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MEDICAL SUBJECT HEADINGS

HIGHLIGHTS-INDEX

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WHAT I WOULD DO DIFFERENTLY BASED ON THE JANUARY-JUNE 2004 ARTICLES

- Administer a high dose of a stain drug immediately (with aspirin) for a patient with suspected acute coronary syndrome. [6-1]
- Discourage long-term use of donepezil and memantine for treatment of Alzheimer's disease [1-6] [6-11] [6-12]
- Advise smokers that they are at increased risk of macular degeneration. [3-9]
- Consider aromatase inhibitor therapy for breast cancer [3-9]
- Use estrogen-progestin hormone replacement therapy more freely in younger healthy postmenopausal women for symptom control [3-3]
- Use estrogen alone in hysterectomized women for menopausal symptom control without undue concern [4-4]
- Use statin drug for primary prevention of stroke in high risk persons, and for secondary prevention in all regardless of cholesterol levels [3-7]
- Encourage fitness and loss of intra-abdominal fat in persons with the metabolic syndrome. [5-4] [6-4]
- Discourage coronary artery calcium score as a screening method for coronary disease [1-11] [6-2]
- Point out the "actual" causes of death to patients: tobacco, alcohol abuse, poor diet, sedentary lifestyle [3-1]
- Consider statin therapy for all (or almost all) patients with diabetes [4-2]
- Point out that, although the Atkin's diet is associated with short-term weight loss, there is as yet no evidence of long-term benefit. [1-12] [5-1]
- Eradicate *H pylori* in all patients to prevent gastric cancer [1-9]
- Gain a better understanding of the frequency and pathogenesis of diastolic heart failure. [5-2]
- Be cautious of use of any NSAID in patient with heart failure and renal disese [5-13]
- Advise use of home BP monitoring [2-1]
- Remember use of "ring" prophylactic therapy with neuraminidase inhibitors in the forthcoming influenza epidemic. [6-13]
- Constantly improve my listening skills. Encourage patients to tell their life stories. [2-4]
- Advise women who are at risk of pregnancy to take folic acid. [1-10]
- Use alendronate for years (along with vitamin D and calcium) for continued protection against osteoporosis [3-8]
- Gauge severity of symptoms and recent onset of abdominal bloating, increased abdominal size and urinary urgency as possible clues of ovarian cancer. [6-7]
- Suggest to patients who fear "shots' that they cough when receiving the injection. [2-11]
- Be more circumspect when ordering PSA determinations [5-6] [5-7] [6-3]
- Consider tamsulosin (*Flomax*) adjunctive therapy for renal colic due to stone lying near the bladder [3-12]
- Consider statin therapy for patients facing elective major non-cardiac surgery [5-5]
- Consider carefully prescribing a newly introduced drug. Is it safer, more effective, less costly, or more conveniently administered than already available drugs. [6-14]
- Consider that carotid endarterectomy in asymptomatic patients with carotid stenosis is associated with significant surgical mortality and may not lead to net benefit for 2 years.
- Advise patients that compression + vein surgery is better than compression alone for chronic venous ulceration. [6-6]

Statement from the Editor/publisher

This index is intended to be a reference document. Each medical subject heading is linked to one or more "Highlights and *Editorial Comments*" of articles abstracted during the first 6 months of 2004. It 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, [1-12] indicates the 12th abstract published in the January issue.

Each monthly issue for the past 5 years can be found on the website (www.practicalpointers.org). This makes 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.

MEDICAL SUBJECT HEADINGS (MeSH) JANUARY-JUNE 2004

JANUARY TO JUNE 2004

HIGHLIGHTS OF ABSTRACTS AND *EDITORIAL COMMENTS*

ACUTE CORONARY SYNDROMES

4-3 INTENSIVE VERSUS MODERATE LIPID LOWERING WITH STATINS AFTER ACUTE CORONARY SYNDROMES

Enrolled over 4000 patients (mean age 58) who had been hospitalized for an acute coronary syndrome (ACS) within the preceding 10 days. ACS defined as acute myocardial infarction (with or without ECG evidence of ST-elevation), or high risk unstable angina.

Randomized to: 1) moderate-intensity treatment with 40 mg pravastatin (*Pravachol*), or 2) high-intensity treatment with 80 mg atorvastatin (*Lipitor*) daily.

Mean achieved LDL-cholesterol was 95 mg/dL in the pravastatin group and 62 in the atorvastatin group

Over 2 years, the more intensive regimen with atorvastatin resulted in a lower risk of death and major cardiovascular events as compared with the moderate pravastatin regimen. The NNT for 2 years to prevent one death, myocardial infarction, angina requiring rehospitalization, revascularization, or stroke = 53

"Although prior placebo-controlled studies have shown that a standard-dose statin is beneficial, we demonstrated that more intensive lipid-lowering significantly increases this clinical benefit."

Although both drugs were "generally well tolerated", there were significantly more liver-related side effects with high-dose atorvastatin. About 1/3 of all patients in both groups dropped out over the 2 years.

"Our results suggest that after an acute coronary syndrome, the target LDL-cholesterol level may be lower than that recommended in the current guidelines."

This was a secondary prevention trial in a very high risk group. Benefits would be considerably less if high-dose atorvastatin were used in primary prevention. Certainly, these results cannot be extrapolated to primary prevention.

The authors suggest that the high-dose regimen "significantly" increased clinical benefit. Primary care clinicians must ask—is this "clinical" benefit applicable to every day practice? Patients with an acute coronary syndrome and their doctors must decide if one chance in 53 over 2 years is worth while, Note that harms (liver disturbance) were statistically significant, and, I believe, as clinically significant as the reported benefits in the high-dose patients. Cost, adverse effects, and likelihood of discontinuation of treatment must be considered. Some patients, knowing they are at very high risk of death or recurrence, would be inclined to accept the high-dose.

The high drop-out rate because of an adverse event, or the patient's preference, or "other reasons" is disturbing. This occurred despite patients' knowledge that they were at high risk of recurrence and death. Drop-outs would likely be higher still in primary care practice.

Pravastatin has the advantage of not being significantly metabolized by the P450 system in the liver. Thus, concern about interactions between pravastatin and concomitantly administered drugs is much less than with atorvastatin, which is metabolized by the P450 system. RTJ

6-1 ASSOCIATION OF STATIN THERAPY WITH OUTCOMES OF ACUTE CORONARY SYNDROMES: The GRACE Study

Statin drugs may have effects in addition to their effect on lipids. These include modulation of inflammation, inhibition of platelet function and thrombosis, and enhancement of endothelial function. The ability of statins to *immediately* affect basic pathophysiologic mechanisms has increased interest in their potential role in acute coronary syndromes. (ACS)

This study examined the association between previous and early in-hospital statin therapy and outcomes of ACS.

Patients who presented with an ACS who were already taking statins were less likely to present with ST-segment elevation MI, experience a large infarct, and have important clinical complications, or die.

Much of the observed effect was lost if statin therapy was not continued during hospitalization. Such patients had death rates similar to patients who had never received statins. Withdrawal of statins reduces the protective effect of statin pretreatment.

In statin-naïve patients, early statin therapy was associated with an improvement in outcomes.

Should primary care clinicians act on these conclusions? Primary care clinicians often act on inconclusive evidence if the putative benefit/harm-cost ratio of the intervention is high. Although the outcomes of the study require confirmation and further experience, I believe the benefit/harm-cost ratio of immediate statin therapy (as of immediate aspirin therapy) for patients with ACS is potentially high. The benefit is potentially life-saving.

The harm and cost of short-term therapy is very low. I would give a high-dose statin immediately on presentation of a patient with presumed ACS.

Those on statins long-term should be continued on statins when admitted for ACS. Those not on statins should start them immediately. And, of course, continue after discharge.

A study "Lipid-Lowering Therapy And In-Hospital Mortality Following Major Non-Cardiac Surgery" (See Practical Pointers May 2004) also presents evidence of immediate protective effects of statins given within the first 2 days after major surgery. RTJ

ATKIN'S DIET (See DIET [1-12]; [5-1])

ALCOHOL

4-6 ALCOHOL INTAKE AND RISK OF INCIDENT GOUT IN MEN

Health Professionals Follow-up Study followed over 47 000 male subjects (mean age 55 at baseline) for 12 years. None had gout at baseline

Compared with men who did not drink alcohol, the relative risk (RR) of incident gout increased linearly as consumption rose from 1 drink daily (RR compared with none = 1.3) to 2.5 in those imbibing 5 or more drinks daily.

Beer consumption showed the strongest independent association with risk of gout. The RR per each 12 ounce serving per day = 1.49 (Beer is the only alcoholic beverage that contains a large amount of purine.) Consumption of spirits was also associated with increased risk. (RR per each drink daily = 1.15.) Wine consumption was *not*

associated. (RR = 1.04 for each 4-ounce serving daily.) The null association persisted regardless of the type of wine.

Risk of gout was greater in men with a body mass index (BMI) over 25 compared with a BMI under 25: In subjects with a BMI under 25, RR of gout was 2.5 in heavy drinkers. In subjects with BMI over 25, RR increased to 5.6..

"Prospective data indicate that alcohol intake is strongly associated with incidence of gout. The risk varies substantially with the type of alcoholic beverage. Beer confers the greatest risk, moderate wine drinking does not increase risk."

Both genetic and environmental factors play a part in the pathogenesis of gout. As with atherosclerotic disease, hypertension, obesity, and type II diabetes, gout can be considered a disease of "civilization"—part of the epidemic of overnutrition and sedentary lifestyles. Gout is associated with a high intake of meat and seafood, and low intake of dairy products.. Now this study reinforces the long-observed relation with alcohol.

As with obesity, gout is becoming more prevalent in developing countries as they become more "Westernized". . RTJ

ALENDRONATE (*Fosamax*) (See OSTEOPOROSIS [3-8])

ALTERNATIVE/COMPLEMENTARY MEDICINE

2-15 SEX, LIES, AND NIAGRA

All capsules of an "all natural" remedy for erectile dysfunction (*Actra-R*) contained sildenafil (*Viagra*), an average of about 55 mg per capsule.

Charlatanism remains alive. Nostrums fill the shelves of our pharmacies. Fraud pervades "alternative/complementary" medicines and the "all-natural herb" industry. Some products have been found toxic (eg, ephedra). Some are ineffective (eg, echinacea for upper respiratory infections in children). I remember one report of an "all natural" topical preparation for dermatitis which was found to contain hydrocortisone. RTJ

ALZHEIMER'S DISEASE

1-6 MEMANTINE TREATMENT IN PATIENTS WITH MODERATE TO SEVERE ALZHEIMER DISEASE ALREADY RECEIVING DONEPEZIL

In October 2003, the FDA approved memantine (*Namenda*) for treatment of moderate to severe AD. Memantine is a blocker of the receptor for aspartate. It is a new class of drug.

This study hypothesized that adding memantine (*Namenda*) to donepezil (*Aricept*) would result in clinical benefit and would be well tolerated.

Memantine resulted in significant statistical, but only slight clinical benefit when added to donepezil. It appeared safe.

Investigators, as in this report, often stress statistically significant improvement, not clinical improvement. This may be misleading. In my view, the outcome of this study is disappointing.. The investigators place a spin on

benefits by noting the statistically significant outcomes. This may appear to be an impressive result, but it is not clinically important. RTJ

6-11 LONG TERM DONEPEZIL (*Aricept*) TREATMENT IN 565 PATIENTS WITH ALZHEIMER'S DISEASE (AD 2000)

All three available cholinesterase inhibitors produce small improvements in cognitive and global assessments in selected patients mild-to-moderate AD over 3-12 months. Little is known about long-term effectiveness, or their usefulness in patients with severe AD. Nonetheless, the demand from clinicians and patients remains strong.

This study asked whether the cholinesterase inhibitor donepezil (*Aricept*) is cost effective and produces worthwhile clinical and social improvements.

Compared with placebo, donepezil group achieved a slightly higher score on the mini-mental-examination within the first 36 weeks (about 1 point above baseline on a 30-point scale). Thereafter, scores deteriorated back to baseline at 48 weeks and to minus 4 points at 112 weeks. The placebo group lost points continuously during the 112 weeks.

Comparatively, over 112 weeks, donepezil group (compared with placebo) maintained a slightly better score (a fraction of one point) despite declining in absolute terms.

Donepezil was associated with *no* improvement in activities-of-daily living scale *at any time* up to 2 years, although, compared with placebo, decline in ADL score was slightly slower.

No significant benefits were seen *vs* placebo in institutionalization, progression of disability, behavioral and psychological symptoms, psychopathology of carers, formal care costs, adverse events, or deaths.

No evidence that costs of caring for patients with Alzheimer's disease in the community are reduced by donepezil. Any effect of donepezil on informal caregiver time is likely to be small.

Benefits of the acetylcholinesterase inhibitor, donepezil, are "below minimally relevant thresholds". It is not cost effective "The disappointingly little overall benefit from donepezil cannot be taken lightly." Clinicians can validly question whether other uses of scarce resources allocated for dementia would provide better value than routine prescription of cholinesterase inhibitors.

I believe many patients are continuing to receive CIs far beyond the time of any hope of benefit.

COST: about $1600 per year quoted by drugstore.com. As is often the case, the 10 mg dose costs just a few dollars more per year than the 5 mg dose. A pill cutter may cut cost in half. There is no statistically significant difference in effects of 10 mg vs 5 mg. Adverse effects (eg, gastrointestinal) are greater with the 10 mg dose. RTJ

6-12 AD 2000: DONEPEZIL IN ALZHEIMER'S DISEASE

Patients seen in everyday practice differ from those selected for inclusion in drug-company-sponsored trials. Drug companies use highly refined selection criteria, often include specialized tests to aid diagnosis, restrict allowable comorbidity and concomitant medications as well as the extent of behavioral or functional impairment. They pay for all protocol-related care, including medications. "Typical selection criteria for industry sponsored trials would exclude over 90% of out-patients with mild-to-moderate Alzheimer's disease in California who would otherwise be eligible to receive treatment. The controversy about effectiveness, costs, and the clinical meaning of trial results has been fueled by the use of participants who do not represent typical patients."

In the trial, donepezil and placebo were both associated with a worsening over time. The mean differences on the MMSE and activities of daily living scale represent a delay in symptom-worsening of about 3 months.

This commentary presents a clinically important point. It emphasizes the gulf which may separate results of randomized controlled trials from benefits evident in primary care practice. There may be a large difference between results reported by a clinical trial for AD and clinical benefits for Mr. Jones, whose family brings him into your office because of memory loss. A practical office-based, "real world" trial is more meaningful and convincing. Beware of "spin". RTJ

AROMATASE INHIBITOR (See BREAST CANCER [3-9])

ASPIRIN

1-14 EFFICACY AND SAFETY OF LOW-DOSE ASPIRIN IN POLYCYTHEMIA VERA

The increase in the red cell mass in PV causes hyperviscosity of the blood, a major determinant of circulatory disturbance. PV is associated with an increase in thromboxane synthesis. This suggests that thromboxane-dependent platelet activation is a major cause of thrombosis.

Thrombotic complications are a major cause of illness and death in untreated patients.

Long-term, low-dose aspirin, used as primary prevention, safely prevents thrombotic complications in patients with PV. NNT to prevent myocardial infarction, stroke, major venous thrombosis, pulmonary embolism, or death from cardiovascular causes over 3 years = 21 to 34.

Major bleeding events associated with low-dose aspirin occurred in one in 26.

PV is the most common of the chronic myeloprolipherative disorders. Primary care clinicians will likely refer patients to a hematologist, but may be responsible for long-term follow-up. RTJ

1-15 DAILY ASPIRIN—ONLY HALF THE ANSWER

Thrombosis causes much of the illness and death in patients with polycythemia vera. No part of the vascular system is spared. Thrombosis develops in about 40% of patients, most often before or at the time of diagnosis. Rates of fatal thrombosis may be high.

Increased blood viscosity is a paramount cause of large-vessel arterial and venous thrombosis. Attempts to control erythrocytosis by phlebotomy often fail to diminish the high rate of thrombosis.

An apparently normal hematocrit may *not* be normal in patients with this disease.. A safe target is under 45% in men and under 42% in women. Viscosity of the blood rises dramatically at hematocrit levels above 45%.

This indicates treatment with both aspirin and adequate hematocrit control. RTJ

BLINDNESS

3-5 SMOKING AND BLINDNESS

Age-related macular degeneration **(MD)** is related to smoking.

Three cross-sectional studies of over 12 000 patients reported that current smoking leads to a 3- to 4-fold incidence of MD compared with non-smokers. Indeed, the relative risk of smoking associated with MD is higher than the relative risk with ischemic heart disease. A dose-response relationship has been established.

Observational studies show a protective effect of smoking cessation on development of MD.

I was unaware of this association. Informing patients may be a powerful incentive to quit. RTJ

BODE INDEX (See CHRONIC OBSTRUCTIVE PULMONRY DISEASE

BREAST CANCER

2-14 HABITS (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?)

In this 2-year randomized study, 12% of women in the HRT group experienced a new BC vs 4% in the no-HRT group. In the HRT group, 11 were local recurrences; 5 were contralateral BC; and 10 were distant metastases. In the no-HRT group 2; 1; and 5. (One in 8 women taking HRT developed recurrence of BC vs 1 in 25 in the no-HRT group.)

Women with a history of BC should not receive HRT. Those already receiving HRT should be advised to discontinue.

For women with history of BC, what can be advised for menopausal-symptom relief other than HRT? The North American Menopause Society suggests several non-hormonal therapies:

Antidepressants venlafaxine (Effexor), paroxetine (Paxil), and fluoxetine (Prozac; generic). Start at very low doses and gradually increase. Cessation requires gradual tapering off.

Gabapentin (Neurontin) may be considered in women older than 65

Clonidine is less effective than gabapentin. RTJ

2-18 ANTIBIOTIC USE IN RELATION TO THE RISK OF BREAST CANCER

This case-control study compared 2266 cases of primary invasive breast cancer **(BC)** with 7953 matched controls without BC in regard to their use of antibiotics. Antibiotic use was ascertained by computerized pharmacy records. Observation period ranged from 10 years to 23 years.

Increasing cumulative days of antibiotic use were associated with increased incident BC.

The investigators report the risk as odds ratios of breast cancer. By this measure, the chance of developing BC in high-dose uses of antibiotics is twice that of non-users.

Is this a clinically important point? Certainly, other risks are more important. To make clinical sense, readers must take the time and trouble of converting odds ratios into absolute risk. Few do. A*ccording to my unadjusted calculations, an extraordinarily high use of antibiotics use was associated with a 1% higher risk of developing BC. Patients using antibiotics for less than 500 days (the great majority) had an increased risk of 2 in 1000. Editors and investigators should plainly state absolute risks in their discussion. And editors should insist upon it. RTJ*)

3-9 A RANDOMIZED TRIAL OF EXEMESTANE (an aromatase inhibitor) AFTER TWO OR THREE YEARS OF TAMOXIFEN THERAPY IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER

Aromatase is the enzyme that catalyses the conversion of androgens to estrogens in females. Exemestane is a 3rd generation aromatase inhibitor. It inhibits aromatization almost completely.

Exemestane therapy, begun after 2 or 3 years of tamoxifen therapy, significantly reduced risk of metastatic recurrence and contralateral breast cancer as compared with continued tamoxifen. [NNT (3 years exemestane to benefit one patient) = 21]

This is consistent with the hypothesis that BC frequently becomes resistant to tamoxifen within 5 years.

I included this abstract because I believe therapy with aromatase inhibitors will continue to improve BC survival. Primary care clinicians should be aware of developments even though they may not be directly involved in this therapy. RTJ

4-13 DUCTAL CARCINOMA IN SITU OF THE BREAST: Review Article

Prevalence of DCIS has markedly increased since screening mammography has become routine (one case detected for every 1300 screening mammograms).

DCIS consists of the clonal proliferation of cells that appear malignant and that accumulate within the lumens of mammary ducts. There is no evidence of invasion beyond the epithelial basement membrane into the adjacent breast stroma. It is a precursor of invasive ductal carcinoma.

The crucial task of pathological assessment is to distinguish DCIS from invasive cancer. Classification remains a challenge due to differing pathologic criteria, interobserver variability, and the heterogeneous nature of tumor growth.

The natural history of *untreated* low-grade DCIS has been defined in long-term, follow-up studies of women who underwent diagnostic biopsy in the era before widespread screening mammography. After 10 years of follow-up, 14 to 60 percent of the women had received a diagnosis of invasive cancer in the affected breast. Such a risk is widely thought to justify the present treatment approaches.

Simple mastectomy is highly effective—curing at least 98% of lesion—and is a potential treatment option for all patients.

Women with DCIS in one breast are at risk for a second tumor (either invasive or in situ) in the contralateral breast—about 0.5% to 1% per year. This warrants follow-up mammography in the opposite breast.

Women with DCIS have considerable deficits in their knowledge of the disease. Their levels of psychological distress and fear of recurrence and death are similar to those among women with invasive breast cancer.

Because incidence of DCIS is related to hormone replacement therapy, and is benefited by tamoxifen, I would guess that aromatase-inhibitor therapy would be efficacious. Undoubtedly, studies will be forthcoming.

The generally favorable prognosis should be emphasized. Women with DCIS should be repeatedly reassured. This is an important responsibility for primary care clinicians. RTJ

BUPROPION (See SMOKING [2-10[ )

CANCER (See organ: BREAST CANCER, PROSTATE CANCER, CERVICAL CANCER, ETC.)

CAPSAICIN

4-7 SYSTEMATIC REVIEW OF TOPICAL CAPSAICIN FOR THE TREATMENT OF CHRONIC PAIN

Six randomized, double-blind, placebo controlled trials (656 patients) compared topically applied capsaicin (0.075%) with placebo in adults with neuropathic conditions. And 3 trials (368 patients) reported use of capsaicin (0.025%) in patients with musculoskeletal conditions.. Capsaicin was applied 3 times daily

Patients had moderate or severe chronic pain.

Primary outcome = number of patients with at least 50% reduction in pain.

At 8 weeks, for those with neuropathic pain the relative benefit of capsaicin *vs* placebo was 1.4. NNT = 6. (Ie, one of 6 patients would achieve a reduction in pain of 50%.) At 4 weeks, for those with musculoskeletal pain, the relative benefit of capsaicin *vs* placebo was 1.5. NNT = 8.

There was a substantial response to placebo—25% to 42%.

Topical capsaicin maybe useful as an adjunct or sole therapy for a small number of patients who are unresponsive to, or intolerant of, other treatments.

"Systematic Review of Topical Rubifacients Containing Salicylates for the Treatment of Acute and Chronic Pain", a companion article in this issue of BMJ (pp 995-98), reports efficacy for musculoskeletal pain was moderate to poor. Adverse effects were rare. There was, however, a lack of good clinical trials.

I believe, in some patients topical applications may be helpful. No way to find out without trying. First inform the patient about possible benefits and harms. Over-the-counter availability is a plus. The placebo effect is an added benefit. RTJ

CARDIOVASCULAR DISEASE

1-5 OMEGA 3 FATTY ACIDS AND CARDIOVASCULAR DISEASE—Fishing For A Natural Treatment

Omega 3 fatty acids from fish and fish oils can protect against coronary heart disease**.** In this era of polypharmacy, many persons believe that simple dietary interventions or nutritional supplements may be a more natural and acceptable method of providing benefits.

The American Heart Association recommends:

Patients without documented CHD should eat a variety of fish (preferably oily) at least twice weekly. Diet should also include vegetable oils.

Patients with documented CHD should consume 1 g of O3FA and O6FA daily.

Physicians may prescribe 2-4 g/d of O3FA and O6FA daily, provided as capsules, for patients with hypertriglyceridemia.

3-3 EVALUATION OF CARDIOVASCULAR EVENT RATES WITH HORMONE THERAPY IN HEALTHY, EARLY POSTMENOPAUSAL WOMEN

Two large randomized trials have evaluated adverse cardiovascular effects of hormone replacement therapy **(HRT)** in postmenopausal women. The average age of the subjects in these two studies was 63 years, well past onset of the menopause. Overall, the studies concluded that HRT results in net *harms*. The greatest risk of adverse effects occurred in the first year.

This was contrary to older *observational* studies which reported considerable benefit in reducing cardiovascular morbidity and mortality. It led to reevaluation of the use of HRT.

It is important to determine if adverse events occur in *younger* women. Most women with menopausal symptoms take HRT at an earlier age, relatively soon after the menopause. This article reviewed 2 other large clinical trials of younger women (mean age 54). It asks—What is the risk of adverse events at this age?

Conclusion: In young, healthy postmenopausal women, the adverse effects of HRT on the cardiovascular system *in the first year* of use were no greater than the expected harms in women not taking HRT.

What should primary care clinicians advise their patients about HRT?

A. Risks of adverse events during the first few perimenopausal years are low in younger, healthier women taking combined HRT, and even lower in those taking estrogen alone.

B. These risks can be further reduced by therapy aimed at reducing cardiovascular risk: smoking cessation, low-dose aspirin; lipid, weight, and BP control; and using the lowest effective dose of estrogen and progesterone. Indeed, I believe it likely that women who, at the age of 50 adopt these protective measures and take HRT will be less likely to experience cerebrovascular events than women who do not take HRT and do not adopt these protective measures.

I believe that recent reports overemphasized the adverse effects of HRT, and that many women who would benefit by symptom relief are being denied treatment. RTJ

3-7 EFFECTS OF CHOLESTEROL-LOWERING WITH SIMVASTATIN ON STROKE AND OTHER MAJOR VASCULAR EVENTS IN 20 536 PEOPLE WITH CEREBROVASCULAR DISEASE OR OTHER HIGH-RISK CONDITIONS

In a large group of patients at *high risk* of vascular disese, statin therapy rapidly reduced risk of ischemic stroke with no apparent increase in risk of hemorrhagic stroke. Benefits occurred even among those who did *not* have high cholesterol concentrations. Statin therapy also reduced the risk of major vascular events among people who had previously experienced a stroke or other cerebrovascular event.

A reduction in LDL-cholesterol from about 154 mg/dL to about 115 mg/dL reduced risk of stroke and other major vascular events by about one-quarter. Lowering it from about 115 mg/dL to about 77 mg/dL also reduced risk by about one quarter. "Current guidelines could, therefore, lead to substantial undertreatment of high-risk patients who present below, or close to, particular targets for LDL reduction."

"These results have important implications for revising treatment guidelines which do not currently take into account cerebrovascular disease risk reduction when considering the initiation of statin therapy."

"Statin therapy should now be considered routinely for all patients at high risk of stroke, irrespective of their initial cholesterol concentrations. "

This study confirms the widely-held belief that statin therapy reduces risk of stroke as well as coronary disease. It also strengthens the observation that lowering LDL-cholesterol below levels usually considered "satisfactory" will further reduce risk of atherosclerotic disease.

The risk of events associated with cardiovascular risk factors increases linearly. There are no artificial cut-points dividing "satisfactory" levels vs "unsatisfactory" levels. RTJ

3-11 URIC ACID AND DIET—INSIGHTS INTO THE EPIDEMIC OF CARDIOVASCULAR DISEASE.

The effects of diet are relevant to the epidemiology of hyperuricemia and gout. Gout and obesity have become epidemic among native people, such as the Maori of New Zealand, since the introduction of Western culture and diets. The immigration of non-Western peoples to Western countries—for example that of Filipino and Japanese to North America—has been associated with increases in the incidence of gout in parallel with the shift in diet to higher intakes of meat and saturated fats. Gout was rare among blacks in the USA until the 1940s when changes in diet led to the rapid development of obesity, diabetes, and hypertension. Now, gout is more common among blacks than in whites. It is also becoming more common in urban communities of Africa in association with an increasing frequency of hypertension and cardiovascular disease.

Gout is no longer a disease of the wealthy; rather its appearance reflects a worldwide increase in fatty meats and a decrease in intake of dairy products associated with Westernization.

Gout should be considered a part of the current epidemic of obesity, hypertension, and diabetes.

The preceding articles convincingly reinforce the view that lifestyle is indeed important in the pathogenesis of gout. RTJ

4-4 EFFECTS OF CONJUGATED EQUINE ESTROGEN IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY

This study reports the conjugated equine estrogen (**CEE**)-alone phase of the Women's Health Initiative trial which was continued for 7 years. Mean baseline age = 63.

The burden of incident disease events was equivalent in the CEE-alone and placebo groups. There was no significant difference in risks other than a slight increase in incidence of stroke. The absolute *excess* was 12 additional strokes per 10 000 person-years. And an absolute *reduction* of hip fracture of 6 per 10 000 person-years.

The estimated excess risk for all monitored events (CHD, stroke, pulmonary embolism, colorectal cancer, hip fracture, and deaths from other causes). was a non-significant 2 events per 10 000 person-years.

This differs importantly from the WHI trial of combined estrogen/progestin in which the risk of CHD was significantly elevated.

Women and their health-care professionals now have usable risk estimates for the benefit/harm ratio of CEE-alone in treatment of menopausal symptoms. "Women can be reassured that incidence of CHD and breast cancer is not increased at least for 6.8 years". But, the data reinforce that there is no overall benefit of CEE for chronic disease prevention.

Nevertheless, CEE-alone *cannot* be recommended for disease *prevention*. CEE should be used only for menopausal symptoms at the smallest effective dose for the shortest possible time.

The study reported a lower risk of breast caner in the CEE-alone group vs the placebo group This is contrary to other observational studies in which risk of BC is increased. I believe clinicians should remain wary and should consider that HRT in any form increases risk of breast cancer.

I believe risks of CEE-alone as well as combined estrogen/progestin have been overemphasized, and that many women are being unnecessarily denied relief from their menopausal symptoms. RTJ

5-4 CARDIORESPIRATORY FITNESS ATTENUATES THE EFFECTS OF THE METABOLIC SYNDROME ON ALL-CAUSE AND CARDIOVASCULAR DISEASE MORTALITY IN MEN

The estimated prevalence of the "metabolic" ("insulin-resistance") syndrome is over 20% among adults in the USA. Middle-aged men with the metabolic syndrome have significantly elevated risk of all-cause and cardiovascular disease **(CVD)** mortality.

It is defined by the *National Cholesterol Education Program* among persons with 3 or more of 5 risk factors:

1. BP at or over 130/85
2. Central obesity—waist circumference > 40 inches in men
3. High triglyceride levels—>150 mg/dL
4. Low HDL-cholesterol— < 40 mg/dL
5. High fasting plasma glucose—at or above 110 mg/dL

After adjustment for age, smoking status, alcohol consumption, and parental CVD, the relative risks **(RR)** of all-cause mortality and CVD mortality were higher in men with the metabolic syndrome who were unfit compared with the fit men. (RR = 2.0 and 2.3)

There was a graded increase in deaths according to fitness categories. Men in the middle tertile of fitness had 2.0 times the CVD death rate as those in the upper tertile of fitness Those in the lower tertile of fitness had 3.5 times the risk.

The estimated population-attributable risk for CVD deaths in males with the metabolic syndrome is 11%. This suggests that about 1 in 10 CVD deaths are directly attributable to the metabolic syndrome. The public health burden is considerable.

Low cardio-respiratory fitness was an important risk factor for premature mortality in men with the metabolic syndrome. Being fit provides a strong protective effect.

As expected, physical fitness attenuated risk of death in men without the metabolic syndrome as well as those with. I omitted this data.

The study is a reminder of the definition of the metabolic syndrome and its importance as a health risk. I have to periodically jog my memory about the definition lest I forget the 5 requirements. Not all 5 risk factors carry equal weight.

Fitness also attenuates risks of adverse outcomes in smokers; and in patients with obesity, coronary disease, hypertension, and diabetes. It is a basic health measure about which we continue to advise patients, but which they do not often follow. RTJ

CAROTID ENDARTERECTOMY (See STROKE [5-11])

CHOLESTEROL (See STATIN DRUGS)

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

3-13 THE BODY-MASS INDEX, AIRFLOW OBSTRUCTION, DYSPNEA, AND EXERCISE CAPACITY INDEX IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: the BODE index

A simple multidimensional grading system predicted risk of death better than the FEV1 alone.

B Body mass index (Low BMI— weight in kg/height in meters ^{2}; cutpoint under 21)

O FEV1 as a percentage of predicted (Obstruction)

D Score on a dyspnea scale (Dyspnea scale 0 to 4)

E Distance walked in 6 minutes. (Exercise)

This simple grading system is a better predictor of death from any cause and death from respiratory causes than the FEV1 alone. Mortality increased progressively with quartiles of the score. The highest quartile (score = 7 to 10) was associated with a mortality of 80% over 4 years.

Despite its importance as a public health problem, COPD is vastly underappreciated. It is underdiagnosed, and when diagnosed, is commonly undertreated. Although it is not a single entity, all patients share a common physiological abnormality—limitation of expiratory airflow. It is a complex disorder, affecting far more than a single organ system. Patients with a similar FEV1 can have obvious and marked differences in body habitus, exercise performance, and oxygenation. Additional information complements the assessment by spirometry alone.

I believe primary care clinicians will rarely calculate this index. They will rely for prognosis on their general assessment of the patient. A patient who is wasted down from his normal weight to a BMI under 21 (probably, in old parlance, a "pink puffer"), who can do little without dyspnea, and who cannot walk even slowly for 6 minutes without stopping, has a very dim prognosis indeed. Assessment of the general condition may lead primary care clinicians to advise oxygen at an earlier stage, to treat more vigorously with inhalation therapy, and to use antibiotics earlier and more frequently. RTJ

CLONING

2-16 FACTS VERSUS IDEOLOGY IN THE CLONING DEBATE

HUMAN CELLS FROM CLONED EMBRYOS IN RESEARCH AND THERAPY.

Korean investigators recently reported derivation of stem cells from a cloned human embryo. This may lead to development of ability to study genetic diseases in entirely new ways. "Experience will be needed to learn how such cells should best be used." The investigators strongly condemned efforts to clone a human.

COLONOSCOPY

4-12 COMPUTED TOMOGRAPHIC COLONOSCOPY (VIRTUAL COLONOSCOPY)

This study assessed the accuracy of CTC *vs* conventional colonoscopy in a large number of participants.

45% to 61% of the lesions were missed by CTC. (False negative tests.) 10% of the CTC patients were diagnosed falsely as having a 6 mm or larger lesion. (False positive tests)

Accuracy to CTC varied considerably between centers.

Patients expressed no clear preference for either technique.

CTC is not yet ready for widespread clinical application.

I abstracted this article mainly because enthusiasts in local communities are investing in costly scanners and advertising CTC to the general public as well as to professionals.

A study abstracted in Practical Pointers December 2003 (12-10) reported the experience of the Uniformed Services University of Health Sciences. This group has had considerable experience with CTC, and uses sophisticated equipment. They claimed that CTC detects polyps of 6 mm or larger as accurately as conventional colonoscopy. If a polyp of this size is detected, conventional colonoscopy is required to remove it.

A critical issue remains. Should all polyps detected be referred for conventional colonoscopy? If not, what is the cut-point size? How should smaller polyps be followed? Patients with smaller polyps (not removed) would be required to undergo screening at shorter intervals than patients whose polyps are removed.

As noted, the bowel-cleansing preparation is the same in both procedures. In observational studies, arrangements for immediate conventional colonoscopy can be made beforehand. In usual practice settings, many patients would require a second bowel cleansing.

I do not believe community-based primary care clinicians should advocate CTC at this time. RTJ

CONGESTIVE HEART FAILURE (See HEART FAILURE)

CONTRACEPTION

6-9 WAITING FOR PLAN B—THE FDA AND NONPRESCRIPTION ON EMERGENCY CONTRACEPTION

The proposal to switch to levonorgestrel emergency contraception (EC; *Plan B*) to over-the-counter status is in limbo. In May, the FDA rejected the application for non-prescription sales. The acting director, wrote that the company had "not provided adequate data to support a conclusion that *Plan B* can be used safely by young adolescent women for emergency contraception without the professional supervision of a practitioner licensed by law to administer the drug". In rejecting the application, the FDA also rejected the advice of its medical review-staff. (A vote of 23 to 4 in favor of nonprescription status.)

I would be willing to wager that this decision will be reversed. RTJ

CORONARY ARTERY CALCIUM SCORE (See CORONARY HEART DISEASE [1-11]; [6-2]))

CORONARY ATHEROSCLEROSIS (See CORONARY HEART DISEASE)

CORONARY HEART DISEASE

1-5 OMEGA 3 FATTY ACIDS AND CARDIOVASCULAR DISEASE—Fishing For A Natural Treatment

Omega 3 fatty acids **(O3FA)** from fish and fish oils can protect against coronary heart disease **(CHD).** In this era of polypharmacy, many persons believe that simple dietary interventions or nutritional supplements may be a more natural and acceptable method of providing benefits.

The American Heart Association recommends:

Patients without documented CHD should eat a variety of fish (preferably oily) at least twice weekly. Diet should also include vegetable oils.

Patients with documented CHD should consume 1 g of O3FA and O6FA daily. Physicians may prescribe 2-4 g/d of O3FA and O6FA daily, provided as capsules, for patients with hypertriglyceridemia.

1-11 CORONARY ARTERY CALCIUM SCORE COMBINED WITH FRAMINGHAM SCORE FOR RISK PREDICTION IN ASYMPTOMATIC INDIVIDUALS.

In an intermediate-to-high-risk cohort of patients with coronary risk factors, the risk of a non-fatal MI or CHD death in those with a FRS risk score over 20% was 14 times that of those with a FRS of less than 10%.

The CACS significantly modified the risk prediction in all categories of the FRS score of at least 10%, but not when the FRS was less than 10%. When the CRCS was more than 300, the increment in predicted risk was equal to a 3% to 9% increase in the 10-year event risk compared with FRS alone for every category of FRS estimate. The risk of a non-fatal MI or CHD death in those with a CACS over 300 was 4 times that of participants with a CACS of zero.

Would adding CACS determination modify my approach to the patient? I believe it would have no effect. My advice about risk-factor control would remain the same as that predicted by the FRS alone.

Primary care clinicians have a broad base of risk factors to estimate prognosis. We do not yet adequately apply them to individual patients. I do not believe adding another factor will bring any clinical advantage. RTJ

3-6 EFFECT OF INTENSIVE COMPARED WITH MODERATE LIPID-LOWERING THERAPY ON PROGRESSION OF CORONARY ATHEROSCLEROSIS. (REVERSAL)

Is there any benefit in lowering LDL-cholesterol below the recommended 100 mg/dL?

This study, in patients with established coronary atherosclerosis, compared the effect of *moderate* lipid-lowering by 40 mg pravastatin (*Pravachol*) with *intensive* lowering by 80 mg atorvastatin (*Lipitor*). Final mean LDL-c was 110 in the *Pravachol* group and 79 in the *Lipitor* group.

The main outcome (progression of coronary atherosclerosis as determined by intracoronary ultrasound) favored atorvastatin. Over 18 months, the atherosclerotic burden in the *Pravachol* group increased by +2.7% compared with – 0.4% in the atorvastatin group.

"These findings have considerable implications for treatment guidelines for patients with dyslipidemia and established CAD."

Note this was a study of lipid-lowering and atherosclerotic progression in patients with established CHD (a high risk group). It did not report any clinical benefits. The extent of coronary atherosclerosis is not the most important determinant of occurrence of acute coronary syndromes, plaque instability is.

The larger problem of primary prevention is unanswered.

The benefit/harm-cost ratio of intensive statin therapy is not known.

We are becoming a nation of statin takers. Should the recommended dose be the highest demonstrated to produce surrogate end-point benefits? Should primary care clinicians now recommend 80 mg of atorvastatin for all? I believe not. The excess cost would be considerable. And, despite the report that the drug "was well

tolerated", there will be serious adverse effects. Indeed, higher doses of all statins are related to higher risk of adverse effects.

Note that LDL-c reached a level below 100 mg/dL in 65% of the group receiving 40 mg Pravachol. I believe it reasonable to start with a moderate dose and gradually increase if needed.

6-2 THE SEARCH FOR THE "HOLY GRAIL" OF CLINICALLY SIGNIFICANT CORONARY ATHEROSCLEROSIS.

In some individuals, coronary atherosclerosis **(CA)** is stable for years, and in others it is very unstable, with rapidly progressive lesions that result in sudden death or an acute coronary syndrome. The diagnostic "Holy Grail" of coronary atherosclerosis is *not* to be able to identify coronary atherosclerosis (which almost all Americans have eventually) but to identify individuals with *unstable* coronary atherosclerotic lesions.

The editorialist describes the evolution of our understanding the pathophysiology of CA—from the concept of a gradual process that over decades narrows the arteries, to silent CA diagnosed by treadmill exercise testing, to coronary angiography, and finally to efforts to detect unstable plaques.

More myocardial infarctions occur in the larger sub-population with negative results on a treadmill test than in those with positive results. More myocardial infarctions are caused by hemodynamically insignificant lesions than from high grade stenosis.

This editorial was written in response to a meta-analysis in this issue of Archives (pp 1285-92) which concluded that the coronary artery calcium score detected by electron-beam computed tomography is an independent predictor of coronary events.

The point of the editorial was to state that fast computed tomography as a screening tool is not ready for prime time. While scanning may reveal calcification, individuals with unstable coronary disease are not always identified. A patient with potentially unstable coronary atherosclerotic lesions may have mildly calcified or non-calcified arteries. Patients with stable and unstable coronary atherosclerosis may have similar calcium scores.

Prevention of an essentially universal disease must be universal. Must we wait for screening tests to detect "higher risk", and only then encourage patients to change his or her lifestyles?

6-4 ABSENCE OF AN EFFECT OF LIPOSUCTION ON INSULIN ACTION AND RISK FACTORS FOR CORONARY HEART DISEASE.

Abdominal obesity (increased abdominal subcutaneous fat, and increased visceral fat) is associated with insulin resistance and other risk factors for coronary heart disease **(CHD).**

This study asked: Which of these fat deposits is associated with insulin resistance and increased risk of CHD?

Liposuction in 15 grossly obese women reduced volume of subcutaneous abdominal fat by 44%. Weight loss = 10 kg; total body fat decreased by 18%.

Liposuction did not significantly alter insulin sensitivity (assessed by stimulation of glucose uptake in muscle); did not suppress glucose production by the liver; and did not suppress lipolysis of adipose tissue.

Levels of C-reactive protein and other indicators of inflammation did not change.

Other risk factors for CHD were unchanged (BP, plasma glucose, insulin, and lipid concentrations).

Large-volume reduction in subcutaneous abdominal fat mass did not have any beneficial metabolic effects

despite a considerable decrease in body weight, waist circumference, and plasma leptin concentrations.

This provides insight into the mechanism by which conventional weight loss improves insulin sensitivity. Induction of a negative energy balance, not simply a decrease in the mass of fat tissue, is critical for achieving the metabolic benefits of weight loss. Even small amounts of weight loss induced by a negative energy balance affect many variables pertaining to body-fat composition and lipid metabolism—variables that contribute to metabolic abnormalities associated with obesity. Conventional weight loss decreases visceral fat mass, intrahepatic fat, fat-cell size, and the rate of release of fatty acids from intra-abdominal adipose tissue. Liposuction does not.

Fat loss by conventional obesity treatment decreases plasma concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor. It improves insulin sensitivity and inhibits vascular inflammation.

I abstracted this article mainly to point out the risks associated with intra-abdominal fat accumulation. Visceral fat drains directly into the portal circulation and into the liver; subcutaneous fat drains into the general circulation. There is a vast metabolic difference. RTJ

CULTURE OF CONSUMPTION

1-17 SHOPPING 'TIL WE DROP

This article is based on a collection of essays edited by Allen Kanner and Tim Kasser--*Psychology and Consumer Culture: the Struggle for a Good Life in a Materialistic World.*

"A culture of consumption, which exalts the acquisition of material goods over almost all other values, is causing severe psychological harm" "People who orient their lives in pursuit of the goals that consumer society tells us to pursue are less happy."

People who are materialistic report less satisfaction with life, less feeling of vitality, and lower energy compared with those who prize "intrinsic" values (personal development, family relationships, and community involvement). They report more problems with depression, anxiety, and alcohol and tobacco use.

Conversely, people who place a higher value on self-knowledge, family, and friendship, are happier and have higher quality relationships, and a greater sense of freedom.

Since the 1950s, as our economy has grown, happiness has not changed at all. And depression and anxiety have gone up. More wealth is not going to make us happier. It's about improving other aspects of our world.

I asked myself—Why did I abstract this article? What has it to do with primary care medicine? I am not sure of the answer. Perhaps it may provide some guidance to physicians and their families. It may enable some primary care clinicians to provide guidance to troubled patients. RTJ

DEATH AND DYING

3-1 ACTUAL CAUSES OF DEATH IN THE UNITED STATES, 2000

This article defines the "actual" causes of death as underlying-modifiable-behavioral risk factors which predispose to the "disease" which is labeled as the cause of death.

About half of all deaths could be attributed to a limited number of largely preventable behaviors: tobacco, poor diet and physical inactivity, alcohol, firearms, sexual behavior, and illicit drug use.

Interventions to prevent and increase cessation of smoking, improve diet, and increase physical activity must become a much higher priority in the public health and health care systems.

The most striking finding is the substantial increase (to about 400 000) in the number of estimated deaths attributable to poor diet and physical inactivity. The gap between deaths due to poor diet and inactivity and those due to smoking has narrowed substantially. "It is clear that if the increasing trend of overweight is not reversed over the next few years, poor diet will likely overtake tobacco as the leading cause of mortality."

In addition to premature death, years of lost life, diminished productivity, and decreased quality of life are strongly associated with the actual causes.

One important cause of death not directly related to obesity is the deficiency of calcium and vitamin D in the American diet. This leads eventually to death and disability as a complication of hip and other fractures.

Primary care clinicians bear a responsibility and opportunity to: 1) follow a healthy lifestyle themselves as an example to patients, and 2) to constantly encourage patients to do likewise. RTJ

3-2 THE IMMEDIATE VS THE IMPORTANT

"One of the most difficult challenges is to ensure that the urgent does not crowd out the important. That challenge is especially difficult because urgent matters can be so riveting."

Every death has a definable history that usually can be traced back to decades and sometimes even generations. Reporting of deaths, diseases and disabilities in traditional diagnostic categories tend to obscure the importance of factors that often play determinant antecedent roles in the occurrence of reported conditions. When it comes to ranking health problems and committing resources, attention seems more naturally drawn to the conditions most proximate to serious illness or death.

5-9 DYING AND DECISION MAKING—Evolution Of End-Of-Life Options

The editorialist reviews decision-making options at the end of life:

Option	Legal Status	Ethical Consensus	Decision maker
1. Proportionately intensive symptom management	Legal	Consensus	Patient or surrogate.
2. Stopping (or not starting) potentially life-saving therapy	Legal	Consensus	Patient or surrogate
3. Sedation to unconsciousness to relieve intractable symptoms	Legal	Uncertain	Patient or surrogate
4. Voluntarily stopping eating and drinking	Legal	Uncertain	Patient only
5. Physician-assisted suicide	Illegal (except in Oregon)	Uncertain	Patient only

The first question to ask—Is the patient mentally competent to make decisions about care? If so, this simplifies the problem. If not, decisions fall on surrogates and become much more difficult. RTJ

DEEP VENOUS THROMBOSIS (See VENOUS THROMBOEMBOLISM [6-10])

DIABETES

4-2 PHARMACOLOGIC LIPID-LOWERING THERAPY IN TYPE 2 DIABETES

Most adverse outcomes from diabetes are due to vascular complications, either micro-vascular or macro-vascular. Macro-vascular complications are more common and severe. Up to 80% of patients with type 2 diabetes will develop or die of macrovascular disease. Associated costs are 10 times greater than for microvascular complications.

The foremost goal of therapy in type 2 diabetes should be prevention of cardiovascular disease through optimization of risk factors. This includes aggressive treatment of hypertension, lipid-controlling therapy, smoking cessation, and use of daily aspirin.

Current evidence suggests that lipid control leads to about a 25% reduction in major cardiovascular events.

For primary prevention (statins vs no statin in patients without established cardiovascular disease) the NNT over 4 years to prevent one cardiovascular event = 35; for secondary prevention the NNT = 14 to prevent one event over 5 years.

"Given the absolute risk reductions observed, treatment will probably be cost-effective under most circumstances." This simplifies and reduces the cost of treatment, and would be similar, for example, to simply prescribing a daily aspirin for a patient with diabetes."

Statins for all patients with diabetes? This article comes close to this recommendation. RTJ

This study presents a simplifying common- sense clinical approach. for primary care. We need more guidelines like this. RTJ

5-12 INHALED INSULIN

Insulin can be effective given by inhalation. Two versions, a powder and an aerosol, may be nearing launch.

The bioavailability is 10-15%. The dose equivalent is about three times that of injected insulin. Advantages of inhaled insulin relate to patient preferences. It may improve compliance and result in more patients achieving glycemic control.

6-4 ABSENCE OF AN EFFECT OF LIPOSUCTION ON INSULIN ACTION AND RISK FACTORS FOR CORONARY HEART DISEASE. (And Diabetes and Metabolic syndrome)

Abdominal obesity (increased abdominal subcutaneous fat and increased visceral fat) is associated with insulin resistance and other risk factors for coronary heart disease **(CHD).**

This study asked: Which of these fat deposits is associated with insulin resistance and increased risk of CHD?

Liposuction in 15 grossly obese women reduced volume of subcutaneous abdominal fat by 44%. Weight loss = 10 kg; total body fat decreased by 18%.

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Other risk factors for CHD were unchanged (BP, plasma glucose, insulin, and lipid concentrations).

Large-volume reduction in subcutaneous abdominal fat mass did not have any beneficial metabolic effects despite a considerable decrease in body weight, waist circumference, and plasma leptin concentrations.

This provides insight into the mechanism by which conventional weight loss improves insulin sensitivity.

Induction of a negative energy balance, not simply a decrease in the mass of fat tissue, is critical for achieving the metabolic benefits of weight loss. Even small amounts of weight loss induced by a negative energy balance affect many variables pertaining to body-fat composition and lipid metabolism—variables that contribute to metabolic abnormalities associated with obesity. Conventional weight loss decreases visceral fat mass, intrahepatic fat, fat-cell size, and the rate of release of fatty acids from intra-abdominal adipose tissue. Liposuction does not.

Fat loss by conventional obesity treatment decreases plasma concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor. It improves insulin sensitivity and inhibits vascular inflammation.

I abstracted this article mainly to point out the risks associated with intra-abdominal fat accumulation. Visceral fat drains directly into the portal circulation and into the liver; subcutaneous fat drains into the general circulation. There is a vast metabolic difference. RTJ

6-5 THERMODYNAMICS, LIPOSUCTION, AND METABOLISM

Hyperglycemia improves *rapidly* during caloric restriction. It outpaces the rate of weight loss. About half of the improvements in glycemic control are achieved during the first week of a negative energy balance, although the actual fat loss is typically quite small. Substantial proportions of the early benefits of weight loss on insulin resistance and hyperglycemia in type 2 diabetes may be attributed to a negative energy balance.

Similar observations have been made concerning hypertension. Much of the decrease in BP occurs fairly rapidly in response to a negative energy balance. There is, however, a return toward hypertensive levels once weight has reached a plateau.

Visceral adiposity is strongly associated with insulin resistance. In animals, surgical resection of visceral fat tissue yields marked and nearly immediate reduction in insulin resistance. The removal of an equivalent amount of subcutaneous fat has little effect. The relation may be related, at least in part, to the release of fatty acids into the portal circulation.

Adipose tissue has endocrine functions—synthesizing leptin, adiponectin, and cytokines such as tumor necrosis factor, interleukin-6, and C-reactive protein.

During World War II type 2 diabetes practically disappeared in the Netherlands. This was related to the near starvation conditions produced by the invasion by Germany. RTJ

DIASTOLIC HEART FAILUE (See HEART FAILURE [5-2]; [5-3])

DIET

1-12 EFFECTS OF AN AD LIBITUM LOW-FAT, HIGH-CARBOHYDRATE DIET ON BODY WEIGHT, BODY COMPOSITION, AND FAT DISTRIBUTION IN OLDER MEN AND WOMEN.

This article describes what might be considered the obverse of the Atkins (high fat, low carbohydrate) diet.

The high carbohydrate-low fat diet consisted of 18% fat; 19% protein; and 63% carbohydrate.

Subjects on the HCLF diet consumed about 600 K/cal daily less than those in the liberal control diet.

"Low-fat, high-carbohydrate diets may reduce body weight via reduced food intake, since complex carbohydrate-rich foods are more satiating and less energy dense than higher-fat foods."

Food choices in the HCLF diet were limited—no sweets and few snacks allowed.

I doubt many free-living overweight persons would adhere to the diet for very long.

I consider this an interesting, but not a clinically significant study. It was performed under strict observation. Food was provided by a metabolic kitchen. It lasted only 12 weeks. There were few subjects.

Weight-loss diets have become a multimillion dollar industry. There are many types of diet and approaches to dieting. Gullible overweight persons in the USA seek a quick fix. There is none. Most individuals gradually gain back any weight lost, regardless of the diet. A calorie is a calorie, is a calorie, is a calorie. RTJ

3-10 PURINE-RICH FOODS, DAIRY AND PROTEIN INTAKE, AND RISK OF GOUT IN MEN.

This study prospectively investigated the association between dietary factors and *new* cases of gout.

Higher intakes of meats and seafoods were associated with *increased* risk of gout. Higher consumption of low-fat dairy products was associated with *decreased* risk. Those in the highest quintile of meat intake (beef, pork, and lamb as main dishes), compared with the lowest quintile, had an elevated risk of developing gout (relative risk = 1.4). Each additional daily serving of meat was associated with a 21% increase in risk

Corresponding RR associated with seafood was 1.5. Each additional weekly serving was associated with a 7% increase in risk.

Higher intake of total protein and higher intake of purine-rich vegetables were *not* associated with increased risk..

The investigators speculate that the risk associated with increased meat and seafood may be greater in men who already have gout because they have impaired renal clearance of uric acid and the absorption of dietary purines causes a steeper increase in blood uric acid levels than in persons with normal uric acid concentrations. (Ie, diet is likely to be a secondary prevention measure.)

This was essentially a primary prevention study. It provides no information on risk of exacerbations due to dietary factors in men with established gout. The authors, however, speculate that increased intake of meat and seafood may increase risk of recurrence of acute gouty arthritis, and low-fat dairy products may decrease risk. I believe it prudent for primary care clinicians to advise these dietary limitations in patients with established gout. RTJ

3-11 URIC ACID AND DIET—INSIGHTS INTO THE EPIDEMIC OF CARDIOVASCULAR DISEASE.

The effects of diet are relevant to the epidemiology of hyperuricemia and gout. Gout and obesity have become epidemic among native people, such as the Maori of New Zealand, since the introduction of Western culture and diets. The immigration of non-Western peoples to Western countries—for example that of Filipino and Japanese to North America—has been associated with increases in the incidence of gout in parallel with the shift in diet to higher intakes of meat and saturated fats. Gout was rare among blacks in the USA until the 1940s when changes in diet led to the rapid development of obesity, diabetes, and hypertension. Now, gout is more common among blacks than in whites. It is also becoming more common in urban communities of Africa in association with an increasing frequency of hypertension and cardiovascular disease.

Gout is thus no longer a disease of the wealthy; rather its appearance reflects a worldwide increase in fatty meats and a decrease in intake of dairy products associated with Westernization.

Gout should be considered a part of the current epidemic of obesity, hypertension, and diabetes.

The preceding articles convincingly reinforce the view that lifestyle is indeed important in the pathogenesis of gout. RTJ

5-1 A LOW-CARBOHYDRATE, KETOGENIC DIET VERSUS A LOW-FAT DIET TO TREAT OBESITY AND HYPERLIPIDEMIA: The Atkin's Diet

Recently, the low-carbohydrate ("low-carb"; **[LC];** Atkin's) diet has gained recognition despite modest supportive scientific evidence of efficacy. A popular version of this diet recommends extreme restriction of carbohydrate intake to less than 20 grams daily. This level can induce ketosis and weight loss.

This randomized trial compared the effects of the LC, ketogenic diet *vs* a low-fat, low-cholesterol reduced-calorie diet.

Over 24 weeks, otherwise healthy obese, hyperlipemic persons who followed a LC diet lost more body weight and fat than those on a low-fat diet. Triglyceride levels decreased; HDL-cholesterol levels increased. The LDL-c increased in some subjects. "Because the low-carbohydrate diet may adversely affect the LDL cholesterol level, it is prudent to monitor the serum lipid profiles. . . ."

The drop-out rate in persons on the LC diet was lower. This is important because the value of any diet depends on the degree to which patients adhere to it over time.

Weight loss in both groups resulted from reduced energy intake. The method of reducing energy intake differed greatly. The low fat diet group received counseling to restrict intake of fat, cholesterol, and energy. The LC diet group received counseling to restrict intake of only carbohydrates, not energy. "The voluntary reduction in energy intake among recipients of the LC diet merits future research."

Further observation is needed to determine the long-term (beyond 6 months) effects of the LC diet. Weight loss may be difficult to maintain.

No matter what the diet, weight loss will vary considerably between individuals. An editorialist suggests that we can encourage overweight patients to experiment with various methods for weight control, including the LC diet, as long as they emphasize healthy sources of fat and protein and incorporate regular physical activity.

"We can no longer dismiss the very-low-carbohydrate diets. "

The determining factor in diet therapy is its effect on long-term (years) weight control. We wait results of these studies, Thus far, it seems doubtful that many persons on the LC diet will maintain their weight loss over time.

I believe studies of the LC diet will be forthcoming as related to diabetes, coronary disease, hypertension, and the metabolic syndrome, as well as obesity. RTJ

DONEPEZIL (Aricept) (See ALZHEIMER'S DISEASE [1-6]; [6-11]; [6-12])

DUCTAL CARCINOMA IN SITU OF THE BREAST (See BREAST CANCER [4-13]

EMERGENCY CONTRACEPTION

6-9 WAITING FOR PLAN B—THE FDA AND NONPRESCRIPTION ON EMERGENCY CONTRACEPTION

The proposal to switch to levonorgestrel emergency contraception (EC; *Plan B*) to over-the-counter status is in limbo. In May, the FDA rejected the application for non-prescription sales. The acting director, wrote that the company had "not provided adequate data to support a conclusion that *Plan B* can be used safely by young adolescent women for emergency contraception without the professional supervision of a practitioner licensed by law to administer the drug". In rejecting the application, the FDA also rejected the advice of its medical review-staff. (A vote of 23 to 4 in favor of nonprescription status.)

I would be willing to wager that this decision will be reversed. RTJ

END OF LIFE CARE (See DEATH AND DYING)

ERECTILE DYSFUNCTION (See FITNESS [6-8] ; OBESITY [6-8])

ESTROGEN (See HORMONE REPLACEMENT THERAPY [4-4])

FALLS

4-5 EFFECT OF VITAMIN D ON FALLS

This meta-analysis of randomized, controlled trials concludes that vitamin D supplementation reduces risk of falling in elderly persons. Based on 5 of the trials in over 1200 persons, vitamin D, was associated with a reduction in rate of falls by 22%.

In two studies, vitamin D plus calcium (compared with calcium alone) improved body sway by 9% within 2 months, and increased muscle function up to 11%.

What is a possible mechanism**?** 1,25-hydroxyvitamin D, the active metabolite, binds to a highly specific nuclear receptor in muscle tissue. This may mediate de novo protein synthesis through this specific nuclear receptor leading to an increase in the number, size and strength of muscle fibers. This benefit may occur within several months. (Too early to be attributed to increased bone strength.)

I considered this a weak study, but interesting. If indeed vitamin D strengthens muscle and thus prevents falls, its benefit/harm-cost ratio (which is already high.) will be substantially increased.

Vitamin D and calcium intake is generally too low in the US population. I believe that supplementation is warranted in persons of all ages to help maintain bone mass and strength. If muscles are strengthened, so much the better. RTJ

FITNESS

1-1 TOTAL ENERGY EXPENDITURE AND PHYSICAL ACTIVITY IN YOUNG SCOTTISH CHILDREN

The epidemic of childhood obesity has been attributed largely to a decline in total energy expenditure **(TEE).** This study postulated that the lifestyle of contemporary young children is sedentary.

Levels of TEE were low at ages 3 and 5 in both sexes. Lifestyles in this sample of youngsters were sedentary. This would increase risk of obesity. Their total energy expenditure was significantly lower than the UK estimate average requirement for energy for children.

Children typically spent only 20-25 min per day in moderate to vigorous physical activity. Present recommendations are that they should accumulate at least 60 min daily. "There is a widespread perception among parents and health and educational professionals that young children are spontaneously active. Actually, modern children establish a sedentary lifestyle at an early age."

Prevalence of childhood obesity has increased strikingly in recent years.

1-2 PHYSICAL ACTIVITY AND OBESITY

The nature of human physiology is such that it is extremely difficult, if not impossible, to maintain a healthy bodyweight with a low level of physical activity.

Obesity arises from an imbalance in which energy intake exceeds energy expenditure. This means that sedentary people must maintain a low intake of energy to avoid obesity. Human physiology did not develop to support restriction of energy intake. It is difficult for most people to do so consistently over time

We have to teach children (and adults) to use their intellect to push back against the environment. Such a change can be done by eating a little less and being a little more physically active than ordinarily. Small changes would counter the natural tendency to succumb to the environment.

"We suggest that weight gain in 90% of the US adult population could be prevented by reducing positive energy balance by only 100 kcal per day." Small and achievable changes in behavior can have a big impact.

Removing high fructose drinks from ready availability to youngsters is a good first step. RTJ

5-4 CARDIORESPIRATORY FITNESS ATTENUATES THE EFFECTS OF THE METABOLIC SYNDROME ON ALL-CAUSE AND CARDIOVASCULAR DISEASE MORTALITY IN MEN

The estimated prevalence of the "metabolic" ("insulin-resistance") syndrome is over 20% among adults in the USA. Middle-aged men with the metabolic syndrome have significantly elevated risk of all-cause and cardiovascular disease **(CVD)** mortality.

It is defined by the *National Cholesterol Education Program* among persons with 3 or more of 5 risk factors:

1. BP at or over 130/85
2. Central obesity—waist circumference > 40 inches in men
3. High triglyceride levels—>150 mg/dL
4. Low HDL-cholesterol— < 40 mg/dL
5. High fasting plasma glucose—at or above 110 mg/dL

After adjustment for age, smoking status, alcohol consumption, and parental CVD, the relative risks **(RR)** of all-cause mortality and CVD mortality were higher in men with the metabolic syndrome who were unfit compared with the fit men. (RR = 2.0 and 2.3)

There was a graded increase in deaths according to fitness categories. Men in the middle tertile of fitness had 2.0 times the CVD death rate as those in the upper tertile of fitness Those in the lower tertile of fitness had 3.5 times the risk.

The estimated population-attributable risk for CVD deaths in males with the metabolic syndrome is 11%. This suggests that about 1 in 10 CVD deaths are directly attributable to the metabolic syndrome. The public health burden is considerable.

Low cardio-respiratory fitness was an important risk factor for premature mortality in men with the metabolic syndrome. Being fit provides a strong protective effect.

As expected, physical fitness attenuated risk of death in men without the metabolic syndrome as well as those with. I omitted this data.

The study is a reminder of the definition of the metabolic syndrome and its importance as a health risk. I have to periodically jog my memory about the definition lest I forget the 5 requirements. Not all 5 risk factors carry equal weight.

Fitness also attenuates risks of adverse outcomes in smokers; and in patients with obesity, coronary disease, hypertension, and diabetes. It is a basic health measure about which we continue to advise patients, but which they do not often follow. RTJ

6-8 EFFECT OF LIFESTYLE CHANGES ON ERECTILE DYSFUNCTION IN OBESE MEN

Erectile dysfunction **(ED)** is common, even in young men. Several modifiable lifestyle factors are associated with maintenance of erectile function. Men with a body mass index over 28 have a 30% higher risk of ED. The prevalence of overweight and obesity in men reporting ED may be as high as 79%, although vascular factors associated with obesity may play an important role.

This study of obese men with ED determined if a long-term reduction in BMI and an increase in physical activity would positively affect erectile functions.

At 2 years an intensive dietary-fitness program led to over 10% loss of body weight and an increase in physical fitness. About 1/3 of the men regained erectile function.

For many patients, ED is a manifestation of more generalized pathology. Hypertension, hyperglycemia, and dyslipidemia are common co-morbidities. Endothelial dysfunction is likely a pathogenic mechanism common to these co-morbid states, risk of cardiovascular disease, and ED. The study demonstrated improvements in endothelial function related to weight loss..

This is not, however, a practical application. Few patients in primary care practice would be able to complete such a program

The main message is—maintain a healthy lifestyle, don't wait to repair damage until after it is done. RTJ

FOLIC ACID (See NEURAL TUBE DEFECTS [1-10]))

FONDAPARINUX (See VENOUS THROMBOEMBOLISM [6-10])

GASTRIC CANCER

1-9 HELICOBACTER PYLORI ERADICATION TO PREVENT GASTRIC CANCER IN A HIGH-RISK REGION OF CHINA

Over 7 years, in a subgroup of patients *without any precancerous lesions* in the stomach, eradication significantly reduced risk of developing GC.

Other investigators suggest that Hp-infected patients with normal findings on endoscopy are at risk of development of GC. Therefore, in high-risk populations, all patients with *H pylori* infection with no precancerous lesions should consider the use of eradication treatment for gastric cancer prevention.

Further studies are required to determine the role of eradication in those with precancerous lesions.

I believe essentially all patients in the USA with demonstrated H pylori infection should receive eradication therapy. RTJ

GOUT

3-10 PURINE-RICH FOODS, DAIRY AND PROTEIN INTAKE, AND RISK OF GOUT IN MEN.

This study prospectively investigated the association between dietary factors and *new* cases of gout.

Higher intakes of meats and seafoods were associated with *increased* risk of gout. Higher consumption of low-fat dairy products was associated with *decreased* risk. Those in the highest quintile of meat intake (beef, pork, and lamb as main dishes), compared with the lowest quintile, had an elevated risk of developing gout (relative risk = 1.4). Each additional daily serving of meat was associated with a 21% increase in risk.

Corresponding RR associated with seafood was 1.5. Each additional weekly serving was associated with a 7% increase in risk.

Higher intake of total protein and higher intake of purine-rich vegetables were *not* associated with increased risk..

The investigators speculate that the risk associated with increased meat and seafood may be greater in men who already have gout because they have impaired renal clearance of uric acid and the absorption of dietary purines causes a steeper increase in blood uric acid levels than in persons with normal uric acid concentrations. (Ie, diet is likely to be a secondary prevention measure.)

This was essentially a primary prevention study. It provides no information on risk of exacerbations due to dietary factors in men with established gout. The authors, however, speculate that increased intake of meat and seafood may increase risk of recurrence of acute gouty arthritis, and low-fat dairy products may decrease risk. I believe it prudent for primary care clinicians to advise these dietary limitations in patients with established gout. RTJ

3-11 URIC ACID AND DIET—INSIGHTS INTO THE EPIDEMIC OF CARDIOVASCULAR DISEASE.

The effects of diet are relevant to the epidemiology of hyperuricemia and gout. Gout and obesity have become epidemic among native people, such as the Maori of New Zealand, since the introduction of Western culture and diets. The immigration of non-Western peoples to Western countries—for example that of Filipino and Japanese to North America—has been associated with increases in the incidence of gout in parallel with the shift in diet to higher intakes of meat and saturated fats. Gout was rare among blacks in the USA until the 1940s when changes

in diet led to the rapid development of obesity, diabetes, and hypertension. Now, gout is more common among blacks than in whites. It is also becoming more common in urban communities of Africa in association with an increasing frequency of hypertension and cardiovascular disease.

Gout is thus no longer a disease of the wealthy; rather its appearance reflects a worldwide increase in fatty meats and a decrease in intake of dairy products associated with Westernization.

Gout should be considered a part of the current epidemic of obesity, hypertension, and diabetes.

The preceding articles convincingly reinforce the view that lifestyle is indeed important in the pathogenesis of gout.

4-6 ALCOHOL INTAKE AND RISK OF INCIDENT GOUT IN MEN

Health Professionals Follow-up Study followed over 47 000 male subjects (mean age 55 at baseline) for 12 years. None had gout at baseline

Compared with men who did not drink alcohol, the relative risk (RR) of incident gout increased linearly as consumption rose from 1 drink daily (RR compared with none = 1.3) to 2.5 in those imbibing 5 or more drinks daily.

Beer consumption showed the strongest independent association with risk of gout. The RR per each 12 ounce serving per day = 1.49 (Beer is the only alcoholic beverage that contains a large amount of purine.) Consumption of spirits was also associated with increased risk. (RR per each drink daily = 1.15.) Wine consumption was *not* associated. (RR = 1.04 for each 4-ounce serving daily.) The null association persisted regardless of the type of wine.

Risk of gout was greater in men with a body mass index (BMI) over 25 compared with a BMI under 25: In subjects with a BMI under 25, RR of gout was 2.5 in heavy drinkers. In subjects with BMI over 25, RR increased to 5.6..

"Prospective data indicate that alcohol intake is strongly associated with incidence of gout. The risk varies substantially with the type of alcoholic beverage. Beer confers the greatest risk, moderate wine drinking does not increase risk."

Both genetic and environmental factors play a part in the pathogenesis of gout. As with atherosclerotic disease, hypertension, obesity, and type II diabetes, gout can be considered a disease of "civilization"—part of the epidemic of overnutrition and sedentary lifestyles. Gout is associated with a high intake of meat and seafood, and low intake of dairy products.. Now this study reinforces the long-observed relation with alcohol.

As with obesity, gout is becoming more prevalent in developing countries as they become more "Westernized". There are more obese persons in the world now than hungry persons. RTJ

HEART FAILURE

2-5 B-TYPE NATRIURETIC PEPTIDE—A Biomarker For All Seasons?

Recently, natriuretic peptides have been introduced as biomarkers:

1) In patients presenting to the emergency department with acute dyspnea, elevated BTNP was helpful in discriminating between heart failure and other causes of dyspnea (chiefly COPD)
2) In asymptomatic middle-aged persons, BTNP was prognostic of future death, heart failure, and stroke over a mean of 5 years. Levels of BTNP higher than 20 pg/mL (above the 80th percentile) were associated with an increase of over 60% in the long-term risk of death. There was also a significant prognostic gradient of BTNP levels - low (under 4 pg/ml), intermediate (4 to 13), and high (over 13)—with respect to risk of heart failure, and stroke. This is remarkable because levels below 100 pg/mL are considered to rule out heart failure.

The first use may be of value to the primary care clinician in making triage decisions.

Regarding the second application—investigators struggle to find more meaningful and accurate risk markers for cardiovascular disease. I doubt BTNP adds anything of clinical importance to risk assessment

I believe we already have enough risk markers to act upon (and often do not) in order to improve prognosis. When the BTNP is elevated what does one do to reduce risk? — simply revert to measurement and treatment of the traditional risk factors. RTJ

4-11 EFFECTS OF TOLVAPTAN, A VASOPRESSOR ANTAGONIST, IN PATIENTS HOSPITALIZED WITH WORSENING HEART FAILURE

Levels of arginine vasopressin (**AVP**; the water-retaining hormone secreted by the pituitary) are increased in heart failure (**HF**). Water retention and hyponatremia result.

Tolvaptan is a non-peptide, orally administered, once daily vasopressin *antagonist*. It binds predominantly with the AVP receptor in the kidney, resulting in decreased renal vascular resistance, increased renal blood flow, improved glomerular filtration rate, and loss of free water. Rather than being classified as a traditional diuretic, tolvaptan is more precisely characterized as an *aquaretic*.

This study assessed the clinical effectiveness of tolvaptan in patients hospitalized for HF.

Tolvaptan, *vs* placebo, given *in addition* to standard therapy (including diuretics) resulted in a greater net volume loss. It produced a rapid and sustained increase of serum levels of sodium (due to loss of free water) in patients with hyponatremia. It did not adversely affect BP, heart rate, electrolyte levels, or renal function.

When I started to study medicine, the treatment of HF consisted of rest, digitalis pills, salt restriction, and the intramuscular mercury-containing diuretic, mercuhydrin. (How many out there remember mercuhydrin?)

Therapeutic advances have been remarkable—beta-blockers, ACE inhibitors and angiotensin II blockers, spirinolactone, and loop diuretics, as well as use of low-dose digoxin. Nevertheless, prognosis of patients with HF remains poor. These newer drugs are really "rear guard" therapies. It may well be that the main benefit of vaptans is symptomatic relief. Lessening dyspnea and edema may make patients more comfortable. Certainly, vaptans will make therapy easier by reducing worry about hyponatremia, hypokalemia, and renal dysfunction.

Note, the study assessed only systolic HF. The large issue of diastolic HF remains.

Primary care clinicians stay tuned. RTJ

5-2 DIASTOLIC HEART FAILURE—Abnormalities Of Active Relaxation And Passive Stiffness Of The Left Ventricle.

This prospective clinical study analyzed measurement of diastolic function (pressures and volumes of the left ventricle) in patients with HF who had a normal ejection fraction.

Patients with clinical HF and a normal ejection fraction (50%) had abnormalities in the diastolic properties of the left ventricle that were sufficient to explain the occurrence of HF. Pressure-volume relations were abnormal during ventricular relaxation in earliest diastole, and during the entire time of passive ventricular filling The term "diastolic heart failure" can be appropriately used to describe these abnormalities in such patients.

Increased left ventricular stiffness in patients with diastolic heart failure makes them especially vulnerable to the development of pulmonary edema. Significant changes in pressure may be seen with little change in volume of the left ventricle. The ventricle is unable to accept venous return adequately without high diastolic pressures. Such high pressures result in decreased lung compliance, increased work of breathing, dyspnea, and exercise intolerance. Pulmonary edema is the direct consequence of increased passive chamber stiffness.

Patients with diastolic HF have a substantial increase in pulmonary venous pressures during exercise and a significant limitation in exercise tolerance. The non-compliant stiff ventricle has limited ability to use the Frank-Starling mechanism. During exercise, the left ventricle is unable to fill optimally, and despite the increased filling pressure, the cardiac output cannot increase. Exercise intolerance is the direct consequence of abnormal left ventricular diastolic function.

I freely interpreted the pathophysiology the authors described. I believe my interpretation to be accurate, although the article expresses it differently and gives more details. Simply put, in diastolic HF, for every volume of the left ventricle, pressures are higher than normal; and for every pressure, volumes are lower than normal .

I welcomed this article. It clarified my understanding. of diastolic HF It emphasized the importance of control of hypertension as a preventive measure. It did not lead to any suggestions for treatment. Pathological changes in the left ventricular myocardium are yet to be fully described. RTJ

5-3 MANAGEMENT OF DIASTOLIC HEART FAILURE IN OLDER ADULTS

The signs and symptoms of diastolic HF are similar to those of systolic HF. In diastolic HF, the ejection fraction remains normal (> 50%). Both experience volume overload. Distended neck veins are the most reliable sign of overload.

A more specific diagnosis would require documentation of an abnormal left ventricular relaxation pattern. This is often determined by a reduced ratio of early (E; filling immediately after the mitral valve opens) to late (A; due to atrial contraction) filling velocities by Doppler echocardiography The E:A ratio is reduced (<1) in advanced diastolic HF (eg E:A < 0.5). Normal is > 1. The ratio is difficult to assess in patients with atrial fibrillation. (*Ie, in diastolic HF, the early filling is less efficient than the late (atrial contraction) filling. The reverse is normal.)*

There is little evidence from large randomized trials to guide treatment. The author suggests some interventions.

5-8 CARDIAC-RESYNCHRONIZATION THERAPY WITH OR WITHOUT AN IMPLANTABLE DEFIBRILLATOR IN ADVANCED CHRONIC HEART FAILURE

Intraventricular conduction delay is associated with dys-synchronous left ventricular contraction due to regional delays in the electrical activation of the chamber. It occurs in 15% to 30% of patients with heart failure **(HF)** due to dilated cardiomyopathy. It impairs systolic function.

Patients with HF and bundle-branch block have a mechanical disadvantage resulting from abnormal activation of the left ventricle. In these patients, the septum contracts before the lateral left ventricle wall. The lateral wall contracts during relaxation of the septum. This mechanical dysfunction increases left ventricular volume, reduces contractility, and worsens mitral regurgitation. Proper placement of the pacemaker leads permits pacing the right ventricle, the septum, and the lateral wall of the left ventricle simultaneously.

This study assessed the effectiveness of CRT in patients with advanced chronic HF who had intraventricular conduction delays. In the pacemaker group (compared with the drug-only group), CRT resulted in a reduction of death, hospitalization, a slightly higher systolic BP, a slight increase in distance walked in 6 minutes, and improvement in quality-of-life and in the NYHA class.

Note—this applies only to systolic HF.

The purpose of the normal Purkinje subendocardial conducting system is to rapidly conduct the electrical impulse to all parts of the ventricles so that all parts of the myocardium contract simultaneously. CRT is a feeble attempt to mimic this function.

In spite of some incremental improvements in therapy of HF over the past 10 years, prognosis remains miserable. Death and hospitalization for HF continued to increase in the subgroup of patients followed for 3 years. In the CRT group, only about 20% had event-free survival at 3 years, and the death rate increased from 12% at 1 year to about 30% at 3 years. Patients will welcome some improvement in quality-of-life. RTJ

5-13 CYCLO-OXYGENASE-2 INHIBITORS VERSUS NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CONGESTIVE HEART FAILURE OUTCOMES IN ELDERLY PATIENTS.

Non-selective NSAIDs are associated with an increased risk of heart failure **(HF).** In susceptible individuals, they raise systemic vascular resistance and reduce renal perfusion. BP may be elevated, and edema and HF may result.

The selective COX-2 inhibitors, celecoxib (*Celebrex*) and rofecoxib (*Vioxx*) are reported to be associated with a lower risk of gastrointestinal events than the non-selective NSAIDs. Might they also be associated with fewer cardiovascular and renal complications? Might celecoxib and rofecoxib differ in their risks?

Relative to non-NSAID users, the rate of admission for HF was significantly higher for users of rofecoxib (RR = 1.8) and non-selective NSAIDs (RR = 1.4) , but *not* celecoxib (RR = 1.0)

Patients with a history of HF were much more likely to be admitted for recurrent HF. Those taking celecoxib were more likely to be readmitted than controls (RR = 1.2), but much less likely than those taking non-selective NSAIDs (RR = 2.2) and rofecoxib (RR = 1.8)

The authors state that , in other studies, patients with long-standing hypertension showed greater increases in systolic BP among those receiving rofecoxib compared with those receiving celecoxib.

We too often concentrate on the adverse effects of NSAIDs on the gastrointestinal tract, and forget those on the cardiovascular and renal systems.

Although celecoxib may have a slight edge as far as adverse effects are concerned, I would avoid its use (and that of any NSAID) in patients with a history of HF, or at risk of HF (including diastolic HF), as well as patients with uncontrolled hypertension. RTJ

HELICOBACTER PYLORI

1-9 HELICOBACTER PYLORI ERADICATION TO PREVENT GASTRIC CANCER IN A HIGH-RISK REGION OF CHINA

Over 7 years, in a subgroup of patients *without any precancerous lesions* in the stomach, eradication significantly reduced risk of developing GC.

Other investigators suggest that Hp-infected patients with normal findings on endoscopy are at risk of development of GC. Therefore, in high-risk populations, all patients with *H pylori* infection with no precancerous lesions should consider the use of eradication treatment for gastric cancer prevention.

Further studies are required to determine the role of eradication in those with precancerous lesions.

I believe essentially all patients in the USA with demonstrated H pylori infection should receive eradication therapy. RTJ

HOMOCYSTEINE (See OSTEOPOROSIS [5-10])

HOMOSEXUALITY

2-13 TREATMENTS OF HOMOSEXUALITY IN BRITAIN SINCE THE 1950s--AN ORAL HISTORY

In Britain, "treatments" to change homosexuals into heterosexuals peaked in the 1960s and early 1970s. "Some participants chose to undergo treatments instead of imprisonment." (Sexual behavior in private between adult men was not decriminalized in Britain until 1967.) DSM classified homosexuality as a disease until 1973.

Treatments included behavioral aversion therapy with electroshock (including electroconvulsive therapy) and apomorphine (one died of side effects); psychoanalysis; estrogen to reduce libido; religious counseling; and hypnosis.

No participant benefited from treatment. "There is no evidence that treatments were effective at changing sexual orientation."

"Social and political assumptions sometimes lie at the heart of what we regard as mental pathology and serve as a warning for future practice." "Assumptions about public morality and professional authority can lead to the medicalization of human differences and the infringement of human rights."

We are not as far removed from barbarism as we think we are. (Note the eugenics movement in the USA in the 20th century.)

In the USA as elsewhere, social mores, religion, politics, and culture still influence medical decisions, and override some of the established benefits scientific medicine brings for both individuals and the general population. RTJ

HORMONE REPLACEMENT THERAPY

2-14 HABITS (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?)

In this 2-year randomized study, 12% of women in the HRT group experienced a new BC vs 4% in the no-HRT group. In the HRT group, 11 were local recurrences; 5 were contralateral BC; and 10 were distant metastases. In the no-HRT group 2; 1; and 5. (One in 8 women taking HRT developed recurrence of BC vs 1 in 25 in the no-HRT group.)

Women with a history of BC should not receive HRT. Those already receiving HRT should be advised to discontinue.

What about HRT in women with ductal carcinoma in situ? I would be cautious in using HRT in these patients as well.

For women with history of BC, what can be advised for menopausal-symptom relief other than HRT? The North American Menopause Society suggests several non-hormonal therapies:

Antidepressants venlafaxine (Effexor), paroxetine (Paxil), and fluoxetine (Prozac; generic). Start at very low doses and gradually increase. Cessation requires gradual tapering off.

Gabapentin (Neurontin) may be considered in women older than 65

Clonidine is less effective than gabapentin. RTJ

3-3 EVALUATION OF CARDIOVASCULAR EVENT RATES WITH HORMONE THERAPY IN HEALTHY, EARLY POSTMENOPAUSAL WOMEN

Two large randomized trials have evaluated effects of hormone replacement therapy **(HRT)** in postmenopausal women.

The average age of the subjects in these two studies was 63 years, well past onset of the menopause. Overall, the studies concluded that HRT results in net *harms*. . The greatest risk of adverse effects occurred in the first year.

This was contrary to older *observational* studies which reported considerable benefit in reducing cardiovascular morbidity and mortality. It led to reevaluation of the use of HRT.

It is important to determine if adverse events occur in *younger* women. Most women with menopausal symptoms take HRT at an earlier age, relatively soon after the menopause. This article reviewed 2 other large clinical trials of younger women (mean age 54). It asks—What is the risk of adverse events at this age?

Conclusion: In young, healthy postmenopausal women, the adverse effects of HRT *in the first year* of use were no greater than the expected harms in women not taking HRT.

What should primary care clinicians advise their patients about HRT?

A. Risks of adverse events during the first few perimenopausal years are low in younger, healthier women taking combined HRT, and even lower in those taking estrogen alone.

B. These risks can be further reduced by therapy aimed at reducing cardiovascular risk: smoking cessation, low-dose aspirin; lipid, weight, and BP control; and using the lowest effective dose of estrogen and progesterone. Indeed, I believe it likely that women who, at the age of 50 adopt these protective measures and take HRT will be less likely to experience cerebrovascular events than women who do not take HRT and do not adopt these protective measures.

I believe that recent reports overemphasized the adverse effects of HRT, and that many women who would benefit by symptom relief are being denied treatment. RTJ

4-4 EFFECTS OF CONJUGATED EQUINE ESTROGEN IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY

This study reports the conjugated equine estrogen (**CEE**)-alone phase of the Women's Health Initiative trial which was continued for 7 years. (Age at baseline = 63.)

The burden of incident disease events was equivalent in the CEE-alone and placebo groups. There was no significant difference in risks other than a slight increase in incidence of stroke. The absolute *excess* was 12 additional strokes per 10 000 person-years. And an absolute *reduction* of hip fracture of 6 per 10 000 person-years.

The estimated excess risk for all monitored events (CHD, stroke, pulmonary embolism, colorectal cancer, hip fracture, and deaths from other causes). was a non-significant 2 events per 10 000 person-years.

This differs importantly from the WHI trial of combined estrogen/progestin in which the risk of CHD was significantly elevated.

Women and their health-care professionals now have usable risk estimates for the benefit/harm ratio of CEE-alone in treatment of menopausal symptoms. "Women can be reassured that incidence of CHD and breast cancer is not increased at least for 6.8 years". But, the data also reinforce that there is no overall benefit of CEE for chronic disease prevention.

Nevertheless, CEE-alone *cannot* be recommended for disease *prevention*. CEE should be used only for menopausal symptoms at the smallest effective dose for the shortest possible time.

The study reported a lower risk of breast caner in the CEE-alone group vs the placebo group This is contrary to other observational studies in which risk of BC is increased. I believe clinicians should remain wary and should consider that HRT in any form increases risk of breast cancer.

I believe risks of CEE-alone as well as combined estrogen/progestin have been overemphasized, and that many women are being unnecessarily denied relief from their menopausal symptoms. RTJ

HYPERPARATHYROIDISM

4-9 ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

The diagnosis of AHP is made on the basis of a combination of elevated total serum calcium + an inappropriately elevated PTH.

Criteria of parathyroid surgery (cutoff points):

Serum calcium	1.0 mg/dL above upper normal
24-hour calcium	> 400 mg
Reduction in creatinine clearance	30%
Bone mineral density	T score below -2.5 (Radius is particularly vulnerable)
Age	Under 50

Surgery is routinely warranted in patients with kidney stones.

Most patients with AHP who do not meet the criteria for surgery do well, with no evidence of progressive disease. In most patients, the average serum and parathyroid hormone levels do not change over 10 years. And

BMD is typically stable. Hypercalciuria usually does not worsen. Younger patients (< age 50) are more likely to progress.

Many patients with AHP will not require surgery. Patients who do not meet the criteria for surgery should be monitored periodically (serum calcium, creatinine clearance, and BMD) because about 25% of patients will progress.

To advise surgery or advise continued surveillance is a clinical call. It depends on patient preference and individual circumstances. If expert surgery is available, I would tilt toward surgery. This would relieve the patient of continuing concerns. RTJ

4-10 MINIMALLY INVASIVE PARATHYROIDECTOMY

The arrival of tecnitium-99m sestamibi scanning revolutionized preoperative localization of parathyroid glands. It accurately identifies the side and size of the adenoma in 9 out of 10 cases.

Patients with reliably localized single adenomas may be treated with a minimal access approach. This is achieved through a 2 cm incision. It can usually be done as a day case procedure in less than 20 minutes with local anesthesia. It has become the first line treatment in specialized units.

Primary care clinicians, if they practice long enough, will encounter patients with asymptomatic HPT. The advent of minimalist surgery further tilts the decision toward operating. RTJ

HYPERTENSION

2-1 ANTIHYPERTENSIVE TREATMENT BASED ON BLOOD PRESSURE MEASUREMENT AT HOME OR IN THE PHYSICIAN'S OFFICE.

Intermittent, self-measurement of BP with an inexpensive ocillometric reader at home accomplishes several of the advantages of 24-hour ambulatory monitoring.

This study compared BP measurements taken in the physician's office with those self-measured at home in patients with hypertension. The goal was a diastolic between 80 and 89.

HomeBP led to less intensive drug treatment and marginally lower costs. It determined presence of white-coat hypertension (office BP higher than home BP), and led to discontinuation of drug therapy in twice as many patients as office BP measurement, but slightly poorer long-term BP control. It may also help identify masked hypertension (home BP higher than office BP).

Should primary care clinicians offer home BP recordings to their patients with hypertension?
I believe it would be helpful. The greatest benefit would be in eliminating or reducing drug therapy in a sizable number of patients. It would also increase compliance and interest in treatment, and reduce the number of office visits. The downside might be slightly less adequate control.

BP goals would differ depending on the individual patient. The great majority of older patients with hypertension have isolated systolic hypertension.

Would patients accept and comply with this approach? They might, with difficulty. Enthusiastic support will be required. Machines would have to be recalibrated periodically. RTJ

3-4 CARDIOVASCULAR PROGNOSIS OF "MASKED HYPERTENSION" DETECTED BY BLOOD PRESSURE SELF-MEASUREMENT IN ELDERLY TREATED HYPERTENSIVE PATIENTS.

There are numerous criticisms of clinical BP measurement. Major inter- and intra-observer variability exist. There are difficulties with standardization of the measurement conditions, and insufficiency in the number of measurements. Office BP fails to recognize the patient's average daily BP.

In this study, home BP self-measurement defined the prognosis in terms of cardiovascular morbidity and mortality better than office measurement. This was due in part to the poor performance of office BP measurements.

The study reported a high prevalence of two classes of patients with hypertension not recognized by BP measurements confined to the office: 1) "White coat" hypertension (office BP higher than home BP); 2) "Masked" hypertension (the opposite—home BP higher than office BP). "The frequency of this double error, which is both diagnostic (with respect to the control of hypertension), and prognostic (with respect to the incidence of cardiovascular events), suggests that monitoring of patients being treated for hypertension must include home BP self measurement."

"Masked" hypertension was associated with a statistically significant increase in risk of adverse cardiovascular events. Indeed, the risk over 3 years was about the same as the group with uncontrolled hypertension. It remains to be seen, however, that adaptation of *treatment* to the results of home BP self-measurement allows better cardiovascular prevention than *treatment* based on office BP.

Although, as the authors state, there are no data reporting outcomes of patients treated for "masked hypertension", I believe it would be reasonable to treat them. What about "white coat"? Previous observations suggest that these patients are subject to development of sustained hypertension. They should be carefully observed. Some would advocate treatment.

I believe home BP will become more standardized as a method for following patients treated for hypertension. RTJ

HYPOGONADISM

1-7 RISKS OF TESTOSTERONE-REPLACEMENT THERAPY AND RECOMMENDATIONS FOR MONITORING.

Hypogonadism is a clinical condition in which low levels of serum testosterone are found in association with specific signs and symptoms: diminished libido and sense of vitality, erectile dysfunction, depression, anemia, and reduced muscle mass and bone density. Prescriptions for testosterone supplementation have increased substantially over the past decade.

Reports indicate that testosterone replacement may produce a wide range of benefits: improvement in libido, bone density, muscle mass, body composition, mood, erythropoiesis, and cognition.

No studies have yet been initiated to assess benefits and risks, especially possible stimulation of prostate cancer. But, "Despite decades of research, there is no compelling evidence that testosterone has a causative role in prostate cancer". There is no compelling evidence to suggest that men with higher testosterone levels are at greater risk of PC or that treating men with hypogonadism with exogenous androgens increases risk. Nevertheless, the authors advocate routine biopsy in all men presenting for replacement therapy

Should primary care clinicians deal with this problem? Should they refer patients seeking therapy to a urologist with considerable experience? At the present stage of development, I would follow the second course.

The value of a therapy has been described as: Value = benefits

harms-costs

I believe the benefits are somewhat nebulous and unknown long-term. Harms are potentially great. Cost is considerable considering consultation and laboratory fees as well as the cost of the testosterone. RTJ

1-8 HYPOGONADISM IN ELDERLY MEN—WHAT TO DO UNTIL THE EVIDENCE COMES

A long-awaited report from the Institute of Medicine (IOM) concluded that there is insufficient evidence that testosterone benefits elderly men.

Many studies document that serum testosterone levels decrease as men age. In contrast to the precipitous and profound decrease in estradiol concentrations in women at the menopause, the decrease in testosterone levels in men occurs moderately and gradually over a period of several decades—from about 600 ng/dL at age 30 to about 400 at age 80. One study reported that about 20% of men over age 60 had total serum testosterones below the normal range for young men.

A still unanswered question is whether this decrease is physiologic (perhaps conveying a benefit) or pathologic (causing harm).

Another unanswered question is whether increasing the low-level testosterone in elderly men to the level of younger men will exacerbate testosterone-dependent diseases such as prostate cancer and benign prostatic hyperplasia.

INFLUENZA

2-17 STRUCTURE OF THE 1918 FLU VIRUS

Scientists at the Medical Research Council (UK) have discovered a crucial structural change in the avian influenza virus that resulted in the death of 20 million people worldwide in 1918.

The hemaglutanin molecule protrudes from the surface of the flu virus as a series of spikes. A change in the configuration of the spikes enabled the avian flu virus to lock on the surface of human cells. Usually, bird viruses cannot be transmitted to humans. But, in 1918 this subtle change in shape of HA gave the virus the ability to attach to receptors on human cells as well as bird cells. The virus then spread rapidly from human to human to infect an estimated billion people—half of the world's population at the time.

All of the devastating flu pandemics of the last century were caused by viruses that came from birds.

Could this happen again? Many believe so. Eternal vigilance and vaccine adjustment will hopefully blunt the epidemic. RTJ

6-13 TACKLING THE NEXT INFLUENZA PANDEMIC

"We must now hasten the preparations for another inevitable influenza pandemic."

A recent systemic review concluded that the prophylactic use of neuraminidase inhibitors **(NIs)** could lead to a reduction of 70-90% in risk of symptomatic flu. These drugs have shown efficacy in preventing transmission of influenza in institutions and community setting. The availability of a highly effective supplement to vaccination opens to debate the appropriate role of NIs and other antiviral drugs in the control of pandemic influenza.

What might be an alternative strategy? It is known that "ring" vaccination, which has been used in the past, will quell smallpox outbreaks. The strategy entails post-exposure vaccination of close contacts. For smallpox, this

approach has provided a wide safety net of prevention, while focusing vaccination where it was needed most. Ring prophylaxis may be applicable to the initial management of an influenza pandemic. NI treatment of influenza cases with the infection and prophylactic use for their contacts may decrease attack rates substantially. It limits usage of the drug to where it is needed most.

Antiviral ring prophylaxis for flu has proved to be effective in family settings. It requires only short term daily treatment for a period of 5-10 days, and targets a relatively limited proportion of the population. Used in this way, NIs may be dispensed more rapidly and require less of a stockpile.

COST: Tamiflu, 75 mg cost about $6 each capsule— $60 for a treatment course; $42 for 7-day prophylaxis. I believe most patients would consider this a bargain.

Healthcare workers should be the first in line to receive "ring" prophylaxis, and to continue it until assured that the current vaccine is effective.

Primary care clinicians will likely use NIs freely to unvaccinated family members during an epidemic of flu. RTJ

LIPID-LOWERING (See STATIN DRUGS)

LIPOSUCTION (See METABOLIC SYNDROME [6-4}; [6-5])

LOW-CARBOHYDRATE DIET (See DIET)

MEMANTINE (See ALZHEIMER'S DISEASE [1-6])

METABOLIC SYNDROME

5-4 CARDIORESPIRATORY FITNESS ATTENUATES THE EFFECTS OF THE METABOLIC SYNDROME ON ALL-CAUSE AND CARDIOVASCULAR DISEASE MORTALITY IN MEN

The estimated prevalence of the "metabolic" ("insulin-resistance") syndrome is over 20% among adults in the USA. Middle-aged men with the metabolic syndrome have significantly elevated risk of all-cause and cardiovascular disease **(CVD)** mortality.

It is defined by the *National Cholesterol Education Program* among persons with 3 or more of 5 risk factors:

1. BP at or over 130/85
2. Central obesity—waist circumference > 40 inches in men
3. High triglyceride levels—>150 mg/dL
4. Low HDL-cholesterol— < 40 mg/dL
5. High fasting plasma glucose—at or above 110 mg/dL

After adjustment for age, smoking status, alcohol consumption, and parental CVD, the relative risks **(RR)** of all-cause mortality and CVD mortality were higher in men with the metabolic syndrome who were unfit compared with the fit men. (RR = 2.0 and 2.3)

There was a graded increase in deaths according to fitness categories. Men in the middle tertile of fitness had 2.0 times the CVD death rate as those in the upper tertile of fitness Those in the lower tertile of fitness had 3.5 times the risk.

The estimated population-attributable risk for CVD deaths in males with the metabolic syndrome is 11%. This suggests that about 1 in 10 CVD deaths are directly attributable to the metabolic syndrome. The public health burden is considerable.

Low cardio-respiratory fitness was an important risk factor for premature mortality in men with the metabolic syndrome. Being fit provides a strong protective effect.

As expected, physical fitness attenuated risk of death in men without the metabolic syndrome as well as those with. I omitted this data.

The study is a reminder of the definition of the metabolic syndrome and its importance as a health risk. I have to periodically jog my memory about the definition lest I forget the 5 requirements.

Fitness also attenuates risks of adverse outcomes in smokers; and in patients with obesity, coronary disease, hypertension, and diabetes. It is a basic health measure about which we continue to advise patients, but which they do not often follow. RTJ

6-4 ABSENCE OF AN EFFECT OF LIPOSUCTION ON INSULIN ACTION AND RISK FACTORS FOR CORONARY HEART DISEASE.

Abdominal obesity (increased abdominal subcutaneous fat, and increased visceral fat) is associated with insulin resistance and other risk factors for coronary heart disease **(CHD).**

This study asked: Which of these fat deposits is associated with insulin resistance and increased risk of CHD?

Liposuction in 15 grossly obese women reduced volume of subcutaneous abdominal fat by 44%. Weight loss = 10 kg; total body fat decreased by 18%. Liposuction did not significantly alter insulin sensitivity (assessed by stimulation of glucose uptake in muscle); did not suppress glucose production by the liver; and did not suppress lipolysis of adipose tissue.

Levels of C-reactive protein and other indicators of inflammation did not change.

Other risk factors for CHD were unchanged (BP, plasma glucose, insulin, and lipid concentrations).

Large-volume reduction in subcutaneous abdominal fat mass did not have any beneficial metabolic effects despite a considerable decrease in body weight, waist circumference, and plasma leptin concentrations.

This provides insight into the mechanism by which conventional weight loss improves insulin sensitivity. Induction of a negative energy balance, not simply a decrease in the mass of fat tissue, is critical for achieving the metabolic benefits of weight loss. Even small amounts of weight loss induced by a negative energy balance affect many variables pertaining to body-fat composition and lipid metabolism—variables that contribute to metabolic abnormalities associated with obesity. Conventional weight loss decreases visceral fat mass, intrahepatic fat, fat-cell size, and the rate of release of fatty acids from intra-abdominal adipose tissue. Liposuction does not.

Fat loss by conventional obesity treatment decreases plasma concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor. It improves insulin sensitivity and inhibits vascular inflammation.

I abstracted this article mainly to point out the risks associated with intra-abdominal fat accumulation. Visceral fat drains directly into the portal circulation and into the liver; subcutaneous fat drains into the general circulation. There is a vast metabolic difference. RTJ

6-5 THERMODYNAMICS, LIPOSUCTION, AND METABOLISM

Hyperglycemia improves *rapidly* during caloric restriction. It outpaces the rate of weight loss. About half of the improvements in glycemic control are achieved during the first week of a negative energy balance, although the actual fat loss is typically quite small. Substantial proportions of the early benefits of weight loss on insulin resistance and hyperglycemia in type 2 diabetes may be attributed to a negative energy balance.

Similar observations have been made concerning hypertension. Much of the decrease in BP occurs fairly rapidly in response to a negative energy balance. There is, however, a return toward hypertensive levels once weight has reached a plateau.

Visceral adiposity is strongly associated with insulin resistance. In animals, surgical resection of visceral fat tissue yields marked and nearly immediate reduction in insulin resistance. The removal of an equivalent amount of subcutaneous fat has little effect. The relation may be related, at least in part, to the release of fatty acids into the portal circulation.

Adipose tissue has endocrine functions—synthesizing leptin, adiponectin, and cytokines such as tumor necrosis factor, interleukin-6, and C-reactive protein.

During World War II type 2 diabetes practically disappeared in the Netherlands. This was related to the near starvation conditions produced by the invasion by Germany. RTJ

"ME TOO" PRODUCTS

1-3 "ME TOO" PRODUCTS—FRIEND OR FOE?

Me-too products create competition among drug and device manufacturers. Competition is a powerful driver for better quality and lower costs. Health care leaders who struggle to provide good care with limited resources see me-too products not as a problem, but as an important part of the solution.

The first product in a new class defines the baseline value equation. [Value = benefit / harm-cost] The manufacturer may set a high price and may have no trouble selling the product at its asking price. When a second product in the same class comes along, its manufacturers must offer a better value. That product must lead to a better outcome or it must be less expensive.

For market forces to really work, physicians have to choose products as if costs matter.

When should primary care clinicians add a new drug to their practice? Is it a unique and important addition to therapeutics? Or is it just a "me-too" drug? It takes several years after entry into general use for all adverse effects to be known. Ask:

1. Is the new drug more clinically effective? (Not just "statistically" more effective.)

2.Is it as safer or safer than established drug?

3. Is it more convenient to administer?. Does it require fewer doses?

4. Is it less costly?

Primary care clinicians are often advised not to be the first to prescribe a new drug, no matter how highly touted, unless it is known to be safe and carry unique and important benefits

I have faced (as have most older clinicians) the embarrassment of having a new drug I had prescribed suddenly withdrawn from the market. The patient will ask for an explanation. RTJ

NARRATIVE MEDICINE

2-4 NARRATIVE MEDICINE

More health care professionals are recognizing the importance of the stories patients tell about their illnesses. Not only is the diagnosis encoded in the narrative, but also deep and therapeutic understandings of the persons who bear the symptoms are made possible through the stories they tell. Only in the telling is the patient's suffering made evident.

Narrative competence, defined as the set of skills required to recognize, absorb, interpret, and be moved by the stories one hears, is increasingly recognized as a basis for diagnosis and therapy.

Primary care clinicians bear the greatest opportunity and responsibility for understanding and responding to patients' stories. Some writers term this making a "connexion" with the patient.

It is the "worried well" and the patient with chronic illness whose narratives should be developed and understood over time as a basis of therapy and support.

Patiently listening and understanding narratives will benefit our family members, children, associates, and friends as well as patients. The art of listening and responding empathetically is a difficult, life-long quest. RTJ

NATRIURETIC PEPTIDE (See HEART FAILURE [2-5]

NEURAL TUBE DEFECTS

1-10 FOLIC ACID AND THE PREVENTION OF NEURAL TUBE DEFECTS

A public health policy should include both the mandatory fortification of flour and a recommendation that all women planning a pregnancy take 5 mg a day. Each year about a quarter of a million pregnancies result in the birth of an infant with NTD, or an abortion performed because of such a defect. 85% of them could be prevented if all women took 5-mg daily before pregnancy and during the first trimester.

A high percentage of women of childbearing age have unplanned pregnancies. Since the beginning of pregnancy cannot be predicted in these women, I believe a good case can be made to recommend all women at risk for pregnancy routinely take FA daily. Primary care clinicians should take the opportunity to so advise their younger women patients regardless of the reason for the consultation.

The benefit/harm-cost ratio of FA is high. Although overall risk is low, benefit may be great for individuals The harm is nil. Cost is low. Considering the devastating effect of NTD for the child and the family, I believe all women at risk of pregnancy should be informed. RTJ

NICOTINE REPLACEMENT (See SMOKING [2-9])

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

5-13 CYCLO-OXYGENASE-2 INHIBITORS VERSUS NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CONGESTIVE HEART FAILURE OUTCOMES IN ELDERLY PATIENTS.

Non-selective NSAIDs are associated with an increased risk of heart failure **(HF).** In susceptible individuals, they raise systemic vascular resistance and reduce renal perfusion. BP may be elevated, and edema and HF may result.

The selective COX-2 inhibitors, celecoxib (*Celebrex*) and rofecoxib (*Vioxx*) are reported to be associated with a lower risk of gastrointestinal events than the non-selective NSAIDs. Might they also be associated with fewer cardiovascular and renal complications? Might celecoxib and rofecoxib differ in their risks?

Relative to non-NSAID users, the rate of admission for HF was significantly higher for users of rofecoxib (RR = 1.8) and non-selective NSAIDs (RR = 1.4) , but *not* celecoxib (RR = 1.0)

Patients with a history of HF were much more likely to be admitted for recurrent HF. Those taking celecoxib were more likely to be readmitted than controls (RR = 1.2), but much less likely than those taking non-selective NSAIDs (RR = 2.2) and rofecoxib (RR = 1.8)

The authors state that , in other studies, patients with long-standing hypertension showed greater increases in systolic BP among those receiving rofecoxib compared with those receiving celecoxib.

We too often concentrate on the adverse effects of NSAIDs on the gastrointestinal tract, and forget those on the cardiovascular and renal systems.

Although celecoxib may have a slight edge as far as adverse effects are concerned, I would avoid its use (and that of any NSAID) in patients with a history of HF, or at risk of HF (including diastolic HF), as well as patients with uncontrolled hypertension. RTJ

OBESITY

1-1 TOTAL ENERGY EXPENDITURE AND PHYSICAL ACTIVITY IN YOUNG SCOTTISH CHILDREN

The epidemic of childhood obesity has been attributed largely to a decline in total energy expenditure **(TEE).** This study postulated that the lifestyle of contemporary young children is sedentary.

Levels of TEE were low at ages 3 and 5 in both sexes. Lifestyles in this sample of youngsters were sedentary. This would increase risk of obesity. Their total energy expenditure was significantly lower than the UK estimates average requirement for energy expenditure for children.

Children typically spent only 20-25 min per day in moderate to vigorous physical activity. Present recommendations are that they should accumulate at least 60 min daily. “There is a widespread perception among parents and health and educational professionals that young children are spontaneously active. Actually, modern children establish a sedentary lifestyle at an early age.”

1-2 PHYSICAL ACTIVITY AND OBESITY

The nature of human physiology is such that it is extremely difficult, if not impossible, to maintain a healthy bodyweight with a low level of physical activity.

Obesity arises from an imbalance in which energy intake exceeds energy expenditure. This means that sedentary people must maintain a low intake of energy to avoid obesity. Human physiology did not develop to support restriction of energy intake. It is difficult for most people to do so consistently over time.

We have to teach children (and adults) to use their intellect to push back against the environment. Such a change can be done by eating a little less and being a little more physically active than ordinarily. Small changes would counter the natural tendency to succumb to the environment.

"We suggest that weight gain in 90% of the US adult population could be prevented by reducing positive energy balance by only 100 kcal per day." Small and achievable changes in behavior can have a big impact.

Removing high fructose drinks from ready availability to youngsters is a good first step. RTJ

5-1 A LOW-CARBOHYDRATE, KETOGENIC DIET VERSUS A LOW-FAT DIET TO TREAT OBESITY AND HYPERLIPIDEMIA: The Atkin's Diet

Recently, the low-carbohydrate ("low-carb"; **[LC];** Atkin's) diet has gained recognition despite modest supportive scientific evidence of efficacy. A popular version of this diet recommends extreme restriction of carbohydrate intake to less than 20 grams daily. This level can induce ketosis and weight loss.

This randomized trial compared the effects of the LC-ketogenic diet *vs* a low-fat, low-cholesterol reduced-calorie diet.

Over 24 weeks, otherwise healthy obese, hyperlipemic persons who followed a LC diet lost more body weight and fat than those on a low-fat diet. Triglyceride levels decreased; HDL-cholesterol levels increased. The LDL-c increased in some subjects. "Because the low-carbohydrate diet may adversely affect the LDL cholesterol level, it is prudent to monitor the serum lipid profiles. . . ."

The drop-out rate in persons on the LC diet was lower. This is important because the value of any diet depends on the degree to which patients adhere to it over time.

Weight loss in both groups resulted from reduced energy intake. The method of reducing energy intake differed greatly. The low-fat, high-carbohydrate diet group received counseling to restrict intake of fat, cholesterol, and energy. The LC diet group received counseling to restrict intake of only carbohydrates, not energy. "The voluntary reduction in energy intake among recipients of the LC diet merits future research."

Further observation is needed to determine the long-term (beyond 6 months) effects of the LC diet. Weight loss may be difficult to maintain

No matter what the diet, weight loss will vary considerably between individuals. An editorialist suggests that we can encourage overweight patients to experiment with various methods for weight control, including the LC diet, as long as they emphasize healthy sources of fat and protein and incorporate regular physical activity.

"We can no longer dismiss the very-low-carbohydrate diets. "

The determining factor in diet therapy is its effect on long-term (years) weight control. We wait results of these studies, Thus far, it seems doubtful that many persons on the LC diet will maintain their weight loss over time.

I believe more studies of the LC diet will be forthcoming as related to diabetes, coronary disease, hypertension, and the metabolic syndrome, as well as obesity. RTJ

6-8 EFFECT OF LIFESTYLE CHANGES ON ERECTILE DYSFUNCTION IN OBESE MEN

Erectile dysfunction **(ED)** is common, even in young men. Several modifiable lifestyle factors are associated with maintenance of erectile function. Men with a body mass index over 28 have a 30% higher risk of ED. The prevalence of overweight and obesity in men reporting ED may be as high as 79%, although vascular factors associated with obesity may play an important role.

This study of obese men with ED determined if a long-term reduction in BMI and an increase in physical activity would positively affect erectile functions.

At 2 years an intensive dietary-fitness program led to over 10% loss of body weight and an increase in physical fitness. About 1/3 of the men regained erectile function.

For many patients, ED is a manifestation of more generalized pathology. Hypertension, hyperglycemia, and dyslipidemia are common co-morbidities. Endothelial dysfunction is likely a pathogenic mechanism common to these co-morbid states, risk of cardiovascular disease, and ED. The study demonstrated improvements in endothelial function related to weight loss..

This is not, however, a practical application. Few patients in primary care practice would be able to complete such a program.

The main message is—maintain a healthy lifestyle, don't wait to repair damage until after it is done. RTJ

OMEGA 3 FATTY ACIDS (See CARDIOVSCULAR DISEASE [1-5]))

OSTEOARTHRITIS

4-1 CORTICOSTEROID INJECTIONS FOR OSTEOARTHRITIS OF THE KNEE

This is the first meta-analysis aimed to determine the efficacy of intra-articular corticosteroids. Are intra-articular injections of corticosteroids more efficacious than placebo in improving symptoms of OA of the knee? How long does the beneficial effect last?

Six short-term studies showed a significant improvement. The pooled relative benefit (steroid *vs* placebo injection) was 1.6 with the number needed to treat to obtain improvement in one patient = between 1.3 and 3.5. No important harms were reported other than transient redness and discomfort. Only one of the 6 studies investigated potential loss of joint space and found no difference between corticosteroid and placebo up to 2 years.

Two longer-term, high-quality trials reported a relative benefit of 2.1 with a NNT to benefit one patient in 4.4 over 16 to 24 weeks. One study investigated potential loss of joint space and found no difference between corticosteroid and placebo up to 2 years. This study used higher dose triamcinolone (40 mg—equivalent to 50 mg prednisone) than most other studies and also gave repeated injections (every 3 months for 2 years). No difference in loss of joint space over 2 years. "Currently, no evidence supports the promotion of disease progression by steroid injections.. Repeat injections seem to be safe over two years." This requires confirmation.

Evidence supports short term (up to two weeks) improvement in symptoms of OA of the knee after corticosteroid injections. Significant improvement was also shown in the only methodologically sound studies addressing longer term use. Multiple doses of the equivalent of 50 mg prednisone may be needed to show benefit at 16-24 weeks.

The data regarding high doses of corticosteroid, repeated periodically, may encourage some clinicians to increase the dose. I believe many physicians are reluctant to recommend multiple high-dose injection for fear of further damaging the joint. The report that high-dose repeated injections over 2 years did not lead to further damage is interesting and reassuring. This is an important clinical point which urgently requires confirmation. I believe there is currently concern that joint damage does occur after repeated injections. If this is not the case, many patients would benefit from repeated injections of higher dose steroids, and would welcome a delay in the need for knee replacement RTJ

OSTEOPOROSIS

1-13 THE EFFECTS OF STRONTIUM RANELATE ON THE RISK OF VERTEBRAL FRACTURE IN WOMEN WITH POSTMENOPAUSAL OSTEOPOROSIS

Strontium ranelate is an orally active agent recently re-introduced for treatment of osteoporosis. It consists of two atoms of strontium and an organic moiety. It acts in a dual manner to stimulate formation of new bone and decrease bone resorption . SR treatment of postmenopausal osteoporosis led to early and sustained reductions in risk of vertebral fractures. In a high-risk group of women with osteoporosis, the NNT to prevent one new vertebral fracture over 3 years = 10

There were no significant differences between groups in the incidence of serious adverse effects. Diarrhea was more common in the SR group (6%). Withdrawals were similar. There was no change in vitamin D metabolites.

"The current trial establishes the efficacy of strontium ranelate, a familiar element relaunched as a new compound, in reducing the risk of vertebral fractures and its role in the armamentarium of therapy for osteoporosis."

Not yet ready for prime time. Watch for developments. RTJ

2-6 EXPERTS URGE EARLY INVESTMENT IN BONE HEALTH

The American Academy of Pediatrics has issued a policy statement urging physicians to contact schools in their communities and push for the elimination of sweetened soft drinks. Carbonated soft drink consumption has increased by 16% since 1970; milk consumption has decreased by an equal amount. In addition to displacing milk in the diet, the phosphorus content of soft drinks may impair absorption of calcium. Milk is the main source of calcium in the typical American diet. Milk consumption—and therefore calcium intake—decreases as soft drink consumption increases.

Much of the focus was on the contribution of sugary (high fructose) beverages to the obesity crisis.

Prevention of osteoporosis begins in childhood and adolescence. This is one of the most important preventive measures primary care clinicians can offer their patients.

Anyone living in a retirement home will realize how common and disabling the kyphotic-osteoporotic spine can become. Development of osteoporosis can largely be prevented or retarded. I believe it is a major prevention opportunity for primary care clinicians. Prevention begins in childhood.

Commercial interests have intruded into our school system in subtle ways. Vending machines dispense not only soft drinks, but high calorie snacks. Textbooks are not an exception. Advertising enters them in apparently innocuous ways. TV and radio programs provided for children in school contain commercial messages. Children can not perceive the hype. RTJ

3-8 TEN YEAR'S EXPERIENCE WITH ALENDRONATE FOR OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

How long is the benefit of bisphosphonates sustained? This article reports results of a trial of postmenopausal women with osteoporosis who were treated for 10 years with alendronate (*Fosamax*).

Bone mineral density (**BMD)** continued to increase throughout the 10-year period. Lumbar spine density was increased by doses of 5 mg and 10 mg daily (+ 9% and +14%). The density of the femoral neck was increased by +3 and + 5%.

Even when alendronate is discontinued, the increased BMD persists for some time.

The drug was well tolerated over 10 years. There is some concern that bone may become more brittle as BMD increases due to prolonged therapy. No evidence, however, of an *increase* in fracture rate in this study.

The study reported a low calcium intake in these women. Deficient intake of calcium and vitamin D is common in the USA. Providing adequate calcium and vitamin D will retard development of osteoporosis. Women (and men) should maintain adequate intake of calcium and vitamin D throughout their lives. This can usually be attained only by supplementation. RTJ

5-10 HOMOCYSTEINE LEVELS AND THE RISK OF OSTEOPOROTIC FRACTURE

Homocystinuria is a rare autosomal recessive disease characterized by very high plasma homocystine levels. It is also characterized by early onset of generalized osteoporosis. The underlying pathophysiological mechanism is not completely understood. It may be related to a disturbance in collagen cross-linking in bone.

In the general population, a mildly elevated plasma homocysteine, termed hyper-homocysteinemia, is a common condition. Hyper-homocysteinemia is recognized as a major risk factor for atherosclerotic and thrombotic disease, as well as cognitive impairment, including Alzheimer's disease.

Are mildly elevated homocysteine levels related to age-related fractures?

This study determined homocysteine levels, and followed over 2400 subjects, all over age 55 (a general, older population) who participated in two separate prospective studies:

When grouped with regard to sex and age-specific quartiles, those in the highest quartile had an increase in risk of fracture twice as high as the risk in the three lower quartiles.

The population-attributable risk of fracture related to a high homocysteine level was estimated at 19%

A companion study "Homocysteine as a Predictive Factor for Hip Fracture in Older Persons" comes to the same conclusion. Compared with the lowest quartile, those in the highest quartile had a greater risk of hip fracture (4 times higher in men and 2 times higher in women).

The authors comment that homocysteine levels are easily modifiable by dietary interventions. The FDA mandate in 1996 led to folic acid fortification of grain products. This has helped reduce the prevalence of low folate levels (< 7 mmol/L) from 22% to 2% and reduce the prevalence of homocysteine concentrations higher than 13 mmol/L from 19% to 10%. It remains to be seen if interventions by supplements will reduce rates of fracture.

Would this study lead primary care clinicians to more strongly advise a daily multivitamin supplement? (In addition to folic acid, supplements contain vitamin B12 and B6 which are also related to a lowering of homocysteine levels.)

Decisions regarding therapy in primary care often do not depend on conclusive evidence of efficacy. They are also based on reasonable assumptions (accepting that observational studies may be misleading), and a judgment of the benefit/harm-cost ratio of the therapy. For daily vitamin supplements, the harm is nil and the cost minimal. Even if the benefit is very modest, it might be reasonable to take them. I would advise older patients that a supplement might reduce risk of fracture and advise them to take a supplement. RTJ

OVARIAN CANCER

6-7 FREQUENCY OF SYMPTOMS OF OVARIAN CANCER IN WOMEN PRESENTING TO PRIMARY CARE CLINICS.

Ovarian cancer **(OC)** has been called the "silent killer" because symptoms are thought not to develop until advanced stages when chance of cure is poor. Standard textbooks state that symptoms do not occur until the disease is advanced. However, several retrospective studies have indicated that the majority of patients with OC do have early symptoms, although not necessarily gynecologic in nature.

Identification of early symptoms may have important clinical implications because the 5-year survival for early stage disease is 70% to 90% compared with 20% to 30% for advanced-stage disease.

This study compared the frequency, severity, and duration of symptoms typically associated with OC *vs* typical symptoms of women attending primary care clinics.

Women with OC described differences in symptoms compared with the typical women presenting for care. Symptoms in patients with OC were more frequent, more severe, and more often had an onset within 6 months. Patients were much more likely to have a combination of abdominal bloating, increased abdominal size, and urinary urgency.

These symptoms warrant further diagnostic intervention because they are more likely to be associated with ovarian tumors.

This requires the patient to carefully recall and describe her symptoms. And requires the physician to be especially alert about fully understanding the onset, severity, and duration of the symptoms. Clarity may be achieved only after several visits.

Physicians should ask women presenting with relatively new-onset symptoms specifically about bloating, abdominal size and urinary symptoms. RTJ

PAIN CONTROL (See CAPSAICIN [4-7])

PAIN OF INJECTION

2-11 COUGHING CAN REDUCE PAIN OF INJECTION

The British Journal of Plastic Surgery reports that, when patients cough vigorously as the needle comes into contact with the skin, the pain of injection is decreased.

There is little doubt that distraction works. It may be explained by the gate-control theory. Stimuli traveling over fast nerve fibers partially override painful sensations traveling along slower nerve fibers.

Coughing may also decrease pain when blood is being drawn.

PHYSICAL ACTIVITY (See FITNESS)

PLAN B (See EMERGENCY CONTRACEPTION [6-9])

POLYCYTHEMIA VERA (See ASPIRIN [1-14]; [1-15])

PREMENSTRUAL DYSPHORIC DISORDER

2-12 *PROZAC* (FLUOXITINE) DROPPED AS INDICATION FOR PREMENSTRUAL DYSPHORIC DISORDER.

Last summer, a European committee reported that "PMDD is not a well-established disease entity". It is listed in the DSM IV only as a research diagnosis. The committee strongly criticized two key trials of the selective serotonin reuptake inhibitor fluoxitine (*Prozac*), noting that in one study almost half of the participants dropped out, and, in the second study, little attempt was made to distinguish between mild and severe health problems. There was concern that women with less severe premenstrual symptoms might receive the diagnosis and be treated inappropriately.

Some researchers welcomed the decision, saying that PMDD (which was only recently described) was an invented illness—a strong example of the medicalization of ordinary life.

Prozac was first approved for PMDD in 2000 by the FDA. An aggressive promotional campaign followed.

This leaves us with PMS ("premenstrual syndrome"). PMS can be severe and accompanied by depression. A variety of lifestyle changes and drugs, including hormonal therapy, have been suggested.

I believe many MDs will continue to prescribe selective serotonin reuptake inhibitors (including Prozac) off label at low dose (20 mg as a trial therapy for select patients). PMS can be disabling. There are few effective alternative therapies. RTJ

PROSTATE CANCER

5-6 PREVALENCE OF PROSTATE CANCER AMONG MEN WITH A PROSTATE-SPECIFIC ANTIGEN ≤ 4.0 NG PER MILLILITER

This study investigated the prevalence of prostate cancer **(PC)** among 3000 men (baseline age 62 to 91) whose PSA consistently remained at 4.0 or less over 7 years. A prostate biopsy was performed at year 7.

Overall prevalence of PC was a mean of 15%, increasing linearly from 6.6% to 26.9%

Overall prevalence of high-grade PC was a mean of 2.2%, increasing linearly from 1% to 6.7%

The positive predictive value of a PSA less than 4.0 has not been well defined. Previous large studies suggested for men over age 50, a value of 4.0 should be used as the upper limit of the normal range. Another study among men with a PSA 2.6 to 4.0 reported that detection of clinically important PC was the same as that among men with PSA over 4.0 It is not surprising that the predictive value of PSA levels is not known.

"There is no PSA value below which a man can be assured that he has no risk of prostate cancer." This is despite the impression of many clinicians that men with a level under 4.0 (92% of all men) have almost no risk of PC.

"Although the use of PSA testing in the United States has led to earlier diagnosis and a marked shift in the stage at which prostate cancer is identified, it is unclear whether PSA testing reduces the rate of death from prostate cancer."

The uncertain benefits of PSA screening have resulted in different recommendations from policymaking organizations. The large difference between a man's risk of death from PC (3% to 4%) and his lifetime risk of the diagnosis of PC (17%) suggests that many PCs detected in routine practice may be clinically unimportant. Lowering the PSA threshold for proceeding to biopsy would increase the risks of overdiagnosis and overtreating clinically unimportant disease.

In this study, the prevalence of PC in asymptomatic men with a PSA level consistently 4.0 and below, ranged from 66 per 1000 men to 269 per 1000 men, depending on level of PSA. And the risk of high-grade PC ranged from about 10 per 1000 men to 67 per 1000 men. Prevalence must be much greater still in men with PSA above 4. This must be the highest prevalence of any asymptomatic cancer, by far.

Progression to clinical disease must be low, since only up to 3% of men die of PC.

Obviously the disease is grossly overdiagnosed and overtreated.

Considering that 92% of men tested have a PSA of 4.0 or less, and that the prevalence of PC in this group varies up to 27%, does it not follow that the great majority of prostate cancers occur in men with a PSA 4.0 or less?

This study, I believe, will encourage primary care clinicians to be more circumspect in recommending routine PSA screening RTJ

5-7 PROSTATE CANCERS IN MEN WITH LOW PSA LEVELS—Must We Find Them?

There is disagreement as to what level of PSA should prompt a biopsy. Controversy stems from a dilemma: 1) Use of higher PSA thresholds risks may miss an important cancer until it is too late. 2) Use of lower PSA thresholds increases the number of biopsies and the proportion of biopsies that identify clinically insignificant disease.

It should not be surprising that 10% to 27% of patients age 62 to 91with a PSA of 4.0 or less were found to have PC. Ninety percent of men age over 50 have PSA values 4.0 or less. Thus, quite a few of these men harbor PC. "Although it would be desirable to detect high-grade cancers that are likely to be life threatening in men with PSA below 4.0, the identification of such cancers will require the development of new biomarkers."

The commentator suggests that we should maintain a cutoff point of 4.0 and above for older men, and 2.5 be used for men age 40-50. Men with baseline PSA 1.0 to 4.0 are at significantly higher risk for a diagnosis of PC

over the next 10 years than are men whose baseline PSA is below 1.0. Thus, in these men, it makes sense to track the rate of rise in PSA values. This has been shown to correlate directly with the risk of cancer.

The cutoff value of PSA that results in 95% sensitivity (detection of 95 % of the cancers) is close to 4.0 for men between ages 50 to 70. The cutoff value of PSA that results in 95% sensitivity for men age 40 to 50 is close to 2.5 Because most of the variability in PSA levels is due to benign prostate enlargement that occurs with age, and men below age 50 are unlikely to have such enlargement, a threshold of 2.5 seems reasonable for these men..

With a PSA in the range of 2.6 to 6.0, younger men are more likely to have curable PC—driven by the fact that younger men are more likely to have less aggressive cancers. The evidence suggests that the detection of PC at younger ages would have a greater effect on the likelihood of remaining free from disease after treatment than would the detection of PC in older men.

Considering the lifetime risk of death from PC is 3%, and the lifetime risk of a diagnosis of PC is 16%, it is apparent that any approach that finds more cancers without quantifying the clinical significance of the detected disease will increase overdiagnosis and overtreatment. This, together with the absence of proof that PSA screening saves lives, suggests that physicians should be circumspect about routinely recommending a prostate biopsy for men over age 50 who have a PSA level 4.0 or less.

Men who present for periodic health examinations should be made aware about the availability of the PSA test. They should be informed (about risks as well as benefits) so they can make an informed decision about the need for routine screening. The enthusiasm for screening in general in the USA suggests that most men will decide to be tested.

If up to one fourth of all men over age 62 with a PSA of 4.0 or less have PC, and about 90% of men have PSA below 4.0, it follows that the vast majority of PCs exists in men with a "low" PSA.

Few screening procedures have been more controversial. Undoubtedly screening with PSA has led to extension of life length in some men. I believe it has led to more unnecessary procedures and adverse complications, and has imposed great long-lasting anxiety.

The controversy continues. I believe it more prudent to screen men under age 60 than those above 60. As patients attain greater age, enthusiasm for screening should wane. RTJ

6-3 NATURAL HISTORY OF EARLY, LOCALIZED PROSTATE CANCER

Even without any initial treatment, only a small proportion of patients diagnosed with PC at an early stage die of the disease within 10 to 15 years following diagnosis.

This observational study of the long-term natural history of localized PC (diagnosed at a mean age 72) assessed disease progression and mortality over years of watchful waiting.

Over 21 years, most patients died of causes other than PC. Only 9% of the cohort survived.

Poor differentiation (in only 4% of the cohort) was a strong predictor of cancer-specific death. This became evident within the first 5 years.

Further follow-up *after* 15 years revealed a substantial worsening of the cancer. The cause-specific mortality from PC increased by 3-fold during years 15 to 20 after diagnosis. .

"If our data reflect a real phenomenon, they would imply that the probability of progression from localized and indolent to metastatic and mortal disease increases markedly after long-term follow-up."

This would support radical treatment, notably among patients with an estimated life-expectancy of over 15 years.

This would argue for greater screening of younger men; less aggressive screening in older men. Long term follow-up may be necessary to observe the full benefits of early diagnosis and definitive treatment in younger men. Older men likely die of other causes.

According to these data, even if your PC is highly differentiated, you still run a risk of about 2 in 100 of developing metastatic disease each year, and about 1 to 2 chances in 100 of dying of PC each year. If you survive over 15 years, these chances are increased by 300%.

Prostate cancer is never cured spontaneously.

If you live long enough and are not treated, your chance of developing metastatic disease (requiring orchiectomy or estrogen therapy) and fatal PC is high, even if you have a highly differentiated PC. If you have a poorly differentiated grade PC and are not treated, you will likely die of it within 5 years.

No doubt some lives are saved by radical treatment. Who to treat and when to treat remains a dilemma. RTJ

PROSTATE SPECIFIC ANTIGEN (See PROSTATE CANCER)

PROVIGIL (See WAKEFULNESS [1-16])

RENAL COLIC

3- 12 TAMSULOSIN (*FLOMAX*) IS EFFECTIVE FOR RENAL COLIC

In patients with renal colic due to juxtavesical stone**,** tamsulosin (*Flomax*) 0.4 mg given 3 times daily was associated with greater chance of passing the stone. And fewer hours to expulsion, fewer number of injections of diclofenac, lower hospitalization rate, and reduced need for endoscopic stone removal.

A therapeutic measure worth keeping in mind.

The major adverse effect of Flomax is postural hypotension. The PDR suggests the highest dose should be 0.8 mg daily. A daily dose of 1.2 mg (0.4 mg 3 times daily) will likely be associated with greater likelihood of hypotension. RTJ

SLEEP (See WAKEFULNESS [1-16]

SMOKING and SMOKING CESSATION

1-4 WHY PEOPLE SMOKE

"If it were not for the nicotine in tobacco, people would be little more inclined to smoke than they are to blow bubbles."

Experimenting with smoking usually begins in the early teenage years. It is driven predominantly by psychosocial motives. Smoking a cigarette is a symbolic act of rebellion, and a statement of independence. The

desired image is sufficient for the novice smoker to tolerate the aversion of the first few cigarettes, after which the pharmacological factors assume much greater importance. As the force from the psychological symbolism subsides, the pharmacological effect takes over to sustain the habit. Absorption of nicotine from the lung and transfer to the brain is almost instantaneous and complete.

Tolerance soon develops, and chronic users probably do not obtain absolute improvements in performance, cognitive processing, or mood. A plausible explanation for why smokers perceive cigarettes to be calming may come from a consideration of the effects of nicotine withdrawal. Smokers start to experience impairment of mood and performance within hours of their last cigarette, and certainly overnight. These effects are completely alleviated by smoking a cigarette.

"Early cessation is especially important."

2-7 ASSESSMENT OF DEPENDENCE AND MOTIVATION TO STOP SMOKING

Whether a smoker succeeds in stopping smoking depends on the balance between: 1) motivation to stop, and 2) degree of dependence. Clinicians must be able to assess both of these characteristics. Motivation is important because "treatments" to assist with smoking cessation will not work unless the smoker is highly motivated. Dependence is especially important in smokers who do not wish to stop. The degree of dependence influences the choice of intervention.

The practical objective of assessing motivation is to identify smokers who are ready to make a quit attempt.

The main value of measuring dependence is to judge the need for pharmacotherapy.

Motivation to stop can be assessed by simple direct questions about the interest in stopping and intention to quit. However, the degree of motivation seems to play a small role in success; once a quit attempt is made, markers of dependence are far stronger determinants of success.

I believe primary care clinicians should frequently assess smoker's motivation to quit. If the patient expresses no interest in stopping there is no benefit in pursuing the subject. Raise the question again at a later consultation. Don't give up.

Smokers who develop angina, have an MI, or stroke, or other serious illness are more likely to quit. This is a great opportunity. It is amazing, however, how many relapse after a time. RTJ

2-8 USE OF SIMPLE ADVICE AND BEHAVIORAL SUPPORT

The most effective method of helping smokers quit is to combine drug therapy (nicotine or buproprion [*Zyban*]), with advice and behavioral support.

Simple advice: "The best thing you can do for your health is to stop smoking. I would advise you to stop as soon as possible." The success rate of brief advice, however, is modest, achieving cessation in about 1 in 40. Nevertheless, it is one of the most cost effective interventions in medicine because the cost is so low. It takes only 1 to 2 minutes in routine consultations.

Behavioral support: Intensive behavioral support is provided outside routine clinical care by trained counselors. About 1 in 13 smokers who are motivated enough to attend counseling sessions are likely to quit. No one type of intensive behavioral support is clearly more effective than any other.

The most effective interventions combine behavioral support with drug treatment.

Primary care clinicians are already aware of the great benefits of quitting smoking. Yet, I believe few routinely ask about smoking and fewer still attempt to offer help. They then miss "The greatest opportunity to improve their patient's health"

We should persist. Don't be discouraged by the poor success rate. I believe obtaining one success in cessation is a benefit equivalent to one coronary by-pass. RTJ

2-9 NICOTINE REPLACEMENT THERAPY

Nicotine products are available to all smokers who want to stop smoking. The purpose is to blunt withdrawal symptoms. Nicotine replacement therapy **(NRT)** is most effective when used in conjunction with behavioral and other types of non-pharmacological-cessation interventions.

NRT makes cigarettes less rewarding. It does not completely eliminate symptoms of withdrawal, possibly because none of the available delivery systems reproduce the rapid and high levels of nicotine in the brain achieved by inhaling cigarette smoke.

The most recent Cochrane review data suggest that NRT doubles achievement of cessation.

NRT should be offered to any regular cigarette smoker who is prepared to make a quit attempt.

It is less harmful than continued smoking even in pregnancy and cardiovascular disease. Increased efforts to quit should be made in these patients,

2-10 BUPROPION AND OTHER NON-NICOTINE PHARMACOTHERAPIES

Bupropion is as effective as nicotine replacement when given in association with intensive behavioral support, achieving a 19% long-term abstinence. It also seems to attenuate the weight gain associated with cessation of nicotine. Use beyond the recommended 8 weeks may confer further protection against relapse.

One study suggested that combined bupropion-nicotine patch produces higher quit rates.

Nicotine replacement is still the treatment of first choice.

3-5 SMOKING AND BLINDNESS

Age-related macular degeneration **(MD)** is related to smoking.

Three cross-sectional studies of over 12 000 patients reported that current smoking leads to a 3- to 4-fold incidence of MD compared with non-smokers. Indeed, the relative risk of smoking associated with MD is higher than the relative risk with ischemic heart disease. A dose-response relationship has been established.

Observational studies show a protective effect of smoking cessation on development of MD.

I was unaware of this association. Informing patients may be a powerful incentive to quit. RTJ

4-8 ABC OF SMOKING CESSATION: HARM REDUCTION

Smoking is primarily a nicotine-seeking behavior.

For individuals addicted to nicotine, cutting down, switching to "low tar" cigarettes, and switching to pipe or cigars do not reduce risk.

There is good evidence that use of smokeless tobacco is less risky than cigarettes.

The technology to develop safe, inhaled forms of nicotine that could provide a more satisfactory alternative to cigarettes is available. In the current regulatory framework, such products would not be licensed and therefore are not commercially available. "This imbalance in the regulation of nicotine needs to be redressed urgently in favor of public health."

Should primary care clinicians advocate their patients who are recalcitrant smokers to judiciously use nicotine replacement in conjunction with cigarette smoking? My PDR (specifically for Nicotrol inhaler) states that patients should be urged to stop smoking completely while using this product. Adverse effects may occur due to high peak nicotine levels. I believe this statement by the drug manufacturer is primarily a defense against litigation.

Should we advise switching to snuff?

Would it be reasonable to encourage manufacture of very high-content nicotine cigarettes? This could easily be done.

These approaches open legal difficulties. We are still constrained by outside forces from applying the best medical care possible. RTJ

STATIN DRUGS

3-6 EFFECT OF INTENSIVE COMPARED WITH MODERATE LIPID-LOWERING THERAPY ON PROGRESSION OF CORONARY ATHEROSCLEROSIS. (REVERSAL)

Is there any benefit in lowering LDL-cholesterol below the recommended 100 mg/dL?

This study, in patients with established coronary atherosclerosis, compared the effect of *moderate* lipid-lowering by 40 mg pravastatin (*Pravachol*) with *intensive* lowering by 80 mg atorvastatin (*Lipitor*). Final mean LDL-c was 110 in the *Pravachol* group and 79 in the *Lipitor* group.

The main outcome (progression of coronary atherosclerosis as determined by intracoronary ultrasound) favored atorvastatin. Over 18 months, the atherosclerotic burden in the *Pravachol* group increased by +2.7% compared with – 0.4% in the atorvastatin group.

"These findings have considerable implications for treatment guidelines for patients with dyslipidemia and established CAD."

Note this was a study of lipid-lowering and atherosclerotic progression in patients with established CHD (a high risk group). It did not report any clinical benefits..

The larger problem of primary prevention is unanswered.

The benefit/harm-cost ratio of intensive statin therapy is not known.

We are becoming a nation of statin takers. Should the recommended dose be the highest demonstrated to produce surrogate end-point benefits? Should primary care clinicians now recommend 80 mg of atorvastatin for all? I believe not. The excess cost would be considerable. And, despite the report that the drug "was well tolerated", there will be serious adverse effects.

Note that LDL-c reached a level below 100 mg/dL in 65% of the group receiving 40 mg Pravachol. I believe it reasonable to start with a moderate dose and gradually increase if needed.

3-7 EFFECTS OF CHOLESTEROL-LOWERING WITH SIMVASTATIN ON STROKE AND OTHER MAJOR VASCULAR EVENTS IN 20 536 PEOPLE WITH CEREBROVASCULAR DISEASE OR OTHER HIGH-RISK CONDITIONS

In a large group of patients at *high risk* of vascular disese, statin therapy rapidly reduced risk of ischemic stroke with no apparent increase in risk of hemorrhagic stroke. Benefits occurred even among those who did *not*

have high cholesterol concentrations. Statin therapy also reduced the risk of major vascular events among people who had previously experienced a stroke or other cerebrovascular event.

A reduction in LDL-cholesterol from about 154 mg/dL to about 115 mg/dL reduced risk of stroke and other major vascular events by about one-quarter. Lowering it from about 115 mg/dL to about 77 mg/dL also reduced risk by about one quarter. "Current guidelines could, therefore, lead to substantial undertreatment of high-risk patients who present below, or close to, particular targets for LDL reduction."

"These results have important implications for revising treatment guidelines which do not currently take into account cerebrovascular disease risk reduction when considering the initiation of statin therapy."

"Statin therapy should now be considered routinely for all patients at high risk of stroke, irrespective of their initial cholesterol concentrations. "

This study confirms the widely-held belief that statin therapy reduces risk of stroke as well as coronary disease. It also strengthens the observation that lowering LDL-cholesterol below levels usually considered "satisfactory" will further reduce risk of atherosclerotic disease.

The risk of events associated with cardiovascular risk factors increases linearly. There are no artificial cut-points dividing "satisfactory" levels vs "unsatisfactory" levels. RTJ

4-2 PHARMACOLOGIC LIPID-LOWERING THERAPY IN TYPE 2 DIABETES

Most adverse outcomes from diabetes are due to vascular complications, either micro-vascular or macro-vascular. Macro-vascular complications are more common and severe. Up to 80% of patients with type 2 diabetes **(DM2)** will develop or die of macrovascular disease. Associated costs are 10 times greater than for microvascular complications.

The foremost goal of therapy in type 2 diabetes should be prevention of cardiovascular disease through optimization of risk factors. This includes aggressive treatment of hypertension, lipid-controlling therapy, smoking cessation, and use of daily aspirin.

Current evidence suggests that lipid control leads to about a 25% reduction in major cardiovascular events.

For primary prevention (statins vs no statin in patients without established cardiovascular disease) the NNT over 4 years to prevent one cardiovascular event = 35; for secondary prevention the NNT = 14 to prevent one event over 5 years.

"Given the absolute risk reductions observed, treatment will probably be cost-effective under most circumstances." This simplifies and reduces the cost of treatment and would be similar, for example, to simply prescribing a daily aspirin for a patient with diabetes."

This study presents a simplifying common- sense clinical approach. for primary care. We need more guidelines like this. It comes close to advising statins for all patients with DM2 RTJ

4-3 INTENSIVE VERSUS MODERATE LIPID LOWERING WITH STATINS AFTER ACUTE CORONARY SYNDROMES

Enrolled over 4000 patients (mean age 58) who had been hospitalized for an acute coronary syndrome (ACS) within the preceding 10 days. ACS defined as acute myocardial infarction (with or without ECG evidence of ST-elevation), or high risk unstable angina.

Randomized to: 1) moderate-intensity treatment with 40 mg pravastatin (*Pravachol*), or 2) high-intensity treatment with 80 mg atorvastatin (*Lipitor*) daily.

Mean achieved LDL-cholesterol was 95 mg/dL in the pravastatin group and 62 in the atorvastatin group.

Over 2 years, the more intensive regimen with atorvastatin resulted in a lower risk of death and major cardiovascular events as compared with the moderate pravastatin regimen. The NNT for 2 years to prevent one death, myocardial infarction, angina requiring rehospitalization, revascularization, or stroke = 53

"Although prior placebo-controlled studies have shown that a standard-dose statin is beneficial, we demonstrated that more intensive lipid-lowering significantly increases this clinical benefit."

Although both drugs were "generally well tolerated", there were significantly more liver-related side effects with high-dose atorvastatin. About 1/3 of all patients in both groups dropped out over the 2 years.

"Our results suggest that after an acute coronary syndrome, the target LDL-cholesterol level may be lower than that recommended in the current guidelines."

This was a secondary prevention trial in a very high risk group. Benefits would be considerably less if high-dose atorvastatin were used in primary prevention. Certainly, these results cannot be extrapolated to primary prevention.

The authors suggest that the high-dose regimen "significantly" increased clinical benefit. Primary care clinicians must ask—is this "clinical" benefit applicable to every day practice? Patients with an acute coronary syndrome and their doctors must decide if one chance in 53 over 2 years is worth while, Note that harms (liver disturbance) were statistically significant, and, I believe, as clinically significant as the reported benefits in the high-dose patients. Cost, adverse effects, and likelihood of discontinuation of treatment must be considered. Some patients, knowing they are at very high risk of death or recurrence, would be inclined to accept the high-dose.

The high drop-out rate because of an adverse event, or the patient's preference, or "other reasons" is disturbing. This occurred despite patients' knowledge that they were at high risk of recurrence and death. Drop-outs would likely be higher still in primary care practice.

Pravastatin has the advantage of not being significantly metabolized by the P450 system in the liver. Thus, concerns about interactions between pravastatin and concomitantly administered drugs is much less than with atorvastatin, which is metabolized by the P450 system. RTJ

5-5 LIPID-LOWERING THERAPY AND IN-HOSPITAL MORTALITY FOLLOWING MAJOR NON-CARDIAC SURGERY

Lipid-lowering therapy inhibits development of atherosclerotic plaques. It is anti-inflammatory and can improve endothelial function and produce a stabilizing effect on vulnerable plaques. These properties may be especially beneficial in the perioperative period because the disruption of unstable plaques is believed to be responsible for most cases of perioperative MI.

This retrospective cohort study was based on hospital and pharmacy records of over 790 000 patients who underwent major non-cardiac surgery at one of 329 hospitals in the USA.

Lipid-lowering therapy in the first 2 days was associated with a lower mortality: 2.18% of the lipid lowering group died compared with 3.15% of those who did not receive it, or for whom treatment was delayed beyond the

first 2 days. The number needed to treat to prevent one death ranged from 30 in patients at high risk of cardiovascular disease to 186 for those at low risk.

What a remarkable effort! A noble attempt, subject to bias and confounding. A provocative study, not definitive—more hypothesis-generating than conclusive.

I suspect that most patients who used statins in the first 2 days were using statins before admission to the hospital for the surgery.

The study used a statistical device termed "propensity matching" to analyze effects of statin use vs no--statin use. I do not fully understand propensity matching. It is an attempt to subclassify participants into groups with common attributes. And to determine risk differences within the groups as one would do in a case-control study.

So. . . would you take a statin before undergoing an elective major surgery? Note that patients at the highest cardiovascular risk gained the most benefit. The majority of older persons in the USA have an indication for statin therapy. This being the case, should not many patients facing elective surgery take a statin beforehand? I believe I would. RTJ

6-1 ASSOCIATION OF STATIN THERAPY WITH OUTCOMES OF ACUTE CORONARY SYNDROMES: The GRACE Study

Statin drugs may have effects in addition to their effect on lipids. These include modulation of inflammation, inhibition of platelet function and thrombosis, and enhancement of endothelial function. The ability of statins to *immediately* affect basic pathophysiologic mechanisms has increased interest in their potential role in acute coronary syndromes. (ACS)

This study examined the association between previous and early in-hospital statin therapy and outcomes of ACS.

Patients who presented with an ACS who were already taking statins were less likely to present with ST-segment elevation MI, experience a large infarct, and have important clinical complications, or die.

Much of the observed effect was lost if statin therapy was not continued during hospitalization. Such patients had death rates similar to patients who had never received statins. Withdrawal of statins reduced the protective effect of statin pretreatment.

In statin-naïve patients, early statin therapy was associated with an improvement in outcomes.

Should primary care clinicians act on these conclusions? Primary care clinicians often act on inconclusive evidence if the putative benefit/harm-cost ratio of the intervention is high. Although the outcomes of the study require confirmation and further experience, I believe the benefit/harm-cost ratio of immediate statin therapy (as of immediate aspirin therapy) for patients with ACS is potentially high. The benefit is potentially life-saving.

The harm and cost of short-term therapy is very low. I would give a high-dose statin immediately on presentation of a patient with presumed ACS.

Those on statins long-term should be continued on statins when admitted for ACS. Those not on statins should start them immediately. And, of course, continue after discharge.

A study "Lipid-Lowering Therapy And In-Hospital Mortality Following Major Non-Cardiac Surgery" (See Practical Pointers May 2004) also presents evidence of immediate protective effects of statins given within the first 2 days after major surgery. RTJ

6-14 DANGERS OF ROSUVASTATIN (*Crestor*) IDENTIFIED BEFORE AND AFTER FDA APPROVAL

A letter to the editor from Sidney M Wolfe, Public Citizen's Health Research Group, Washington DC. Lancet June 26, 2004; 363: 2189-90 comments:

The lipid-lowering drug rosuvastatin (*Crestor*; Astra-Zeneca) is currently in the midst of the most heavily financed launch of a prescription drug *ever*.

The correspondent presents available pre–marketing and post-marketing evidence of the adverse effects of the drug.

Pre-marketing:

Documents included a acknowledgement of a risk of severe myopathy and rhabdomyolyis which clearly increased at the highest dose (80 mg). The preapproval document also stated that 80 mg is associated with a high frequency of creatine kinase elevations (CK 10 times upper normal). *Crestor* was approved with the belief that lower doses would be much safer. The 80 mg dose was subsequently discontinued.

Post-marketing:

Myopathy: Since marketing of rosuvastatin, there have been 18 additional cases of rhabdomyolyis. Two patients were using 40 mg; five using 20 mg; 11 using 10 mg.

Renal toxicity: Rosuvastatin is associated with renal abnormalities.

A small percentage exposed primarily to 80 mg had increased frequency of persistent proteinuria and hematuria, and, in some patients, an increase in serum creatinine. There is a reported dose-associated risk.. The 10, 20, and 40 mg doses have been associated with increasing risk up to 1% of patients. In individuals who develop ++ proteinuria or more, the percentage with an increase of creatinine of over 30% rose incrementally with dose—from 14% in the 5 mg daily dose to 33% in the 40 mg dose.

There have been 8 reported cases of acute renal failure and 4 of renal insufficiency since marketing began. Nine were using 10 mg. .

Other "currently approved statins do not have similar renal effects".

"By now, the number of reported cases of rhabdomyolyis and renal insufficiency or renal failure—20 of which have occurred in people using 10 mg—is certain to have increased substantially from the number filed by April 13, 2004."

Efficacy:

A statistical review of comparative efficacy found no significant difference in LDL-cholesterol lowering between 5, 10, and 20 mg of rosuvastatin and 20, 40 and 80 mg of atorvastatin.

"The renal toxicity, high rate of cases of rhabdomyolyis compared with other statins, and lack of unique benefits are compelling reasons to remove rosuvastatin from the market before additional patients are injured or killed." The correspondent recalls that cerivastatin (*Baycol*) was removed from the market because of increased risk of myopathy.

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A letter to the editor July 10, 2004; 364: 135 from Gunnar O Olsson, Astra-Zeneca, Molindal, Sweden offers a rebuttal:

Crestor has a safety profile comparable to those of other marketed statins. (The US FDA has reviewed post-marketing safety data and has supported this conclusion.)

Crestor was the most extensively studied statin ever submitted for regulatory review. More than 60 countries have approved it on the basis of an excellent benefit/risk profile. "More than 80% of patients can reach their LDL cholesterol goal on the usual start dose of 10 mg."

The reported rate of rhabdomyolyis has remained very low (< 1 in 10 000) is consistent with the rates of all currently marketed statins.

Proteinuria has been associated with *Crestor*, but is transient, and often resolves on continued treatment. It is not predictive of acute or progressive renal disease.

Astra-Zeneca is surprised that The Lancet published a letter containing inappropriate comparisons that serve to cause undue alarm. "The letter, which is a rehash of misinformation presented by Public Citizen in the past includes reference to a non-marketed dose (80 mg) and is "highly speculative".

"Rosuvastatin has an excellent benefit-risk profile compared with other marketed statins, having a better efficacy lowering LDL cholesterol and raising HDL cholesterol and a safety profile comparable to those of other marketed statins."

Comment:

These letters raise an important clinical point. When should primary care clinicians add a new drug to their practice?

Is Crestor a unique and important addition to therapeutics? Or is it just a "me-too" drug? Should primary care clinicians prescribe it a the present time?

1. *Is Crestor more effective in lowering LDL? No. Other statins lower LDL just as much, although they might require a higher dose. Remember, this is a laboratory endpoint, not a clinical endpoint. Clinical efficacy has not been established.*
2. *Is Crestor as safe as other statins? This is the dispute. That the 80 mg dose has been withdrawn because of toxicity raises caution. It will take several years of general use in the USA for the FDA to determine toxicity. Certainly, Crestor is not safer.*
3. *Is Crestor more convenient to administer. Does it require fewer doses? No*
4. *Is Crestor less costly? No. Costs are comparable.*

The first letter may raise an entirely unwarranted red flag. I do not know. I abstracted these letters mainly to reinforce the long-honored and oft-repeated admonishment to primary care clinicians not to be the first to prescribe a new drug, no matter how highly touted, unless it is known to be safe and carry unique and important benefits. Regardless of the question of toxicity, I do not believe the benefits of Crestor are unique or comparatively important.

I would not prescribe Crestor at this time. If it proves equally or less toxic, maintains its reported comparative efficacy in reducing LDL-c, and has a significant cost benefit, I would consider prescribing it.

I have faced (as have most older clinicians) the embarrassment of having a new drug I had prescribed suddenly withdrawn from the market. The patient will ask for an explanation. RTJ

STROKE

2-2 POPULATION-BASED STUDY OF EARLY RISK OF STROKE AFTER TRANSIENT ISCHAEMIC ATTACK OR MINOR STROKE.

Ischemic strokes are frequently preceded by a transient ischemic attacks **(TIA).** This warning gives an opportunity to prevent stroke. This study determined frequency of stroke following a TIA of minor stroke.

	7 days	1 month	3 months
Stroke after a TIA (%)	8	12	17
Recurrent stroke after minor stroke. (%)	12	15	19

"For stroke prevention to be most effective, patients will need to be seen within the first few hours or days."

Many of these patients had risk factors for stroke at baseline (previous TIA, hypertension, smoking, diabetes, angina, previous myocardial infarction, and hyperlipidemia).

They were a high risk group. Interventions (primary prevention) prior to the incident TIA or minor stroke would have lowered the risk considerably. RTJ

2-3 SECONDARY PREVENTION FOR STROKE AND TRANSIENT ISCHAEMIC ATTACKS

Epidemiologic studies show no demonstrable floor exists for the relationship between BP and risk of stroke. Risk continues to halve for every 10 mm Hg fall in diastolic even if initial BP is within conventionally normal limits.

"Definitions of hypertension and hypercholesterolemia in any patient with stroke or TIA seem artificial." Irrespective of starting levels, almost all patients may benefit from reduction of BP and cholesterol.

A general therapeutic principle is emerging. There is no cut-point below which risk is eliminated. Try to reduce BP, LDL-cholesterol, HbA1c, body mass index, abdominal girth and other risk markers to as low a level as reasonable without encountering adverse effects. The cut-point for smoking is an exception. There is only one cut-point—cessation. RTJ

3-7 EFFECTS OF CHOLESTEROL-LOWERING WITH SIMVASTATIN ON STROKE AND OTHER MAJOR VASCULAR EVENTS IN 20 536 PEOPLE WITH CEREBROVASCULAR DISEASE OR OTHER HIGH-RISK CONDITIONS

In a large group of patients at *high risk* of vascular disese, statin therapy rapidly reduced risk of ischemic stroke with no apparent increase in risk of hemorrhagic stroke. Benefits occurred even among those who did *not* have high cholesterol concentrations. Statin therapy also reduced the risk of major vascular events among people who had previously experienced a stroke or other cerebrovascular event.

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This study confirms the widely-held belief that statin therapy reduces risk of stroke as well as coronary disease. It also strengthens the observation that lowering LDL-cholesterol below levels usually considered "satisfactory" will further reduce risk of atherosclerotic disease.

The risk of events associated with cardiovascular risk factors increases linearly. There are no artificial cut-points dividing "satisfactory" levels vs "unsatisfactory" levels. RTJ

5-11 PREVENTION OF DISABLING AND FATAL STROKES BY SUCCESSFUL CAROTID ENDARTERECTOMY IN PATIENTS WITHOUT RECENT NEUROLOGICAL SYMPTOMS.

Patients with substantial (60-99%) carotid narrowing are at increased risk of stroke. Risk is greater if they are already symptomatic (ie, have recently suffered some relevant neurological symptoms).

Carotid endarterectomy **(CEA)** can remove arterial narrowing. The surgical procedure involves risk of perioperative stroke and death. Moreover, even successful CEA might not permanently eliminate all thromboembolic risk. The balance of risk and long-term benefit is uncertain.

What is the benefit/risk ratio of CEA for *asymptomatic* patients?

Because of the immediate risk of stroke or perioperative death, benefits for CEA did not outweigh that of watchful waiting until after 2 years.

Among patients up to 75 years of age with severe carotid stenosis but no relevant neurological symptoms, CEA reduced incidence of stroke or death over 5 years by about 6%. (This takes into account the 3% perioperative hazard of death or stroke.)

Combining the perioperative events and the non-perioperative strokes, the net 5-year risks were 6.4% *vs* 11.8%. (Absolute difference = 5.4%; NNT = 18). For fatal strokes 2.1% *vs* 4.2% (NNT = 48).

Benefits will exceed risks only if perioperative hazards remain low. Surgical expertise may indeed be improving, but so is medical therapy (scrupulous and compliant regulation of lipids, glucose, BP, and cigarette smoking, as well as appropriate platelet inhibition).

What might the primary care clinician advise patients with asymptomatic carotid stenosis?

You have (at the minimum) one chance in 33 of dying or having a stroke as a result of surgery.

If you survive the operation and do not have a stroke due to the surgery, your prognosis will be more favorable in the next 5 years if you have successful surgery:

A. Chance of having a stroke without surgery is 11% over 5 years. (About one in ten)

B. Chance of having a stroke after successful surgery is 3.8% over 5 years. (About one in 25)

Chances of harm and benefit are equal for the first 2 years.

If you are elderly (over75), there is a much greater chance of your dying of a cause other than stroke.

RTJ

STRONTIUM (See OSTEOPOROSIS [1-13])

TAMSULOSIN (*Flomax*) (See RENAL COLIC)

TESTOSTERONE (See HYPOGONADISM)

THROMBOEMBOLIC DISEASE (See VENOUS THROMBOEMBOLISM)

TOBACCO (See SMOKING)

TOLVAPTAN (See HEART FAILURE [4-11])

TRANSIENT ISCHEMIC ATTACK (TIA) (See STROKE [2-2 AND 2-3]

URIC ACID (See GOUT)

VENOUS THROMBOEMBOLISM

6-10 FONDAPARINUX OR ENOXAPARIN FOR THE INITIAL TREATMENT OF SYMPTOMATIC DEEP VENOUS THROMBOSIS

Fondaparinux is a selective inhibitor of activated factor X (Xa). Once-daily injections produce a predictable anticoagulant effect.

This randomized, double-blind multicenter study entered over 2200 patients (mean age 61) with established acute symptomatic DVT of the lower extremity. Randomized to fondaparinux once-daily, or the low-molecular-weight heparin enoxaparin twice-daily. Many received injections at home. All were started on oral anticoagulant therapy within 72 hours.

Double-blind subcutaneous injections were continued for at least 5 days, or until the warfarin-induced INR reached 2.0 or greater. Oral therapy was continued for 3 months

Over 3 months, outcomes were very similar between groups: recurrent thromboembolic events, pulmonary embolism, recurrent DVT, major bleeding, and death.

"This study adds to the growing body of evidence that inhibitors of activated factor X are effective, safe, and easy-to-use antithrombotics."

There are several cautions about at-home treatment with either LMWH or fondaparinux: 1) concern about undertreatment of DVT and resultant pulmonary embolism, and 2) the need for careful laboratory monitoring of oral anticoagulation status during the first days of treatment.

Should fondaparinux be considered a "me too" drug? For a new drug to be adopted into primary care practice to replace an old effective drug, important attributes must be considered—must be just as effective, or more effective; must be established as just as safe or safer; must be more convenient to administer and require fewer doses; must be less costly.

Study sponsored by Sanofi-Synthelabo and MV Organon. I always look for "spin" in drug-company sponsored studies. This study looks straight forward. We look for confirmation. RTJ

VENOUS ULCERATION

6-6 COMPARISON OF SURGERY AND COMPRESSION WITH COMPRESSION ALONE IN CHRONIC VENOUS ULCERATION (ESCHAR study)

Multilayered elastic compression bandaging, leg elevation, and exercise achieve healing in up to 80% at 24 weeks. However, despite continued use of elastic compression stockings, the 12-month recurrence rate is high. .

Simple superficial venous surgery (saphenous vein ablation) theoretically removes the underlying venous incompetence in legs in patients with isolated superficial reflux.

This randomized study reported that healing over 24 weeks was similar between groups. Recurrence of the ulcer within 1 year was much less likely in the surgery group. [NNT = 6]

The investigators state that about a quarter of patients with venous ulcers will refuse surgery. Primary care clinicians then deal with these individuals as best they can. RTJ

VIRTUAL COLONOSCOPY (See COLONOPSCOPY [4-2])

VITAMIN D

4-5 EFFECT OF VITAMIN D ON FALLS

This meta-analysis of randomized, controlled trials concludes that vitamin D supplementation reduces risk of falling in elderly persons. Based on 5 of the trials in over 1200 persons, vitamin D, was associated with a reduction in rate of falls by 22%.

In two studies, vitamin D plus calcium (compared with calcium alone) improved body sway by 9% within 2 months, and increased muscle function up to 11%.

What is a possible mechanism**?** 1,25-hydroxyvitamin D, the active metabolite, binds to a highly specific nuclear receptor in muscle tissue. This may mediate de novo protein synthesis through this specific nuclear receptor leading to an increase in the number, size and strength of muscle fibers. This benefit may occur within several months. (Too early to be attributed to increased bone strength.)

I considered this a weak study, but interesting. If indeed vitamin D strengthens muscle and thus prevents falls, its benefit/harm-cost ratio (which is already high.) will be substantially increased.

Vitamin D and calcium intake is generally too low in the US population. I believe that supplementation is warranted in persons of all ages to help maintain bone mass and strength. If muscles are strengthened, so much the better. RTJ

WAKEFULNESS

1-16 POISED TO CHALLENGE NEED FOR SLEEP, "WAKEFULNESS ENHANCER" ROUSES CONCERN

The drug maker *Cephalon* has made an unusual request. It wants the FDA to approve a drug, not for a condition or a disease, but for a symptom—sleepiness. Not just routine sleepiness, but excessive, or "profound sleepiness"—the kind that makes drivers crash.

The drug is modafinil. It is marketed as *Provigil.* It is already approved for the treatment of narcolepsy. Modafinil somehow—no one knows how—targets the hypothalamus and other sleep-regulating areas of the brain. Patients feel more alert without "hyperarousal".

According to sales figures, more and more sleep experts, psychiatrists, and primary care clinicians are prescribing modafinil for sleepiness for conditions other than narcolepsy. Depression tops the list.

Cephalon's trials reported few adverse effects. A handful of patients discontinued because of headache and nausea. Modafinil induces the P450 system in the liver and may affect metabolism of many drugs. Caution is advised in patients with left ventricular hypertrophy, ischemic heart disease and hypertension. There is an abuse potential. The drug has psychoactive and euphoric effects in some patients.

Modafinil is classified as a schedule IV drug. Long-term studies are limited. The drug blurs the lines between illness and enhancement.

Provigil taken regularly costs several hundreds of dollars per month. The company is ramping up for a marketing blitz which includes direct-to-consumer advertising.

I do not believe primary care clinicians should prescribe this drug. Wait for further experience. RTJ