore be viewed as "proinflammatory." Regrettably, our consumption of fruit and vegetables¹³⁻¹⁵ and our intake of essential fatty acids^{16,17} is remote from recommended levels, which likely leads to a proinflammatory state and places us at risk for a host of diseases.

A Proinflammatory Soup

It is likely that inflammatory mediators work in concert. Handwerker and Reeh coined with each other to create the inflammatory drive associated with chronic disease. The term "inflammatory soup" is used to describe the combination of mediators that work together to excite nociceptors. Numerous mediators are known to activate and sensitize nociceptors, including 5-hydroxytryptamine, histamine, bradykinin, interleukin-1 (IL-1), tumor necrosis factor (TNF), an acidic pH, free radicals, and eicosanoids, such as prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and thromboxane A2 (TXA2).¹⁸⁻²¹ Combinations of these mediators cause pain and inflammation, whether the cause is direct injury, osteoarthritis, or rheumatoid arthritis. Aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) have been the

cornerstone of treatment for these conditions because of their ability to inhibit eicosanoid production.

Many of the same inflammatory mediators that promote pain and inflammation are also involved in the pathogenesis of heart disease, a condition regarded as an undesirable inflammatory condition of arteries.^{7,22-24} Ross²² explains that inflammation precedes and accompanies the normal tissue healing processes of arteries and that advanced atherosclerotic lesions “result from an excessive inflammatory-fibroproliferative response to numerous different forms of stimuli,” such as oxidized cholesterol fractions. In response to arterial injury, platelets aggregate in the area and release their proinflammatory mediators, such as serotonin, TXA₂, PGE₂, IL-1, platelet-derived growth factor, transforming growth factor, platelet activating factor, and several anti-proteases that act to promote fibrin deposition and fibrosis.²²⁻²⁵ IL-1 and TNF are released from macrophages, endothelial cells, and smooth muscle cells and participate in the atherogenic process.²² Clearly, an inflammatory soup involving similar mediators that promote pain can also cause heart disease. Thus, it is not surprising that eicosanoid-inhibiting aspirin is a commonly recommended drug to prevent heart disease.

The inhibition of proinflammatory eicosanoids is also a desired outcome in the treatment of cancer, such that NSAIDs are often incorporated into the treatment regimen of cancer patients. Although the initial cause of cancer is still not understood, many environmental and phenotypic factors are thought to play a role in the initiation of this disease. At some point, genetic mutations occur and oncogenic activity ensues—a subject best covered in articles and texts devoted to the specific subject of cancer. Germane to the focus of this article is the role of NSAIDs in preventing cancer development and reducing cancer progression, presumably as a result of their inhibitory effect on eicosanoid synthesis.²⁶⁻²⁸ With regard to eicosanoid modulation, research has clearly demonstrated that n-6 fatty acids enhance carcinogenesis, whereas n-3 fatty acids are inhibitory. Accordingly, it is believed that the American diet, which heavily favors n-6 fatty acid consumption, creates a proinflammatory state that promotes cancer.³⁹⁻⁴⁵

Not surprisingly, a proinflammatory state may promote certain neurodegenerative diseases. For example, Alzheimer’s disease (AD) is thought to manifest as a “chronic inflammatory state of the brain,” such that the incidence of this disease is low in rheumatoid arthritis patients who take anti-inflammatory drugs.⁵ In fact, it is now well known that patients who use NSAIDs have a reduced risk of AD,^{46,47} which suggests that proinflammatory eicosanoids may play a causative role in the pathogenesis of AD. Not surprising, research suggests that cyclooxygenase-2 expression is elevated in the brain of patients with AD,⁴⁸⁻⁵⁰ which would reflect an increase in production of PGE₂ and related inflammatory changes.

A recent experiment found that there was no difference in total cerebrospinal fluid levels between patients with AD and healthy control subjects, whereas there was a marked disparity in the levels of proinflammatory PGE₂. Patients with AD had approximately 5-fold more PGE₂ and 4-fold less 6-keto-prostaglandin F₁ than control subjects.⁵¹ Altered PGE₂ levels may play a direct role in the pathogenesis of AD. Astrocyte culture data have shown that PGE₂ increases astrocyte expression of amyloid precursor protein, and *in vitro* data suggest that PGE₂ may promote amyloid β -peptide deposition and neurodegeneration.⁵¹

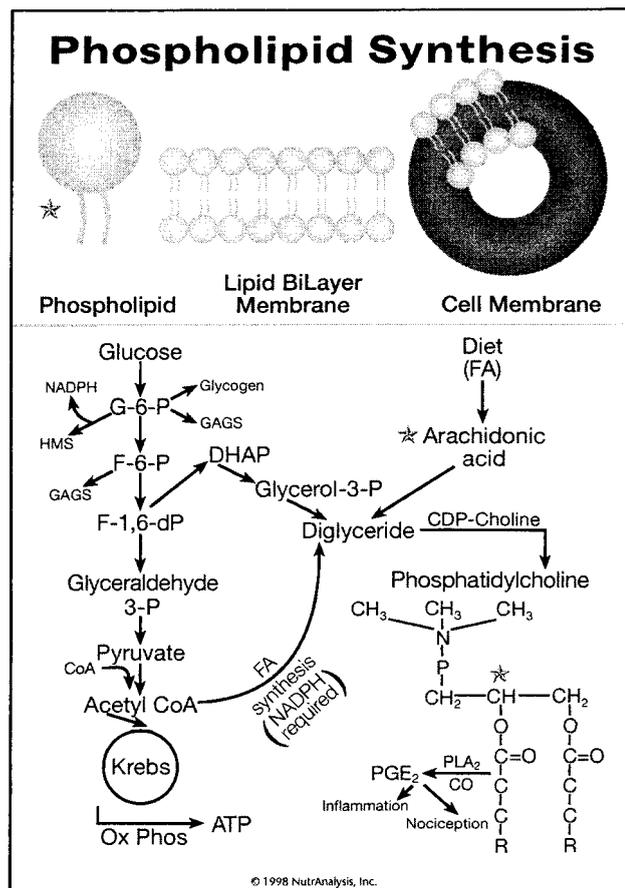
On the basis of this information, a great deal of research has been devoted to studying the role NSAIDs may play in the treatment and prevention of AD.⁴⁶⁻⁵⁴ Although a beneficial role of NSAID therapy for AD is understood to exist, a method of clinical application for treatment and prevention has yet to be determined.

Very little has been done in the way of studying n-6:n-3 in patients with AD. However, it is known that the brain of a patient with AD has a conspicuous loss of fatty acids, most notably docosahexanoic acid, which is an important n-3 fatty acid. A decline in structural and functional integrity of brain tissue in AD appears to correlate with loss in membrane docosahexanoic acid (DHA) concentrations.⁵⁵ A survey of 900 elderly men showed that those who consumed the highest amount of linoleic acid were the most likely to have senile dementia, whereas those who ate an n-3-rich fish diet had the best mental function.⁵⁶

As outlined previously, eicosanoid inhibition is an integral component in the treatment of seemingly diverse and unrelated diseases. Rarely do researchers and practitioners focus their attention on the cause of what amounts to an overproduction of proinflammatory eicosanoids. Accordingly, it is not appreciated that a significant body of literature indicates that poor food choices shift the fatty acid balance to one that favors the production of inflammatory eicosanoids.

Fatty Acid Imbalances

Omega-6 versus omega-3 fatty acids. Fatty acid imbalances may actually form the foundation on which the proinflammatory state develops, as an excess of omega-6 fatty acids (linoleic acid and arachidonic acid) and a deficiency of omega-3 fatty acids may be involved the development of numerous diseases. For example, Eskimos eating their traditional diet, which is high in omega-3 fatty acids and very low in omega-6 fatty acids, are almost free of the chronic degenerative diseases that plague those in Western societies who consume virtually no omega-3 fatty acids and excessive amounts of omega-6 fatty acids. Eskimos do not suffer from heart disease, cancer, diabetes, appendicitis, diverticulitis, ulcerative colitis, gallstones, psoriasis, multiple sclerosis, or rheumatoid arthritis.⁵⁷⁻⁵⁹ Researchers indicate that the anti-inflammatory fatty acid balance of the traditional Eskimo



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Fig 1. Phospholipid synthesis.

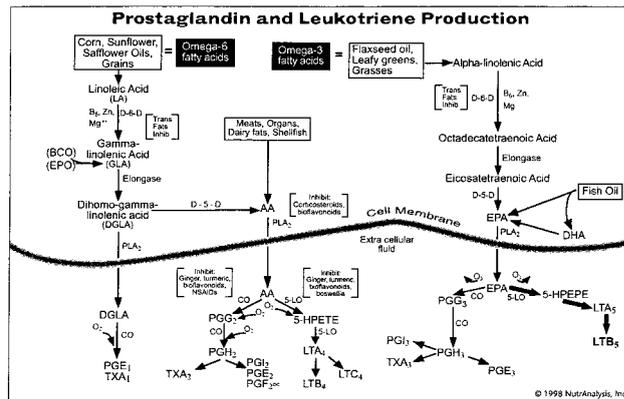
diet provides them with protection from these proinflammatory degenerative diseases.⁵⁸⁻⁶⁰

Fernandes and Venkatraman⁶¹ state that omega-6 fatty acids are “considerably more pro-inflammatory” than omega-3 fatty acids.

The increased consumption of many vegetable oils particularly of the n-6 series is however to be viewed as pro-inflammatory and is suspected as one of the possible causes for the gradual rise in certain malignant tumors, rheumatoid arthritis and autoimmune diseases primarily due to the increased production of pro-inflammatory cytokines . . . In contrast, n-3 fatty acid-enriched fish oil and/or n-3 precursors from certain vegetable oils (linolenic acid) are found to provide protection against cardiovascular disease, rheumatoid arthritis, cancer and possibly against the severity of viral infections.⁶¹

Unfortunately, those of us who live in Western society consume a diet with an omega-6 to omega-3 fatty acid ratio of about 10:1 to 25:1, which is significantly greater than the 1:1 ratio on which humans evolved and on which our genetic patterns were established.¹⁶ Simopoulos⁶² indicates that our omega-6 to omega-3 ratio must be less than 4:1 to avoid the promotion of heart disease and cancer, and presumably other proinflammatory diseases.

Omega-6 and omega-3 fatty acids are concentrated in cell membrane phospholipids. The human body contains tril-



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Fig 2. Prostaglandin and leukotriene production.

lions of cells, each of which is housed in a lipid bilayer membrane composed of phospholipid molecules. It is known that specific biochemical pathways produce phospholipids and that our diet directly influences their production. Figure 1 illustrates the manner in which polyunsaturated fatty acids are incorporated into membrane phospholipids. As mentioned previously, dietary omega-6 fatty acids strongly predominate omega-3 fatty acids. Consequently, arachidonic acid, along with its proinflammatory potential, will be inserted into membrane phospholipids.

Figure 2 illustrates the manner in which omega-6 and omega-3 fatty acids synthesize their respective proinflammatory and anti-inflammatory eicosanoids. Notice that linoleic acid is the vegetable oil precursor of arachidonic acid, both of which are omega-6 fatty acids. Although seeds and grains are rich in linoleic acid, they are devoid of arachidonic acid. However, the consumption of seeds, seed oils, and grains will result in the production of arachidonic acid. This is because animal cells readily convert linoleic acid into arachidonic acid. Thus, there are 2 ways in which humans increase tissue concentrations of arachidonic acid. First, we consume foods rich in linoleic acid, which is subsequently converted into arachidonic acid; second, we consume liberal amounts of arachidonic acid-containing animal products, such as beef, chicken, and eggs. In contrast, we consume minimal amounts of foods that are rich in linolenic acid, eicosapentanoic acid (EPA), and DHA, such as green leafy vegetables, fish, and fish oil. The outcome of this eating pattern is an excessive production of proinflammatory eicosanoids from arachidonic acid and a deficiency in the production of anti-inflammatory eicosanoids, that is, a diet-induced proinflammatory state.

Although the term “diet-induced proinflammatory state” is new and perhaps conceptually different than the standard view, it is still generally understood that our population suffers from the proinflammatory state. This understanding is demonstrated daily by the use of copious amounts of prescription and over-the-counter anti-inflammatory drugs to treat aches, pains, osteoarthritis, rheumatoid arthritis,

heart disease, and cancer; that is, our population is proinflammatory and subsequently requires anti-inflammatory medication. Figure 2 illustrates that NSAIDs function to inhibit the cyclooxygenase enzyme and thereby inhibit the production of a variety of proinflammatory eicosanoids. Although NSAIDs may offer a symptomatic relief from pain and inflammation and may delay the onset of heart disease, cancer, and AD, it should be obvious that NSAID therapy will never influence the proinflammatory state that is established by an unbalanced dietary intake of omega-6 and omega-3 fatty acids. The treatment of chronic pain and chronic disease clearly needs to change, and even US government publications believe this should begin with nutrition.¹⁰

Regularly consuming foods and/or supplements that provide linolenic acid, EPA, and DHA may be the most important nutritional habit we can develop. A significant body of literature exists to support this contention. The following is an example:

Additional clinical investigations and experimental studies confirmed the initial observations: when diets are supplemented with omega-3 fatty acids, the latter partially replace the omega-6 fatty acids in the membranes of practically all cells (ie, erythrocytes, platelets, endothelial cells, monocytes, lymphocytes, granulocytes, neuronal cells, fibroblasts, retinal cells, hepatic cells, and neuroblastoma cells); omega-3 fatty acids modulate prostaglandin metabolism and decrease triglycerides; and in high doses omega-3 fatty acids lower cholesterol and have antithrombotic and anti-inflammatory properties. These studies were extensively reviewed and reported.¹⁶

In 1991, Simopoulos¹⁶ reviewed the physiologic outcome of omega-3 fatty acid incorporation into cell membranes. Ingesting EPA and DHA from fish or supplemental fish oil leads to the following:

1. A decreased production of PGE₂;
2. A decrease in TXA₂, a potent platelet aggregator and vasoconstrictor;
3. An increased production of TXA₃, a weak platelet aggregator and a weak vasoconstrictor;
4. A decreased production of LTB₄, an inducer of inflammation and a powerful inducer of leukocyte chemotaxis and adherence;
5. An increased production of LTB₅, a weak inducer of inflammation and a weak chemotactic agent;
6. An increased production of prostacyclin PGI₃, leading to an overall increase in total prostacyclin by increasing PGI₃ without a decrease in PGI₂ (both PGI₂ and PGI₃ are active vasodilators and inhibitors of platelet aggregation).

More recently, it was determined that supplementation of young and old women with 1.68 g EPA and 0.72 g DHA per day for 12 weeks "decreased lymphocyte production of pro-inflammatory cytokines, IL-1, TNF, IL-6 as well as PGE₂ production."²⁴ The same findings were observed in subjects who consumed a high-fish diet for 6 months.²⁴ Calder^{59,63} recently reported similar reductions in proin-

flammatory eicosanoids and cytokines after increasing omega-3 fatty acid intake.

"IL-1 and TNF are principal mediators of inflammation. Recent work also suggests involvement of these cytokines in the pathogenesis of atherosclerosis. Eicosanoids such as LTB₄, PGE₂, and TXB₂ have also been indicated as contributory factors to the development of inflammatory and atherosclerotic diseases. Therefore, decreased production of these cytokines and eicosanoids following consumption of n-3 polyunsaturated fatty acids may reduce pathogenesis of these diseases. Epidemiologic, clinical, and animal studies support this notion."⁶⁴

On the basis of the previous information, it is clear that the anti-inflammatory benefits of n-3 fatty acids have been known for many years. However, it is common to read through texts and journal articles devoted to various proinflammatory diseases and not find n-3 fatty acids mentioned. Even the publication that describes the United States Department of Agriculture Food Pyramid does not mention n-3 fatty acids and the importance of maintaining a proper balance between n-6 and n-3 fatty acids,⁶⁵ an omission that has been strongly criticized.⁶⁶

Numerous authors have also discussed the anti-inflammatory benefits of omega-3 fatty acid supplementation.^{24,61,64,67-76} In fact, Linder⁷¹ indicates that fish oils may be more useful in suppressing chronic inflammation than aspirin and other nonsteroidal anti-inflammatory agents. In the clinical setting, proper dosing of n-3 fatty acids is often a confusing proposition. How much should be taken? Should recommendations differ depending the condition or disease? Finally, is n-3 supplementation safe, and are there potential drug interactions?

At present, the practice of n-3 supplementation remains more art than science. Supplementation guidelines do not exist and, in reality, may never exist. Ultimately, the purpose of n-3 supplementation is to shift the balance of n-6:n-3 ratios, and the precise dose will be different for each person depending on individual dietary levels. It is quite conceivable that a patient who reduces the consumption of n-6 rich grains and oils and ingests more n-3 rich fish and green vegetables may need less n-3 supplements compared with someone who subsists predominately on n-6 rich foods. Meanwhile, studies with patients who have rheumatoid arthritis have provided us with some idea about supplementation levels. Kremer⁷⁷ has studied the effects of n-3 supplementation on rheumatoid patients for many years. The number of tender joints on physical examination and the amount of morning stiffness is consistently reduced in patients who take n-3 supplements.

In these cases, supplements were consumed daily in addition to background medications and the clinical benefits of the n-3 fatty acids were not apparent until they were consumed for > or = 12 wk. It appears that a minimum daily dose of 3 g eicosapentaenoic and docosahexaenoic acids is necessary to derive the expected benefits.⁷⁷

For those who count pills, this represents a minimum of 10 fish oil capsules per day, if one were to take the common variety that contains 180 mg of EPA and 120 mg of DHA. Fortunately, there are virtually no reports of toxicity in the dose range used to treat rheumatoid arthritis, and the oil is generally very well tolerated.⁷⁷ In one study, the subjects ingested 6 g of EPA/DHA per day for 7 years with no reported side-effects.⁷⁸ On the basis of the available literature, it would be reasonable to suggest supplementing the diet with 1 to 3 g of omega-3 fatty acids per day as both a therapeutic and preventive measure.

The Anti-inflammatory Nature of Fruits and Vegetables

As stated earlier, fruit and vegetable consumption by people in the United States is “remote from recommended levels.”¹⁴ Craig¹⁵ provides a more vivid picture of our population’s deficiency:

The average American eats only about 1-1/2 servings of vegetables per day and less than 1 serving of fruit per day. A recent survey of American eating habits showed that only 1 in 11 Americans met the guidelines for eating at least 3 servings a day of vegetables and 2 servings a day of fruit. In fact, one in every nine Americans surveyed ate no fruit and no vegetables on the day of the survey, and 45% reported eating no fruit that day. When asked how many servings of fruits and vegetables someone should eat everyday for good health, people gave amazing answers. Two of three Americans surveyed said they thought that only 2 or fewer servings were sufficient for good health.¹⁵

Such dietary habits can have catastrophic ramifications, because “one of the most consistent research findings is that those who consume higher amounts of fruits and vegetables have lower rates of heart disease and stroke as well as cancer,”⁷⁹ all of which have been identified as proinflammatory conditions. Not surprisingly, the same diet that helps to prevent these inflammatory diseases can also be used to effectively reduce inflammation and pain in patients with rheumatoid arthritis.

Kjeldsen-Kragh et al⁸⁰ compared the effects of a vegetarian-based diet (diet group: 27 patients with rheumatoid arthritis) and an ordinary diet (control group: 26 participants). The diet group was initially placed on a 7- to 10-day modified fast, amounting to 800 to 1260 kJ and consisting of herbal teas, garlic, vegetable broth, decoction of potatoes and parsley, and juice extracts from carrots, beets, and celery. After this modified fast, the patients were placed on a vegetarian diet. However, because of the difficulty in meeting nutritional needs, despite advice from a dietitian, they were placed on lactovegetarian diets. The dietary modifications resulted in a significant reduction in proinflammatory indices, suggesting that the chronic pain was, in part, driven by a diet-induced proinflammatory state.

After 4 weeks at the health farm the diet group showed a significant improvement in the number of tender joints, Ritchie’s articular index, number of swollen joints, pain score, duration of morning stiffness, grip strength, erythrocyte sedimentation rate, C-reactive protein, white blood cell count, and a health assessment questionnaire score . . . The benefits in the diet group were still present after one year, and evaluation of the whole course showed significant advantages for the diet group in all measure

indices . . . The patients in the control group showed a decrease in pain score after their stay in the convalescent home, but none of the other indices improved significantly, and at the end of the study they had deteriorated.”⁸⁰

Kjeldsen-Kragh et al⁸⁰ suggested that the improvements seen in all patients was the result of a shift in fatty acid consumption that was associated with eating more plant foods, which resulted in the production of less inflammatory prostaglandins and leukotrienes,⁸⁰ presumably those derived from omega-3 fatty acids and dihomogamalinolenic acid. In a follow-up article, Kjeldsen-Kragh⁸¹ stated that the positive outcomes in the diet group could not be explained entirely by placebo mechanisms, immunosuppression as a result of energy deprivation, or changes in eicosanoid metabolism. A suggested reason for clinical improvement involved alterations of the gut microflora and reduced antibody activity against *Proteus mirabilis*, an organism that has been implicated in the etiopathogenesis of rheumatoid arthritis.⁸¹ Another possible reason for the improved outcome, although one not explored by the authors, is an increased consumption of anti-inflammatory antioxidants and phytochemicals associated with a vegetarian-based diet.

On the basis of this information alone, there can be no doubt that a diet rich in fruits and vegetables tends to be anti-inflammatory, while a diet deficient in these foods is proinflammatory.

The nutritional quagmire in which researchers often find themselves revolves around the following question. What specific factors in fruits and vegetables account for their anti-inflammatory and disease-preventing effects? As of yet, no one can thoroughly answer this question. For example, in the case of cancer, we are told the following by the American Cancer Society:⁸²

Vegetables and fruits are complex foods containing more than 100 beneficial vitamins, minerals, fiber, and other substances. Scientists do not yet know which of the nutrients or other substances in fruits and vegetables may be protective against cancer. The principle possibilities include specific vitamins and minerals, fiber, and phytochemicals—carotenoids, flavonoids, terpenes, sterols, indoles, and phenols—that are present in foods of plant origin. How fruits and vegetables exert their protective role constitutes an active area of scientific inquiry. Until more is known about specific food components, the best advice is to eat 5 or more servings of fruits and vegetables each day.⁸²

The same can be said of heart disease, rheumatoid arthritis, and other inflammatory diseases; that is, all of the precise details about the disease-specific, anti-inflammatory effects of fruits and vegetables are not known. Consider citrus fruits as an example, which contain more than 170 phytochemicals in addition to the known nutrients such as vitamin C. Citrus contains some 60 flavonoids, 40 limonoids, 20 carotenoids, as well as terpenoids,¹⁵ and it is possible that no one may ever know the precise flavonoid, limonoid, or terpenoid that exerts the greatest anti-inflammatory effect in a given disease. Each fruit and vegetable is equal in its bewildering complexity, which also helps to shed light on the foolish notion that nutritional supplements

can take the place of whole foods. In no way can an ascorbic acid supplement, for example, make up for the plethora of vitamins, minerals, and phytochemicals that are found in an orange or grapefruit. Not surprising, the protective effects of vegetables and fruits observed in epidemiologic studies are not seen when plant foods or their constituents are given in pharmacologic doses.⁸³

In general, we now know that nuts, seeds, whole grains, herbs, spices, fruits, and vegetables, contain a host of health promoting and disease-fighting nutrients, such as vitamins, minerals, antioxidants, essential fatty acids, and numerous phytochemicals. Lycopene, allium compounds, indoles, ellagic acid, flavonoids, terpenoids, carotenoids, and a host of phenolic compounds comprise the family of phytochemicals that are thought to offer preventive and therapeutic benefits with respect to chronic inflammatory diseases.^{15,79,84,85} A recent review described potential disease-preventive mechanisms of vegetables and fruits, many of which are anti-inflammatory. Vegetables and fruits possess antioxidant activity, modulate detoxification enzymes, stimulate the immune system, decrease platelet aggregation, modify cholesterol metabolism, reduce blood pressure, and possess antibacterial and antiviral activity.⁸³

Despite the fact that the much more needs to be known about the anti-inflammatory factors in our diet, a good bit of general information and some specific details are already available. Several nutrients found in fish, vegetables, and fruits are known to offer anti-inflammatory benefits, especially the previously mentioned omega-3 fatty acids involved in eicosanoid synthesis and the broad family of anti-oxidants and phytochemicals.

Inadequate Antioxidant Intake

Free radical pathology. A free radical is a very reactive and unstable molecule because it has an unpaired electron in its outer orbital.⁸⁶ Examples of free radicals include superoxide and hydrogen peroxide, which naturally form as a consequence of human aerobic metabolism. *Hydroxyl radicals* can form when a transitional metal ion, such as copper or iron, interacts with hydrogen peroxide.⁸⁶ Hydroxyl radicals may form in response to mechanical injury to tissues. Macro- and micro-trauma can cause cells to rupture and release their contents, including metal ions, such as copper and iron, which then react with hydrogen peroxide to form hydroxyl radicals.⁸⁷

The human body encounters an additional barrage of free radicals from a variety of environmental agents, such as air pollutants, pesticides, and tobacco smoke. "These xenobiotics either already exist as free radicals or are converted to radical species by intracellular metabolic or detoxification processes."⁸⁸

When a free radical is formed it very readily gives up or accepts an electron to stabilize its unpaired electron.⁸⁶ This exchange of electrons is very damaging to cellular structures. Free radicals are thought to damage lipids, proteins, membranes, and DNA.^{2,89-92} Free radicals are thought to

involve "a final common pathway of cell injury in such varied processes as chemical and radiation injury, oxygen and other gaseous toxicity, cellular aging, microbial killing by phagocytic cells, inflammatory damage, tumor destruction by macrophages and others."²

Directly related to the thesis of this paper is the fact that inflammation is an important outcome of free radical damage. Free radicals promote the release of arachidonic acid from cell membranes, which results in the production of proinflammatory PGE2 and LTB4.^{92,93,94} In addition, macrophages and neutrophils produce free radicals that can damage local tissues and promote inflammation.⁹⁵

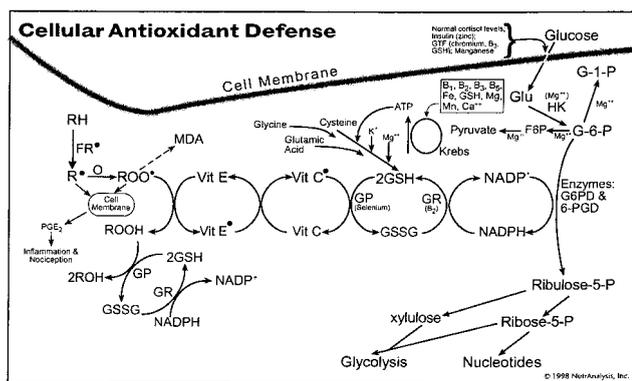
Free radicals may also promote inflammatory damage by enhancing the production of various cytokines, such as tumor necrosis factor. "It is becoming increasingly apparent that in addition to promoting cytotoxicity, reactive oxygen metabolites may also initiate and/or amplify inflammation via the upregulation of several different genes involved in the inflammatory process, such as those that code for pro-inflammatory cytokines and adhesion molecules."⁹⁶ Research suggests that antioxidant nutrients such as vitamins E and C can inhibit this proinflammatory process.⁹⁶ Clearly, free radicals are proinflammatory substances.

Free radical pathology and human diseases. Free radicals are involved in a general mechanism of tissue injury in most, if not all, human diseases.⁸⁷ Indeed, free radicals have been implicated in more than 100 conditions, from arthritis and hemorrhagic shock to AIDS.⁸⁷ For example, research suggests that free radicals participate in the pathogenesis of heart disease,⁹⁷⁻¹⁰⁰ aging,¹⁰¹ Parkinson's disease,¹⁰² amyotrophic lateral sclerosis,¹⁰³ altered immunity,¹⁰⁴ cataracts,¹⁰⁵ and cancer.^{89,106,107} A recent review discusses most of these diseases and their relationship to free radicals and antioxidant therapy.⁹⁵

Research also suggests that free radical activity may predispose the spine to injury. Lipofuscin, known as the aging pigment, is produced by the oxidation of lipids or lipoprotein. At the time of surgery, lipofuscin has been found in the nucleus pulposus and the inner and middle layers of the annulus fibrosis, regions associated with strong histologic degeneration. Lipofuscin was found in the discs of individuals older than 20 years of age.¹⁰⁸ Painful muscle dysfunction may also be promoted by free radicals. A recent article presented evidence indicating that fibromyalgia was mediated, in part, by free radical activity.¹⁰⁹

Even a health-promoting activity such as exercise can promote free radical production. This occurs as a result of a 10- to 15-fold increase in oxygen uptake during exercise.¹¹⁰ Sen¹¹⁰ indicates that "regular physical activity in association with dietary habits to ensure adequate supply of a combination of appropriate antioxidants may be expected to be a prudent course."

It should be clear that we cannot escape free radicals and their proinflammatory nature, because they are a normal component of human life. The only way to combat free



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Fig 3. Cellular antioxidant defense.

radical damage is to ensure a continuous and adequate supply of antioxidants through diet and perhaps supplementation.

Antioxidant nutrient deficiencies in America. Antioxidant micronutrients, which offer substantial disease protection, are found in fruits and vegetables, and research indicates that the United States population's intake of these foods is remote from recommended levels.¹⁴ Such a low level of vegetable and fruit consumption places one at risk for being deficient in antioxidants. A deficiency of antioxidant nutrients permits free radical proliferation, a situation that could reach a catastrophic threshold. Indeed, "without continuous and abundant antioxidant and radical scavenging capability, survival would be impossible."⁸⁹

Regarding antioxidant nutrients, the primary focus is typically centered around β -carotene, vitamin E, vitamin C, and selenium. However, such a focus is not consistent with the biochemical needs of the body's antioxidant defense mechanism. Figure 3 illustrates a component of the human body's antioxidant defense system.^{88,111-118} In addition to the nutrients listed in Figure 3, flavonoids, carotenoids, lycopene, and other phytochemicals also have antioxidant, cytoprotective, and anti-inflammatory properties.

Bioflavonoids also exert an inhibitory effect on eicosanoid synthesis (Fig 2).^{75,119,120} In fact, anti-inflammatory activity was the first known biologic effect of flavonoids.¹²¹ In both human and animal studies, flavonoids have demonstrated an anti-inflammatory effect.⁷⁵ Athletes who consumed flavonoids recovered significantly faster after injury compared with those who did not take flavonoids.⁷⁵ At the present time, some 500 different flavonoids have been identified.^{75,119} In addition to inhibiting eicosanoid synthesis, flavonoids function as accessory anti-oxidants and help to protect collagen.⁷⁵ Flavonoids also affect inflammation by reducing capillary permeability and fragility.^{121,122}

Although animal products do not contain antioxidants and phytochemicals, fruits and vegetables contain appreciable amounts. Considering that the United States population's intake of fruits and vegetables is remote from recom-

mended levels,¹⁵ it is reasonable to suggest that we consume inadequate levels of antioxidants and phytochemicals. The most rational way to correct this imbalance is to consume greater quantities of fruits and vegetables. It is generally recommended that we consume at least 3 servings of vegetables and 2 servings of fruit per day.¹⁵ Simopoulos,⁶² however, suggests that we consume 7 or more servings of fruits and vegetables.

Mechanical Pain May Be a Biochemical Condition

A new study commissioned by the Merck Corporation¹²³ revealed that 9 in 10 Americans suffer with pain. Despite the high prevalence of pain, there is still no consensus about the genesis and etiology of most pain syndromes,^{124,125} which is probably a result of the fact that frank pathology and obvious tissue changes are not associated with most kinds of pain. Terms such as *simple backache*, *somatic pain*, *nonspecific pain*, *muscular pain*, *nociceptive pain*, and *mechanical pain* are used to describe such pain. The most common medical treatment approach involves the use of NSAIDs, which are known to provide both peripheral anti-inflammatory and central analgesic effects. Concerning this treatment approach, it is important to consider the mechanism by which NSAIDs inhibit pain. As described earlier, pain results from the stimulation of peripheral nociceptors that are activated by numerous chemical mediators, including lactic acid, potassium ions, PGE₂, LTB₄, histamine, 5-hydroxytryptamine, bradykinin, IL-1, and TNF.¹⁸⁻²¹ NSAIDs are known to directly or indirectly antagonize some of these mediators, particularly prostaglandins.

Research within the last 10 years suggests that the treatment of musculoskeletal, or so-called *mechanical pain*, requires a safe and effective biochemical method.¹²⁶ Phospholipase A₂ (PLA₂) is the enzyme that cleaves the unsaturated fatty acid from the C-2 position of cell membrane phospholipids (Fig 1).¹²⁷ PLA₂ can act on DGLA or EPA, resulting in the production of noninflammatory eicosanoids, or PLA₂ may act on arachidonic acid and result in the generation of proinflammatory eicosanoids, such as PGE₂. As described earlier, the standard American diet heavily favors the consumption of omega-6 fatty acids, which leads the production of arachidonic acid and an associated proinflammatory response. With this in mind, consider the fact that both herniated disks and synovial fluid from degenerative joints contain PLA₂, and that human lumbar disk PLA₂ is 20- to 100,000-fold more active than any other phospholipase yet to be described.¹²⁸ Perhaps this is why simple or mechanical back pain can often be debilitating and lead both doctors and patients to believe that a much more serious pathologic condition is responsible for the pain.

Sierkerka¹²⁹ suggests that nutritional therapy should accompany any chosen treatment regimen to accelerate the healing of a damaged disk, the most integral aspect of acute therapy being the dietary addition of foods containing n-3

and the avoidance of those that contain arachidonic acid.¹²⁹ Except for the work of Sierkerka,¹²⁹ biomechanically oriented professionals, such as chiropractors and orthopedic surgeons, have placed little emphasis on the importance of restoring fatty acid balance for the purpose of reducing pain and inflammation.

The main biochemical intervention for back pain, osteoarthritis, and rheumatoid arthritis continues to be NSAIDs, an approach that needs to change. Consider that NSAIDs are taken to reduce inflammation and that these medications merely act to inhibit a biochemical process acting on fatty acids that ultimately come from our diet. We literally eat ourselves into an inflamed and painful state and then seek out passive care from doctors to intervene on our behalf. Medications and chiropractic manipulation may reduce pain and inflammation, but they cannot influence the underlying diet-induced proinflammatory state. Dietary modification and nutritional supplementation appear to be the only interventions that can address the underlying cause.

CONCLUSION

In the past century, numerous inflammatory mediators have been discovered and studied, such as PGE₂, LTb₄, histamine, bradykinin, serotonin, TXA₂, TNF, IL-1, platelet-derived growth factor, and many more cytokines and growth factors. Each has been linked to the pathogenesis of chronic diseases such as heart disease, cancer, rheumatoid arthritis, osteoarthritis, disc disease, chronic pain, and many other conditions. Dietary imbalances that favor the production of these mediators could be referred to as prothrombotic,¹³⁰ protherogenic,¹⁷ procarcinogenic, proarthritic, or pronociceptive; however, this method of nomenclature is far too cumbersome and does not reflect the fact the same nutritional imbalances can promote numerous diseases. The term "diet-induced proinflammatory state" is far more appropriate because it is more precise and inclusive.

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