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INSIDE

Effect of new diagnosis of Barrett's esophagus on insurance status
page 147

Increased dietary intake of folate reduces the risk of developing Alzheimer's disease
page 148

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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 AstraZeneca and serves on the speaker's bureau of McNeil, Sanofi-Aventis, and Ortho-McNeil.

Even If You Use It, You May Lose It!

ABSTRACT & COMMENTARY

By Ralph R. Hall, MD, FACP, ASM

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Dr. Hall is a consultant for Aventis.

Synopsis: *The decline in VO_2 in healthy adults is not constant across age spans but accelerates markedly with each successive age decade despite increases in leisure time physical activity. The decline in aerobic capacity is greater in men than women.*

Source: Fleg JL, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults.*Circulation.* 2005;112:674-682.

THE ABILITY OF OLDER PERSONS TO FUNCTION INDEPENDENTLY is dependent on the maintenance of sufficient aerobic capacity and strength to perform daily activities. Peak aerobic capacity has been shown to decline with age. The rate of decline has previously been estimated from cross sectional studies. Cross sectional studies may provide an overly optimistic estimate of the changes that take place with age.

To determine the longitudinal rate of change in aerobic capacity and the influence of age, gender, and physical activity on these changes, Fleg et al performed serial measurements of peak treadmill oxygen consumption (peak VO_2). The tests were performed in 375 women and 435 men ages 21 to 87 years of age who were enrolled in the Baltimore Longitudinal Study of Ageing, a community-dwelling cohort free of clinical heart disease, over a median follow-up period of 7-9 years.

A mixed effects regression model was used to calculate the change in peak VO_2 expressed in ml per minute, for each age decade from the 20s through the 70s after adjustment for self-reported leisure time physical activity. A longitudinal decline in peak VO_2 was observed in each of the 6 age decades in both sexes. However, the rate of decline accelerated from 3-6% per 10 years in the 20s and 30s to > 20% per 10 years in the 70s and beyond. The rate of decline in the men was greater than in the women from the 40s onward.

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Similar rates of decline prevailed whether peak VO_2 was indexed per kilogram of body weight or per kilogram of fat free mass, and in all quartiles of self reported physical activity. The longitudinal rate of heart rate decline averaged only 4% to 6% per 10 years and accelerated only minimally with age.

Fleg and colleagues concluded that the rate of decline in peak VO_2 in healthy adults is not constant across age span but accelerates markedly with each age decade regardless of physical activity habits.

COMMENTARY

There is both good news and bad news associated with this study. The bad news is that with ageing there is a continuing decline in aerobic fitness. The good news is that the more leisure time physical activity the better your aerobic fitness at all ages. These studies confirm the findings of Tanaka et al who found, in a cross sectional study, that the absolute but not he relative rate of decline was greater in highly active women (competitive runners) than that of sedentary women. In fact, many of the active women in their 60s and 70s had VO_2 max levels similar to 20 and 30 year old sedentary women. The other good news, from a scientific point of view, is that this study provides an important data base from which a number of future studies can be done.

Fleg et al attempted to correct for fat free mass by calculating the ratio of the peak VO_2 (mL/min) divided by the fat free mass. As Ades and Toth note, in their accompanying editorial,[2] this may not be "a precise method for correction of fat free mass. However, it does make it unlikely that fat free mass accounts for the decline in aerobic fitness." Ades and Toth postulate that the delivery of oxygen to exercising muscle or the ability of muscle to use oxygen are more likely the determinants of declining aerobic activity.

There is still considerable controversy regarding the age related decline in peak VO_2. Fleg and associates note there are prior studies in small homogenous samples in which middle aged and older men who continue to exercise vigorously experience significantly attenuated reductions in peak VO_2.[3] The work of Wang et al who followed runners over a 13-year period is also noteworthy. The runners not only had less reduction in their fitness and a longer life span but also a decrease in morbidity prior to death when compared to their sedentary controls.[4]

Recent physiological studies support the concept that endurance activity is an important factor in decreasing the decline in aerobic fitness. Eskurza et al[5] found that brachial artery flow-mediated dilatation was 45% lower in sedentary older men than sedentary younger men but was preserved in endurance trained older men. Franzoni et al[6] also noted that ageing is associated with oxidative stress and endothelial dysfunction. However, they also found that antioxidant activity and oxyradical scavenging was associated with preserved endothelial function in older endurance athletes. These positive changes may be associated with improved aerobic fitness and protection from adverse cardiac events.

Keep in mind that despite the more rapid decline in aerobic capacity with age, the level of fitness of the exercising individuals will be far better than those who are sedentary. The exercising group will likely have 5 or more years of life and be free of disabilities compared to their sedentary counterparts.

Encouraging people to exercise more is difficult. As we age we tend to give up endurance activities and many forms of exercise that are beneficial, such as yard work

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Questions & Comments

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and heavy household chores.

We need to remember, however, that when you give up the hard things the easy things become hard. ■

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Effect of a New Diagnosis of Barrett's Esophagus on Insurance Status

ABSTRACT & COMMENTARY

By Malcolm Robinson MD, FACP, FACG

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Synopsis: *Although patients with Barrett's esophagus have a normal life expectancy, diagnosis of Barrett's esophagus more than doubles life insurance premiums and may limit or prevent access to health insurance.*

Source: Shaheen NJ, et al. Effect of a new diagnosis of Barrett's esophagus on insurance status. *Am J Gastroenterol.* 2005;100:577-580.

Barrett's esophagus (BE), metaplastic replacement of esophageal squamous mucosa with specialized columnar epithelium, is increasingly common. BE is clearly associated with an increased risk of esophageal adenocarcinoma, and screening endoscopies have been recommended to identify BE (and to initiate endoscopic surveillance to allow early identification of dysplasia or early malignancy). Unfortunately, direct data do not yet substantiate that such screening and surveillance will lengthen life or provide improved quality of life. Shaheen and colleagues hypothesized that identification of BE might adversely impact life and health insurability. To assess such impact, this study assessed effects of newly diagnosed BE on insurance rates from 20 insurers in California and North Carolina. In each location, a BE patient requested the best rate for a $1 million 20-year term life insurance policy with the preferred rate for a nonsmoker. After the best rate was obtained, the rate for an identical policy with the new diagnosis of nondysplastic BE was requested. In North Carolina, the patient was a 43-year-old Caucasian male nonsmoker. In California, the patient was a 36-year-old female nonsmoker. Companies refusing to insure a patient with BE or increasing life insurance premiums for this diagnosis were sent a physician's letter including data demonstrating normal life expectancy with BE. Health insurance quotes were also requested. The mean life insurance annual premium for the healthy male was $1,255 with a range of $1,050 to $1,495. With BE, the mean rate rose 118% to $2,731 ($1,250-$4,340; P < 0.001). The healthy female premium was $517 ($452-$551), rising by 177% with BE diagnosis to $1,434 ($1,144-$1,896; *P* < 0.001). No company lowered its premium after physician letters requesting reconsideration had been sent. Health insurance could not be obtained at all from a number of companies, and no companies would consider issuing health insurance without additional evaluation. Shaheen et al state that 3 million Americans have BE. It is clear that most of these will never get cancer (rate of cancer developing in BE is < 0.005 cases/year). Overall 'statistical" life expectancy is almost certainly normal in BE. The authors strongly assert that insurers need to be educated regarding the generally benign prognosis of BE, and patients who are considered for screening must be told that there are some potentially drastic consequences inherent to the diagnosis of BE that may not be counterbalanced by any medical advantage provided by such identification.

■ COMMENTARY

Physicians often tend to be 'activists,' assuming that most or all possible medical interventions are worth undertaking. Unfortunately, they are also frequently motivated by the fact that intervening (as in screening endoscopy for BE) will be financially

rewarding for the physician involved. In this regard, the situation may be similar to asking a barber about the utility of haircuts. This study and many others question the value of universal endoscopic screening for BE. If such screening cannot reproducibly improve quality or length of life and if there are powerful negative consequences to undertaking such screening, involved professional societies ought to re-think their current strong support for this program. At the least, it is mandatory that patient understand all of the admittedly limited benefits and the unquestioned risks of undertaking such screening. BE occasionally can be the precursor of a dreaded cancer, but most patients with BE can be expected to have a long and healthy life. As physicians, we should think twice before recommending screening of heartburn sufferers for BE. Without a doubt, the medical profession needs to help inform insurance companies that life insurance should be available to nondysplastic BE patients without huge increases in premiums. Furthermore, the loss of health insurance by patients with BE is viciously counterproductive since it may well prevent access for whatever screening and care may be needed for their long-term management. ■

Increased Dietary Intake of Folate Reduces the Risk of Developing Alzheimer's Disease

ABSTRACT & COMMENTARY

By M. Flint Beal, MD

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Dr. Beal reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

Synopsis: *An increased dietary intake of folate reduces the risk of developing AD.*

Source: Corrada M, et al. Reduced Risk of Alzheimer's Disease with High Folate Intake: The Baltimore Longitudinal Study of Aging. *Alzheimer's & Dementia*. 2005;1:11-18.

THE PRESENT REPORT COMES FROM THE BALTIMORE longitudinal Study of Aging. This is a large study prospectively following patients for development of Alzheimer's disease (AD). The study was initiated in 1958 by the National Institute of Aging to prospectively examine the normal aging process. It was originally limited to men, but the study began enrolling women in 1978. The study cohort comprises well-educated, predominantly white community-dwelling volunteers who return every 2 years for 2.5 days of multidisciplinary tests. These include medical, physiological, and biomedical examinations, as well as cognitive evaluations. The present study was based on a dietary intake report, which previously has been determined to be an accurate assessment of vitamin intake. Corrada and colleagues evaluated whether total intake from diet plus supplements of antioxidant vitamins including vitamin E, C, carotenoids, and B vitamins, including folate, B6, and B12 were associated with a reduced risk of developing AD. The participants were 579 non-demented elderly volunteers who recorded their dietary supplement intake for a 7-day period. After a mean follow-up of 9.3 years, 57 participants developed AD, as assessed by standard criteria. A higher intake of folate resulted in a relative risk of developing AD of 0.41, and vitamin E with a relative risk of 0.56. Vitamin B6 had a relative risk of 0.41. These were individual associations of decreased risk of developing AD after adjusting for age, gender, education, and caloric intake. When the 3 vitamins were analyzed together, however, only intake of folate at or above the recommended dietary allowance was associated with significant decreased risk of AD. These findings suggest that an increased dietary intake of folate reduces the risk of developing AD.

■ COMMENTARY

In previous columns in *Internal Medicine Alert*, the association of increased homocysteine levels with AD has been discussed. This appears to be independent of the increased risk of vascular diseases associated with elevated homocysteine levels. This prospective study provides evidence of a reduced risk of AD among people with high intake of folate. This may very well be an effect on homocysteine levels. Some studies of antioxidant supplements have found effects of vitamin C or vitamin E with vitamin C; however, this was not observed in the present study. The present results were obtained before mandatory folate fortification of grain products began in the United States in 1998. This was done with the intention of reducing neural tube defects. It is, therefore, as yet unclear, whether folate supplementation will be beneficial. Corrada et al, however, felt that almost half of the participants would have been deficient regardless of the increased

folate fortification in present diets. These results provide further evidence that modulation of diet may have a major effect on risk of developing AD. As noted, some but not all prior studies of antioxidant vitamins have shown a reduced risk of developing AD. Furthermore, diets with high amounts of omega 3 fatty acids also reduce the risk of developing AD. The present results provide further evidence that intake of folate may also have a major effect on risk of developing AD. ■

Pharmacology Update

Ramelteon Tablets (Rozerem™)

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

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Associate 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 the first melatonin receptor agonist for the treatment of insomnia. Ramelteon differs from benzodiazepine and nonbenzodiazepine sedative hypnotics in that it is a non-scheduled drug and it is approved for long term use. It is marketed by Takeda Pharmaceutical America, Inc as Rozerem™.

Indications

Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset.[1]

Dosage

The recommended dose is 8 mg taken within 30 minutes of going to bed. It should not be taken with or immediately after a high fat meal as the absorption is significantly reduced. Ramelteon should not be used in patients with severe hepatic dysfunction and it should be used with caution in patients with moderate hepatic dysfunction.[1]

Potential Advantages

This is the first melatonin agonist approved and is mechanistically different from the barbiturates, benzodiazepine, and benzodiazepine-related (eg, zolpidem) agents. Ramelteon appears to be well tolerated and with no significant abuse potential, withdrawal, or rebound insomnia.[1]

Potential Disadvantages

Common side effects include somnolence (5% vs 3% for placebo), fatigue (4% vs 2%), and dizziness (5% vs 3%).[1] Some evidence of fatigue was observed with chronic use and mean increase of 34% of prolactin levels have been reported in women.[1]

Comments

Ramelteon is the first melatonin receptor agonist approved. It has a 10-fold greater affinity for MT1 receptor and 100-fold greater affinity for MT2 receptor, associated with sleep promotion, compared to melatonin.[1,2] It has low affinity for MT3 which has other systemic effects and no affinity for GABA receptors. Melatonin is regarded as an internal sleep facilitator and is believed to have a direct effect on sleep-inducing thermoregulatory mechanism.[3] In placebo-controlled studies, ramelteon reduced sleep latency compared to placebo in subjects with chronic insomnia and transient insomnia.[1] In subjects with chronic insomnia (n = 693), ages 64-69 yrs, ramelteon reduced sleep latency by about 8 minutes (78.5 min to 70.2 min) compared to placebo; $P = 0.008$.[4] In a similarly designed study in younger subjects (ages 18-64 yrs), no difference was found between ramelteon and placebo.[1] Ramelteon was studied in a model of transient insomnia using high doses (16 mg and 64 mg) (n = 370).[5] Latency to sleep was 26.6 ± 21.0 min for placebo compared to 14.1 ± 15.1 min and 15.5 ± 15.4 min respectively for ramelteon 16 mg and 64 mg respectively. Total sleep times were 411.3 ± 41.7 min, 425.4 ± 37.6 min, and 422.4 ±34.8 min respectively. These were all statistically different at $P < 0.05$. Wake after sleep onset and time spent in each sleep stage were not significantly different. In a 35-day study, patients who received ramelteon reported more fatigued at week 1 and 3 but not at week 5 compared to placebo.[1] A lower mean number of words recalled were observed at week 3. Elevations of serum prolactin levels have been reported in women. There are currently no published comparisons with other sedative hypnotics. The wholesale cost of ramelteon is $2.25 per 8 mg tablet which is priced similar to or lower than the nonbenzodiazepine drugs such as zolpidem (Ambien), zaleplon (Sonata), and eszopiclone (Lunesta).

Clinical Implications

Ramelteon is the first of the new class of agents to treat insomnia. The benefit of the drug appears modest, providing less than a 10-minute reduction in sleep latency with the FDA approved dose. It is not approved for increasing sleep duration. However the drug is unique in that it appears safe for long-term use. More clinical experience is needed to define the role of the agent in the treatment of insomnia. ■

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CME Questions

13. The incremental benefit of long-term anticoagulant therapy for VTE:

a. Increases as the duration of anticoagulation increases
b. Persists to some degree for at least six months
c. Is the same for high-risk and low risk populations
d. Is minimal.

14. Which of the following is *false*?

a. The fall in peak VO_2 is apparent in both endurance trained and those with high leisure time physical activity.
b. Endothelial function is preserved in older endurance trained men.
c. The loss of lean body mass does not seem to be the cause of the decrease in aerobic fitness with ageing.
d. The fall in aerobic capacity with ageing precludes any benefit from continuing to exercise as we age.

Answers: 13: b; 14: d

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
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Gabapentin for Hot Flashes for Women with Breast Cancer

THE PATHOPHYSIOLOGY OF menopausal hot flashes (HFL) is not fully understood, but restoration of estrogen, with or without progesterone, provides dramatic relief. Recent disenchantment with utilization of hormone replacement therapy (HRT) as a result of the Women's Health Initiative has left a population of HFL sufferers looking for additional relief measures. Although there remains some controversy over its appropriateness, breast cancer (BCA) is generally considered an absolute contraindication to HRT. Many women with BCA are receiving treatments like tamoxifen, which are associated with induction of HFL whether or not the patient is menopausal.

Gabapentin (GABA) is one of several therapeutic choices that has shown efficacy in reducing HRT. Because it has no direct hormonal effects, GABA becomes a rational consideration for BCA patients, further supported by a favorable pilot study in women with BCA.

Women (n = 420) with BCA and HFL at least twice daily (mean number of daily hot flashes = 8.7) were randomly assigned to GABA 100 mg t.i.d., GABA 300 mg t.i.d., or placebo for 8 weeks. HFL frequency and severity were compared at weeks 4 and 8.

Both doses of GABA provided a statistically significant 33% reduction in HFL severity. For frequency of HFL, only the higher (300 mg t.i.d.) GABA dose was statistically superior to placebo, providing a 44% reduction. GABA was very well tolerated, with only a 3% placebo-subtracted dropout rate. Similar results have been seen with clonidine, but no head-to-head comparisons of clonidine vs GABA have been published. ■

Pandya KJ, et al. Lancet. 2005;366: 818-824.

CHF: Risk-Treatment Mismatch

HEART FAILURE (CHF) HAS SOMEtimes been called the 'hemodynamic malignancy,' since mortality outcomes from the time of diagnosis are as bad as or worse than many cancers. Voluminous trial data support the favorable impact of ACE inhibitors, ARBs, and beta blockers upon CHF mortality. Because studies of other major mortal disease states, eg, acute coronary syndromes, has shown us that patients at highest risk may actually receive less frequent pharmacotherapeutic tools that have been shown to favorably affect mortality, it was not unreasonable to assess whether the treatment of CHF patients is well matched to the severity of their disease.

Using the validated EFFECT heart-failure mortality risk-stratification method (EFFECT = Enhanced Feedback for Effective Cardiac Treatment), Lee et al, examined the predicted 1 year mortality rates of a large population of CHF patients in Ontario, Canada (n = 9,942) at hospital discharge. Then, they looked at the relative frequency with which ACE inhibitors, ARBs, and Beta Blockers were prescribed in those determined to be a low, intermediate, and highest risk of mortality in the next year.

Disturbingly, patients at the highest risk of 1-year mortality were least likely to receive treatment with ACE inhibitors, ARBs, or Beta Blockers. For instance, the frequency of ACE inhibitor prescription for those in low, intermediate, and highest mortality risk were 81%, 73%, and 60%, respectively ($P \leq 0.001$ for trend). Even after accounting for potential perceived contraindications to one or more pharmacotherapies, there remained discordance between risk and treatment intensity. Identifying and overcoming clinician barriers to providing appropriate CHF treatment, especially for higher risk patients, is in order. ■

Lee DS, et al. JAMA. 2005;294: 1240-1247.

Diagnosing DPN: The Tuning Fork Wins!

DIABETES REMAINS THE NUMBER one cause of limb loss in the United States, to some degree related to diabetic peripheral neuropathy (DPN). Good diabetic control has been shown to reduce the progression of DPN, and early identification may help forestall consequences, if vigilance towards optimum foot care is maintained.

The literature supports the use of a variety of tests to diagnose DPN, including the 128-Hz tuning fork (128 TF), testing the great toe with pin-prick (TPP), cotton swab light-touch testing of the great toe (CST), monofilament testing using the Semmes-Weinstein monofilament on the sole of the foot (MFT), Achilles reflex testing (ART), and nerve conduction velocity testing (NCV). For those of us who haven't looked at the tuning fork for awhile, the 128TF is the one with the biggest 'ears.' Smaller tuning forks (higher frequency) are not suitable for vibration testing.

Different combinations of these tests were used to diagnose DPN in patients with diabetic foot ulcers (n = 24), diabetics without known neuropathy (n = 24), and a non-diabetic control group (n = 21).

After comparing various tests, alone and in combination, the authors determined that the predictive value and validity of the 128TF alone is best, and is clearly superior to monofilament testing. I guess it's time to step back to simplicity! ■

Meijer JWG, et al. Diabetes Care. 2005;28:2201-2205.

When Did the Chest Pain Begin?

By Ken Grauer, MD

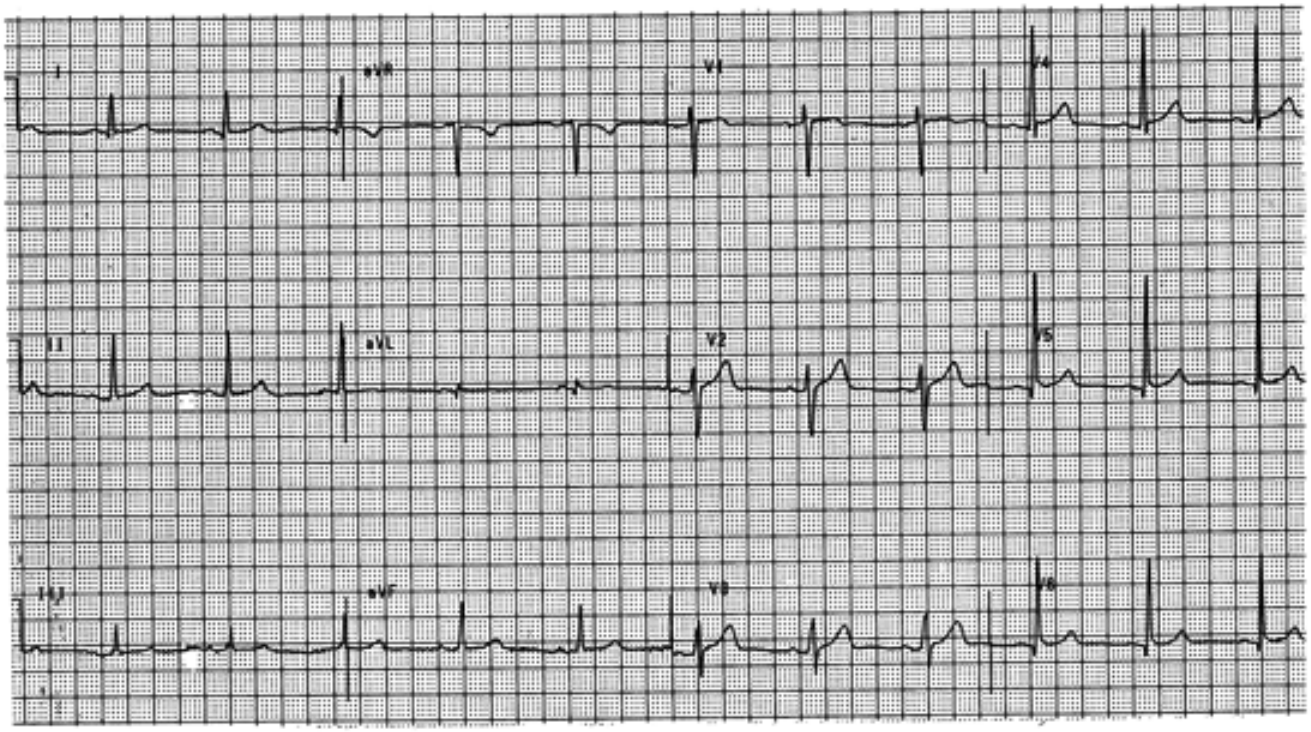

Figure: 12-lead ECG recorded from a 50-year-old man with severe chest pain 5 days earlier, but whose symptoms resolved 2-3 days before this ECG was obtained.

Clinical Scenario: The ECG in the Figure was obtained from a 50-year-old man who presented to the office for evaluation of chest pain. His symptoms began 5 days before the ECG shown here was recorded. The patient's chest pain was initially severe, and had lasted about 2 days—but then resolved. He has several cardiac risk factors, but no prior history of coronary artery disease. In view of this information, how would you interpret his ECG? No prior tracing is available.

Interpretation/Answer: Although P waves are of small amplitude, the rhythm is sinus at a rate of 65/minute. All intervals and the mean QRS axis are normal. There is no ECG evidence of chamber enlargement. There are small q waves in virtually all of the lateral leads. The most remarkable finding on the tracing is slight but definite ST segment elevation in the precordial leads.

ST segment deviations (elevation or depression) are judged with respect to the preceding PR segment. A small amount of ST segment elevation with an upward concavity (ie, "smiley" configuration) is commonly seen as a normal finding in one or more precordial leads, especially V_2 through V_4. The normal variant pattern known as "early repolarization" often produces J-point ST segment elevation in inferior or lateral leads. The problem arises when an adult of suitable age with cardiac risk factors presents with chest pain but without availability of a prior tracing for comparison. This is the situation here.

We suspect that the ECG in this case is benign. The lateral q waves in leads I, aVL, V_5 and V_6 are probably normal septal q waves. Although impossible to rule out recent MI (myocardial infarction) without a prior tracing for comparison, the shape of the ST segments, the diffuse nature of the changes seen here in multiple leads, and the lack of reciprocal ST segment depression make recent infarction unlikely. If an acute MI had occurred 5 days ago, one would have expected evolutionary changes to occur by now (ie, deepening Q waves, ST segment coving, and T wave inversion). ■

In Future Issues:

Sleepiness in Diabetics

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

The Use of Prophylactic Antibiotics for Neutropenia

Antibacterial prophylaxis is generally not recommended for neutropenic patients undergoing chemotherapy. Two studies in the Sept. 8 issue of the *New England Journal of Medicine* may change that recommendation. The first study from Italy looked at 760 adult patients who were undergoing treatment for acute leukemia, solid tumors, or lymphoma and were at risk for chemotherapy-induced neutropenia lasting more than 7 days. Many were undergoing stem cell transplantation. Patients were randomized received either oral levofloxacin 500 mg daily or placebo from the start of chemotherapy until the resolution of neutropenia. The rate of fever present for the duration of neutropenia was reduced in the levofloxacin group (65% levofloxacin prophylaxis, 85% placebo; RR, 0.76, 95% CI; $P = 0.001$). The levofloxacin group also had a lower rate of microbiologically documented infections (17% absolute difference in risk; $P < 0.001$), bacteremia (16% absolute difference in risk; $P < 0.001$), and single agent gram-negative bacteremias (7% absolute difference in risk; $P < 0.01$), compared to the placebo group. There was no difference in mortality, and there was no difference in outcomes between patients with acute leukemia or those with solid tumors or lymphoma. Treatment was generally well-tolerated. The authors conclude that prophylactic treatment with levofloxacin is an effective and well-tolerated way of preventing febrile episodes and other relevant infection-related outcomes in patients with cancer and profound and protracted neutropenia (Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia. *N Engl J Med*. 2005;353:977-987).

The second study from England looked at 1565 patients undergoing cyclic chemotherapy for solid tumors or lymphoma who were at risk for temporary, severe neutropenia. Since these patients were receiving cyclic chemotherapy, the rate of neutropenia was significantly lower than the first study. Patients were randomized to receive levofloxacin 500 mg daily or placebo for 7 days during the expected neutropenia period. During the first cycle of chemotherapy, 3.5% of patients in the levofloxacin group had a least one febrile episode, compared with 7.9% in the placebo group ($P < 0.001$). During the entire chemotherapy course, 10.8% of patients in the levofloxacin group had a least one febrile episode, compared with 15.2% of patients in the placebo group ($P = 0$ .01); the rate of probable infection was 34.2% and 41.5%, respectively ($P = 0.004$). Hospitalization rates were significantly higher in the placebo group, and the rate of severe infection was twice as high in the placebo group (1.0% vs 2.0% [$P = 0$ .15]). The death rate was same in both groups. The authors concluded that prophylactic use of levofloxacin reduces the rate of fever, probable infection, and hospitalization (Cullen M, et al. Antibacterial Prophylaxis After Chemotherapy for

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Solid Tumors and Lymphomas. *N Engl J Med*. 2005;353:988-998).

An accompanying editorial suggests that these are important studies which provide more data on prophylactic antibiotics in neutropenia that had previously been available. However, further study still needs to define which patients are at highest risk and the period of greatest risk during chemotherapy. Most importantly, the emergence of resistant organisms, which was seen in the Italian study, is a major concern. The author states "If prophylactic antimicrobial therapy is to be adopted at a cancer center, it should be accompanied by vigorous infection-control practices and careful monitoring for the emergence of resistant organisms" (Baden LR. Prophylactic Antimicrobial Agents and the Importance of Fitness. *N Engl J Med*. 2005:353: 1052-1054).

Is It Hot In Here?

Hot flashes are common problem for women undergoing treatment for breast cancer. A new study suggests that gabapentin adjusted 900 mg per day may help alleviate symptoms. Four hundred twenty women, with breast cancer and 2 or more hot flashes per day, were randomly assigned to receive gabapentin 300 mg per day or gabapentin 900 mg/day or placebo in 3 divided doses for 8 weeks. The 900 mg per day does reduce hot flashes by 49% and 46% at 4 and 8 weeks, respectively. The 300 mg dose was not effective at a statistical level. The authors suggest that gabapentin 900 mg per day should be considered for treatment of hot flashes in women with breast cancer (Pandya KJ, et al. Gabapentin for Hot Flashes in 420 Women with Breast Cancer: A Randomised Double-Blind Placebo-Controlled Trial. *Lancet*. 2005;366:818-824).

Homeopathy vs Conventional Medicine

A new study suggests that homeopathy is no better than placebo in treating disease. Researchers from the University of Berne in Switzerland, reviewed over 100 clinical trials of homeopathy and conventional medicine. Eight large homeopathy trials were eventually used in a meta-analysis, along with 6 large conventional medicine trials. The odds ratio for homeopathy was 0.88 and for conventional medicine 0.58. When only the largest trials were used, the odds ratio for homeopathy was 0.96 and for conventional medicine 0.67. This suggests that the benefit from homeopathy is no better than random chance (Shang A, et al. Are the Clinical Effects of Homeopathy Placebo Effects? Comparative Study of Placebo-Controlled Trials of Homeopathy and Allopathy. *Lancet*. 2005; 366: 726-732). An accompanying editorial states "Now doctors need to be bold and honest with their patients about homeopathy's lack of benefit. . ." (The End of Homeopathy. *Lancet*. 2005;366:690). Homeopathy which uses very dilute solutions to treat disease has been popular in Europe; however, this study marks a trend away from homeopathy in England. The Swiss government also recently withdrew insurance coverage for homeopathy after a 5-year trial because it did not meet efficacy and cost effectiveness criteria.

FDA Actions

The FDA has approved a new 4-component vaccine for children aged 12 months to 12 years that includes measles, mumps, rubella, and varicella viruses. The approval was based on data showing effectiveness of the vaccine was similar to that of MMR (measles, mumps, and rubella) and varicella vaccine (Varivax). The new vaccine will be marketed under the trade name ProQuad by Merck & Co.

Sanofi-Synthelabo has received approval to market an extended release formulation of zolpidem (Ambien) for the treatment of insomnia. The new preparation is a bi-layered tablet that delivers the drug in 2 stages, a quick dissolving layer to induce sleep, and a slower release layer to provide sleep continuity. Ambien CR will be marketed in a 12.5 mg dose for adults and a 6.25 mg strength for patients 65 years and older.

The Senate has approved a bill to limit over-the-counter sales of pseudoephedrine, a key ingredient in the illicit manufacturing of methamphetamine. The bill which has bipartisan support, will require decongestant medications containing pseudoephedrine to be sold behind pharmacy counters and would limit how much any individual can buy to 7.5g a month (250 30 mg tablets).The bill also encourages a computer tracking system to limit multiple purchases at different stores and pharmacies. A similar bill is working its way to the House of Representatives.

The FDA is one step closer to approving Pfizer's inhaled insulin powder after an advisory panel voted 7-2 to urge approval. The preparation, which will be marketed under the trade name Exubera, is a short-acting insulin powder that is used before meals. The drug does not replace the need for long acting insulin injections. There have been concerns that Exubera may hamper lung function in diabetics, but Pfizer has been able to show 2-year data that suggest patients experience only minimal decrease in lung capacity that is reversible if the drug is stopped. ■