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INSIDE

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Internal Medicine Alert's Editor, Stephen Brunton, MD, is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and Astra-Zeneca, and serves on the speaker's bureau of McNeil, Sanofi-Aventis, and Ortho-McNeil. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

Fitness Now Comes in a Pill!

ABSTRACT & COMMENTARY

By Ralph R. Hall, MD, FACP, FACSM

Emeritus Professor of Medicine University of Missouri-Kansas City School of Medicine

Dr. Hall is a consultant for Aventis.

Synopsis: *Rosiglitazone improves exercise capacity in individuals with Type 2 Diabetes.*

Source: Regensteiner JG, et al. Rosiglitazone improves exercise capacity in individuals with type 2 diabetes. *Diabetes Care*. 2005;28:2877-2883.

REGENSTEINER AND COLLEAGUES OBSERVED THAT EVEN IN THE absence of cardiovascular disease, persons with type 2 diabetes have an impaired ability to carry out maximal exercise, and that the impairment is correlated with insulin resistance and impaired endothelial function. They postulated that administration of a thiazolidinedione (TZD) would improve exercise capacity in type 2 diabetes.

Twenty patients with uncomplicated type 2 diabetes were randomly assigned in a double blind study to receive 4 mg/day of rosiglitazone or matching placebo after baseline measurements to assess endothelial function, maximal oxygen consumption (VO_{2max}), oxygen uptake (VO_2) kinetics, and insulin sensitivity by hyperinsulinemic-euglycemic clamp. Measurements were reassessed after 4 months of treatment.

Participant groups did not differ at baseline in any measure. Rosiglitazone-treated patients (n = 10) had significantly improved VO_{2max} (19.8 ± 5.3 mL $\times$ kg^{-1} $\times$ min^{-1}) before rosiglitazone vs 21.2 ± 5.1 mL $\times$ kg^{-1} $\times$ min^{-1} after rosiglitazone ($P = 0.01$). Insulin sensitivity and endothelial function also improved significantly. A change in VO_{2max} correlated with improved insulin sensitivity and endothelial function. Placebo treated (n = 10) patients showed no improvement in VO_{2max}, insulin sensitivity, or endothelial function after treatment with rosiglitazone.

This is the first report demonstrating that a TZD improved exercise function in type 2 diabetes. Whether this is due to observed improvements in insulin sensitivity and/or endothelial function or is

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due to another action of this class of anti-diabetic drugs is unknown.

COMMENTARY

This is an interesting study but it should be viewed with some skepticism. It is small, the improvement in exercise capacity is small, and the it was of short duration. If the study were of longer duration, would the exercise capacity have improved more or would there have been a gradual return to baseline?

Despite these shortcomings this is a worthwhile study using a medication that has already demonstrated its value in the treatment of type 2 diabetes. This experiment was carried out by experienced investigators in a laboratory with demonstrated expertise in exercise testing and in the treatment of diabetics. They had reason to believe that the TZDs would increase exercise capacity based on the drug's mechanism of action.

The authors note that "the study was not designed to evaluate the mechanism by which rosiglitazone increased exercise capacity; the potential relationships between improved exercise capacity, endothelial function and insulin resistance, separately or together, require further investigation."

It is presumed that other TZDs will improve exercise capacity. If insulin resistance is an important factor then metformin should also improve exercise capacity.

LeBrasseur and Ruderman in an accompanying editorial[1] discuss the potential mechanisms of action that lead to the improved exercise performance as the result of TZD treatment. Possible mechanisms include increased exercise capacity a result of improved mitochondrial function, improvement in muscle blood flow and oxygen extraction, a decrease in inflammatory cytokines and other mechanisms.

The other question for physicians treating type 2 diabetics is whether this small change in VO_{2max} is clinically significant. ■

Reference

1. LeBrasseur NK, Ruderman NB. *Diabetes Care*. 2005;28:2975-2976.

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Cardiovascular Risk Factors for Predicting a Long Life

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

Dr. Ferris reports no financial relationship to this field of study.

Synopsis: *Participants in the Framingham Heart Study who had low levels of cardiovascular risk factors in middle age had longer overall survival and less morbidity when followed to age 85. Control of risk factors may have a major influence on reaching older age in good health.*

Source: Terry DF, et al. Cardiovascular risk factors predictive for survival and morbidity-free survival in the oldest-old Framingham Heart Study participants. *J Am Geriatr Soc*. 2005:53:1944-1950.

USING DATA FROM THE MASSACHUSETTS FRAMINGHAM Heart Study of 2,531 men and women, information gathered during at least 2 examinations between age 40-

50 years was compared to overall survival and morbidity up to age 85. Risk factors analyzed included nationally accepted guidelines for values of systolic and diastolic blood pressure, serum cholesterol level, body mass index, presence of diabetes, and smoking status; additional factors analyzed were educational level, physical activity index, pulse pressure, antihypertensive medication, and electrocardiographic evidence of left ventricular hypertrophy.

Predicted probability of survival to age 85 was greatest in women with no risk factors (65% vs 14% with 5 factors), and less in men (37% with no factors vs 2% with 5 factors). Increased risk of early death and morbidity increased with the number of risk factors, of which the most influential were lower midlife blood pressure and total cholesterol levels, absence of glucose intolerance, nonsmoking status, and higher educational attainment. Fully one-third of the Framingham participants survived to age 85, and 22% of those were free of morbidity.

COMMENTARY

These data provide further evidence to use in motivating our patients to modify their cardiovascular risk factors in middle age. There has been concern that the longer survival we hope for may be marked by increased disease at older ages, but this study, along with others[1] with long-term follow-up, support the premise that favorable cardiovascular risk profiles in middle age lead to both better quality of life and lower risk of diseases in older age. It is disappointing that the survival for men was markedly less than for women with similar risk factors, which suggests other unidentified influences are contributing to this difference.

The relative importance of the different risk factors varies in the current medical literature. A recent Finnish study which followed 47,212 men and women for a mean of 18 years pointed to a lack of physical activity as the most influential predictive factor for early mortality and morbidity; this was associated with obesity which was accompanied by more cardiovascular risk factors.[2] In this group, women with obesity had more early mortality than men (18% vs 6%).

Other than living in the Framingham area of Massachusetts, where a remarkably large portion of the population live to age 85, it seems most likely that increased years of survival with minimal morbidity can be gained from a combination of factors, many of which may be modifiable in middle age. ■

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Carbs are OK: Certainly for Women

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego

Dr. Scherger reports no financial relationship to this field of study.

Synopsis: *In the largest randomized dietary intervention trial conducted to date, a low-fat predominately carbohydrate diet resulted weight maintenance over 7.5 years in postmenopausal women compared with a control diet higher in fat.*

Source: Howard BV, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial. *JAMA*. 2006;295:39-49.

The Women's Health Initiative (WHI) included a Dietary Modification Trial with the primary end points looking at breast and colorectal cancer. More than 48,000 postmenopausal women were randomized into either a dietary intervention with a goal of 20% calories from fat with a high intake of vegetables, fruit and grains, or a control group simply given nutrition information. At baseline, the women had a mean age of 62.3 years, mean body mass index of 29.1 (overweight), and a dietary fat intake of at least 32% of total calories.

This was not a weight loss trial, but the monitoring of the 2 groups included measuring body weight. The intervention group lost a mean of 2.2 kg during the first year and maintained this weight over 7.5 years. The control group had modest weight gain between ages 50 and 70. Among the women in the intervention group, the lower the fat intake the greater the weight loss. A greater intake of vegetables and fruit also resulted in greater weight loss. Grain intake was neutral with respect to weight.

The authors conclude that a low-fat predominately carbohydrate eating pattern does not result in weight gain in postmenopausal women.

COMMENTARY

The low carb craze is finally winding down, and this study helps bring balance and sanity back into nutritional advice. Three recent studies did report that people assigned to a low-calorie, low-carbohydrate diet (with high protein and fat content) lost more weight during a 6-month period than did those assigned to a reduced fat diet.[1-3] However, in the study which was extended to 1 year, no differences in weight loss were demonstrated.[1] The long-term health effects of a high-protein and high-fat diet have not been determined, but raise considerable cause for concern with respect to cardiac risk factors.

What have we learned from the recent dietary swings with respect to carbohydrates, fat, and protein? Some might think confusion and cynicism, and there is no solution except eating less and exercising more. I think we have learned a lot about healthy eating and some clues for weight loss and weight maintenance. This study is large and gives us limited, but important, information. A healthy diet consists of vegetables, fruits and grains, is low in fat, and does not result in weight gain. Note that doughnuts, cookies, sodas, and candies were not included in the recommended carbohydrates. These unhealthy foods have a high glycemic index and drive hunger. Time honored evidence demonstrates that diets high in saturated fats are not healthy. We have learned about healthy fats such as monounsaturated and polyunsaturated oils which reduce cardiac risk factors.[4] Finally, we know that ingesting protein with each meal is beneficial in reducing the glycemic index of carbohydrates resulting in less hunger and the tendency to eat less overall calories, the bottom line in weight loss and maintenance.

We live in a society with an unprecedented abundance and variety of food. People vary greatly in their food tastes. Promoting healthy nutrition requires flexibility in food choices. Understanding the basic principles of healthy carbohydrates, fats and proteins will go a long way in counteracting the epidemic of overweight and obesity. If people limited their food choices to healthy foods and kept active, we would not have today's epidemic obesity problem. This important study provides great reassurance and validation that the low fat diet recommendation is still valid, certainly in postmenopausal women. ■

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An Oral Solution for Partial Small Bowel Obstruction

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Residency Program Director, Associate Professor of Family Medicine, University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus, Huntsville

Dr. Wilke reports no financial relationship to this field of study.

Synopsis: *The use of a laxative, a digestive aid, and a surfactant leads to speedier recovery from partial small bowel obstruction with less need for surgery.*

Source: Chen SC, et al. Nonsurgical management of partial adhesive small-bowel obstruction with oral therapy: a randomized controlled trial. *CMAJ*. 2005;173:1165-1169.

CHEN AND COLLEAGUES IN TAIPEI CONDUCTED THIS single-blind, randomized control study of a combination of oral magnesium oxide (a laxative), *Lactobacillus acidophilus* (a digestive aid), and simethicone (a surfactant) in the treatment of partial small bowel obstruction (PSBO) secondary to adhesions. Criteria for admission into the study were: signs and symptoms consistent with PSBO (pain, distention, nausea, vomiting, and constipation), a history of abdominal surgery at least 4 weeks before enrollment, and a plain upright abdominal X-ray that showed dilated loops of small bowel, air-fluid levels, and colonic gas. In this study, 128 patients were identified. They excluded patients with no X-ray evidence of gas in the colon, signs of intestinal strangulation or peritonitis, fever, intractable pain, or leukocytosis.

Patients were also excluded if adhesions were not the cause of the PSBO (eg, inflammatory bowel disease, hernia, cancer, or irradiation). All patients had a thorough history and physical and had a complete blood count and abdominal X-ray. They all received intra-

venous Ringer's lactate and a nasogastric tube for decompression. They were randomized to a usual conservative therapy group (nothing by mouth) or the intervention group (MgO 250 mg 2 tablets, plus *Lactobacillus acidophilus* 0.3 mg tablet, plus simethicone 40 mg tablet 3 times daily). All patients had daily abdominal X-rays. The decision to take a patient to surgery was made if the patient became toxic (fever, leukocytosis, intractable pain, signs of peritonitis) or if the PSBO persisted for 5 days. Discharge criteria were no pain, tolerating solids, and an abdominal X-ray showing no gas in the small bowel. Patients were followed for 6 months post discharge.

The 2 groups were well matched with a slight preponderance of males. Average age was 54 years (range, 18 to 83). The intervention group underwent surgery less frequently (9.2% vs 23.8%; number-needed-to-treat, 7) and had shorter length of stay (LOS) (1.0 vs 4.2 days). Both results were statistically significant. Complications and recurrence of PSBO were low and not statistically different between the 2 groups.

COMMENTARY

Every so often a really neat clinical trial comes across my desk. This one had a tightly focused clinical question whose results are important to patients and third-party payers. It's not surprising that the control group had longer LOS; after all, they had a higher rate of surgery with the subsequent postoperative recovery period. What I found surprising was the speed at which symptoms in the intervention group resolved. This therapeutic regimen has the potential of saving a great deal of money, based on a difference of 3.2 days of hospitalization, no operating room charges, and, presumably, less time off work. In the long term, because the vast majority of PSBO is caused by adhesions from prior abdominal surgery,[1] perhaps there will be fewer recurrences in the non-operative group, although this was not demonstrated in this study during the 6-month follow-up period.

One obstacle to adoption of this treatment in the United States is the dosing of *L. acidophilus*. A search of the US Pharmacopeia[2] failed to find any reference for *L. acidophilus*. The tablets (sold as Bacid®, Kala®, Lactinex®, MoreDophilus®, Pro-Bionate®, Superdophilus®) are available at on-line pharmacies, but usually the dosage is not listed, and when it is, it is given as the number of live organisms. Becton Dickinson, the manufacturer of Lactinex®, reports that each tablet contains 1 million CFUs, which equates to 0.5 grams.[3] The hospital where I admit patients does stock it; I suggest you check with your hospital pharmacy before trying this regimen. MgO, *L. acidophilus*, and simethicone are dirt cheap. MgO 250 mg tablets are available in 200-tablet bottles for less than $10.00; Lactinex® comes in bottles of 50 tablets and also sells for less than $10.00. Simethicone (Flatulex®, Mylicon®, Gas-X®, and others) is even cheaper.

This is not the first time an oral regimen has been advanced for treating PSBO. A Cochrane Review[4] from January 2005 found that the use of a water-soluble contrast (eg, Gastrografin®) predicts non-operative resolution of adhesive small bowel obstruction and appears to reduce hospital stay, but does not cause resolution of PSBO. Interestingly, the lead author of the Cochrane Review was the second author of a study[5] published in August 2005 that found that Gastrografin® accelerates resolution of PSBO. ■

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Pharmacology Update

Sunitinib Maleate Capsules (Sutent®)

By William T. Elliott, MD, FACP, and James Chan, PhD, PharmD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationships to this field of study.

THE FDA HAS APPROVED A NEW DRUG FOR THE TREATment of gastrointestinal stromal tumor and metastatic renal cell cancer. Sunitinib is an orally active, highly selective, multi-targeted tyrosine kinase inhibitor. The drug was given a priority review and was approved in less than 6 months. Sunitinib is marketed by Pfizer as Sutent®.

Indications

Sunitinib is indicated for the treatment of gastrointestinal stromal tumor (GIST) after progression on or intolerance to imatinib. It is also indicated for the treatment of advanced renal cell carcinoma (RCC).[1]

Dosage

The recommended dose for GIST and advanced RCC is 50 mg capsule taken once daily for 4 weeks on and 2 weeks off. Dose reduction to a minimum of 37.5 mg should be considered if sunitinib is co-administered with a strong CYP3A4 inhibitor (eg, ketoconazole, itraconazole, protease inhibitors). A dose increase should be considered to a maximum of 87.5 mg if sunitinib is co-administered with a CYP3A4 inducer (eg, rifampin). Sunitinib may be taken without regard to meals.

Sunitinib is supplied as 12.5 mg, 25 mg, and 50 mg capsules.

Potential Advantages

Sunitinib has been shown to prolong time to tumor progression in patients with GIST resistant to or intolerant to imatinib. In patients with RCC sunitinib has been shown to reduce tumor size.

Potential Disadvantages

Serious adverse events have been reported with sunitinib. These include left ventricular dysfunction, hemorrhagic events, hypertension, myelosuppression, and reduced adrenal function. Other adverse events include diarrhea, nausea, stomatitis, dyspepsia, vomiting, skin discoloration, fatigue, mouth pain/irritation, and taste disturbance.[1]

Comments

Sunitinib is a multitargeted tyrosine kinase inhibitor. Targets include vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2), platelet-derived growth factor receptors, and stem cell factor receptors.[1,2] It has demonstrated antitumor and antiangiogenic activity. In a randomized, double-blind, placebo-controlled trial in patients with GIST whose disease progressed on imatinib or who were intolerant of imatinib (n = 312), sunitinib (50 mg daily; 4 weeks on and 2 weeks off) was found to significantly improve time-to-tumor progression and progression-free survival compared to placebo.[1] The median time to tumor progression for sunitinib vs. placebo respectively was 27.3 (95% CI, 16.0%-32.1%) weeks vs 6.4 (95% CI, 4.4%-10.0%) weeks and median progression-free survival was 24.7 (95% CI, 11.1%-28.3%) and 6.6 (95% CI, 4.4%-9.9%) weeks respectively. The partial response rate was 6.85 (95% CI, 3.7%-11.1%). In 2 single-arm studies in patients with metastatic RCC (n = 106 and 63) who had progressed on cytokine-based therapy, sunitinib showed response rates of 25.5% and 36.5%.[1] Objective response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST).[3] Median duration of response was 54 (95% CI, 24.7-49.6) weeks in one study. The second study was still in progress when data were collected.[1] Common adverse events include fatigue, myelosuppression, skin discoloration, taste disturbance, bleeding, and gastrointestinal symptoms. Patients should be monitored for left ventricular dysfunction, hypertension, CBC and platelet counts, thyroid function, and pancreatic function. Dosage adjustment is required if sunitinib is co-administered with a strong CYP3A4 inhibitors and inducers.

Clinical Implications

Imatinib is a first-line treatment for unresectable and/or metastatic GIST.[4,5] Sunitinib provides a treatment option in patients who have failed or are intolerant of imatinib. For metastatic RCC, adjunct therapy with conventional chemotherapy, interferon alfa, or interleukin-2 has not been effective.[3,6] Sunitinib provides an agent with a measurable response rate. It joins sorafenib as recent approvals for advanced RCC. There are approximately 32,000 new cases of advanced renal cancer and 5,000 cases of GIST annually.[7] ■

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CME Questions

7. **When compared to usual conservative therapy, use of magnesium oxide, *L. acidophilus*, and simethicone in the treatment of partial small bowel obstruction was associated with:**
   a. a longer length of stay.
   b. more recurrences of small bowel obstruction.
   c. less need for surgery.
   d. fewer complications.

8. **The evidence from the Women's Health Initiative Dietary Modification Trail supports which of the following dietary recommendations:**
   a. A diet with 30% of calories from fat supports the maintenance of body weight.
   b. A diet with less than 50% carbohydrates supports the maintenance of body weight.
   c. A diet with 2 grams of protein per pound of body weight supports the maintenance of body weight.
   d. A diet low in fat and high in carbohydrates from vegetables, fruits and grains supports the maintenance of body weight.

9. **Middle aged men in the Framingham Heart Study who had 5 cardiovascular risk factors were found to have what percent chance of survival to age 85?**
   a. 2%
   b. 5%
   c. 10%
   d. 20%
   e. 30%

Answers: 7 (c); 8 (d); 9 (a)

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CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances; and
- to describe cost-effective treatment regimens.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Erectile Dysfunction and Subsequent Cardiovascular Disease

THE PRESENCE OF ERECTILE DYSfunction (ED) has recently been recognized to commonly be a consequence of endothelial dysfunction. Indeed, some have suggested that ED may be an indicator of existing vasculopathy in the same way angina, intermittent claudication, or TIA reflect vascular compromise.

The Prostate Cancer Prevention Trial population (n = 18,882) was designed to investigate the impact of finasteride upon incidence of prostate cancer in healthy men. As part of the data accrual, assessment of sexual function at baseline and on followup was performed. Because finasteride can affect sexual function, only the placebo group data (n = 9,457) were used for analysis. In this group, 85% were free of cardiovascular disease at baseline.

Although approximately half of the men were free of ED at baseline, by the 5-year mark of the study, 57% of these had developed it. Amongst these men (incident ED), there was a 25% increased hazard ratio for new cardiovascular events. Amongst all men with ED (incident plus present at study initiation), the hazard ratio for a new cardiovascular event was increased by 45%.

ED predicts increased risk of new cardiovascular events. The magnitude of association is as strong as that of cigarette smoking or family history. Men with ED should be encouraged to have close scrutiny and appropriate modification of their cardiovascular risk factors. ■

Thompson IM, et al. JAMA. 2005;294: 2996-3002.

Oseltamivir Resistance during Influenza A Infection

NO ONE DOUBTS THAT INFLUENZA can extract dread consequences on a grand scale. Some degree of complacency may have been fostered by the development of highly effective oral agents for the treatment of influenza A and B, such as the neuraminidase inhibitors oseltamivir (OTV) and zanamivir. Clinicians share a great respect for the capacity of bacteria to develop resistance to antibiotics; there is little corresponding awareness of the role of viral resistance in antiviral therapeutics.

The H5N1 influenza virus (FLU-H5N1) is particularly ominous in its adverse outcomes and potential for pandemic spread. There has been great hope that agents like OTV might provide adequate treatment or prophylaxis for FLU. Unfortunately, resistance to antivirals, including OTV, might become problematic.

De jong et al provide data from Vietnam about 8 cases of FLU-H5N1. In 2 of the patients, neuraminidase amino acid substitution resulted in OTV resistance; both of these patients died. Amongst the other 6 patients, prompt reductions in FLU-H5N1 viral load was correlated with survival: 2 of 6 patients (without resistance) who failed to evidence a prompt reduction in viral load succumbed

These sobering data suggest that OTV alone may be insufficient to ensure successful treatment of some evolving strains influenza virus. It may be that a 2-drug regimen will be required to grapple with the potential for emergence of resistant strains, or when failure of monotherapy to promptly reduce viral load occurs. ■

de Jong MD, et al. N Engl J Med. 2005;353:2667-2672.

Dietary Intake of Antioxidants and AMD

AGE-RELATED MACULAR DEGENERAtion (AMD) is the most prevalent cause of blindness in first-world nations. Although vitamin and antioxidant supplementation has not fulfilled its blush of initial promise for cardiovascular end points, data on supplements of beta carotene, vitamin C, vitamin E, and zinc indicate a beneficial slowing of AMD progression. Whether dietary intake (apart from supplements) is associated with AMD was the subject of this study.

Rotterdam, the Netherlands was the source of this population-based study (n = 10,725) of socioeconomically middle-class adults older than age 55 (mean age, 68). Early AMD was defined by the presence of drusen (white retinal deposits). All study subjects underwent photographic evaluation of their fundi. All subjects completed food diaries. Follow up was 8 years.

There was an inverse relationship between vitamin E and zinc intake and AMD. Each 1-standard deviation increase in dietary intake was associated with an 8-9% decrease in AMD. Overall intake of vitamin C, E, beta carotene, and zinc above the median was associated with approximately one-third less risk of new AMD. Interestingly, among those in the highest quintile of dietary intake, adding supplements did not appear to affect risk reduction. These observational data suggests that diet may have a meaningful impact upon risk of AMD. ■

van Leeuwen R, et al. JAMA. 2005;294:3101-3107.

In Future Issues: **A Normal Temperature May Not Be What We Were Taught**