

# **PRACTICAL POINTERS FOR PRIMARY CARE**

**ABSTRACTED MONTHLY FROM THE JOURNALS**

**OCTOBER 2000**

**DOCTOR DO YOU KNOW HOW MUCH YOUR PRESCRIPTIONS COST THE PATIENT?**

**THE BEST SINGLE MEASURE TO PREDICT MORTALITY — PULSE PRESSURE**

**LOW-DOSE THIAZIDES HELP PRESERVE BONE MINERAL DENSITY**

**HISTORICAL FEATURES TO DIAGNOSE TYPE OF HEADACHE**

**HEALTH CARE WORKERS SHOULD TAKE FLU VACCINE EVERY YEAR**

**PRIMARY PREVENTION OF CORONARY DISEASE BY STATIN DRUGS**

**STATINS ARE UNDERUSED — MANY MORE WOULD BENEFIT.**

**DOES ULTRASOUND HELP TO DIAGNOSE ACUTE APPENDICITIS?**

**PRACTICAL MANAGEMENT OF INTERMITTENT CLAUDICATION**

**GLYBURIDE VS INSULIN FOR WOMEN WITH GESTATIONAL DIABETES**

**SHOULD WE SCREEN HIGH-RISK PATIENTS FOR LUNG CANCER?**

**CHOLESTEROL EMBOLI SYNDROME**

**UPRIGHT POSTURE AND POSTPRANDIAL HYPOTENSION IN THE ELDERLY**

**MELATONIN, CIRCADIAN RHYTHMS, AND SLEEP**

**GRAVE'S DISEASE — A REVIEW**

**ORAL CONTRACEPTIVES AND BREAST CANCER**

**RELIGION, SPIRITUALITY, AND MEDICINE.**

**RECOMMENDED READING**

**REFERENCE ARTICLES**

**JAMA, NEJM, BMJ, LANCET**

**ARCHIVES INTERNAL MEDICINE**

**ANNALS INTERNAL MEDICINE**

**ANNALS OF INTERNAL MEDICINE**

**EDITED BY RICHARD T. JAMES JR. MD**

**400 AVINGER LANE, SUITE 203**

**DAVIDSON NC 28036 USA**

**WWW.PRACTICALPOINTERS.ORG**

## HIGHLIGHTS OCTOBER 2000

### 10-1 PHYSICIANS' ATTITUDES ABOUT PRESCRIBING AND KNOWLEDGE OF THE COSTS OF COMMON MEDICINES.

Physicians were predisposed to being cost-conscious in their prescribing habits, but lacked knowledge about actual costs. Considering the benefit/harm-cost ratio is the basic consideration of therapy. We often fail to consider the cost denominator. We should know the costs especially of drugs used long term (eg, hypertension, diabetes, lipid disorders).

It is easy to access costs on the internet, for both generics and brand-names. The web pages of major pharmacies (eg, [www.cvs.com](http://www.cvs.com) 1-888-607-4287 ) post actual retail costs.

### 10-2 PULSE PRESSURE AND MORTALITY

The best single measure of blood pressure to predict mortality in older people appears to be the pulse pressure. A high systolic combined with a low diastolic BP therefore correlates with increased risk.

In middle-aged persons, systolic BP alone is a major risk factor.

In older persons, the pulse pressure is the major risk factor.

Systolic BP correlates closely with pulse pressure in older patients

Thus, systolic BP alone can be considered a common denominator of risk at all ages.

Treatment is aimed at reducing systolic BP

### 10-3 LOW-DOSE HYDROCHLOROTHIAZIDE AND PRESERVATION OF BONE MINERAL DENSITY IN OLDER ADULTS

Low-dose hydrochlorothiazide given for 3 years preserved BMD. Low-dose thiazides are still considered the first choice anti-hypertensives — preservation of BMD is an added benefit.

### 10-4 THE DIAGNOSTIC VALUE OF HISTORICAL FEATURES IN PRIMARY HEADACHE SYNDROMES

The most sensitive clinical features for migraine are nausea, phonophobia, and photophobia. Foods, especially cheese and chocolate, are triggers for migraine. Aura, especially visual, predominate in migraine and when present establish the diagnosis.

TTHA, the most common HA, is recurring, pressing, and band-like with few migrainous features. Phonophobia, photophobia and nausea are not common. Stress and hunger are triggers.

Cluster HA is a distinct syndrome.

"A carefully taken history can establish the diagnosis of migraine, cluster or tension-type headache with sufficient confidence that no need will exist for additional evaluation."

### 10-5 PREVENTING INFLUENZA IN HEALTHY ADULTS: The Evolving Story

Flu vaccine for healthy adults will prevent influenza in some individuals each year. The absolute number will vary with the severity of the epidemic and the match between the native influenza virus and the vaccine virus.

Healthy health care workers should take vaccine every year.

### 10-6 USE OF LIPID LOWERING DRUGS FOR PRIMARY PREVENTION OF CORONARY HEART DISEASE: Meta-Analysis of Randomized Trials

Treatment with lipid controlling drugs over 5 to 7 years reduced coronary heart disease events in persons with no known cardiovascular disease. (Primary prevention)

National Guidelines have suggested starting primary prevention treatment in persons with a 3% annual risk of CHD events. But the decision to take drugs depends to a large extent on personal preference. Clinicians should assess risks in each patient and if they are considered at higher risk than average, should inform them of the benefit/harm-cost ratio to guide their individual decision. Statin drugs are costly. RTJ

### 10-7 STATINS: UNDERUSED BY THOSE WHO WOULD BENEFIT

Statins are effective, easy to take, and relatively safe (*and very expensive*). Many people who would benefit from taking them are not doing so. Underuse is most apparent in the *secondary* prevention of heart disease in patients with known atherosclerotic disease for whom there is overwhelming evidence that statins are highly beneficial. Treatment should start as soon as a clinical diagnosis is made.

Undertreatment is also a problem for the larger population of people who do not have manifest atherosclerotic disease (*primary* prevention). "There is no longer any doubt that statin treatment benefits those who are at substantial coronary risk<sup>1</sup> but do not have established atherosclerotic disease.

. In practice, clinicians might consider treatment for those of younger age who have strong risk factors such as familial hypercholesterolemia or diabetes. Problems include cost and issues of long-term safety, although statins are reasonably safe and less likely to cause serious harm than aspirin.

For primary prevention of persons at higher than average risk of atherosclerotic events, MDs should explain the benefit/harm-cost ratio to each individual and allow him/her to make a personal informed choice.

### **10-8 CAN WE IMPROVE DIAGNOSIS OF ACUTE APPENDICITIS?**

Given the false positive (12%) and false negative rate (5%) of ultrasound, should ultrasound be allowed to override clinical judgement? There is probably no role for ultrasound where clinical evidence is convincing.

The main role of ultrasound may be for the equivocal case, where a combination of repeated clinical assessment and ultrasound may provide the additional information required to determine whether surgery is necessary. Patients should not be sent home after negative ultrasonography unless there are also clinical grounds for their discharge.

### **10-9 THE PRACTICAL MANAGEMENT OF CLAUDICATION**

#### ***As A Marker For Cardiovascular Disease It Needs Active Treatment***

Since peripheral vascular disease is a strong risk factor for myocardial infarction and stroke, it might be expected that patients would benefit by reducing risk of MI and stroke.

Claudication is a marker for generalized atherosclerotic disease. We should look at the patient's overall vascular risk and act accordingly. Preventive interventions include: smoking cessation; exercise; lipid control; and antiplatelet therapy.

### **10-10 A COMPARISON OF GLYBURIDE AND INSULIN IN WOMEN WITH GESTATIONAL DIABETES MELLITUS**

Gyburide (*DiaBeta; generic*) is a clinically effective alternative to insulin in women with gestational diabetes. It is as safe as insulin.

### **10-11 SCREENING STRATEGIES FOR EARLY DETECTION OF LUNG CANCER**

The editorialist argues that with CT scanning and improved cytology, many lung cancers can be diagnosed at an early stage and cured.

"Now is the time to screen for early-stage lung cancer." Screening heavy smokers with airflow obstruction with sputum cytology testing for central lesions and CT for peripheral lesions can identify and harvest the "low hanging fruit".

### **10-12 ROUTINE SCREENING FOR LUNG CANCER?**

#### **Lead Time Bias; Length Time Bias; Contamination Of The Control Population; Overdiagnosis**

There is not enough data to predict the benefit/harm-cost ratio of routine screening for LC. This commentator argues that screening is not of proven benefit. There are too many biases in the way of proof.

On an individual basis, patients at high risk (long-time smokers with decreased FEV1) may be made aware of the benefits, harms, and costs of screening, and be given the opportunity to choose for themselves.

See the original for a definition of lead-time bias, length-time bias, overtreatment, and contamination of the control population.

### **10-13 CHOLESTEROL EMBOLI SYNDROME**

Cholesterol embolization (CE) is a common complication of arteriography, vascular surgery, thrombolysis, and anticoagulation in elderly patients. The diagnosis is not often considered.

CE is a serious multisystem disorder, more common than has been supposed. It is characterized by a classic triad: 1) livido reticularis, 2) acute renal failure, and 3) eosinophilia

CE should feature strongly in the differential diagnosis of acute renal failure in elderly patients after angiography or other interventions. Clinicians should be aware of the delayed onset which often obscures the causative link. It may, however, occur without instrumentation.

### **10-14 UPRIGHT POSTURE AND POSTPRANDIAL HYPOTENSION IN ELDERLY PERSONS**

Meal ingestion was significantly related to a fall in systolic BP in elderly persons. After the meal, 22% had resultant symptomatic hypotension (systolic < 80 mm Hg) vs 12% when tested before the meal.

The problem of post-prandial hypotension and syncope leading to falls is common in nursing home patients. We should take care to keep individuals with this risk sedentary or recumbent for a time after meals, not allowing them to rise quickly.

### **10-15 MELATONIN, CIRCADIAN RHYTHMS, AND SLEEP**

Disturbances in circadian rhythms often result in disturbances in sleep. Some examples; jet lag; shift work; and the sleep disorders that occur in totally blind persons with free-running circadian rhythms (ie, rhythms that are not synchronized to the 24-hour day). The hormone melatonin can be used both to characterize and treat such disorders.

### **10-16 GRAVES' DISEASE**

I enjoyed this review. I abstracted some points I felt needed emphasis, and some I did not know or had forgotten. RTJ

### **10-17 ORAL CONTRACEPTIVES AND BREAST CANCER.**

There was a significant correlation between ever-use of OCs and risk of BC in sisters and daughters of probands (RR = 3.3 compared to marry-ins), but not among granddaughters or nieces. Women using OCs who had 3 family members with BC had a RR of 5; for those with 5 affected family members RR = 11. "These data offer strong support for the amplified effect of estrogen in the presence of genetic risk for BC."

However, the increased risk was seen only in users before 1975 when formulations contained higher doses of estrogen and progestins. Among first degree relatives who used OCs after 1975, the RR of BC was 0.9 compared with non-users.

First degree relatives of a woman with BC should use other contraceptive methods.

#### **10-18 RELIGION, SPIRITUALITY, AND MEDICINE: Application To Clinical Practice**

Patients want to be seen and treated as whole persons, not as diseases. A whole person is someone whose being has physical, emotional, and spiritual dimensions. Ignoring any one of these aspects of humanity leaves the patient feeling incomplete, and may even interfere with healing. For many patients spirituality is an important part of wholeness.

The editorialist quotes 4 simple questions the ACP suggests be asked of those with terminal illness which acknowledges the spiritual life of the patient and might be appropriate and helpful.

#### **RECOMMENDED READING**

**10-18 RELIGION, SPIRITUALITY, AND MEDICINE: Application To Clinical Practice**

#### **REFERENCE ARTICLES**

**10-4 THE DIAGNOSTIC VALUE OF HISTORICAL FEATURES IN PRIMARY HEADACHE SYNDROMES**

**10-16 GRAVES' DISEASE**

---

---

### **10-1 PHYSICIANS' ATTITUDES ABOUT PRESCRIBING AND KNOWLEDGE OF THE COSTS OF COMMON MEDICINES.**

Compliance with therapy is often compromised because patients cannot afford to pay for medications. Primary-care physicians often lack knowledge about drug costs.

Inattention to cost-effectiveness contributes to the inefficient use of societal resources and the rise in pharmaceutical spending. This topic is now receiving national attention, especially regarding costs for the elderly.

This study assessed the extent to which physicians were willing to consider the cost of drugs, and their knowledge about actual costs of drugs.

Conclusion: Physicians often were predisposed to consider costs, but lacked accurate knowledge about costs.

#### **STUDY**

1. Conducted a survey of internal medicine and general medicine clinicians. (134 responded; 70% house officers)
2. Questions concerned estimates of the average wholesale price of a 30-day supply of commonly used drugs.

#### **RESULTS**

1. The great majority considered costs an important consideration in the prescribing decision.
2. About 3/4 were willing to sacrifice some degree of effectiveness to make drugs more affordable.
3. Over 75% often were unaware of actual costs. Only 1/3 had easy access to drug cost information.
4. Almost all gave consideration to the cost when patients were self-paying. Only 30% considered this when patients had Medicaid or an HMO with a prescription plan.<sup>1</sup> A few physicians preferred brand names over generics regardless of cost. Estimates were more accurate for generics than for brand-name drugs.

5. Estimates of a month's supply of commonly used drugs were too low in 40% of cases; accurate in 45%. The costs of brand-name and expensive drugs were most likely to be underestimated.
6. Attending physicians were more cost-conscious than house officers.
7. Physicians rarely asked patients about the cost of the drugs.

## DISCUSSION

1. Straining to pay the cost of their drugs is a common occurrence for the poor and elderly and contributes to suboptimal care. High costs may prevent patients from filling their prescriptions and may reduce compliance, especially in treatment of chronic diseases.
2. In general, physicians appeared predisposed to practice cost-effective medicine. But they were often ill-equipped with the requisite knowledge to do so. They were likely to underestimate costs of expensive drugs.

## CONCLUSION

Physicians were predisposed to being cost-conscious in their prescribing habits, but lacked knowledge about actual costs.

Archives Int Med October 9, 2000; 160: 2799-2803 Original investigation, first author Steven Reichert, Englewood Hospital and Medical Center, Englewood, New Jersey. [www.archinternmed.com](http://www.archinternmed.com)

Comment:

I placed this as the lead article of this month's issue. Considering the benefit/harm-cost ratio is the basic consideration of therapy. We often fail to consider the cost denominator. We should know the costs especially of drugs used long term (eg, hypertension, diabetes, lipid disorders).

**1** It is wrong to fail to consider costs to insurance carriers. Costs will inevitably be passed on.

It is easy to access costs on the internet, for both generics and brand-names. The web pages of major pharmacies (eg, [www.cvs.com](http://www.cvs.com) 1-888-607-4287 ) post actual retail costs. Wholesale prices given in the Physicians Desk reference ( [www.pdf.com](http://www.pdf.com) ) may be widely off the mark when a patient reaches the check-out counter.

All learning of evidence-based medicine, and expertise in applying it to an individual patient goes for naught if the patient cannot afford the drug prescribed. RTJ

---

## 10-2 PULSE PRESSURE AND MORTALITY IN OLDER PEOPLE

In middle-aged populations, both systolic and diastolic BPs have strong, linear relationships with cardiovascular and total mortality. Since systolic BP and diastolic BP are highly correlated, studies find that diastolic BP provides little additional prognostic information after consideration of systolic BP. (Ie, in middle-aged persons, systolic alone can be taken as the BP risk factor.)<sup>1</sup>

In older persons, observational studies have commonly found a J-shaped relationship of BP with mortality. I.e, mortality rises as diastolic BP falls. The fall in diastolic is due to loss of aortic compliance and increased arterial stiffness which begins at about age 60. Thus pulse pressure (**PP**) rises as the diastolic falls, and the systolic rises with age. Consideration of PP may explain the apparent increased risk associated with low diastolic BP.

It is possible that PP is the measure most strongly related to cardiovascular risk in older people. Increased PP may be associated with risk of myocardial infarction, heart failure, and cardiovascular and total mortality. Since PP is strongly correlated with systolic BP, it is not clear whether PP provides prognostic information independent of systolic BP.

This study examined which combinations of systolic, diastolic, pulse, and mean arterial BP best predict total and cardiovascular mortality.

Conclusion: PP appears to be the best single measure of BP in predicting mortality in older persons.

## STUDY

1. Measured BP in over 9000 persons age 65 to 102 in 1981.
2. Followed for an average of 10 years.

## RESULTS

1. Over 10 years over 4500 subjects died; 2300 of cardiovascular causes.
2. The lowest overall death rate occurred in those with systolic less than 130, and diastolic 80 to 90.
3. The highest mortality occurred in those with a systolic 160 or more and diastolic less than 70.
4. Both low diastolic and elevated systolic independently predicted increases in cardiovascular and total mortality.
5. PP correlated strongly with systolic pressure. But, PP was a slightly stronger predictor of both cardiovascular and total mortality than systolic pressure.

## DISCUSSION

1. "These prospective data indicate that, in older people, both (*high*) systolic and (*low*) diastolic pressure provide important and independent prognostic information about the risk of cardiovascular and total mortality."
2. As in middle-aged people, in older persons, higher systolic pressure predicts linear increases in risk, with little evidence of confounding by other comorbid conditions. There is a clear increase in risk among those with borderline high (140-159 mm Hg) systolic pressure.
3. Low diastolic pressure is also a marker of increased risk of death, independent of systolic pressure.  
This association is largely explained by the confounding effects of frailty and comorbid conditions.
4. Pulse pressure, although highly correlated with systolic pressure, has the advantage of incorporating the effects of both high systolic pressure and low diastolic pressure. Prognostic models including PP are simpler and have nearly the same predictive value as models including both systolic and diastolic pressure.
5. PP appears to be the single best BP measurement to predict mortality risk in the elderly.
6. In healthy, middle-aged populations, PP is *not* a consistent and independent risk factor for

cardiovascular disease. (*Ie, in younger persons, systolic is a better predictor than PP.*)

7. Several studies have indicated that the prognostic significance of systolic pressure increases with age, while that of diastolic pressure and mean arterial pressure decreases.
8. Also, "Pulse pressure appears to be the best measure of BP to predict heart failure in the elderly."
9. Several plausible mechanisms: arterial stiffness increases afterload and myocardial work, impairs ventricular relaxation, and causes ischemia. PP is strongly correlated with left ventricular hypertrophy, a known risk factor for cardiovascular events. It is also correlated with the presence of atherosclerosis. The increase in shear stress and pulsatile strain may promote primary atheroma development, and may contribute to rupture of vulnerable plaques.
10. Borderline elevations of systolic pressure (140-159) were associated with significant elevations in risk, particularly among individuals with a low diastolic pressures.
11. Therapies of potential value in improving arterial compliance include ACE inhibitors, nitrates, and a low salt diet.

## CONCLUSION

The best single measure of blood pressure to predict mortality appears to be the pulse pressure.

Archives Int Med October 9, 2000; 160: 2765-72 Original investigation, first author Robert J Glynn, Brigham and Women's Hospital and Harvard Medical School, Boston Mass. [www.archinternmed.com](http://www.archinternmed.com)

Comment:

So . . . Systolic BP *alone* is a major risk factor in younger persons.

PP is a major risk factor in the elderly.

Systolic BP correlates with PP in the elderly.

Therefore, systolic BP *alone* may be considered a major risk factor at all ages.

Treatment should aim at reducing systolic RTJ

---

## 10-3 LOW-DOSE HYDROCHLOROTHIAZIDE AND PRESERVATION OF BONE MINERAL DENSITY IN OLDER ADULTS

Thiazides have been reported to be associated with higher bone mineral density (**BMD**) in both men and women. However experimental evidence has been lacking.

This study assessed the effect of hydrochlorothiazide on the rates of bone loss in older adults.

Conclusion: Low-dose hydrochlorothiazide had a modest effect in preserving BMD at the hip and spine.

## STUDY

1. Randomized, double-blind, placebo-controlled trial followed over 300 healthy normotensive adults age 60 to 79. (Mean = 68)
2. All received increased calcium intake.

3. Randomized to: 1) 12.5 mg hydrochlorothiazide daily, 2) 25 mg hydrochlorothiazide daily, or 3) placebo.
4. Measured BMD by X-ray absorptiometry at baseline and at 3 years.
5. Follow-up = 3 years.

## RESULTS

1. At 3 years, differences in hip bone BMD compared with placebo: + 0.8 percentage points for 12.5 mg; +0.9 percentage points for 25 mg.
2. Percentage change in the spine was significantly greater in the 25 mg group (+0.8%) compared with placebo.
3. No significant differences in total BMD.
4. Treatment differences were greater in women than in men.

## DISCUSSION

1. There was a dose response relationship to hydrochlorothiazide over 3 years.
2. Low-dose hydrochlorothiazide in healthy elderly subjects prevented bone loss at the hip and spine.  
At 3 years, the 25 mg hydrochlorothiazide group gained about 1% in BMD when compared with placebo.
3. The mechanism is likely the action of thiazides on the kidney tubule to decrease calcium excretion.
4. Despite accumulating evidence that low-dose thiazides reduce risk for stroke, congestive heart failure, coronary disease, and total mortality among patients with high BP, use has declined in recent years.  
“The benefits of thiazide on bone should be considered in decisions about long-term pharmacologic therapy for high blood pressure.”
5. If preservation of BMD accumulated over 10 to 20 years, the modest effects observed in this trial could possibly explain the one-third reduction in hip fracture observed in many observational studies.

## CONCLUSION

Low-dose hydrochlorothiazide given for 3 years preserved BMD.

Annals Int Med October 3, 2000; 133: 516-26 Original investigation, first author Andrea Z LaCroix, . Group Health Cooperative of Puget Sound, Fred Hutchinson Cancer Research Center, Seattle, Washington

[www.annals.org](http://www.annals.org)

=====

### Reference Article — A Comprehensive Review

## 10-4 THE DIAGNOSTIC VALUE OF HISTORICAL FEATURES IN PRIMARY HEADACHE SYNDROMES

The near universal nature of headache (**HA**) poses a challenge for clinicians. Over 90% of individuals experience HA in their lifetime. In 40% to 50% of persons the headaches are, over a lifetime, severe enough at times to cause interruption of work.

Many physicians are uncomfortable when evaluating patients with HA and may be concerned about misdiagnosing the rare patient with worrisome cause. "A disparity often exists between the severity of the HA and the need to worry." Eg, patients with uncomplicated migraine may have some of the most severe and disabling forms of HA, but do not have a pathologic cause of the HA. This disparity heightens physician anxiety and can lead to overuse of imaging studies in order to reassure the patient. <sup>1</sup>

The international headache society (**IHS**) established 13 broad categories of HA, and 128 distinct HA syndromes. (*See table 1 p 2731*) Clinicians may find these criteria too complicated and restrictive to use in day-to-day office evaluation.

This review summarizes the literature with the aim of determining the value of the history in patients with "primary" HA. Defined primary HAs as those without underlying pathological abnormalities; secondary HA as those due to a pathological cause. Results of the neurological examination are normal when HAs are not present.

[An exception is occasional persistence of Horner syndrome among asymptomatic patients with a history of cluster HA.]

The principal primary HAs are migraine, tension-type, and cluster.

Conclusion: Five historical features are most predictive of migraine vs tension HA. Cluster HA is a distinct clinical syndrome.

## STUDY

1. Searched the literature concerning the sensitivity of clinical and historical features for the diagnosis of migraine, tension-type, and cluster HA. Classified them according to the ISH criteria as the standard for diagnosis.
2. Clinical features include pain character, location, onset, precipitants, aura, other associated symptoms, duration, frequency, and time-course.
3. Calculated sensitivities and specificities of particular clinical features with a gold standard described by the IHS.

## RESULTS

### MIGRAINE

1. For migraine, the most frequent and specific features are: 1) nausea, 2) exacerbation by physical activity, 3) photophobia, 4) phonophobia, and 5) aura.

- |                                |        |             |             |
|--------------------------------|--------|-------------|-------------|
| 2. Positive likelihood ratios: | Nausea | Phonophobia | Photophobia |
|                                | 19     | 5           | 6           |

(Ie, in 20 patients with a headache accompanied by nausea, 19 will have migraine, and one will have a headache of other origin. RTJ )

(Likelihood ratio of a *positive* test = % of patients with the symptom (the test in this instance) who do have migraine divided by the % of patients with the symptom who do not have migraine. Ie, true positive % divided by false positive %

3. The specificity of these 3 symptoms is high. Ie, few patients who have these symptoms have HA other

than migraine.

4. Despite the origin of the word "migraine" from "hemicrania", unilateral pain is the least sensitive criterion. Throbbing pain is also less sensitive a criterion.
5. The absence of any of the features — nausea, phonophobia, photophobia and exacerbation by physical activity makes the diagnosis of migraine less likely.
5. Migraine precipitants: 1) stress, 2) certain foods, 3) missing a meal, and 4) menses, especially the week before. Food triggers (especially cheese, chocolate) are noted in about half the patients. The positive likelihood ratio of food precipitation = 3.6. Chocolate is the most specific precipitant. However, with the exception of food triggers, the other precipitants are equally prevalent among patients with tension-type HA.
6. Aura: About 1/3 of migraine patients experience an aura before the HA. Visual aura are the most common. Positive visual aura include zigzags, stars, and flashes. Negative aura are scotoma and hemianopsia. Sensory aura occur mainly in the hand and face. (They may progress from hand, to arm, to face). Sensory aura are usually unilateral. Aphasic, and motor aura occur in 5% to 20%. When one of these auras is present, the diagnosis is established. Most aura last less than 30 minutes.
7. Over half the migraine patients have a positive family history. Recurrent vomiting attacks and motion sickness in childhood may predict development of migraine later in life.

## DISCUSSION

1. "The history and results of the general physical and the neurological examinations correctly identify patients who need no further diagnostic evaluation."
2. About 18% of women and 6% of men have migraine HA. In about half, the migraine is severe enough to require bed rest or severely restricted working ability.
3. Mean age of onset of migraine is in the teen years. A first HA occurring after age 40 deserves particular diagnostic diligence to rule out secondary HA.

## TENSION-TYPE HA (TTHA)

1. Are the most common HA. Lifetime prevalence is about 75%. Although episodes are less likely to result in loss of work, the total national loss is greater than for migraine because of the greater prevalence of TTHA.
2. Migraine and TTHA can occur in the same patient.
3. The HA is chronic and recurring with few or no migrainous features. They are commonly bandlike, non-throbbing, and bilateral. The great majority last less than 24 hours. (Similar duration to migraine.) Phonophobia and photophobia are uncommon. If either is present, suspect migraine.
4. Except for food triggers, precipitants are similar to those for migraine. (Again if a food trigger is present, suspect migraine.)

## CLUSTER HA

1. Is distinctive, and easily distinguished from migraine.

2. In contrast to migraine: cluster HA is more common in men. Mean age of onset is age 30, older than for migraine.
3. Pain is commonly periorbital and strictly unilateral. It is usually excruciating. Patients become restless and agitated, and cannot find a comfortable position. Attacks commonly begin during sleep.
3. Autonomic symptoms commonly accompany cluster HA — lacrimation, rhinorrhea, and a partial Horner syndrome.
4. Duration is most commonly 30 to 60 minutes, distinctly shorter than for migraine. (Trigeminal neuralgia pain is much briefer.)
5. Stress and alcohol are common precipitants.
6. Cluster HA derives its name from their periodicity or tendency to cluster over time. Each cluster lasts an average of 1 to 2 months. Patients commonly experience 1 to 2 clusters a year.

## CONCLUSION

The most sensitive clinical features for migraine are nausea, phonophobia, and photophobia. Foods, especially cheese and chocolate, are triggers for migraine. Aura, especially visual, predominate in migraine and when present establish the diagnosis.

TTHA, the most common HA, is recurring, pressing, and band-like with few migrainous features. Phonophobia, photophobia and nausea are not common. Stress and hunger are triggers.

Cluster HA is a distinct syndrome.

"A carefully taken history can establish the diagnosis of migraine, cluster or tension-type headache with sufficient confidence that no need will exist for additional evaluation."

Arch Int Med October 9, 2000; 160: 2729-37 Review article by Gerald W Smetana, Beth Israel Deaconess Medical Center, Boston. [www.archinternmed.com](http://www.archinternmed.com)

Comment:

I enjoyed this review. The differential of HA is important since treatments differ.

A simple history is the most important feature leading to a correct diagnosis. Recognition by history will lessen need and reliance on expensive and invasive diagnostic procedures and permit reassurance for the patient.

1 Nevertheless, some patients with severe recurring HA will insist on further diagnostic studies (especially imaging). Although the clinician may be quite sure of the diagnosis, the patient may not be convinced. And although we may object to imaging as a routine, for some individuals it may bring considerable reassurance. Just as a negative EKG brings reassurance to a patient with chest pain. RTJ

---

**10-5 PREVENTING INFLUENZA IN HEALTHY ADULTS: The Evolving Story**

Controlled trials between 1943 and 1969 demonstrated the flu vaccine was 70% to 90% efficacious in preventing laboratory-confirmed clinical influenza as long as the vaccine-virus resembled the circulating virus. The current vaccine is similar to the old, but has a higher potency and fewer adverse effects. Its efficacy in healthy adults was recently confirmed.<sup>1</sup>

A study reported in this issue of JAMA<sup>2</sup> demonstrated that vaccination provided some clinical benefit, but, from the societal perspective, in some years provided no overall economic benefit. A multiyear approach is needed when evaluating the benefits of vaccination programs. The size of the yearly outbreak on populations is unpredictable.

We now have several new drugs to combat influenza (neuraminidase inhibitors; attenuated live vaccine for intranasal use). These new agents have provided new opportunities to prevent and treat influenza, in the form of prophylaxis for high risk individuals who do not receive vaccine, and as targeted prophylaxis after influenza exposure. This approach should be subject to the same economic scrutiny as the vaccine.

Many healthy persons may elect, given the need for annual vaccination and the likelihood that in many years they would not be infected even without receiving the vaccine, to consider use of neuraminidase inhibitors should they develop influenza. Neuraminidase inhibitors are as effective as vaccine for influenza prophylaxis, and appear not to be affected by changes in the circulating virus. But it is critical that older individuals and those with risk conditions not take this risk.

Given that the size of a forthcoming outbreak is not predictable, vaccine has to be given each year. But, unless there is much illness to prevent, the costs may outweigh the benefits.

JAMA October 4, 2000; 284: 1699-1701 editorial by Arnold S Monto, University of Michigan, Ann Arbor  
**www.jama.com**

**1** "Effectiveness And Cost-Benefit Of Influenza Vaccination Of Healthy Working Adults." JAMA October 4, 2000; 284: 1655-63 Vaccination of healthy, young, working adults can reduce the rates of influenza-like illness, lost workdays, and physician visits. Economic benefits are less in years when the risk of infection is low.

**www.jama.com**

**2** See also: "Effectiveness Of Influenza Vaccine In Health Care Professionals" JAMA 1999;282:908-13

**www.jama.com**

"Effectiveness Of Live, Attenuated Intranasal Influenza Virus Vaccine In Healthy Working Adults" JAMA 1999;282:137-144 **www.jama.com**

Comment:

The cost-benefit ratio in populations does not greatly concern clinicians and their individual patients.

We cannot predict the extent of a forthcoming epidemic.

We cannot predict the match between the vaccine and the circulating virus.

Nevertheless, I believe there are good reasons why all health care workers, including physicians, should be immunized each year:

Health care workers by definition have an increased exposure to flu.

Protection against an uncomfortable few days of lost-work due to a febrile illness.

Vaccination will increase herd-immunity.

Cost:

My pharmacy quotes a price of \$59.00 for ten 75 mg tablets of oseltamivir (*Tamiflu*).

---

---

## **10-6 USE OF LIPID LOWERING DRUGS FOR PRIMARY PREVENTION OF CORONARY HEART DISEASE: Meta-Analysis of Randomized Trials**

Effectiveness<sup>1</sup> of lipid controlling agents in *secondary* prevention is strongly supported. What about *primary* prevention of coronary heart disease (**CHD**)? Systematic reviews have reported conflicting conclusions.

This study summarized the effect lipid control on *primary* prevention of CHD events and all-cause mortality.

Conclusion: Treatment with lipid-controlling drugs over 5 to 7 years was associated with a reduction in CHD events, but was not associated with any reduction in total mortality.

### STUDY

1. Literature search identified 4 randomized trials of at least 1-year's duration reporting use of drug treatment for patients without known cardiovascular disease. (Primary prevention)
2. Mean age = 53; initial total cholesterol levels ranged from 220 mg/dL to 290 mg/dL.
3. Studies used cholestyramine, gemfibrozil, pravastatin (*Pravachol*), and lovastatin (*Mevacor*).
4. End point = all cause mortality, CHD mortality, and non-fatal myocardial infarction.

### RESULTS

1. Drug treatment with cholestyramine and gemfibrozil reduced total cholesterol levels by about 10% ; statin drugs reduced total cholesterol by about 20%.
2. Drug treatment reduced the odds of a coronary event by 30%.
3. Drug treatment over 5 to 7 years was not associated with any statistically significant reduction in total all-cause mortality.
4. Trials using statin drugs suggest a slightly stronger benefit on all outcomes, but did not show a significant reduction in all-cause mortality.

### DISCUSSION

1. In primary prevention trials, lipid controlling drugs reduced the relative risk of CHD events and CHD mortality by about 30% over 5 to 7 years.
2. The effect on all-cause mortality was small and not significant.
3. The failure of drug treatment to reduce all-cause mortality in primary prevention trials is most likely due to the generally low risk of mortality in the patient populations that were studied.

4. "Treatment targeted specifically at primary prevention in patients with higher levels of risk of coronary disease events might reduce all-cause mortality." Lower risk populations might experience a lower all-cause mortality if they were treated for a longer period.
5. Because the absolute risk of all-cause mortality in primary prevention patients is relatively low (2.4%) over 5 years, the absolute benefit in lives saved will also be low initially. The absolute risk reduction from treatment is proportional to the underlying risk in the person being considered for treatment. <sup>2</sup>
6. The decision about whether to use lipid-controlling drugs for patients without a history of CHD is difficult and requires consideration of outcomes other than all-cause mortality.<sup>3</sup>
7. The concomitant use of other drugs (eg, aspirin and beta-blockers), which were not used widely in the trials, may lower absolute risks.

## CONCLUSION

Treatment with lipid controlling drugs over 5 to 7 years reduced coronary heart disease events in persons with no known cardiovascular disease. (Primary prevention)

BMJ October 21, 2000; 321: 983-86 Original investigation, first author Michael Pignone, University of North Carolina, Chapel Hill [www.bmj.com/cgi/content/full/321/7267/983](http://www.bmj.com/cgi/content/full/321/7267/983)

Comment:

- 1 To review: 1) Effectiveness relates to results of treatments in the real world of clinical practice. 2) Efficacy refers to the results of treatments in the narrower experimental trial world. The two may be quite different.
- 2 Obviously, some determination of absolute risk should be made. Patients with established CHD are at most risk and should routinely (and immediately) after an event receive lipid control. Those without established CHD, who are smokers, and those with diabetes, hypertension, family history of CHD, and who are overweight with increased abdominal girth are next in line.
- 3 Most persons with a myocardial infarction survive, but then go on to considerable disability and lowered quality-of-life. This is most important when considering prevention. Morbidity is a less definitive end-point than mortality.

National Guidelines have suggested starting primary prevention treatment in persons with a 3% annual risk of CHD events. But the decision to take drugs depends to a large extent on personal preference. Clinicians should assess risks in each patient and if they are considered at higher risk than average, should be informed of the benefit/harm-cost ratio to guide their individual decision.

Costs:

For the statin drugs used in this review, my pharmacy quotes:

Pravastatin (*Pravachol*) 40 mg \$356 for 100

Lovastatin (*Mevacor*) 40 mg \$385 for 100.

The trials used 40 mg daily. Thus a month's supply would cost over \$100.

When negotiating a shared decision about long-term care, the patient must be informed about the benefit/harm-cost ratio. In the case of statins, he/she should realize that they might cost about \$1200.00 a year. RTJ

---

## **10-7 STATINS: UNDERUSED BY THOSE WHO WOULD BENEFIT**

Statins are effective, easy to take, and relatively safe (*and very expensive*). Many people who would benefit from taking them are not doing so. Underuse is most apparent in the secondary prevention of heart disease in patients with known atherosclerotic disease for whom there is overwhelming evidence that statins are highly beneficial.

Undertreatment is also a problem for the larger population of people who do not have manifest atherosclerotic disease (primary prevention). "There is no longer any doubt that statin treatment benefits those who are at substantial coronary risk<sup>1</sup> but do not have established atherosclerotic disease.

The recently revised Sheffield table<sup>2</sup> is easy to use as an excellent predicting tool. It provides cut-off points for ratios of total-cholesterol to high density cholesterol (based on age, sex, diabetes, hypertension, and smoking) that identifies people whose coronary risk exceeds 15% per decade and 30% per decade. The 15% cut-off point has the virtue of more closely resembling the 10-year coronary risk of participants in trials of primary prevention.

Age is the most important determinant of coronary risk. Primary prevention trials used cut-points starting at 45 for men and 55 for women. In practice, clinicians might consider treatment for those of younger age who have strong risk factors such as familial hypercholesterolemia or diabetes. Problems include cost and issues of long-term safety, although statins are reasonably safe and less likely to cause serious harm than aspirin. Adverse effects are usually reversible.

Statins have outstripped other lipid-controlling drugs<sup>3</sup> and have eclipsed the role of diet in coronary prevention. Diet is much less effective in controlling lipids, and has greater problems with adherence.

BMJ October 21, 2000; 321: 971-72 Editorial, first author Stephen B Hulley, University of California, San Francisco. [www.bmj.com/cgi/content/full/321/7267/971](http://www.bmj.com/cgi/content/full/321/7267/971)

Comment:

**1** We often seem to concentrate on "coronary" risk, forgetting that the atherosclerotic risk extends to all arteries.

**2** BMJ 2000; 320:671-76 [www.bmj.com/cgi/content/full/320/7236/671](http://www.bmj.com/cgi/content/full/320/7236/671)

**3** BMJ 2000; 320: 659-61 [www.bmj.com/cgi/content/full/320/7236/659](http://www.bmj.com/cgi/content/full/320/7236/659)

Most authors use the term "lipid lowering" I believe a more accurate and descriptive term is "lipid control" because one aim is to *increase* HDL-cholesterol. RTJ

---

## **10-8 CAN WE IMPROVE DIAGNOSIS OF ACUTE APPENDICITIS?**

"Clinical diagnosis of acute appendicitis is based on showing that movement between adjacent inflamed peritoneal surfaces causes pain. Laboratory investigations usually contribute little, and can be misleading." Normal white counts can occur in patients with gangrenous and perforated appendixes.

The vagaries of presentation and the variability of signs are such that even the most experienced surgeons may remove normal appendixes, or "sit on" those that have perforated. It is apparent that in most surgical units the normal appendix removal rate remains 15% to 30%.

Can we improve on our clinical performance? Can graded compression ultrasonography improve diagnostic accuracy? A study in this issue of BMJ,<sup>1</sup> which combined ultrasound with a clinical score, failed to produce better outcomes than unaided clinical diagnosis. Ultrasound performed by experienced observers still produced a 5% false negative result. (Ie, 5% of patients with acute appendicitis were reported to have a normal ultrasound.) And the false positive rate was about 12%. (Ie, in patients with a positive ultrasound, 10% had a normal appendix removed.)

Given the false positive and false negative rate, should ultrasound be allowed to override clinical judgement? There is probably no role for ultrasound where clinical evidence is convincing. The low false positive rate (6%) in patients with clinically obvious appendicitis does not warrant routine ultrasound. (One large study of 2280 patients found no benefit from routine ultrasound added to clinical assessment.)

The main role of ultrasound may be for the equivocal case, where a combination of repeated clinical assessment and ultrasound may provide the additional information required to determine whether surgery is necessary. Patients should not be sent home after negative ultrasonography unless there are also clinical grounds for their discharge.

BMJ October 14, 2000; 321: 907-08 Editorial by Spencer W Beasley, Christchurch Hospital, New Zealand.

**[www.bmj.com/cgi/content/full/321/7266/907](http://www.bmj.com/cgi/content/full/321/7266/907)**

**1** "Randomized, Controlled Trial of Ultrasonography in Diagnosis of Acute Appendicitis, Incorporating the Alvarado Score" BMJ October 14, 2000; 321: 919-22 **[www.bmj.com/cgi/content/full/321/7266/919](http://www.bmj.com/cgi/content/full/321/7266/919)**

---

## **10-9 THE PRACTICAL MANAGEMENT OF CLAUDICATION**

### ***As A Marker For Cardiovascular Disease It Needs Active Treatment***

The goal of managing claudication extends beyond increasing the restricted blood flow. The goal includes prevention of coronary and cerebrovascular events. Intermittent claudication is under-recognized as a risk factor. Sixty percent of people with claudication die of coronary heart disease; 10% die of stroke. What strategies are available to improve prognosis?

Exercise is widely held to be beneficial, but it has been applied with little enthusiasm. A meta-analysis of 21 studies reported an improvement of distance walked by 122%. Programs in which patients exercised 30 minutes at least 3 times weekly had the greatest benefit. The main role of supervised programs is to maintain and reinforce enthusiasm for exercise regimens.

Smoking cessation is important, but fewer than 1/3 of patients actually quit. Quitting reduces risk of limb threatening complications, and reduces likelihood of developing pain at rest, myocardial infarction, and death over a subsequent 7 years. Nicotine replacement therapy is safe, and combined with counseling is effective.

Antiplatelet therapy significantly reduces non-fatal cardiovascular events and death in patients with myocardial infarction and stroke. Use in patients with peripheral vascular disease with or without co-morbidity is gaining support. “Antiplatelet treatment has proved to be extremely useful in managing clinical manifestations of atherosclerosis and preventing further thrombotic events. The spectrum of anti-platelet drugs available for clinical use is expanding.”

Lipid control: There is no direct evidence that drugs improving lipid profiles are beneficial in patients with claudication. However, they reduce risk of cardiovascular events in patients with established ischemic heart disease and in patients at high risk of vascular disease. Since peripheral vascular disease is a strong risk factor for myocardial infarction and stroke, it might be expected that patients would benefit from lipid control by reducing risk of MI and stroke.

Claudication is a marker for generalized atherosclerotic disease. We should look at the patient’s overall vascular risk and act accordingly.

BMJ October 14, 2000; 321: 911-12 Editorial by Alun Davies, Imperial College School of Medicine, London.

[www.bmj.com/cgi/content/full/321/7266/911](http://www.bmj.com/cgi/content/full/321/7266/911)

Comment:

Another reminder that atherosclerosis is a generalized disease. If you have it in the peripheral arteries, it is also present in the coronaries, carotids, cerebral arteries, aorta, and renal arteries. RTJ

---

## **10-10 A COMPARISON OF GLYBURIDE AND INSULIN IN WOMEN WITH GESTATIONAL DIABETES MELLITUS**

Gestational diabetes and pre-existing diabetes are associated with adverse outcomes of pregnancy. . The principal approach to glycemic control in pregnancy has been dietary therapy with added insulin when diet alone is not sufficient.

Several authorities in the past have warned against use of sulfonylurea drugs in pregnancy, fearing neonatal hypoglycemia and fetal anomalies. This was before the availability of drugs such as glyburide (*DiaBata*; *generic*). In contrast to older sulfonylureas and metformin, glyburide does *not* cross the placenta in appreciable quantities. The primary action of sulfonylureas is to increase the secretion of insulin, thereby decreasing hepatic glucose production and indirectly improving insulin sensitivity.

This study hypothesized that glyburide might be a safe and effective alternative to insulin in patients with gestational diabetes.

Conclusion: Glyburide was a clinically effective alternative to insulin.

## STUDY

1. Randomized trial followed over 400 women with gestational diabetes. All failed to achieve acceptable glucose levels with diet and exercise, and were considered in need of drug treatment.
2. All had singleton pregnancies and a fasting plasma glucose between 95 and 140 mg/dL. Those with levels  $\leq 95$  were initially treated with diet, but subsequently enrolled in the trial if the glucose rose to over 95.
3. Mean baseline plasma glucose values (mg/dL):

|  |     |
|--|-----|
| Screen (1-h after 50-g glucose)        | 169 |
| Oral glucose tolerance (100-g glucose) |     |
| Fasting                                | 98  |
| 1 hour                                 | 199 |
| 2 hour                                 | 174 |
| 3 hour                                 | 137 |
4. Randomized at between 11 and 33 weeks to: 1) glyburide, or 2) insulin according to an intensified treatment protocol. Primary end point = desired level of glycemic control.
5. Mean dose of insulin = 85 units/d; mean dose of glyburide = 9 mg/d

## RESULTS

1. Mean pretreatment blood glucose concentration was 115 mg/dL.
2. Mean concentration during treatment was 105 mg/dL in both groups.
3. Eight women (4%) in the glyburide group required switch to insulin therapy.
4. No differences in percentage of infants who were large for gestational age; who had macrosomia (birth weight  $\geq 4000$ -g); lung complications; hypoglycemia; admissions to neonatal intensive care; or fetal anomalies.
5. Cord serum insulin concentrations were similar.
6. Glyburide was not detected in cord serum of any infant.

## DISCUSSION

- 1 Glyburide was as effective as insulin in producing glycemic control.
2. No materno-fetal transfer of glyburide was detected.
3. Past studies with metformin in women with GD reported 18% of infants were large for gestational age, 30% had jaundice; 9% major congenital anomalies.
4. The women in the present study were treated well after organogenesis. Rates of anomalies were similar in both groups and similar to women without diabetes.

## CONCLUSION

Gyburide is a clinically effective alternative to insulin in women with gestational diabetes. It is as safe as insulin.

NEJM October 19, 2000; 343: 1134-38 Original investigation, first author Oded Langer, St. Luke's-Roosevelt Hospital Center, New York. [www.nejm.com](http://www.nejm.com)

Comment:

Pregnant women were screened for diabetes with a 50-g oral glucose challenge. Those having glucose concentrations above 130 mg/dL at one hour underwent a 100-g glucose tolerance test. Those with 2 or more abnormal plasma glucose values were diagnosed as gestational diabetes. (Citation # 32) RTJ

---

---

## 10-11 SCREENING STRATEGIES FOR EARLY DETECTION OF LUNG CANCER.

Technology is available which could change the outcome of lung cancer (LC). But, screening in patients at high risk is still not recommended. Thus, LC is not diagnosed until it is symptomatic and usually when it is advanced and not curable. LC is the most common fatal malignancy in both men and women (1996 data). The 5-year survival rate is only 15%. About 150 000 persons in the US die each year of this rapidly progressive, painful malignancy.

The surgical survival rate in early-stage LC (ie, in situ and stage IIA) is at least 60%. "Diagnosing and treating lung cancer in the early stages of the disease could save tens of thousands of lives each year."

Why then is screening considered not beneficial and not recommended? The recommendations are based on studies done in the 1970s which used standard chest X-ray and sputum cytology for screening. But, standard X-ray does not often identify early-stage LC.

Recent studies (*citations 10 & 11*) using low-radiation, high resolution CT have shown that peripheral nodules as small as 3 mm can be detected. Virtually all of these lesions can be successfully resected. CT scanning is the standard screening practice in Japan. Most patients in Japan identified by screening have early-stage resectable lesions.

It is well established that CT is far more sensitive and specific than conventional radiography in the diagnosis of early peripheral LCs, which are usually adenocarcinomas.

In addition, the sensitivity and specificity of sputum cytologic testing has been improved by automated techniques.

Screening should be limited to those at high risk — history of smoking over 30 pack-years and evidence of airflow obstruction by spirometry. Airflow obstruction (FEV1 < 70%) in heavy smokers is associated with a 4 to 6 times higher prevalence of LC compared with patients without obstruction. In one study, screening heavy smokers with reduced FEV1 discovered about 2% with LC, far more than the yield of mammography for breast cancer.

Many patients with a history of smoking would be candidates for yearly screening. "Today, more lung cancer is found in former smokers than in current smokers."

The National Lung Health Education Program recommends identification and treatment of patients with early mild-to-moderate chronic obstructive pulmonary disease (COPD). It encourages all primary care practitioners to perform

spirometry in smokers older than 45, and in anyone with cough, dyspnea, wheeze, or mucus hypersecretion. These patients would also be candidates for LC screening.

Cost remains an important consideration. Prospective studies are needed to establish cost.

"Now is the time to screen for early-stage lung cancer." Screening heavy smokers with airflow obstruction with sputum cytology testing for central lesions and CT for peripheral lesions can identify and harvest the "low hanging fruit".

JAMA October 18, 2000; 284: 1977-80 Commentary as part of "Controversies" by Thomas L Petty, University of Colorado Health Sciences Center, Denver. [www.jama.com](http://www.jama.com)

See the following for a rebuttal.

---

## 10-12 ROUTINE SCREENING FOR LUNG CANCER?

### Lead Time Bias; Length Time Bias; Overdiagnosis

The editorialist points out that many prospective studies have reached a common conclusion: early screening for LC does *not* lead to reduced mortality. (*All studies were reported before 1987. RTJ*) He suggests that, until the value of screening is established, screening programs should be limited to well-designed, controlled studies.

For screening to be effective: 1) the disease in question must progress through a presymptomatic phase of sufficient duration to be detected, and 2) the treatment of cases detected by screening must have better outcomes than cases treated after detection after symptom onset. (*By definition, screening applies only to patients who have no symptoms at the time of the screen. RTJ*)

The editorialist points out important causes of bias in screening for LC:

1. Lead-time bias. This pertains to patients who are destined to die at a fixed date regardless of a screen, and any treatment given as a result of the screen. For example, suppose a patient with LC, even in the early stages, is destined to die of the LC on January 11, 2002, regardless of any treatment. (*This may be due to metastatic disease already present before resection of the cancer.*) A screen discovers the cancer on January 11, 2000. The local cancer is resected. If the screen were not performed, the patient develops symptoms on January 11, 2001. In both cases the patient dies on January 11, 2002. However, those who perform the screen claim that the screen and the resultant surgery prolonged the patient's life by 1 year, and therefore was worthwhile.

2. Length-time bias. This is a less evident bias. It has to do with the length of time between screens. For example, consider two patients with LC: 1) has aggressive disease, 2) has slowly progressive disease. When an initial screen is done at baseline, both screens are negative. The screen done 2 years later discovers the less aggressive cancer and surgery is performed. However, the patient with more aggressive cancer develops symptoms leading to the diagnosis one year after the original screen (*interval cancer*). Ie, the cancer is diagnosed, not as a result of the screen, but because of the onset of symptoms. Thus, the aggressive case is excluded from the analysis of the cohort of screened patients. The less aggressive case is included in the screened and treated cohort, and the results of the screening are thus considered to be more favorable than they actually are. Ie, length-time bias leads to elimination of aggressive cancers and favors the discovery of patients with less aggressive disease.

This results in a bias favoring screening. Increased detection of more aggressive cancer can be achieved only by shortening the interval between screens, or improving the sensitivity of the test.<sup>1</sup>

Contamination of the control population is another common bias in community settings. This occurs when many individuals in the control group actually do not remain untreated controls, but receive treatment outside of the study. Thus, the comparative difference between treated and control group diminishes.

Overdiagnosis is another consideration. This refers to the fact that some indolent cancers progress so slowly that the patient eventually dies of some other cause. The cancer discovered by screen is not involved. (*Overdiagnosis is a problem with screening for prostate cancer by PSA.*)

The editorialist goes on to comment that, although CT scanning for LC is more sensitive, the specificity of CT scan for LC is low (many false positives). Thus the predictive value of a positive CT is low. (The predictive value of a positive test is the ratio between true positive tests expressed as a percentage divided by the sum of true positive tests + false positive expressed as a percentage.) This was 12% in one study. This leads to overtreatment with its attendant harms and costs.

Screening is beneficial only if earlier detection of the disease leads to effective treatment that decreases mortality from the disease or provides longer survival and improved quality of life. Improved survival is a benefit only if it is *not* iatrogenic pseudosurvival — that is, pseudosurvival because of overdiagnosis, lead-time bias, or length-time bias.

However, "I believe it should be ethical for physicians to discuss lung cancer screening with selected high-risk patients. As long as the patient understands that screening is no substitute for tobacco avoidance, understands that it is not known whether screening leads to better outcomes, understands that screening may lead to a cascade of other evaluations and potential complications, and is aware that third-party payers may not pay for the tests, it is appropriate for this physician to offer screening if that is what the patient wants."

JAMA October 18, 2000; 284: 1980-83    Commentary by Paul S Frame, University of Rochester School of Medicine and Dentistry, New York    [www.jama.com](http://www.jama.com)

Comment:

**1** Do not CT and more definitive sputum cytology increase sensitivity?

So . . . which one is right? I believe both are. Routine screening of high-risk persons on a national level is not appropriate at this time. This will await more definitive data on the benefit/harm-cost ratio. On the other hand, on an individual basis, patients at high risk may be made aware of the benefits, harms, and costs of screening, and be given the opportunity to choose for themselves. RTJ

---

### **10-13 CHOLESTEROL EMBOLI SYNDROME**

Cholesterol embolization (**CE**) is a common complication of arteriography, vascular surgery, thrombolysis, and anticoagulation in elderly patients. The diagnosis is not often considered.

This brief article presents 3 illustrative cases, all seen with an initial presentation of acute renal failure.

CE is a serious multisystem disorder, more common than has been supposed. It is characterized by a classic triad: 1) livido reticularis, 2) acute renal failure, and 3) eosinophilia.<sup>1</sup> It arises in patients with generalized atheroma. The principal underlying mechanism seems to be destabilization of cholesterol plaques, leading to release of cholesterol crystals. These embolize until they become impeded by small vessels. They may provoke a foreign body response and lead to progressive fibrosis. This may explain the striking eosinophilia, which is reported in about 3/4 of cases.

The time interval between the intervention causing the embolization and the disease onset may be from one to four weeks (occasionally several months). This obscures the causative link.

Treatment options are limited. Statins might stabilize plaques. Steroids have been reported to benefit by some investigators, but others report no benefit. Early diagnosis is crucial if further episodes of embolization are to be avoided. CE is a potent contraindication to any further vascular intervention.

CE should feature strongly in the differential diagnosis of acute renal failure in elderly patients after angiography or other interventions. Clinicians should be aware of the delayed onset which often obscures the causative link. It may, however, occur without instrumentation.

BMJ October 28, 2000; 321: 1065-67 First author Peter J DuPont, Imperial College School of Medicine, London.  
[www.bmj.com/cgi/contnet/full/321/7268/1065](http://www.bmj.com/cgi/contnet/full/321/7268/1065)

Comment:

1 I was not aware of the association of eosinophilia with this syndrome. RTJ

See illustration of peripheral embolic lesions in the toes (blue toes) p 1066

---

#### **10-14 UPRIGHT POSTURE AND POSTPRANDIAL HYPOTENSION IN ELDERLY PERSONS**

Syncope and falls are common in the elderly, resulting in significant morbidity and mortality. Aging is associated with changes in cardiovascular function that predispose elderly persons to orthostatic and postprandial hypotension. Numerous investigations have confirmed postprandial reductions in BP in elderly persons.

This study hypothesized that the postprandial state and hypotension would result in symptomatic hypotension in some elderly persons.

Recruited 50 functionally independent elderly persons (mean age = 78). Performed head-up tilt-table testing before and 30 minutes after a standardized warm meal high in carbohydrate. (Warm food high in carbohydrate causes substantially more hypotension than colder foods high in protein and fat.)

Meal ingestion was significantly related to a fall in systolic BP. After the meal, 22% had resultant symptomatic hypotension (systolic < 80 mm Hg) vs 12% when tested before the meal.

Annals Int Med October 1, 2000; 133: 533-36 Original investigation, first author Matthew S Maurer, college of Physicians and Surgeons, Columbia University New York [www.annals.org](http://www.annals.org)

Comment:

The mechanism is a shift in blood volume to the gi tract and some loss of fluid into the gut following the meal. I abstracted this article briefly to remind me that the problem of post-prandial hypotension and syncope is common in nursing home patients. We should take care to keep individuals with this risk sedentary or recumbent for a time after meals, not allowing them to rise quickly.

---

---

## **10-15 MELATONIN, CIRCADIAN RHYTHMS, AND SLEEP**

Disturbances in circadian rhythms often result in disturbances in sleep. Some examples; jet lag; shift work; and the sleep disorders that occur in totally blind persons with free-running circadian rhythms (ie, rhythms that are not synchronized to the 24-hour day). The hormone melatonin can be used both to characterize and treat such disorders.

The circadian rhythm of melatonin secretion is generally set by the central pacemaker, or "clock", located in the hypothalamus. Like many other circadian rhythms, it is synchronized to a 24-hour period largely by clues from the light-dark cycle that are received by the hypothalamus.

Melatonin secretion responds to signals from the hypothalamic clock. Conversely, it is notable that melatonin can provide feed back to the clock, and modify the rhythm of its own production. This issue of NEJM reports a study<sup>1</sup> which took advantage of this action of melatonin to restore a more normal pattern of sleep in totally blind persons. (Blind persons have free running circadian rhythms, somewhat longer than the normal 24-hour cycle, and have associated sleep disorders.)

Normally, melatonin is produced during the night. In humans, its secretion is related to the length of the night. The longer the night, the longer the duration of secretion. (*Melatonin is a night-blooming hormone.*) The evening increase in secretion is associated with an increase in the propensity for sleep. Secretion during the day, which occurs in diverse pathological or occupational health situations, is strongly associated with sleepiness and napping. Administration of melatonin induces sleepiness.

Melatonin is used to treat circadian-rhythm disorders. Treatment of the disturbed circadian rhythms of blind people is one of the most important applications of melatonin therapy. Sleep-wake disorders involving a circadian cycle longer than 24 hours are a lifetime problem for blind persons.<sup>2</sup>

The true potential of melatonin is becoming evident, and the importance of timing is becoming clear.

NEJM October 12, 2000; 343: 1114-16 Editorial by Josephine Arendt, Guilford, Surry, UK [www.nejm.com](http://www.nejm.com)

**1** "Entrainment Of Free-Running Circadian Rhythms By Melatonin In Blind People." NEJM October 12, 2000; 343: 1070-77 [www.nejm.com](http://www.nejm.com)

**2** Blind persons have a free-running sleep-wake rhythm which averages somewhat over 24 hours. In each 24-hour period, the wake period is extended and the sleep period delayed. Thus, the wake period gradually lengthens into the middle of the night. This disrupts the daily schedule of blind persons. See the article for the use of melatonin ( 10 mg daily) to set the cycle straight and maintain a more normal sleep-wake cycle to concur with

sighted persons in the same household. The dose of melatonin in these blind persons could be reduced to 0.5 mg daily and still preserve the improved cycle

Comment:

Since melatonin is considered a dietary supplement, it is not subject to FDA approval and surveillance. I still worry about strength and purity of drugs purchased off the shelf.

The study used "analytic grade melatonin" administered under an Investigational New Drug application.

The study strengthens my belief that melatonin is a legitimate pharmaceutical and has important physiologic actions. RTJ

---

---

## Review Article

### 10-16 GRAVES' DISEASE

*(I enjoyed this review. I abstracted some points I felt needed emphasis, and some I did not know or had forgotten. RTJ )*

Graves' hyperthyroidism is caused by thyroid-stimulating antibodies produced by T-cells. The antibodies bind to, and activate thyrotropin receptors on thyroid cells. (Ie, Graves' is an autoimmune disease.) It shares many immunologic features with autoimmune hypo-thyroidism, including high serum concentrations of antibodies against thyroglobulin and thyroid peroxidases.

Graves' ophthalmopathy is characterized by edema and inflammation of the extraocular muscles and an increase in orbital connective tissue and fat. Cause is unknown, although an autoimmune response to one or more antigens located in the orbit is suspected. Smoking is strongly associated with ophthalmopathy. Clinically evident ophthalmopathy occurs in about 50% of patients. It may be evident a year before the diagnosis of hyperthyroidism, or may occur after Graves' becomes evident.

The increased prevalence of Graves' in females is in part the result of modulation of the autoimmune response by estrogen. Stress (bereavement, divorce, job loss) may precede the onset.

With increasing age, symptoms may change. The classical irritability and heat intolerance may lessen, and weight loss and decreased appetite become more common. (*Apathetic hyperthyroidism*) Atrial fibrillation is rare under age 50, but occurs in about 20% of older patients.

Measurement of serum thyrotropin is a useful screening test for hyperthyroidism. Small increases in thyroid secretion reduce secretion of thyrotropin. The diagnosis must be confirmed by measurement of *free* thyroxine (T4). Patients in the earliest stage may have only increased secretion of tri-iodothyronine (T3). Serum *free* T3 must be measured in patients with a normal *free* T4 and low thyrotropin levels.

Occasionally, thyroid radionuclide studies may be indicated to distinguish between painless, destructive (autoimmune) thyroiditis and Graves, especially in postpartum women. Patients with thyroiditis may have a small diffuse goiter. But painless thyroiditis is unlikely to last longer than 2 months.

Natural history: About 20% of patients with mild hyperthyroidism treated with beta-blockers for one year will become clinically and biochemically euthyroid. The duration of this response is not known. About 1/3 of patients treated with an

antithyroid drug will remain euthyroid for prolonged periods after cessation of the drug. The course of ophthalmopathy is largely independent of thyroid status, although it tends to be more severe when hyperthyroidism is poorly controlled.

Therapy: Definitive therapy (correction of the abnormal autoimmune response) is not possible. Current therapy consists of 1) radioactive iodine, 2) antithyroid drugs, or 3) surgery. In the U.S. radioactive iodine is favored. Carbimazole, methimazole, and propylthiouracil are the 3 available drugs. Propylthiouracil, in addition to its action on the thyroid, blocks the extrathyroidal de-iodination of thyroxine. This may lead to a more rapid reduction of tri-iodothyronine and more rapid resolution of symptoms. Drug selection is largely determined by local practice. About 1/3 of patients treated with drugs remain euthyroid 10 years after discontinuation. This means the disease has remitted. The author prefers "block-replace" therapy<sup>1</sup> when using drugs. Fewer visits to the clinic are required. Euthyroidism is easier to maintain.

The author recommends antithyroid drugs for patients with a first episode of Graves' hyperthyroidism who are younger than age 50. And radioactive iodine for those over 50 because recurrent hyperthyroidism carries a risk of atrial fibrillation in this age group. Radioactive iodine is also recommended for patients with recurrent hyperthyroidism unless there is an indication for surgery.

Patients with severe hyperthyroidism should be treated with an antithyroid drug for weeks before giving radioactive iodine because of the risk of thyrotoxic crisis soon after the iodine treatment.

NEJM October 26, 2000; 343: 1236-48 "Medical Progress" review article by Anthony P Weetman, University of Sheffield, UK [www.nejm.com](http://www.nejm.com)

**1** Block-replace consists of an antithyroid drug titrated in sufficient dose to cause hypo-thyroidism, then adding thyroxine to maintain euthyroidism.

See table 1 p 1241 for major symptoms and signs of Graves' and conditions associated with it. RTJ

---

## **10-17 ORAL CONTRACEPTIVES AND BREAST CANCER.**

Women have long been concerned about the association of OCs with risk of breast cancer (**BC**). A large meta-analysis<sup>1</sup>, using data from more than 50 studies, provided reassurance. The relative risk of BC in that study associated with current use (vs non-users) was 1.2. The risk disappeared after discontinuation for 10 years. Since most users are young and at that age are at less risk, the absolute risk was small— about 1 additional case per 20 000 women who used OCs between ages 20 and 25 . In addition, BCs in OC users tend to be diagnosed at an earlier stage.

What about the subset of women with inherited susceptibility? The meta-analysis found no difference in BC risk by family history. But accurate reporting of family history cannot be assured in epidemiological studies. Family history is not always an indicator of high risk. Indeed, the effect of having a first-degree relative with BC is small for most women because the relative's cancer usually occurs late in life. A woman whose mother or sister had BC in her 60s, has a risk of BC only modestly above average.

But the available data leaves open the possibility that hormone exposure could increase the risk of BC to a much greater degree in women with an inherited predisposition (eg, those carrying mutations in the BRCA1 and BRCA2 genes). Hormone replacement does result in a cumulative increase in risk over time. Conversely, there is strong evidence that OCs can substantially reduce risk of ovarian cancer. This protective effect may be an important consideration.

A study in this issue of JAMA<sup>2</sup> provides further information. It followed over 400 families with BC probands diagnosed 40 years before. There was a significant correlation between ever-use of OCs and risk of BC in sisters and daughters of probands (RR = 3.3 compared to marry-ins), but not among granddaughters or nieces. Women using OCs who had 3 family members with BC had a RR of 5; for those with 5 affected family members RR = 11. "These data offer strong support for the amplified effect of estrogen in the presence of genetic risk for BC."

However, the increased risk was seen only in users before 1975 when formulations contained higher doses of estrogen and progestins. Among first degree relatives who used OCs after 1975, the RR of BC was 0.9 compared with non-users. The lower age of those using BCs after 1975, however, may conceal a future risk.

Thus, the data presented argues for avoidance of OCs in high-risk women, but at the price of forgoing a reduction in risk of ovarian cancer.

"The use of OCs needs to be considered on an individual basis, taking into account baseline risk of breast cancer and ovarian cancer, alternative strategies for cancer risk reduction, and other benefits OCs may provide."

JAMA October 11, 2000; 284: 1837-38 Editorial by Wylie Burke, University of Washington. Seattle

**www.jama.com**

**1** The Lancet 1996;347: 1713 **www.thelancet.com**

**2** "Risk of Breast Cancer with Contraceptive Use in Women with a Family History of Breast Cancer." JAMA October 11,2000; 1791-98 **www.jama.com** The absolute risk is low, especially with low-dose OCs. But, first degree relatives of a woman with BC are at increased risk and should take OCs with extreme caution, or not at all.

Comment:

I am sure that for those with high-risk of BC, most clinicians would not prescribe, and most women would not take BCs. However, the data do reassure those that do take the low-dose OCs. RTJ

---

---

### **Recommended Reading**

#### **10-18 RELIGION, SPIRITUALITY, AND MEDICINE: Application To Clinical Practice**

Patients want to be seen and treated as whole persons, not as diseases. A whole person is someone whose being has physical, emotional, and spiritual dimensions. Ignoring any one of these aspects of humanity leaves the patient feeling incomplete, and may even interfere with healing. For many patients spirituality<sup>1</sup> is an important part of wholeness.

More than 800 studies have examined the relationship between religious involvement and various aspects of health. The majority found that people experience better mental health and adapt more successfully to stress if they are religious. They also report that religious persons are physically healthier, lead healthier life-styles, and require fewer health services.

But, no study has shown that people who become religious only in anticipation of health benefits will experience better health. <sup>2</sup>

What does this mean for clinical practice?

First, what should physicians *not* do? Physicians should not prescribe religious beliefs or activities for health reasons. They should not impose their religious beliefs on patients or initiate prayer without the knowledge of the patient's religious background and the likely appreciation of such activity.

What should physicians do? They should acknowledge and respect the spiritual lives of patients, and should keep interventions patient-centered. Acknowledging the spiritual life often involves taking spiritual history, although this is not appropriate for every patient. For those with illness that threatens life or way of life, it probably is. The American College of Physicians suggests 4 simple questions:

1. Is faith (religion, spirituality) important to you in this illness?
2. Has faith been important to you in the past?
3. Do you have someone to talk to about spiritual matters?
4. Would you like to explore religious matters with someone?

Taking a spiritual history is often a powerful intervention in itself. Many patients appreciate their physician's sensitivity to these issues. The physician can thus send an important message that he/she is concerned with the whole person, a message that enhances the physician-patient relationship.

Should physicians pray with patients? It is not appropriate to pray without the patient's consent. Alternatively, prayer can be led by the patient. Our calling as physicians is to "cure sometimes, relieve often, and comfort always". If a distressed patient asks for prayer and the physician sees that such prayer could bring comfort, then it is difficult to justify a refusal to do so.

JAMA October 4, 2000; 284: 1708 Essay by Harold G Koenig, Duke University Medical Center, Durham, NC

[www.jama.com](http://www.jama.com)

Comment:

**1** The author uses spirituality and religion interchangeably since most Americans do not make a distinction between the two. I prefer "spirituality". In extreme cases, "religion" has an adverse connotation.

**2** Beware! One does not become spiritual to attain better health. One attains better health if spirituality comes first. Do not bargain with God!

## NOTE

Practical Pointers can also be accessed on the Internet **[www.practicalpointers.org](http://www.practicalpointers.org)**

The internet version is formatted in HTML. This presents many helpful links, especially when one wishes to use the cumulative index.

The pdf format permits printing out the text in a readable format. RTJ

