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Internal Medicine

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ABSTRACT & COMMENTARY

Mental Stress-Induced Myocardial Ischemia in Patients with Coronary Artery Disease

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

SYNOPSIS: In a systematic review and meta-analysis of prospective studies examining the association between mental stress-induced myocardial ischemia (MSIMI) and adverse outcome events in patients with stable CAD, all existing investigations point to an approximate doubling of cardiovascular risk in patients with MSIMI.

SOURCE: Wei J, et al. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. *Am J Cardiol* 2014;114:187-192.

It has been reported that one-third to one-half of patients with coronary artery disease (CAD) develop myocardial ischemia in response to mental stress.[1] Mental stress-induced myocardial ischemia (MSIMI) differs from physical exercise or pharmacologic stress-induced myocardial ischemia in that it is less likely to result in chest pain and/or electrocardiographic changes and is not always related to the severity of the coronary atherosclerosis that is present.[2,3]

Because the prognostic significance of MSIMI has not been previously clarified and because the effects of the various treatment modalities are emerging,[4,5] Wei and colleagues performed a systematic review and meta-analysis of the subject with the primary objective of summarizing the existing evidence of the association between MSIMI and adverse outcomes in patients with CAD. Only five studies each with a sample size of less than 200 patients and with fewer than 50 outcome events met the inclusion criteria. The results demonstrated that MSIMI was associated with a two-fold increased risk of a combined endpoint of cardiac events or total mortality.

■ COMMENTARY

Despite a systematic review of the literature, Wei et

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al were only able to find five prospective studies that had investigated MSIMI as a prognostic factor in patients with CAD. Their pooled analysis confirmed a strong association between MSIMI and adverse outcome events in patients with CAD. However, it should be carefully noted that there were only five prospective studies, all of which were relatively small in number and were mostly based on selected small samples with only a few female and minority participants. In addition, most of the studies were incompletely adjusted for potential confounding factors such as medication use and history of other chronic illnesses. Also, since these studies were mostly concerned with patients who were enrolled many years previously, none of the studies used myocardial perfusion imaging, which is believed to be more accurate for the detection of MSIMI than other diagnostic testing methods, based solely on changes in left ventricular function.[6]

Although several other studies have examined the subject,[1,7] the current meta-analysis by Wei et al was the first study to summarize the existing literature on the prospective association between MSIMI and adverse outcomes in patients with CAD. In addition, the precise mechanisms for the association between MSIMI and adverse outcomes are unclear; one possibility is that mental stress causes both coronary artery vasoconstriction and increased heart rate and/or blood pressure, thereby resulting in a myocardial oxygen supply/demand mismatch.[6,8] Mental stress has been linked to impaired endothelial function,[9] exaggerated peripheral microvascular tone,[3,10] and vasoconstriction of normal coronary artery segments.[11] Finally, mental stress has also been associated with induced cardiac electrical instability, possibly resulting in cardiac arrhythmias and even sudden cardiac death.[12-14]

Physicians should be aware of the possible untoward effects of MSIMI and, although more data are needed, MSIMI recognition and management may provide a novel therapeutic approach that may improve patient outcomes over and above the outcomes expected when using only the standard treatments of CAD complications. ■

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ABSTRACT & COMMENTARY

New Recommendations for HIV Testing

By Stan Deresinski, MD, FACP, FIDSA

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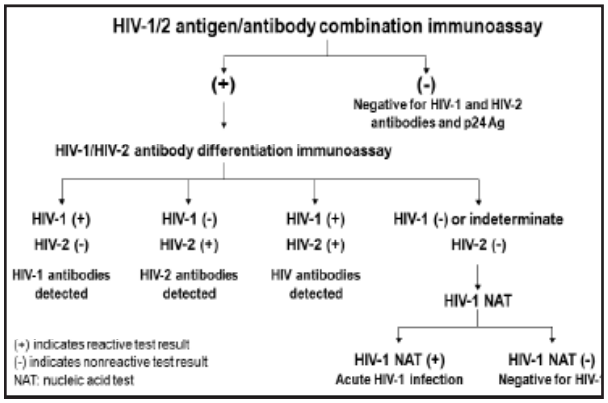
Dr. Deresinski does research for the National Institutes of Health and is an advisory board member and consultant for Merck. This article originally appeared in the August 2014 issue of *Infectious Disease Alert*.

SYNOPSIS: Detecting HIV early creates opportunity for treatment and reduces transmission risk.

SOURCE: Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: Updated recommendations. Available at http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf.

Recommendations for testing for HIV infection have continually evolved as the result of improving technology and clinical knowledge. The latest generation assays allow earlier detection of infection and avoid the frequent false-negative and indeterminate results seen with use of Western blot or immunofluorescence assays (IFA) for confirmation in patients with early infection. This is of importance because of the recognition that the risk of transmission is highest during the acute early phase of infection and because treatment is beneficial in all phases of infection, including the early phase. Furthermore, while HIV-2 infection remains rare in the United States, use of the HIV-1 Western blot misclassifies the majority as HIV-1 infection. Western blot and IFA tests are no longer included in the testing algorithm.

As a consequence of this evolution, the Centers for Disease Control and Prevention and the Association of Public Health Laboratories have provided new recommendations for HIV testing of serum or plasma that supersede previous ones (*see algorithm*). The changes take into full account the sequence of appearance of laboratory markers in the course of HIV-1 infection. Thus, HIV-RNA becomes detectable by nucleic acid amplification tests (NAT) approximately 10 days after infection and increases to very high concentrations. Four to 10 days after viral RNA is detectable, fourth-generation immunoassays are able to detect P24 antigen, but this is transient as the result of the appearance of antibody — unless special methods to disrupt antigen-antibody complexes are used. IgM antibody may be detected by third- and fourth-generation immunoassays 3-5 days after P24 antigen is first detectable and 10-13 days after the appearance of viral RNA. The sequence can be more broadly considered to consist of an initial eclipse period when no markers are detectable, a seroconversion window between initial infection and first detection of antibodies, acute HIV infection describing the interval between HIV RNA and antibody detectabilities, and established HIV infection beginning with a fully developed IgG antibody response.



Initial testing should be with an FDA-approved antigen/antibody combination (fourth-generation) immunoassay that detects antibodies to both HIV-1 and HIV-2 as well as HIV-1 p24 antigen. If this test is negative, no further testing is indicated. If the test is reactive, additional testing with an FDA-approved antibody immunoassay that differentiates antibody to HIV-1 and HIV-2 should be performed. If the fourth-generation immunoassay is reactive but the antibody differentiation test is negative or indeterminate, an FDA-approved HIV-1 NAT should be performed.

■ COMMENTARY

These recommendations emerge from the continuing advance in the technological and clinical aspects of testing for HIV-1 infection. The elimination of Western blot and IFA testing for confirmation of the presence of specific antibody is important given the subjectivity and both indeterminate falsely negative results seen with these assays. The ability to detect HIV-1 infection in its earliest phase provides the opportunity to initiate treatment that is clinically beneficial to the patient and reduces the risk of transmission during a time when viral loads reach their highest levels in plasma in the absence of therapeutic intervention. ■

ABSTRACT & COMMENTARY

Is the Routine Pelvic Exam Obsolete?

By Joseph E. Scherger, MD, MPH

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Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: The American College of Physicians recommends against performing screening pelvic examination in asymptomatic, nonpregnant, adult women.

SOURCE: Qaseem A, et al. Screening pelvic examination in adult women: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2014;161:67-72.

Representing the American College of Physicians, a Minneapolis-based, evidence-based synthesis program center performed a systematic review of the English language literature from 1946 through January 2014 regarding the evidence for or against performing routine pelvic examination in adult women. With the exception of screening for cervical cancer, there was no evidence of benefit in screening for ovarian cancer or any other pathology. Potential harms were cited, although minor, and hence this new clinical guideline. As would be expected, this guideline conflicts with the policies of the American College of Obstetricians and Gynecologists, who recommend a pelvic exam as part of an annual well-woman visit.[1]

The following clinical recommendations are made as part of this guideline:

1. Clinicians do not need to perform a pelvic examination before prescribing oral contraceptives.
2. Screening for sexually transmitted disease can be performed with urine testing or vaginal swabs and does not require a pelvic examination.
3. All or part of a pelvic examination is often indicated in women with such symptoms as vaginal discharge, abnormal bleeding, pain, urinary problems, and sexual dysfunction.
4. When screening for cervical cancer, examination should be limited to visual inspection of the cervix and cervical swabs for cancer and HPV.

■ COMMENTARY

This guideline is a major change in medical practice. Gone is the need for adult women to have a gynecologist just for well-women exams. Internists and family physicians should still be proficient in pelvic examination for the assessment of related health problems and for screening for cervical cancer. Routine Pap smears are no longer recommended annually,[2] but every 3 years in women between the ages of 21 and 65.[2] I predict that monogamous women who are HPV negative will be able to discontinue Pap testing in the future since the vast majority of cervical cancer is caused by the sexually transmitted HPV virus.

Much time and money are wasted in routine health care of no clinical benefit. If the routine pelvic exam becomes obsolete, the shortage of primary care physicians, especially in women's health, will need to be recalculated. ■

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PHARMACOLOGY UPDATE

Suvorexant Tablets (Belsomra®)

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

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

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

The first in a new class of orexin receptor antagonists has been approved by the FDA for the treatment of insomnia. Orexins are hypothalamic neuropeptides that appear to have a role in maintaining wakefulness.[1] Suvorexant is marketed by Merck & Co. as Belsomra.

INDICATIONS

Suvorexant is indicated for the treatment of insomnia (i.e., difficulty falling asleep and/or staying asleep).[1]

DOSAGE

The recommended dose is 10 mg once nightly within 30 minutes of going to bed.[1] There should be at least 7 hours before planned awakening. If the 10 mg dose is tolerated but not effective, the dose may be increased to 20 mg nightly. Patients taking a moderate CYP3A inhibitor should start with a 5 mg dose and may increase to a 10 mg dose. Suvorexant should be avoided in patients taking a strong CYP3A inhibitor. The onset of effect may be delayed if taken with or after a meal.

Suvorexant is available as 5 mg, 10 mg, 15 mg, and 20 mg tablets.

POTENTIAL ADVANTAGES

There has been no evidence of physical dependence with prolonged use or withdrawal symptoms after discontinuation.[1] The drug appears to be safe and well tolerated over 1 year with nightly use.[2]

POTENTIAL DISADVANTAGES

Suvorexant at doses of 40 mg, 80 mg, and 150 mg had similar abuse liability in recreational poly drug users as zolpidem.[1] It carries the same class warning for abnormal thinking, behavioral changes, and worsening of depression/suicidal ideation as other hypnotics.[1] Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms can occur with suvorexant.[1]

COMMENTS

Suvorexant is a highly selective antagonist of orexin receptors OX1R and OX2R. Orexin are hypothalamic neuropeptides that are important in regulating wakefulness.[3] The drug's efficacy and safety were evaluated primarily in two 3-month, randomized, placebo-controlled, clinical trials in subjects with insomnia characterized by difficulties falling asleep and staying asleep.[1] In two studies with similar design, subjects were randomized 2:1 to suvorexant (20 mg if ages 18-64 or 15 mg if age ≥ 65 years) or placebo.[1] Sleep latency and sleep maintenance were assessed by polysomnography and patient estimation. In study 1 (n = 483), sleep latency was reduced by 34 minutes (baseline 69 minutes) compared to -23 minutes for placebo (baseline 66 minutes), a statistically significant difference of 10 minutes at 1 month. The effect was less at 3 months, -35 vs -27 (difference of 8 minutes). In the second study (n = 431), the drug was less effective, with a difference of 8 minutes at 1 month and no difference at 3 months. In terms of patient-estimated time-to-sleep onset, the difference ranged from 5-8 minutes over the course of the study. Polysomnographic assessment of sleep maintenance showed a reduction of 24-26 minutes in time awake after sleep onset at 1 month (mean baseline, approximately 118 minutes) and 17-31 minutes at 3 months. Patient-estimated total sleep time changes were 16-21 minutes at 1 month and 11-22 minutes at 3 months (baseline of approximately 310 minutes). No clear rebound effects were observed after nightly dose for 3 months. Some patients may experience impaired driving performance the next day, particularly at the 20 mg dose.[1] Also, next-day effect on memory or balance may be experienced by some. Suvorexant did not appear to have any respiratory depressant effect in healthy subjects and those with mild-to-moderate chronic obstructive pulmonary disease.[1] The drug seems well tolerated, with somnolence as the most common side effect (7% vs 3% for placebo).

CLINICAL IMPLICATIONS

Suvorexant is the first in a new class of drugs for the treatment of insomnia. It has been suggested that it may be safer (i.e., greater therapeutic margin for sleep vs cognitive disturbance in animals) than the nonbenzodiazepine hypnotics (Z-drugs) such as zolpidem and eszopiclone.[4] There are currently no published comparative trials; however, numerical results reported for suvorexant seem modest compared to those reported for the Z-drugs. For example, suvorexant decreased sleep latency by 5-10 minutes compared to about 22 minutes reported for the Z-drugs.[5,6] How suvorexant differs from eszopiclone or zolpidem in terms of sleep quality and sleep depth is not known. The ultimate role of suvorexant in the treatment of insomnia remains to be determined. The cost was not available at the time of this review.[1] Suvorexant is a Schedule IV controlled substance. ■

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I Wish I Knew the Best BP for Hypertensive Senior Citizens

Source: Mohebi R, et al. *J Am Soc Hypertens* 2014;8:491-497.

The Joint National Committee (for purists, AKA "the group originally assigned to create JNC8") suggests that for persons aged ≥ 60 years, systolic blood pressure (SBP) should be lowered to < 150 mmHg. Is this the right number? After all, the relationship between SBP and cardiovascular disease (CVD) demonstrated in epidemiologic observational studies appears to be linear, so might CVD risk be better reduced by achieving lower SBP than simply "< 150 mmHg"?

To address this question, Mohebi et al followed a population of senior citizens (n = 1845) for approximately 10 years, looking at the hazard ratio for suffering a CVD event or mortality when comparing various levels of BP to a BP of 120/80 (which they designate as ideal BP). All study participants were aged ≥ 60 years at baseline (mean age = 66 years), and ostensibly free of CVD.

In this population, persons with prehypertension were not at demonstrably greater risk than persons with ideal BP. However, when SBP was 140-150 mmHg, risk for CV events was more than 1.5 times as great as SBP 120 (even though there was no increased mortality signal).

Based on these observations, the authors suggest that the risk of CV events even at a SBP of 140-150 is substantially greater than "ideal BP." At the same time, they acknowledge that clinical trials in senior citizens attempting to clarify whether lower BP levels will improve outcomes more than simply attaining < 150 mmHg have been inconsistent. ■

Be Careful Before Placing Confidence in a Urine Drug Screen that is PCP Positive

Source: Fischer M, et al. *J Clin Psychiatry* 2014;75:7:728-730.

The approach to management of a patient who incurs a positive urine drug test (UDT) screen for an illicit substance is complex. It is even more complex, however, if false positives could be the explanation.

Fischer et al report on their experience with 40 psychiatric patients found to be phencyclidine (PCP, also called "angel dust") positive on UDT. Out of this population, only one patient confirmed taking PCP. The others were receiving psychiatric medications known to potentially produce a false-positive result for PCP such as venlafaxine. The authors report that the list of medications potentially causing a false-positive PCP UDT — most of which are used for psychiatric disorders — is substantial, and includes lamotrigine, tramadol, ibuprofen, imipramine, diphenhydramine, and others.

This particular report, however, draws attention to another psychiatric medication, chlorprothixene, which they found to be the most common cause of a false-positive UDT for PCP, being associated with 16 of the 40 cases (venlafaxine was associated with 14 cases). Chlorprothixene has not previously been reported as a cause of false-positive PCP UDT.

These results must be considered preliminary because the investigators did not confirm the absence/presence of actual PCP by a highly sensitive method such as liquid chromatography. Nonetheless, these findings support consideration of chlorprothixene and other commonly used psychiatric drugs as the cause of false-positive PCP UDT results. Positive PCP results on UDT in a patient who denies using PCP may require confirmation with more sensitive assays than are typically used in routine UDT. ■

The Ongoing Salt Saga

Source: Mente A, et al. *N Engl J Med* 2014;371:601-611.

If you thought that another very large clinical trial would finally settle uncertainties about salt — well, I hate to disappoint you. Opinions about the role of salt in cardiovascular disease range from "there is little relationship" to "the relationship is strong and consistent," with all sorts of conjecture in between.

Mente et al report on data obtained from 18 different countries in which a single morning urine specimen measurement of sodium and potassium was used as a metric for dietary ingestion of those same electrolytes. They found a positive linear relationship between salt ingestion and blood pressure (BP), such that every 1 g/d increase in sodium was associated with a 2.11 mmHg increase in SBP.

Their data did not, however, demonstrate a "one size fits all" linearity. Persons with the highest sodium ingestion (> 5 g/d) demonstrated an almost 4-fold greater increment in BP per gram of sodium consumption than persons at the lowest levels (< 3 g/d sodium). Also, older persons and persons with pre-existing hypertension were more sensitive to BP-raising effects of sodium.

Potassium ingestion was inversely associated with BP. So are we *finally* finished with this roller coaster-like journey about sodium? Yes — well, that is until you turn the page on that article in the *New England Journal of Medicine* to find that the very next article also examined sodium in more than 100,000 persons, and did *not* come up with the same answer — oh well, we'll keep searching. ■

A Healthy 23-year-old with a Wide Tachycardia

By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

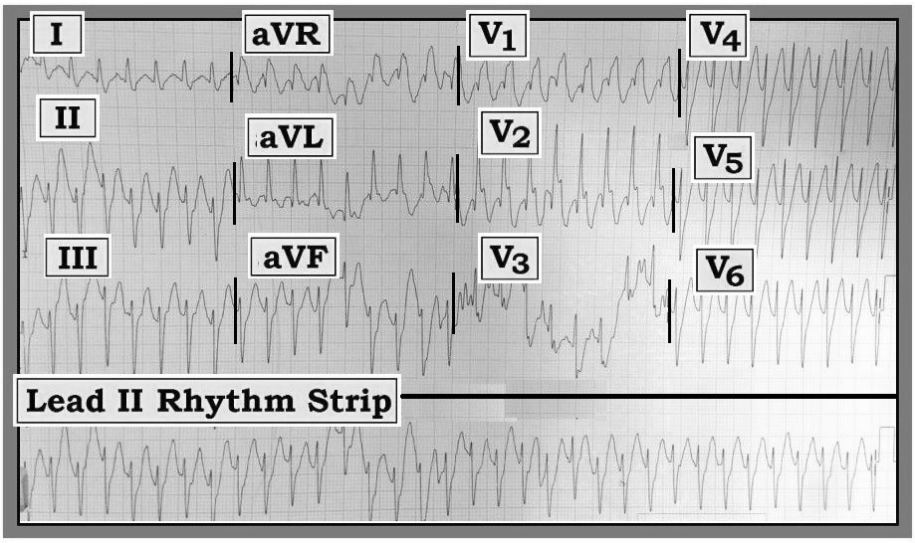

Figure — ECG obtained from a young adult with palpitations.

Scenario: Interpret the ECG and accompanying lead II rhythm strip in the Figure. The patient was a 23-year-old man who presented with "palpitations." He was presumably healthy prior to the occurrence of this arrhythmia — and he was hemodynamically stable at the time this ECG was recorded. Is the rhythm likely to be ventricular tachycardia (VT) or supraventricular tachycardia (SVT) with aberrant conduction?

Interpretation: The rhythm is a wide-complex tachycardia (WCT) without clear sign of atrial activity. Although there is some angling of the ECG paper, the rhythm appears to be regular. The rate is just over 200/minute. QRS morphology resembles the bifascicular block pattern of right bundle branch block (RBBB) with left anterior hemiBlock (LAHB).

Impression: The differential diagnosis of a regular WCT rhythm without sinus P waves should *always* be VT until proven otherwise. The patient should be treated accordingly. Statistically, at least 80-90% of such cases will be VT — especially if the patient is an older adult with a history of underlying heart disease. That said, there are several unique aspects to this case.

- This patient is not an "older adult with underlying heart disease." Instead, he is a healthy young adult with palpitations, but who was hemodynamically stable. Certain types of VT rhythms are known to occur in younger adults without underlying heart disease. Many of these rhythms are catecholamine-related and exercise-induced. A significant percentage of these VT rhythms (thought to account for up to 5-10% of all VT rhythms) are responsive to adenosine. This is an important reason to consider early trial of adenosine in the treatment approach to a regular WCT of *uncertain* etiology.
- In addition to the young age of the patient and absence of underlying heart disease, certain ECG features sometimes provide clues to the likelihood that one of these special forms of VT may be operative. This is true in this case — as the RBBB/LAHB pattern of QRS widening seen here is highly suggestive of a fascicular form of VT. QRS morphology in lead V1 is distinctly atypical for aberrant conduction — because the S wave fails to descend to the baseline and the terminal R is far wider than expected when the rhythm is SVT with aberrant conduction.

There is consensus that immediate cardioversion is indicated for treatment of a WCT rhythm whenever the patient is at all unstable. However, medical treatment with an antiarrhythmic agent is reasonable when the patient is stable, as was the case for this patient. Awareness of the existence of certain special forms of VT that are most often seen in otherwise healthy young adults can provide clues to the realization that: 1) aberrant conduction of an SVT is highly unlikely in this case; and 2) adenosine is the initial drug of choice, and may work even though the rhythm turned out to be VT. ■

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CME QUESTIONS

1. A meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with CAD revealed:

a. an approximately doubling of cardiovascular risk.

b. no effect on cardiovascular risk.

c. a quadrupling of cardiovascular risk.

d. that the results were uncertain.

2. Which of the following is correct regarding the updated CDC recommendations for HIV testing?

a. Initial testing should use a fourth-generation immunoassay that detects HIV-1 p24 antigen as well as antibodies to both HIV-1 and HIV-2.

b. If the combination fourth-generation assay is negative, a Western blot should be performed.

c. A Western blot test should routinely be used to confirm a positive combination fourth-generation immunoassay.

d. Initial testing should include a Western blot.

3. The new clinical guideline from the American College of Physicians on the routine pelvic examination recommends which of the following?

a. Primary care physicians no longer need to perform pelvic examinations.

b. There is no need for a routine pelvic examination in adult women without symptoms and who are not pregnant.

c. Women should get a complete pelvic examination when they are screened for cervical cancer.

d. Any suspicion of a sexually transmitted disease requires a complete pelvic examination.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Colonoscopies after age 75 may present more risk than benefit

Effects of low-carbohydrate and low-fat diets: A randomized trial