Natural Interventions for Treating Autoimmune Diseases

Current Knowledge and New Possibilities

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Conventional medical intervention for a variety of autoimmune diseases has been disappointing at best. Therapy is generally initiated to control some of the symptoms and slow the progression of disease. However, conventional treatment does not offer a "cure" and long-term prognoses for remissions still remain poor. Many of the drugs used to treat these disorders have serious side-effects, such as bone loss, ulcers, joint and organ damage, and additional worsening of immune function and symptoms over time.[1,2] Autoimmune disease is more prevalent in women compared to men[3] and studies suggest that increased serum estrogens play a role in autoimmune disease.[3]

What Research Shows

Research into autoimmune diseases and their treatment provide some useful leads regarding their causation and treatment.

Negative Effects of Estrogen Replacement

Studies have shown that estrogen replacement therapy in menopausal women significantly raises the risk of developing systemic lupus erythematosus (SLE) and/or developing discoid lupus (DL)[4] and that the use of oral contraceptives also raises these risks.[5] In the Nurses Health Study, more than 69,000 postmenopausal users of estrogen replacement had a relative risk (RR) of 2.1 for developing SLE, current users had a RR of 1.2, and past users had a RR of 1.8. A proportional increase in risk was observed with the duration of use of postmenopausal hormones.[6]

Estrogen Dominance May Be a Factor

Many American women have "hyperestrogenism" or estrogen dominance because they consume meat, chicken, veal, and dairy products that still retain estrogens that have been added to livestock as well as xenoestrogens from pesticides and other environmental toxins.[7]

In addition, only 32 percent of Americans eat the recommended 5 servings of fruit and vegetables[8] and consumption among these women of whole grain food is very low.[9] Fruits, vegetables, and whole grains are important sources of phytohormones, which can modulate estrogen levels in the body by enhancing the metabolism of estradiol to estrone and produce estriol as a final byproduct.

High levels of estradiol have repeatedly been implicated in breast cancer.[10] Japanese women, who eat a more plant-based diet that is also rich in soy, appear to have a lower risk of developing breast cancer and have decreased serum estradiol levels compared to American women.[11] It would be interesting to see if there is a connection between phytohormone ingestion (e.g., vegetables, soy) and prevention of autoimmune disease.

Potentially Helpful Supplements

Current research indicates that two supplements, dehydroepiandrosterone (DHEA) and melatonin, may confer benefits on patients with some types of autoimmune disorders.

DHEA

More recent studies have shown that, for some types of autoimmune disorders, exogenous DHEA replacement may actually be therapeutic for treating rheumatoid arthritis (RA)[12] and SLE.[13]

In a double-blind, placebo-controlled study, 21 patients with severe SLE received either 200 mg per day of DHEA or placebo in addition to conventional treatment (corticosteroids, immunosuppressives) for 6 months. The mean improvement of a SLE activity index was greater in the DHEA-treated group and 7 of 9 patients who took DHEA versus 4 of 10 who took the placebo were responders.

DHEA also demonstrated a protective effect with respect to corticosteroid-induced osteopenia.[13] Adjuvant DHEA therapy given at similar levels in addition to conventional treatment has been shown to reduce symptoms associated with RA.[12]

It has been suggested that DHEA increases androgen levels rather than estrogen levels in these patients, thus reducing the symptoms of disease.[12,13]

Melatonin's Potential Benefit

In a case report of a patient with multiple sclerosis (MS), 3 mg of melatonin taken at 2 PM each day, when the patient experienced severe blurring of vision, resulted in dramatic improvement in visual acuity within 15 minutes of ingesting the supplement. It has been suggested that melatonin may be of benefit to patients with MS because melatonin modulates the thermogenic regulatory mechanisms of the pineal gland.[14]

The Mercury Debate

The potent neurotoxin mercury has been shown to induce systemic autoimmune conditions in genetically suscepti-

Vegan and gluten-free diets have been shown to be of benefit to patients with autoimmune diseases.

Female:Male Ratios in Autoimmune Diseases

Autoimmune condition	Female:male incidence ratio
Hashimoto's disease/hypothyroiditis	50:1
Systemic lupus erythematosus	9:1
Sjøgren's syndrome	9:1
Antiphospholipid syndrome	9:1
Primary biliary cirrhosis	9:1
Mixed connective tissue disease	8:1
Chronic active hepatitis	8:1
Graves' disease/hyperthyroiditis	7:1
Rheumatoid arthritis	4:1
Scleroderma	3:1
Myasthenia gravis	2:1
Multiple sclerosis	2:1
Chronic idiopathic thrombocytopenic purpura	2:1

Notes: Many autoimmune diseases have a disproportionately high incidence among women.

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ble mice.[15] These animals also have a narrow safety margin compared to non–genetically susceptible mice. One study revealed that death rates from MS were linearly related to the numbers of decayed, missing, and filled teeth in patients from 6 Australian states, 48 American states, and 45 Asian and European countries.[16] Another study demonstrated a 21-percent increase in MS in relation to dental carries compared to controls in England.[17] This compelling evidence has prompted many practitioners to advise patients to have mercury amalgams removed. Anecdotal evidence of patient improvement has been reported by numerous practitioners.

Natural Approaches

Scientific studies have shown that specific dietary supplements, dietary modifications, and life style changes may be of benefit to patients with autoimmune disease as demonstrated by extended clinical remissions, reductions in symptoms, and/or reductions in dosages of steroids and other drugs used to control the diseases.[11,15,18–47] Although a more natural intervention is best utilized at the very onset of disease, this type of treatment can also be combined with conventional therapy to help provide symptom relief and lessen the side-effects of pharmaceutical agents that are used to treat patients in later stages of disease. Despite the significance of results, further research into nutritional intervention for autoimmune disease has been quite slow in coming.[11,15,18–47]

Dietary Interventions

Low fat diets have been reported to be beneficial in both human and animal studies with respect to autoimmune diseases such as SLE[18] and MS.[19,20]

For example, very–long-term studies following patients with MS for 34 and 36 years have shown that patients who followed very–low-fat diets (<20 g fat per day) experienced significantly less deterioration and much lower death rates than patients who consumed higher amounts of dietary fat.[19,20] Approximately 95 percent of patients who were followed during these 34- and 36-year studies survived for the duration of the studies and remained physically active.[19,20] An even lower-fat diet (10–15 g of fat per day) resulted in better improvement in energy and reduced fatigue levels.[16,17] In patients who consumed >20 g of fat per day, the death rate approached 80 percent by the end of the 34- and 36-year studies.[19,20]

Low-fat diets could potentially modulate prostaglandin metabolism, specifically arachidonic acid and inflammatory prostaglandins. High-meat diets are rich in arachidonic acid and high-fat diets are generally quite high in linoleic acid—both of which may result in an imbalance of prostaglandin metabolism by encouraging the production of inflammatory prostaglandins.[21] In addition, lower-fat diets would result in lower levels of oxidative stress.

Vegan diets and gluten-free diets have been shown to be of benefit to patients with RA,[22] psoriasis,[23] eczema,[24] dermati-

Food and chemical sensitivities are more common in patients with autoimmune diseases.

tis herpetiformis,[25] type 1 diabetes,[26] or Crohn's disease.[27] Milk consumption has been shown to increase the incidence of MS.[28] Food and chemical sensitivities are more common in patients with autoimmune diseases, in particular, those with SLE.[29]

Omega-3 and Omega-6 Fatty Acids

Numerous animal models of SLE have demonstrated marked protection from kidney disease, increased life spans, and autoimmune suppression.[30] Human clinical studies have shown that fish oil can induce clinical remission of SLE without any negative side-effects.[30] Fish-oil supplementation has also been shown to benefit patients with MS, in particular, newly diagnosed patients, by significantly reducing neurologic scores and exacerbation rates.[31] There are many studies show-

Mainstream Medicine on Autoimmune Disease

National Institutes of Health

Despite exellent data on alternative treatments for autoimmune diseases, mainstream organizations are unaware of this research. However, these organizations can offer other kinds of support. Because autoimmune diseases affect so many different structures and functions of the body, numerous institutes at the National Institutes of Health (NIH) conduct research into treatments for autoimmune diseases. Many of these diseases fall under the aegis of the National Institute of Allergy and Infectious Diseases (NIAID), which maintains a Web site that provides extensive links to other relevant institutes and to nongovernmental organizations that provide disease-specific information to patients with specific autoimmune disease diagnoses. The institutes and private organizations also coordinate and may fund research into the specific diseases. Institutes of the NIH that oversee medical research and provide information about specific autoimmune diseases include:

National Institute of Allergy and Infectious Diseases
Office of Communications
Building 31/Room 7A50
31 Center Drive, MSC 2520
Bethesda, MD 20892-2520
Phone: (301) 496-5717
Web site: www.niaid.nih.gov

National Institute of Arthritis and Musculoskeletal and Skin Diseases
Information Clearinghouse/NIH
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Clearinghouse: (301) 495-4484
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Private organization

American Autoimmune-Related Diseases Association (AARDA)
22100 Gratiot Avenue
East Detroit, MI 48021
Phone (800) 598-4668 or (586) 776 3318
Web site: www.aarda.org

The AARDA is the principal private organization that distributes information about autoimmune diseases. This organization initiates and fosters research and sends packets of information on autoimmunity and autoimmune diseases.

Supplementation with just one antioxidant can potentially induce oxidative stress.

ing a beneficial effect of fish oil supplementation for patients with RA.[32] These benefits include reduced use of nonsteroidal anti-inflammatory drugs and reductions in such symptoms as joint tenderness and swelling.[32]

Clinical benefit of fish-oil supplementation (in particular, enteric-coated supplements) has also been observed in patients with such disorders as Crohn's disease by lowering the relapse rates and maintaining remissions.[33] Patients who have received long-term administration of fish oil had clinical improvement in psoriasis lesions.[34]

In general, studies have used high-dose fish oil supplementation of at least 3.6 g per day. This amount is at least 9 fish oil capsules per day, depending upon the g of fish oil provided by each capsule. The eicosapentaenoic acid content of 1.5 g of fish oil is 450 mg and the docosahexaenoic acid content is generally 300 mg.

Fish oil appears to work as well as, if not better than, conventional drug treatment, produces no side-effects[30–34] and can be combined with conventional therapy.[30–34] However, coadministration of a very-low-fat diet may reduce the quantity of fish oil required to improve a patient's condition and/or induce remission of symptoms of autoimmune disease.

Gamma–Linolenic Acid

The results of studies using evening primrose (*Oenothera biennis*) oil (EPO) for treating autoimmune disease have been mixed, perhaps because of different doses used in these studies. EPO is a significant source of γ-linolenic acid (GLA) with each capsule providing 45 mg per capsule of GLA. However, in order to produce a therapeutic benefit, 6–12 capsules of EPO (4–8 g) have been needed in studies (both human and animal) for treating autoimmune disorders. Patients with scleroderma who took 1g per day of EPO had clinical benefits, including pain relief, improved skin texture, and ulcers healing. The authors of this study suggest that 6 g per day may offer greater benefit in patients with scleroderma.[45]

Borage (*Borago officinalis*) oil capsules supply 240 mg of GLA per capsule thereby reducing the number of capsules a patient needs to take to gain therapeutic benefit. GLA supplementation for patients with RA has produced reduced inflammation of joints, with better results at higher intakes (1.4 g versus 2.4 g).[35]

Similar intakes of GLA for patients with MS have produced improvements in hand-grip strength.[36] Theoretically, one may be able to obtain similar results by lowering the fat content of the diet and using lower doses of GLA. Some practitioners recommend using both fish oil and GLA supplementation.

Antioxidants

Patients who are chronically ill with autoimmune disease have consistently higher levels of oxidative stress and lower levels of antioxidants. However, studies have generally examined the effects of one antioxidant at a time on disease progression. The problem that arises with this type of research is that, unfortunately, supplementation with just one antioxidant can potentially induce oxidative stress.

For example, because vitamin E is a polyunsaturated fat, if given alone, it could potentially oxidize. When given concomitantly with vitamin C to a patient, the ascorbic acid will prevent vitamin E oxidation and regenerate vitamin E in the body. Studies have shown that vitamin E may be beneficial for patients with SLE and DL, producing complete clearing of lesions and/or clinical remission at very high doses of 800–1600 international units (IU).[37] The vitamin may also reduce symptoms associated with scleroderma and Raynaud's syndrome.[37–39] Case reports on vitamin E use have described clearing of scleroderma lesions and reductions of RA symptoms. Similar doses of the vitamin produced these results.[38,39]

High-dose vitamin A (more 100,000 IU per day) or etritinate may significantly reduce psoriasis symptoms. However patients must be monitored for potential side-effects and toxicity, such as headaches and elevated results in liver-function tests.[40]

It is possible that conducting studies with multiple antioxidants along with other nutrients may yield better results. For example, as mentioned earlier, vitamin C can regenerate vitamin E and protect it from oxidation. In addition, antioxidants such as vitamin E help to protect polyunsaturated fatty acids from fish oil, EPO, or borage oil from being oxidized.

What is surprising is that, while excellent results were achieved using vitamin E supplementation to treat patients with SLE, DL, and scleroderma, there is a surprising lack of studies that have used vitamin E to treat patients who have MS, except for just a few studies that combined selenium, vitamin C, and vitamin E.[41]

With regard to using each antioxidant individually, it is equally surprising that, when great results were obtained for a particular autoimmune disease, they were not necessarily repeated for another disease.

It would be prudent to administer all major antioxidants to patients who have autoimmune disease because of the synergistic effects of these supplements, their role in modulating essential fatty acid (EFA) metabolism to favor the production of anti-inflammatory prostaglandins (which is why they work

As is the case with antioxidants, B vitamins do not operate in a vacuum but rather are synergistic.

well with EFA supplements), and their ability to quench free radicals and prevent organ and cellular damage.

B Vitamins

A number of B-vitamins have been the focus of research on different autoimmune diseases. In general, this research has shown that some B-vitamin deficiencies have been associated with autoimmune disorders and that therapy with certain B vitamins appears to reduce the symptoms of autoimmune disease.[41]

For example, one study suggests that a vitamin B_6 deficiency may predispose a person to develop MS.[42] In another study, 2 g of pantothenic acid significantly decreased stiffness and degree of disability and pain in patients with RA.[43] In yet another study, 67 patients with SLE and DL received 10–15 g per day of a pantothenic-acid supplement along with 1000–1200 mg of vitamin E for 7–19 months. All of the subjects showed marked reductions of symptoms and relapse rates for the duration of the study. Only transient gastric distress was reported as a side-effect.[44]

There have been several human studies that demonstrated the effectiveness of high-dose para-aminobenzoic acid (PABA) supplementation (Potaba). The researchers administered 12 g per day to patients with scleroderma. In a retrospective study, analyses were made of the records of 390 patients, 224 of whom were taking Potaba for extended periods of time—as long as 10 years. The researchers found that 90 percent of the 224 patients treated with Potaba experienced mild, moderate, or marked skin softening with a significant difference noted between the patients who did not take Potaba.[47] Some patients reported side-effects such as skin rashes, anorexia, nausea, and fever; liver toxicity was rarely reported.[15,47] In light of these results, patients who are given high-dose PABA should be monitored for these side-effects.

In a follow up study, of patients who were maintained on Potaba therapy, 81.4 percent survived 5 years from diagnosis and 69.4 percent survived 10 years from diagnosis.[47] While these results are outstanding, and side-effects are still minimal compared to other standard forms of therapy, it remains a mystery as to why this therapy is not utilized by physicians.

The B-vitamin research has also followed the "magic bullet" protocol of generally researching only one particular B-vitamin at a time. But, as is the case with antioxidants, B vitamins do not operate in a vacuum but rather are synergistic. The synergy in these vitamins is the result of their being coenzymes that modulate EFA metabolism and neurotransmitter metabolism. The B vitamins also participate in the Kreb's cycle to produce adenosine triphosphate.

Conclusion

According to what is currently known, dietary interventions, omega-3 and omega-6 fatty acids, antioxidants, and B-vitamins can be helpful for treating patients with autoimmune disorders. These interventions can slow the progression of disease and extend clinical remission in some cases. In others, these treatments can relieve symptoms, thus, reducing the need for (or doses of) of pharmaceutical agents.

In addition, being that mercury is a known neurotoxin, removal of such amalgams may be beneficial to patients with autoimmune disorders. DHEA and melatonin may also be helpful for such patients; however, closer monitoring of blood, salivary, or urinary levels of these hormones is imperative during hormonal therapy.

None of these interventions require that a patient stop conventional therapy, making them ideal. Many of the study outcomes are as good as—or better than—many conventional therapies for autoimmune disease. What appears to make them superior, is their apparent lack of serious side-effects. More research is needed to determine which combination therapies are the most effective for specific types of autoimmune diseases. In the meantime, many practitioners can combine interventions with the hope of achieving maximum results. □

References

1. Anonymous. Fractures in adults on systemic steroid therapy. *Prescrire Int* 8(43):153–156, 1999.

2. Anonymous. Pain medicine—the dangers of acetominophen. *Harvard Health Lett* 26(9):6, 2001.

3. Greenstein, B.D. Lupus: Why women? *J Women's Health Gender Based Med* 10(3):233–239. 2001.

4. Meier, C.R., Sturkenboom, M.C., Cohen, A.S., et al. Postmenopausal estrogen replacement therapy and the risk of developing systemic lupus erythematosus or discoid lupus. *J Rheumatol* 25(8):1515–1519, 1998.

5. Petri, M. Exogenous estrogen in systemic lupus erythematosus: Oral contraceptives and hormone replacement therapy. *Lupus* 10(3):222–226, 2001.

6. Sanchez-Guerro, J., Liang, M.H., Karlson, E.W., et al. Postmenopausal estrogen therapy and the risk for developing systemic lupus erythematosus. *Ann Int Med* 122(6):430–433, 1995.

7. Rao, T., Richardson, B. Environmentally induced autoimmune diseases: Potential mechanisms. *Environ Health Perspect* Suppl.5:737–742, 1999.

8. Krebs-Smith, S.M., Cook, A., Subar, A.F., et al. U.S. adults fruit and vegetable intakes,

1989–1991: A revised baseline for the Healthy People 2000 objective. *Am J Public Health* 85(12):1623–1629, 1995.
9. Albertson, A.M., Tobelmann, R.C. Consumption of grain and whole-grain foods by American population during the years 1990–1992. *J Am Diet Assn* 95(6):703–704, 1995.
10. Chang, Y.C., Riby, J. et al. Cytostatic and antiestrogenic effects of 2-(indolyl-3-methyl)3',3'-diindolylmethane, a major in vivo product of dietary indole-3-carbinol. *Biochem Pharmacol* 58(5):825–834, 1999.
11. Nagata, C., Kabuto, M., Durisu, Y., et al. Decreased serum estradiol concentration associated with high dietary intakes of soy products in premenopausal Japanese women. *Nutr Cancer* 29(3):228–233, 1997.
12. Cutolo, M. Sex hormone adjuvant therapy in rheumatoid arthritis. *Rheum Dis Clin North Am* 26(4):881–895, 2000.
13. Van Vollenhoven, R.F., Park, J.L., Genovese, M.C., et al. A double-blind, placebo-controlled, clinical trial of dehydroepiandrosterone in severe systemic lupus erythematosus. *Lupus* 8(3):181–187, 1999.
14. Sandyk, R. Diurnal variation in vision and relations to circadian melatonin secretion in multiple sclerosis. *Int J Neurosci* 83(1–2):1–6, 1995.
15. Bagenstose, L.M., Salgame, P., Monestier, M. Murine mercury-induced autoimmunity: A model of chemically related autoimmunity in humans. *Immunol Res* 20(1):67–78, 1999.
16. Craelium, W. Comparative epidemiology of multiple sclerosis and dental carries. *J Epidemiol Comm Health* 32:155–165, 1972.
17. McGrother, C.W., Dugmore, C., Phillips, M.J., et al. Multiple sclerosis, dental carries and fillings: A case control study. *Br Dent J* 187(5):261–264, 1999.
18. Corman, L.C. The role of diet in animal models of systemic lupus erythematosus: Possible implications for human lupus. *Semin Arthritis Rheum* 15(1):61–69, 1985.
19. Swank, R.L., Dugan, B.B. Effect of low saturated fat diet in early and late cases of multiple sclerosis. *Lancet* 336:37–39, 1990.
20. Swank, R.L., Grimsgaard, A. Multiple sclerosis: The lipid relationship. *Am J Clin Nutr* 48:1387–1393, 1988.
21. Lucas, C., Power, L. Dietary fat aggravates active rheumatoid arthritis. *Clin Res* 29(4):754, 1981.
22. Muller, H., de Toledo, F.W., Resch, K.L. Fasting followed by vegetarian diet in patients with rheumatoid arthritis: A systematic review. *Scand J Rheumatol* 30(1):1–10, 2001.
23. Lithell, H., Bruce, A., Gustafsson, I.B., et al. A fasting and vegetarian diet treatment trial on chronic inflammatory disorders. *Acta Derm Venereol* 65(5):397–403, 1983.
24. Finn, R.A. Serum IgG antibodies to gliadin and other dietary antigens in adults with atopic eczema. *Clin Exp Dermatol* 10(3):222–228, 1985.
25. Leonard, J., Haffenden, G., Tucker, W., et al. Gluten challenge in dermatitis herpetiformis. *N Engl J Med* 308(14):816–819, 1983.
26. Jaeger, C., Hatziagelaki, E., Petzoldt, R. et al. Comparative analysis of organ specific autoantibodies and celiac disease–associated antibodies in type 1 diabetic patients, their first-degree relatives and healthy control subjects. *Diabetes Care* 24(1):27–32, 2001.
27. Curtis, W.B., Schuman, B.M., Griffin, J.W. Association of gluten-sensitive enteropathy and Crohn's colitis. *Am J Gastroenterol* 87(11):1634–1637, 1992.
28. Agranoff, B., Goldberg, D. Diet and the geographical distribution of multiple sclerosis. *Lancet* ii:1061–1066, 1974
29. Carr, R.I., Wold, R.T., Farr, R.S. Antibodies to bovine gamma globulin (BCG) and the occurrence of a BCG-like substance in systemic lupus erythematosus sera. *J Allergy Clin Immunol* 50(1):18–30, 1972.
30. Clark, W.F., Parbtani, A. Omega-3 fatty acid supplementation in clinical and experimental lupus. *Am J Kidney Dis* 23(5):644–647, 1994.
31. Nordvik, I., Myhr, K.M., Nyland, H. et al. Effect of dietary advice and n-3 supplementation in newly diagnosed multiple sclerosis patients. *Acta Neurol Scand* 102(3):143–149, 2000.
32. Kremer, J.M. N-3 fatty acid supplements in rheumatoid arthritis. *Am J Clin Nutr* 71(suppl.1):349–351, 2000.
33. Belluzi, A., Brignola, C., Campieri, M., et al. Effect of an enteric-coated fish oil preparation on relapses in Crohn's disease. *N Engl J Med* 334(24):1557–1560, 1996.
34. Kojima, T., Terano, T., Tanabe, E. et al. Long-term administration of highly purified eicosapentaenoic acid provides improvement of psoriasis. *Dermatologica* 182(4):225–230, 1991.
35. Belch, J.J., Hill, A. Evening primrose oil and borage oil in rheumatologic conditions. *Am J Clin Nutr* 71(suppl.1): 352–356, 2000.
36. Simpson, L.O. Dietary supplementation with Efamol and multiple sclerosis. *NZ Med J* 98(792):1053–1054, 1985.
37. Ayres, S., Mihan, R. Is vitamin E involved in the autoimmune mechanism? *Cutis* 21:321–325, 1978.
38. Darlington, L.G., Stone, T.W. Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. *Br J Nutr* 85(3):251–269, 2001.
39. Ayres S. Raynaud's phenomenon, scleroderma and calinosis cutis: Response to vitamin E. *Cutis* 11:54–62, 1973.
40. Kaplan, R.P. Etretinate therapy for psoriasis: Clinical responses, remission time, epidermal DNA and polyamine response. *J Am Acad Dermatol* 8(1):95–102, 1983.
41. Klenner, F.R. Response of peripheral and central nerve pathology to mega-doses of the vitamin B-complex and other metabolites. *J Appl Nutr* 25:16–40, 1973.
42. Mitchell, D.A., Schandl, E.K. Carbon monoxide, vitamin B_6 and multiple sclerosis—a theory of interrelationship. *Am J Clin Nutr* 26(8):890–896. 1973.
43. Anonymous. Calcium pantothenate in arthritic conditions: A report from the General Practitioner Research Group. *Practitioner* 224:208–211, 1980.
44. Welsh, A.L. Lupus erythematosus: Treatment by combined use of massive amounts of pantothenic acid and vitamin E. *Arch Dermatol Syphilol* 70:181–198, 1954.
45. Strong, A.M., Campbell, A., Thompson, J. The effect of oral linoleic acid and gamma-linolenic acid (Efamol). *Br J Clin Pract* 39(11–12):444–445, 1985.
46. Zarafonetis, C.J., Dabich, L., Skowronski, J.J., et al. Retrospective studies in scleroderma: Skin response to potassium para-aminobenzoate therapy. *Clin Exp Rheumatol* 6(3):261–268, 1988.
47. Zarafonetis, C.J., Dabich, L., Negri, D., et al. Retrospective studies in scleroderma: Effect of potassium para-aminobenzoate on survival. *J Clin Epidemiol* 41(2):193–205, 1988.

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