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INSIDE

What Are the Chances That a Mole Will Turn to the Dark Side?

ABSTRACT & COMMENTARY

Synopsis: *Melanocytic nevi rarely transform into cutaneous melanoma.*

Source: Tsao H, et al. *Arch Dermatol*. 2003;139:282-288.

Although the phenomenon of cutaneous melanoma (CM) arising from melanocytic nevi (MN) is known, the transformation rate of MN into CM is not. Tsao and associates set out to calculate the rate, using published data and making some assumptions to ease the calculation. Their first assumption is that the number of MN in any year is stable. The second assumption is that the number of CM arising from MN is the same as the number of MN that transform into CM per year. (This may appear to be an intuitive equivalence, but some MN are obliterated in the process of becoming CM, leaving no histologic trace.) They examined the records of a community-based general dermatopathology practice and identified 1615 CM. Of these, 425 (26%) had an associated MN. They also calculated rates based on gender and age stratification. The percentages ranged from 20 to 65 for men and 9 to 47 for women with a peak in the third decade for both. They used data from the National Cancer Institute's Surveillance, Epidemiology, and End Result Study (SEER, available at seer.cancer.gov) to derive the number of CM in the US white population by sex and age group and data from the US Census Bureau to calculate incident rates. Previous studies of mole counts from British and Australian studies were used to establish the number of MN per person, again with sex and age stratified. Their calculations yielded annual transformation rates of 0.0005% or less for both sexes aged 40 years and younger to 0.003% for men older than 60. They also calculated cumulative risk rates. The risk of a mole on a 20 year old becoming malignant by age 80 is 0.03% (1 in 3164) in men and 0.009% (1 in 10,800) in women.

COMMENT BY ALLAN J. WILKE, MD

I know what you're thinking—GIGO! (Garbage In, Garbage Out, a derisive term from the early days of computer programming). Of course, if you really want to know the transformation rate, the gold

standard would be to conduct a prospective cohort study in an unbiased population. However, this would involve following a very large group of people for many years. Until that study is done (not likely), this will have to do. In this article, Tsao et al set out to estimate the rate at which MN transform into CM. They cobbled together data from a collection of disparate sources and using a mathematical formula, estimated that the risk of any one MN becoming malignant is approximately 1 in 200,000 before age 40. The lifetime chance of developing a CM in the US is 1 in 75.[1] The American Cancer Society (ACS) estimates that in 2003 there will be 54,200 (29,900 men, 24,300 women) new cases of CM.[2] Early detection, which should be easy considering that they are pigmented and lie on the skin surface, and excision usually means cure. There is a well-established, albeit complex, association between sun exposure and melanoma, and the ACS recommends sun protection behaviors, including avoiding sunburn during childhood and intense intermittent sun exposure.[3] A particularly vexing association with CM is MN, or in the vernacular, moles. MN are ubiquitous; almost every young adult has 20-40 of them. When CM are excised, MN are often found in histologic continuity with them. Along with excessive exposure to ultraviolet radiation (including tanning booths), fair skin, exposure to coal tar, pitch, creosote, arsenic, or radium, family history, and multiple or dysplastic nevi are all risk factors for CM. The ACS recommends that patients regularly perform self-examination and report suspicious lesions to their physicians. A suspicious lesion is scaling, oozing, bleeding, or changing in appearance and may be associated with a spread of pigmentation or itching, tenderness, or pain. Physicians are reminded of the ABCD rule. Be suspicious when A, the lesion is Asymmetric; B, the Border is irregular or blurred; C, the Color is not uniform; and D, the Diameter is greater than 6 mm. What should a harried primary care physician take from this study? First, it is a rare event for a mole to transform into a melanoma. Second, most people are covered with moles, making surveillance (even with a camera) a high-cost, low-yield venture. Third, excising moles isn't likely to make a dent in the incidence of melanoma. Fourth, pay closer attention to older patients with traditional risk factors. Fifth, educate your patients in self-examination and self-restraint when it come to sun exposure. ■

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The Urine Color Test with Isoniazid Treatment of Latent Tuberculosis Infection

ABSTRACT & COMMENTARY

Synopsis: *Noncompliance with treatment for latent tuberculosis can be monitored with the aid of a special urine test that checks for metabolites of isoniazid.*

Source: Eidlitz-Markus T, et al. *Chest*. 2003;123:736-739.

TUBERCULOSIS CONTINUES TO BE ONE OF THE LEADING causes of mortality and morbidity and still con-

tinues to pose a major threat to public health.[1] The treatment regimens for tuberculosis are very effective with a 95% cure rate when patients are compliant with the medications. The problem arises when patients are not compliant and endanger their lives and also the lives of those around them due to the infectious nature of the disease. The problem of nonadherence with medications may be even worse in patients being treated for latent tuberculosis. Patients with latent tuberculosis may not perceive themselves as being sick, as they have no symptoms and may be even more reluctant to be compliant with their medications.

The aim of this study was to monitor compliance with isoniazid by a simple urine test—the Arkansas method of detecting metabolites of isoniazid.[2] This method has been used for many years but is relatively unknown outside of the United States. It is a simple test, very inexpensive, gives immediate results, and is easy to read. It has a sensitivity of > 97% and a specificity of > 98%.[3] Factors that affected compliance with medications were also evaluated in this study.

Patients who were referred to the Tel Aviv Tuberculosis Center and children (younger than 18 years) attending the ambulatory Day Care Center were included in the study. The study was done during the period of September 1999 to April 2000. Only patients on monotherapy with isoniazid were enrolled. Demographic data, dose of isoniazid, duration of therapy, means of administration of therapy (whether self-administered or given by parents in the case of children), and the time of the last dose of isoniazid were collected during interviews with patients or the parents in the case of children. Urine samples were collected on routine analysis, and the urine was checked for metabolites of isoniazid.

The test consisted of placing the urine in a plastic tube containing barbituric acid, N-chlorotoluene-sulfonamide sodium salt solution (Chloramine-T; Sigma; St. Louis, Mo), and potassium cyanide. A positive test resulted in the color of the urine changing from yellow to blue, and a negative test resulted in no change of color.

The study enrolled 105 patients (38 male patients and 67 female patients). The mean age was 26.9 years (range, 1-75 years) and the mean weight was 58.6 kg (range, 9-100 kg). Isoniazid had been prescribed for persons with latent tuberculosis who were at increased risk of developing active tuberculosis as follows: 42 children and adolescents (40%), 25 patients with recent conversion (23.8%), 36 patients with close contact with a patient who had tuberculosis (34.2%), and 2 patients with positive PPD results who had been on prolonged steroid treatment (1.9%) .

The mean dose of isoniazid was 288 mg (range, 100-300 mg) or 5.6 mg/kg (range, 3-15 mg/kg). The mean duration of treatment prior to the study was 2.5 months (range, 2 weeks to 8 months). Adults supervised 77.14% of the children during drug administration. The mean interval between drug intake and the urine test was 14.6 hours (range, 2-48 hours).

The urine test results revealed noncompliance with isoniazid in 30 patients (28.5 %). In the remainder of the patients, the Arkansas test revealed metabolites of isoniazid. There was no statistically significant correlation between compliance and any of the following parameters: age ($P = .10$), gender ($P = .20$), diagnosis ($P = .55$), mode of administration of isoniazid (self-administration or with parent supervision) ($P = .27$), duration of treatment in months ($P = .57$), dosage of isoniazid/weight ratio ($P = .30$), or interval since last dose taken ($P = .12$).

Repeat urine tests were conducted on 26 patients on follow-up to check for treatment compliance. Noncompliant patients were counseled regarding the importance of compliance with medications. Only 1 of the 6 patients who was found to be noncompliant on the first visit continued to remain noncompliant when tested on the second visit. Three of 20 originally compliant patients were found to be noncompliant on the second visit.

COMMENT BY NAJMA USMANI, MD, AND DAVID OST, MD

Tuberculosis is a very common disease worldwide. Approximately 8 million new cases of tuberculosis infection and 2.6-2.9 million deaths from this disease occur annually worldwide.[4] The major barrier to achieving a cure is not a lack of medications but rather the nonadherence with therapy. This problem with nonadherence is not limited only to patients with active disease but may be even more of a problem in patients being treated for latent tuberculosis, as they are asymptomatic. This study has attempted to address this issue of nonadherence with medications. Information is given on the use of a urine test that is simple, easy to do in the office, gives immediate results, and which may be very helpful. Noncompliant patients can be counseled immediately about the dangers of skipping medications in this potentially fatal disease. Patients who are given clear and comprehensive information regarding the disease demonstrate improved compliance with medications.[5]

However, this study gives no recommendations on methods of improving compliance due to flaws in the methodology of the study. It did not have a control arm where no testing was done to compare results with the group that was being tested. It draws no conclusions about which groups are at increased risk and need repeated testing for compliance. There is no surrogate marker (improvement in morbidity or mortality) used to

demonstrate that repeated testing improves outcome. This study does not give solutions to the issue of noncompliance with medications. ■

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Silent Strokes Predispose to Dementia

ABSTRACT & COMMENTARY

Synopsis: *This study concludes that there may be a direct association between ischemia and the development of Alzheimer's pathology (plaques and neurofibrillary tangles), or alternatively, ischemia may unmask otherwise mild cases of AD.*

Source: Vermeer SE, et al. *N Engl J Med*. 2003;348: 1215-1222.

THERE IS LITTLE DOUBT THAT CEREBROVASCULAR disease is a major contributor to cognitive decline in the elderly. Recurrent symptomatic strokes affecting cortical or subcortical function inevitably result in a stepwise burden of accumulating damage and disability. Less clear, however, is a possible relationship between silent brain infarcts as diagnosed incidentally on MRI and a risk for the subsequent development of dementia.

In the Rotterdam Scan Study, 1015 elderly participants were followed prospectively over a 4-year period to correlate the presence of ischemic brain injury on an initial MRI with their subsequent risk of developing dementia. All participants were free of dementia at baseline, and any patient with a known history of stroke was excluded. The entire cohort was analyzed for the development of dementia, but only 75% were available for subsequent detailed mental status examination and/or MRI primarily due to the death or institutionalization of more than 100 enrollees.

Thirty participants developed dementia; of these, 14 had 1 or more silent infarcts on initial MRI scan, and 7 had multiple infarcts. The presence of silent brain infarcts at baseline increased the risk of dementia more than 2-fold (hazard ratio, 2.26), even when controlling for other MRI findings, such as periventricular or subcortical white matter lesions or brain atrophy. White matter disease also predicted dementia, although less powerfully, with a hazard ratio of 1.59 for periventricular and 1.21 for subcortical disease.

Among those participants who underwent a follow-up MRI scan, strokes appeared in 7/30 (23%) who became demented (3 symptomatic, 4 silent) compared with 79/618 (12%) who did not develop dementia (1 symptomatic, 71 silent). Documented decline in memory as measured by neuropsychiatric testing was restricted to patients with new infarcts, whether they had baseline silent strokes or not. Strokes in the thalamus were more likely to produce cognitive effects than in other locations. Dementia was diagnosed as Alzheimer's disease (AD) in the majority (26/30), while vascular dementia was only identified in 2/30.

As Vermeer and colleagues note, this study did not focus on subtypes of dementia, but rather an overall association between silent vascular disease and cognitive loss. They postulate that there may be a direct association between ischemia and the development of Alzheimer's pathology (plaques and neurofibrillary tangles) or alternatively, ischemia may unmask otherwise mild cases of AD.

■ COMMENT BY ALAN Z. SEGAL, MD

Dementia nomenclature can be confusing, especially as it relates to cerebrovascular disease. Patients with vascular damage may be diagnosed as suffering from strategic infarct dementia, multi-infarct dementia, or merely vascular dementia. Those with severe hypertension might be labeled as Binswanger's disease or may be thought to have white matter changes consistent with "leukoariosis." Additional overlap between these vascular diagnoses and AD pathology further muddies these classifications. From a practical therapeutic standpoint, however, acetylcholinesterase inhibitors, such as donepezil, should be considered for all patients regardless of subtype. Given the likely heterogeneous factors at work, it is not surprising that these agents appear to improve memory in patients thought to have AD, vascular-type disease, or some mixture of the two.

Middle-aged and elderly patients who undergo MRI not for dementia, but often for unrelated reasons, are frequent-

ly discovered to have ischemic-type disease, whether lacunar strokes in deep gray matter structures or more nonspecific white matter hyperintensities. While such findings are still not cause for alarm in the majority of patients, the Rotterdam study reminds us that they are not benign and should motivate a comprehensive program of vascular risk factor reduction (including, but not limited to, control of lipid and blood pressure, and smoking cessation) as well as antiplatelet therapy such as daily baby aspirin. ■

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Obesity: Death, Dollars, and the Prospects for Treatment

ABSTRACTS & COMMENTARY

Synopsis: *The management of the obesity epidemic is complex, but there are some interventions that can be helpful.*

Sources: Mitka M. *JAMA*. 2003;289:1761-1880; Hill J, et al. *Science*. 2003;299:853-855.

The year 2003 has been accompanied by an avalanche of data and information concerning the incidence, consequences, causes, cost, and potential treatments of obesity.

The urgency to reverse the trend in increasing obesity is documented in 2 major scientific journals: the *Journal of the American Medical Association* and a recent issue of *Science*. Both journals have devoted significant portions of a single issue to the review of what is known and the potential for significant improvements in the way we manage this disorder. Newspapers, television, and radio have given many hours of time reporting the cost of this epidemic, in death and dollars, and as a result our public has more information about the dire consequences of this disorder than ever before.

A seminal publication in the *New England Journal of Medicine* spelling out the association between obesity and most types of cancer may help motivate our patients to a greater extent than the fear of vascular disease or diabetes. Cancer scares the hell out of us, while we seem more blasé about vascular disease.[1]

The *JAMA* articles reported the obvious relationship between sedentary behaviors such as watching television and the resulting increase in body weight and type 2 diabetes.[2] It also reviewed the results of weight loss and the ability of patients to maintain weight loss with commercial programs and an internet weight loss counseling programs to prevent diabetes. Commercial programs were better than self-help programs, but the results were best for the e-mail counseling group.[3]

Weight loss and increased physical activity decreased markers of inflammation (interleukin 6 and 18 and C-reactive protein) and increased the anti-inflammatory marker adiponectin.[4]

Not surprisingly, the quality of life in severely obese adolescents is comparable to adolescents being treated for cancer.[5]

The soaring demand for surgical treatment of morbid obesity is receiving both scientific and ethical review. Improvement in laparoscopic methods and a 1991 Consensus Statement by the National Institutes of Health that established criteria for eligibility for surgical treatment of morbid obesity (BMI > 40) opened the door for insurance coverage. This has lead to an explosive increase in the number of operations for obesity. Some institutions have a year-long waiting list. Weight loss at 5 years varies between 48-74% of the patient's original weight.[6]

The single most important article in this issue is the editorial by George Bray. He notes that "obesity is a chronic, relapsing, neurochemical disease that occurs in genetically susceptible people." Further, current treatments do not cure obesity and are only palliative. Two kinds of treatment are available for obesity: cognitive and noncognitive.

Cognitive treatments—such as lifestyle change, diet and exercise—produce weight loss when they are being used, but when they are stopped, relapse occurs. Noncognitive treatments include drugs, surgery, and some environmental manipulations, and they may produce long-standing weight loss.

Bray further discusses the controversy regarding low carbohydrate diets. The rapid weight loss with the low carbohydrate diet is largely a diuresis as the body mobilizes endogenous glycogen stores from the muscle and liver. The rapid weight-loss period lasts 7-14 days. The disadvantage is the potential for bone mineral loss over a period of time, and one potential advantage is the loss of gustatory stimulation by sweets. Not noted in these discussions is the potential for a decline in renal function in those patients who have decreased renal function at the onset of the low-carbohydrate diet, which is by definition a high-protein diet.

In *Science,* Nestle outlines one of the biggest challenges in the management of obesity. "When the interests of corporate institutions that control the distribution of food and its advertisement (with the goal of maximizing

food consumption) conflict with public good who is to intervene and how?"[7]

Researchers are picking apart the roles of the molecular signals that the body uses to regulate its weight. Leptin, the first anti-obesity hormone which was identified in 1994, has not resulted in significant changes in our treatments. Other hormones that control appetite are under intense investigation. Ghrelin is produced in the upper portion of the stomach and acts through the arcuate nucleus to stimulate short-term appetite. It is removed by gastric surgical procedures, which remove the upper portion of the stomach from the stimuli of food and may account for the decreased appetite in patients undergoing these operations. Ghrelin is increased in persons who lose weight with dieting and may undermine the dieters' ability to lose weight.[8]

The potential for new drugs and their mechanisms of action is reviewed. The search for new drugs is frustrating, but because of the huge potential for their use, pharmaceutical companies are salivating over the prospect of creating anti-obesity medications. However, it is hard to treat such a complex disease, and the potential for adverse results is great. There are drugs in the second and third phases of FDA trials now, but they will not reach the general public in the next year.[9]

In the "Where Do We Go From Here?" article, Hill and colleagues state: "Biology clearly contributes to individual differences in weight and height, but the rapid weight gain that has occurred over the past 3 decades is the result of the changing environment." These changes encourage consumption and discourage expenditure of energy. Using data from the National Health and Nutrition Examination Survey, they calculate that the average weight gain in persons 20-40 years of age is 1.8-2 pounds/year. This is only 50 Kcal/d. This means that reducing the energy gain by 50 Kcal/d would offset weight gain in 90% of the population. Walking 1 mile per day increases energy expenditure at least 100 kcal and would result in a gradual weight loss. They make very useful recommendations for putting this information into a daily plan.[10]

COMMENT BY RALPH R. HALL, MD, FACP

The article by Hill et al gives us information that enables us to approach our patients with a reasonable plan for life style changes that cost little in time or money. The key to implementing a plan is to take time to identify the barriers to change in our patients' life styles. This may take more time than we usually have and may ultimately mean that we have to partner with others to get the desired results. The article by Hill et al is essential reading for anyone treating patients for obesity.

The implication of Nestle and other nutritionists is that, somehow, laws should be passed to prevent advertising and to change our environment. This is impractical. We would have to stop advertising automobiles, large houses, etc. The individual has to take responsibility for their acts. Hill and his associates have given the majority of the population the knowledge and tools to successfully prevent and reverse obesity. ■

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Pharmacology Update

Aprepitant Capsules (Emend—Merck & Co)

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

THE FDA HAS APPROVED APREPITANT FOR PREVENTing both acute and delayed nausea and vomiting associated with chemotherapy. Aprepitant is a unique antiemetic, the first selective antagonist of the neurokinin-1 (NK-1) receptor, and the first to be approved for acute and delayed nausea and vomiting. Merck & Co markets aprepitant capsules as "Emend."

Indications

Aprepitant is indicated, in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.[1]

Dosage

Aprepitant is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. The recommended dose is 125 mg orally 1 hour prior to chemotherapy on day 1 and 80 mg in the morning on day 2 and day 3.[1] Based on clinical studies, the recommended dose of dexamethasone is 12 mg orally on day 1 and 8

mg orally on day 2, 3, and 4. The recommended dose of ondansetron is 32 mg IV on day 1.

Aprepitant is available as 80-mg and 125-mg capsules.

Potential Advantages

Aprepitant is the first drug to be approved for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. The combination of aprepitant 125 mg orally, dexamethasone 12 mg orally, and ondansetron 32 mg IV on day 1 and aprepitant 80 mg orally and dexamethasone 8 mg in the morning on days 2 and 3 was reported to be more effective than dexamethasone 20 mg orally and ondansetron 32 mg IV on day 1 and dexamethasone 8 mg morning and evening on days 2 and 3.[1] The percent of patients with complete response (no emetic episodes and no use of rescue therapy) in the acute phase (0-24 hrs) ranged from 83-89% for the aprepitant regimen compared to 68-75% for the standard regimen ($P < .001$). For the delayed phase (25 -120 h), complete response ranged from 68-75% for aprepitant and 47-56% ($P < .001$) for the standard regimen.

Potential Disadvantages

The combination of aprepitant and dexamethasone appears to be less effective than a 5-HT3 and dexamethasone combination in acute nausea and vomiting.[2] Aprepitant is a substrate, moderate inhibitor, and inducer of CYP3A4 inhibitor and may affect drug plasma levels of drug metabolized by this isoenzyme.[1] Drugs that inhibit or are inducers of this isoenzyme may affect the metabolism of aprepitant. Aprepitant is also an inducer of CYP2C9. The oral dose of dexamethasone or methylprednisone should be administered at about 50% of the dose normally given without aprepitant. Intravenous methylprednisolone should be given at about 25% of the usual dose.

Comments

Aprepitant is the first of the neurokinin-1 (NK-1) receptor antagonists. Substance P is the neurokinin neurotransmitter that selectively binds to NK-1.[3] In animal models, substance P has been found to produce emesis, and NK-1 receptor antagonists show antiemetic activity.[4] When aprepitant is added to a "standard" regimen of a 5-HT3 receptor antagonist and dexamethasone, both acute and delayed phase nausea and vomiting were reduced. FDA approval was based on 2 studies involving a total of 1105 patients who received cisplatin and other chemotherapeutic agents (eg, etoposide, fluorouracil, gemcitabine, vinorelbine, paclitaxel).[1] In both studies, a statistically significantly higher proportion of patients with added aprepitant had better outcomes overall, in the acute phase and delayed phase. The primary end point was no emesis and no rescue therapy (complete response). Aprepitant appears to be well tolerated although drug interactions, involving primarily CYP3A4 and CYP2C9, are a possibility.

The wholesale cost for a course of aprepitant (1 × 125 mg and 2 × 80 mg) is $250.

Clinical Implications

Acute and delayed nausea and vomiting commonly occur with the administration of cisplatin, carboplatin, cyclophosphamide, or doxorubicin. Cisplatin is one of the most emetogenic drugs at doses of 50 mg/m^2 or higher. Antiemetic prophylaxis with a 5-HT3 receptor antagonist in combination with a corticosteroid is standard therapy in these patients.[5] However, this combination is not as effective in preventing delayed nausea and vomiting, and approximately 50% of patients will suffer delayed nausea and vomiting. The addition of aprepitant appears to reduce the incidence of delayed nausea and vomiting compared to the 2-drug combination. In addition, the 3-drug regimens also appeared to reduce the incidence of acute nausea and vomiting compared to the 2-drug combination. This is particularly significant as poor control of acute nausea and vomiting has been reported as an important predictor of delayed nausea and vomiting.[6,7] Whether the combination of a neurokinin-1 receptor antagonist, 5-HT3 receptor antagonist, and a corticosteroid will become the standard of care will be determined with broader clinical experience. ■

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CME Question

25. Which one of the following questions is *false*?

a. The average weight gain of individuals between 20 and 40 years of age is 1.8 to 2 lbs/y.
b. Adolescent obesity is associated with a quality of life similar to adolescents being treated for cancer.
c. The use of leptin to treat obesity has improved our treatment results.
d. Surgery for obesity results in a weight loss at 5 years of between 48 and 70% of body weight.

Answer: 25 (c)

By Louis Kuritzky, MD

Influenza Vaccination and Reduction in Hospitalizations

DESPITE THE FACT THAT INFLUENZA and its consequences are well recognized, the number of at-risk individuals for serious sequelae to an influenza infection who receive vaccination remains suboptimal. Perhaps some clinicians remain unconvinced of the efficacy of influenza vaccine to reduce important outcomes. Nichol and colleagues studied the effect of influenza vaccine in 2 successive years (1998-2000) upon a large cohort (n = 140,000) of senior citizens aged 65 or older, which represent pooled data from 3 large managed-care organizations.

In each of these 2 influenza seasons, just over half of the population were immunized (55.5, 59.7%, respectively). Outcomes measured included odds of hospitalization for cerebrovascular disease, cardiac disease, and pneumonia or influenza. All-cause mortality was also assessed.

Influenza vaccination was associated with reductions in all outcomes measures, including 16-23% for cerebrovascular disease, 19% for cardiac disease, and 29-32% for pneumonia or influenza. Influenza vaccination was associated with a 48-50% reduction in all-cause mortality.

Only about two-thirds of senior citizens in the United States received influenza vaccination in 2001, leaving a very substantial gap from the intended current goal of 90% immunization. Perhaps such robust associations of influenza vaccine with favorable outcomes will stimulate clinicians to re-invigorate their energies toward enhanced vaccination. ■

Nichol KL, et al. N Engl J Med. 2003;348:1322-1332.

Screening Men for Prostate and Colorectal Cancer

PROSTATE CANCER (P-CA) AND COLorectal cancer (C-CA) do not share the same evidence base for potential efficacy in reducing mortality. For P-CA, there remain no data to confirm whether screening with PSA will lead to reductions in all-cause mortality. Even the recent trials, which have confirmed reductions in P-CA related mortality from cancers discovered by PSA screening, have not shown a reduction in all-cause mortality, leading to great uncertainty about the overall benefits for an individual patient and divergence of opinion by major policy making bodies about the best course of action for PSA screening. C-CA, on the other hand, is endorsed by essentially all policy-making and consensus groups, based upon multiple randomized controlled trials that show reductions in C-CA mortality with FOBT, and probably even greater benefit with sigmoidoscopy or colonoscopy.

The Behavioral Risk Factor Surveillance system is an annual study that obtains information for the CDC by random-digit dialing telephone surveys. In these data, questions about P-CA and C-CA screening in men older than 40 were included in 2001 (n = 49,315).

In this large population, 75% of men older than age 50 had undergone PSA testing, and the likelihood increased with increasing age. In contrast, only 63% of men in the same age group had been screened with either FOBT or endoscopy. Considering that an approximately equal number of deaths occur from these 2 disorders (C-CA = 27,800; P-CA = 30,200 estimated for the year 2002), and the considerably less robust evidence for the efficacy of P-CA screening, clinicians would be wise to expend more intensive energies to enhance C-CA screening practices. ■

Sirovich BE, et al. JAMA. 2003;289: 1414-1420.

Weight Loss in CHF and Treatment with ACE-I

WEIGHT LOSS TO THE DEGREE OF cachexia complicates cancer, some infectious diseases (eg, HIV, thyrotoxicosis), and less obviously, perhaps, heart failure (CHF). It has been previously noted in a small, prospective study of CHF patients that substantial weight loss (SWL) is associated with adverse effect upon survival, independent of other risk factors.

By analyzing the data from patients in a large treatment trial of CHF using ACE inhibitors (the SOLVD trial, n = 2569), Anker and colleagues investigated weight changes, the relationship of weight change to mortality, and the effect of ACE inhibitor treatment upon weight loss in a subgroup of the SOLVD trial (n = 1929).

In this data set, weight loss was independently related to reduced survival, independent of age, sex, New York Heart Association Class, ejection fraction, and even treatment allocation. In crude adjusted analysis, a weight loss of 6% or greater was the strongest predictor of reduced survival.

Anker et al comment that weight loss in CHF is not abrupt, but rather gradual, and represents diverse tissue compartment losses, including muscle, fat, bone, and the heart itself. They suggest that a 6% or greater weight loss be considered definitional for cardiac cachexia. ■

Anker S, et al. Lancet. 2003;361: 1077-1083.

In Future Issues: Lipid-Lowering Therapy