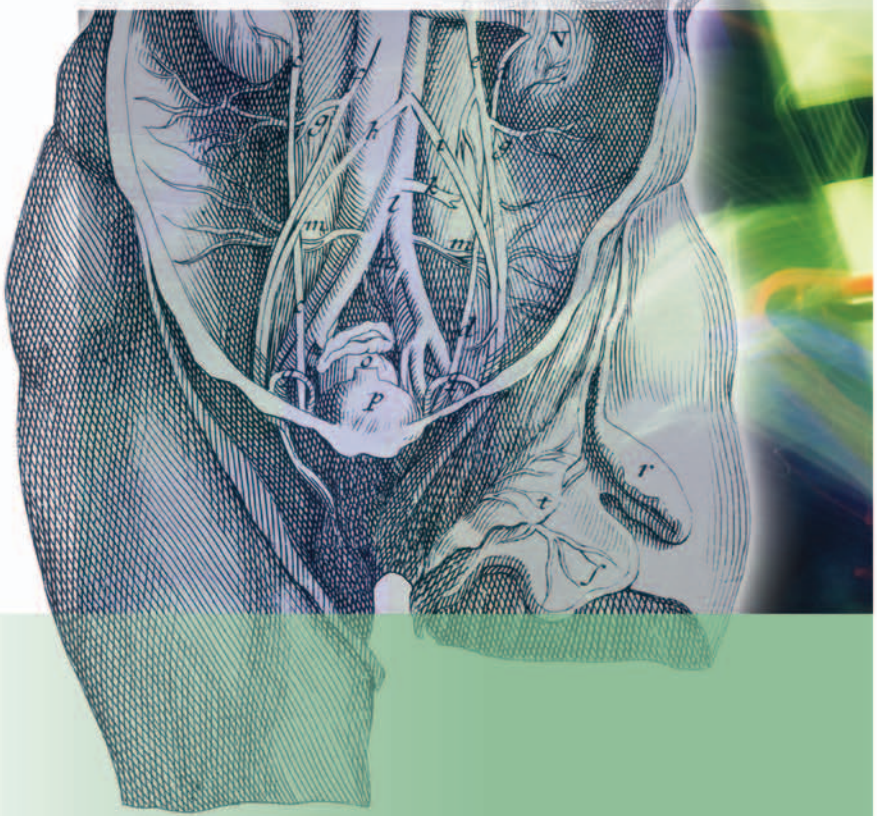
CONDITION MANAGEMENT SERIES

Autoimmune Diseases

Nutritional Strategies From Metagenics Functional Medicine Research Center



The term ***Autoimmune Disease*** refers to a varied group of more than 80 distinct, chronic illnesses in which the underlying problem is similar—the body's immune system is misdirected, attacking the body tissues it was designed to protect. Autoimmune disease can affect any system, organ, or tissue in the body, including the gastrointestinal (GI), nervous, and endocrine systems as well as the eyes, blood, blood vessels, and skin and other connective tissues.

Examples of autoimmune conditions include the following:

- **Rheumatoid arthritis (RA)**
- **Lupus (e.g., systemic lupus erythematosus [SLE])**
- **Type 1 diabetes**
- **Inflammatory bowel disease (IBD) (e.g., Crohn's disease, ulcerative colitis)**
- **Hashimoto's thyroiditis & Grave's disease**
- **Raynaud's phenomenon**
- **Neurological diseases (e.g., myasthenia gravis, multiple sclerosis [MS])**

The purpose of this guide is to offer a *functional medicine* approach to addressing the various issues associated with autoimmune disease. The strategies discussed in this guide are not intended to treat disease, but to identify possible triggers and address underlying and mediating factors, such as:

- **Sex hormones**
- **Drugs & chemicals**
- **GI barrier function & microflora balance**
- **T helper (Th1) dominance**
- **Inflammation**
- **Impaired biotransformation**
- **Nutritional deficiencies**
- **Oxidative stress**

For ease of use, each section in this guide begins with a brief general discussion, followed by therapeutic considerations, and concluded by nutritional recommendations.

Metagenics®
Genetic Potential Through Nutrition

Triggers—Minimize the impact of physiological and environmental triggers

Sex Hormones

The sex hormones—particularly estrogen—appear to play a role as mediators and perpetuators of inflammatory and autoimmune disorders. This may explain the higher incidence of autoimmune diseases among women and fluctuations of disease severity observed in pregnant women. In fact, it has been shown that synovial fluid levels of pro-inflammatory estrogens relative to androgens are significantly elevated in both female and male RA patients.

Sex Hormone Activity

Research suggests that sex hormones influence the immune response in a number of ways. Estrogen appears to enhance Th1 activity, whereas androgens and progesterone possess immunosuppressive properties. The local effects of sex hormones appear to consist primarily of the modulation of cell proliferation and cytokine production.

Estrogen Metabolism

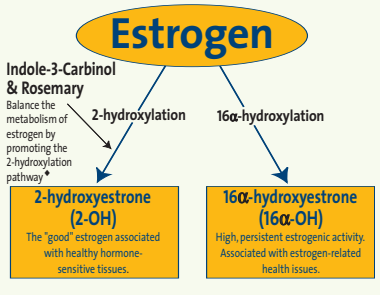
An interesting aspect of the observations concerning estrogens and autoimmunity relates to estrone metabolism and to the 16α-hydroxylated metabolite—a mitogenic estrogen that appears to increase estrogen-induced autoimmunity—in relation to levels of the 2-hydroxylated metabolite, which is not mitogenic or immunogenic. A number of studies on patients with RA and SLE have demonstrated elevated levels of the mitogenic 16α-hydroxyestrone (16α-OHE), likely contributing to the cellular proliferative state observed in these autoimmune diseases.

Considerations:

- Promote estrogen detoxification to prevent estrogen dominance in relation to androgen and progesterone
- Support the hydroxylation and methylation of estrogens to help favor the conversion of 2-OH over 16α-OH estrogens
- Assess with section XII of Health Appraisal Questionnaire (HAQ)

Nutritional Support:

- Indole-3-carbinol (I3C) to promote 2-OH estrogen conversion
- Non-soy isoflavones with bioactive folate for healthy estrogen balance
- Medical food for healthy hormone balance
- Metabolic detoxification program
- Anti-inflammatory diet program



Drugs & Chemicals

It is now apparent that a number of drugs and environmental pollutants can induce immunotoxic effects, resulting in the appearance of autoantibodies and in some instances, in the appearance of autoimmune clinical syndromes. One of the most studied diseases in relation to environmental factors is lupus; although, there is increasing research on conditions such as scleroderma, RA, vasculitis, as well as muscle, blood, and neurologic disorders.

Drugs

Over 70 drugs have been reported to be related to autoimmune conditions, and have been particularly implicated in the development of drug-related lupus (DRL), a condition sometimes accompanied by central nervous system and renal involvement. Specific families of drugs that have been identified as autoimmune-inducing agents include anticonvulsants, beta-blockers, and sulfonamides. Interestingly, common drugs associated with DRL are estrogens, gold salts (also used to treat RA), penicillin, and interferon.

Environmental Pollutants

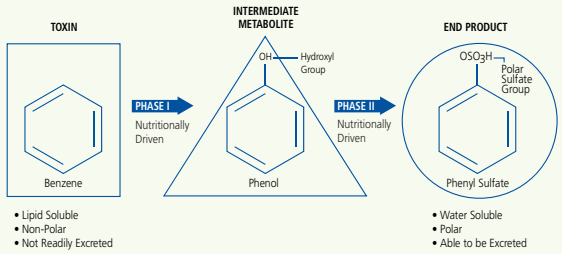
Many environmental pollutants—such as xenobiotics, mercury, cadmium, gold, organic solvents, vinyl chloride, pristane (a compound of mineral oil), and pesticides—may cause adverse reactions in susceptible individuals that are characteristic of autoimmune disease. Although the mechanisms by which environmental pollutants contribute to autoimmune disorders are still under investigation, it is thought they may trigger macrophages and other inflammatory cells to release pro-inflammatory products. In addition, they may shift the balance between type 1 and type 2 immune responses.

Considerations:

- Identify and avoid environmental triggers
- Assess detoxification capacity
- Modulate Th1/Th2 balance
- Assess with section II of HAQ
- Assess general physical symptoms with Medical Symptoms Questionnaire (MSQ)

Nutritional Support:

- Medical food for metabolic detoxification
- Elimination or anti-inflammatory diet program
- Bioactive folates for detoxification support
- Comprehensive antioxidant support
- Reduced iso-alpha acids (RIAA) and vitamin D nutraceutical



Mediators—Address the underlying physiological and dietary mediators

GI Barrier Function & Microflora Balance

Research suggests there is a correlation between mucosal barrier function and autoimmune disease. The GI tract is responsible for regulating the traffic of molecules between the environment and the body through a barrier mechanism. Together, the GI barrier with its selectively permeable intracellular tight junctions, lymphoid tissue, and neuroendocrine network control the balance between tolerance and immunity to potential antigens. When the precise trafficking of molecules becomes dysregulated, autoimmune disease can occur.

Intestinal Permeability

The permeability of the intestinal barrier depends on the regulation of intercellular tight junctions, which are responsible for selectively trafficking beneficial and potentially harmful molecules—such as nutrients and antigens, respectively—between the environment and host. It is now widely accepted that tight junction dysfunction, commonly referred to as "leaky gut," plays a role in the pathogenesis of several diseases, particularly autoimmune diseases.

Emerging scientific findings from mucosal biopsies of IBD patients have shown altered expression of critical tight junction proteins, possibly due to the effects of pro-inflammatory cytokines on barrier integrity. This suggests a vicious cycle is created, in which increased intestinal permeability allows further leakage of intestinal contents, contributing to a pro-inflammatory immune response on intestinal tissue that, in turn, promotes further gut leakiness.

Microflora Balance

A healthy intestinal tract harbors a large variety of beneficial microflora, or "friendly" bacteria, residing in close proximity to rapidly renewing intestinal epithethial cells and other components of the mucosal immune system. Components of beneficial microflora are essential to maintain a balanced immune and inflammatory response; when this balance is disrupted, excessive immune activation could pose a risk to the development of intestinal or systemic inflammation.

Considerations:

- Manage GI function through GI Restoration Program
- Reduce inflammatory response
- Assess with section I of HAQ

Nutritional Support:

- Medical food for metabolic detoxification
- Elimination or anti-inflammatory diet program
- *Lactobacillus acidophilus* NCFM® and *Bifidobacterium* supplement
- Herbal antimicrobial with berberine or oregano
- Omega-3 (high EPA) supplement

Th1 Dominance

Emerging data suggest the same immune mechanisms that protect against invasive microorganisms are involved in the generation of organ-specific autoimmune disease, as well as result in the destruction of tissue and loss of organ function during the course of autoimmune disease. This immune response, known as cellular immunity, is controlled by Th1 cells, which develop preferentially over Th2 cells during infections with intracellular pathogens.

Cellular Immunity Action

Upon activation, Th1 cells control the type of immune response by secreting pro-inflammatory cytokines, activating macrophages to produce reactive oxygen intermediates and nitric oxide, and stimulating their phagocytic functions. When the Th1 pathway is over-stimulated, the Th1-driven immune response can become aggressive and autoreactive in susceptible individuals, as has been seen in organ-specific autoimmune diseases such as RA and type 1 diabetes.

Role in Autoimmune Inflammation

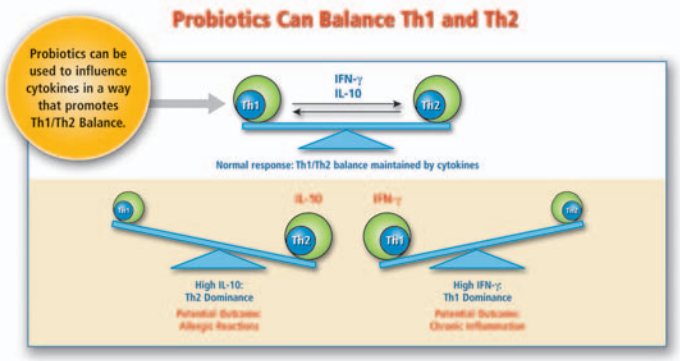
A number of scientific observations suggest that Th1-driven immunity plays a dominant role in the pathogenesis of autoimmune inflammation. Emerging research indicates that Th1 cells are stimulated by pro-inflammatory cytokines, whereas Th2 cells are stimulated by anti-inflammatory cytokines, suggesting a strong association of Th1 dominance in autoimmune inflammation. Interestingly, activated Th1 cells have been found in the inflamed synovium of RA patients.

Considerations:

- Reduce Th1 dominance and balance overall immune activity
- Assess with section VII of HAQ

Nutritional Support:

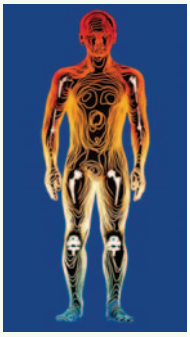
- Medical food for inflammation and biotransformation
- Anti-inflammatory diet program
- Omega-3 (high EPA) supplement
- RIAA and vitamin D nutraceutical
- *Lactobacillus acidophilus* NCFM® and *Bifidobacterium* supplement
- Non-soy isoflavones with bioactive folate for healthy estrogen balance



Inflammation

Research indicates that inflammation is intrinsic to autoimmune diseases. During inflammation, the inflammatory cascades release a wide array of cytokines, eicosanoids, reactive oxygen species (ROS), and other mediators that can overwhelm and offset Th1/Th2 balance and potentially damage body tissues.

Cytokine Dysregulation



Recent evidence indicates the involvement of cytokines—mediators that control immune and inflammatory responses—in the pathogenesis of autoimmune disease. Specifically, cytokines associated with the Th1 immune response—such as IL-12, TNF-α, and IFN-γ—stimulate other inflammatory responses, indicating they play a synergistic role to drive chronic inflammatory responses in autoimmune disease.

Eicosanoid Pathways

Major mediators of collateral damage in autoimmunity are eicosanoids—lipid mediators that are central to the inflammatory pathway and the regulation of numerous physiological processes. Inhibition of the cyclooxygenase-dependend eicosanoid products is known to improve the quality and prolong the life of patients with autoimmune disease, such as lupus and autoimmune arthritis.

C-Reactive Protein

High sensitivity C-reactive protein (hsCRP) is a non-specific marker of inflammation that may be markedly elevated in chronic inflammatory conditions, and has been reported to be predictive of future coronary heart disease (CHD) events in several studies.

Because the inflammation in autoimmune diseases has been found to result from the underlying issue of immune activation, "disease modifying anti-arthritic drugs" (DMARDs) have been used to suppress the immune system, thereby eventually leading to a decrease in inflammation. A number of natural ingredients may provide similar immune-balancing and anti-inflammatory effects.

Considerations:

- Calm systemic inflammatory status
- Support antioxidant pathways
- Address fatty acid profile
- Assess status of hsCRP and other inflammatory markers
- Assess general physical symptoms with MSQ

Nutritional Support:

- Medical food for inflammation
- Anti-inflammatory diet program
- RIAA and vitamin D nutraceutical
- Omega-3 (high EPA) supplement

Impaired Biotransformation

The depletion or insufficiency of any cofactor involved in biotransformation can significantly impair overall health and well-being. Biotransformation describes the series of chemical alterations that a compound undergoes in order for the body to adequately excrete the compound. These chemical alterations most often involve the cytochrome P450 family of enzymes, which includes the detoxification enzymes that act to metabolize drugs and foreign chemicals. Cytochrome P450-containing enzymes are also involved in the detoxification of estrogen, metabolism of arachidonic acid and eicosanoids, and conversion of vitamin D into its active metabolite.

Vitamin D Metabolism

One of the important roles of the CYP450 family related to immune function regulation is the metabolism of vitamin D. Vitamin D is first hydroxylated in a rate limiting step to 25-hydroxyvitamin D_3 in the liver by CYP25 (25-hydroxylase) and then further hydroxylated in the kidney to 1,25 dihydroxyvitamin D_3 (1, 25$[OH]_2$ D_3), which is the active hormonal form of the vitamin. Expression of the vitamin D hydroxylating enzymes in the liver and kidney determine, in part, the role that the hormonal form of vitamin D has in modulating immune function.

B Vitamins and Estrogen Detoxification

B vitamins—such as folate, B_6, and B_{12}—function as important co-factors for enzymes involved in estrogen detoxification. Therefore, decreased levels of B vitamins can disrupt estrogen detoxification, leading to increased levels of circulating estrogen and an unhealthy balance of estrogen metabolites, such as 2-OHE and 16α-OHE. Because up to 40% of the U.S. population has a genetic variation that impairs the ability to metabolize folic acid, supplementation with the active metabolite of folate, L-5-methyl tetrahydrofolate (L-5-MTHF), can be especially beneficial.

Considerations:

- Initiate patient-specific metabolic detoxification program
- Support antioxidant pathways
- Assess vitamin D status
- Assess with section II of HAQ
- Assess general physical symptoms with MSQ

Nutritional Support:

- Elimination or anti-inflammatory diet program
- Medical food for metabolic detoxification
- Milk thistle extract
- Bifunctional detoxification support formula
- Vitamin D_3 supplement with soy isoflavones

Nutritional Deficiencies

A variety of common nutritional deficiencies can exacerbate the autoimmune response, such as the following:

Vitamin D

Mounting scientific data indicates vitamin D deficiency increases the risk of autoimmune diseases such as type 1 diabetes, MS, and RA. The metabolized, hormonal form of vitamin D(1, 25$[OH]_2$ D_3) acts as an important immune modulator through its interactions with immune cells and involvement in regulating lymphocyte function, cytokine production, and macrophage activity.

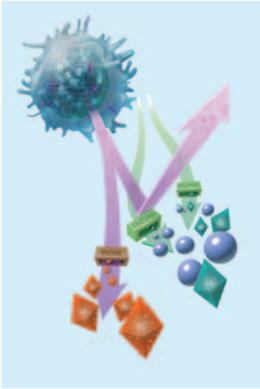
Unfortunately, vitamin D deficiency has reached epidemic proportions in the U.S. With this new emphasis on the importance of vitamin D, many researchers are now recommending levels of intake much higher than 400 IU per day, which is the recommended amount.

Folate

Moderate hyperhomocysteinemia related to low folate levels has been reported in patients with autoimmune diseases. Interestingly, a recent study of patients with RA showed a correlation between high homocysteine levels, low folate status, and increased concentrations of immune activation markers—suggesting that both folate status and immune activation could be involved in the development of hyperhomocysteinemia.

Omega-3 Fatty Acids

Omega-3 fatty acids, particularly EPA, possess potent anti-inflammatory and immunomodulatory effects. The properties of omega-3s include regulation of the amount and types of eicosanoids produced, as well as actions on transcription factor activity and gene expression. A number of clinical trials in inflammatory and autoimmune diseases—including RA, Crohn's disease, ulcerative colitis, psoriasis, SLE, and MS—have revealed significant benefits of omega-3 supplementation.



Selenium and Zinc

The role of these minerals in chronic inflammatory conditions is of great scientific interest because they are co-factors in metabolic processes involving joint tissues and immune system function. Selenium and zinc deficiencies have been linked to an exacerbation of inflammation in active RA, and supplementation has been reported to reduce joint tenderness and stiffness.

Considerations:

- Assess diet and supplement regimen with diet dairy (found in the *FirstLine Therapy*® book)

Oxidative Stress

Emerging research suggests that chronic oxidative stress may play a substantial role in the pathogenesis of autoimmune disease and related complications. Oxidative stress favors a sequence of immune system activities, such as production of pro-inflammatory cytokines, macrophage activation, cellular proliferation, and endothelial activation—the same events found in autoimmune diseases, particularly SLE. This has led some researchers to hypothesize that oxidative stress may trigger inflammatory activity, inducing a flare of autoimmune disease in susceptible individuals.

Considerations:

- Reduce oxidative stress and inflammation
- Assess antioxidant nutrient intake

Nutritional Support:

- Comprehensive antioxidant blend of vitamins A, C, E with selenium and zinc
- Green tea, D-limonene, and turmeric formula
- Medical food for inflammation and biotransformation
- Anti-inflammatory diet program

Dietary Program Options

A specialized dietary program can play an important part in the management of autoimmune disease. Consider the following diet options:

Elimination Diet—A 3-step, focused, low-allergy-potential dietary program to decrease inflammation and reduce the body's burden of allergens and toxins.

- **Step 1: Initial Clearing (Days 1-6)**
  Eliminate potentially allergenic foods and increase intake of nutritional support product(s).
- **Step 2: Detoxification (Days 7-13)**
  Consume a select number of low-allergy-potential foods along with three servings a day of nutritional support product(s).
- **Step 3: Reintroduction (Days 14-28)**
  Slowly reintroduce the foods eliminated in Step 2 back into the diet, and slowly decrease intake of nutritional support product(s) paying careful attention to any possible food reactions. These reactions may indicate food allergy or intolerance.

Anti-Inflammatory Diet—A long-term, easy-to-follow dietary program to reduce inflammation and protect body tissues from an autoreactive immune system. **(See *Dietary Modifications to Manage Inflammation* on the back page.)**

Dietary Modifications *to Manage Inflammation**

Food Category	Serving Size	Servings per day	Calories per serving	Choices
VEGETABLES	1/2 cup	5-7	10-25	All vegetables are allowed except white potato, turnip, parsnip, rutabaga, and corn. Fresh vegetable juices are also allowed.
FRUITS	Approximately 1 medium	3-4	80	All whole fruits except banana, pineapple, and papaya. Fruit juice not recommended.
CONCENTRATED PROTEIN **	3.5 oz (after cooking)	Aim to consume no more than 60 mg arachidonic acid (AA) daily; (please refer to chart to calculate AA content). Note: dairy and soy products have negligible amounts of AA	150	**POULTRY (remove all skin):** Turkey breast and chicken breast **LEAN MEATS:** Sliced boiled ham, pork tenderloin, beef flank steak, ground beef, 5% fat **FISH (avoid farmed fish):** (See chart below.) **DAIRY:** Cottage cheese 1%, 3/4 cup; ricotta, reduced fat, 1/2 cup **TOFU PRODUCTS:** tofu, 1 cup; tempeh, 1/2 cup; soy burger, 4 oz.; TVP, 1/3 cup
DAIRY	6 oz.	1-2 (if tolerated)	80-100	Plain yogurt (lowfat or nonfat), milk (nonfat, 1%, or 2%), buttermilk, milk substitutes (soy, rice, nut)
LEGUMES	1/2 - 1 cup	1-2	100-200	All peas and beans, hummus, bean soups
GRAINS	1/2 cup	1-3	75-100	Whole grains such as 100% whole wheat bread and pasta, brown rice, whole oats, rye crackers, and pearled barley with at least 3 grams or more of fiber per serving.
NUTS/SEEDS	1 small handful	1	150-200	All nuts except cashews and macadamias, 1-2 Tbsp nut butter
OILS	1 tsp	4-6	40	Olive and canola oils for cooking, flax seed (refrigerate) and walnut oils for salads, mayonnaise from canola oil (no egg or sugar added), avocado (1/8 of whole), green or black olives (8-10).
BEVERAGES	Unlimited	Water intake recommended at 1/2 body weight in ounces	0	Water, herbal tea, decaffeinated coffee or tea, mineral water, club soda, or seltzer, plain or flavored **(no added artificial sweeteners)**.
CONDIMENTS	Unlimited	As desired	0	Cinnamon, carob, mustard, horseradish, vinegar, lemon, lime, flavored extracts, herbs/spices, stevia. **No refined sugars or artificial sweeteners are allowed.**

Food	Arachidonic Acid Content (mg per 3.5 oz. for meats)
Meat and poultry:	
Ham, sliced boiled	0
Pork tenderloin	30
Turkey breast, roast	40
Beef, flank steak	40
Ground beef, 5% fat	50
Chicken breast	60
Fish:	
Mahi Mahi	0
Pacific mackerel	10
Pink salmon	10
Pacific cod	20
Sockeye salmon	30
Atlantic cod	30
Haddock	30
Snapper	40
Yellowfin tuna	40
White tuna, canned in water	50
Flounder	50
Atlantic mackerel	50
Grouper	60

* If you suspect that your patient has issues with food allergies or sensitivities, follow the elimination diet.

** Please eat only the cheeses that are listed, as most other cheeses are quite high in saturated fat and not allowed on this program.

It's a Matter of Fat

Arachidonic Acid is a fat associated with inflammation in the body. Various opinion leader organizations, such as the American College of Rheumatology, support eating certain fish and foods that contain omega-3 fatty acids due to the new evidence indicating that these fats can reduce the pain and inflammation of RA. The American Heart Association (AHA) advocates a general recommendation of at least two servings per week to receive the cardiovascular benefits of these fatty acids. Increased consumption of omega-3 fatty acids results in a decrease in the amount of arachidonic acid. Along with a diet low in glycemic index, research supports the limitation of arachidonic acid to no more than 60 mg daily.

Adjacent is a list of animal foods (meat, poultry, and fish) that are at or below 60 mg per 3.5 oz average serving. Please limit your food in this category to only those on this list. Remember if you eat more than 3-4 oz at a time, you must add the additional arachidonic acid to your calculations. Egg yolks are high in arachidonic acid (70 mg per yolk) and therefore must be avoided. Soy and dairy products contain no significant arachidonic acid.

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