PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JANUARY TO JUNE

2005

PRACTICAL POINTS FOR PRACTICE

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

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This document is divided into three parts:

1) **"Practical Points"—one sentence statements of how the articles abstracted during the 6 months may influence primary care practice.**
2) **Seventy seven medical subject headings (MeSH) from "Absolute Cardiovascular Risks" to "Ximelagatran". Each of the medical subject headings is linked to one or more "Highlights and *Editorial Comments*" of articles abstracted during the first half of 2005.**
3) **A "Highlights-*Editorial Comments*" Section, arranged alphabetically following the list of MESH, provides a means of recalling to memory, in an evening or two, what the editor considered new and important for primary care presented in 6 flagship journals over the 6 months.**

The numbers in the brackets refer to the full abstract. For example, [6-2] indicates the 2nd abstract published in the June issue.

The indexes and each monthly issue for the past 5 years can be found on the website (www.practicalpointers.org). HTML links make possible easy and speedy access to the full abstract and the journal reference of all articles abstracted under an individual MeSH.

I hope you find the publication useful and interesting.

Richard T. James Jr. M.D.

The editor thanks Whitney Lowell for internet applications and Lois M. James for proofreading.

PRACTICAL POINTS JANUARY-JUNE 2005

HOW THE ARTICLES ABSTRACTED INFLUENCED MY PRACTICE

- **Consider use of herpes zoster vaccine when it becomes available. [6-1]**
- **Consider use of delayed prescriptions for acute lower respiratory infections [6-2]**
- **Encourage patients to consider their abdominal girth a risk factor [6-3]**
- **Be cautious in using aspirin for primary protection of CHD in elderly women. [6-5]**
- **Care in using antipsychotic drugs in nursing homes [6-6]**
- **Consider a thiazide a first-line treatment in hypertensive diabetics and blacks [6-8] [4-1]**
- **Use opioids more freely for patients with neuropathic pain [6-9] Consider use of gabapentin combined with morphine for severe neuropathic pain [3-4]**
- **Advise patients that high dose vitamin E is useless in the elderly with memory defects or for reduction of risk of cardiovascular disease and cancer. And it may be toxic [6-10] [3-10]**
- **Advise younger overweight patients that weight loss will prevent later development of hypertension [6-11]**
- **Continue to advise vitamin D (800 IU) for primary prevention of osteoporosis and fractures [5-3]**
- **For first-line therapy, advise symptomatic treatment for traveler's diarrhea, not antibiotics. [5-4]**
- **For patients with persistent cough, pertussis is a possibility [5-5**
- **Oral vitamin B12 in high dose is effective therapy [5-6]**
- **Progesterone, not estrogen, is the risk factor for breast cancer in women receiving HRT**
- **Inform men about risks of PSA screening as well as benefits. Consider that "most prostate cancers now removed need not be removed" [5-9]**
- **Treat acute pain of herpes zoster aggressively to lower severity of post-herpetic neuralgia pain [5-10]**
- **Stress the benefits of a modified Mediterranean diet which contains poly-unsaturated fats as well as mono-unsaturated fats. [4-4]**
- **Consider the "Money needed to treat" as well as the "Number needed to treat needlessly" [4-6]**
- **Consult with your cardiologist consultants about availability and advisability of cardiac resynchronization in patients with left bundle-branch-block and heart failure. [4-10]**
- **Consider myasthenia gravis in a patient with fluctuating weakness which improves with rest and application of cold. [4-11]**
- **Consider that all adults have at least one risk factor for cardiovascular disease. All should be considered in each individual patient. Changing life-styles is basic therapy. Many will benefit from drug therapy [3-1] [3-2]**
- **Know the drugs available for prophylaxis and treatment of influenza [2-1]**
- **Never give up encouraging smokers to quit [2-3]**

- **For atrial fibrillation, rate control is preferable to rhythm control [2-4]**
- **Simple first aid and local wound care the best approach for bites of the brown recluse spider. [2-6]**
- **Extent of treatment of hypertension and dyslipidemia should depend on the patient's absolute cardiovascular risk. [1-1]**
- **In considering application of results of trials beware of surrogate endpoints, composite outcome measures, underreporting of adverse effects, and reports by pharmaceutical companies. [1-2]**
- **Uncertainty is inherent in primary care practice. Evidence helps quantify the uncertainty, but cannot remove it. [1-4]**
- **Know the benefits of a new class of drugs to treat breast cancer (aromatase inhibitors) [1-5]**
- **Fast foods are an ominous public health issue [1-8]**
- **For patients with persistent dyspepsia consider testing of H pylori and treating if positive. [1-9]**
- **The U. S Preventive Services Task Force recommends one-time screening for abdominal aortic aneurysm in persons who smoke. [1-11]**

MEDICAL SUBJECT HEADINGS (MeSH) JANUARY- JUNE 2005

ABSOLUTE CARDIOVASCULAR RISK
ACUTE CORONARY SYNDROMES
ADVERTISING
ALCOHOL
ALLHAT STUDIES **(SEE HYPERTENSION [6-8])**
ANEURYSM
ANTIBIOTICS
ANTICOAGULANT THERAPY
ANTIPSYCHOTIC DRUGS
AROMATASE INHIBITOR **(SEE BREAST CANCER [1-5])**
ASPIRIN
ATKIN'S DIET **(SEE DIET [1-7])**
ATRIAL FIBRILLATION

BREAST CANCER
BROWN RECLUSE SPIDER

CANCER
CARDIOVASCULAR DISEASE
CHOLESTEROL
COGNITIVE DECLINE
COGNITIVE IMPAIRMENT
CONGESTIVE HEART FAILURE **(SEE HEART FAILURE)**
CORONARY HEART DISEASE **(SEE ALSO ISCHEMIC HEART DISEASE [5-2])**
C-REACTIVE PROTEIN **(SEE STATIN DRUGS [1-13])**

DIABETES
DIABETIC NEUROPATHY
DIET
DYING
DYSPEPSIA

ENDOMETRIAL CANCER
ESTROGEN **(SEE HORMONE REPLACEMENT THERAPY)**
EVIDENCE-BASED MEDICINE

FAST FOOD
FOLIC ACID **(See HOMOCYSTEINE [3-9])**
FRACTURE **(SEE VITAMIN D [5-3])**

GASTRO ESOPHAGEAL REFLUX DISEASE
GESTATIONAL DIABETES MELLITUS

HEART FAILURE
HERPES ZOSTER
HOMOCYSTEINE
HORMONE REPLACEMENT THERAPY
HYPERPARATHYROIDISM
HYPERTENSION
.
INFLUENZA
INSULIN RESISTANCE
INTRACRANIAL STENOSIS.
ISCHEMIC HEART DISEASE

MACULAR DEGENERATION
MEDITERRANEAN DIET
"MONEY" NEEDED TO TREAT
MYASTHENIA GRAVIS
MYOCARDIAL INFARCTION

NEUROPATHIC PAIN
NUMBERS NEEDED TO TREAT (NEEDLESSLY)

OBESITY
OPIOID AGONISTS

PAIN (SEE OPIOID AGONISTS [6-9])
PERTUSSIS (SEE WHOOPING COUGH [5-5])
PNEUMONIA
POLYPILL (SEE CORONARY HEART DISEASE)
POSTHERPETIC NEURALGIA AND PAIN (SEE HERPES ZOSTER)
POWER AND AUTHORITY IN MEDICINE
PREMENSTRUAL SYNDROME
PROSTATE CANCER

RANDOMIZED CONTROLLED TRIALS
RESPIRATORY INFECTION
.

SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUES: A REVIEW

SMOKING

STATIN DRUGS

STROKE

TRAVELERS' DIARRHEA

TUBERCULOSIS

VITAMIN B12

VITAMIN D

VITAMIN E

WAIST CIRCUMFERENCE

WHOOPING COUGH

XIMELAGATRAN

HIGHLIGHTS AND *EDITORIAL COMMENTS*

JANUARY- JUNE 2005

ABSOLUTE CARDIOVASCULAR RISK

Treat the Patient, Not the BP, Not the cholesterol

1-1 TREATMENT WITH DRUGS TO LOWER BLOOD PRESSURE AND BLOOD CHOLESTEROL BASED ON AN INDIVIDUAL'S ABSOLUTE CARDIOVASCULAR RISK.

Absolute risk of a cardiovascular disease is the probability that an *individual* patient will have an event over a defined period. It is determined by a synergistic effect of *all* CVD risk factors present in the individual. It may be true that, in a large group of individuals with a systolic BP of 160, the CVD risk is twice as high as in a large group with a systolic of 110 (*relative risk*). In an individual, however, absolute risk depends on much more than a single risk factor. Indeed, absolute differences in risk can vary more than 20-fold in patients with the same BP.

"Cardiovascular treatment benefit is directly proportional to the pre-treatment absolute risk."

A new approach to preventive therapy is to modestly reduce all modifiable risk factors rather than concentrating on reaching "target levels' of one or two.

This is a sea change in our approach to lowering risk.

Please read the full abstract.

ACUTE CORONARY SYNDROMES

Proposing an ABCDE Memory Device to Simplify Adherence to Guidelines

1-6 A SIMPLIFIED APPROACH TO THE MANAGEMENT OF NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES

The study assembled a comprehensive plan through an "ABCDE" approach. The intention was to provide a memory device to overview therapies and lifestyle changes that are clinically useful for patients with NSTE-ACS.

Elements of the plan:

A Antiplatelets; Anticoagulation; ACE inhibitors; Angiotensin II blockers.

B Beta-blockers; Blood pressure control

C Cholesterol management; Cigarette cessation

D Diet; Diabetes management

E Exercise.

This practical approach allows physicians to more effectively create disease management protocols, define roles and responsibilities for different medical personnel, and ensure implementation of evidence-based short- and long-term medical and risk-reducing strategies.

This plan is almost identical to a check list presented in the Archives Int Med July 2004 for secondary prevention of cardiovascular disease. (See Practical Pointers July 2004 [7-8])

I believe check lists can be a valuable addition to primary care. In the hurried pace of practice, we all omit (simply forget to consider) aspects of treatment and lifestyle which should be addressed at almost every patient visit. A mneumonic check list is a practical approach.

Some clinicians may make their own. I tried to create a mneumonic check list for diabetes:

D Diet; Depression

I Insulin

A Aspirin; ACE inhibitors

B BMI; BP

E Exercise

T Tests (blood glucose; HbA1c; lipids; microalbuminuria; liver function; ejection fraction)

E Eye (retinopathy); Extremities (foot health; foot pulses; peripheral neuropathy)

S Sulfonylureas, Statins, and other oral drugs; Smoking

Plus (Add others which might be indicated.)

ADVERTISING

"Ask Your Doctor if X is Right for You"

4-12 DIRECT-TO-CONSUMER ADVERTISING

A Haphazard Approach to Health Promotion

DTCA drives sales of newer, more expensive products for symptomatic relief of chronic conditions. The market potential is huge. Erectile dysfunction, arthritis, and allergies are the most common conditions advertised.

"Relying on emotional appeals, most advertisements provide a minimal amount of health information, describe benefits in vague, qualitative terms, and rarely offer evidence of support claims."

The great majority of physicians believe that DTCA does not provide balanced information. The FDA rarely writes regulatory letters. "Millions of patients are exposed to misleading advertisements." Nearly 80% of physicians think that DTCA encourages patients to seek treatments they do not need. Less than 10% of physicians consider DTCA a positive trend in health care.

Is ED a manufactured "disease"? Is drug treatment mainly recreational?

I confess that advertisements on TV touting a drug in market terms and then asking the listener to "Ask your doctor if the drug is right for you" irritates me. It would require considerable time and patience to educate individual patients about the benefit/harm-cost ratio of a given drug. It may be easier to submit as gracefully as possible.

I believe claims by drug companies that DTCA is for instruction and benefit of the consumer are specious. The purpose is to market the drug and increase profits.. After all, we live in a capitalistic society.

ALCOHOL

One or Two Drinks per Day may Reduce Risk of Cognitive Decline

1-12 EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON COGNITIVE FUNCTION IN WOMEN.

This study asks—What is the effect of *moderate* consumption of alcohol on cognition? A benefit is plausible considering the strong link between moderate alcohol and decreased risk of cardiovascular disease. Cognitive impairment and cardiovascular disease share common risk factors.

Compared with abstainers, moderate drinkers (less than 15 g alcohol per day; one drink) had better mean cognitive scores. (Relative risk of impairment = 0.81 based on a global cognitive score.) Also, compared with abstainers, moderate drinkers (15 to 30 g per day) had a reduced relative risk of cognitive impairment (although slightly less favorable, with wider confidence intervals).

In older women consumption of one alcoholic drink per day did not impair cognitive function, and may actually decrease risk of cognitive decline.

Benefits of moderate alcohol consumption have been reported with remarkable consistency over the past 10 years. Indeed, some epidemiologists consider abstinence to be a risk factor for cardiovascular disease.

As always, we should be cautious about generalizing the conclusions of observational studies.

"Almost No Pattern of Drinking (Even Low-To-Moderate) is Entirely Risk Free."

2-2 ALCOHOL AND PUBLIC HEALTH

Over the past 30 years, advances in our understanding of drinking problems have been substantial.

This review considers 3 subtopics: 1) the epidemiology of alcohol's role in health and illness, 2) treatment of alcohol use disorders as part of public health, and 3) prevention and policy research.

Alcohol is causally linked to more than 60 different medical conditions—most, but not all, detrimental.
For most diseases there is a dose-response relationship. Not only the volume of consumption, but patterns of drinking (especially binge drinking) determine the burden of disease. Almost no pattern of drinking (even low-to-moderate) is entirely risk free.

*Breast cancer (**BC**):*

Meta-analyses have shown a linear increase in risk of BC associated with increasing average consumption of alcohol.

*Coronary heart disease (**CHD**):*

Comprehensive meta-analyses reiterate the protective effect of low-to-moderate alcohol intake—a J-shaped curve.

Injury (violence)

Several pharmacological effects are likely to increase probability of aggressive behavior.

Alcohol accounts for about as much of the burden of disease globally as tobacco. Its burden is surpassed only by unsafe sex, high blood pressure, and malnutrition.

Among heavy drinkers who have no evidence of severe alcohol dependence, an intervention in primary care aimed at reduction of drinking to moderate levels may benefit. Evidence suggests that clinically significant effects on drinking behavior can follow a brief intervention—but not in alcohol-dependent persons.

Overall, a discouraging report. Primary care clinicians may have some place in prevention of alcohol dependence by early assessment and intervention.

Many experts have urged screening, especially for patients who are hospitalized for any reason.

AUDIT and CAGE questionnaires available on Google. Screening in itself may broach the subject and lead patients to self-examination.

The relation between breast cancer and alcohol has not been well publicized. I believe it prudent to inform women at high risk (family history; breast cancer genes) about the risk.

No level of alcohol consumption is known to be safe in pregnancy.

Associated With A Slight Reduction In Days Of Heavy Drinking

4-13 EFFICACY AND TOLERABILITY OF LONG-ACTING INJECTABLE NALTREXONE FOR ALCOHOL DEPENDENCE

The opioid antagonist naltrexone has been shown to be effective for treatment of alcohol dependence (**AD).** The FDA approved naltrexone in 1994 to treat AD after it was shown to reduce drinking frequency and likelihood of relapse to heavy drinking.

However, adherence to daily oral therapy is problematic, as it is with other medications.

Recently a new formulation of naltrexone has been made available. When given by injection, it releases the drug over a period of one month without daily peaks in concentration.

A randomized, double-blind, placebo-controlled multicenter trial followed over 400 patients (mean age = 45). All were considered to be AD and almost all were still actively drinking (median heavy drinking days per month = 20). All were seeking treatment for their AD.

Randomized to: 1) monthly injections of 380 mg long-acting naltrexone, or 2) placebo injections.

All also received low-intensity psychosocial intervention.

Follow-up = 6 months.

Conclusion: Long-acting naltrexone, given by injection once a month, was associated with a slight reduction in days of heavy drinking.

Authors (with concurrence from journal editors) persist in reporting efficacy as percentages. ("Naltrexone resulted in a 25% reduction in the event rate of heavy drinking days").

Results of the trial were not impressive. Dropout rate was high. Women did not benefit. Adverse effects were frequent. "Spin" was evident.

The most evident benefit shown by the study was in the "placebo" group (motivated patients who received counseling). At 6 months there was a median reduction in days of heavy drinking per month from about 19 to about 6. Naltrexone was associated with a further reduction from 6 to 3 days. (My assessment of the figure 2 page 1622). Over the 6 months, in the placebo group there was a median of 56 cumulative days of heavy drinking vs 47 cumulative days in the naltrexone group, a difference of only about 9 days.

Should primary care clinicians administer long-acting naltrexone by injection? I believe only in exceptional circumstances. If a patient with AD approaches the primary care clinician for help, the desire to quit must be understood to be strongly motivated. The clinician must be able to provide adequate counseling. Follow-up must be rigid. The clinician and patient must enter a contract to guide compliance. The small added benefit from naltrexone must be made clear.

We await better treatments, perhaps with the addition of two or more pharmacological agents (eg, acamprosate).

The study was sponsored by Alkermes and Pharmacological Product Development Inc. who collected and monitored the data. Data were managed and analyzed by Alkermes clinical and statistical staff.

ALLHAT STUDIES **(See HYPERTENSION [6-8])**

ANEURYSM

The USPSTF Now Recommends One-Time Screening in Select Subsets of Men

1-11 SCREENING FOR ABDOMINAL ANEURYSM

The U.S. Preventive Services Task Force **(USPSTF)** now recommends one-time ultrasonographic screening for abdominal aortic aneurysm **(AAA)** for men ages 65 to 75 who presently smoke or who have smoked in the past.

The task force makes no recommendation for or against screening men who have never smoked. It recommends *against* routine screening for women.

One-time screening is sufficient.

Is there any medical treatment? Will beta-blockers decrease the rate of expansion by reducing the stress caused by the steep increase in wall expansion during systole? Many patients in this age group with AAAs would be candidates for beta-blocker therapy because of an increase in risk factors for CVD, including sub-optimal BP control.

As always, primary care clinicians must judge benefits vs harms of individual patients. The availability of expert, safe surgery is a major factor influencing the recommendation.

Advice for screening carries ethical considerations. Although opportunistic preventive medicine is considered a part of good medical practice, is it always ethically justifiable? Consider a male smoker age 70 who consults for arthritis. Should the primary care clinician at the time of the consultation advise the patient to undergo screening for AAA? Should the primary care clinician advise a prostate specific antigen?

Physicians who offer a screening test carry a considerable responsibility. They must offer enough information about risks and benefits in order to enable the patient to give informed consent. Every test carries a chance of a false-positive result leading to interventions that do not benefit the patient, and may cause harm.

I believe many primary care clinicians would limit screening for AAA to patients who consult for a specific indication—assessment of their general health status.

ANTIBIOTICS

Antibiotics Provided Little Advantage Compared With No-Antibiotics.

6-2 INFORMATION LEAFLET AND ANTIBIOTIC PRESCRIBING STRATEGIES FOR ACUTE LOWER RESPIRATORY INFECTION

Pharyngitis and acute bronchitis are the main causes of excess antibiotic prescribing.

This pragmatic study assessed the effectiveness of 3 different antibiotic strategies for acute bronchitis.

Randomized, controlled trial followed over 800 patients presenting to primary care with acute uncomplicated LRI. Patients with findings suggestive of pneumonia were excluded—new focal chest signs (focal crepitations or bronchial breathing); and systemic features (high fever, vomiting, severe diarrhea). Also excluded patients with asthma, other chronic or acute lung diseases, cardiovascular disease, or with previous pneumonia.

Randomized to: 1) no antibiotic prescribed [control group], 2) delayed prescription [to be picked up later], or 3) immediately prescribed antibiotic. The antibiotic of choice was amoxicillin 250 mg 3 times daily for 10 days, or, if allergic, erythromycin 250 mg 4 times a day for 10 days.

Compared with no antibiotics [control group], the other strategies did not significantly alter cough duration: Delayed prescription shortened duration by 0.75 days; immediate prescription by 0.11 days. Treatment group had no effect on duration of other symptoms.

"Compared with immediate antibiotics, a strategy of either no offer of antibiotics or a delayed prescription was associated with little difference in duration or severity of symptoms." Overall, antibiotics probably do provide modest symptomatic relief. If a benefit is present, it represents a shortening of only one day in a relatively long history. "It is difficult to justify widespread antibiotic prescribing for uncomplicated lower respiratory infection on this basis, given the dangers of antibiotic resistance."

I was somewhat surprised at the duration of cough symptoms in this group of patients—a mean total of 3 weeks. However, I believe most patients would experience a gradual improvement over this period. We are admonished to consider pertussis in patient with LRI when the cough lasts 3 weeks or more. I presume in pertussis the cough continues unabated.

I believe advising patients that antibiotics may be associated with serious adverse effects (eg, colitis) will do more to tilt them toward accepting only symptomatic therapy than would advising them of the danger of antibiotic resistance in the community.

I have had success in prescribing delayed prescriptions of patients with uncomplicated lower respiratory infections. The great majority never fills the prescription. This may be an acceptable means of satisfying a demanding patient.

In the US, It is likely that many patients presenting after a week or more of cough and sputum production will receive a cheat X-ray.

The decision by primary care clinicians to prescribe or not prescribe, I believe, will often depend on how "sick" the patient appears.

ANTICOAGULANT THERAPY

Potentially A Less Intimidating Alternative to Warfarin. Concerns about Hepatotoxicity

2-7 XIMELAGATRAN—Promises and Concerns

Melagatran is a highly-specific direct thrombin inhibitor, an analogue of hirudin, the thrombin inhibitor found in the medicinal leech. It is a small dipeptide which binds reversibly to the active site of thrombin. It inhibits clot-bound thrombin as well as free thrombin. Ximelagatran is a prodrug form of melagatran. It is rapidly absorbed from the GI tract. When given orally it is rapidly converted to melagatran. Its antithrombin activity is immediate. Peak blood levels are attained in 3 hours. It is cleared entirely by renal excretion in 12 hours.

Since the effect is predictable at a fixed dose, monitoring is not necessary.

This is not yet a practical point for primary care since the drug is not yet approved by the FDA. Many attributes of the drug make it a very attractive anticoagulant: immediate action when given orally; a fixed dose without need for monitoring; rapid renal clearance; no food or drug interactions; active against clot-bound as well as free thrombin; reversible binding to thrombin.

If the risk of hepatotoxicity can be controlled by monitoring, I believe it will be a major therapeutic advance.

Warfarin Provided No Benefit Over Aspirin. Was Associated With More Adverse Effects.

3-7 COMPARISON OF WARFARIN AND ASPIRIN FOR SYMPTOMATIC INTRACRANIAL STENOSIS.

Randomized, double-blind multicenter (59 sites) trial entered over 550 patients (mean age 63). All had experienced a TIA or a non-disabling stroke caused by angiographically verified 50% to 99% stenosis of a major intracranial artery (internal carotid, middle cerebral, vertebral, or basilar).

Randomized to: 1) warfarin—target INR of 2.0 to 3.0, or 2) aspirin 650 mg twice daily.

Warfarin provided no benefit over aspirin. It was associated with significantly higher rates of adverse events. "Aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis."

This is a good example of a pragmatic (real world of practice) trial. Difficulty in control of warfarin dosage may have been the cause of its lack of benefit.

ANTIPSYCHOTIC DRUGS

"Our Most Important Finding Was The High Level Of Antipsychotic Prescribing In NHs."

6-6 THE QUALITY OF ANTIPSYCHOTIC DRUG PRESCRIBING IN NURSING HOMES

Antipsychotic drug prescribing in nursing homes **(NHs)** has been rising.

Federal statutes are in effect to protect NH residents from receiving inappropriate antipsychotics. They may be appropriately prescribed for delirium and dementia only if psychotic features or dangerous behaviors are present. Guidelines also stipulate maximum daily doses.

For residents with dementia, behavioral assessments must also show evidence of verbal or physical aggression or delusions or hallucinations.

Impaired memory, wandering, restlessness, unsociability, uncooperativeness, and indifference to surroundings are NOT indications.

Use of antipsychotic drugs in NHs was widespread. Most atypicals were prescribed outside the prescribing guidelines with doses, and for indications without strong clinical evidence of benefit. About 1 in 4 received doses exceeding recommended. About 2/3 of use was appropriate—dementia with aggressive behavior; dementia with delusions; psychotic disorder. About 1/3 received the drugs inappropriately—impaired memory; depression without psychotic features; indifference to surroundings; insomnia; anxiety; wandering; restlessness; uncooperativeness; unsociability.

The study failed to detect positive relationships between behavioral symptoms and antipsychotic therapy.

"This study raises questions about the current uses of antipsychotics in NHs."

These are powerful drugs. Elderly patients are subject to more adverse effects. They require a lower dose because of impaired renal function and concomitant illness. The PDR reiterates that schizophrenia is the only indication. There is no mention of use in nursing homes. Few studies have concerned patients over age 65.

I believe the most appropriate question to ask when contemplating use of antipsychotics in NHs is . . .
Am I prescribing this drug to benefit the patient, or the nursing staff and the family? This can be a most difficult decision to make. If they are prescribed, individual- patient's response must be carefully monitored.

AROMATASE INHIBITOR (See BREAST CANCER [1-5])

ASPIRIN

The NNT to Prevent One Stroke is Very High

3-6 RANDOMIZED TRIAL OF LOW-DOSE ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN.

Use of aspirin in *primary* prevention in women is controversial. The current recommendations for use of aspirin in *primary* prevention in women are based on limited data.

The Women's Health Study was a large, randomized, double-blind placebo-controlled trial of low-dose aspirin in the primary prevention of cardiovascular disease among over 39 000 apparently healthy women followed for a mean of 10 years for major cardiovascular events.

For the entire group of women over age 45, aspirin reduced risk of ischemic stroke. It did not protect against myocardial infarction and death from cardiovascular causes until after age 65.

Women taking aspirin experienced significantly more GI hemorrhages (RR = 1.40)

By my calculation, between 500 and 900 individuals would need to be treated for 10 years to prevent one ischemic stroke. Is this clinically significant?—especially when the increased risk of hemorrhage is considered. RTJ)

Thus far, studies indicate that, in men, the prophylactic benefit against first occurrence of myocardial infarction is much greater than in women. But in men, aspirin does not provide primary protection against stroke.

"No Indication Of A Net Benefit."

6-5 EPIDEMIOLOGICAL MODELLING OF ROUTINE USE OF LOW-DOSE ASPIRIN FOR THE PRIMARY PREVENTION OF CORONARY HEART DISEASE AND STROKE IN THOSE AGE > 70

Current US guidelines recommend the use of low-dose aspirin for people with a 5-year absolute risk of coronary heart disease **(CH D)** of > 3%, or a 10-year absolute risk of > 10%.

"Prophylactic use of a potentially toxic agent can be problematic, particularly in people in whom comorbidity and polypharmacy are common." In a prospective observational study in two large UK general hospitals, aspirin use was the causal agent in 18% of all admissions for adverse drug effects, and was implicated in 61% of all associated deaths. Older females are the most vulnerable.

This epidemiological modeling study was conducted in a hypothetical population (10 000 men and 10 000 women) selected from a reference population from a state in Australia. All were age 70-74. None had known cardiovascular disease.

Proportional benefit gained from aspirin in prevention of MI and ischemic stroke *vs* excess hemorrhage from age 70-74 to age 100 or to death:

Benefit in preventing	Men (n = 10 000)	Women (n = 10 000)
Myocardial infarction	- 389	- 321
Ischemic stroke	- 19	- 35
Harm		
Excess GI hemorrhage	+ 499	+ 572
Excess hemorrhagic stroke	+ 76	+ 54

When comparing net harms *vs* net benefits of aspirin, the effects on length and quality of life were equivocal.

"Despite sound evidence for efficacy, the temptation to blindly implement low-dose aspirin treatment for the *primary* prevention of cardiovascular disease in elderly people must be resisted." Benefits may be offset by harms.

I believe low-dose aspirin has an important place in primary prevention of women at higher risk, and in secondary prevention of cardiovascular disease.

There is an important clinical downside related to universal prophylactic aspirin therapy: suppose primary care clinicians prescribe low-dose aspirin to 1000 women over 10 years. Three or 4 ischemic strokes might be prevented. But there would be no way of knowing which individuals of the 1000 benefited. Conversely, a serious hemorrhagic event occurring in 2 of the1000 patients would be self-evident. The clinician might feel responsible, and the patient and family might blame the clinician for the disaster.

I believe primary prevention with aspirin in women at average risk should be avoided. Obviously, careful clinical judgment based on individual-patient attributes is required.

ATKIN'S DIET **(See DIET [1-7])**

ATRIAL FIBRILLATION

Rate Control of AF Appears to be at Least Equivalent to Rhythm Control.

2-4 RATE VS RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

Patients with AF have a 4- to 5-fold increase in risk of stroke and a 2-fold increase in risk of death. Because of the frequency of AF at present, and its increasing incidence as the population ages, there are enormous implications regarding AF-associated stroke, and its prevention.

The two fundamental approaches to management are 1) reestablishment and maintenance of sinus rhythm (rhythm control), and 2) control of ventricular rate by intraventricular node blocking agents (rate control).

"The results of our meta-analysis suggest that in most patient populations with persistent AF, or at high risk of recurrent AF, a strategy of maintaining rhythm control does not translate into significant benefit on survival compared with a strategy of rate control in combination with anticoagulation. . . ."

Indeed, the suggestion is that rhythm control may actually be inferior in regard to survival.

Compared to patients in normal sinus rhythm (NSR) , patients with AF have more heart-related symptoms and less efficient ventricular function, decreased exercise tolerance, higher risk of stroke, lesser quality of life, a requirement for anticoagulation, and shorter survival. If restoration and maintenance of NSR, could be accomplished easily and safely and could be constantly maintained, outcomes would be more favorable than among patients with persistent AF. The problem is that NSR may be difficult to achieve and maintain, and the drug therapy required is toxic and often has to be withdrawn.

Many patients for whom rhythm control is attempted revert to AF and are later crossed over to rate control. If anticoagulation is adequate in the AF patients, risk of stroke is low.

Practical Pointers has previously abstracted two studies which arrived at the same conclusion—rate control is not inferior to rhythm control. I thought the point deserved emphasis. See www.practicalpointers.org December 2002 [12-2]

BREAST CANCER

Aromatase Inhibitor Safer and More Effective Than Tamoxifen

1-5 RESULTS OF THE ATAC (ARMIDEX, TAMOXIFEN, ALONE OR IN COMBINATION) TRIAL OF 5 YEARS' ADJUVANT TREATMENT FOR BREAST CANCER

This study compared the aromatase inhibitor anastrozole with tamoxifen over 5 years.

Compared with tamoxifen, anastrozole led to significant improvements for disease-free survival, and time-to-recurrence, especially in women whose BC was hormone-receptor-positive. Benefits were also demonstrated in hormone-receptor-negative patients.

Benefits were therefore *in addition* to the risk reduction previously shown in tamoxifen vs placebo trials. (*Ie, anastrozole vs placebo would have shown greater absolute benefits compared with tamoxifen vs placebo*)

The incidence of contralateral BC was substantially reduced by anastrozole as compared with tamoxifen. (This was also an improvement over the benefit of tamoxifen alone vs placebo as demonstrated in previous studies.)

Withdrawals were significantly fewer in the anastrozole group (11% vs 14%).

Drug-related serious adverse events were also fewer (5% vs 9%).

Anastrozole was associated with significant reductions in endometrial cancer, thromboembolic events, ischemic cerebrovascular events, vaginal bleeding, and hot flushes.

Arthralgias and fractures were more frequent in the anastrozole group. (*The authors suggest concomitant bisphosphonate therapy because of this finding*.)

It is reasonable to switch patients currently on tamoxifen to an aromatase inhibitor. It is not appropriate to wait until after a 5-year period of treatment with tamoxifen. The most effective and well-tolerated therapy should be offered at the earliest opportunity.

Anastrozole should be considered the preferred *initial* adjuvant endocrine therapy for post-menopausal women with hormone-receptor positive localized BC.

Aromatase is the enzyme which catalyses conversion of androgens to estrogens in females. Aromatase inhibitors block production of estrogen.. There are three 3rd generation compounds under investigation: exemestane, anastrozole, and letrozole. The action of exemestane is irreversible.

A similar study reported in NEJM March 11, 2004 reported similar benefits when exemestane was substituted for tamoxifen after 2 to 3 years.(See Practical Pointers March 2004 [3-9])

I believe this represents a major improvement in therapy of BC, and likely an improvement in prevention.

I wonder—would there be any benefit in treatment of ductal carcinoma in situ?

BROWN RECLUSE SPIDER

Usually Self-Limited and Typically Heal Without Medical Intervention

2-6 BITES OF BROWN RECLUSE SPIDERS AND SUSPECTED NECROTIC ARACHNIDISM

"Among both physicians and the general public the perceived threat of spider bites far exceeds the actual risk." Loxosceles spider bites are the only proven medically important cause of necrotic arachnidism in North America. The brown recluse spider (*Loxosceles reclusa)* is most commonly blamed. Diagnosis is made by collection and proper identification of the spider. This is rarely possible.

Bites occur much less commonly than as perceived by physicians and patients. The misdiagnosis of spider bites is given to a wide spectrum of dermatologic conditions, some of which are far more dangerous than a spider bite. (*See the long list p. 703*)

"Since many diseases mimic loxoscelism, and since documented bites are rare, any diagnosis of loxoscelism should be considered highly suspect."

Treatment remains controversial. Initial care should include routine first aid: elevation and immobilization; application of ice; local wound care; and tetanus prophylaxis. A wide range of other interventions has been reported, none with consensus regarding efficacy. Many are costly, painful, and potentially toxic.

"Because the injury from the bite of a brown recluse spider is usually self-limited and typically heals without medical intervention, controlled trials would be essential to justify treatment before advocating any particular therapy." There is no therapy with proven efficacy.

Even severe necrosis is rarely life-threatening. The bite is typically self-limiting and self-healing.

Patients often overemphasize spider involvement in idiopathic wounds, a tendency that can misdirect physicians toward an erroneous diagnosis. "Physicians should be skeptical of any undocumented history of spider bite and should entertain a broad differential diagnosis before attributing a skin ulcer as loxoscelism."

Conservative use of simple first aid and local wound care may be the best approach.

This sensible report may save some patients considerable discomfort.

CANCER

Fasting Serum Glucose Level and Diabetes were Associated with Cancer Risk

1-15 FASTING SERUM GLUCOSE LEVEL AND CANCER RISK IN KOREAN MEN AND WOMEN

Is there any connection between diabetes and cancer? Some observational studies have suggested there is. This prospective cohort study investigated this possibility.

A ten-year prospective study enrolled over 829 000 men and over 468 000 women age 30 to 95 at baseline. (Mean = 46; mean body mass index = 23)

After adjusting for smoking and alcohol use, the stratum with the highest fasting glucose (> 140) had higher death rates from all cancers compared with the stratum with the lowest level (< 90). Hazard ratio = 1.25

Age-adjusted cancer deaths per 100 000 men rose linearly from about 600 in the groups with fasting glucose < 90 to about 1400 per 100 000 in the group with glucose levels above 140. (*Although absolute numbers are low, the linear relationship depicted on page 196 and 200 is impressive. RTJ*). Similar linear increases were recorded in women, although not as high in absolute terms. Incidence of cancer was similar to mortality.

The association was strongest for pancreatic cancer. (Hazard ratio = 2 comparing the highest glucose stratum with the lowest.) Significant associations were also found in other cancers (esophagus, colo-rectal, liver, cervix).

"We have shown that fasting serum glucose level and diabetes are associated with cancer risk in a population far leaner than the Western populations."

This is my first encounter with the relation between glucose intolerance and cancer. It is not a clinically important point now. I felt it was interesting enough to abstract. I will watch for follow-up studies.

CARDIOVASCULAR DISEASE

1-1 TREATMENT WITH DRUGS TO LOWER BLOOD PRESSURE AND BLOOD CHOLESTEROL BASED ON AN INDIVIDUAL'S ABSOLUTE CARDIOVASCULAR RISK.

Absolute risk of a cardiovascular disease is the probability that an *individual* patient will have an event over a defined period. It is determined by a synergistic effect of *all* CVD risk factors present in the individual. It may be true that, in a large group of individuals with a systolic BP of 160, the CVD risk is twice as high as in a large group with a systolic of 110 (*relative risk*). In an individual, however, absolute risk depends on much more than a single risk factor. Indeed, absolute differences in risk can vary more than 20-fold in patients with the same BP.

"Cardiovascular treatment benefit is directly proportional to the pre-treatment absolute risk."

A new approach to preventive therapy is to modestly reduce all modifiable risk factors rather than concentrating on reaching "target levels' of one or two.

This is a sea change in our approach to lowering risk.

Please read the full abstract.

The NNT to Prevent One Stroke is Very High

3-6 RANDOMIZED TRIAL OF LOW-DOSE ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN.

Use of aspirin in *primary* prevention in women is controversial. The current recommendations for use of aspirin in *primary* prevention in women are based on limited data.

The Women's Health Study was a large, randomized, double-blind placebo-controlled trial of low-dose aspirin in the primary prevention of cardiovascular disease among over 39 000 apparently healthy women followed for a mean of 10 years for major cardiovascular events.

For the entire group of women over age 45, aspirin reduced risk of ischemic stroke. It did not protect against myocardial infarction and death from cardiovascular causes until after age 65.

Women taking aspirin experienced significantly more GI hemorrhages (RR = 1.40)

By my calculation, between 500 and 900 individuals would need to be treated for 10 years to prevent one ischemic stroke. Is this clinically significant?—especially when the increased risk of hemorrhage is considered. RTJ)

Thus far, studies indicate that, in men, the prophylactic benefit against first occurrence of myocardial infarction is much greater than in women. But in men, aspirin does not provide primary protection against stroke.

CHOLESTEROL

Treat the Patient, Not the Blood Pressure—Not the Cholesterol.

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Injecting New Enthusiasm into the Dietary Management of Hyperlipidemia

5-1 THE EFFECT OF A PLANT-BASED DIET ON PLASMA LIPIDS IN HYPERCHOLESTEROLEMIC ADULTS

Dietary modifications to lower LDL-cholesterol have focused on avoiding saturated fats and cholesterol. They often result in only modest improvement.

This traditional focus of lipid management may have been overly simplistic. Diets may be more effective if more attention were focused on *including* certain foods rather than just *avoiding* saturated fat and cholesterol. Several foods such as soy protein, plant sterols, soluble fiber, oats, nuts, and garlic have potential lipid benefits. Each is derived from plants. They contain little saturated fat and no cholesterol.

This study theorized that the lipid-lowering benefits of a plant-based diet would be greater than a more conventional low fat-diet under conditions in which both diets contained the same amount of total fat, saturated fat, and cholesterol, and the weight was held steady.

Subjects were randomized to:

1) Low Fat diet. Consistent with former American Heart Association step 1 guidelines:

2) Low-Fat Plus diet. Consistent with the AHA year 2000 guidelines:

Kept saturated fat under 10% but added increased intakes of vegetables and whole grains—in general a plant-based diet. It contained considerably more vegetables, legumes, whole grains, and fruits. Soy protein (~ 16 g per/2000 kcal) and fresh garlic (~ 1.5 cloves) were used daily.

Butter, cheese, and eggs were added to the low-fat plus diet to increase the saturated fat and cholesterol content to match the low-fat diet. Both diets provided 30% of energy from total fat; 10% from saturated fat; and about 100 mg cholesterol per 1000 kcal.

Change at 4 weeks (means):	Low-fat Plus	Low-fat
Total cholesterol (mg/dL)	-18	-9
LDL-cholesterol (mg/dL)	-14	-7

In moderately hypercholesterolemic individuals a plant-based low-fat diet achieved a significantly greater reduction in LDL-c than the standard low saturated fat diet.

The differences are not attributable to saturated fat, cholesterol, energy intake, or body weight because each of these variables was kept constant in the 2 groups.

This puts a new slant on treatment of dyslipidemia. Patients may be told that including 1, 2 or 3 selected foods daily will actually treat their cholesterol.

When To Intervene? How To Intervene?

6-7 THRESHOLDS FOR NORMAL BLOOD PRESSURE AND SERUM CHOLESTEROL.

In 2003, European guidelines suggested a BP of above 140/90, and a cholesterol above 5 mmol/L (193 mg/dL) as the appropriate thresholds for intervention. "The bottom line is that the doctor is expected to inform the patient that these measurements mean that he or she is at increased cardiovascular risk regardless of the management proposed. In other words, a disease label is to be attached to the patient."

In Norway, if this threshold for cholesterol and BP were to be applied at age 24, half the population would be identified as being at increased risk. At age 49, the proportion is raised to 90%. As much as 75% of the total population would be identified as being at risk.

The potential benefits for treated patients become less at lower risk levels. The number needed to treat is increased. The rates of adverse effects (of drug treatment) remain the same. Adverse effects tend to be under-reported and under-published.

Certainly, experts who developed these guidelines did not suggest that all persons with BP and cholesterol levels above these cut-points should be treated with drugs.

I believe however, that all should be treated with judicious advice about changing in lifestyle. This will apply to almost all persons in the US over age 50. Very rarely will individuals over age 50 have no risk factors. Cut-points are defined at levels below which no further reduction in risk occurs. Admittedly, those with baseline risk-levels at the low range will have less to gain when their levels are lowered than persons with high baseline risk-levels.

I do not believe life-style advice will be interpreted as a labeling of disease. There are few if any adverse effects of lifestyle changes. Effectiveness is established. The benefit/harm-cost ratio is very low.

The task of educating patients about healthy lifestyles and getting them to adopt them is daunting, and in the main unsuccessful. We should not be deterred from trying. This includes primary care clinicians' adopting a healthy lifestyle themselves.

Who should be treated with drugs?—patients who are indeed at high risk. The definition of "high risk" depends not only on the number or risk factors present and their levels, but also on the individual patient's assessment of his own risk. Patients must be convinced of the benefits of drug therapy; must understand that drug therapy is long-term, expensive, and carries risks of its own.

COGNITIVE DECLINE

One or Two Drinks per Day may Reduce Risk of Cognitive Decline

1-12 EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON COGNITIVE FUNCTION IN WOMEN.

This study asks—What is the effect of *moderate* consumption of alcohol on cognition? A benefit is plausible considering the strong link between moderate alcohol and decreased risk of cardiovascular disease. Cognitive impairment and cardiovascular disease share common risk factors.

Compared with abstainers, moderate drinkers (less than 15 g alcohol per day; one drink) had better mean cognitive scores. (Relative risk of impairment = 0.81 based on a global cognitive score.) Also, compared with abstainers, moderate drinkers (15 to 30 g per day) had a reduced relative risk of cognitive impairment (although slightly less favorable, with wider confidence intervals).

In older women consumption of one alcoholic drink per day did not impair cognitive function, and may actually decrease risk of cognitive decline.

Benefits of moderate alcohol consumption have been reported with remarkable consistency over the past 10 years. Indeed, some epidemiologists consider abstinence to be a risk factor for cardiovascular disease.

As always, we should be cautious about generalizing the conclusions of observational studies.

COGNITIVE IMPAIRMENT

Donepezil May Delay Clinical Progression To Alzheimer's Disease

6-10 VITAMIN E AND DONEPEZIL (*ARICEPT*) FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT

Amnestic (memory loss) mild cognitive impairment **(MCI)** represents a transitional state between the cognitive changes of normal aging and the earliest clinical features of Alzheimer's disease **(AD).** Amnestic MCI refers to the subtype that has a primary memory component, either alone or in conjunction with other cognitive-domain impairments, of insufficient severity to constitute dementia. About 80% of those who meet the criteria for MCI will have AD within 6 years.

MCI is a transition state between normal aging and dementia (for Alzheimer's disease in particular), one in which cognitive deficits are present, but function preserved. In clinical settings, the term is often used to describe patients who present with memory loss, but do not have dementia. Even when defined carefully, MCI is a heterogeneous category that includes some persons with memory changes of normal aging, some with non-progressive cognitive defects, some with prodromal AD, and some with prodromal forms of other neurodegenerative dementias.

This study was designed to determine if vitamin E or the cholinesterase inhibitor donepezil could delay the clinical diagnosis of AD in patients with MCI.

Vitamin E had no effect at any time.

For donepezil . . . "The observed relative reduction in the risk of progression of 56% at one year and 36% at two years in the entire cohort is likely to be clinically significant."

"Although our findings do not provide support for a clear recommendation for the use of donepezil in persons with mild cognitive impairment, they could prompt a discussion between the clinician and the patient about this possibility."

Symptoms of memory loss in older persons should be taken seriously. They may represent the beginning of AD. This may be an important clinical measure once more effective treatments become available.

The important question is . . . What are the cognitive changes of normal aging?

I believe some degree of memory impairment is almost universal among individuals over age 80. It usually

begins by forgetting names, and recalling them minutes or hours later ("senior moments"). The spectrum of memory impairment is wide. The definition of amnestic MCI is not settled. At what point does it predict development of AD? The criteria for diagnosis of amnestic MCI in the study included patients with difficulties greater than temporarily forgetting names.

This study may foretell important developments in drug therapy which may delay the onset of disabling dementia. The spectrum of forgetfulness of old age is very broad. When should intervention be considered?
Some elderly patients may well accept early intervention. A delay of one to two years represents a large proportion of remaining quality-life. Patients may be willing to accept some adverse effects of drugs to gain a few years free of dementia of AD. (Note that anticholinergics do not benefit vascular dementia.)

Others may wish to wait until adverse effects on daily living become more evident.

I do not believe memory defects inevitably progress to AD. Keeping mentally and physically active, continuing a healthy diet, retaining active family and social connections, and controlling risk factors for cardiovascular disease will delay or prevent development of dementia in many individuals.

CORONARY HEART DISEASE **(See also ISCHEMIC HEART DISEASE [5-2])**

All Adults in the USA Have One or More Risk Factors for Atherosclerotic Disease.

3-1 RELATIVE IMPORTANCE OF BORDERLINE AND ELEVATED LEVELS OF CORONARY HEART DISEASE RISK FACTORS

Prospective cohort study (The Framingham Study) and a national cross sectional survey (Third National Health and Nutrition Examination Survey) considered a large group of white, non-Hispanic persons between ages 35 and 74. (Mean age = 50)

Determined the first CHD event (defined narrowly as a myocardial infarction or cardiac death over 10-years) related to five major CHD risk factors: BP, LDL-cholesterol, HDL-cholesterol, glucose intolerance, and smoking.

Assigned three categories to each risk factor—elevated, borderline, and optimal.

	Optimal	Borderline	Elevated
Systolic BP	under120	120-139	over 139
Diastolic BP	under 80	80-89	over 89
LDL-cholesterol	under100	100-159	over159
HDL-cholesterol	over 59	59-40	under 40
Other borderline factors:			
	Impaired fasting glucose (110-123)		
	Past history of smoking		
Other elevated risk factors			
	Diabetes		
	Smoking		

Optimal levels of all 5 risk factors were rarely present in any age group or in either sex.

Seventy four % of men and 59% of women had one or more elevated risk factors. Twenty six % of men and 41% of women had at least one borderline risk factor. (*Note: this adds up to 100%)*

The authors estimate that, for ages 35-74, over a 10-year period, nearly 4.7 million white men and over 1 million white women in the US will experience a first MI or cardiac death. More than 90% of CHD events will occur in individuals with at least one elevated risk factor, and 8% in those with only borderline risk factors.

I believe this study presents too narrow a view of the cardiovascular disease problem in the US population, The study underestimates risk of atherosclerotic events.

1) Ten years is too short a time to assess the overall risk of disease. The atherosclerotic process begins decades earlier and ends decades later.

2) Only 5 risk factors were considered. There are many others for which we should intervene: body mass index, dietary factors, physical fitness, intra-abdominal fat, triglycerides, C-reactive protein, abstinence from alcohol. The object of prevention should be to lower every individual risk factor as much as possible considering safety and cost. The number of risk factors far exceeds those chosen by the study.

3) The definition of disease was too narrow. (Only cardiac death and myocardial infarction.) This eliminates consideration of other acute coronary syndromes, stroke, vascular dementia, peripheral vascular disease, and aortic aneurysm.

4) The study arbitrarily divided the cohort into 3 subgroups of risk—elevated, borderline and optimal and assumed the risk was equal in every individual in each cohort. The study did not consider the considerable differences in risk of disease associated with varying levels of the risk factors in each of the 3 groups. Risk rises and falls linearly. An individual with a LDL-cholesterol of 110 (borderline) has lower risk than one with a LDL-c of 145 (still borderline). A person with a systolic BP of 145 (elevated) is at much lower risk than one with a systolic of 175 (also elevated).

This article tilts toward the traditional practice of screening to identify higher risk associated with a relatively few risk factors, and vigorously treating each individual risk factor. Is screening, and treating, and retesting every one of 5 "elevated" risk factors the best approach? This is certainly not practical when applied to the entire at-risk population. (Essentially the whole population in the USA.) How vigorously should "borderline" factors be treated?

All risk factors add to risk in all individuals in our high-risk culture. They should be treated empirically .and lowered concomitantly. Laboratory testing may be minimized.

Atherosclerosis is an essentially preventable disease. We have failed miserably in our efforts to prevent it.

We need to apply a new population-based approach to prevention.

The approach changes for patients with established atherosclerotic disease. Risk reduction should be applied vigorously to all factors. RTJ

Drug And Lifestyle Modifications Are Beneficial Regardless Of The Initial Level Of The Risk Factor.

3-2 THE MIDDLE-AGED AND OLDER AMERICANS; WRONG PROTOTYPE FOR A PREVENTIVE POLYPILL?

(This editorial comments and expands on the preceding article.)

Most Americans older than age 55 have one or more risk factors for cardiovascular disease" 1/3 or more have hypercholesterolemia, 1/5 smoke, most have inactive lifestyles, 1/3 have high BP. About 1/3 are obese, about 1/10 have diabetes.

Americans have a dizzying array of options to reduce risk. Preventive approaches aimed primarily at identifying and treating individual risk factors were popular in the 1980s and 1990s but had limited success.

Experts now recommend assessment of an individual's *global* risk for vascular disease when deciding whether to treat risk factors, and when selecting specific target levels for those risk factors.

In 2003 Wald and Law[1] proposed a radical population-based strategy that they claimed would reduce cardiovascular disease by 80%, and have greater impact on public health than any other preventive strategy. They advised discarding the

view that risk factors need to be measured (and treated individually if found to be 'abnormal'). Instead they advocated treating *all* adults older than age 55 with a "Polypill" containing low doses of a statin, folic acid, aspirin, and 3 antihypertension drugs. (Low-dose presumably would be associated with fewer adverse effects.) This was based on the premise that risk factors are present in *everyone* in Western societies, and determination of individuals' global risk is not necessary, and that 96% of deaths from vascular disease occur in people over age 55. Monitoring each individual's risk factor level to assess treatment benefits is of limited usefulness.

Risk factor interventions with drugs and lifestyle modifications are effective whatever the initial level of the risk factor.

The editorialists comment that treating everyone older than age 55 with a low-dose Polypill without measuring risk factors may be too audacious for Americans. Adverse effects will likely occur from these multi-drug pills in low risk patients who have little potential for benefit.

When I first read of the Polypill, I thought the authors were suggesting the concept "tongue in cheek". Subsequently the concept gained considerable attention and comment.

The premise of the Polypill:

1) *All persons have risk factors for CVD. There is no cut point below which risk is not evident, and no cut point above which risk does not increase.*
2) *The Polypill reduces 4 risk factors (BP, LDL-c, platelet aggregation, and homocysteine). The benefit from lowering all 4 is additive, although not equally.*

The Polypill is limited to drug therapy. And only in persons over age 55. The range of risk factors is much larger, and the atherosclerotic process begins at a much younger age. Many individuals experience a CVD event at an early age.

Each risk factor(lifestyle and clinical) adds to risk. When each risk factor is reduced, (even if only modestly) benefit increases additively.

Primary care clinicians and their patients tend to focus on measuring and treating only a few risk factors (eg, BP and cholesterol). Indeed "know your cholesterol" has become a national imperative. In the mind of the public achieving a "low" cholesterol is the best one can do to prevent CVD. But, individuals may have a LDL-c considerably below 100 and still be at high risk due to presence of other factors.

.What to do? 1) Treat everyone empirically , or 2) Treat only select individuals after screening. If you concede that everyone is at risk, you must choose 1). Treating everyone with drug therapy is too drastic a measure. Lifestyle measures begin at an early age and modifying them can reduce risk without adverse effects. More clinicians may now be encouraged to list all risk factors in their individual patients and point out the additive effect of lowering each of them.

I believe atherosclerosis is essentially a preventable disease. Our attempts at control are failing miserably. Americans refuse to adopt preventive lifestyles. Primary care clinicians have failed to adequately educate the public.

Once atherosclerotic disease becomes established, treatment changes to all-out reduction of risk factors. RTJ

"No Indication Of A Net Benefit."

6-5 EPIDEMIOLOGICAL MODELLING OF ROUTINE USE OF LOW-DOSE ASPIRIN FOR THE PRIMARY PREVENTION OF CORONARY HEART DISEASE AND STROKE IN THOSE AGE > 70

Current US guidelines recommend the use of low-dose aspirin for people with a 5-year absolute risk of coronary heart disease **(CH D)** of > 3%, or a 10-year absolute risk of > 10%.

"Prophylactic use of a potentially toxic agent can be problematic, particularly in people in whom comorbidity and polypharmacy are common." In a prospective observational study in two large UK general hospitals, aspirin use was the causal agent in 18% of all admissions for adverse drug effects, and was implicated in 61% of all associated deaths. Older females are the most vulnerable.

This epidemiological modeling study was conducted in a hypothetical population (10 000 men and 10 000 women) selected from a reference population from a state in Australia. All were age 70-74. None had known cardiovascular disease.

Proportional benefit gained from aspirin in prevention of MI and ischemic stroke *vs* excess hemorrhage from age 70-74 to age 100 or to death:

Benefit in preventing	Men (n = 10 000)	Women (n = 10 000)
Myocardial infarction	- 389	- 321
Ischemic stroke	- 19	- 35
Harm		
Excess GI hemorrhage	+ 499	+ 572
Excess hemorrhagic stroke	+ 76	+ 54

When comparing net harms *vs* net benefits of aspirin, the effects on length and quality of life were equivocal.

"Despite sound evidence for efficacy, the temptation to blindly implement low-dose aspirin treatment for the *primary* prevention of cardiovascular disease in elderly people must be resisted." Benefits may be offset by harms.

I believe low-dose aspirin has an important place in primary prevention of women at higher risk, and in secondary prevention of cardiovascular disease.

There is an important clinical downside related to universal prophylactic aspirin therapy: suppose primary care clinicians prescribe low-dose aspirin to 1000 women over 10 years. Three or 4 ischemic strokes might be prevented. But there would be no way of knowing which individuals of the 1000 benefited. Conversely, a serious hemorrhagic event occurring in 2 of the1000 patients would be self-evident. The clinician might feel responsible, and the patient and family might blame the clinician for the disaster.

I believe primary prevention with aspirin in women at average risk should be avoided. Obviously, careful clinical judgment based on individual-patient attributes is required.

DIABETES

A mnemonic for diabetes. The editor tried to create a check list for diabetes:

D Diet; Depression
I Insulin
A Aspirin; ACE inhibitors
B BMI; BP
E Exercise
T Tests (blood glucose; HbA1c; lipids; microalbuminuria; liver function; ejection fraction)
E Eye (retinopathy); Extremities (foot health; foot pulses; peripheral neuropathy)
S Sulfonylureas, Statins, and other oral drugs; Smoking

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The association was strongest for pancreatic cancer. (Hazard ratio = 2 comparing the highest glucose stratum with the lowest.) Significant associations were also found in other cancers (esophagus, colo-rectal, liver, cervix).

"We have shown that fasting serum glucose level and diabetes are associated with cancer risk in a population far leaner than the Western populations."

This is my first encounter with the relation between glucose intolerance and cancer. It is not a clinically important point now. I felt it was interesting enough to abstract. I will watch for follow-up studies.

Treatment Reduced Serious Perinatal Morbidity In Infants And May Improve The Woman's Health-Related Quality Of Life.

6-12 GESTATIONAL DIABETES MELLITUS; Effect Of Treatment On Pregnancy Outcomes.

Gestational diabetes mellitus **(GDM)** occurs in up to 9% of all pregnancies. It is associated with substantial maternal and perinatal complications. Neonatal complications include macrosomia, shoulder dystocia, birth injuries, bone fractures, nerve palsies, and hypoglycemia. Long-term adverse health outcomes among infants born to mothers with GDM include sustained glucose intolerance, subsequent obesity, and impaired intellectual achievement.

This study asked . . . Does screening and treatment for GDM reduce these risks?

This randomized trial enrolled 1000 women who were between 16 and 30 weeks pregnant. Randomized to: 1) An intervention group received expert diabetes care including education, self-monitoring blood glucose, and adjusted insulin therapy, and 2) A usual care group.

Serious perinatal complications in infants were significantly lower in the intervention group (1% vs 4%). The NNT to prevent one serious outcome in infants = 34. Birth weights were lower in the intervention group (less likely to have macrosomia). No difference in rate of hypoglycemia requiring intravenous glucose.

Women in the intervention group gained less weight and had less risk for preeclampsia. At 3-months postpartum, women had lower rates of depression and higher scores on quality-of-life. Rates of caesarean deliveries were similar.

Impaired glucose tolerance and diabetes are important risk factors at the time of conception. Primary care clinicians can serve their young adult female patients by advising them of the risks of glucose intolerance (and excessive weight) before and at the time of conception.

DIABETIC NEUROPATHY

Development May be Delayed by Good Glycemic Control and Modification of Cardiovascular Risk Factors.

1-14 VASCULAR RISK FACTORS AND DIABETIC NEUROPATHY

The Diabetes Control and Complications Trial reported a 60% reduction in DN in the intensively treated group at 5 years. But the incidence still remained substantial. This suggests that DN can develop despite intensive control of glucose levels. Risk factors other than glucose are involved.

This study assessed potentially modifiable risk factors for development of distal, symmetric DN.

Dyslipidemia, elevated BMI, smoking, and hypertension were associated with development of DN.

Cardiovascular disease at baseline was associated with double the risk of neuropathy.

What can be done prospectively to try to prevent DN?

Control glycemia as best it can be controlled

Stop smoking

Control BP

Control weight, obtain lower body mass index

Reduce other cardiovascular risk factors.

(*Ie, essentially standard diabetes management*.)

I enjoyed reviewing the diagnosis of neuropathy.

The mean age at baseline was about 30. Of an initial cohort, 28% already had DN. Prospectively, over 7 years 23% developed DN. Thus at age about 40, over half had DN. I would expect almost all patients with type 1 diabetes will eventually develop DN.

DIET

Adherence was Poor. Those Who Adhered for One Year Lost Weight

1-7 COMPARISON OF THE ATKINS, ORNISH, WEIGHT WATCHERS, AND ZONE DIETS FOR WEIGHT LOSS AND HEART DISEASE RISK REDUCTION

This study assessed adherence rates and effectiveness of 4 diets in producing weight loss and reducing cardiac risk factors:

1. Atkins Low carbohydrate—20 g carbohydrate daily
2. Zone High protein, low glycemic load
3. Weight Watchers Balanced diet—total daily ”points” in a range determined by current weight (Aimed for 24 to 32 points daily.)
4. Ornish Low fat, vegetarian diet containing 10% of calories as fat.

About half of the subjects in each group failed to complete the 1-year course. The most common reasons were “too hard to follow” and “not yielding enough weight loss”. Adherence was particularly low for Atkins and Ornish.

At 1 year, completers lost more than those who failed to complete (- 3. 9 kg for Atkins and -6.6 kg for Ornish)

Each diet significantly reduced LDL/HDL-cholesterol ratio by about 10%. The Atkins diet did not lower LDL-cholesterol significantly. The Ornish diet did not increase the HDL-cholesterol. No diet significantly altered triglyceride levels. Reductions of total cholesterol, C-reactive protein, and insulin levels were significantly associated with the degree of weight loss.

Under realistic conditions a variety of popular diets can reduce weight and several cardiac risk factors. But only about half of the subjects in this study sustained a high adherence level.

The problem is not the diet, it is the patient’s inability to follow it. Recidivism would be higher still at 5 or 10 years. The bloom seems to be coming off the Atkins diet.

The authors suggest that one way to improve dietary adherence in clinical practice may be to use a broad spectrum of diet options to better match individual patient’s food preferences, lifestyles, and cardiovascular risk factors. They suspect adherence would have been better if subjects had been given the option to choose their diet.

I wonder—would switching from one type of diet to another every few months increase compliance?

Associated with longer survival.

4-4 MODIFIED MEDITERRANEAN DIET AND SURVIVAL

The Mediterranean diet **(MD)** is characterized by a high intake of vegetables, legumes, fruits, and cereals (largely unrefined); a moderate to high intake of fish; a low intake of saturated fats; a high intake of unsaturated fats (particularly olive oil); low to moderate dairy products; a low intake of meat; and a modest intake of ethanol, mostly as wine.

This study examined whether adherence to a modified MD (poly-unsaturated fats substituted for mono-unsaturates) was associated with longer life expectancy among elderly Europeans.

Means scores on the 10-point MD scale varied considerably between countries. Greece was highest (6.25); Spain next (5.61); Netherlands was lowest (2.92).

An increase in this modified MD score was associated with lower overall mortality. A two-unit increment corresponded to a reduction on 8% in mortality.

I believe the modification (substituting poly-unsaturated fats for mono-unsaturated fat) is a clinically important point. Poly-fats are more accessible in our culture than mono-fats.

Injecting New Enthusiasm into the Dietary Management of Hyperlipidemia

5-1 THE EFFECT OF A PLANT-BASED DIET ON PLASMA LIPIDS IN HYPERCHOLESTEROLEMIC ADULTS

Dietary modifications to lower LDL-cholesterol have focused on avoiding saturated fats and cholesterol. They often result in only modest improvement.

This traditional focus of lipid management may have been overly simplistic. Diets may be more effective if more attention were focused on *including* certain foods rather than just *avoiding* saturated fat and cholesterol. Several foods such as soy protein, plant sterols, soluble fiber, oats, nuts, and garlic have potential lipid benefits. Each is derived from plants. They contain little saturated fat and no cholesterol.

This study theorized that the lipid-lowering benefits of a plant-based diet would be greater than a more conventional low fat-diet under conditions in which both diets contained the same amount of total fat, saturated fat, and cholesterol, and the weight was held steady.

Subjects were randomized to:

1) Low Fat diet. Consistent with former American Heart Association step 1 guidelines:

2) Low-Fat Plus diet. Consistent with the AHA year 2000 guidelines:

DYING

"The Moral Basis of the Right to Die is the Right to Good Quality Life" "Mere Existence Is Not An Automatic Good."

4-7 "RIGHT TO DIE"

A general question is whether there such a thing as a right to die. The editorialist believes there is for the following reasons:

1) Every human rights convention recognizes a fundamental right to life.

2) Paradoxically, as it might at first seem, this also entails a right to die.

A. Life in the phrase "the right to life" does not mean bare existence. It means existence that has a certain minimum quality.

B. Mere existence is not an automatic good

"It is perhaps characteristic of humankind that it regards reasoned choices about when and how to die as morally problematic, whereas ignoring the question and hoping for the best is seen as acceptable or even right."

Lawyers and doctors distinguish between withholding treatment with death as the result, and giving treatment that causes death. The first is considered permissible in law and ethics. The second is not. “But in fact, there is no difference between them.” Withholding treatment is an act, based on a decision, just as giving treatment is an act based on a decision. “Like the doctrine of double effect, which allows death-hastening levels of analgesia with the putative aim of controlling pain, the distinctions are fictitious. Death, after all, is the ultimate analgesic.”

This one page commentary sums it up nicely

DYSPEPSIA

Stool Antigen Test is Recommended

1-9 TEST AND TREAT FOR DYSPEPSIA: But Which Test?

The National Institute for Clinical Excellence **(NICE)** of the UK recommends that patients with *persistent or recurrent uncomplicated dyspepsia* should have a non-invasive test for *Helicobacter pylori*. If the test is positive they should receive eradication (triple antibiotic) therapy

Now the stool antigen test is available. It detects *H pylori* antigens passed in feces. A commercial monoclonal antibody test is available. It is reported to be as accurate as the urea breath test. It can be introduced with ease into routine laboratory practice. It is less expensive and less time consuming than the urea breath test. It is useful also in confirming eradication of the infection.

“We need to have an easy, accurate diagnostic test and the stool antigen test is just that.”

There are some advantages of “test and treat”:

Will treat an unsuspected peptic ulcer. And reduce risk of subsequent ulcer disease.

Will reduce or eliminate symptoms in some patients (~ 10%). Since about 50% of patients with functional dyspepsia will be positive, eradication will remove symptoms in only 5% of patients with dyspepsia.

Remove a risk factor for gastric cancer.

ENDOMETRIAL CANCER

Causes More Cancer Than It Prevents

5-7 ENDOMETRIAL CANCER AND HORMONE REPLACEMENT THERAPY IN THE MILLION WOMEN STUDY

Estrogen-only hormone-replacement therapy **(HRT)** increases the risk of endometrial cancer **(EC).** To counteract this effect, many postmenopausal women who have not had a hysterectomy use combined HRT (progestagen + estrogen). The addition of progestagen attenuates or even reverses the estrogen-associated increase in EC.

This large study assessed the relation between different types of HRT and incidence of EC.

Relative risk of EC compared with never-users:

Continuous combined HRT (progestagen daily + estrogen daily—RR = 0.71 (A reduction in risk.)

Combined cyclic HRT (progestagen 10 to 14 days/month—RR = 1.05 (No significant alteration.)

Estrogen alone—RR = 1.45 (Increased risk.)

But the benefit in lowering risk of EC was greatly offset by a rise in breast cancer.

Incidence rates for endometrial cancer and breast cancer per 1000 women over 5 years:

	Continuous combined	Cyclic combined	Estrogen alone	Never users
Endometrial cancer	2.0	3.0	4.9	3.0
Breast cancer	29	28	18	14

Thus, although continuous combined HRT reduced risk of endometrial cancer by 1 in 1000 over 5 years, it was associated with 15 more breast cancers. This is an increase in total cancers of 14 per 1000. Estrogen alone was associated with a lower risk (4 total cancers per 1000 women over 5 years).

Combined estrogen-progestagen causes a greater increase in breast cancer than a reduction in EC. The net effect is an *increase in total cancer risk* with use of HRT, especially combined HRT.

Progestagens, not estrogens, are the main factor increasing risk of BC.

Just think—another extraordinary sea change in clinical application. For decades standard HRT practice insisted that, for women with a uterus, a progestagen be added to estrogen. This on the pain of being accused of malpractice.

EVIDENCE-BASED MEDICINE

Is the Evidence "Generalizable" to my Patient?

1-3 EVIDENCE-BASED PRACTICE AND THE INDIVIDUAL

Is my patient so different from those in the trial that its results cannot help me make my treatment decision? The more family practitioners feel they know their patients, the less likely they are to apply external evidence to guide management.

Disingenuous surrogate markers and misleading composite outcomes may create good advertising material, but cannot obscure data and hinder genuine patient-centered care.

Let us not neglect the central role of individual patients as decision-makers in their own care. "It is the responsibility of healthcare workers to communicate objective evidence in a manner which allows recipients to make an informed choice, and then to respect that choice."

"Now and then, clinicians will have to accept and explain that uncertainty is an inherent facet of the uniqueness of human nature. Evidence helps to quantify that uncertainty, but cannot remove it.

Why do we Underuse Treatments That are Beneficial in Trials?

1-2 EXTERNAL VALIDITY OF RANDOMIZED CONTROLLED TRIALS: To Whom do the Results of this Trial Apply?

Randomized controlled trials **(RCTs)** and systematic reviews must be *internally* validated. (Ie, the design and conduct of RCTs must keep the possibility of bias to a minimum). To be clinically useful, however, the results must be relevant to a definable group of patients in a particular clinical setting. This is termed *external validity*.

The most frequent criticism by clinicians of RCTs, systematic reviews, and guidelines is the lack of external validity. This explains the widespread underuse in routine practice of treatments that are beneficial in trials and recommended by guidelines.

Assessment of external validity requires clinical rather than statistical expertise.

The response to, and compliance with, treatment can be influenced strongly by the doctor-patient relationship, placebo effects, and patient preferences. The importance of these factors outside of trials should not be underestimated. Note the popularity of "alternative" therapies in which such factors are the only active ingredients.

The primary care clinician is a final arbiter of external validity. (Would this application be clinically useful for Mrs. Jones?)

Beware of surrogate outcomes in RCTs, of composite outcome measures, underreporting of adverse effects, and reports by pharmaceutical companies.

Primary care difficult, challenging, and so rewarding.

FAST-FOOD

A Particularly Ominous Public Health Issue

1-8 FAST-FOOD HABITS, WEIGHT GAIN, AND INSULIN RESISTANCE

This study investigated the association between fast-food habits of young U.S. adults and changes in body weight and insulin resistance over a 15-year period.

At baseline, weekly visits to fast-food restaurants = 2.4 for men and 1.7 for women. Younger subjects made more visits. There was a direct and independent monotonic association between fast-food frequency and weight and insulin resistance. Subjects who visited three times a week had a mean weight about 2 kg higher than those who visited less than once a week.

Over 15 years, frequent visitors gained more weight compared with those who visited less than once a week. Insulin resistance was directly associated with visits of 3 times a week. There was a direct and independent monotonic association between fast-food frequency and weight and insulin resistance. Compared with subjects whose fast-food visits were less than once a week, those who visited over 2 times weekly gained an extra 4.5 kg and had a 104% greater increase in insulin resistance.

Fast-food habits have strong, positive and independent association with weight gain and insulin resistance in young adults. This suggests an increased risk of type 2 diabetes and obesity.

I am sure that this does not surprise anyone.

The study points out some differences between blacks and whites, and between males and females. See the text.

"Overload your truck & it will break down."

The fast-food industry is beginning to make some adjustments in their menus. This is difficult for a highly competitive industry. To stay in business, the competition must be met. Customers will frequent the establishments offering the best tasting foods and the largest portion size. The solution lies, not in forcing the fast-food to change their menus, but by making a sea-change in public awareness and compliance with a "healthy diet"—an almost impossible task which will take years to accomplish even partially.

FOLIC ACID **(See HOMOCYSTEINE [3-9])**

FRACTURE **(See VITAMIN D [5-3])**

GASTRO ESOPHAGEAL REFLUX DISEASE

The Test Could Be Used As An Initial Approach To Diagnosis.

6-13 IS PROTON PUMP INHIBITOR TESTING AN EFFECTIVE APPROACH TO DIAGNOSE GASTRO ESOPHAGEAL REFLUX DISEASE IN PATIENTS WITH NON-CARDIAC PAIN? A Meta-analysis

Gastro esophageal reflux disease **(GERD)** is the most common cause of non-cardiac chest pain **(NCCP).** Patients with NCCP are often treated empirically and successfully with proton pump inhibitors.

This study asked. . .Can proton pump inhibitors (a PPI test) be used as a *diagnostic* test?

Results of the PPI test:

	GERD present	GERD absent
Positive test (> 50% relief)	80% (true positive)*	26% (false positive)
Negative test (< 50% relief)	20% (false negative)	74% (true negative test)**

(* sensitivity of the PPI test = true + % = 80%; ** specificity of the PPI test = true negative % = 74%)

Results of the placebo test:

Positive test (> 50% relief)	19% (true positive)***	23% (false positive)
Negative test (< 50% relief)	81% (false negative)	77% (true negative test)****

(*** sensitivity of placebo test =19%; **** specificity of placebo test = 77%)

Thus 80% responded favorably to PPI *vs* 19% to placebo.

Treatment with PPIs and placebo showed similar effects (26% and 23%) on improving NCCP symptoms in patients *without* GERD, indicating a possible placebo effect.

The use of PPI as a diagnostic test for detecting GERD in patients with NCCP has an "acceptable" sensitivity and specificity and could be used as an initial approach by primary care physicians to detect GERD in selected patients with NCCP.

"Acceptability of the test would be more meaningfully determined by calculating pre-test probability., likelihood ratios, and post-test probability. See the full abstract.

Regardless of the modest diagnostic help given by a PPI test, I believe, in practice, the test is used extensively by primary care clinicians and their patients.

GESTATIONAL DIABETES MELLITUS

Treatment Reduced Serious Perinatal Morbidity In Infants And May Improve The Woman's Health-Related Quality Of Life.

6-12 GESTATIONAL DIABETES MELLITUS; Effect Of Treatment On Pregnancy Outcomes.

Gestational diabetes mellitus **(GDM)** occurs in up to 9% of all pregnancies. It is associated with substantial maternal and perinatal complications. Neonatal complications include macrosomia, shoulder dystocia, birth injuries, bone fractures, nerve palsies, and hypoglycemia. Long-term adverse health outcomes among infants born to mothers with GDM include sustained glucose intolerance, subsequent obesity, and impaired intellectual achievement.

This study asked . . . Does screening and treatment for GDM reduce these risks?

This randomized trial enrolled 1000 women who were between 16 and 30 weeks pregnant. Randomized to: 1) An intervention group received expert diabetes care including education, self-monitoring blood glucose, and adjusted insulin therapy, and 2) A usual care group.

Serious perinatal complications in infants were significantly lower in the intervention group (1% vs 4%). The NNT to prevent one serious outcome in infants = 34. Birth weights were lower in the intervention group (less likely to have macrosomia). No difference in rate of hypoglycemia requiring intravenous glucose.

Women in the intervention group gained less weight and had less risk for preeclampsia. At 3-months postpartum, women had lower rates of depression and higher scores on quality-of-life. Rates of caesarean deliveries were similar.

Impaired glucose tolerance and diabetes are important risk factors at the time of conception. Primary care clinicians can serve their young adult female patients by advising them of the risks of glucose intolerance (and excessive weight) before and at the time of conception.

HEART FAILURE

Reduced Complications and Risk Of Death.

4-9 THE EFFECT OF CARDIAC RESYNCHRONIZATION ON MORBIDITY AND MORTALITY IN HEART FAILURE

Despite improvements in pharmacologic treatment, many patients with heart failure **(HF)** have severe and persistent symptoms. Their prognosis is poor. Such patients commonly have regions of delayed myocardial activation (left bundle branch block), leading to cardiac dyssynchrony.

Resynchronization was accomplished by a pacemaker containing 3 leads (right atrium, right ventricle, and left ventricle. This resulted in a reduction in intraventricular mechanical delay and end-systolic volume, and an increase in the left ventricular ejection volume. It improved symptoms and quality-of-life.

CR substantially reduced the risk of complications and deaths among patients with HF due to left ventricular systolic dysfunction and cardiac dyssynchrony. The benefits were in addition to those afforded by pharmacologic therapy. Over the study period, for every nine devices implanted, one death and 3 hospitalizations for major cardiovascular events were prevented. The reduction in risk of death is similar to that associated with beta-blocker therapy.

Obviously not a panacea. Experienced consultants must be chosen with care. Patients should be aware of the high rate of complications, and the likelihood of improvement. The greatest benefit may be improving quality-of-life.

See illustration of lead placement on page 1595

Enables The Ventricles To Contract Simultaneously.

4-10 RESYNCHRONIZING VENTRICULAR CONTRACTION IN HEART FAILURE

The biventricular-pacemaker implantation is technically demanding. It provides atrial-based, biventricular stimulation. Three leads are placed to pace 1) the right atrium, the 2) right ventricle, and the 3) left ventricle The left ventricular lead is inserted into the coronary sinus (in the right atrium) and advanced into a cardiac vein on the lateral wall of the lateral wall of the left ventricle. This enables the ventricles to contract simultaneously.

Complications of insertion are more frequent than for conventional pacemaker insertion

See illustration of the placement of the pacemaker leads on page 1595.

Primary care clinicians should be able to advise this subset of patients if the procedure is available.

HERPES ZOSTER

Aggressive And Effective Relief Of The Acute Pain May Reduce The Risk Of Chronic Pain.

5-10 POSTHERPETIC PAIN: WHEN SHINGLES WANES, BUT PAIN DOES NOT

The intensity of the acute pain shortly after onset of shingles is a robust predictor of postherpetic neuralgia **(PHN).** This leads to the tantalizing hypothesis that aggressive and effective relief of the acute pain may prevent, or at least reduce, the risk of chronic pain.

Oral opioid analgesics, in conjunction with antiviral drugs are likely candidates to decrease the incidence of PHN. They are also more effective in treatment of the acute pain. Opioids are relatively well tolerated by elderly patients.

Previous studies have suggested that control of acute pain will reduce the severity and prevalence of chronic pain. I believe this is an important point for primary care. We should go all-out to control the acute pain of HZ, giving adequate doses of opioids without restraint.

We await availability of the live, attenuated HZ vaccine. It does prevent HZ in elderly adults with waning cellular immunity. It lessens incidence and severity of postherpetic neuralgia.

Reduced Incidence And Severity Of HZ And PHN.

6-1 A VACCINE TO PREVENT HERPES ZOSTER AND POSTHERPETIC NEURALGIA IN OLDER ADULTS.

This study tested the hypothesis that vaccination would decrease the incidence and severity of both HZ and PHN.

Over 38 000 subjects were randomized to: 1) a subcutaneous injection of live, attenuated varicella-zoster vaccine, or 2) placebo. The potency of the live attenuated Oka vaccine was about 14 times that of the varicella vaccine given to children.

A. Herpes zoster: (3 years)	Vaccinated	Placebo	Absolute difference	NNT
Confirmed cases of acute HZ	315	642	1.7%	58
Overall incidence of HZ				
per 100 person-years	0.54	1.11	0.57%	175
Median duration of pain (days)	21	24		
Severity of illness	141	180	(area under the curve)	
Burden of illness score	2.2	5.7		
B. Postherpetic neuralgia (3 years)				
Confirmed cases	27	80	0.3%	333

Persistence of pain was shorter in the vaccinated group.

There was no evidence that the live vaccine caused HZ.

Adverse effects were generally mild, mainly due to local reactions.

We would expect more cases of HZ would be prevented as time progressed, and as more individuals enter the ranks of the elderly. I asked myself—at my advanced age should I take the vaccine? Having seen the devastating complications of zoster, I would be more than willing to take it, even though the likelihood of prevention of HZ over 3 years is only 1 in 58. .

Questions remain:

At what age should the vaccine be recommended?

How long is the boost in immunity protective?

Is it cost-effective enough for Medicare to cover costs?

HOMOCYSTEINE

The Benefit/Harm-Cost Ratio of Vitamin B12 and Folate May Be Very High

3-9 HOMOCYSTEINE AND FRACTURE PREVENTION

This issue of JAMA presents evidence that an elevated homocysteine level might be associated with brittle bones. The randomized trial of Japanese patients who had suffered hemiplegia due to stroke compared a group given folate and B12 (effectively lowering homocysteine levels) with a control group. The untreated group had 5 times the fracture rate as the treated group.

At baseline, patients had low levels of serum B12 and folate, and high levels of homocysteine. In the treatment group serum homocysteine fell by 38%; increased by 31% in the placebo group. Serum B12 and folate levels increased in the treatment group; fell in the placebo group.

Homocysteine is a simple sulfur-containing amino acid. Folate and B12 are co-factors involved in its metabolism. They facilitate conversion of homocysteine to methionine (another sulfur-containing amino acid).

Years ago, the genetic abnormality homocysteinuria was demonstrated to be associated with atherosclerotic disease and osteoporosis. Homocysteine acts as an atherogenic and thrombogenic agent. Increased levels are associated with coronary artery disease, cerebrovascular disease, peripheral arterial disease and deep-vein thrombosis.

A substantial portion of the elderly in the USA has a marginal sufficiency of folate.

Supplementation with B12 and folate reduces serum homocysteine levels.

The benefit/harm-cost ratio of folate and B12 supplementation may be very high. Both are relatively inexpensive and safe.

The study did not assess vitamin D and calcium intake, although intake of both is traditionally low in the elderly in Japan, as is the exposure to sunlight. Their benefit/harm-cost ratio in preventing fractures is high. This would lead to a reasonable recommendation to supplement the diets of the elderly with B12, folate, calcium and vitamin D.

Practical Pointers has abstracted a number of studies in the past 5 years which conclude that folic acid and B12 do reduce homocysteine levels and produce clinical benefits:

Homocysteine Levels and the Risk of Osteoporotic Fractures May 2004 [5-10]

Associated with reduced risk of congestive heart failure March 2003 [3-14]

Observing a reduction in dementia and Alzheimer's disease February 2002 [2-10]

Reducing risk of major cardiac events and restenosis after PTCA November 2001 [11-11]

HORMONE REPLACEMENT THERAPY

Causes More Cancer Than It Prevents

5-7 ENDOMETRIAL CANCER AND HORMONE REPLACEMENT THERAPY IN THE MILLION WOMEN STUDY

Estrogen-only hormone-replacement therapy **(HRT)** increases the risk of endometrial cancer **(EC).** To counteract this effect, many postmenopausal women who have not had a hysterectomy use combined HRT (progestagen + estrogen). The addition of progestagen attenuates or even reverses the estrogen-associated increase in EC.

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Progestagens, not estrogens, are the main factor increasing risk of BC.

Just think—another extraordinary sea change in clinical application. For decades standard HRT practice insisted that, for women with a uterus, a progestagen be added to estrogen. This on the pain of being accused of malpractice.

HYPERPARATHYROIDISM

Primary Hyperparathyroidism Does Not Progress In Most Patients. "Most Have No Symptoms"

4-8 A 64-YEAR OLD WOMAN WITH PRIMARY HYPERPARATHYROIDISM

This “Clinical Crossroads” conference presents the history of Mrs. Q, a 64-year old woman with mild hypercalcemia over 7 years. Her serum calcium has varied from time to time (10.1 to 11.3 mg/dL; normal = 9.0 – 10.5 mg/dL). Her parathyroid hormone level was 102 pg/mL (normal = 10 – 60 pg/mL); phosphate level = 3.4 mg/dL;
albumin level = 4.1 g/dL

She was asymptomatic; never had any fracture or renal stone. No depression or mood swings. She did not take vitamin D or calcium. Her bone mineral density had decreased by 7% at the spine and by 5% at the femoral neck. 24 hour calcium excretion = 226 mg. Creatinine clearance normal.

A sestamibi scan revealed a localized increased uptake in the lower pole of the thyroid.

The consultant parathyroid surgeon concurred that the patient had mild chronic primary hyperparathyroidism.

How to proceed?

The article discusses epidemiology, pathophysiology, evaluation, end-organ effects, progression of the disease, effects on general well-being, surgical treatment, and recommendations of the National Institutes of Health for surgery.

Our understanding of the natural history of primary hyperparathyroidism has been clarified and expanded over the years. The article describes several points which were new to me:

Hyperparathyroidism in all its forms is characterized by a re-setting of the activity of the parathyroid glands to maintain a calcium level above normal range. A new balance is reached wherein the parathyroid hormone (PTH) excretion is increased to maintain the serum calcium at a higher than normal level. The higher calcium level restrains the gland and maintains its secretion at a higher set level. In all other forms of hypercalcemia PTH is suppressed.

Prospective studies over 10 years have reported that primary hyperparathyroidism does not progress in most patients. “The stability of most cases of primary hyperparathyroidism is surprising, considering the neoplastic nature of the disorder.” It may be related to the previously mentioned set-point for secretion of PTH. (Secretion of the adenoma is suppressed by the elevated serum calcium levels.) The adenoma may grow until the serum calcium set-point is reached. Then secretion of PTH secretion remains steady and the tumor stops growing.

A new approach, minimally invasive parathyroidectomy, requires preoperative localization of the adenoma by scanning with Technicium Tc99m-labeled sestamibi. If an adenoma is located, a limited incision may be made. Morbidity is lowered, operating time shortened, and hospital stay reduced.

If you practice primary care long enough you will unexpectedly encounter a patient with primary hyperparathyroidism. Most are identified by a chemical screen, which reveals high serum calcium.

I believe many primary care clinicians would inform this patient:

1) The disease will not go away. It may progress and lead to increased bone loss over time.

2) You have already undergone 7 years of testing, worry, inconvenience, and expense.

3) Surgery will cure you and end all these concerns. The minimally invasive technique is safe.

Recovery is rapid.

Primary care clinicians choose your surgical consultant carefully.

HYPERTENSION

If Confirmed, This Represents An Enormous Public Health Benefit.

1-4 FOLATE INTAKE AND THE RISK OF HYPERTENSION AMONG U.S. WOMEN

Oral folic acid supplementation improves endothelial function. Folate may have beneficial effects on blood pressure by increasing nitric oxide synthesis in endothelial cells, and by reducing plasma homocysteine levels. (Homocysteine by itself can cause endothelial cell injury.)

This study assessed the association of folate intake with incident hypertension in 2 large groups of women.

Younger women (mean age 36 at baseline):

Identified 7373 incident cases of hypertension (8%) over 8 years.

Subjects whose daily consumption was at least 1000 ug of total folate (diet + supplement) had a relative risk of developing hypertension of 0.54 compared with women who consumed less than 200 ug daily.

Absolute risk reduction of incident hypertension was about 8 cases per 1000 person-years.

Older women (mean age 55 at baseline):

Identified 12347 incident cases of hypertension (19%) over 8 years.

Relative risk of hypertension (1000 ug folate daily *vs* less than 200 ug) = 0.82.

Absolute risk reduction of incident hypertension was about 6 per 1000 person-years.

The most significant relationship was associated with supplemental (not dietary) folate intake.

(Bioavailability of supplemental folate is twice that of food folate.)

Younger women achieved the most benefit. Younger women whose intake was at least 1000 ug experienced 1/3 the risk of developing hypertension over 8 years. (*Ie, start supplementation early. RTJ*)

High intake of folate was associated with a decreased risk of incident hypertension, especially in younger women. Supplemental folate was independently beneficial.

If confirmed as true, this has enormous public health benefit.

The benefits of folate extend to prevention of spina bifida and coronary heart disease. The benefit/harm-cost ratio is very high.

A Practical Definition Of Hypertension: The Value Of BP Below Which No Further Benefit Of Lowering The BP Can Be Demonstrated

3-3 HYPERTENSION—TIME TO MOVE ON

In view of the *continuous* associations between BP and cardiovascular disease risks, the value of categorical systems for classifying BP is questionable. Such categorical systems provide little useful information about an *individual's* risk of actually developing a blood-pressure-related cardiovascular disease. Most guidelines acknowledge that risks are determined by many factors and not by BP alone.

A practical definition of hypertension is the value of BP below which no further benefit of lowering the BP can be demonstrated. There is now compelling epidemiological evidence of continuous associations between usual BP values down to about 115/75 and risks of major cardiovascular disease. Non-hypertensive individuals with multiple risk factors or a history of cardiovascular disease will often be at higher *absolute* risk of BP-related cardiovascular events than hypertensive patients without other risk factors.

"So why do we persist with this focus on the treatment of hypertension (defined arbitrarily) rather than the prevention of blood-pressure-related diseases?"

This reinforces the argument presented in the preceding article—risk factors are additive and should not be considered alone.

Neither Amlodipine Nor Lisinopril Was Superior To Chlorthalidone

4-3 RENAL OUTCOMES IN HIGH-RISK HYPERTENSIVE PATIENTS WITH AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR A CALCIUM CHANNEL BLOCKER VS DIURETIC

This subset of the study assessed outcomes in the entire group (n = 33 000) for renal outcomes. The methods used were identical to those in the study of blacks. Chlorthalidone, lisinopril, and amlodipine were used separately as first line therapy.

In both diabetic and non-diabetic participants, the 6-year rate of ESRD for those assigned to chlorthalidone was no different from those assigned to lisinopril. The benefits of ACE inhibitors (and angiotensin blockers) have been attributed to their effects on the renin-angiotensin system and their unique anti-proteinuric effects. Epidemiological studies have demonstrated a strong association between BP and ESRD outcomes. There was, however little difference in BP between the chlorthalidone and lisinopril groups.

What is the message for primary care clinicians? Fortunately, we are not limited to an either-or choice of therapy as in the trial. Most high-risk hypertensive patients (with and without diabetes) will require two or three drugs to reduce BP as much as possible. A combination of a diuretic, an ACE, and a calcium blocker would be appropriate.. The diuretic should not be omitted. Addition of a beta-blocker should be considered in some patients.

Thiazides the Drugs of First Choice for Blacks as well as Whites.

4-1 OUTCOMES IN HYPERTENSIVE BLACK AND NON-BLACK PATIENTS TREATED WITH CHLORTHALIDONE, AMLODIPINE, AND LISINOPRIL

Blacks have the highest morbidity and mortality from hypertension of any population group in the USA. The choice of the most effective and efficacious first-choice antihypertension drug is therefore important. This has been controversial in blacks.

This study asks if the benefits of thiazide diuretic therapy (chlorthalidone) compared with an ACE –inhibitor (lisinopril) and Calcium blocker (amlodipine) extended to black patients.

In blacks, neither the ACE nor the CB was more effective than the thiazide diuretic in preventing the primary outcome of fatal CVD + non-fatal-MI, or any other major cardiovascular or renal outcome.

Chlorthalidone was superior to ACE and CB in reducing incidence of heart failure.

Chlorthalidone was associated with a lower incidence of stroke than lisinopril.

Much of the comparative benefit may have been due to the greater reduction in systolic BP associated with chlorthalidone.

"Thiazide-type diuretics remain the drugs of choice for initial therapy of hypertension in both black and non-black hypertensive patients."

Using a diuretic as first-line therapy in both blacks and whites is associated with considerably lower costs over the years.

Costs; Chlorthalidone and hydrochlorothiazide cost 9 to 12 cents a day

Prinivil 53 cents a day ; Norvasc $1.40 a day.

" Hypertensive End-Organ Damage Begins With A BP Below 140/90."

4-2 ELEVATED BLOOD PRESSURE AND RISK OF END-STAGE RENAL DISEASE IN SUBJECTS WITHOUT BASELINE KIDNEY DISEASE

Establishing a detrimental effect of lesser degrees of BP elevation on the kidneys is difficult because kidney disease itself can elevate BP. This study asks: What is the importance of hypertension as a risk factor for ESRD?

A graded association between baseline BP and risk of ESRD existed among subjects without clinical evidence of kidney disease at baseline. Even relatively modest elevations of BP were associated with an increased risk of ESRD. " Hypertensive end-organ damage begins with a BP below 140/90."

At any given level of BP there was a much higher risk of ESRD among blacks and patients with diabetes. . *Again demonstrating that risk of disease follow a linear pattern. There is no "normal" BP cut point.*

Extra vigilance is required for black patients and for those with diabetes.

In Modestly Overweight Persons, Reduction In Weight May Lower Risk Of Developing Hypertension.

6-11 WEIGHT LOSS IN OVERWEIGHT ADULTS AND THE LONG-TERM RISK OF HYPERTENSION: The Framingham Study

Obesity is associated with higher levels of insulin resistance, hyperinsulinemia, rises in cardiac output, increases in cholesterol and triglycerides, and increased sympathetic nervous system activity. Most of these changes have been associated with increases in BP. "In recent years, there has been a great deal of focus on the roles of hyperinsulinemia and insulin resistance in the development of hypertension."

The goal of this study was to estimate the effects of both the amount on weight loss and the persistence of weight loss on the risk of incident hypertension among already obese adults. (*Primary prevention.)*

After multiple adjustments, weight loss of 6.8 kg (18 pounds) or more led to a 28% reduction in risk of developing long-term hypertension in younger subjects (mean age 27) , and a 37% reduction in older subjects (mean age 52).

If the weight loss was sustained over the years, the risks of developing hypertension were reduced by 22% and 26%.

"The results of this study suggest that at least 15% of the cases of hypertension in overweight middle-aged adults and 22% of the cases occurring in overweight older adults could be prevented by a modest amount of sustained weight loss."

Overweight + hyperinsulinism + dyslipidemia + hypertension = a common and deadly combination

No Evidence Of Superiority For Treatment With A Calcium Channel-Blocker, Or An ACE Inhibitor Compared With A Thiazide-Type Diuretic

6-8 CLINICAL OUTCOMES IN ANTIHYPERTENSIVE TREATMENT OF TYPE 2 DIABETES, IMPAIRED FASTING GLUCOSE CONCENTRATION, AND NORMOGLYCEMIA

The Antihypertensive and Lipid-lowering Treatment to prevent Heart Attack Trial (ALLHAT)

This is one of a series of articles reported by the ALLHAT group.

There was no evidence of superiority for treatment with a calcium channel-blocker, or an ACE inhibitor compared with a thiazide-type diuretic during first-step antihypertension therapy in DM, IFG, or NG.

Most hypertensive patients with DM or IFG or impaired glucose tolerance, I believe, would receive more than one antihypertension drug. Many clinicians would use a combination of an ACE inhibitor and a diuretic.. Any combination should include a thiazide.

The abstract of this study is brief since I already abstracted similar studies by the same ALLHAT group:

A. JAMA December 18, 2002; 2981-97 presented the original ALLHAT study. (See Practical Pointers December 2002 [12-1]) The study compared the same 3 drugs in similar patients with hypertension and at least one additional risk factor (high-risk) . Conclusion: "Thiazide-type diuretics should be considered first for pharmacological therapy in patients with hypertension. " They are unsurpassed in lowering BP, reducing clinical events, and in tolerability. They are much less costly. Since many patients with hypertension will

require more than one drug to control their BP, it is reasonable to infer that a diuretic should be included in all multidrug regimens.

B. JAMA April 6, 2005; 293: 1595-1608 (See Practical Pointers April 2005 [4-2]) "Thiazide-type diuretics remain the drugs of first choice for initial therapy of hypertension in both black and non-black hypertensive patients."

C. Archives Int Med April 25, 2005; 165: 936-46. "Renal Outcomes in High-Risk Hypertensive Patients with an Angiotensin-Converting Enzyme Inhibitor or a Calcium Channel Blocker vs Diuretic." In hypertensive patients with reduced glomerular filtration rate, neither amlodipine nor lisinopril was superior to chlorthalidone in reducing the rate of development of end-stage renal disease or a 50% or greater reduction of glomerular filtration rate.

See also:

NEJM December 30, 2004; 351: 2805-16 (Practical Pointers December 2004 [12-2]) "Association between Cardiovascular Outcomes and Antihypertensive Treatment in Older Women" Conclusion: Monotherapy with diuretics was equally or more effective than other monotherapies. The combination of diuretics + beta-blockers was superior to, or equally effective as, other combinations.

When To Intervene? How To Intervene?

6-7 THRESHOLDS FOR NORMAL BLOOD PRESSURE AND SERUM CHOLESTEROL.

In 2003, European guidelines suggested a BP of above 140/90, and a cholesterol above 5 mmol/L (193 mg/dL) as the appropriate thresholds for intervention. "The bottom line is that the doctor is expected to inform the patient that these measurements mean that he or she is at increased cardiovascular risk regardless of the management proposed. In other words, a disease label is to be attached to the patient."

In Norway, if this threshold for cholesterol and BP were to be applied at age 24, half the population would be identified as being at increased risk. At age 49, the proportion is raised to 90%. As much as 75% of the total population would be identified as being at risk.

The potential benefits for treated patients become less at lower risk levels. The number needed to treat is increased. The rates of adverse effects (of drug treatment) remain the same. Adverse effects tend to be under-reported and under-published.

Certainly, experts who developed these guidelines did not suggest that all persons with BP and cholesterol levels above these cut-points should be treated with drugs.

I believe however, that all should be treated with judicious advice about changing in lifestyle. This will apply to almost all persons in the US over age 50. Very rarely will individuals over age 50 have no risk factors. Cut-points are defined at levels below which no further reduction in risk occurs. Admittedly, those with baseline risk-levels at the low range will have less to gain when their levels are lowered than persons with high baseline risk-levels.

I do not believe life-style advice will be interpreted as a labeling of disease. There are few if any adverse effects of lifestyle changes. Effectiveness is established. The benefit/harm-cost ratio is very low.

The task of educating patients about healthy lifestyles and getting them to adopt them is daunting, and in the main unsuccessful. We should not be deterred from trying. This includes primary care clinicians' adopting a healthy lifestyle themselves.

Who should be treated with drugs?—patients who are indeed at high risk. The definition of "high risk" depends not only on the number or risk factors present and their levels, but also on the individual patient's assessment of his own risk. Patients

must be convinced of the benefits of drug therapy; must understand that drug therapy is long-term, expensive, and carries risks of its own.

INFLUENZA

2-1 DOES THIS PATIENT HAVE INFLUENZA?

This systematic review deals chiefly with precision and accuracy of diagnosis of flu by symptoms and signs. It leads to other publications by the CDC which are helpful in diagnosis, treatment, and prophylaxis of flu

Diagnosis by signs and symptoms: "Fever, headache, myalgias and cough are the classic symptoms that physicians associate with influenza. Unfortunately, these symptoms are frequently seen in patients presenting with other infections during influenza season, making the clinical diagnosis of influenza a challenge to the primary care physician."

Epidemiology ; Clinician's knowledge of the current epidemiological status of flu in the community is basic to accurately estimate the probability of influenza in a given patient.

Laboratory diagnosis: Rapid diagnostic tests are now available for office use. Results are available within 30 minutes: The tests require swabs of the nasopharynx. The sensitivity (% of patients with flu who have a positive test) and specificity (the % of patients who do not have flu who have a negative test.) vary. Two commercial tests have waivers from the Clinical Laboratory Improvement Amendments, and can be used in office settings.

Treatment: Four drugs are approved for early treatment—oseltamivir (*Tamiflu*); zanamivir (*Relenza*); amantadine (*Symmetrel*; Generic); and rimantadine (*Flumadine*; generic). Tamiflu is effective against both A and B, and can be given by mouth.

Test and treat or treat empirically without testing: Depending on the acuity of the illness, vaccination status, and presence of co-morbid conditions, some physicians might choose to treat empirically with an antiviral drug. Empirical treatment may be favored because the test may be a false negative.

Decision must be based on epidemiologic estimates of the likelihood of the infection in the community. The decision is sensitive to prior vaccination status.

Physicians who were provided with rapid test results prescribed fewer antibiotics, ordered fewer lab studies and chest X-rays, and kept the patient in the emergency department for shorter periods of time and generated fewer charges.

Chemoprophylaxis: Three drugs are approved—amantadine, rimantadine, and oseltamivir.

CDC has, in the past, encouraged use of amantadine and rimanatadine for chemoprophylaxis. Oseltamivir

(Tamiflu) may be a better choice since it covers both A and B. It is well tolerated. Less than 1% of patients experience nausea and vomiting which leads to withdrawal. The UK is stockpiling the drug in anticipation of a pandemic of the Asian bird flu.

Prophylaxis is indicated for persons at high risk of serious complications and immunosuppressed patients including those in institutions. <u>Vaccinated</u> as well as unvaccinated immunosuppressed residents in institutions where an outbreak occurs should receive chemoprophylaxis for the duration of the outbreak.

If non-immunosuppressed patients can be vaccinated, the prophylaxis may be continued for 2 weeks until immunity develops.

INSULIN RESISTANCE

A Circumference Under 100 Cm Rules Out Insulin Resistance And Hyper-Insulinemia.

6-3 USE OF WAIST CIRCUMFERENCE TO PREDICT INSULIN RESISTANCE

This study assessed how effectively different anthropometric markers used in clinical practice can predict insulin sensitivity. The authors suggest abdominal circumference is the most powerful independent predictor to rule out insulin resistance.

Determined height, weight, and waist circumference (midway between lateral lower ribs and iliac crest). Also determined results from analyses of plasma for glucose, insulin, and lipid concentrations. Used a homoeostasis index as a measure of insulin sensitivity [plasma glucose (mol/L) X plasma insulin (mU/L)/22.5]. A score of 4.0 and greater was defined as insulin resistance.

Using 100 cm as a test, the authors determined the sensitivity to diagnose insulin resistance was between 94-98%; and the specificity was between 61-63%. The positive predictive values of the test were 61% for men and 42% for women. The negative predictive value of the test was 98% in men and 97% in women. A waist circumference under 100 cm was therefore a strong independent predictor in *ruling out* insulin resistance.

Waist circumference is a simple tool to *exclude* insulin resistance. If the patient has a circumference under 100 cm (40 inches), he or she is very *unlikely* to have insulin resistance and hyper-insulinemia. Circumferences above 100 cm may, or may not, be related to insulin resistance.

I found this short article provocative. The results require confirmation. Abdominal girth is an important risk factor for the metabolic syndrome and cardiovascular disease .

INTRACRANIAL STENOSIS.

Warfarin Provided No Benefit Over Aspirin. Was Associated With More Adverse Effects.

3-7 COMPARISON OF WARFARIN AND ASPIRIN FOR SYMPTOMATIC INTRACRANIAL STENOSIS.

Randomized, double-blind multicenter (59 sites) trial entered over 550 patients (mean age 63). All had experienced a TIA or a non-disabling stroke caused by angiographically verified 50% to 99% stenosis of a major intracranial artery (internal carotid, middle cerebral, vertebral, or basilar).

Randomized to: 1) warfarin—target INR of 2.0 to 3.0, or 2) aspirin 650 mg twice daily.

Warfarin provided no benefit over aspirin. It was associated with significantly higher rates of adverse events. “Aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis.”

This is a good example of a pragmatic (real world of practice) trial. Difficulty in control of warfarin dosage may have been the cause of its lack of benefit.

ISCHEMIC HEART DISEASE

Combinations of A Statin, A Beta-Blocker, and Aspirin Improve Survival in High-Risk Patients

5-2 EFFECT OF COMBINATIONS OF DRUGS ON ALL-CAUSE MORTALITY IN PATIENTS WITH ISCHEMIC HEART DISEASE

This case-control study assessed the effect of combinations of drugs (statins, aspirin, beta-blockers and angiotensin converting enzyme inhibitors [**ACE**]) in the *secondary* prevention of all-cause mortality in patients with ischemic heart disease.

All-cause mortality:	Adjusted odds ratio (controls/cases)
Statins alone	0.53
Aspirin alone	0.59
ACE alone	0.80
Beta-blocker alone	0.81

Combined statin, aspirin & beta-blocker	0.17
Combined statin, aspirin, beta-blocker, and ACE	0.25

In this secondary prevention study, combinations of statins, aspirin, and beta-blockers improved survival in high-risk patients with IHD.

Millions of Americans are now using multiple drugs for primary, as well as secondary prevention. This includes drugs for hypertension [thiazides, beta-blockers, ACE inhibitors], statins for dyslipidemia, and low-dose aspirin. The absolute benefit will be lower than when used for secondary prevention.

We could include other interventions for both primary and secondary prevention: weight control; physical fitness; modest daily intake of alcohol.

MACULAR DEGENERATION

"May Lead To Treatment Which Slows Disease Progress"

4-14 GENE DISCOVERY PROVIDES CLUES TO CAUSE OF AGE-RELATED MACULAR DEGENERATION

A gene variant may be responsible for about half of the 15 million cases of AMD in the US. Using techniques from the Human Genome Project, investigators have identified a common variant of the complement factor H **(CFH)** gene that explains about 50% of cases:

Individuals who possess a certain variant of the CFH gene are at increased risk of AMD. The protein [tyrosine replaced by histidine] encoded by the variant fails to bind to receptors on cells on the retina and surrounding blood vessels. The protective effect of normal CFH is lost. This leads to increased inflammation in the retina and choroid.

Discovery of this variant may lead to treatment which slows disease progress. A modest slow-down would be sufficient to preserve a patient's vision for the rest of his life.

While not a practical point at this time, I felt the "News" was provocative enough to abstract.

MEDITERRANEAN DIET

Associated with longer survival.

4-4 MODIFIED MEDITERRANEAN DIET AND SURVIVAL

The Mediterranean diet **(MD)** is characterized by a high intake of vegetables, legumes, fruits, and cereals (largely unrefined); a moderate to high intake of fish; a low intake of saturated fats; a high intake of unsaturated fats (particularly olive oil); low to moderate dairy products; a low intake of meat; and a modest intake of ethanol, mostly as wine.

This study examined whether adherence to a modified MD (poly-unsaturated fats substituted for mono-unsaturates) was associated with longer life expectancy among elderly Europeans.

Means scores on the 10-point MD scale varied considerably between countries. Greece was highest (6.25); Spain next (5.61); Netherlands was lowest (2.92).

An increase in this modified MD score was associated with lower overall mortality. A two-unit increment corresponded to a reduction on 8% in mortality.

I believe the modification (substituting poly-unsaturated fats for mono-unsaturated fat) is a clinically important point. Poly-fats are more accessible in our culture than mono-fats.

“MONEY” NEEDED TO TREAT

The Cost Of Treating Patients Who Benefit + Those Who Do Not Benefit.

4-6 “MONEY” NEEDED TO TREAT (MNT)

The costs of treatment (money needed to treat to benefit one patient) can be easily calculated from analysis of trials which report the NNT(to benefit one patient over a given duration of therapy) in absolute terms. And by determining the cost of the drug.

A trial reported in NEJM April 7, 2005 “Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease” compared use of 80 mg the statin drug atorvastatin (*Lipitor*) with 10 mg. The LDL-cholesterol was lowered to a greater extent in the 80 mg group.

Over 5 years, major cardiac events occurred in 8.7% in the 80 mg group, and 10.9% in the 10 mg group Absolute difference = 2.2%; NNT(over 5 years to benefit one patient) = 45. Thus, 44 would be treated needlessly.

Based on the NNT (benefit) + the NNT(needlessly), the total cost of the 80 mg dose (44 + 1) = $65 700

Conversely, patients may be told that they will spend $1460 over 5 years to achieve a one in 45 chance of benefit.

MYASTHENIA GRAVIS

The Clinical Hallmark Is Fatigable Muscle Weakness Which Improves With Rest and Application Of Cold

4-11 DOES THIS PATIENT HAVE MYASTHENIA GRAVIS?

This article reviews: anatomical and physiological origins of symptoms and signs; how to elicit symptoms and signs; anticholinesterase tests; and analysis of articles reviewed.

The approaches to diagnosis and treatment have evolved over the years. Testing now includes the ice pack test, the rest test, the sleep test, and the peek sign.

“Fluctuating weakness that worsens with exertion and improves with rest or with application of ice or cold is never normal.” The fluctuation is dramatic and occurs rapidly.

Bear in mind that the initial fluctuating weakness of MG may become fixed over time if severe enough.

Certain historical features (speech becoming unintelligible after prolonged periods) of signs (peek test) maybe useful in diagnosis. Their absence does not rule it out.

The ice test, sleep test, and response to anticholinesterase agents are useful in confirming the diagnosis.
A positive test result should prompt proceeding with acetylcholine receptor antibody testing and specialist referral.

The authors did not mention a common associated abnormality—enlargement of the thymus. This is frequent enough, I believe, to warrant imaging in suspected cases of MG.

The patient with MG, on first presentation, should present suggestive symptoms and signs. Speaking from personal experience, it is embarrassing to miss the diagnosis.

MYOCARDIAL INFARCTION

Addition of Clopidogrel Improved Patency of The Affected Artery and Reduced Ischemic Complications.

3-5 ADDITION OF CLOPIDOGREL TO ASPIRIN AND FIBRINOLYTIC THERAPY FOR MYOCARDIAL INFARCTION WITH ST-SEGMENT ELEVATION

A substantial proportion of patients receiving fibrinolytic therapy for MI with ST-segment elevation have inadequate reperfusion or re-occlusion of the infarct-related artery. Aspirin significantly improves outcomes. But, aspirin is a relatively weak antiplatelet agent. It has limitations. It irreversibly inhibits cyclo-oxygenase in platelets thereby inhibiting synthesis of

thromboxane, a powerful promoter of platelet activation. It exerts no effect on thromboxane-independent mediators of platelet activation. Up to 30% of persons with coronary artery disease are relatively resistant or unresponsive to aspirin.

Clopidogrel (*Plavix*) acts differently from aspirin in inhibiting activation and aggregation of platelets. Does addition of clopidogrel benefit patients with acute ST-segment elevation MI who are receiving fibrinolysis and aspirin?

The short-time study enrolled over 3400 patients (mean age 57) who presented within 12 hours after onset of an acute ST-segment elevation MI. Randomized to: 1) clopidogrel (300 mg loading dose followed by 75 mg once daily), or 2) placebo.

Over a period of about a week, the addition of clopidogrel improved patency of the affected artery and reduced ischemic complications and death.

Treatment was not associated with an increased rate of major bleeding or intracranial hemorrhage.

Plavix has been extensively advertised to the public for ongoing use in patients with CVD. It is expensive. A 75 mg tablet costs almost $4.

I believe primary care clinicians may provide a meaningful advanced therapeutic measure to a patient presenting to the office with an acute MI. While transfer to the hospital is arranged, the patient may be given:
1) full dose aspirin (325 mg); 2) clopidogrel (300 mg); 3) a statin drug; and 4) a beta-blocker. A few packets containing these drugs may be kept handy. .

NEUROPATHIC PAIN

The Combination Was Associated With Significantly Less Pain-Related Interference with Mood, And Higher Scores for Vitality and Social Functioning

3-4 MORPHINE, GABAPENTIN, OR THEIR COMBINATION FOR NEUROPATHIC PAIN

This study assessed the effectiveness of a combination of morphine + gabapentin *vs* either alone and placebo for pain due to diabetic neuropathy and post-herpes zoster neuralgia.

Treatment with a combination of morphine + gabapentin resulted in greater relief of pain than treatment with either alone.

	Baseline	Placebo	Gabapentin	Morphine	Morphine + gabapentin
Mean daily pain scores	5.7	4.5	4.2	3.7	3.06
On a scale of 1 to 10					
McGill Pain Questionnaire	18.9	4.4	10.7	10.7	7.5
On a scale of 0 to 45					

The maximum doses of morphine and gabapentin were lower with the combination than for each given separately.

The combination was associated with significantly less pain-related interference with mood, and higher scores for vitality and social functioning. The combination was also associated with improvement in depression as measured by the Beck Depression Inventory.

This may bring considerable relief to some patients with very disturbing pain.

Gabapentin(Neurontin) is an analogue of butyric acid. It modulates calcium channel subunits thought to be important in neuropathic pain. It has both analgesic and anti-convulsant action and is approved for treatment of partial seizure epilepsy and post-herpetic neuralgia.

Gabapentin and morphine have mechanically distinct analgesic actions The combination may result in synergistic or additive pain relief at lower doses and with fewer side effects.

Repeated administration of gabapentin does not lead to tolerance.

NUMBERS NEEDED TO TREAT (NNT)

Too Often, Large Numbers Of Patients Are Being Treated Without Benefit.

4-5 NUMBERS NEEDED TO TREAT (NEEDLESSLY?)

The authors suggest a new index NNT(needlessly) to complement NNT(benefit). The higher the number, the greater the treatment burden.

For example, if the absolute difference between drug compared to placebo is 2% over 5 years, the NNT(benefit one patient) = 50. Of these, only one of 50 is benefited; 49 are treated (needlessly).

NNT(benefit) puts the emphasis on the positive side. But it tends to obscure the reality, that, too often, large numbers of patients are being treated without benefit.

The authors believe the new parameter will remind us that we should not be complacent about our inability to better identify patients who will benefit from our well-meaning interventions.

NNT(needlessly) may also help patients decide on their course of therapy.

This is a good illustration of the uncertainty principle of therapeutics, which is related to all treatments. We cannot judge beforehand which patients will benefit and which ones will be treated unnecessarily. The numbers in the latter will almost always be higher than the former.

The number needed to harm [NNT(harm)] is another helpful index. It can be easily calculated from data presented in trials. Usually, the older a patient becomes the greater the NNT(harm).

We might also consider the "Money Needed to Treat" (MNT). (Ie, the cost of a drug to benefit one patient + the cost of treating many patients needlessly. See the following. RTJ

OBESITY

Adherence was Poor. Those Who Adhered for One Year Lost Weight

1-7 COMPARISON OF THE ATKINS, ORNISH, WEIGHT WATCHERS, AND ZONE DIETS FOR WEIGHT LOSS AND HEART DISEASE RISK REDUCTION

This study assessed adherence rates and effectiveness of 4 diets in producing weight loss and reducing cardiac risk factors:

1. Atkins	Low carbohydrate—20 g carbohydrate daily
2. Zone	High protein, low glycemic load
3. Weight Watchers	Balanced diet—total daily "points" in a range determined by current weight (Aimed for 24 to 32 points daily.)
4. Ornish	Low fat, vegetarian diet containing 10% of calories as fat.

About half of the subjects in each group failed to complete the 1-year course. The most common reasons were "too hard to follow" and "not yielding enough weight loss". Adherence was particularly low for Atkins and Ornish.

At 1 year, completers lost more than those who failed to complete (- 3. 9 kg for Atkins and -6.6 kg for Ornish)

Each diet significantly reduced LDL/HDL-cholesterol ratio by about 10%. The Atkins diet did not lower LDL-cholesterol significantly. The Ornish diet did not increase the HDL-cholesterol. No diet significantly altered triglyceride levels. Reductions of total cholesterol, C-reactive protein, and insulin levels were significantly associated with the degree of weight loss.

Under realistic conditions a variety of popular diets can reduce weight and several cardiac risk factors. But only about half of the subjects in this study sustained a high adherence level.

The problem is not the diet, it is the patient's inability to follow it. Recidivism would be higher still at 5 or 10 years. The bloom seems to be coming off the Atkins diet.

The authors suggest that one way to improve dietary adherence in clinical practice may be to use a broad spectrum of diet options to better match individual patient's food preferences, lifestyles, and cardiovascular risk factors. They suspect adherence would have been better if subjects had been given the option to choose their diet.
I wonder—would switching from one type of diet to another every few months increase compliance?

In Modestly Overweight Persons, Reduction In Weight May Lower Risk Of Developing Hypertension.

6-11 WEIGHT LOSS IN OVERWEIGHT ADULTS AND THE LONG-TERM RISK OF HYPERTENSION: The Framingham Study

Obesity is associated with higher levels of insulin resistance, hyperinsulinemia, rises in cardiac output, increases in cholesterol and triglycerides, and increased sympathetic nervous system activity. Most of these changes have been associated with increases in BP. "In recent years, there has been a great deal of focus on the roles of hyperinsulinemia and insulin resistance in the development of hypertension."

The goal of this study was to estimate the effects of both the amount on weight loss and the persistence of weight loss on the risk of incident hypertension among already obese adults. (*Primary prevention.)*

After multiple adjustments, weight loss of 6.8 kg (18 pounds) or more led to a 28% reduction in risk of developing long-term hypertension in younger subjects (mean age 27) , and a 37% reduction in older subjects (mean age 52).

If the weight loss was sustained over the years, the risks of developing hypertension were reduced by 22% and 26%.

"The results of this study suggest that at least 15% of the cases of hypertension in overweight middle-aged adults and 22% of the cases occurring in overweight older adults could be prevented by a modest amount of sustained weight loss."

Overweight + hyperinsulinism + dyslipidemia + hypertension = a common and deadly combination

OPIOID AGONISTS

Likely To Produce Clinically Important Pain Relief.

6-9 EFFICACY AND SAFETY OF OPIOID AGONISTS IN THE TREATMENT OF NEUROPATHIC PAIN OF NON-MALIGNANT ORIGIN A Systematic Review.

Effective pain relief in these patients is difficult to achieve. Use of opioids is controversial. This is in part because studies have been small, have yielded equivocal results, and have not established long-term efficacy and safety. There have been concerns about adverse effects: potential for abuse and addiction, hormonal abnormalities, dysfunction of the immune system, and paradoxical hyperalgesia.

This systematic review assessed the efficacy and safety of opioids for treatment of NP.

Opioid treatment for 1 to 8 weeks had a beneficial effect over placebo for spontaneous neuropathic pain. The magnitude of this opioid effect was nearly a 14-point difference in pain intensity at study end compared with placebo. Is an average decline of 14 points on a 100-point scale meaningful to patients? The mean initial pain intensity ranged from 46 to 69. A 14-point difference corresponds to a 20% to 30% reduction in pain.

The trial did not address issues of addiction. It is reasonable to assume that the studies did not include individuals who might be potential abusers.

The most common adverse effects were nausea, constipation, drowsiness, vomiting, and dizziness. (NNT to harm one patient = 4 to 7.)

I believe primary care clinicians underuse opioids for patients with non-cancer pain. Fears of addiction have been overemphasized.

PAIN **(See OPIOID AGONISTS [6-9])**

PERTUSSIS **(See WHOOPING COUGH [5-5])**

PNEUMONIA

Should Beta-Lactams be the Antibiotics of Initial Choice in Adults with Community-Acquired Pneumonia?

2-5 EFFECTIVENESS OF BETA-LACTAM ANTIBIOTICS COMPARED WITH ANTIBIOTICS AGAINST ATYPICAL PATHOGENS IN NON-SEVERE COMMUNITY ACQUIRED PNEUMONIA.

One of the barriers to better define treatment of community-acquired pneumonia (**C-AP)** is the inability to accurately determine which organisms might be the cause. *Streptococcus pneumoniae* has long been considered a common pathogen. It is now apparent that other organisms are causative—*Mycoplasma pneumoniae, Chlamydia pneumoniae,* and Legionella species. Their major distinguishing feature is a lack of response to beta-lactam antibiotics.

This meta-analysis compared the efficacy of beta-lactam antibiotics (eg. penicillin; amoxicillin) with antibiotics active against atypical pathogens in adults with C-AP: 7 different fluoroquinolones (eg, levofloxacin); 2 macrolides (eg, erythromycin; azithromycin).

The study assessed only the necessity for coverage of atypical pathogens in the *initial* management of community-acquired pneumonia.

"Data from our analysis do not support the need for antibiotics that possess specific activity against atypical pathogens in the *initial* managements of adults with mild-to-moderate community-acquired pneumonia."

"We suggest that the role of *M pneumoniae* and *C pneumoniae* in community-acquired pneumonia may have been overplayed." There was no evidence that specific therapy is required for *M pneumoniae and C pneumoniae.* Legionella infections do require specific therapy.

Antibiotic treatment should always be reassessed in any patient who shows signs of deterioration or failure to improve.

"Beta-lactams should remain the antibiotics of *initial* choice in adults with community-acquired pneumonia."

This approach to therapy reflects the British view. It remains controversial. When I was abstracting the study, I wondered if beta-lactam therapy would be generally acceptable in the USA. I believe amoxicillin would often be prescribed initially in out patients with suspected pneumonia. The study gives some assurance that it is not a bad choice. However, as the study states, careful follow-up is required to judge if the patient's illness is improving or deteriorating.

The article did not mention the increasing resistance of S pneumoniae to beta-lactams (as well as many other antibiotics including erythromycin). Primary care clinicians should be aware of the likelihood of penicillin resistance in their community. There are now reports that some strains of S pneumoniae are susceptible only to vancomycin.

POLYPILL **(See CORONARY HEART DISEASE)**

POSTHERPETIC NEURALGIA AND PAIN **(See HERPES ZOSTER)**

POWER AND AUTHORITY IN MEDICINE

Physician's Power Can be Enhanced, Diminished, Used Well or Ill, but It Cannot be Disowned.

1-10 CONSENT OR OBEDIENCE? Power and Authority in Medicine

This essay considers the role of inappropriate obedience as a source of abuse in the teaching hospital and the effect of obedience on patients' autonomy and consent.

Patients provide consent not only about big issues, but, in the course of an illness, sick patients consent innumerable times to interventions that they would rather not undergo.

Serious illness is marked by losses of normal function in many dimensions of existence, including the ability to reason and to act (without which "autonomy" loses meaning). Sick patients do not reason their way to decisions based on their appraisals of the relevant information, but because an authority helps them to decide.

A power comes from the hospital setting and the trappings of medical authority. "Such power can be enhanced, diminished, used well or ill, but it cannot be disowned."

Bearing in mind the effect of sickness on function, we should accept the propensity of sick patients to seek our approbation, celebrate our expertise, and acknowledge the legitimacy of our authority by doing as they think we wish. These tendencies present us with difficult responsibilities.

"The biggest thief of autonomy is sickness."

I enjoyed this thoughtful essay.

We live in a world in which authority leads multitudes to follow blindly and commit unspeakable atrocities. The resistance of one man is a badge of courage.

I believe physicians apply their power to some extent in every patient encounter. Physicians, wield your power carefully and always with the aim of benefit to the patient.

PREMENSTRUAL SYNDROME

May Reduce Risk Of Development Of PMS.

6-14 CALCIUM AND VITAMIN D INTAKE AND RISK OF INCIDENT PREMENSTRUAL SYNDROME

Several studies have suggested that calcium and vitamin D levels are lower in women with PMS, and that calcium supplementation may prevent the initial development of PMS.

This case-control study was nested within the large prospective Nurses' Health Study. Participants were a subset of women age 27 to 44 (mean = 35). All were free of PMS at baseline (1991). Cases: 1057 women who developed PMS over a 10-year follow-up. Controls: 1968 women who reported no diagnosis of PMS and no, or minimal, menstrual symptoms.

Determined dietary and supplemental intakes of calcium and vitamin D by periodic questionnaires.

Women in the highest quintile of total vitamin D intake (median of 706 IU) had a relative risk of new-onset PMS of 0.59 compared with those in the lowest quintile (median of 112 IU). Benefit was associated with vitamin D from food. Supplemental vitamin D did not seem to be associated with risk.

Similar benefit was associated with calcium intake from food.

I abstracted this article because its conclusions are provocative—certainly not definitive. It raises more questions: Why did the benefit not extend to supplements? Is there a reasonable biological mechanism for the action of calcium and vitamin D? Why no benefit from whole milk? At a more practical level—could diet be beneficial in treatment as well as prevention?

I will watch for more developments.

PROSTATE CANCER

"These Results Do <u>Not</u> Support Aggressive Treatment Of Localized, Low-Grade Prostate Cancer."

5-8 20-YEAR OUTCOMES FOLLOWING CONSERVATIVE MANAGEMENT OF CLINICALLY LOCALIZED PROSTATE CANCER. A Natural History Study

This study estimated 20-year survival of men who were diagnosed with clinically localized PC and treated with observation or androgen withdrawal therapy. None received prostatectomy for attempted cure. They were stratified by age at diagnosis and histological findings. It provides an estimate of the natural progression of PC treated conservatively.

Fifty eight % of patients received no treatment; others received androgen suppression (orchiectomy or estrogens). None received radical prostatectomy for attempted cure.

The median observation period was 24 years.

Men with low-grade PC (Gleason score 2 to 4) had a minimal risk of dying from PC during 20 years. Those with high-grade PC (Gleason score 7, 8 to 10) had a high probability of dying from PC within 10 years. Those with scores 5 to 6 had an intermediate risk of dying from PC.

Cumulative mortality from PC up to 20 years after diagnosis stratified by age and Gleason score (*My analysis of Figure p 2099 RTJ*):

Men age 55-59 at diagnosis:	Died from PC
Gleason score 2-4	5%
Gleason score 8-10	90% (10% died of other causes)
Men age 70-74 at diagnosis	
Gleason score 2-4	8%
Gleason score 8-10	58% (42% died of other causes)

The majority of men with high grade PC die from the cancer regardless of their age at diagnosis. The percentage of deaths from PC in older men is *lower* than in younger men because older men have more competing causes of death. Much depends on the man's age at diagnosis.

"Tumor histology still remains the most powerful predictor of disease progression." Men with well-differentiated tumors rarely die of the disease. Men with poorly differentiated tumors frequently die of the disease within 5 to 10 years despite aggressive interventions including androgen deprivation. (The study did not include radical prostatectomy.)

Counseling men with Gleason scores of 5, 6, and 7, and a life expectancy of more than 15 years poses the greatest challenge. Physicians will continue to recommend aggressive treatments in these patients at the time of diagnosis.

The annual rate of progression of PC does not increase after 15 years. "These results do not support aggressive treatment of localized, low-grade prostate cancer."

None of these patients received PSA screening. At present, the natural history of PC is influenced by PSA determinations. I wondered . . . What would have been the natural history if PSA had been available for this study?

A. Many men would have been biopsied. A diagnosis of "cancer' would have caused great continuing anxiety to the patients and family. Some may have changed their lifestyles as a result.

B. Many with low-grade Gleason scores would have undergone radical prostatectomy without benefit, and with risk of serious adverse effects from surgery.

C. Many men with high-grade scores would have undergone radical prostatectomy with no chance of cure.

D. Many older men would have undergone radical prostatectomy without any effect on their life span. They would have died of other causes.

E. Few men would have been cured.

Primary care clinicians should understand the natural history of PC—as much as it can be presently understood—in order to advise men regarding PSA screening, and benefits and adverse effects of surgery.

Screening and surgery should tilt toward younger men.

"In Absolute Terms The Reduction In Mortality Is Moderate. Clinical Decision-Making Will Remain Difficult."

5-9 RADICAL PROSTATECTOMY VERSUS WATCHFUL WAITING IN EARLY PROSTATE CANCER

This article reports estimated 10-year results of a trial comparing radical prostatectomy *vs* watchful waiting **(WW)** in patients with early PC.

Cumulative incidence at 10 years:	Surgery (%)	WW (%)	Absolute difference (%)	NNT
Disease-specific mortality	9.6	14.9	5.3	19
Distant metastases	15.2	25.4	10.2	10
Local progression	19.2	44.3	25.1	4
Disease specific survival at 10 y	91%	86%		

(*Note that 45% of the surgery group were not cured [10% died; 15% had metastases; 20% local progression]. 15% of the WW group had no evidence of disease at 10 years.)*

"We found that the reduction in disease-specific mortality as a result of radical prostatectomy was . . . *limited to patients younger than 65 years."* But this observation had limited interpretability because it was based on small numbers of patients.

"In absolute terms the reduction in mortality is moderate. Clinical decision-making will remain difficult."

The slight difference in 10-year disease-specific survival between groups (5%) impressed me. That 45% of the surgery group was not cured is also impressive.

All of these patients received PSA screening. The end-result at 10 years was a very modest (5%) cure rate. The survival rate in the WW group was 85%.

When first introduced, PSA screening was said to be the most important ontological screen yet developed. Now, the bloom seems to be coming off PSA screening. The US Preventive Task Force states that evidence is inconclusive either for or against screening. Dr. Thomas Stamey, who is considered the father of PSA screening, now states: "Most prostate cancers now removed need not be removed." "It is a cancer that all men will get if they live long enough."

PSA screening is an important consideration in primary care. Before screening, all men should receive adequate information about risks as well as benefits. This applies to older men—especially those with co-morbidity—who request screening. Screening and surgery should tilt toward younger men.

Primary care clinicians who enthusiastically advise PSA screening assume a much greater responsibility for the adverse effects that screening may lead to than when screening is done after persistent requests from the patient.

Still, PSA remains the best screen for PC available today. Many men will continue to request it. Many primary care clinicians will continue to order it without much thought.

Undoubtedly, PSA screening, biopsy, and attempts at curative surgery are grossly over used.

"Is cure necessary when possible?" Not always. "Is cure possible when necessary?" Sometimes

RANDOMIZED CONTROLLED TRIALS

Why do we Underuse Treatments That are Beneficial in Trials?

1-2 EXTERNAL VALIDITY OF RANDOMIZED CONTROLLED TRIALS: To Whom do the Results of this Trial Apply?

Randomized controlled trials **(RCTs)** and systematic reviews must be *internally* validated. (Ie, the design and conduct of RCTs must keep the possibility of bias to a minimum). To be clinically useful, however, the results must be relevant to a definable group of patients in a particular clinical setting. This is termed *external validity*.

The most frequent criticism by clinicians of RCTs, systematic reviews, and guidelines is the lack of external validity. This explains the widespread underuse in routine practice of treatments that are beneficial in trials and recommended by guidelines.

Assessment of external validity requires clinical rather than statistical expertise.

The response to, and compliance with, treatment can be influenced strongly by the doctor-patient relationship, placebo effects, and patient preferences. The importance of these factors outside of trials should not be underestimated. Note the popularity of "alternative" therapies in which such factors are the only active ingredients.

The primary care clinician is a final arbiter of external validity. (Would this application be clinically useful for Mrs. Jones?)

Beware of surrogate outcomes in RCTs, of composite outcome measures, underreporting of adverse effects, and reports by pharmaceutical companies.

Primary care difficult, challenging, and so rewarding.

RESPIRATORY INFECTION

Antibiotics Provided Little Advantage Compared With No-Antibiotics.

6-2 INFORMATION LEAFLET AND ANTIBIOTIC PRESCRIBING STRATEGIES FOR ACUTE LOWER RESPIRATORY INFECTION

Pharyngitis and acute bronchitis are the main causes of excess antibiotic prescribing.

This pragmatic study assessed the effectiveness of 3 different antibiotic strategies for acute bronchitis.

Randomized, controlled trial followed over 800 patients presenting to primary care with acute uncomplicated LRI. Patients with findings suggestive of pneumonia were excluded—new focal chest signs (focal crepitations or bronchial breathing); and systemic features (high fever, vomiting, severe diarrhea). Also excluded patients with asthma, other chronic or acute lung diseases, cardiovascular disease, or with previous pneumonia.

Randomized to: 1) no antibiotic prescribed [control group], 2) delayed prescription [to be picked up later], or 3) immediately prescribed antibiotic. The antibiotic of choice was amoxicillin 250 mg 3 times daily for 10 days, or, if allergic, erythromycin 250 mg 4 times a day for 10 days.

Compared with no antibiotics [control group], the other strategies did not significantly alter cough duration: Delayed prescription shortened duration by 0.75 days; immediate prescription by 0.11 days. Treatment group had no effect on duration of other symptoms.

"Compared with immediate antibiotics, a strategy of either no offer of antibiotics or a delayed prescription was associated with little difference in duration or severity of symptoms." Overall, antibiotics probably do provide modest symptomatic relief. If a benefit is present, it represents a shortening of only one day in a relatively long history. "It is difficult to justify widespread antibiotic prescribing for uncomplicated lower respiratory infection on this basis, given the dangers of antibiotic resistance."

I was somewhat surprised at the duration of cough symptoms in this group of patients—a mean total of 3 weeks. However, I believe most patients would experience a gradual improvement over this period. We are admonished to consider pertussis in patient with LRI when the cough lasts 3 weeks or more. I presume in pertussis the cough continues unabated.

I believe advising patients that antibiotics may be associated with serious adverse effects (eg, colitis) will do more to tilt them toward accepting only symptomatic therapy than would advising them of the danger of antibiotic resistance in the community.

I have had success in prescribing delayed prescriptions of patients with uncomplicated lower respiratory infections. The great majority never fills the prescription. This may be an acceptable means of satisfying a demanding patient.

In the US, It is likely that many patients presenting after a week or more of cough and sputum production will receive a cheat X-ray.

The decision by primary care clinicians to prescribe or not prescribe, I believe, will often depend on how "sick" the patient appears.

SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUES

6-4 SENSITIVITY, SPECIFICITY, AND PREDICTIVE VALUES A Review

The authors of the preceding article calculated the sensitivity, specificity, and predictive values of the waist circumference test.—the ability of the test to detect insulin resistance and insulin sensitivity among healthy subjects by using 100 cm as a cut-off point. I welcome opportunities to review these important statistical measures. I have done so many times. I still have some difficulty in thinking them through and calculating them accurately. I used the determinations in the article as an example.

See the abstract.

SMOKING

Cessation is Difficult to Achieve. When Successful, it Saves Lives.

2-3 THE EFFECTS OF A SMOKING CESSATION INTERVENTION ON 14.5-YEAR MORTALITY: A Randomized Trial

The Lung Health Study entered over 5500 community-dwelling adult volunteers. All were heavy smokers (mean of 31 cigarettes daily and a history of 40 pack-years). At baseline, all had modestly impaired FEV1 and FVC, but were asymptomatic. None considered themselves to be ill.

Randomized to: 1) Intervention group received an intensive 10-week smoking cessation program consisting of a strong physician message and 12 two-hour group sessions using behavior modification and nicotine gum and 2) Usual care group.

At 5 years, 22% of the special intervention group had stopped smoking *vs* 5% of the usual care patients.

Mortality rates per 1000 person-years at 14 years:

	Sustained quitters	Intermittent quitters	Continuing smoker
Cardiovascular disease	1.0	1.5	2.9
Lung cancer	1.5	3.0	3.6

The most prominent difference between groups was observed in the youngest participants. "It could be argued that smoking cessation was more effective in preventing truly premature death."

This type of intervention would not be feasible in primary care practice.

The discouraging (yet realistic) outcome of this all-out effort—78% of heavy smokers failed to achieve cessation even though they received an all-out intervention, and were aware of a beginning disability from smoking.

This would tilt efforts to intervene much earlier in life, particularly to prevent smoking in the first place.

Cessation benefits all ages. Younger patients can be told their risk of dying at a relatively young age (35-44) is high as a result of smoking. This might deter a few.

STATIN DRUGS

Statins Reduce C-Reactive Protein Levels and Improve Outcomes Independently of LDL-Cholesterol

1-13 STATINS FOR ATHEROSCLEROSIS—Autoimmunity, Inflammation, and C-reactive Protein.

Statin drugs, in addition to inhibiting synthesis of cholesterol, now appear to directly inhibit inflammation. Two articles in this issue of NEJM confirm that reducing the inflammatory component of cardiovascular disease with statin therapy improves clinical outcomes independently of the reduction in cholesterol. Both studies found that the statin-induced decrease in C-reactive protein (**CRP**), a marker of inflammation, is only weakly correlated with changes in lipid levels.

The LDL-c lowering effect of statins and their effect on lowering CRP are largely independent of each other. Patients achieving the lowest CRP levels through statin therapy had a higher event-free survival at all levels of LDL-cholesterol.

Only by assaying both C-reactive protein and cholesterol can the full effect of statins be identified.

Statins are the "penicillin" of the last of the 20th century

This is not a practical point at this time. Although it is still "far out", I included the abstract because of its potential. We need a more specific agent to reduce C-reactive protein levels.

CRP is formed in the liver in response to acute inflammation. It is a non-specific marker.

C(capsule)-reactive protein has an interesting history. It was first described in 1930 as an indicator of pneumococcal infection because it reacts with the polysaccharide in the capsule of the pneumococcus.

STROKE

"No Indication Of A Net Benefit."

6-5 EPIDEMIOLOGICAL MODELLING OF ROUTINE USE OF LOW-DOSE ASPIRIN FOR THE PRIMARY PREVENTION OF CORONARY HEART DISEASE AND STROKE IN THOSE AGE > 70

Current US guidelines recommend the use of low-dose aspirin for people with a 5-year absolute risk of coronary heart disease **(CH D)** of > 3%, or a 10-year absolute risk of > 10%.

"Prophylactic use of a potentially toxic agent can be problematic, particularly in people in whom comorbidity and polypharmacy are common." In a prospective observational study in two large UK general hospitals, aspirin use was the causal agent in 18% of all admissions for adverse drug effects, and was implicated in 61% of all associated deaths. Older females are the most vulnerable.

This epidemiological modeling study was conducted in a hypothetical population (10 000 men and 10 000 women) selected from a reference population from a state in Australia. All were age 70-74. None had known cardiovascular disease.

Proportional benefit gained from aspirin in prevention of MI and ischemic stroke *vs* excess hemorrhage from age 70-74 to age 100 or to death:

Benefit in preventing	Men (n = 10 000)	Women (n = 10 000)
Myocardial infarction	- 389	- 321
Ischemic stroke	- 19	- 35

Harm

Excess GI hemorrhage	+ 499	+ 572
Excess hemorrhagic stroke	+ 76	+ 54

When comparing net harms *vs* net benefits of aspirin, the effects on length and quality of life were equivocal.

"Despite sound evidence for efficacy, the temptation to blindly implement low-dose aspirin treatment for the *primary* prevention of cardiovascular disease in elderly people must be resisted." Benefits may be offset by harms.

I believe low-dose aspirin has an important place in primary prevention of women at higher risk, and in secondary prevention of cardiovascular disease.

There is an important clinical downside related to universal prophylactic aspirin therapy: suppose primary care clinicians prescribe low-dose aspirin to 1000 women over 10 years. Three or 4 ischemic strokes might be prevented. But there would be no way of knowing which individuals of the 1000 benefited. Conversely, a serious hemorrhagic event occurring in 2 of the1000 patients would be self-evident. The clinician might feel responsible, and the patient and family might blame the clinician for the disaster.

I believe primary prevention with aspirin in women at average risk should be avoided. Obviously, careful clinical judgment based on individual-patient attributes is required.

TRAVELERS' DIARRHEA

"Rapid and Judicious Treatment of Diarrhea, Not Antibiotic Prophylaxis, Is the Best Recommendation"

5-4 TRAVELERS' DIARRHEA: HOW TO HIT THE RUNS FOR FIFTY MILLION TRAVELERS

Prophylaxis and Treatment of Travelers' Diarrhea

An article in this issue of Annals reports a new (to the US) antibiotic *treatment* for traveler's diarrhea. **(TD)**. Rifaximin [*Xifaxan*], a non-absorbable antibiotic, was recently licensed for treatment of uncomplicated traveler's diarrhea. The study reports excellent *prophylactic* properties.

The high protection rate of antibiotic prophylaxis has led to the inescapable conclusion that TD is an infectious disease. Putative agents appear to be gram negative enteric bacteria sensitive to many antibiotics. (Doxycycline, trimethoprim-sulfamethoxazole, and fluoroquinolones are effective. However, unlike rifaximin, they are absorbed.) These microorganisms are likely food or water borne. Beware of "dietary mistakes"—fresh unpeeled fruit and ice.

The editorialist has misgivings about a preventive policy that would lead to millions of persons receiving antimicrobial drugs. The most persuasive argument against universal antibiotic prophylaxis is the existence of excellent treatment alternatives that can reduce an episode of TD to a few hours of inconvenience. Antimotility drugs (eg, loperamide—over-the-counter *Imodium-AD* each tablet contains 2 mg) act rapidly and are safe. Bismuth subsalicylate (*Pepto-Bismol*) is also useful for mild disease. For more severe disease, a fluoroquinolone or azithromycin can be added to the loperamide regimen.

"The current recommendation is to supply the at-risk traveler with these drugs to be taken as required for diarrhea, along with the warning to seek medical attention for more severe symptoms." "Rapid and judicious treatment of diarrhea, not antibiotic prophylaxis, is the best recommendation for most travelers."

Travelers to countries where TD is prevalent should take a packet of treatment drugs along.

TUBERCULOSIS

Hope For Reducing The Prevalence Of This World-Wide Scourge.

6-15 BASIC SCIENCE GUIDELINES DESIGN OF NEW TB VACCINE CANDIDATES

Several new vaccines which improve immune response are under investigation. They may be helpful in primary prevention of infection as well as boosting immunity in those with latent infection.

See the abstract.

(*The entire June 8 2005 issue of JAMA is devoted to tuberculosis.)*

VITAMIN B12

Approximately 1% of Crystalline B12 Given Orally is Absorbed

5-6 ORAL CYANOCOBALAMIN SUPPLEMENTATION IN OLDER PEOPLE WITH VITAMIN B12 DEFICIENCY: ***A Dose-finding Trial***

Vitamin B12 deficiency affects mainly older people. Symptoms include anemia, neuropathy, and neuropsychiatric disorders, but deficiency more commonly leads to nonspecific tiredness or malaise.

In the presence of intrinsic factor, and normal functioning of stomach, pancreas and terminal ileum, B12 in food can be absorbed actively with a limited capacity of about 3 ug per meal. The bioavailability of crystalline B12 is unaffected by the underlying causes of deficiency. Approximately 1% is absorbed by passive absorption.

Although deficiency is usually treated by monthly injections of 1000 ug (1 mg), dietary supplements of 1000 to 2000 ug/d administered orally are as effective in correcting biochemical markers of deficiency.

"The lowest dose of oral cyanocobalamin required to normalize mild vitamin B12 deficiency is more than 200 times the recommended daily allowance, which is approximately 3 ug daily."

Harrison's textbook "Principles of Internal Medicine" states that, generally, treatment is given intramuscularly—1000 ug monthly, although daily oral doses of crystalline B12 are also effective. In patients with pernicious anemia, clinicians may prefer to administer B12 intramuscularly as often as weekly until the anemia is controlled. Thereafter, patient preference may guide therapy.

VITAMIN D

The Benefit/Harm-Cost Ratio of Vitamin D May Be Very High

3-8 RECENT DEVELOPMENTS IN VITAMIN D DEFICIENCY AND MUSCLE WEAKNESS AMONG ELDERLY PEOPLE

Vitamin D deficiency is common in the elderly (especially in the house-bound and nursing home patients). Its prevalence is much greater than previously realized. It may be associated with poor muscle strength, and a tendency to fall, as well as osteomalacia.

Higher plasma levels of calcidiol are associated with muscle strength, physical activity, and ability to climb stairs. Lower levels of calcidiol are associated with falls among the elderly. A randomized trial reported a 47% reduction in falls and fractures in elderly women given 800 IU of vitamin D daily (compared with controls receiving calcium alone) over 12 months.

The author states that supplementation is often inadequate. 400 IU daily may be ineffective. In contrast, 800 IU has been shown to significantly reduce the risk.

Treatment with a supplement of 800 IU daily should be seriously considered.

It is important to remember that patients with kidney and liver disease require special consideration. The kidney is the first step in metabolism of cholecalciferol to calcidiol. And the liver is involved in the final conversion to the active hormone, calcitriol.

See also:

"Effect of vitamin D on falls" Practical Pointers April 2004 [4-5]

"Effect of four-monthly oral vitamin D supplementation on fractures and mortality in man and women living in the community" March 2003 [3-4]

"Occult vitamin D deficiency in postmenopausal U.S. women with acute hip fracture April 1999 [4-7]

Supplements Containing 800 IU Appear To Reduce Risk Of Fracture; 400 IU Is Inadequate.

5-3 FRACTURE PREVENTION WITH VITAMIN D SUPPLEMENTATION

A Meta-analysis of Randomized, Controlled Trials.

This study estimated the effectiveness of oral vitamin D supplements in preventing hip and non-vertebral fractures in older persons.

A dose of 800 IU was associated with a reduction in relative risk of both hip fracture (RR = 0.74) and non-vertebral fracture (RR = 0.77) compared with calcium supplements alone or placebo. No significant benefit was observed from a dose of 400 IU.

The pooled risks indicate the NNT(to benefit one patient) = 45 for hip fracture and 27 for any non-vertebral fracture.

I believe there will be greater benefit from vitamin D + calcium if they are started at a younger age. Any benefit in older persons who already are osteoporotic and have already sustained a fracture would be minimal.

I believe supplemental calcium is required for most Americans. Our diet is often woefully deficient in calcium.

Benefit/harm-cost ratio is high for both calcium and vitamin D. There is increasing evidence that the dose should be raised to 800 IU in older persons who live indoors.

Vitamin D given in the usual daily doses is a very safe drug.

May Reduce Risk Of Development Of PMS.

6-14 CALCIUM AND VITAMIN D INTAKE AND RISK OF INCIDENT PREMENSTRUAL SYNDROME

Several studies have suggested that calcium and vitamin D levels are lower in women with PMS, and that calcium supplementation may prevent the initial development of PMS.

This case-control study was nested within the large prospective Nurses' Health Study. Participants were a subset of women age 27 to 44 (mean = 35). All were free of PMS at baseline (1991). Cases: 1057 women who developed PMS over a 10-year follow-up. Controls: 1968 women who reported no diagnosis of PMS and no, or minimal, menstrual symptoms.

Determined dietary and supplemental intakes of calcium and vitamin D by periodic questionnaires.

Women in the highest quintile of total vitamin D intake (median of 706 IU) had a relative risk of new-onset PMS of 0.59 compared with those in the lowest quintile (median of 112 IU). Benefit was associated with vitamin D from food. Supplemental vitamin D did not seem to be associated with risk.

Similar benefit was associated with calcium intake from food.

I abstracted this article because its conclusions are provocative—certainly not definitive. It raises more questions: Why did the benefit not extend to supplements? Is there a reasonable biological mechanism for the action of calcium and vitamin D? Why no benefit from whole milk? At a more practical level—could diet be beneficial in treatment as well as prevention?

I will watch for more developments.

VITAMIN E

An increased Risk of Heart Failure Associated with Vitamin E

3-10 IS THERE ANY HOPE FOR VITAMIN E?

Over the past 3 to 6 years, placebo-controlled trials have consistently shown that commonly used antioxidant vitamins (E, C, and beta carotene, or a combination) do *not* significantly reduce overall cardiovascular events or cancer.

This editorial comments on a study which reports a 7-year follow-up of a trial of vitamin E (daily 400 IU of alpha-tocopherol—a natural source). The study was based on a cohort of patients age 50 to 75 who had established cardiovascular disease or diabetes. There was no statistical benefit from the vitamin in reducing risk of total cancer or cardiovascular events.

A subgroup finding reported a possible *harmful* effect—an increased risk of heart failure associated with vitamin E.

"In nearly 60 000 studied to date, there was no compelling evidence that higher doses of vitamin E reduced cardiovascular disease or cancer."

"Vitamin E supplements should not be used in patients with vascular disease of diabetes."

The "antioxidant" theory has become entrenched in the minds of the public in the USA. It may take a while to un-entrench the idea. The editorialists comment that enthusiasts may continue to claim that vitamin E has a protective effect against specific cancers (lung, oropharyngeal, and prostate).

Donepezil May Delay Clinical Progression To Alzheimer's Disease

6-10 VITAMIN E AND DONEPEZIL (*ARICEPT*) FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT

Amnestic (memory loss) mild cognitive impairment **(MCI)** represents a transitional state between the cognitive changes of normal aging and the earliest clinical features of Alzheimer's disease **(AD).** Amnestic MCI refers to the subtype that has a primary memory component, either alone or in conjunction with other cognitive-domain impairments, of insufficient severity to constitute dementia. About 80% of those who meet the criteria for MCI will have AD within 6 years.

MCI is a transition state between normal aging and dementia (for Alzheimer's disease in particular), one in which cognitive deficits are present, but function preserved. In clinical settings, the term is often used to describe patients who present with memory loss, but do not have dementia. Even when defined carefully, MCI is a heterogeneous category that includes some persons with memory changes of normal aging, some with non-progressive cognitive defects, some with prodromal AD, and some with prodromal forms of other neurodegenerative dementias.

This study was designed to determine if vitamin E or the cholinesterase inhibitor donepezil could delay the clinical diagnosis of AD in patients with MCI.

Vitamin E had no effect at any time.

For donepezil . . . "The observed relative reduction in the risk of progression of 56% at one year and 36% at two years in the entire cohort is likely to be clinically significant."

"Although our findings do not provide support for a clear recommendation for the use of donepezil in persons with mild cognitive impairment, they could prompt a discussion between the clinician and the patient about this possibility."

Symptoms of memory loss in older persons should be taken seriously. They may represent the beginning of AD. This may be an important clinical measure once more effective treatments become available.

The important question is . . . What are the cognitive changes of normal aging?

I believe some degree of memory impairment is almost universal among individuals over age 80. It usually

begins by forgetting names, and recalling them minutes or hours later ("senior moments"). The spectrum of memory impairment is wide. The definition of amnestic MCI is not settled. At what point does it predict development of AD? The criteria for diagnosis of amnestic MCI in the study included patients with difficulties greater than temporarily forgetting names.

This study may foretell important developments in drug therapy which may delay the onset of disabling dementia. The spectrum of forgetfulness of old age is very broad. When should intervention be considered?
Some elderly patients may well accept early intervention. A delay of one to two years represents a large proportion of remaining quality-life. Patients may be willing to accept some adverse effects of drugs to gain a few years free of dementia of AD. (Note that anticholinergics do not benefit vascular dementia.)

Others may wish to wait until adverse effects on daily living become more evident.

I do not believe memory defects inevitably progress to AD. Keeping mentally and physically active, continuing a healthy diet, retaining active family and social connections, and controlling risk factors for cardiovascular disease will delay or prevent development of dementia in many individuals.

WAIST CIRCUMFERENCE

A Circumference Under 100 Cm Rules Out Insulin Resistance And Hyper-Insulinemia.

6-3 USE OF WAIST CIRCUMFERENCE TO PREDICT INSULIN RESISTANCE

This study assessed how effectively different anthropometric markers used in clinical practice can predict insulin sensitivity. The authors suggest abdominal circumference is the most powerful independent predictor to rule out insulin resistance.

Determined height, weight, and waist circumference (midway between lateral lower ribs and iliac crest). Also determined results from analyses of plasma for glucose, insulin, and lipid concentrations. Used a homoeostasis index as a measure of insulin sensitivity [plasma glucose (mol/L) X plasma insulin (mU/L)/22.5]. A score of 4.0 and greater was defined as insulin resistance.

Using 100 cm as a test, the authors determined the sensitivity to diagnose insulin resistance was between 94-98%; and the specificity was between 61-63%. The positive predictive values of the test were 61% for men and 42% for women. The negative predictive value of the test was 98% in men and 97% in women. A waist circumference under 100 cm was therefore a strong independent predictor in *ruling out* insulin resistance.

Waist circumference is a simple tool to *exclude* insulin resistance. If the patient has a circumference under 100 cm (40 inches), he or she is very *unlikely* to have insulin resistance and hyper-insulinemia. Circumferences above 100 cm may, or may not, be related to insulin resistance.

I found this short article provocative. The results require confirmation. Abdominal girth is an important risk factor for the metabolic syndrome and cardiovascular disease .

WHOOPING COUGH

It Has Been Known For Decades That Pertussis Occurs In Adults. It Is Not A "Zebra" Diagnosis.

5-5 ADULTS ARE WHOOPING, BUT ARE INTERNISTS LISTENING?

Evidence strongly supports the inclusion of pertussis in the differential diagnosis of chronic cough illness (1 month of more) in adults and adolescents. One study reported that patients had visited their physicians as often as 9 times for cough symptoms, and that none of the 153 referrals for cough symptoms persisting for 2 weeks or longer had pertussis

documented as a suspected diagnosis. Many respondents were not aware that childhood immunization with pertussis vaccine does not provide lifetime immunity. Many did not know that the nasopharyngeal swab or aspirate is the preferred method for collection of a sample for culture. A minority knew that antimicrobial therapy is indicated for all close contacts of a case-patient.

Clinicians should think of pertussis when a cough illness exceeds 2 weeks.

"Pertussis is a community-acquired disease of persons of all ages and deserves greater attention by physicians for adults."

Confirmation of diagnosis by culture and PCR is difficult and waiting for confirmation will delay treatment. I believe many clinicians will treat chronic-cough illness empirically with antibiotics.

XIMELAGATRAN

Potentially A Less Intimidating Alternative to Warfarin. Concerns about Hepatotoxicity

2-7 XIMELAGATRAN—Promises and Concerns

Melagatran is a highly-specific direct thrombin inhibitor, an analogue of hirudin, the thrombin inhibitor found in the medicinal leech. It is a small dipeptide which binds reversibly to the active site of thrombin. It inhibits clot-bound thrombin as well as free thrombin. Ximelagatran is a prodrug form of melagatran. It is rapidly absorbed from the GI tract. When given orally it is rapidly converted to melagatran. Its antithrombin activity is immediate. Peak blood levels are attained in 3 hours. It is cleared entirely by renal excretion in 12 hours.

Since the effect is predictable at a fixed dose, monitoring is not necessary.

This is not yet a practical point for primary care since the drug is not yet approved by the FDA. Many attributes of the drug make it a very attractive anticoagulant: immediate action when given orally; a fixed dose without need for monitoring; rapid renal clearance; no food or drug interactions; active against clot-bound as well as free thrombin; reversible binding to thrombin.

If the risk of hepatotoxicity can be controlled by monitoring, I believe it will be a major therapeutic advance.