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Treating the Irritable Bowel Syndrome: What Really Works?

ABSTRACT & COMMENTARY

Synopsis: *Contrary to popular belief, bulking agents failed to pass muster while the use of smooth-muscle relaxants was supported by evidence from clinical trials.*

Source: Jailwala J, et al. *Ann Intern Med* 2000;133:136-147.

Jailwala and colleagues set out to evaluate the efficacy of pharmacologic agents for irritable bowel syndrome (IBS). Their analysis was based on a review of 70 randomized, double-blind, parallel, or cross-over trials of a pharmacologic intervention for adult patients that reported outcomes of improvement in global or irritable bowel-specific symptoms. They found that the strongest evidence for efficacy was shown for smooth-muscle relaxants in patients with abdominal pain as the predominant symptom. Loperamide seemed to reduce diarrhea but did not relieve abdominal pain. They concluded that the efficacy of bulking agents had not been established. They also felt that evidence for the use of psychotropic agents was inconclusive and that more high-quality trials of longer duration were needed. There was also evidence to support efficacy for 5-HT-receptor antagonists, but they felt that more studies were needed.

COMMENT BY EAMONN M. M. QUIGLEY, MD

IBS continues to pose a therapeutic challenge. Given that the etiology of this common disorder remains unclear, therapy remains largely symptomatic with fiber and bulking agents being recommended for constipation, antispasmodics for pain, and antidiarrheals for those with diarrhea. Recently, antidepressants have become popular, based primarily on their proposed effects on visceral sensation; more recently, alosetron, a 5-HT3-antagonist, has been approved for use in IBS in the United States, as a gut-specific anti-nociceptive agent.[1] This excellent review attempts to place these therapies in context through a rigorous review of evidence of efficacy. On review, many studies were found to exhibit methodological and analytical shortcomings; most were far from adequately powered and evaluated short-term

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therapy only. Indeed, the number of truly high-quality studies in this area proved to be remarkably few. Contrary to popular belief, bulking agents failed to pass muster, while the use of smooth-muscle relaxants was supported by evidence from clinical trials. Other agents, including anti-depressants, were difficult to assess due to a lack of high-quality studies. Initial studies with alosetron looked promising. Jailwala et al did not assess psychological or behavioral approaches. Clearly, IBS deserves further rigorous attention from the clinical trialist; we need both better studies on available agents and new studies with better agents. ❖

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Alcohol Consumption and Risk of Coronary Heart Disease in Diabetic Patients

ABSTRACTS & COMMENTARY

Synopsis: *The findings in both of these studies suggest that light to moderate alcohol intake is associated with a slightly more than 50% reduction in the risk of developing symptomatic CHD. The positive effect among diabetics of either sex was comparable to that seen in the general population.*

Sources: Ajani UA, et al. *Circulation* 2000;102:500-505; Solomon CG, et al. *Circulation* 2000;102:494-499.

Coronary heart disease (chd) is a major cause of morbidity and mortality in diabetics, in fact, CHD was listed as a cause of death on at least 69% of death certificates of diabetic patients.[1] Epidemiologic studies have consistently reported that moderate alcohol consumption significantly reduces the risk for CHD incidences and mortality[2-4] in the general population. Until now, a similar association between consumption of alcohol and occurrence of CHD among individuals with diabetes had not been demonstrated.

Ajani and associates from Harvard Medical School and several teaching hospitals in the Boston area examined the records of 87,938 U.S. physicians (2790 with diagnosis mellitus) who were participating in the Physicians' Health Study. In the same issue of *Circulation*, Solomon and colleagues from the Harvard School of Public Health reported on the results of their evaluation of a prospective cohort study of 121,700 female nurses; they evaluated 39,092 person-years of follow-up in women who reported a diagnosis of diabetes mellitus. The results of both of these studies strongly suggested that light to moderate alcohol consumption is associated with risk reductions in CHD occurrence among diabetic patients that were similar to those which have been demonstrated to occur in the nondiabetic population.

COMMENT BY HAROLD L. KARPMAN, MD

The effects of light to moderate daily alcohol consumption were similar among men in the Ajani et al study as they were among women in the Solomon et al study. The findings in each of these studies suggest that light to moderate alcohol intake is associated with a slightly more than 50% reduction in the risk of developing symptomatic CHD. The positive effect among dia-

betics of either sex was comparable to that seen in the general population.[5-7]

The beneficial effect of alcohol on CHD risk in individuals with Type II diabetes mellitus may be due to the favorable effects of alcohol consumption on serum lipids,[8,9] on decreasing platelet aggregation,[10] and/or on increasing fibrolytic activity.[11] These mechanisms may even be more important in a diabetic population than in the general population because dyslipidemia and coagulation disorders are more prevalent in diabetics. In addition, it is possible that alcohol may reduce insulin in diabetics afflicted with hyperinsulinemia,[12] which could result in a decrease in the risk of CHD.

In conclusion, light to moderate alcohol consumption has been demonstrated in these two prospective cohort studies to significantly reduce the risk of CHD morbidity and mortality similarly among men and women, whether or not they are afflicted with diabetes. Because modest alcohol consumption appears to have a favorable cardiovascular effect in diabetics, it should not be routinely discouraged in the diabetic population; however, in light of major clinical and public health problems associated with heavy drinking, recommendations regarding alcohol use, no matter how beneficial, must be made on an individual basis after carefully assessing the risks and benefits of any changes in drinking behavior in that individual. If alcohol consumption can be limited to only a light or moderate daily intake, both diabetic and nondiabetic patients of both sexes will benefit by the significant reduction in CHD morbidity and mortality. ❖

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Effect of Lung-Volume Reduction Surgery in Patients with Severe Emphysema

ABSTRACT & COMMENTARY

Synopsis: *This study found that in selected patients with severe emphysema, lung-volume reduction surgery can improve FEV_1, walking distance, and quality of life. Whether it reduces mortality is uncertain.*

Source: Geddes D, et al. *N Engl J Med* 2000;343:239-245.

This was a randomized controlled trial in 48 patients comparing the effects of lung-volume reduction surgery (LVRS) vs. standard medical therapy. The inclusion criteria were severe emphysema as shown on computed tomography (CT) with no restrictions on the pattern or distribution of the emphysema, age younger than 75 years, a FEV_1 greater than 500 mL, use of oxygen less than 18 hours per day, steroid dose of less than 10 mg per day, and PCO_2 of less than 45 mm Hg. The exclusion criteria were patients with isolated bullae, asthma, previous thoracic surgery, or other serious medical conditions.

The patients were given medical treatment consisting of a smoking-cessation program, a trial of therapy with prednisolone (30 mg/d for 2 weeks), inhaled beta-adrenergic agonists, anticholinergics, oral theophylline, oral antibiotics to be kept at home for use when needed for chest infections, and vaccination against influenza and pneumococcus. Patients without any clear contraindication on initial assessment were entered into a six-week program of outpatient rehabilitation, consisting of physiotherapy and occupational therapy, with nursing, nutritional, and social services. After rehabilitation, patients were randomly assigned to surgery or to continued medical treatment. Both groups were reassessed at three, six, and 12 months after randomization and yearly thereafter.

Primary outcome measures were mortality, changes in FEV_1, shuttle-walking distance, and quality of life at six months. The secondary measures were changes in forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV), inspiratory and expiratory mouth pressures, and arterial-blood gas values.

Bilateral lung resection was performed through a median sternotomy or by thoracoscopy. Lung resection was performed with the use of various mechanical sta-

plers, with or without bovine-pericardial-strip reinforcement. The baseline characteristics of patients did not differ significantly between the groups.

There were five deaths in the surgical group (21%) and three in the medical group (12%). Analysis of the entire study group showed no significant difference in survival between groups ($P = 0.29$). The changes from baseline differed significantly between the medical and surgical groups at six months for FEV_1 (-80 mL and +70 mL, respectively; $P = 0.02$), shuttle-walking distance (-20 m and +50 m; $P = 0.02$), and SF-36 scores (-12 and +22; $P = 0.003$), for FEV_1 at three months; and for shuttle-walking distance and SF-36 score at 12 months. Differences between surgical and medical groups were significant for total lung capacity, residual volumes, and inspiratory mouth pressure at three, six, and 12 months.

COMMENT BY DAVID OST, MD, & SYED RIZVI, MD

LVRS has recently re-emerged as a surgical option for the treatment of end stage chronic obstructive pulmonary disease (COPD) due to underlying severe emphysema. Advocates of the surgery claim that it represents a significant breakthrough in the management of this challenging group of patients. The mechanism of action is thought to be an increase in lung elastic recoil after the targeted emphysematous tissue is resected. This leads to an increase in FEV_1, decrease in functional residual capacity, increase in maximum voluntary ventilation, and increase in exercise capacity.[1]

Young and colleagues conducted a systematic review of 19 case series meeting rigorous methodological criteria for inclusion from 75 potentially relevant studies. The pattern of results was consistent across individual studies, despite a significant degree of clinical heterogeneity, and it was concluded that LVRS appears to represent a promising option in the management of patients with severe emphysema.[2] Ferguson and colleagues demonstrated that LVRS produces significant improvements in exercise performance, dyspnea, and quality of life in selected patients with severe emphysema.[3] Benditt and colleagues showed that LVRS improves maximal O_2 consumption and maximal minute ventilation.[4] This trial supports the benefits of lung volume reduction surgery as evidenced by statistically significant benefits in terms of FEV_1, shuttle-walking distance, and quality of life at various follow-up times. The mortality was similar in the two groups, but the study had too few patients to evaluate this end point adequately. Although most patients who underwent surgery had considerable benefit, a few did not. In contrast, the condition of most of the patients treated medically worsened. Overall, this study supports the promising results demonstrated by other investigators using LVRS. More conclusive evidence will be available when the National Emphysema Treatment Trial (NETT) is completed. ❖

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An Expensive Way to Evaluate Cardiovascular Risks!

ABSTRACT & COMMENTARY

Synopsis: *Data from Electron Beam Computed Tomography (EBCT) is a modest predictor of future cardiovascular events.*

Source: Wong ND, et al. *Am J Cardiol* 2000;86:495-498.

Recent reports support a relationship between coronary artery calcification (CAC) in predicting the future incidence of cardiovascular disease events in asymptomatic persons. This report expands on previously reported preliminary findings by Wong and colleagues.[1]

The study population was derived from a series of 2016 men and women, primarily self-referred or referred by their physician for EBCT coronary calcium screening.

Wong et al evaluated the relation of CAC to future cardiovascular disease events in 926 asymtomatic persons (735 men and 191 women, mean age 54 years) who underwent a baseline EBCT. All subjects in the report returned a follow-up questionnaire 2-4 years (mean, 3.3 years) after scanning, inquiring about myocardial infarction, stroke, and revascularization. Approximately 60% of the men and 40% of the women had positive scans at baseline. Twenty-eight cardiovascular events occurred. The presence of CAC and an increasing score (increase in degree of calcification)

was related to the occurrence of new myocardial infarction ($P < 0.05$), and total cardiovascular events ($P < 0.001$). Those with the highest quartile score had a relative risk of 4.5. These events were adjusted for age, gender, and coronary risk factors.

COMMENT BY RALPH R. HALL, MD, FACP

In their discussion, Wong et al make several relevant observations. To begin with, although cardiovascular events occur with greater frequency in those with CAC, they still do occur in those with little or no CAC. Second, and very importantly, CAC did not provide incremental information over risk factors in predicting cardiovascular events.

During the recruitment of patients who were ultimately in this study, I heard the radio announcements advertising the merits of EBCT. The advertisements left no question that this procedure was of merit. It is likely that those attracted to this procedure by these advertisements were highly motivated to do something about their disease, if they indeed had CAC. Some physicians who referred patients for this study did so at the patients' request. Therefore, after the procedure it is likely that many of these persons undertook preventive measures that would have lowered their incidence of cardiovascular events. This may have lowered the number of cardiovascular events that did occur and significantly altered the results of this study.

In any event, this is an expensive method of selecting patients for primary or secondary prevention measures. ❖

Reference

1. Wong ND, et al. *Am J Cardiol* 1996;78:1220-1223.

Pharmacology Update

Balsalazide Disodium Capsules (Colazal—Salix Pharmaceuticals)

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

The fda has approved balsalazide disodium for the treatment of ulcerative colitis, the first new drug approved for this indication in more than 10 years. Balsalazide is the prodrug of mesalamine in which the sulfapyridine moiety of sulfasalazine is replaced with aminobenzoyl-beta-alanine. It will be marketed by Salix Pharmaceuticals as Colazal.

Indications

Balsalazide is indicated for the treatment of mildly to moderately active ulcerative colitis.

Dosage

The usual dose is three 750 mg capsules taken three times a day for eight weeks. Some patients may require treatment up to 12 weeks.[1]

Balsalazide will be supplied as 750 mg capsules.

Potential Advantages

A report suggests that balsalazide is more effective and better tolerated than delayed-release mesalamine (Asacol).[2] In this study, more patients had symptomatic remission (78% vs 45%; $P = 0.012$) and complete remission (54% vs 22%; $P = 0.0018$) as assessed by sigmoidocopy at eight weeks with balsalazide vs. mesalamine. In addition, fewer patients reported adverse events (48% vs 71%; $P = 0.024$). Balsalazide also had a more rapid action with the median time to the first completely symptom-free day of 10 vs. 25 days ($P = 0.0039$). Patients with more severe disease who were treated with balsalazide had a higher probability of achieving complete remission than patients with milder disease treated with mesalamine.

Potential Disadvantages

Balsalazide requires three times a day dosing. The most common adverse event is abdominal pain (11%).[3] Balsalazide has not been FDA approved for the maintenance of ulcerative colitis.

Comments

Balsalazide is a prodrug of mesalamine where the sulfapyridine of sulfasalazine is replaced with an inert carrier, 4-aminobenzoyl-beta alanine. After oral administration, mesalamine is released by cleavage by colonic bacterial azoreductase. In a randomized, double-blind study (n = 99) balsalazide (6.75 g/d) was found to be more effective and better tolerated in the treatment of ulcerative colitis than a delayed-release mesalazine (Asacol; 2.4 g/d). Balsalazide has not been approved by the FDA for the maintenance of ulcerative colitis, although data suggest that it may be comparable to mesalazine over a 12-month study period for this indication.[4]

Clinical Implications

Ulcerative colitis is an inflammatory disease of the colon and rectum with an estimated annual incidence of 2-6 per 100,000 in the United States.[5] The disease is believed to be caused by a genetically based regulatory disturbance of the intestinal mucosa or systemic immune response. Pharmacotherapy includes anti-inflammatory drugs such as 5-aminosalicylate (mesalamine) and corticosteroids and immune-modulating agents such as azathioprine and 6-mercaptopurine. Mesalamine is generally used for mild-to-moderately active disease and for maintaining remission. Sulfasalazine, the oldest mesalamine prodrug, is limited by its side effects, most of which are attributed to sulfapyridine. Several delivery systems of mesalamine have been developed which include two pH-dependent controlled-released formulations (Asacol, Pentasa) and olsalazine which is a linked pair of mesalamine molecules requiring colonic bacterial cleavage. The objective of all these agents is to deliver mesalamine to the colon while reducing systemic absorption.

Sulfasalazine is limited by various side effects, olsalazine causes diarrhea, and controlled-release formulations have shown systemic absorption.[6]

Balsalazide may prove to be a well tolerated and more colon specific delivery system for mesalamine. Balsalazide is expected to be launched in January 2001. ❖

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Correction

The Pharmacology Update, "Malarone—A New Antimalarial Combination," in the August 29 issue of *Internal Medicine Alert* contained an error. In the Dosage section in the sentence reading, "For adult patients, the dose is based upon body weight: 11-20 kg (1 adult strength tablet), 21-30 kg (2 adult strength tablets), 31-40 kg (3 adult strength tablets), and more than 40 kg (4 adult strength tablets) taken for three consecutive days," adult patients should be pediatric patients. We regret any confusion this may have caused. ❖

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CME Questions

27. Which one of the following statements is correct?

a. Electron Beam Computed Tomography is a cost-effective method of predicting future cardiovascular events.
b. Patients who do not have coronary vascular calcification will not have future cardiovascular events.
c. Cardiovascular events also occur in persons who do not have coronary artery calcifications.

28. Which of the following therapeutic modalities has been shown to increase FEV_1 in patients with severe emphysema?

a. Antibiotics
b. Positive pressure ventilation
c. Lung volume reduction surgery
d. Exercise

29. Which of the following is *incorrect* regarding balsalazide?

a. It is a prodrug of mesalamine.
b. It is approved for maintenance therapy of ulcerative colitis.
c. It is approved for therapy of 8-12 weeks.
d. It is dosed three times a day.

By Louis Kuritzky, MD

Health Food Store Recommendations for Breast Cancer

As many as two-thirds of cancer patients may turn to complementary or alternative medicine. Unfortunately, not only can some of these agents have significant toxic effects, they also might interact with traditional allopathic treatments. It is of some concern that quality control and adverse effect surveillance are not on parity with prescription drugs.

Health food store personnel generally do not possess a license to diagnose or prescribe, yet may not infrequently be called upon to consider giving such advice. The purpose of this study was to observe, by means of a simulated medical scenario, the personnel response to a young woman who posed as the daughter of a metastatic breast cancer patient. The details of the "case" included that the diagnosis had been made five years prior, lumpectomy had been performed, and radiation therapy had been done. Complaints of the patient (the mother) included bone pain, despite her medication regimen of tamoxifen. The story also included the detail that the mother wished to consider alternative treatment, since traditional treatment had not cured her cancer.

Of the 40 stores in which the scenario was enacted, only four stores did not make recommendations. The other 36 store employees suggested one or more products, and 20% of the personnel suggested participation in a structured program (usually provided by the store), such as consultation with their store specialist, a program of their products, or diagnostic tests (e.g., iridology, muscle testing). It was fairly common (35%) for indirect recommendations to be given by offering input that certain products were popular with cancer patients, for instance shark cartilage or maitake mushrooms.

Clinicians must be aware that cancer patients or their families may seek the advice of health food store personnel, and be prepared to respond in such a way as to best avoid potential adverse effects of such interventions, while not disallowing the possibility that some tools used in health food stores may be of benefit. ❖

Gotay CC, Dumitriu D. Arch Fam Med 2000;9:692-698.

Rabies Postexposure Prophylaxis

In that there has been but a single confirmed rabies survivor in the United States in the last three decades, rabies may be acknowledged as a uniformly fatal disease. Thanks primarily to control of rabies in domestic animals, the number of annual cases has dropped from more than 100 at the beginning of the 20th century, to only 1-3 yearly.

Rabies among animals, especially raccoons, has increased almost 20% since 1996. No cases of human rabies have ever been documented subsequent to exposure to raccoon rabies. Appropriate administration of rabies prophylaxis treatment is important not only to prevent rabies, but also to avoid unnecessary administration to persons not at risk, since the process is not without discomfort, and is costly ($1500 for a treatment course alone, without physician or office/hospital fees). This trial is the first prospective one to assess appropriateness of rabies prophylaxis administration.

Of 2030 patients with rabies exposure, 6.7% received prophylaxis. Of 136 patients who received prophylaxis, 40% were considered inappropriate, most commonly due to the fact that the culprit animal was available for observation or testing, which could obviate intervention. Of 1894 persons not receiving prophylaxis, 6.3% were considered inappropriate, most commonly because the culprit animal was not available for observation.

Moran and colleagues conclude that enhanced adherence to appropriate use of rabies prophylaxis is needed, and may be advanced by provision of easy access to and availability of suggested locale-specific and circumstance-specific guidance, through health department assistance and guideline promulgation. ❖

Moran GJ, et al. JAMA 2000;284: 1001-1007.

Ondansetron for Reduction of ETOH

The serotonin 5ht-3 receptor is important in mediating alcohol effects, and blockade of this receptor in a variety of animals has reduced alcohol consumption. There has been some support for the concept that early-onset alcoholism might be responsive to intervention with ondansetron, due to its modulation of serotonin.

This placebo-controlled trial of 321 persons suffering alcoholism (at least 3 drinks daily at the time of enrollment) used either 1, 4, or 16 mcg/kg of ondansetron twice daily, in addition to cognitive behavioral therapy for a total of 12 weeks (including run-in).

Early-onset alcoholism patients who were treated with ondansetron demonstrated a significantly decreased amount of alcohol consumption, and improved number of days abstinent. The most effective dose of ondansetron was 4 mcg/kg. Early-onset alcoholism is characterized by earlier onset of problem drinking behavior and antisocial behavior. Patients with late-onset alcoholism did not respond to ondansetron treatment.

Adverse effects of the treatment were infrequent, and none were serious. The most common side effects were gastrointestinal. A single fatality in the trial was not attributed to the medication: the subject fell down a flight of stairs at home.

The biology of early-onset alcoholism appears to be different from late-onset alcoholism, and responds differently to ondansetron modulation. ❖

Johnson BA, et al. JAMA 2000;284: 963-971.

ECG Review

SVT With an Answer

By Ken Grauer, MD

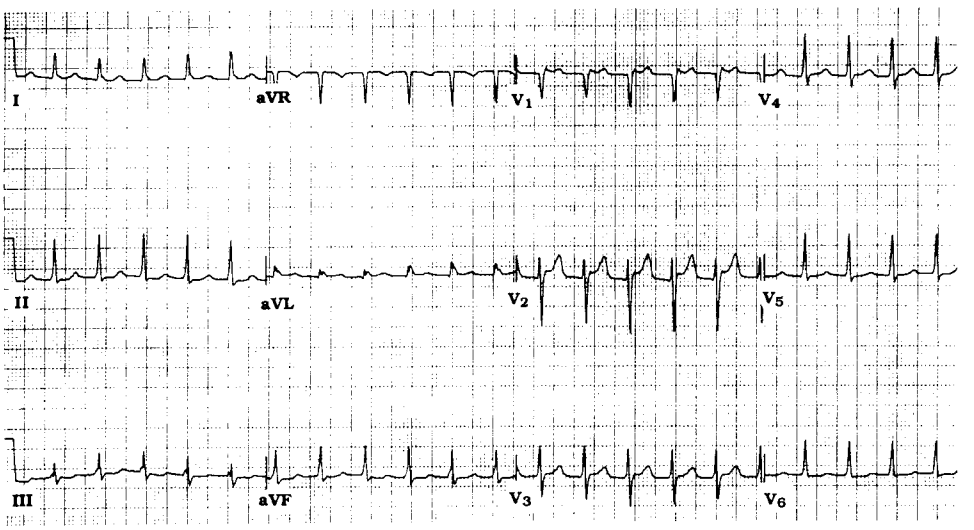

Figure. 12-lead ECG obtained from a young adult man with chest tightness. What is the rhythm most likely to be?

Clinical Scenario: The 12-lead ECG in the Figure shown here was obtained from a young adult man with chest tightness. Might his symptoms be explained by the cardiac rhythm? What is the likely mechanism of this rhythm? (Hint: The probable answer lies with searching for atrial activity on this tracing!)

Interpretation: The rhythm is a regular supraventricular tachycardia (SVT) at a rate of just under 150 beats/minute. Atrial activity is not initially evident. For practical purposes, the differential diagnosis consists of three entities: 1) sinus tachycardia; 2) atrial flutter; and 3) paroxysmal supraventricular tachycardia (PSVT).

Definitive diagnosis of the etiology of this rhythm is not possible on the basis of this single 12-lead tracing. Nevertheless, several key presumptions can still be made. Of the three entities listed above, the one least likely to be present is atrial flutter. Despite the fact that the ventricular response in the Figure is very close to 150/minute (the most common ventricular rate seen with untreated atrial flutter)—there is not the slightest hint of flutter waves anywhere on the tracing. Atrial activity with a sawtooth pattern can usually be discerned if carefully looked for in at least one or more leads of a 12-lead tracing when flutter is present.

Sinus tachycardia is also unlikely to be the etiology of this arrhythmia. Admittedly, one can't rule out the possibility that the small upright deflection at the midpoint of the R-R interval in lead II could be a P wave (or a *combined* P and T wave). However, in view of the rapid rate, we would usually expect a shorter PR interval than would be the case if this upright deflection in lead II was in fact concealing a P wave. Moreover, sinus P wave activity is also clearly lacking in lead V_1 (the second best lead for detection of sinus conducted P waves).

By the process of elimination, PSVT is the most likely etiology of this arrhythmia. The mechanism of PSVT is most often reentry that typically involves at least a portion of the AV node. Confirmation that this mechanism is operative will sometimes be forthcoming from evidence of *retrograde* atrial activity during the tachycardia in several leads. Such activity is suggested here by the subtle slender *negative* deflections that occur at the end of the QRS complex in each inferior lead, as well as from the simulated r' deflection in lead V_1. Verification that these deflections truly represent reentry conduction during the tachycardia was established by their disappearance *after* the patient converted to sinus rhythm. This patient's chest tightness also resolved with resumption of sinus rhythm. ❖

In Future Issues:

Death Be Not Proud