Literature Review & Commentary

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Glucosamine hits the big time

Two hundred-twelve patients with mild to moderate osteoarthritis of the knee were randomly assigned to receive, in double-blind fashion, 1,500 mg of glucosamine sulfate (GS) or placebo once daily for 3 years. Mean and minimum joint-space width of the medial compartment of the tibiofemoral joint were assessed radiographically, at baseline and after 1 and 3 years. Symptoms were scored by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index. In the intent-to-treat analysis, patients receiving placebo showed a mean joint-space loss after 3 years of -0.31 mm, compared with -0.06 mm in the GS group ($p = 0.043$ for the difference between groups). For the change in minimum joint space width, the values at 3 years were -0.40 and -0.07 mm, respectively ($p = 0.003$ for the difference between groups). Symptom scores at the end of the study showed a slight worsening from baseline in the placebo group, and an improvement in the GS ($p = 0.02$ for the difference between groups). There were no serious side effects attributable to GS. In addition, there were no marked changes in any routine laboratory tests. Fasting plasma glucose concentrations decreased slightly in the GS group (data not shown).

Comment: Although numerous double-blind studies have demonstrated symptomatic improvement of osteoarthritis in patients taking GS, the medical community has largely been skeptical of this treatment. One of the criticisms of earlier studies is that they were of relatively short duration, typically only 2 months. The new study answers that concern, showing not only persistent symptomatic improvement, but a reduction in joint-space narrowing. Thus, GS appears to be disease-modifying antiarthritic compound, rather than one that merely suppresses symptoms. Moreover, despite concerns that GS could cause hyperglycemia (based on animal studies using continuous intravenous infusions), the present study showed no adverse effect of GS treatment on plasma glucose levels.

With the publication of this study, there is no longer any excuse for the medical community to refuse to consider GS as first-line therapy for osteoarthritis. In an editorial (*Lancet* 2001;357:247) that accompanied this report, Tim McAlindon, from the Arthritis Center, Boston University Medical Center, wrote: "Although health-care professionals generally expect to be involved in medical decisions...they are not regarded as a repository of objective advice about nutritional products and are generally kept out of the loop. This situation must change. It is time for the profession to accommodate the possibility that many nutritional products may have valuable therapeutic effects and to regain the credibility of the public at large."

Reginster JY, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;357:251-256.

Obesity as a cause of sleep-disordered breathing

In a population-based, prospective cohort study conducted from July 1989 to January 2000, 690 randomly selected Wisconsin residents (mean age, 46 years) were evaluated twice at 4-year intervals for sleep-disordered breathing (SDB). Compared with stable weight, a 10% weight gain predicted approximately a 32% increase (i.e., worsening) in the apnea-hypopnea index (AHI). A 10% weight loss predicted a 26% decrease (i.e., improvement) in the AHI. A 10% increase in weight predicted a 6-fold increase in the risk of developing moderate-to-severe SDB.

Comment: SDB, a condition that includes sleep-apnea, is common among the US population. SDB has been associated with impaired neurobehavioral functioning (such as getting into more automobile accidents), increased cardiovascular problems, and increased mortality. Previous studies have shown that SDB is associated with excess body weight. It has been hypothesized that obesity can impair breathing during sleep by altering airway structure and function, and by inducing disturbances in the respiratory drive. The present study suggests that losing excess body weight can reduce the severity of SDB or prevent it from developing.

Peppard PE, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000;284:3015-3021.

New treatment for itching

Thirty-one patients with pruritus of various etiologies that had failed to respond to antihistamines and other drugs, were treated with tablets containing 250 mg of procaine hydrochloride and 150 mg of ascorbic acid, given every 4 hours or as needed. Dramatic relief occurred within minutes and in most cases lasted 4-6 hours. Patients were able to stop scratching, thus allowing the skin an opportunity to heal. No adverse effects were seen. Twelve of 13 patients with atopic dermatitis, 8 of 9 with contact dermatitis, 3 of 4 with poison ivy, and 3 of 3 with urticaria reported relief. Twelve patients with pruritus vulvae, 3 with pruritus ani, and 2 with scabies were also relieved. One patient with seborrhea did not improve.

Comment: Procaine is a drug that is used primarily as an anesthetic. It is also the main component of the controversial nutritional supplement Gerovital (GH3), which is said to function as an antiaging compound and antidepressant. Procaine is apparently safe when administered orally. This new study suggests that procaine, in combination with relatively low doses of ascorbic acid, is an effective short-term treatment for itching. Actually, this study is not new at all; it was published nearly 50 years ago. However, since no one appears to be using this treatment, and for the benefit of "modern chauvinists" (i.e., those who like to use the latest treatments), I'm going to pretend that the report is new.

Parish FA. An effective method for the treatment of pruritus with the oral use of procaine hydrochloride-ascorbic acid combination. *Ann Allergy* 1953;11:85-90.

New treatment for multiple sclerosis

The formation of the neurological lesions of multiple sclerosis (MS) has been associated with local production of the free-radical product peroxynitrite. In mice with

experimental allergic encephalomyelitis (an animal model for MS), the development of the typical lesions can be prevented and damage in existing lesions resolved by administration of the peroxynitrite scavenger, uric acid. Patients with MS have been found to have significantly lower serum concentrations of uric acid, compared with age- and sex-matched controls consuming the same diet. Furthermore, the coexistence of MS and gout in the same individual is said to be very rare. Oral administration of uric acid to MS patients has been ineffective at raising serum uric acid levels, possibly because of destruction of uric acid by gut bacteria.

In an attempt to raise uric acid levels, inosine (a uric acid precursor) was administered to 10 patients with chronic MS. The initial dose was 1 g/day, increased by week 6 to 3 g/day (in 2 divided doses), and maintained at a level of 2 or 3 g/day for a total treatment period of 46 weeks. After 15 weeks of treatment, the mean serum uric acid concentration had increased from approximately 4 mg/dl to nearly 9 mg/dl, and was maintained at around 8 mg/dl for the remainder of the treatment period. Three of the 10 patients showed some evidence of improved function, and the rest remained stable. A significant reduction in lesion activity was seen in one of the 2 patients with active lesions, as identified by MRI. No adverse effects were seen.

Comment: The results of this preliminary study suggest that supplementation with inosine may be beneficial for patients with MS, presumably by raising uric acid levels. However, of the many treatments for MS that have been proposed over the years, most have been found to be ineffective when subjected to controlled trials. Furthermore, raising uric acid levels could increase the risk of developing gout or cardiovascular disease. On the other hand, MS is a much more serious disease than gout, and cardiovascular disease can largely be prevented through diet, nutritional supplements, and lifestyle modifications. Therefore, this potentially effective treatment for MS deserves further investigation.

Koprowski H, et al. Prospects for the treatment of multiple sclerosis by raising serum levels of uric acid, a scavenger of peroxynitrite. *Ann Neurol* 2001;49:139.

Laugh your allergies away

Twenty-six patients (mean age, 31 years) with atopic dermatitis (eczema), all of whom were allergic to house dust mites, were studied. Skin prick tests with a commercial extract of house dust mite were performed before and after the patients viewed an 87-minute Charlie Chaplin video *(Modern Times)*. The same procedure was then repeated, before and after an 87-minute non-humorous video (presenting information on the weather). Wheal size, measured 15 minutes after the skin prick, was significantly reduced ($p < 0.01$) after viewing the humorous video, but was unchanged after viewing the non-humorous video.

Gaby's Literature Review

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Comment: The results of this study suggest that the physiological responses associated with laughter may play a role in alleviating allergies. If so, then laughter is a true placebo, because "placebo" means "I will please," and people who are laughing are definitely pleased. Norman Cousins noted that 10 minutes of laughter per day relieved his pain from ankylosing spondylitis. In another report, exposure to a 60-minute humorous story decreased blood levels of interleukin-6 and interferon-gamma, and reduced pain in patients with rheumatoid arthritis. The intriguing relationship between psychological factors and immune function is illustrated further by the case of a person with multiple-personality disorder, who allegedly developed anaphylactic reactions to certain substances in one personality, but tolerated these same substances just fine in the other personalities. The power of the mind-immune system connection makes one wonder how much of a placebo effect is involved in some of the popular allergy "desensitization" techniques, such as NAET and electrodermal testing. Certainly, these techniques should be subjected to controlled trials.

Kimata H. Effect of humor on allergen-induced wheal reactions. *JAMA* 2001;285:738

Is exposure to plastic causing precocious puberty?

Serum samples were analyzed from 41 Puerto Rican girls (aged 6 months to 8 years; median, 20 months) with premature breast development (thelarche) and from 35 controls (aged 6 months to 10 years; median, 46 months). Significant concentrations of phthalates (dimethyl, diethyl, dibutyl, and di-[2-ethylhexyl]) and its major metabolite (mono-[2-ethylhexyl] phthalate) were identified in the serum of 68% of the premature thelarche patients, compared with only 3% of the controls. The phthalates that were identified have been classified as endocrine disrupters.

Comment: Since 1979, there has been an alarming increase in the incidence of premature thelarche among Puerto Rican girls. The estimated average annual incidence in Puerto Rican girls aged 6-24 months was 8 per 1,000 births from 1984 to 1993. This is the highest incidence ever reported, 18.5 times higher than the incidence reported in a study conducted in Minnesota through 1984. In Puerto Rico, there is a high level of consumption of imported dietary products stored in plastic containers. These plastics contain endocrine-disrupting chemicals such as phthalate esters and alkyl phenols; some of these compounds have been shown to disrupt normal sexual development in wildlife. The results of the present study suggest that exposure to plastics with known estrogenic and antiandrogenic activity may be contributing to the increasing incidence of premature breast development among Puerto Rican girls.

Colon I, et al. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ Health Perspect* 2000;108:895-900.

Glutamine for alcohol cravings

Ten presumably well-nourished alcoholics received 1 g/day of glutamine in divided doses with meals or a placebo, each for varying periods of time, in a 3-month double-blind crossover trial. In 9 of the 10 cases, glutamine appeared to diminish the desire to drink alcohol. Some patients reported decreased nervousness and improved ability to sleep while on glutamine. One doctor (personal communication) has observed that larger doses of glutamine were effective in some cases where 1 g/day was not.

Comment: This small study, performed many years ago, suggests that supplementation with glutamine can reduce the craving for alcohol. Studies in rats have also demonstrated that administration of glutamine reduces voluntary intake of ethanol. Although larger and better-controlled trials are needed, glutamine is safe and inexpensive and is, therefore, worth a try for individuals who find that "the spirit is willing but the flesh is weak." I treated one recovered alcoholic who, despite having successfully dealt with the emotional causes of his drinking, had a persistent physical craving for alcohol. While taking 500 mg of glutamine 3 times a day, he lost his desire to drink, and was even able to resume occasional light, social drinking, without losing control. Previously, even one drink would knock him off the wagon. While I do not encourage ex-alcoholics to attempt periodic social drinking, this case illustrates that biochemical factors play an important role in alcohol addiction.

Rogers LL, Pelton RB. Glutamine in the treatment of alcoholism. *Q J Stud Alcohol* 1957;18:581-587.

Gamma-hydroxybutyrate (GHB) for alcoholism

Ninety-one alcoholic patients were treated with gamma-hydroxybutyrate (GHB) at a dose of 50 mg per kg of body weight, 3 times a day for 8 weeks. Sixty-six patients (72.6%) were abstinent during this time and continued the same treatment regimen. After 6 months of treatment, these patients remained abstinent, with the exception of 11% who had occasional minor relapses. Twenty-five patients continued to drink alcohol during the first 8 weeks, although 16 of these patients substantially reduced their alcohol intake. These patients were then given the same dose of GHB divided into 6 daily doses for an additional 8 weeks. During that time, 19 (76%) of the 25 nonresponders began and maintained abstinence. After 6 months of treatment with 6 daily doses, all patients have remained abstinent, with the exception of one who had occasional minor relapses. In both groups, abstinence was associated with a significant decrease in the Alcohol Craving Scale.

Comment: GHB has been shown to prevent the alcohol withdrawal syndrome in humans and animals and to induce short-term and medium-term abstinence in 60-70% of patients treated. GHB is usually divided into 3 daily doses, even though its half-life is 35 minutes. More-frequent dosing of GHB might therefore be an effective regimen for nonresponders. Side effects are dose-dependent and have included drowsiness, hypnagogic state, amnesia, involuntary movements, seizure-like activities, and a comatose state. The severity of adverse reactions may be potentiated by the consumption of alcohol.

GHB also has significant abuse potential, and some alcoholics take far more than the prescribed dose. For that reason, if GHB is used, it should be administered by a family member who can watch for signs of abuse. Although GHB overdose (often in combination with various street drugs) has been linked to serious adverse reactions and some deaths, and, although GHB has also been used as a "date rape" drug, it appears to be reasonably safe when administered appropriately. In the United States, GHB is a Schedule I controlled substance, in the same category as cocaine. However, GHB may be the most effective compound available for the treatment of alcoholism, and it should not be overlooked.

Addolorato G, et al. Maintaining abstinence from alcohol with gamma-hydroxybutyric acid. *Lancet* 1996;351:38.

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