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Alternative Strategies for Interstitial Cystitis

By Lucretia Perilli and Vicki Ratner, MD

LITTLE RESEARCH HAS BEEN CONDUCTED USING ALTERNATIVE therapies to treat interstitial cystitis (IC). This paucity of research may be detrimental to IC patients, who inevitably seek alternative treatments on their own with virtually no medical supervision and little research-based evidence of therapeutic efficacy. The following is a review of alternative therapies used to treat IC.

L-Arginine

The amino acid L-arginine is the only alternative therapy for IC that has been subjected to randomized, controlled trials. The basic premise for the use of L-arginine in the treatment of IC is that it helps to increase the production of nitric oxide (NO) and its precursor nitric oxide synthase (NOS). NOS and NO have antibacterial, smooth muscle relaxant, hormone-releasing, and immune-modulating effects.

Elevated NO levels typically are found in some inflammatory disorders. The first study implicating NO in IC was conducted in 1996. Researchers at Yale compared urine samples of 12 IC patients (diagnosed by NIH criteria) to those of 17 patients with a urinary tract infection and eight controls. They found that NOS production appeared to be lower than normal in IC patients (2.3 ± 1.0) and higher in UTI patients (120 ± 10) when compared with controls (14 ± 3.0).[1]

In a subsequent uncontrolled Yale study, researchers administered L-arginine (1.5 g/d po) for six months to 10 IC patients (diagnosed by NIH criteria). They found that L-arginine helped increase the NOS activity in the bladders of IC patients and reduced some IC symptoms, beginning at one month. All of the IC patients taking oral L-arginine for the six-month period had improvement of symptoms based on patient symptom scoring. L-arginine treatment resulted in significant decreases in urinary voiding pain (from 4.8 ± 1.3 to 0.7 ± 0.3), lower abdominal pain (from 5.0 ± 1.0 to 1.5 ± 0.6), and vaginal/urethral pain (from 4.5 ± 1.1 to 1.5 ± 0.6). Urinary frequency decreased during the day (from 13.4 ± 2.0 to 8.1 ± 1.1) and at night (from 5.3 ± 1.0 to 1.9 ± 0.6). From these results and the results of their previous study, these researchers postulated a causal link among bladder infection, inflammation, and IC.

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Subsequent placebo-controlled L-arginine studies by the Yale team, however, found no significant improvement in IC symptom scores when compared with placebo. L-arginine did seem to benefit two subgroups: patients with a history of intermittent urinary tract infections and larger bladder capacities (greater than 800 cc).[2-4] All of the Yale studies were funded by NIH.

Recent studies of L-arginine by other groups have not supported a benefit. A privately and institutionally funded Swedish study treated nine women with IC with 3 g/d or 10 g/d of L-arginine for five weeks. Symptoms were evaluated with an IC symptom score index, and NO production was measured. Patients with stress incontinence (n = 18) were used as controls for NO levels. NO concentration in the urinary bladder was elevated in IC patients (239 ± 60 ppb) compared with controls (15 ± 2 ppb), but L-arginine treatment did not significantly affect NO levels in IC patients (189 ± 72 ppb). Symptom scores did not change significantly with either dose of L-arginine at the five-week time point.[5]

A team of British researchers found similar results. In this placebo-controlled crossover study, published in 2000, 16 IC patients (diagnosed by NIH criteria) were given 2.4 g/d of L-arginine or placebo for one month. After a two-week washout period, each group received the other medication for one month. Patients in the placebo group showed no differences in any recorded variable over the baseline symptom values. L-arginine caused a statistically significant reduction in the overall symptom score from baseline, but this effect was small. Moreover, there was no significant difference in any variable between the L-arginine group and the placebo group.[6]

The roles of L-arginine, NO, and NOS in the etiology and treatment of IC remain controversial. Leading clinicians in the treatment of IC have largely abandoned the use of L-arginine.

Mucopolysaccharides

Mucopolysaccharides, which include glycoproteins, glycolipids, and glycosaminoglycans, are thought to benefit IC by replacing the defective GAG lining in the bladder. Pentosan polysulfate sodium, the only oral FDA-approved treatment for IC, acts in this manner. Over-the-counter mucopolysaccharides include glucosamine, chondroitin, and aloe vera. Other herbs purported to "soothe the bladder lining" include marshmallow root (*Althaea officinalis*) and *Spirulina* species (a type of blue-green algae).

No controlled trials have been done on naturally occurring mucopolysaccharides and IC. Intravesical chondroitin has been tested in a small, open-label pilot study in which 14 IC patients (diagnosed by positive hydrodistension and positive potassium sensitivity test) were given a chondroitin compound (80 mg Urocyst-S®) intravesically once weekly for four weeks, then once a month for eight to 38 weeks). Twelve patients showed positive responses, one patient failed to respond, and one relapsed at 12 weeks. The average response time was 3-12 weeks.[7] Algonot®, a combination of chondroitin, glucosamine and quercetin, has been proposed as a possible treatment for IC.[8]

Quercetin

Quercetin, available in various over-the-counter (OTC) formulas, is reported to act as an antihistamine, anti-inflammatory, and antioxidant. No published, double-blind placebo-controlled studies are available. Quercetin recently has been studied as a treatment for chronic abacterial prostatitis (chronic pelvic pain syndrome in men)[9] and currently is under investigation as a possible IC treatment. Most OTC formulas combine quercetin with vitamin C, which can irritate the IC bladder. An open-label study of Cysta-Q® (which does not contain added vitamin C) in 22 IC patients found that 57% of the 20 patients who completed the study showed improvement of symptoms after four weeks.[10]

Chinese Herbs

Herbal formulas in tea and pill forms are being used

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to treat IC. The Chinese herbs most commonly used include gardenia (*Gardenia jasminoides*), licorice (*Glycyrrhiza glabra*), dianthus (*Dianthus superbus*), poria (*Wolfiporia cocos*), rhubarb (*Rheum palmatum*), rehmannia (*Rehmannia glutinosa*), cornus (*Cornus officinalis*), water plantain (*Alisma plantago-aquatica*), ginseng (*Panax* spp.), and plantain (*Plantago* spp.). One unpublished, open-label study that was reported in the *ICA Update* newsletter used a Chinese herbal formula to treat 25 women who have had IC from four to 20 years and were diagnosed by NIH criteria.[11] The participants drank one cup of tea bid for six days out of every week. After three months, the dosage was reduced to one cup a day. In the first month of the study, 61% of the patients experienced a decrease of more than three points on the pain scale. Twenty-two percent had a similar response after three months. Eighteen percent did not improve. Larger, controlled studies are necessary to further evaluate these herbs.

Other Alternative Therapies

Acupuncture may be a useful complement to conventional medical care for some patients,[12] but there have been no adequate clinical trials of this technique. A crossover study of 12 women with IC randomized subjects to transcutaneous electrical nerve stimulation (TENS) (applied to the posterior tibial nerve, 30 minutes qd) or acupuncture (two to three times weekly); each treatment phase lasted a month.[13] Only five women completed both treatments; four dropped out after receiving acupuncture and three dropped out after receiving TENS because of lack of symptom relief. Neither treatment resulted in differences in frequency, voided volume, or visual symptom scores (analyzed by Wilcoxon signed-rank test). Only one patient experienced both subjective and objective clinically significant improvement (which lasted three months after acupuncture treatment).

Myofascial release is a type of physical therapy focused on trigger points that develop in muscles due to chronic pain or overuse.[14] It is used to treat pelvic floor dysfunction, which can exist concurrently with IC.[15] Anecdotally, some IC patients have benefited from this type of treatment provided by physical therapists specially trained in this technique.

MSM (methyl sulfonyl methane) is a naturally occurring organic sulfur compound that is similar chemically to the intravesical IC treatment, DMSO (dimethylsulfoxide). It is being used topically and orally by some IC patients. No clinical trials of this therapy were identified.

Conclusion

IC patients eagerly await more solid evidence regarding the use of alternative therapies for the treatment of their disease. One possible avenue for encouraging and expanding this area of research exists at the NIH National Center for Complementary and Alternative Medicine. As more and more IC patients turn to various alternative therapies to help with their IC symptoms, it is essential that the research community develop clinical trials utilizing standard research techniques so that unbiased, valid, peer-reviewed data will become available. ❖

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Interstitial Cystitis Resources

For more information about IC please contact:

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Web site: http://www.IChelp.org

Suggested Reading for Practitioners and Patients

Moldwin RM. *The Interstitial Cystitis Survival Guide*. Oakland, CA: New Harbinger Press, Inc.; 2000.

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Interstitial Cystitis: Overview

By Lucretia Perilli and Vicki Ratner, MD

INTERSTITIAL CYSTITIS (IC), A CHRONIC INFLAMMATORY condition of the bladder, is characterized by pelvic/perineal pain, urinary urgency, and frequency in the absence of bacterial infection or other identifiable causes. The etiology of IC is unknown, and there is no cure. For many years IC was dismissed as a "hysterical female condition"; as late as 1985, *Campbell's Urology* described IC as "a disease that ... may represent the end stage of a bladder that has been made irritable by emotional disturbance.... A pathway for the discharge of unconscious hatreds."[1] The text finally has been revised, and attitudes are changing slowly.

Epidemiology

There are an estimated 700,000 cases of IC in the United States, with projections running as high as several million; 90% of IC patients are female. IC can occur at any age, including childhood and adolescence (25% of patients are < 30). The prevalence of IC in the United States is three-fold greater than that reported in Europe.[2] Recently, the National Institutes of Health allocated $7.5 million to be used for epidemiologic studies of IC.

Symptoms and Causes

Pain, urinary frequency, and urgency are the paramount symptoms of IC. Dyspareunia can be so severe that many women abstain from all sexual activity. Bladder and suprapubic pain and pressure can range from mild to severe and may be accompanied by urinary frequency (as often as 60 times a day). Patients also may report urethral, vaginal, or rectal pain, and lower back and thigh pain. These symptoms can disrupt every aspect of patients' personal and professional lives, resulting in sleep deprivation, depression, and in some cases, suicide. Many patients are unable to work full-time, thus limiting their access to affordable health insurance. Others may be unable to work at all. Some have pain so severe it prevents them from riding in a car or even leaving their homes. The quality of life of IC patients has been documented to be worse than that of women undergoing dialysis for end-stage renal disease.[3] IC can be associated with other chronic conditions such as fibromyalgia, vulvodynia, migraines, allergic reactions, and gastrointestinal problems.[4]

The etiology of IC remains unknown but a number of theories are being investigated including: a defect in the bladder lining allowing substances in the urine to damage the bladder wall; an immunologic/autoimmune response; an allergic reaction; an unidentified bacterium, fungus, or virus; and a neurogenic inflammatory response.[5] A familial or genetic component also is being investigated.

Diagnosis

No IC-specific urinary marker has yet been identified but two factors are under investigation: a glycoprotein (GP51) and an anti-proliferative factor.[6,7] Also, a rhamnose/lactulose blood assay to test for bladder permeability (thought to be correlated with IC) is being studied.[8]

Cystoscopy with hydrodistension performed under general or regional anesthesia is considered the "gold standard" for confirmation of diagnosis and is therapeutic as well in some patients. Office cystoscopy may be too painful for IC patients and may not distend the bladder sufficiently to reveal the signs of IC: pinpoint hemorrhages or glomerulations (present in 90% of patients) and Hunner's ulcers (present in 5-10% of patients). Up to 10% of IC patients may show no signs of glomerulations or Hunner's ulcers with cystoscopy under general anesthesia.[9] A potassium chloride sensitivity test has

been proposed as a possible diagnostic tool for IC. The test consists of instilling a solution of potassium chloride into the bladder via urinary catheter and measuring pain response. A positive pain response may indicate a defect in the GAG lining, which may be diagnostic of IC. However, this painful test compounds an already painful condition. A recent study reports only 60% accuracy with this test.[10]

Conventional Treatments

A recent report from the Interstitial Cystitis Database, established in 1993, reported that of 581 women in the database, 105 (18%) were receiving no treatment.[11] An astounding 183 different treatments for urinary symptoms were prescribed by physicians. The most common physician-prescribed treatments for women at baseline were cystoscopy/hydrodistension (32.9%), amitriptyline (16.9%), phenazopyridine (14.3%), special diet (9.3%), intravesical heparin (9.1%), hyoscamine (7.1%), oxybutynin (5.9%), oral pentosan polysulfate sodium (5.5%), propoxyphene plus acetaminophen (4.8%), and urinary antiseptic combinations (4.5%). The authors point out that current pentosan polysulfate sodium is probably much higher; the drug was approved by the FDA in 1996, after most women had entered the database Although this report was recently published, data in this paper date from 1990-1995; the IC Database has been concluded for several years.

The researchers note that there is a paucity of good, placebo-controlled, randomized clinical trials of therapies, and clearly there is no consensus on treatment.

Oral medications. The only oral medication approved specifically for IC, pentosan polysulfate sodium, is a glycosaminoglycan-like material thought to help restore the bladder surface.[12] In double-blind, placebo-controlled trials, 38% of the patients treated with pentosan polysulfate sodium for three months reported improvement of their IC symptoms. In open-label trials, 61% of the patients reported improvement.[12] Low-dose tricyclic antidepressants (10-75 mg qhs) have been used both for their analgesic and anticholinergic effects that can help decrease urinary frequency.[13] Selective serotonin reuptake inhibitors (SSRIs) also are used, but no research has been conducted on SSRIs. The most widely used antihistamine to treat IC is hydroxyzine, which inhibits mast cell degranulation, thought to play a part in some IC symptoms. It also has sedative and anxiolytic effects.[14] Pain medications include anticonvulsants such as gabapentin or carbamazepine, and short- or long-acting narcotics. Other oral medications used in the treatment of IC include: antispasmodics (methenamine), anticholinergics (tolterodine tartrate, oxybutynin, hyoscyamine), H2 blockers (cimetidine, ranitidine), urinary alkalinizing agents (sodium citrate, potassium citrate), and adrenergic blockers (doxazosin, terazosin). None of these has been approved by the FDA specifically for IC.

Intravesical medications. Although oral medications are used more frequently to treat IC, medications instilled directly into the bladder still are considered a mainstay of treatment. DMSO (dimethylsulfoxide)—approved for use in IC in 1978—commonly is used as part of a "cocktail" instillation combined with heparin, steroids, and/or anesthetics. BCG (*bacillus Calmette-Guerin*) is an experimental treatment currently in phase III clinical trials; hyaluronic acid also is undergoing clinical trials.

Transcutaneous electrical nerve stimulation. Some IC patients have reported temporary relief of symptoms

Table 1

The IC Diet

Restricted Foods, Beverages and Other Ingredients

Milk/Dairy Products: aged cheeses, sour cream, yogurt, and chocolate

Vegetables: fava beans, lima beans, onions, tofu, soybeans, and tomatoes

Fruits: apples, apricots, avocados, bananas, cantaloupes, citrus fruits, cranberries, grapes, nectarines, peaches, pineapples, plums, pomegranates, rhubarb, strawberries, and juices made from these fruits

Carbohydrates and Grains: rye and sourdough bread

Meats and Fish: aged, canned, cured, processed or smoked meats and fish, anchovies, caviar, chicken livers, corned beef, and meats that contain nitrates or nitrites

Nuts: most nuts, with the exception of almonds, cashews, and pine nuts

Beverages: alcoholic beverages, beer, carbonated drinks such as sodas, coffee, tea, cranberry juice, and wine

Seasonings: mayonnaise, miso, spicy foods (especially such ethnic foods as Chinese, Indian, Mexican, and Thai), soy sauce, salad dressing, and vinegar

Preservatives and Additives: benzol alcohol, citric acid, monosodium glutamate (MSG), aspartame (Nutrasweet®), saccharin, and foods containing preservatives, artificial ingredients, and colors

Miscellaneous: tobacco, caffeine, diet pills, junk foods, recreational drugs, cold and allergy medications containing ephedrine or pseudoephedrine, and certain vitamins

Adapted from: Interstitial Cystitis Association's IC & Diet brochure.

with the use of transcutaneous electrical nerve stimulation (TENS). A small study comparing TENS (using the posterior tibial nerve) with acupuncture found little benefit for either;[15] other studies have found TENS to be a useful tool in treating the pain of IC.[16-18] Transvaginal biofeedback and electrical stimulation have also been used to treat pelvic pain caused by IC; no trials were identified on this treatment in IC patients.

Surgery. Laser surgery is used specifically to treat Hunner's ulcers. While not a cure, laser therapy can help to alleviate the symptoms of Hunner's ulcers for extended periods of time.[19] Other types of surgery for IC, such as augmentation cystoplasty or urinary diversion, rarely are recommended because of potentially serious complications and its failure to relieve IC pain in many cases.

Sacral nerve stimulation implants. Sacral nerve stimulation implants, recently approved by the FDA for urge incontinence, urinary frequency, and urgency, currently are undergoing preclinical trials testing for use in the treatment of IC and pain. A case series tested percutaneous sacral nerve root neuromodulation (via test stimulation, not permanent implant) in 15 women with refractory IC.[20] Mean voided volume during treatment increased from 90 to 143 ml ($P < 0.001$). Mean daytime urinary frequency significantly decreased (from 20 to 11) and nocturia decreased (from six to two times) ($P = 0.01$ for both). Mean bladder pain decreased from 8.9 to 2.4 points on a 10-point scale ($P < 0.001$). Several quality-of-life parameters significantly improved; 73% of participants requested to proceed to complete sacral nerve root implantation. Another case series in six women found significant improvement in voiding frequency, pelvic pain, and urinary urgency (all $P < 0.05$) after five days of continuous sacral nerve root stimulation.[21] Controlled trials of this therapy should be done.

Self-Help Techniques

There are no treatments that work for all IC patients. Patients with mild cases of IC may find significant symptom relief by implementing self-help strategies. Patients with more severe IC symptoms also may benefit by adding these strategies as adjuncts to their treatment regimen. None of the following treatments have been subjected to controlled clinical trials, but have been reported helpful by patients.

Diet. (*See Table 1.*) Avoiding caffeine, artificial sweeteners, alcohol, and tobacco can help to reduce IC symptoms. A diet low in acidic foods and beverages may help symptoms; some patients add Prelief® (a dietary supplement containing calcium glycerophosphate) to foods and beverages to reduce acidity. Diets low in the amino acids tyramine, tyrosine, and tryptophan are used by some patients. Some IC patients follow salt- and/or sugar-restricted diets; others avoid foods containing yeast.[22] The consumption of vitamin C or some stimulant supplements, such as ephedra, may aggravate IC symptoms.

Stress-reduction techniques. Strategies used by IC patients include meditation, visualization, biofeedback, self-hypnosis, massage therapy, and psychotherapy tailored toward the needs of the chronically ill.

Exercise. Exercise plans may include gentle stretching exercises that avoid tightening or jarring the pelvic region, pelvic floor relaxation exercises, yoga, low-impact aerobics, Tai Chi, and swimming. However, chlorinated swimming pool water may cause IC symptoms to flare.

Bladder retraining. The bladder retraining program is a self-help process by which patients learn to control their urge to urinate. It is essential that pain be under control before this program is attempted. When patients experience bladder pain or urgency, the normal impulse is to urinate to stop the symptom. A pattern of frequent voiding can be difficult to reverse. The goal of the bladder retraining program is to use a series of simple steps to achieve longer and longer periods between urinations. Working with a health care practitioner, a program is established for each patient beginning with a four-week period of holding the urine for a specific number of minutes or hours (based on the individual's current average voiding schedule). The patient is encouraged to wait a specified period after the first urge is felt before urinating (15 minutes, for example). If severe pain is felt before the period has elapsed, voiding is encouraged. If after waiting, the patient finds that the need to urinate has diminished, then she/he should wait until the next urge to void is felt. At the end of one month, the time interval is increased, and at the end of the second month, the interval is increased again. It is acceptable if intervals are occasionally longer or shorter, as long as the minimum interval occurs most of the time.

Pain relief. Self-help sources of IC pain relief include cold packs and/or hot packs placed on the pelvic floor region, sitz baths, and, for those not on salt-restricted diets, drinking a solution of water and a teaspoon of baking soda during flare-ups. There are no established guidelines for this practice, and patients should be cautioned about repeatedly consuming several teaspoons of baking soda because of potential health risks.

Other self-help techniques. Learning new sexual techniques that do not place as much stress and pressure on the bladder is helpful. Female IC patients have found that positions other than the missionary position put less stress on the bladder. Water-based lubricants can be

helpful. Also, "outercourse" (i.e., oral sex, sensual massage, mutual masturbation) can be a helpful sexual strategy for IC patients. Wearing loose-fitting clothing and using unbleached and unscented toilet paper can also help to alleviate IC symptoms. ❖

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CME Questions

20. The majority of placebo-controlled trials have found arginine treatment of interstitial cystitis to be:
a. effective.
b. ineffective.

21. Which of the following alternative treatments has been shown in randomized controlled trials to be effective in treating interstitial cystitis?
a. Spirulina (blue-green algae)
b. Acupuncture
c. Arginine
d. Chinese herbs
e. None of the above

22. Which metabolic pathway of estradiol is associated with antiestrogenic and antiproliferative effects?
a. 2-hydroxyestrone
b. 16-alpha-hydroxyestrone

23. Argyria is:
a. reversible.
b. irreversible.

Broccoli and CIN

Source: Bell MC, et al. Placebo-controlled trial of indole-3-carbinol in the treatment of CIN. *Gynecol Oncol* 2000;78:123-129.

Design: Randomized, placebo-controlled, trial. Patients and colposcopists were blinded to treatment.

Subjects: Thirty women with cervical intraepithelial neoplasia (CIN I-III) by cervical biopsy. Sixteen women (5 placebo, 11 treated) had CIN II, while 11 (5 placebo and 6 treated) had CIN III. Seven of 10 placebo patients, seven of eight patients receiving 200 mg/d indole-3-carbinol, and eight of nine patients receiving 400 mg/d indole-3-carbinol tested positive for human papilloma virus (HPV).

Treatment: Placebo, 200 mg/d indole-3-carbinol, or 400 mg/d indole-3-carbinol for 12 weeks.

Outcome Measures: Cervical biopsy. Colposcopic examination was performed and urinary 2-hydroxyestrone/16-alpha-hydroxyestrone ratios obtained at baseline and monthly for three months.

Results: None of the 10 patients in the placebo group had complete regression of CIN (although three of five initially CIN III improved to CIN I). Four of eight patients (three initially CIN II, one initially CIN III) who received 200 mg/d indole-3-carbinol experienced complete regression. Four of nine patients (three initially CIN II, one initially CIN III) in the group receiving 400 mg/d had complete regression. The protective effect calculated as relative risk was 0.50 in the 200 mg group (95% CI 0.25-0.99, P = 0.023) and 0.55 in the 400 mg group (95% CI, 0.31-0.99, P = 0.032). The presence of HPV did not correlate with treatment response. Urinary 2-hydroxyestrone/16-alpha-hydroxyestrone ratios showed marked individual variability.

Comments: This trial was quite small but is intriguing. Confidence intervals were fairly wide, a function of the small number of subjects in this trial. Results should be confirmed in a larger trial, as CIN II may regress spontaneously (CIN III usually does not). It is interesting that in this series three of five placebo-treated CIN III patients improved to CIN I. Found in vegetables of the cruciferous family (including broccoli, cauliflower, cabbage, and Brussels sprouts), indole-3-carbinol alters estrogen metabolism by up-regulating 2-hydroxylation. In the liver, estradiol is degraded to 2-hydroxyestrone or 16-alpha-hydroxyestrone. 2-hydroxyestrone appears to have anti-estrogenic and anti-proliferative effects, while 16-alpha-hydroxyestrone has proliferative effects in some breast cancer cell lines. A dose of 400 mg indole-3-carbinol is equivalent to about one-third of a head of raw cabbage (400 g) per day. There are no known health risks for incorporating broccoli, cabbage, or other cruciferous vegetables into one's diet. ❖

Colloidal Silver and Argyria

Promoters of colloidal silver have claimed that no cases of argyria have been linked with the colloidal form. While that may well have been true at the earliest stages of marketing (the condition takes months or years to develop), that claim can no longer be made. A 35-year-old woman presented with typical blue-gray discoloration of skin and nail beds after ingesting mild colloidal silver protein (25 mcg/tsp) for one year;[1] in another case a 38-year-old woman presented with a blue-gray facial discoloration after ingesting an unspecified form of colloidal silver (1/4 cup tid for eight months) in an effort to treat Lyme disease with this "natural " antibiotic.[2] Neither patient had other complications. In the third case, a 55-year-old man who had been taking a teaspoon of colloidal silver tid for three years in an effort to treat allergies also developed argyria.[3]

The first sign of argyria is often a slate-blue or silver line in the gingiva. The grayish hue that characterizes argyria is a combination of silver deposits and melanin pigmentation; silver stimulates melanocytes. Discoloration often is more pronounced in sun-exposed areas, as light reduces silver. Argyria is unattractive but the dermatological form is otherwise benign. However, rare cases of silver deposition in internal organs have been reported; neurological deficits may result but are extremely rare.

Argyria is irreversible; chelation therapy with B A L or D—penicillamine has been ineffective. Intradermal injection with 6% sodium thiosulfate or 1% potassium ferrocyanide occasionally has resulted in successful local reversal, but this is not practical for large areas of discoloration.[4] ❖

References

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4. Fung MC, Bowen DL. Silver products for medical indications: Risk-benefit assessment. *Clin Toxicol* 1996;34: 119-126.

In Future Issues:

Acupuncture and Nausea

Cranberries and Urinary Tract Infections

Red Yeast Rice as Cholesterol-Lowering Agent