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## Andrographis and Upper Respiratory Tract Infection

By Mary Scanlon-O'Kelly, MD, and Benjamin Kligler, MD, MPH

BOTANICAL MEDICINES ARE BECOMING INCREASINGLY POPULAR among the public for the treatment of uncomplicated infection, including upper respiratory tract infections (URTIs) such as the common cold.

*Andrographis paniculata* is a shrub indigenous to India and other Asiatic countries. Also known as andrographolide and Indian echinacea, it has been used during epidemics, including the Indian flu epidemic of 1919, in which a tincture of andrographis was credited with arresting the spread of disease.<sup>1</sup> It also has been employed in the treatment of malaria,<sup>2</sup> snake bites,<sup>3</sup> fever, toxic hepatic injury, the common cold, and pharyngotonsillitis, among others.<sup>4</sup>

Over the last two decades, andrographis has been commonly used as an herbal medicinal product in Scandinavia for the treatment of colds. The most widely used product is Kan Jang, a standardized extract from *Andrographis paniculata* and *Eleutherococcus senticosus*.<sup>5</sup> Kan Jang is manufactured by the Swedish Herbal Institute and is standardized to contain 4-5.6 mg of andrographolide.<sup>6</sup> Of note is the fact that isolated andrographolide does not appear to affect the immune system to the same extent as the whole plant extract.

Andrographis is now available in the United States and, as discussed below, there is reasonably good evidence that it can reduce the severity of cold symptoms; in addition, it also may help prevent colds.

### Mechanism of Action

Although the mechanism of action of andrographis is unknown, preliminary evidence suggests that it may stimulate immune function, specifically by increasing antibody activity and phagocytosis by macrophages.<sup>7</sup> The active ingredients are thought to be lactones, especially andrographolide, dehydroandrographolide, neoandrographolide, and deoxyandrographolide.<sup>1</sup>

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## Clinical Applications: Animal Studies

Although the focus of this article is on the use of andrographis for URTI, there are interesting preliminary data from animal research on a number of other potential applications of this herb. For example, animal studies suggest a possible role for andrographis as an agent that may help prevent heart disease.<sup>2,3</sup> In addition, preliminary studies suggest that andrographis may help protect the liver from toxic injury.<sup>8,9</sup> In rats and guinea pigs, andrographis appears to stimulate gallbladder contraction.<sup>10</sup> It is noteworthy that andrographis does not appear to have any antibacterial properties.<sup>11</sup>

## Clinical Studies: Andrographis for URTI

Although andrographis is used for a wide variety of indications in Ayurvedic and herbal medicines, to date clinical effectiveness in humans has been documented only for the common cold. Most of the trials have examined Kan Jang, which contains both andrographis and eleutherooccus; thus, at this point it is difficult to draw definitive conclusions about the efficacy of andrographis as a solitary preparation. Nevertheless, the combination product does appear to be quite effective in reducing both severity and duration of URTI.

**Symptom Reduction.** When used as an oral preparation for the common cold, andrographis seems to improve symptoms significantly when started within 72 hours of the onset of symptoms. Some improvement can be seen after two days of treatment, but it typically takes 4-5 days before there is maximal symptom relief.<sup>1,6,12</sup>

Three double-blind, placebo-controlled studies, enrolling about 400 people have evaluated either the combination remedy Kan Jang or andrographis extract alone. For example, a five-day, double-blind, parallel-group, placebo-controlled trial of 185 adults with acute URTIs, including sinusitis, found that treatment with Kan Jang reduced cold symptoms and also relieved the inflammatory symptoms of sinusitis.<sup>5</sup>

A second trial compared andrographis extract to paracetamol (acetaminophen). In this study, 142 adults with sore throat and fever were randomized to receive low-dose andrographis (3 g daily), high-dose andrographis (6 g daily), or paracetamol (3.9 g daily).<sup>13</sup> Symptoms were similar in all three groups at baseline. The higher dose of andrographis (6 g) decreased symptoms of fever and throat pain to about the same extent as paracetamol after three days of treatment, whereas the lower dose of andrographis (3 g) was not as effective. There were no significant side effects in either group.

**URTI Prevention.** When used orally for prevention of the common cold, there is some evidence that andrographis can decrease the relative risk of developing a cold by approximately 50%. However, this beneficial effect does not seem to occur until after two months of continuous treatment, and it is unclear how long this benefit lasts.

Preventive treatment with Kan Jang in one double-blind, placebo-controlled study of 107 students reduced the risk of catching a cold by a factor of 2 as compared to placebo.<sup>6</sup> Fifty-four students took two 100-mg tablets standardized to 5.6% andrographolide daily—considerably less than the 1,200-6,000 mg per day that has been used in studies on treatment of colds. The other 53 students were given placebo tablets with a coating identical to the treatment. Then, once a week throughout the study, a clinician evaluated all the participants for cold symptoms. In the third month of treatment, only 16 people in the group using andrographis had experienced colds, compared to 33 of the placebo-group participants. This difference was statistically significant ( $P < 0.05$ ).

## Safety Issues

Andrographis extract used in Kan Jang was tested in acute, subacute, reproductive, and toxicological studies without encountering toxic effects. In one study,

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participants were monitored for changes in liver function, blood counts, kidney function, and other laboratory measures of toxicity. No problems were detected.<sup>1</sup>

Contraindications include hypersensitivity to andrographis and pregnancy.<sup>14</sup> Safety in young children, nursing women, or individuals with kidney or liver disease has not been established. Also, because andrographis may stimulate gallbladder contraction, it would be prudent to avoid use in patients with gallbladder disease.

Some animal studies have raised concerns about fertility; however, the results are equivocal and thus no useful conclusions can be drawn.

Finally, based on a single recent study in HIV-positive adults, andrographis may potentially increase viral replication rates.<sup>15</sup> In addition, a universal immune booster like andrographis has the potential, theoretically, to exacerbate autoimmune disease.

### Dosage

Dosing of herbal preparations varies and is dependent on factors such as growing and harvesting conditions, plant parts, and extraction methods. A typical dosage of andrographis is 400 mg three times a day for the common cold. Doses as high as 1,000-2,000 mg three times daily have been used in studies of pharyngotonsillitis. Andrographis usually is standardized to andrographolide content, typically 4-6% as is found in Kan Jang.

### Conclusion

Andrographis is used primarily as an overall tonic in Ayurvedic medicine and also has been used as a cold remedy for many years in Sweden. Patients generally tolerate andrographis without ill effects when taken at the recommended doses. The literature supports its use as a safe, effective herb for alleviating symptoms associated with the common cold, and possibly for prevention of URTI as well.

### Recommendation

Given its favorable safety profile and reasonable evidence of efficacy, clinicians can consider recommending andrographis at a dose of 400 mg three times daily for patients presenting with URTI. For patients who experience frequent URTI, a three-month trial of andrographis extract for prevention could be considered. This herb should be avoided in pregnancy, and probably also in patients with HIV infection. ♦

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# Age-Related Macular Degeneration and Nutrition

By Lynn Keegan, RN, PhD, HNC, FAAN

MACULAR DEGENERATION (MD), ALSO TERMED AGE-related macular degeneration (ARMD), is the leading cause of deteriorating vision and blindness in people older than age 60 in the United States. It affects 25-30 million people worldwide. As Americans age, the incidence rate is expected to triple by 2025.<sup>1</sup>

## Signs, Symptoms, and Disease Process

Macular degeneration begins with the loss of central vision. There are several theories used to explain the origin and progression of the disease process. The simplest theory is that in individuals who are susceptible on the basis of pre-existing genetic, environmental, or metabolic conditions, light entering the eye sets up a process of rapid oxidation that destroys the pigment of the retinal cells, and the resulting buildup of debris causes damage to vision. Table 1 lists the most common risk factors for ARMD.

Common changes as normal eyes age include: changes in color perception, floaters, dry or burning eyes, and/or difficulty adjusting to changes in light. Early symptoms of ARMD include difficulty reading print because the pages appear to be distorted in the center, difficulty recognizing familiar faces, problems with depth perception, and difficulty finding personal objects even in a familiar environment. There are two types of ARMD, wet and dry, with the less severe, slower-progressing, dry-type occurring 85-90% of the time.<sup>1</sup>

Symptoms of macular degeneration can be mistaken for psychiatric disease. Charles Bonnett syndrome, manifested by visual hallucinations such as purple flowers on khaki pants or little girls in white dress playing in the yard, may occur in 10% of ARMD patients.<sup>1</sup> Also, some ARMD patients may be labeled as having early dementia because of the inability to recognize familiar faces.

The physical findings include drusen on the retina. Drusen are small yellow deposits that contain complex lipids, fatty wastes of the photoreceptor cells, and calcium. Drusen are used as markers for ARMD, but their presence alone does not indicate that the patient has ARMD.

Epidemiological studies of dietary, environmental, and behavioral risk factors suggest that oxidative stress is a contributing factor to ARMD. Pathology studies indicate that damage to the retinal pigment epithelium

**Table 1**  
**Risk factors for ARMD**

- Age older than 55 years
- Fair skinned with blond hair and blue or green eyes
- History of smoking
- Previous excessive exposure to ultraviolet light
- Farsighted vision
- Certain diseases
  - High blood pressure
  - Diabetes
  - Cardiovascular problems
- Family history of ARMD
- Genetic abnormalities
- Environmental factors including food additives and car exhaust

(RPE) is an early event in ARMD. In vitro studies show that oxidant-treated RPE cells undergo apoptosis, a possible mechanism by which RPE cells are lost during the early phase of ARMD.<sup>2</sup>

## Dietary Phytochemicals, Minerals, and Macular Degeneration

At one time, researchers believed that all antioxidants served the same function. Now there is evidence that individual antioxidants may be used by the body for specific purposes. Lutein and zeaxanthin, naturally occurring fat-soluble antioxidant carotenoid biochemicals that are found in green leafy vegetables such as spinach, kale, collard greens, romaine lettuce, leeks, and peas, have been found to be helpful in preventing the progression of ARMD.

Lutein is the primary carotenoid in the retina of humans. Lutein in the retina acts to filter and shield harmful blue light from the eye and protect against ARMD. One study indicated that adults with the highest dietary intake of lutein had a 57% decreased risk of macular degeneration compared to those with the lowest intake. The roles played by zinc and copper also will be explored in this article.

## Animal Studies

Research into the mechanisms underlying the development of ARMD has been limited by the lack of animal models for this disease. Studies have been done assessing the severity of macular drusen in elderly rhesus monkeys and comparing these findings to circulating levels of select components of the free radical defense system and levels of thiobarbituric acid reactive substances (TBARS), the latter being a measure of lipid

peroxidase activity. The monkeys with the most severe drusen were found to have alterations in the enzymes associated with copper and had higher plasma levels of TBARS. This research supports the concept that excessive oxidative lipid damage contributes to ARMD.<sup>3</sup>

The role of copper in the development of ARMD is not entirely clear. Copper is a promoter of angiogenesis, a process that appears to play a prominent role in ARMD.<sup>4</sup> Studies have been undertaken utilizing agents that block copper to see if this can prevent the neovascularization prominent in some ARMD.<sup>5</sup> In the neovascular form of ARMD, extensive studies are being undertaken to elucidate the growth factors underlying the progression of the disease.<sup>6</sup> Several approaches are being developed in animal models to prevent ocular angiogenesis by blocking the key steps in the angiogenic cascade.<sup>7</sup>

As noted above, the xanthophyll carotenoids (lutein and zeaxanthin) are hypothesized to delay the progression of ARMD. An investigation on quail determined that diets enriched with zeaxanthin could alter zeaxanthin or lutein concentrations in the retina, serum, liver, and fat tissues. Xanthophyll profiles in quail mimic those in primates. Thus, the quail is a good animal model for further exploration of factors regulating delivery of dietary carotenoids to the retina.<sup>8</sup>

### Genetic Factors

A number of specific genetic abnormalities recently have been described. The phenotype of a premature form of autosomal dominant macular degeneration has been characterized. This disease is manifested by a spectrum of retinal pigment epithelium (RPE) changes from mild to marked atrophy. Drusen-like deposits are present and subretinal neovascular membrane is an established complication. The locus for this disease has been found on chromosome 5.<sup>9</sup>

A study from the University of Michigan's Kellogg Eye Center demonstrated a relationship between gene mutations on the X chromosome and MD. The mutation (Tyr141Cys) is a gene called RDS that causes an inherited eye disease that mimics MD. The suspicion is that some individuals with ARMD might also harbor the RDS mutation.<sup>10</sup>

A recent ground-breaking discovery confirms not only the association of genetic abnormalities of ARMD, but in a large family also confirmed the age-related penetrance of the disease.<sup>11</sup>

### Human Studies

In an effort to explore the pathogenesis of ARMD to facilitate early detection and prevention, scientists in

China studied the enzymes in red blood cells and levels of serum minerals and antiretinal antibodies in ARMD patients, and in controls, comparing electron microscopy and immunohistochemical surveys of the ARMD sub-retinal neovascular membrane. Their findings showed that the levels of superoxide dismutase and catalase as well as serum zinc were decreased in ARMD patients, and that the ratio of copper to zinc was increased.<sup>12</sup>

Oxidation of lipids, nucleic acids, or proteins has been suggested to be involved in the etiology of several chronic diseases including ARMD, and even aging in general. A large body of research has investigated the potential role of antioxidant nutrients in the prevention of chronic diseases.<sup>13</sup> Among the supplements studied has been zinc because of its effect as a catalyst in multiple enzymatic processes. Extensive research as part of the Age-Related Eye Disease Study (AREDS) found no difference between the baseline dietary zinc intake of the general population as compared with the intake of those with AREDS.<sup>14</sup>

A study conducted in Alberta, Canada, reported significant reduction in the progression of certain categories of ARMD with the use of high-dose antioxidant and zinc supplementation. Recommendations were that people not taking in adequate amounts of beta-carotene, vitamins C and E, and zinc be counseled to better meet recommended dosages by using some combination of currently available over-the-counter supplements: ICAPS, TR, Ocuvite, and Vitalux, as well as Centrum multivitamins and individual supplements.<sup>15</sup>

On the other hand, a population-based cohort study in Australia found no association between baseline intake of antioxidant vitamins and zinc (apart from vitamin C) and the five-year incidence of early ARMD.<sup>16</sup> Taken together, most of these studies suggest that although the baseline plasma levels of ARMD and normal patients may be identical, the ARMD patient, who is genetically or environmentally susceptible to the disease, is likely benefited in preventing further deterioration of ARMD by the use of antioxidant and mineral supplements, especially zinc.

One Dutch study found the prevalence of ARMD in patients with low antioxidant and lutein intake to be approximately twice as high as that in patients with high intakes.<sup>17</sup> An Italian investigation found that a deficiency of antioxidants (vitamins C and E and carotenoids) seems to be associated with ARMD, particularly in the advanced form.<sup>18</sup>

The classic study that awakened interest in the possible contribution of nutrient deficiencies to this condition evaluated the relationships between dietary intake of carotenoids and vitamins A, C, and E and the risk of

ARMD.<sup>19</sup> At five ophthalmology centers in the United States a total of 356 subjects, ages 55-80 years, who were diagnosed with the advanced stage of ARMD within one year prior to their enrollment were studied. The 520 control subjects had other ocular diseases, and were frequency-matched to cases according to age and sex. The relative risk for ARMD was estimated according to dietary indicators of antioxidant status, controlling for smoking and other risk factors. Analysis found that higher dietary intake of carotenoids was associated with a lower risk for ARMD. Adjusting for other risk factors for ARMD, those in the highest quintile of carotenoid intake had a 43% lower risk for ARMD compared with those in the lowest quintile.

Among the specific carotenoids, lutein and zeaxanthin, which are primarily obtained from dark green, leafy vegetables, were most strongly associated with a reduced risk for ARMD. Several food items rich in carotenoids were inversely associated with ARMD. In particular, a higher frequency of intake of spinach or collard greens was associated with a substantially lower risk for ARMD. The intake of preformed vitamin A (retinol) was not appreciably related to ARMD. Neither vitamin E nor total vitamin C consumption was associated with a statistically significant reduced risk for ARMD, although a trend toward a lower risk for ARMD was identified among those with higher intakes of vitamin C, particularly from foods.

Inverse associations have been reported between the incidence of advanced, neovascular ARMD, the combined intake of dietary lutein and zeaxanthin, and lutein and zeaxanthin concentration in the blood serum. Research data suggest that people with high levels of lutein and zeaxanthin in either the diet or serum would likely have, in addition, relatively high densities of these carotenoids in the macula (the central area of the retina), the so-called "macular pigment." Several lines of evidence point to a potential protective effect by the macular pigment against ARMD.<sup>20</sup>

One study examined the relationship between dietary intake of lutein and zeaxanthin using a food-frequency questionnaire, concentration of lutein and zeaxanthin in the serum, and macular pigment optical density. The researchers also analyzed the serum and retinas from 23 tissue donors in order to obtain the concentration of lutein and zeaxanthin in these tissues. The results reveal positive, albeit weak, associations between dietary intake of lutein and zeaxanthin and serum concentrations of lutein and zeaxanthin, and between serum concentrations of lutein and zeaxanthin and macular pigment density. The authors estimated that approximately one-half of the variability in the subjects' serum concen-

tration of lutein and zeaxanthin can be explained by their dietary intake of lutein and zeaxanthin, and about one-third of the variability in their macular pigment density can be attributed to their serum concentrations of lutein and zeaxanthin. These results, together with the reported associations between risk of ARMD and dietary and serum lutein and zeaxanthin, support the hypothesis that low concentrations of macular pigment may be associated with an increased risk of ARMD.<sup>20</sup>

A Japanese study evaluated the relationship between fatty acids and ARMD. Findings indicate that polyunsaturated fatty acids, vulnerable to free radicals and reactive oxygen species and easily peroxidized, may be related to ARMD induction.<sup>21</sup>

Another study assessed whether dietary intake of fat or fish is associated with age-related maculopathy (ARM) prevalence.<sup>22</sup> People (n = 3,654) ages 49 years or older with ARM were identified from masked grading of retinal photographs. A self-administered, semi-quantitative food-frequency questionnaire was completed adequately by 88.8% of participants and used to assess dietary intakes of fat and fish. A higher frequency of fish consumption was associated with decreased risk of late ARM. Subjects with higher energy-adjusted intakes of cholesterol were significantly more likely to have late ARM. Thus, the amount and type of dietary fat intake may be associated with ARM.

Yet another study used a large cross-sectional survey to evaluate the association between dietary fat and ARMD, and found that ARMD was not significantly associated with dietary fat.<sup>23</sup>

### Mechanism of Action

The RPE is a monolayer of cuboidal cells that is strategically placed between the rod and cone photoreceptors and the vascular bed of the choriocapillaris. The RPE has many important functions, including phagocytic uptake and breakdown of the sloughed photoreceptor membranes. The RPE also is responsible for the uptake, processing, transport, and release of vitamin A (retinol), and setting up the ion gradients within the interphotoreceptor matrix. In addition, the RPE acts as the blood-retina barrier and provides all transport of substances from blood to the retina and vice versa. The RPE contains pigment granules that seem to be involved in many important functions, such as protection from oxidative stress, detoxification of peroxides, and binding of zinc and drugs.

Recent research shows that melanin granules are connected to the lysosomal degradation pathway. Deficiency of melanin pigment is associated with ARMD.<sup>24</sup> Studies have tested the hypothesis that neovascular-related

**Table 2****Dietary sources of zinc**

Food Source	Portion	Amount of Zinc
Organ meats	3 oz	5.1 mg
Lean lamb meat	3 oz	4.3 mg
Lean ground beef	3 oz	3.8 mg
Dark chicken/turkey meat	3 oz	3.0 mg
Pumpkin seeds	1/4 C	2.6 mg
Sunflower seeds	1/2 C	2.0 mg
Swiss cheese	2 oz	2.2 mg

ARMD is directly associated with oxidative stress involving the macular RPE. In one study, whole surgically removed eyes were studied with a variety of techniques including electron microscopy, immunological studies, and quantitation of enzymes thought to protect from oxidative stress. The authors found that copper and zinc superoxide dismutase immunoreactivity (an immunological measurement of enzyme activity) increased and catalase decreased with age in the cytoplasm and lysosomes from both macular RPE of normal eyes and eyes with ARMD. Both heme oxygenase-1 (HOG1) and heme oxygenase-2 (HOG2) had a highly significant greater immunoreactivity in the RPE cell lysosomes that decreased with age, especially in patients with RPE. The authors concluded that the high HOG1 and HOG2 lysosomal enzyme antigen levels in macular RPE cells of eyes with neovascular ARMD represented an upregulation of these enzymes in response to oxidative stress, and that the protective mechanism of enzymatic upregulation diminished with age. The much higher HOG1 and HOG2 levels in macular RPE cells from younger individuals confirm that the protective mechanisms against oxidation, and consequentially the development of ARMD, decreases with age.<sup>25</sup>

As briefly mentioned above, the body responds to oxidative damage by producing new blood vessels (neovascularization) under the effect of vascular endothelial growth factor (VEGF), leading to further damage. There are studies currently under way evaluating anti-VEGF substances (antibodies and oligonucleotides) in the prevention of the neovascular damage.<sup>26</sup>

All of these studies emphasize the importance of optimizing antioxidant protection during the process of aging well before the onset of neovascularization.

**Conclusion**

The impact of positive dietary changes has profound consequences for optimizing health and well being for the mature years. It appears that increasing the con-

**Table 3****Dietary measures to prevent or delay development of macular degeneration**

- Eat lots of dark green leafy vegetables and red and yellow peppers.
- Eliminate foods containing trans-fatty acids such as commercial hamburgers and fries.
- Decrease intake of omega-6 fatty acids found in some processed foods and vegetable oils.
- Increase dietary intake of omega-3 fatty acids by consuming fish and fish oils.

sumption of foods rich in certain carotenoids, in particular dark green, leafy vegetables, may decrease the risk of developing advanced or exudative ARMD, the most visually disabling form of macular degeneration among older people. The role of the antioxidants lutein and zeaxanthin (as well as vitamins A, C, and E) in the prevention of ARMD support the almost universal dietary guideline to maximize intake of fruits and vegetables. Future dietary guidelines for the elderly need to take into account protective food patterns, rather than target specific foods.<sup>27</sup> Presently, there is little chance of reversing ARMD, but recent advances in the areas of early detection and nutritional intervention, including proprietary supplements containing zinc (*see Table 2 for food sources of zinc*), may slow the progression of ARMD.

**Dietary Recommendations**

Recent studies indicate that preventive measures and dietary changes implemented early in life can reduce an individual's risk of ARMD (*see Table 3*). There is ample epidemiological evidence that the amount of macular pigment is inversely associated with the incidence of ARMD. Macular pigment can be increased in primates by either increasing the intake of foods that are rich in lutein and zeaxanthin, such as dark green leafy vegetables, or by supplementation with lutein or zeaxanthin.<sup>28</sup>

Structural and clinical studies have shown that these carotenoids are concentrated in the retinal macular pigment and that such accumulation is dependent on dietary intake. Consumption of dark green leafy vegetables has been shown in clinical studies to reduce the risk of ARMD.

Studies indicate that the density of the macular pigment is related to preservation of visual sensitivity and (possibly) protection from ARMD.<sup>29</sup> While lifestyle modifications such as smoking cessation, reduction of

alcohol consumption, and the wearing of sunglasses may reduce the risk of ARMD, it is likely that consumption of specific dietary components (i.e., fruits and vegetables) can reduce the risk further. ♦

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## Fasting for Health

By Dónal P. O'Mathúna, PhD

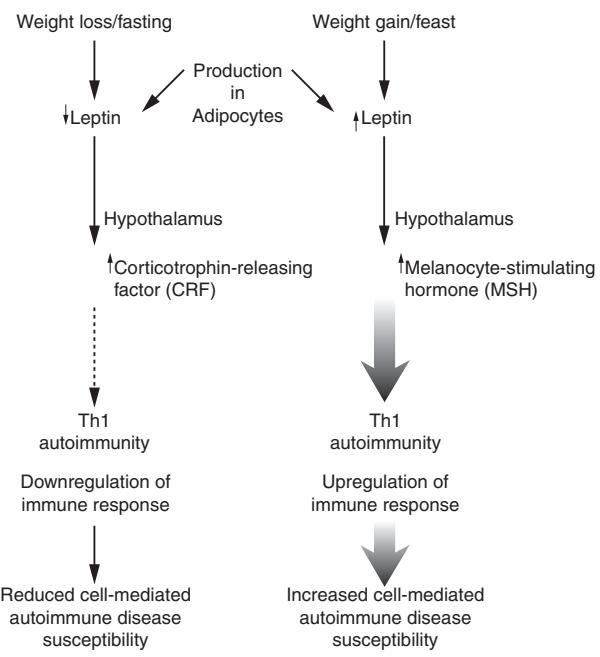
**F**ASTING HAS LONG BEEN ASSOCIATED WITH VARIOUS religious traditions. With recent interest in spirituality and medicine, and the importance of diet being stressed for good health, the role of fasting in promoting health has been receiving attention. While designing controlled studies of any nutritional therapy in disease raises challenges, fasting has been examined in a small number of scientific studies. Although fasting technically means the withholding of all solid food, studies vary in their duration and in what people may consume while fasting. Some fasts require that people consume only water, while others allow limited calorie consumption in the form of juices, usually fresh, natural juices.

### Background

Fasting has been given some credence in health promotion within the naturopathic tradition. Fasting has there retained a role in nutritional therapy to reverse the impact of what is viewed as unhealthy eating patterns. The high-fat, high-sodium diets of developed countries are believed to leave people's palates intolerant to the low-fat, low-sodium foods found in most plant-rich diets.<sup>1</sup> This is believed to underlie the difficulty many people have in sustaining healthier eating patterns. Fasting is then viewed as a form of sensory deprivation, which resensitizes taste nerves, making healthy plant foods more palatable.<sup>1</sup>

However, a completely different proposal recently has been offered for the health effects of fasting. Traditional advice from grandma to "feed a cold" may reflect folk knowledge that immunity and diet are connected.<sup>2</sup> While chronic malnutrition generally impairs the immune system, observations during the 1970s in African refugee camps noted that the incidence of certain infectious diseases increased dramatically when starving people were refed.<sup>3</sup> Fasting has been shown to have a complicated impact on various components of the immune system.<sup>4</sup> This connection has regularly been noted in the context of autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis (MS). How-

**Figure**  
**Fasting and leptin production**



ever, claims that fasting can ease the symptoms of autoimmune diseases generally have been greeted with skepticism—until recent research on leptin.<sup>5</sup>

### Mechanism of Action

Leptin is a hormone produced in human fat cells (and other tissues). It has come to public prominence because of its role in obesity and regulating food intake. Although early research focused on leptin's role in satiety, more recent studies have demonstrated a broader impact on insulin metabolism, reproductive function, response to stress, and the immune system.<sup>6</sup> Leptin has been shown to be a strong regulator of T cells in the immune system.<sup>2</sup> Leptin enhances the activity of T cells that produce cytokines of the type that promote inflammatory reactions.<sup>5</sup> These same T cells are involved in many autoimmune diseases.

In early 2003, research with mice confirmed the proposed role of leptin in autoimmune disease, and gave support to the idea that fasting could ameliorate symptoms of some of these diseases. Mice were given an experimental condition recognized as a model for human MS (abbreviated as EAE).<sup>7</sup> Immediately before the mice developed EAE symptoms, their leptin levels increased. These mice also showed increased levels of pro-inflammatory T cells and cytokines. When similar mice fasted for 48 hours (something known to reduce

leptin levels), EAE symptoms did not develop. Also, in mice that genetically can't produce leptin, EAE did not develop. This elegant set of experiments supported the proposed mechanism of action that fasting reduces leptin production (*see Figure*), which promotes the secretion of anti-inflammatory cytokines and at the same time lowers the production of pro-inflammatory cytokines.<sup>5</sup>

### Clinical Studies

Controlled clinical trials directly examining the role of leptin and fasting in autoimmune diseases have not yet been conducted. The incidence of MS is higher in populations with a higher intake of saturated fat, but the role of nutrition in causing or influencing the disease is unclear.<sup>8</sup> The role of leptin in MS is supported by autopsy findings that genes for leptin and pro-inflammatory cytokines are overly expressed in the brains of MS patients.<sup>9</sup>

Three observational studies in the 1970s and 1980s found that fasting brought relief to rheumatoid arthritis patients.<sup>10</sup> However, as soon as subjects started eating again, symptoms returned to their baseline levels. A subsequent controlled clinical trial was then conducted in which fasting was followed by gradual, controlled reintroduction of various foods. Fifty-three subjects were randomly allocated to either the intervention or control group. The control group stayed at a convalescent home for four weeks, ate normally, and recorded their food intake. The intervention group stayed at a health farm for four weeks, fasting for the first 7-10 days. Natural juices were allowed with subjects ingesting 800-1,260 kJ/d. After fasting, subjects introduced a new food every second day and carefully monitored their arthritis symptoms. If symptoms were exacerbated, the item was excluded from their diet. For 3.5 months, food items were consistent with a gluten-free vegan diet. From 3.5 to 12 months, a lactovegetarian diet was followed.

After four weeks, patients in the intervention group had statistically significant improvements in nine arthritis symptom measurements, grip strength, and a subjective health assessment questionnaire ( $P < 0.05$ ). Patients in the control group had significant improvement in pain scores only. At the end of the study, the intervention group scored significantly better than the control group in all measurements except platelet count and hemoglobin. The researchers originally attributed these findings to food allergies or intolerance, but later proposed that the dietary changes might have caused changes in fecal flora leading to the absorption of different bacterial substances from the intestine.<sup>11</sup> More recent studies have suggested that these clinical results might be related to leptin levels.<sup>5</sup>

A somewhat different area of research has examined the impact of fasting on hypertension. An inpatient clinic enrolled 174 self-referred adults with blood pressure (BP) of at least 140/90 mm Hg (average, 159/89 mm Hg).<sup>12</sup> The treatment protocol involved prefasting (average of 2-3 days consuming only fresh fruit and vegetables), fasting (average of 10-11 days consuming only distilled water), and refeeding (average of 6-7 days introducing a low-fat, low-sodium, vegan diet). During the study, patients also agreed not to smoke or consume alcohol, and to restrict physical activities to avoid side effects. Upon completing the study (ranging from four to 28 days), 89% of the subjects had BP lower than 140/90 mm Hg, averaging 37/13 mm Hg lower than baseline ( $P < 0.05$ ). Follow-up data were collected six months later on 42 of the original 174 subjects. Their average BP was 123/77 mm Hg, although these data are preliminary and the sample was not randomly selected.

The same investigators enrolled another 68 self-referred adults with baseline systolic BP of 120-140 mm Hg and diastolic BP less than 91 mm Hg (average BP, 129/78 mm Hg).<sup>1</sup> The same fasting protocol was used as before, except the group averaged two days of prefasting, 13.6 days water-only fasting, and six days refeeding. At the end of the study, 82% of the patients had BP at or below 120/80 mm Hg (average BP, 109/71 mm Hg), which was statistically significant ( $P < 0.05$ ).

### Adverse Effects

Mild nausea and orthostatic hypotension were reported occasionally in the inpatient studies of hypertension.<sup>1,12</sup> These researchers cautioned that their prolonged water-only fasting regimen should not be undertaken without medical supervision. Physical activities were restricted to minimize the occurrence of orthostatic hypotension, arrhythmia, dehydration, and electrolyte disturbances, which have all been reported during fasting accompanied by unrestricted activity.<sup>12</sup> Patients on the strict gluten-free vegan diet lost upper arm muscle area, a situation not reversed while on the diet, even with consultations from dietitians.<sup>10</sup> However, when these subjects moved to the lactovegetarian phase of the study, this problem was eliminated.

### Conclusion

While fasting is an ancient practice, its health impact has not been subjected to substantial scientific study. Studies examining the role of fasting in treating hypertension used multiple interventions and were not controlled. However, improvements were noted in a substantial majority of the patients. Where fasting may prove to have a more substantial impact involves its

interaction with leptin and the immune system. Although this is a relatively new area of research, it is rapidly expanding. Laboratory and animal studies offer a mechanism of action that suggests how fasting may provide relief for those with a variety of autoimmune diseases. Given that many of these diseases can only be ameliorated with powerful pharmaceuticals, any effective complementary strategies would be welcome.

### Recommendation

For those with hypertension, fasting for a few days may be useful to help kick-start a more healthy diet. However, this should not be done without adequate medical supervision so that the patient's overall health is closely monitored. Those with autoimmune diseases could explore fasting while monitoring the symptoms of their disease. Again, medical supervision would be very useful, both for objective measurement of symptoms and in checking for adverse effects. Although the research evidence is in its very early days, the relative safety of fasting makes it something worth suggesting to select patients. ♦

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## Clinical Briefs

*With Comments from Russell H. Greenfield, MD*

### Electric Blanket Use and Breast Cancer

**Source:** Kabat GC, et al. Electric blanket use and breast cancer on Long Island. *Epidemiology* 2003;14:514-520.

**Goal:** To evaluate the relationship between exposure to low-frequency electromagnetic fields (EMF) and breast cancer risk.

**Design:** Population-based, case-control study performed in two stages—Part I was the Long Island Breast Cancer Study Project (LIBCSP), which focused

primarily on exposure to organochlorines and other environmental pollutants; Part II, the Electromagnetic Fields and Breast Cancer on Long Island Study (EBCLIS), included a subset of LIBCSP participants.

**Subjects:** Women with first breast cancer diagnosed between August 1996 and July 1997 and matched controls were eligible for entry into LIBCSP. Women who were younger than age 75 and had lived in their current homes for more than 15 years (responses from 576/663, 87%, and 585/702, 83%, of available cases and controls, respectively)

were then eligible to participate in EBCLIS.

**Methods:** During the LIBCSP, women were asked to participate in a two-hour comprehensive questionnaire, and to provide blood and urine specimens. Participants in EBCLIS took part in a 30-minute interview administered at their homes that focused on use of electric blankets, exposure to other appliances, and potential occupational EMF exposure. EMF measurements were determined in two rooms of the home as well as at the front door. Later, electrical wiring configuration was diagrammed

from outside the home. Some analyses were stratified according to menopausal status.

**Results:** Analyses of both the LIBCSP and EBCLIS groups showed no association between breast cancer and electric blanket use, frequency of use, duration of use, or other indicators of intense exposure to EMF.

**Conclusion:** Results of this study do not support an association between use of electric blankets and an increased risk of breast cancer.

**Study strengths:** Thorough nature of inquiry into possible EMF exposure from electric blankets; sample size (albeit less than was targeted).

**Study weaknesses:** Inherent limitations of self-reported use of electric blankets; low control of participation rate during

LIBCSP, especially among older women; seasonality not addressed.

**Of note:** Eight prior studies of electric blanket use and breast cancer risk showed either no association at all or a slight association with continuous use throughout the night; electronic blankets purchased before 1989 produce stronger EMF than those purchased at later dates; analysis of household and occupational appliance use in EBCLIS participants has yet to be reported.

**We knew that:** It has been posited that low-frequency EMF may inhibit the normal nocturnal rise in melatonin, thereby leading to increased estrogen levels and greater risk for development of breast cancer (especially in premenopausal women).

**Clinical import:** Long Island is one of a few locales that exhibits a high

breast cancer rate relative to the rest of the country. For years researchers have been trying to identify environmental factors that might explain the apparent regional disparity in breast cancer risk, with one area of focus being exposure to EMFs.

Although prevalence of electric blanket use among today's women is unlikely to be very high, it is conceivably a source of significant exposure to EMFs because the blanket is often applied directly to the body. This study provides welcome respite in that it appears that electric blanket use, in and of itself, does not cause breast cancer. We eagerly await further analyses of the results of EBCLIS (occupational and household EMF exposure).

**What to do with this article:** Keep a hard copy in your file cabinet. ♦

## CME Questions

**CME Instructions:** Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

**5. Andrographis is used primarily as a tonic in Ayurvedic medicine and as a cold remedy in Sweden.**

- a. True
- b. False

**6. The literature supports the use of andrographis:**

- a. to alleviate symptoms associated with the common cold.
- b. for prevention of URTI.
- c. Both a and b

**7. Which of the following vegetables has a high content of lutein and zeaxanthin, both of which have been found helpful in preventing the progression of age-related macular degeneration?**

- a. Dark green leafy vegetables
- b. Red and yellow peppers
- c. Peas
- d. All of the above

**8. Fasting may have a benefit in the treatment of:**

- a. hypertension.
- b. rheumatoid arthritis.
- c. multiple sclerosis.
- d. All of the above

Answers: 5. a, 6. c, 7. d, 8. d.

## In Future Issues:

### Behind the Banning of Ephedra: Misuse, Abuse, and Dangers

### Policosanol: A Natural Alternative for Lipid Management?

### Soy for Menopausal Symptoms

### Echinacea and the Common Cold

# ALTERNATIVE MEDICINE ALERT™

A Clinician's Evidence-Based Guide to Alternative Therapies

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## Chicken Soup and Vitamin C: The Science Behind Folk Remedies

DOES GRANDMA'S CHICKEN SOUP REALLY HELP RELIEVE COLD SYMPTOMS? WAS LINUS PAULING ON TO SOMETHING WITH HIS PROPOSAL THAT MEGA DOSES OF VITAMIN C COULD PREVENT COLDS AND REDUCE SYMPTOMS? A LOOK AT THE MEDICAL LITERATURE MAY OFFER SOME INTERESTING FINDINGS.

### Chicken soup and hot water vapors

The most notable study examining the effects of chicken soup on cold symptom severity was conducted in 1978.<sup>1</sup> Nasal mucus velocity and nasal airflow resistance were measured in 15 healthy subjects before and at five and 30 minutes after drinking hot water by sip or straw, hot chicken soup by sip or straw, and cold water by sip. A sham drinking procedure with straw was also employed.

Hot water by sip increased nasal mucus velocity from 6.2 to 8.4 mm/min, hot chicken soup by sip from 6.9 to 9.2 mm/min, and chicken soup by straw from 6.4 to 7.8 mm/min five minutes after administration. These increases were statistically significant compared to cold water, hot water by straw and sham. All values returned to their baseline at 30 minutes except cold water which significantly decreased the nasal mucus velocity from 7.3 to 4.5 mm/min. There were no significant changes from baseline in nasal airflow resistance five and 30 minutes following the above treatments.

The authors concluded that drinking hot fluids transiently increases nasal mucus velocity in part or totally through the nasal inhalation of water vapor. Hot chicken soup, either through the aroma sensed at the posterior nares or through a mechanism related to taste, appears to possess an additional substance for increasing nasal mucus velocity. Finally, hot liquid might be superior to cold liquids in the management of fluids in upper respiratory tract infections.

Heated, humidified air is used by common cold sufferers since the invention of the steam kettle. There is scientific literature available investigating this mode of therapy using a rhinotherm. The present reviews addresses to the use of hot, humid air in common cold.

A more recent review assessed the effects of inhaling heated water vapor with the help of a rhinotherm (an equipment designed to deliver heated water vapor to a person's nasal cavity), in the treatment of the common cold by comparing symptoms, viral shedding, and nasal resistance after a natural or experimentally induced common cold.<sup>2</sup>

Randomized trials using heated water vapor in a standardized way in patients with the common cold or volunteers with experimental induction of rhinovirus infection were included in the review.

All the articles retrieved were initially subjected to a review for inclusion/exclusion criteria. Review articles, editorials, and abstracts with inadequate outcome description were excluded. Studies selected for inclusion were subjected to a methodological assessment.

The results of a systematic review of six trials with 319 participants support the use of warm vapor inhalations in the common cold in terms of relief of symptoms (odds ratio with

95% confidence interval 0.31, 0.16-0.60, relative risk 0.56, 0.4-0.79). Results on symptom score indices were equivocal. None of the studies demonstrated a worsening of clinical symptom scores. One study demonstrated increased nasal resistance one week after steam inhalation in contrast to an earlier study that showed improvement in the nasal resistance. There was no evidence of decreased viral shedding measured by virus isolation in the nasal secretions or measurement of viral titers in nasal washings among treatment group. The rhinovirus titers in the nasal washings from the treatment group were the same as those of the placebo group on day one prior to the treatment and on all four days after the treatment. The area under curve also was similar in the placebo and treatment groups for titers of virus in the nasal washings as were the average viral titers across five days of follow up, the maximum values after treatment, and viral shedding velocity, i.e. amount of virus shed per day. Minor side effects due to thermal stress were reported in all the studies.

Three trials demonstrated beneficial effects on the symptoms of the common cold. One study from Israel showed a decrease in nasal resistance measured by peak nasal expiratory and inspiratory flow rate. Studies done in North America failed to show any objective improvement in outcome measures with the study intervention.

## Vitamin C

Controversy over the benefit of vitamin C in the prevention and treatment of the common cold has been a constant since Linus Pauling first proposed it in 1970. Investigators increasingly have moved away from Pauling's mega doses and have produced interesting, if not conflicting, results. Two recent studies have added support to vitamin C proponents.

A prospective, randomized, double-blind, multicenter, four-arm, controlled trial was carried out in 1,167 patients with common cold treated with one of the following medications: Grippostad-C, a combination of acetaminophen, caffeine, chlorpheniramine, and ascorbic acid (verum); ascorbic acid (control); chlorpheniramine and ascorbic acid (reference 1); and acetaminophen, caffeine, and ascorbic acid (reference 2).<sup>3</sup> A score of common cold symptoms (headache, throat pain, extremities and joint pain, cough, blocked nose, and disturbances of sleep quality) was the primary outcome. The test drug was first compared with the control using a hierarchic test strategy, then with reference 1, followed by reference 2 with the aim of proving superiority.

A clinically relevant and statistically significant difference was demonstrated at each level of the hierarchy. Grippostad-C was significantly superior to all other treatment groups, the combination of acetaminophen, caffeine, and ascorbic acid was significantly superior to the control, and the combination of chlorpheniramine and ascorbic acid was not statistically different from the control.

The findings demonstrate that the combination is superior to each of its separate components and each of the components has its own distinctive contribution to the efficacy of the combination product.

In another study, 168 volunteers were randomized to receive a placebo or a vitamin C supplement, two tablets daily, over a 60-day period between November and February.<sup>4</sup> They used a five-point scale to assess their health and recorded any common cold infections and symptoms in a daily diary.

Compared with the placebo group, the active-treatment group had significantly fewer colds (37 vs. 50, P < 0.05), fewer days challenged virally (85 vs. 178), and a significantly shorter duration of severe symptoms (1.8 vs. 3.1 days, P < 0.03). Consequently, volunteers in the active group were less likely to get a cold and recovered faster if infected. Few side effects occurred with the active treatment, and volunteers reported greatly increased satisfaction with the study supplement compared with any previous form of vitamin C.

The authors concluded that the well-tolerated vitamin C supplement used in this study may prevent the common cold and shorten the duration of symptoms. They noted that volunteers were generally impressed by the protection afforded them during the winter months and the general acceptability of the study medication.

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