PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JULY TO DECEMBER

2004

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS-INDEX

EDITORIAL COMMENTS

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ANNALS OF INTERNAL MEDICINE

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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 last half 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, [10-12] indicates the 12th abstract published in the October 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.

HOW THE ARTICLES ABSTRACTED JULY-DECEMBER 2004 INFLUENCED MY PRACTICE

- **Discourage use of "antioxidants" to prevent cancer [10-8]**
- **Encourage use of sweeteners (eg, aspartame) for patients with a weight problem [10-4]**
- **Remember to recommend aspirin for patients with diabetes [12-5]**
- **Warn about the dangers of over-the-counter "herbal medicines" [12-7]**
- **Suggest to interested patients they may calculate the risk of disease [7-9]**
- **Use mneumonic "check lists" more frequently [7-8]**
- **Encourage use of statin drugs for patients with diabetes [8-6]**
- **Do not dissuade patients with troublesome back pain from consulting chiropractors [10-5]**
- **Be aware of the costs of drugs I prescribe [9-2]**
- **Resist use of feeding tubes in terminally ill demented patients. [8-10]**
- **Advise strongly against sugar-sweetened soft drinks [8-1; 8-2]**
- **Depend more on 2-hour post-meal glucose rather than HbA1c and fasting glucose [8-3]**
- **Advise a low glycemic index diet as part of a healthy diet. [8-4; 11-1]**
- **Use ACE inhibitors to prevent microalbuminuria in patients with diabetes [11-8]**
- **Consider and treat non-alcoholic fatty-liver disease in patients with diabetes [12-3]**
- **Encourage the "Mediterranean "diet [9-5]**
- **Inform patients with dizziness that a simple home treatment may reduce symptoms [10-10; 10-11]**
- **Consider some patients with fibromyalgia improve with drug treatment [11-12]**
- **Encourage patients to record their "Family History" [11-2]**
- **Encourage more fish consumption. Inform patients risks are low [12-8]**
- **Encourage use of diuretics and beta-blockers as first-line therapy for hypertension [12-2]**
- **Use intradermal flu vaccine if supplies are very short [11-3]**
- **Do not discourage use of low-dose hormone replacement therapy in menopausal women [8-7]**
- **Be very cautious about use of multiple drugs in elderly patients [12-1]**
- **Reconsider the "power of the placebo" [10-2]**
- **Suggest daily ingestion of components of the "Polymeal" [12-4]**
- **Be very cautious in advising men to check their PSA [11-5]**
- **Share medical decisions with patients [11-6]**
- **Encourage less TV viewing [7-1]**

MEDICAL HEADING SUBJECTS (MeSH) JULY-DECEMBER 2004

ALDOSTERONE
ANTIOXIDANTS
ASPARTAME
ASPIRIN
ASTHMA
AYURVEDIC HERBAL MEDICINE PRODUCTS

BARIATRIC SURGERY (See OBESITY)
BREAST CANCER

CALCULATING THE RISK OF DISEASE
CANCER (See also BREAST CANCER, PROSTATE CANCER)
CANCER OF THE CERVIX (See HUMAN PAPILLOMA VIRUS)
CARDIOVASCULAR DISEASE
CHIROPRACTIC
CHOLESTEROL (See STATIN DRUGS)
COGNITIVE FUNCTION
COST OF MEDICATION
COX-2 INHIBITORS

DEMENTIA
DIABETES
DIET
DIZZINESS

FAMILY HISTORY
FATTY LIVER DISEASE (See HEPATOBILIARY DISEASE)
FEEDING TUBE (See DEMENTIA)
FIBROMYALGIA SYNDROME
FISH CONSUMPTION
FRAILTY

GALLSTONES
GLYCEMIC INDEX; GLYCEMIC LOAD (See also DIABETES)

HEADACHE.
HEART FAILURE
HEMOGLOBIN A1C (HbA1C; See DIABETES)
HEPATOBILIARY DISEASE (See DIABETES)
HORMONE REPLACEMENT THERAPY (See MENOPAUSE)
HUMAN PAPILLOMA VIRUS
HYPERTENSION

HIGHLIGHTS AND *EDITORIAL COMMENTS* JULY TO DECEMBER 2004

ALDOSTERONE

7-10 SERUM ALDOSTERONE AND THE INCIDENCE OF HYPERTENSION IN NON-HYPERTENSIVE PATIENTS

"All known monogenic forms of hypertension in humans can be traced to defects in renal sodium handling."

The potential role of aldosterone in the pathogenesis of essential hypertension is of great interest. No studies have prospectively evaluated the effect of serum aldosterone on the incidence of hypertension.

Do aldosterone levels within the *physiological range* influence the risk of hypertension?

Higher aldosterone levels *within the normal physiologic range* predispose to hypertension. For each quartile increment of serum aldosterone there was a 16% increase in the risk of an increase of an elevation of BP category, and a 17% increase in risk of developing hypertension.

Relative to the lowest quartile of aldosterone, the highest quartile was associated with a 1.6-fold risk of an elevation in BP category and a 1.6-fold risk of developing hypertension. There was a linear increase with each quartile.

"Increasing aldosterone levels within the physiologic range may predispose to hypertension through promotion of sodium retention, potentiation of action of angiotensin II, and impairment of endothelial function."

I abstracted this article as a matter of interest. It has no practical importance at this time. Watch for follow-up studies. Are we beginning to take "essential" out of essential hypertension? RTJ

ANTIOXIDANTS

10-8 ANTIOXIDANT SUPPLEMENTS OF PREVENTION OF GASTROINTESTINAL CANCERS

"Oxidative stress can cause cancer." The GI tract is thought to be the major site of antioxidant action. Many observational epidemiological studies have reported that high intakes of fruit and vegetables (rich in antioxidants) are associated with a lower incidence of cancer. Results of randomized trials of one or more selected antioxidant supplements have been contradictory.

This review identified 14 randomized trials (n = 170 000 subjects) comparing antioxidants *vs* placebo for prevention of GI cancers. The quality of the trials was generally high.

The meta-analysis did *not* show any significant benefits of supplementation with beta-carotene, vitamins A, C, and E (alone or in combination) *vs* placebo for esophageal, gastric, colorectal, pancreatic and liver cancer.

An analysis of 7 high-quality trials showed that antioxidants were associated with a significantly *increased* mortality. "Our result for the detrimental effect of antioxidant supplements on mortality was unexpected."

Four trials (only one was high quality) reported that selenium showed significant *benefit* on incidence of GI cancers.

"Our systematic review contains several major findings." Beta-carotene, vitamin A, and vitamin E supplements given alone or in combination do not seem to have much effect on the prevention of gastrointestinal cancers. Further, they seem to *increase* overall mortality. However, 95% confidence intervals

were large in the analysis of single cancer types and could be compatible with either beneficial or harmful effects.

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The results should not be translated to the potential effects of vegetables and fruits, which are rich in antioxidants. Many substances they contain have been postulated to have anticarcinogenic properties. Data on the effect of fruits and vegetables on cancer have been conflicting.

Randomized trials set up to study prevention of lung cancer showed that beta-carotene actually *increased* the risk of disease. A trial of patients at high-risk of cardiovascular disease showed *no* benefit after 5 years treatment with a supplement combination. “Antioxidant supplements are not having a good press.”

The study found no evidence of benefit (or harm) in the combined group of 5 cancers. However, there were 2 important exceptions: vitamin C and selenium. There was almost no data for vitamin C used alone in cancer prevention. For selenium there was evidence of cancer protection, although on further analysis the benefit was confined to liver cancer.

“The prospect that vitamin pills may not only do no good, but also may kill their consumers is a scary speculation given the vast quantities that are used in certain communities.” However, these results must be considered preliminary.

Nutrient deficiency may increase risk of disease. Replacement in deficient states may confer benefits. But for nutritionally replete individuals, excess intake may harm.

A randomized, placebo-controlled 7-year trial from France (Archives Int. Med. November 22, 2004) presented evidence that low-dose antioxidant supplements reduced total cancer incidence and all-cause mortality in men but not in women. The issue is not yet settled. We can advise patients that as of this date no benefit from high-dose individual vitamins has been demonstrated for cancer prevention.

I would discourage use of high-dose individual vitamins. I would encourage use of supplements not exceeding the recommended daily dose.

11-4 THE SU.VI.MAX STUDY: Trial of Health Effects of Supplementary Antioxidants.

This study tested the efficacy of *nutritional doses* of supplements containing a mixture of antioxidant vitamins and minerals in reducing incidence of cancer, CVD, and all-cause mortality in a general population.

Subjects were randomized to: 1) vitamin-mineral supplement, or 2) placebo daily

The daily supplement contained:

Ascorbic acid	120 mg
Vitamin E	30 mg
Beta-carotene	6 mg
Selenium	100 ug
Zinc	20 mg

There was a statistically significant protective effect in men, but not in women:

Cancer incidence in men:

Intervention 3.5%; Placebo 4.9%. Absolute difference = 1.4% NNT 7 years = 71

Total mortality in men

Intervention 1.6%; Placebo 2.5% Absolute difference = 0.9% NNT 7 years = 111

The authors speculate that the difference in outcomes of men *vs* women might be due to a generally lower intake and plasma concentration of antioxidants (especially beta-carotene) in men. Indeed, baseline serum concentrations were lower in men.

The study reinforces the general recommendation of a life-long diversified diet containing an abundance of foods rich in antioxidants.

Is the putative benefit of supplements clinically important? I believe it is.

How can we apply this information to primary care in the USA?

I believe at this time we should advise against high doses of individual vitamins and minerals. There is no evidence of benefit and there is evidence of possible harm.

I believe it is likely that any benefit from supplements will be in individuals whose nutritional status is borderline. In primary care practice, we cannot assess the nutritional status of every individual patient. I believe therefore that a routine recommendation for a daily low-dose supplement for adults is reasonable. Although in adequately nourished individuals this may not bring any benefits in protecting against cancer or cardiovascular disese, the supplements do contain, as an added attraction, vitamin D and folic acid which may bring benefits.

ASPARTAME

10-4 ASPARTAME AND ITS EFFECTS ON HEALTH

Aspartame (*NeutraSweet; Equal; Generic*) consists of two amino acids—phenylalanine and aspartic acid. Both are contained in normal dietary proteins. Aspartame is 200 times sweeter than sucrose. The European population consumes about 2000 tons annually as a substitute for sugar.

Is it harmful? The European Scientific Committee on Food was convinced in 1988 that aspartame was safe. The committee conducted a further review encompassing over 500 reports in 2002. It concluded from biochemical, clinical, and behavioral research that a daily intake of up to 40 mg/kg/day remained entirely safe—except for people with phenyketonuria. Does aspartame embody a healthy way of life and reduce prevalence of obesity? In most Western countries, sugar provides about 10% of total calories (50 g daily, or about 200 kcal). If this were entirely replaced by a non-nutritive, non-caloric sweetner, “obesity could indeed be vanquished - assuming these calories were not replaced”. However, evidence that aspartame prevents weight gain or obesity is generally inconclusive.

One *packet of generic aspartame contains 35 mg. An “acceptable daily intake” = up to 3500 mg, or 100 packets, much less than usually consumed. (Persons who drink many sweetened soft drinks daily may approach this quantity.)*

One rounded teaspoon of sucrose (5 g) contains 20 kcal. If I added a teaspoonful of sugar to each of my 3 cups of coffee daily in place of 3 packets of aspartime (and all other intake remained constant) my caloric

intake would increase by 60 kcal each day. By my calculation, if I added this amount to my daily caloric intake, and assuming perfect metabolism and conversion into fat tissue, I would gain over 5 pounds a year.

I believe sweeteners are a reasonable ingredient in the diet of persons who tend to be overweight and obese, and especially in persons with diabetes. Primary care clinicians should so advise them. Use in place of sucrose will reduce postprandial blood glucose levels and reduce a risk factor for cardiovascular disease.

ASPIRIN

12-5 ASPIRIN USE AMONG PATIENTS WITH DIABETES

Adults with diabetes, but with *no clinical cardiovascular disease*, may have risk of CVD events similar to non-diabetic adults *with established CVD.*

Strategies to prevent CVD events in persons with diabetes are underused. Aspirin effectively reduces risk of first and subsequent myocardial infarction in patients with diabetes as well as in those without. Many adults with diabetes do not use it.

This study assessed regular aspirin use among adults with diabetes between 1997 and 2001.

Use remained less than ideal for patients with CVD. One quarter of diabetic patients with established heart disease or stroke did not use aspirin. Among those with risk factors for CVD (hypertension, dyslipidemia, smoking) 60% did not use aspirin. Almost 2/3 of those without CVD did not use aspirin.

Overall use by women was lower than by men.

Although aspirin use in patients with diabetes is increasing, use is suboptimal, especially in women, younger patients, and in those with major CVD risk factors.

The benefit/harm-cost ratio of aspirin is among the highest of any drug.

Should all patients with diabetes take aspirin? I believe in the great majority the benefits outweigh risks. Risks of aspirin in younger persons with no other risk factors for CVD may outweigh benefits. But even in younger persons the duration of diabetes should be considered.

I believe at times primary care clinicians simply forget to recommend aspirin.

ASTHMA

7-6 PHARMACOLOGICAL MANAGEMENT TO REDUCE EXACERBATIONS IN ADULTS WITH ASTHMA

Exacerbations are one of the most important endpoints for clinical trials of asthma. They represent the period of greatest risk of emergency visits, hospitalization, and death.

Corticosteroids are potent (but nonspecific) anti-inflammatory agents. Inhaled corticosteroids (**ICS**) are the single most effective therapy for adult patients with asthma who require more than an occasional inhalation of a short-acting beta agonist. Low doses are first-line therapy. Since airway inflammation is present even in mild disease, inhaled corticosteroids are first-line treatments of patients who need more than an occasional inhalation of short-acting beta agonists. Higher doses (with or without an added long-acting beta-agonist) can be added. With long-term therapy, risk of adverse effects increases. Proper inhaler

technique, use of a spacer, and mouth rinsing after each actuation significantly reduce systemic absorption. Patients should be so educated.

By themselves, long-acting inhaled beta agonists have only a modest beneficial effect in reducing exacerbations. When added to inhaled corticosteroids, they do help to reduce exacerbations. Monotherapy is best avoided. It its less effective than ICS.

Lifestyle management leads to the use of a minimal amount of medication: smoking cessation, eliminating allergens, weight loss if overweight or obese (this has been demonstrated to reduce symptoms and improve lung function and quality-of-life in patients with asthma). If smoking continues, oral corticosteroids do not lead to significant improvement.

Oral corticosteroids, leukotriene modifiers, and theophylline can occasionally be used as add-on therapy.

The treatment table on page 373 is helpful.

Smokers should be told—"You will not get better unless you stop smoking."

AYURVEDIC HERBAL MEDICINE PRODUCTS

12-7 HEAVY METAL CONTENT OF AYURVEDIC HERBAL MEDICINE PRODUCTS

Ayurvedic medicine originated in India more than 2000 years ago. It relies heavily on herbal medicine products **(HMP).** HMPs are marketed as dietary supplements under the *Dietary Supplement Health and Education Act.* Proof of safety and efficacy is not required.

Ayurvedic HMPs containing heavy metals are readily available in the USA. This study determined the prevalence and concentrations of heavy metals in Ayurvedic HMPs.

Fourteen of 70 (20%) HMPs tested contained heavy metals:

	No. containing	Median concentration—mg/gram	Range mg/gram
Lead	13	0.040	0.005 to 37
Mercury	6	20	0.03 to 104
Arsenic	6	0.4	0.037 to 8

Taken as recommended by the manufacturer, heavy metal intoxication may result. One in 5 Ayurvedic HMPs produced in South Asia contains potentially harmful levels of lead, mercury, and/or arsenic. Users are at risk.

Traditional medicines from China, Malaysia, Mexico, Africa, and the Middle East have also been shown to contain heavy metals.

The recent furor over unreported adverse effects of Merck's Vioxx led me to include this study. Can you imagine the furor which would occur if a product of Merck was reported to contain arsenic, mercury, or lead? Our drug oversight system is schizophrenic.

The term Ayur-veda comes from the Sanskrit meaning Life (health) and knowledge. Google presents over 1 million citations. The wide range of products available, which are said to be all "natural", include nostrums for vitality and strength; healthy blood and skin; healthy hair growth; proper function of the immune system, heart, joints, muscles, kidneys, adrenal, liver, lung, and reproductive system; mental clarity; control of blood glucose; and depression.

BREAST CANCER

7-2 EFFICACY OF MRI AND MAMMOGRAPHY FOR BREAST CANCER SCREENING IN WOMEN WITH FAMILIAL OR GENETIC PREDISPOSITION.

Mammographic screening of women between ages 50-70 can reduce mortality from BC by about 25%. The consensus is that BC screening in this age group is effective. Although screening is frequently offered to women under age 50 who have a genetic predisposition, efficacy is unproven. Preliminary results of screening studies with mammography reported a low sensitivity for detecting BC in these women.

This study compared the efficacy of magnetic resonance imaging **(MRI)** with that of mammography for screening this group of younger, high-risk women (mean age 40).

MRI detected 32 of 45 BCs (22 of these were not visible on mammography). Missed 13 of 45 (including 5 of 6 DCIS, 4 interval cancers, and 1 detected by clinical examination.)

Mammography detected 18 of 45 BCs (10 of which were visible on MRI)' missed 27 (including 22 visible on MRI), but detected more DCIS (5 of 6)

With respect to all BCs:	Sensitivity	Specificity
Clinical examination	18%	98%
Mammography	40%	95%
MRI	71%	90%

In younger women at high risk for BC due to a genetic predisposition or a strong family history. MRI detected more BCs than mammography (71%.*vs* 40%). The specificity of MRI was lower (more false positives—10% vs 5%).

MRI detected 20 cancers that were not detected by mammography or clinical examination. Tumors tended to be smaller and positive nodes were present in only one case.

Comment:

As usual, a test with a high sensitivity (high % of true positive tests) is associated with a lower specificity (high % of false positives). In this group, MRI detected many more BCs than mammography, but the higher false positive rate led to more follow-up examinations and biopsies. Women age 40 have more dense breast tissue. This makes interpretation of mammography more difficult.

I wonder if this study might reduce the frequency of prophylactic mastectomy in high risk women. RTJ

7-3 BREAST CANCER SCREENING WITH MRI: What Are The Data For Patients At High Risk?

The average lifetime risk of BC in American women is one in seven. This risk increases in women with a strong family history of BC, and an inherited mutation (BRCA genes) Women with BRCA mutations make up about 5% to 10% of women with BC. Their risk of ovarian cancer is also high.

Cumulative risk of BC of women with these mutations range from 3% at age 30, to 50% by age 50, and to 85% at age 70. These BCs often occur at a younger age, have "pushing margins", a high nuclear grade, and lack estrogen receptors. Cancers in these women grow rapidly.

MRI is highly sensitive in detecting BC. Disadvantages include cost, variations in technique and interpretation, imperfect specificity, and variations in enhancement during the menstrual cycle (midcycle is optimal). MRI screening will likely be refined and standardized. "Whether the excellent results reported can be achieved in primary care practice remains to be determined."

Discovering and removing a BC in these high-risk women does not end surveillance. Screening the remaining breast tissue must continue after surgery. Considering the lifetime need of frequent screening and the continuous anxiety associated, I can understand that many women would grow weary and opt for bilateral prophylactic mastectomy RTJ

CALCULATING THE RISK OF DISEASE

7-9 CALCULATING THE RISK OF DISEASE www.yourdiseaserisk.harvard.edu

A review note in BMJ July 24, 2004; 329: 237 calls attention to an online tool for determining an individual's risk for five of the most important disease groups in the USA (cancer, diabetes, heart disease, stroke, and osteoporosis). It is presented by The Harvard Center for Cancer Prevention, part of the Harvard School of Public Health. It is an expanded version of the center's cancer risk assessment website.

The site is an interactive educational tool that seeks to encourage healthy lifestyles. It questions the inquirer's eating habits, drinking, and exercise, and offers personalized tips for disease prevention.

I accessed this site on August 13, 2004 and completed the heart disease risk evaluation. Individuals can easily and quickly complete the 21 or more questions asked. It includes all components of the Framingham Risk Score except HDL-cholesterol.

In addition it asks for past history of heart disease, family history, waist size, diabetes, 7 different questions about diet and alcohol, vitamin supplements, and exercise.

On completion it presents a colored risk scale (low to high) and places the individual's estimated risk compared with average.

A useful addition is a list of tips on how you can reduce your individual risk. I received 5 different tips to reduce my risk. RTJ

CANCER

10-8 ANTIOXIDANT SUPPLEMENTS OF PREVENTION OF GASTROINTESTINAL CANCERS

"Oxidative stress can cause cancer." The GI tract is thought to be the major site of antioxidant action. Many observational epidemiological studies have reported that high intakes of fruit and vegetables (rich in antioxidants) are associated with a lower incidence of cancer. Results of randomized trials of one or more selected antioxidant supplements have been contradictory.

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CARDIOVASCULAR DISEASE

7-8 A PRACTICAL AND EVIDENCE-BASED APPROACH TO CARDIOVASCULAR DISEASE RISK REDUCTION: *Secondary Prevention. A check list:*

ABCS OF CARDIOVASCULAR DISEASE RISK MANAGEMENT

A	B	C
Aspirin	Beta blocker	Cholesterol management
ACE inhibitor	BP control	Cigarettes

D	E
Diet and weight	Exercise
Diabetes	Ejection fraction.

I believe checklists are of value to primary care clinicians. Many effective preventive measures are not prescribed when they are indicated.

Most of these applications are also applicable to primary prevention.

I believe aspirin, beta-blockers, ACE inhibitors, statins, and antihypertension drugs are essential components of the list. Full doses may not be needed. Administration can go low and slow. A pill cutter can drastically reduce cost.

Life-style changes mandatory.

My wife and I have found checklists helpful when we go on trips. We have a list of things to do to set the apartment straight before leaving, and a list of things we should not forget to take along. Almost every time, on going through the lists, we note one or two items we have forgotten.

Clinical practice has become so complex, primary care needs more check lists, RTJ

8-6 PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE WITH ATORVASTATIN IN TYPE 2 DIABETES

Current prescription rates for lipid lowering drugs in patients with DM2 remain low, even in patients with established cardiovascular disease **(CVD).**

This study assessed the effectiveness of a 10 mg dose of atorvastatin (*Lipitor*) *vs* placebo in *primary* prevention of CVD in patients with DM2. None had high concentrations of LDL-c. The trial was stopped 2 years early because of demonstration of significant benefit.

None had documented history of CVD. All had at least one risk factor: retinopathy, macro- or micro-albuminuria, current smoking, or hypertension. The risk of a major cardiovascular event in these patients was 10% over 4 years.

Incidence of major cardiovascular events was 25 per 1000 person-years at risk in the placebo group vs 15 per 1000 person-years at risk in the atorvastatin group. Therefore, allocation of 1000 patients to atorvastatin

would avoid 37 first major events over a 4-year follow-up. 27 patients would need to be treated for 4 years to prevent one event. [NNT (for 4 years to benefit one) = 27]

"The debate about whether *all* patients with DM2 warrant statin therapy should now focus on whether any patients can reliably be identified as being at sufficiently low risk for this safe and effective treatment to be withheld."

These data challenge the use of a particular threshold level of LDL-c as the sole arbiter of which patients with DM2 should receive statin therapy (as in the case of most current guidelines). Target levels of LDL-c (100 mg/dL) could be lowered.

An editorialist comments: The conclusions of the study—"Seems too far-fetched in view of the available clinical trials and epidemiological data". He cites 4 large studies of lipid control which contained many patients with DM2. Two of the four did not report a statistically significant reduction in coronary disease. Two did.

Clinical trials enroll carefully selected patients. The results cannot necessarily be extrapolated to primary care practice. Many patients may be at low risk and the benefit/ harm-cost ratio may be too low to warrant long-term treatment. Some may be at higher risk of adverse effects from statins. As always, individualization is required.

I believe the majority of patients with DM2 will benefit from statin therapy for primary prevention. Most will have one or more additional risk factors. There would be no question regarding secondary prevention.

Authors and publishers persist in presenting relative benefits (rather than absolute differences). Thus, they reiterate that treatment with atorvastatin was related to a 37% reduction in major coronary events; a 31% reduction in coronary revascularizations; a 48% reduction in stroke; and a 27% reduction in deaths.

This can be very misleading. I believe statements of relative benefits should be eliminated from published reports.

9-3 ASSOCIATION OF HEMOGLOBIN A1C WITH CARDIOVASCULAR DISEASE AND MORTALITY IN ADULTS

Diabetes raises the risk of *macro*-vascular disease as well as micro-vascular disease. Evidence suggests that the relation between plasma glucose and macro-disease (cardiovascular disease; **CVD**) is continuous and does not have obvious thresholds.

In this study of over 10 000 subjects, the risk of CVD, CHD and mortality increased continuously as HbA1c rose. Cardiovascular disease events increased continuously from 6.7 per 100 men with HbA1c less than 5% to 35 per 100 men with HbA1c over 7%. The risk for CHD was significantly increased in those with HbA1c 5.0% to 5.4% compared with those with HbA1c concentrations less than 5%. This included individuals *without* diabetes.

Each increase of HbA1c of 1% was associated with a relative risk of 1.26 for death from any cause. The relationship was apparent in persons without known diabetes. (Only 193 subjects had known diabetes.)

HbA1c levels were significantly associated with all-cause mortality and coronary and cardiovascular disease even below the threshold commonly accepted for the diagnosis of diabetes. Each increase of HbA1c of 1% was associated with a 20% to 30% increase in mortality and cardiovascular events. The gradient was apparent through the population range from less than 5% up to 6.9%.

Subjects with HbA1c over 7% made up 4% of the sample and contributed about 25% of the excess mortality.

Reduction in HbA1c levels in persons *without* diabetes may lessen their risk.

The metabolism of glucose is related to risk of cardiovascular disease.. A healthful lifestyle should include attempts to control postprandial glucose levels in patients without diabetes as well as those with diabetes. Diets containing a low glycemic load are an important part of healthy living. RTJ

9-4 GLYCOSYLATED HEMOGLOBIN: FINALLY READY FOR PRIME TIME AS A CARDIOVASCULAR RISK FACTOR.

The societal burden of the diabetic epidemic is being fueled by our current lifestyle. Diabetes is just the measured tip of a much larger "dysglycemic iceberg".

It is now clear that fasting and 2-h PG levels well below the diabetes cutoffs are cardiovascular risk factors. And that a progressive relationship between PG and CVD risks extends from normal glucose levels right into the diabetic range, with no clear lower threshold.

Evidence is accumulating that HbA1c is a progressive risk factor for CVD in people *without* diabetes as well as people with diabetes. A HbA1c level of 6.59% in a *non-diabetic* person predicts a higher CVD risk than a HbA1c of 5.5%. Even after excluding individuals with a HbA1c level of 7% and greater, with diabetes, and with a history of heart disease, the increase in risk for CHD, CVD, and total mortality for every 1% rise in HbA1c was 40%, 16%, and 26% respectfully.

We can conclude that HbA1c is an independent and progressive risk factor for incident CVD regardless of diabetes status. "Glycosylated hemoglobin level can now be added to the list of other clearly established indicators of CVD risk." "The presence or absence of diabetes is likely to become less important than the level of glycosylated hemoglobin in the assessment of CVD risk. Reducing HbA1c in both diabetic and non-diabetic persons may reduce cardiovascular risk."

It will be interesting to find out the relative risks of HbA1c and hyperinsulinemia compared with lipids. Could it be that markers of a stressed glucose-insulin metabolism will become clinical risk indicators as important as LDL-c and HDL-c? This would include the 2-hour postprandial glucose as well as the HbA1c level. Could food sugars become as important a risk factor as saturated fats? Excess sugar intake is related to obesity and the metabolic syndrome, and in turn to hypertension, hyperinsulinemia, and dyslipidemia.

I believe, at the present stage of our knowledge, we should consider aberrant glucose metabolism an important risk factor for CVD and act on it. RTJ

10-6 COXIBS AND CARDIOVASCULAR DISEASE

Recently *Vioxx* (a selective COX-2 inhibitor) was removed from the market by Merck following the results of a trial designed to test effects on adenomatous polyp formation in the colon. The data and safety monitoring board took action to stop the study prematurely because of a significantly increased incidence of serious thromboembolic adverse events (*vs* placebo) in the group receiving 25 mg of *Vioxx* daily. The incidence of myocardial infarction and thrombotic stroke in the two groups began to diverge after a year. FDA had approved the 3 COX-2 inhibitors on the basis of trials that typically lasted three to six months.

In the colon polyp study, which enrolled patients without known cardiovascular disease, 3.5% of those receiving *Vioxx* and 1.9% of those receiving placebo had a myocardial infarction or stroke. (*Absolute difference = 1.6%; NNT to harm one patient = 63.*) This amounts to an excess of 16 extra events per 1000 treated. And this was in a group with presumably low risk.

Considering the tens of millions of patients who were taking rofecoxib…"We are dealing with an enormous public health issue." "Even a fraction of a percentage excess in the rate of serious cardiovascular events would translate into thousands of affected persons."

COX-2 inhibitors blunt the production of prostaglandin I_2 (a factor which protects endothelium). They do not blunt the production of thromboxane (a risk factor for thrombosis). A single mechanism of COX-2 inhibitors (depressing I_2 while leaving thromboxane intact) might elevate BP, accelerate atherogenesis, and predispose to thrombosis. The higher the patient's intrinsic risk of cardiovascular disease, the more likely the manifestation of a clinically important adverse event.

"We now have clear evidence of an increase in cardiovascular risk that revealed itself in a manner consistent with a mechanistic explanation that extends to *all* coxibs."

How should clinicians respond? Selective inhibitors of COX-2 remain a rational choice for patients at low cardiovascular risk who have had serious gastrointestinal events, especially while taking traditional NSAIDs. "It would appear prudent to avoid coxibs in patients who have cardiovascular disease, or who are at risk for it."

This is discouraging. Primary care clinicians are often admonished not to prescribe a new drug until it has been in general use for 2 or 3 years (unless it has unique benefits). Two or 3 years of general use would presumably reveal any adverse effects not demonstrated in trials. Now we find that, after 5 or more years of general use, Vioxx has unreported and serious adverse effects. I suspect that more established drugs will be discovered to have unsuspected long-term serious adverse effects. This reinforces the old adage that "The best medicine is no medicine".

It has long been realized that NSAIDs increase risk of hypertension and heart failure. It appears that the risk is augmented in patients taking COX-2 inhibitors.

The FDA and the drug companies manufacturing other COX-2 inhibitors now must conduct trials to determine cardiovascular risk of their products as compared with placebo. Meanwhile, primary care clinicians should be cautious about prescribing any coxib.

CHIROPRACTIC

10-5 COMPARATIVE ANALYSIS OF INDIVIDUALS WITH AND WITHOUT CHIROPRACTIC COVERAGE.

There is evidence supporting the efficacy of chiropractic care for back pain. A comprehensive review reported that spinal manipulation was better, and no trials found it significantly worse, than conventional treatment.

This retrospective study analyzed claims data covering a 4 year period. It compared more than 700 000 health plan members who had additional chiropractic coverage *vs* over 1 million members without coverage.

Compared with those without coverage, members with chiropractic coverage had *lower* annual costs (by $200). They also had a *lower* average back-pain episode-related cost.

Having coverage was associated with a 1.6% decrease in total annual health care costs.

Back pain patients with chiropractic coverage had lower utilization of plain radiographs and MRI; fewer hospitalizations; less surgery and inpatient care.

Chiropractic care sought by members with insurance coverage was more often substituted for usual medical care. It was less often an add-on care.

Patients treated for back pain by chiropractors tend to be more satisfied than those treated by MDs.

The study raises the intriguing possibility that chiropractic may in fact be the more economic approach to the management of the complex, ill-defined, recurrent, and often refractory symptoms of back pain.

My primary advice for a patient consulting me for back pain would be to keep on being as active as possible. Stay out of bed. Take acetaminophen or an NSAID temporarily. In most cases the pain will abate spontaneously. For more protracted back pain, I would not hesitate to refer to a chiropractor well established in the community with whom I was personally acquainted. I would not refer for conditions other than back pain.

COGNITIVE FUNCTION

9-8 PHYSICAL ACTIVITY, INCLUDING WALKING, AND COGNITIVE FUNCTION IN OLDER WOMEN

This study examined the relation of long-term regular physical activity, including walking, to cognitive function in a large cohort of women. Higher levels of activity were associated with better cognitive performance. On a global score combining results of all cognitive tests, women in the second through the fifth quintile of energy expenditures scored an average of 0.06, 0.06, 0.09, and 0.1 standard units higher than women in the lowest quintile.

Compared with women in the lowest physical activity quintile, those in the highest quintile had a 20% lower risk of cognitive impairment.

"In this large prospective study of older women, higher levels of long-term regular physical activity were strongly associated with higher levels of cognitive function and less cognitive decline. This benefit was similar in extent to being about 3 years younger in age." The association was not restricted to women engaging in vigorous activity. Walking the equivalent of at least 1.5 hours per week at a 20 to 30 minute per mile pace was also associated with better cognitive performance.

This is an interesting, provocative study. It is not proof of any relationship between physical activity and cognition. Observational studies cannot prove cause and effect. But I believe patients should be reminded of the many benefits of physical fitness. There is now suggestive evidence of improved cognitive function.

A companion article in this issue of JAMA (pp 1447-52) "Walking and Dementia in Physically Capable Elderly Men", first author Robert D Abbott, University of Virginia School of Medicine, Charlottesville, comes to the same conclusion. RTJ

COST OF MEDICATION

9-2 COST-RELATED MEDICATION UNDERUSE

Patients often restrict their use of prescribed medications because of cost. Those who have chronic conditions, and require long-term medication are most vulnerable. Underuse has been associated with serious health consequences, increased emergency department visits and nursing home admissions, and decrements in self-reported health status.

This nationwide survey identified of a group of patients with chronic illnesses who reported underuse of medication and the reasons for underuse, mostly due to costs. About 1/3 never discussed this problem with their doctors. Most patients were never asked about cost problems. When patients did talk about the costs, the majority found the conversation helpful. However, many stated their prescription was never changed to a generic or to a less expensive alternative. They received no information about which drug(s) might be less necessary and might be excluded. Few patients were given other forms of assistance such as referral to a social service agency, information about programs that help pay drug costs, or where to purchase less expensive medication.

"Very few chronically ill patients who restrict their medication use because of cost appeared to be receiving assistance from their health care providers."

"Clinicians should take a more proactive role in identifying and assisting patients who have problems paying for prescription drugs."

Clinicians consider the benefit/harm ratio of all drugs they prescribe. I believe the ratio is better expressed as benefit/harm-cost. When a prescribed drug is expensive it would be appropriate to mention this to even the most affluent patient. And to routinely discuss cost considerations with those less economically advantaged. Rapport with social services is most helpful.

This study raises a most important consideration in these days of patient-centered medicine. When negotiating a treatment plan with the patient, we must arrive at a conclusion which the patient understands and is willing and able to follow. An expert consultation is worthless if the patient cannot or will not follow the prescription for any reason, including costs.

I believe most doctors have little knowledge about costs of drugs and procedures they prescribe. They should learn. The lowest cost effective and safe program should be offered to all patients, regardless of their economic status.

I am convinced the American public is over-charged and over-medicated.

The drug store pages on the internet are rapidly accessible and list prices. Drugs ordered over the internet may be less costly than at the local pharmacy. I believe much of the cost of drugs with a large therapeutic index (eg, statins) can be reduced by use of a pill cutter. An 80 mg pill may cost the same as a 20 mg pill. When cut into quarters, the cost would be reduced by 75%. It makes little difference in the effectiveness and safety of many drugs whether the daily dose is a few milligrams above or below the prescribed dose. This is not applicable to drugs with a narrow dose-range for safety and effectiveness. RTJ

COX-2 INHIBITORS

10-6 COXIBS AND CARDIOVASCULAR DISEASE

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How should clinicians respond? Selective inhibitors of COX-2 remain a rational choice for patients at low cardiovascular risk who have had serious gastrointestinal events, especially while taking traditional NSAIDs. "It would appear prudent to avoid coxibs in patients who have cardiovascular disease, or who are at risk for it."

This is discouraging. Primary care clinicians are often admonished not to prescribe a new drug until it has been in general use for 2 or 3 years (unless it has unique benefits). Two or 3 years of general use would presumably reveal any adverse effects not demonstrated in trials. Now we find that, after 5 or more years of general use, Vioxx has unreported and serious adverse effects. I suspect that more established drugs will be discovered to have unsuspected long-term serious adverse effects. This reinforces the old adage that "The best medicine is no medicine".

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DEMENTIA

8-10 USE OF RAPID-CYCLE QUALITY IMPROVEMENT METHODOLOGY TO REDUCE FEEDING TUBES IN PATIENTS WITH ADVANCED DEMENTIA

Feeding tubes are often placed in patients with dementia who are hospitalized for an acute illness; often contrary to the wishes of patients and families.

A growing body of research over the past decade has questioned the utility of placing feeding tubes in patients with advanced dementia. There is *no* evidence that feeding tubes in this population prevents aspiration, prolongs life, improves overall function, or reduces pressure sores. Feeding tubes may adversely affect quality-of-life. Patients may require wrist restraints to prevent pulling on the tube. They may develop cellulitis at the site, and be deprived of the social actions and pleasure surrounding meals.

The aim of this study was to describe the effect of efforts of an interdisciplinary team focusing on an educational program to change the staff's approach to use of feeding tunes. After completion of the program, use of feeding tubes declined dramatically. This prevented patients from receiving futile treatment.

I omitted details of the study, and concentrated only on a reminder that feeding tubes may be harmful and overused in primary care practice. I do believe, however, that use is declining. RTJ

DIABETES

8-1 SUGAR-SWEETENED BEVERAGES, WEIGHT GAIN, AND INCIDENCE OF TYPE 2 DIABETES IN YOUNG AND MIDDLE-AGED WOMEN

This study examined the relationships between sugar-sweetened beverage consumption (especially soft drinks), weight gain, and risk of diabetes in a large cohort of young and middle-aged women.

Over the entire 10 year period, women who *increased* their sugar-sweetened soft drink **(S-SSD)** intake from low to high had larger increases in weight compared with women who maintained a low intake, or substantially reduced their intake.

In contrast, women who *decreased* their S-SSD reduced their total energy consumption by 319 kcal/d. Women who *decreased* their intake during the first 5 years and maintained a low level gained less weight than those who increased their intake (2.8 kg. vs 4.4 kg).

Participants whose consumption of *diet* soft drinks *increased* from one drink or less per week to more than one drink per day gained significantly *less* weight (1.6 kg) than women who *decreased* their intake from one or more drinks daily to 1 drink or less per week (4.2 kg). [*Ie, consumption of calorie free drinks apparently to some extent, blunts ingestion of calorie-containing foods.*]

Greater S-SSD consumption was strongly associated with progressively higher risk of type 2 diabetes. (RR = 1.9 in women consuming one or more drinks per day *vs* those consuming less than one per month.)

Sugar-sweetened fruit punch was also associated with increased risk of diabetes. (RR = 2.0)

"Pure" fruit juice was *not* associated with risk of diabetes.

Over 8 years, there were positive associations between sugar-sweetened beverage consumption and both greater weight gain and risk of type 2 diabetes, independent of other known risk factors.

Energy provided by sugar-sweetened beverages does not affect subsequent food and energy intake. (Ie, little or no compensation by reduction in intake of other foods.) Weight gain and obesity result from the positive energy balance.

Fruit juice was *not* associated with diabetes risk in this study. This suggests that naturally occurring sugars in beverages may have different metabolic effects than added sugars

This is an important life-style consideration.. It convinces me to ask a screening question, especially for overweight patients and patients with type 2 diabetes—"How many Cokes and how many Diet Cokes do you drink every week?"

Grocery stores offer a wide range of fruit flavored drinks (fruit punches). Some contain high amounts of fructose and sucrose. Some contain an artificial sweetener. Look at the "Nutrition Facts" label.

A 12-oz can of Coke contains 42 gm of sugar (high fructose corn syrup or sucrose).

A 12-oz can of Diet Coke contains zero calories. (Aspartame).

My "pure" orange juice contains 36 grams of sugar per 12 oz, almost as much as 12 oz of Coke. What is the metabolic difference?

Note also that many other foods (especially breakfast cereals) contain a high concentration of sugar. Do these foods, in contrast to S-SSD, have a higher satiety value? Moral: "Give your pancreas a break". RTJ

8-2 SUGAR-SWEETENED SOFT DRINKS, OBESITY, AND TYPE 2 DIABETES.

When individuals include liquid carbohydrate consumption in their diet, they do *not* reduce their solid food consumption. An increase in liquid carbohydrates leads, perversely, to even greater caloric consumption of other foods.

"A better mechanism for weight gain could not have developed than introducing a liquid carbohydrate with calories that are not fully compensated for by increasing satiety."

Conversely, intake of *diet* (non-sugar containing) sodas is associated with a *lowering* of risk of childhood obesity.

"Reducing sugar-sweetened beverage consumption may be the best single opportunity to curb the obesity epidemic."

This convinces me to ask a routine screening question, especially for overweight patients and patients with type 2 diabetes. How many Cokes and how many Diet Cokes do you drink every week?" RTJ

8-3 DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS OF RELATIONSHIPS BETWEEN 2-HOUR POSTCHALLENGE PLASMA GLUCOSE, AND HEMOGLOBIN A1C VALUES

Hemoglobin A1c is the preferred method to monitor long-term glycemic control. Lower levels are associated with reduced risks for both micro- and macro-vascular diabetic complications. Current recommendations vary: a target of 7%; 6.5%; 6% and below.

This study (of a large cohort of apparently healthy individuals) determined the relationships between fasting plasma glucose (**fasting PG**), 2-hour post-challenge plasma glucose (**2-h PG**), and HbA1c levels. All had HbA1c levels under 7%.

HbA1c *vs* fasting PG:

As HbA1c increased, fasting PG gradually increased. When HBA1c reached about 6.5%, the mean fasting PG was abnormal. (110 and over).

HbA1c *vs* 2-h PG:

As the HbA1c increased, the 2-h PG increased—much more rapidly than the fasting PG. The top 4 deciles of HbA1c were associated with an impaired glucose tolerance. (2-h PG over 140). This included many individuals with HbA1c levels under 6%. The 2-h PG is a more sensitive marker of abnormal glucose metabolism than fasting PG.

HbA1c *vs* diabetes:

DM2 was diagnosed in a few individuals with HbA1c levels as low as 5%. Prevalence of DM2 was higher in individuals with HBA1c levels 5.3% to 6%. About half of those with HbA1c over 6.33% had DM2.

Subdivided by HbA1c levels:

	Impaired glucose tolerance (%)	Diabetes mellitus (%)
HbA1c below 5%	16	1
HbA1c 5% to 5.4%	37	5
HbA1c 5.5% to 6.9%	53	24

Persons with fasting PG and HbA1c levels in the upper range of "normal" may be at increased risk of cardiovascular disease due to increased post-meal PG levels.

An appreciable number of individuals with a normal fasting glucose will have an abnormal 2-hour PG. Their condition may be undiagnosed and untreated. As HbA1c rises, 2-h PG increases at a much greater rate than fasting PG levels, and contributes more to the increase in HbA1c levels. 2-h PG is a more reliable indicator of abnormal glucose metabolism than either fasting PG or HbA1c. And a sensitive indicator of risk of developing diabetes.

The diagnostic use of fasting PG levels, is suboptimal. The upper limit for HbA1c, and fasting PG (at 110) is set too high. Only 17% of subjects in this study who had impaired GT had an abnormal fasting PG level. This supports the recommendations of the WHO that the oral glucose tolerance test be the main diagnostic procedure.

Most individuals with HbA1c levels between 6% and 7% have normal fasting PG levels but abnormal 2-h post challenge PG levels. Attempts to lower HbA1c will require treatment preferentially directed at lowering postprandial glucose levels.

This relatively short article presented a great deal of data.

The message is—clinicians should depend more on the 2-h PG than on either the fasting PG or the HbA1c to determine abnormal glucose metabolism. HbA1c is not a reliable method for diagnosing impaired glucose tolerance or DM2. Fasting PG (even at the new standard of 100) is not as indicative of abnormal glucose metabolism as the postprandial PG.

As a general life-style measure, post-meal glucose levels should be maintained at low levels by a low glycemic load diet.

I believe primary care clinicians, when screening for DM2, can ask their patients to come to the office about 2 hours after a meal to have their blood glucose checked. A GTT can be requested if the post prandial PG is high.

But, beware of formally labeling a patient as being "diabetic" or having "abnormal glucose tolerance" if the 2-h PG levels are not unduly high. The levels may change over time. When diagnosed by blood tests, "Once a diabetic, always a diabetic" is not true. Levels may change according to weight loss, and diet. Labeling may adversely affect insurance and employment and cause anxiety.

Measuring 2-h PG levels can lead to earlier preventive therapeutic interventions than either HbA1c or fasting PG.

8-4 EFFECTS OF DIETARY GLYCAEMIC INDEX ON ADIPOSITY, GLUCOSE HOMEOSTASIS, AND PLASMA LIPIDS IN ANIMALS.

Several trials have reported that persons consuming a low glycemic index **(GI)** diet weigh less than those consuming a high GI diet. However, clinical outcomes in humans cannot be attributed solely to GI because interventions designed to modify GI unavoidably also influence intake of fiber, and alter palatability and energy density.

This study, in rats and mice, examined the effects of GI on adiposity and other endpoints.

Despite maintenance of similar body weight, rats given high GI food gained more body fat, and had less lean body mass compared with the low-GI animals. The GI had an independent effect on body composition. Rats in the high GI group required less food to gain the same weight. This suggests that they had become more metabolically efficient.

The high-GI group had greater increases over time in the areas under the curve for blood glucose and plasma insulin, a lower plasma adiponectin, much higher plasma triglyceride concentrations, and severe disruption of islet-cell architecture.

"We speculate that the striking chronic primary peripheral hyperinsulinemia induced by the high-GI diet alters nutrient partitioning in favor of fat deposition, shunting metabolic fuels from oxidation in muscle to storage in fat."

This study fits in well with the preceding articles.

I rarely abstract studies based on animal research. We cannot confidently extrapolate the results to humans.

As these investigators suggest, long-term studies on effects of GI and GL in humans would be extraordinarily difficult.

If you access "Glycemic index" on Google, you will receive much more information on individual foods than you may wish to know. For those seeking low GI diets, implementation is simpler than the vast tables of numerical values of individual foods suggest: avoid "sugar" (sucrose), use breakfast cereals based on oats,

barley and bran (and without added sugar); use grainy breads made of whole seeds; reduce the amount of potatoes; enjoy all types of nuts, fruits, and vegetables (except potatoes), and eat plenty of salad vegetables with an oil dressing. Most refined foods (bread, refined cereal, potato, and glucose and sucrose) have high GI. Most non-starchy vegetables, fruits, legumes, and nuts have low GI.

Breakfast cereals based on refined grains and with added sugar present a "double whammy" The food industry is gradually improving the number of available healthy foods.

Although controversy still exists as to the clinical importance of GI and GL, it makes common sense to me. (But, beware of "common sense".) RTJ

8-5 PREVALENCE, CARE, AND OUTCOMES WITH DIET-CONTROLLED DIABETES IN GENERAL PRACTICE

By tradition, a substantial number of people with type 2 diabetes **(DM2)** have been managed without medication. They are usually offered dietary advice. Irrespective of whether patients remember or follow the advice, they are referred to as being managed by diet alone.

This study aimed to establish the proportion of patients with DM2 in general practice treated by diet alone. And to determine levels of complications and quality of care received as compared with patients on medication.

Overall, about 1/3 of patients were managed with diet alone. But, there was a great variation between practices (16% to 73%). Diet-alone patients were much less likely to have received monitoring for HbA1c, BP, lipids, smoking, microalbuminuria, and foot pulses.

Patients on diet alone were more likely to have high BP, and were less likely to receive antihypertension drugs. They were 45% more likely to have a high cholesterol, and less likely to receive lipid-controlling drugs.

Although some individuals might be effectively managed by diet alone, there is a case for better surveillance and for more intensive therapy.

I believe that in the U.S. many patients with known diabetes are not treated and followed as carefully as they should be. And many more who have diabetes and do not know it are not treated at all. RTJ

8-6 PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE WITH ATORVASTATIN IN TYPE 2 DIABETES

Current prescription rates for lipid lowering drugs in patients with DM2 remain low, even in patients with established cardiovascular disease **(CVD).**

This study assessed the effectiveness of a 10 mg dose of atorvastatin (*Lipitor*) *vs* placebo in *primary* prevention of CVD in patients with DM2. None had high concentrations of LDL-c. The trial was stopped 2 years early because of demonstration of significant benefit.

None had documented history of CVD. All had at least one risk factor: retinopathy, macro- or micro-albuminuria, current smoking, or hypertension. The risk of a major cardiovascular event in these patients was 10% over 4 years.

Incidence of major cardiovascular events was 25 per 1000 person-years at risk in the placebo group vs 15 per 1000 person-years at risk in the atorvastatin group. Therefore, allocation of 1000 patients to atorvastatin

would avoid 37 first major events over a 4-year follow-up. 27 patients would need to be treated for 4 years to prevent one event. [NNT (for 4 years to benefit one) = 27]

"The debate about whether *all* patients with DM2 warrant statin therapy should now focus on whether any patients can reliably be identified as being at sufficiently low risk for this safe and effective treatment to be withheld."

These data challenge the use of a particular threshold level of LDL-c as the sole arbiter of which patients with DM2 should receive statin therapy (as in the case of most current guidelines). Target levels of LDL-c (100 mg/dL) could be lowered.

An editorialist comments: The conclusions of the study—"Seems too far-fetched in view of the available clinical trials and epidemiological data". He cites 4 large studies of lipid control which contained many patients with DM2. Two of the four did not report a statistically significant reduction in coronary disease. Two did.

Clinical trials enroll carefully selected patients. The results cannot necessarily be extrapolated to primary care practice. Many patients may be at low risk and the benefit/ harm-cost ratio may be too low to warrant long-term treatment. Some may be at higher risk of adverse effects from statins. As always, individualization is required.

I believe the majority of patients with DM2 will benefit from statin therapy for primary prevention. Most will have one or more additional risk factors. There would be no question regarding secondary prevention.

Authors and publishers persist in presenting relative benefits (rather than absolute differences). Thus, they reiterate that treatment with atorvastatin was related to a 37% reduction in major coronary events; a 31% reduction in coronary revascularizations; a 48% reduction in stroke; and a 27% reduction in deaths.

This can be very misleading. I believe statements of relative benefits should be eliminated from published reports.

9-3 ASSOCIATION OF HEMOGLOBIN A1C WITH CARDIOVASCULAR DISEASE AND MORTALITY IN ADULTS

Diabetes raises the risk of *macro*-vascular disease as well as micro-vascular disease. Evidence suggests that the relation between plasma glucose and macro-disease (cardiovascular disease; **CVD**) is continuous and does not have obvious thresholds.

In this study of over 10 000 subjects, the risk of CVD, CHD and mortality increased continuously as HbA1c rose. Cardiovascular disease events increased continuously from 6.7 per 100 men with HbA1c less than 5% to 35 per 100 men with HbA1c over 7%. The risk for CHD was significantly increased in those with HbA1c 5.0% to 5.4% compared with those with HbA1c concentrations less than 5%. This included individuals *without* diabetes.

Each increase of HbA1c of 1% was associated with a relative risk of 1.26 for death from any cause. The relationship was apparent in persons without known diabetes. (Only 193 subjects had known diabetes.)

HbA1c levels were significantly associated with all-cause mortality and coronary and cardiovascular disease even below the threshold commonly accepted for the diagnosis of diabetes. Each increase of HbA1c of 1% was associated with a 20% to 30% increase in mortality and cardiovascular events. The gradient was apparent through the population range from less than 5% up to 6.9%.

Subjects with HbA1c over 7% made up 4% of the sample and contributed about 25% of the excess mortality.

Reduction in HbA1c levels in persons *without* diabetes may lessen their risk.

The metabolism of glucose is related to risk of cardiovascular disease. A healthful lifestyle should include attempts to control postprandial glucose levels in patients without diabetes as well as those with diabetes. Diets containing a low glycemic load are an important part of healthy living. RTJ

9-4 GLYCOSYLATED HEMOGLOBIN: FINALLY READY FOR PRIME TIME AS A CARDIOVASCULAR RISK FACTOR.

The societal burden of the diabetic epidemic is being fueled by our current lifestyle. Diabetes is just the measured tip of a much larger "dysglycemic iceberg".

It is now clear that fasting and 2-h PG levels well below the diabetes cutoffs are cardiovascular risk factors. And that a progressive relationship between PG and CVD risks extends from normal glucose levels right into the diabetic range, with no clear lower threshold.

Evidence is accumulating that HbA1c is a progressive risk factor for CVD in people *without* diabetes as well as people with diabetes. A HbA1c level of 6.59% in a *non-diabetic* person predicts a higher CVD risk than a HbA1c of 5.5%. Even after excluding individuals with a HbA1c level of 7% and greater, with diabetes, and with a history of heart disease, the increase in risk for CHD, CVD, and total mortality for every 1% rise in HbA1c was 40%, 16%, and 26% respectfully.

We can conclude that HbA1c is an independent and progressive risk factor for incident CVD regardless of diabetes status. "Glycosylated hemoglobin level can now be added to the list of other clearly established indicators of CVD risk." "The presence or absence of diabetes is likely to become less important than the level of glycosylated hemoglobin in the assessment of CVD risk. Reducing HbA1c in both diabetic and non-diabetic persons may reduce cardiovascular risk."

It will be interesting to find out the relative risks of HbA1c and hyperinsulinemia compared with lipids. Could it be that markers of a stressed glucose-insulin metabolism will become clinical risk indicators as important as LDL-c and HDL-c? This would include the 2-hour postprandial glucose as well as the HbA1c level. Could food sugars become as important a risk factor as saturated fats? Excess sugar intake is related to obesity and the metabolic syndrome, and in turn to hypertension, hyperinsulinemia, and dyslipidemia.

I believe, at the present stage of our knowledge, we should consider aberrant glucose metabolism an important risk factor for CVD and act on it. RTJ

10-3 POSTPRANDIAL GLUCOSE REGULATION AND DIABETIC COMPLICATIONS.

There is increasing evidence that postprandial hyperglycemia is implicated in the development of cardiovascular disease. Postprandial hyperglycemia may be directly involved in the pathogenesis of diabetes complications through its harmful effects on the vasculature.

Several studies have demonstrated a striking relationship between postprandial glucose levels and cardiovascular complications. Some have reported that 2-hour glucose is a better predictor of complications and mortality than HbA1c or the fasting blood glucose. The risk of death in subjects with postchallenge hyperglycemia was reported to be almost as high as in patients with previously diagnosed type 2 diabetes.

A number of trials have demonstrated that specific pharmacological approaches can reduce the impact of post-prandial glycemic excursions on overall glycemic control. The disaccharidase inhibitor acarbose (*Precose*) delays the digestion of complex carbohydrates in the small bowel, and blunts postprandial hyperglycemia. Repaglinide (*Prandin*), administered immediately before meals, has pharmacological actions that make it more attractive than sulfonylureas as an acute insulin secretogogue. It provides a more potent effect in reducing postprandial glycemic excursions.

To achieve normal or near-normal blood glucose levels, measurement of postprandial hyperglycemia is essential because it not only reflects glycemic exposure during the longest period of the day, but it may also be a required target of diabetes management to prevent the noxious effects of hyperglycemia on the vascular wall. Controlling postprandial glucose levels can help to optimize metabolic control and may be particularly important for prevention of vascular complications.

This is an important sea-change in approach to diabetes control. It goes beyond believing that "normal" fasting glucose and HbA1c within an "acceptable" range predict adequate diabetes control. They do not.

It does emphasize the importance of postprandial levels of glucose. Indeed, I believe that a 2-hour postprandial glucose at the high range of "normal" (eg. 130) will lead to greater risk of cardiovascular disease than a postprandial glucose of 100. I suspect there is a linear relationship between post-prandial glucose levels and vascular disease. This would lead incorporation of a low glycemic load diet for all persons as part of a healthy lifestyle.

This presents a practical application—routinely checking postprandial blood glucose in the office, noting the time after the last meal. This would be much more convenient, and more meaningful, than requiring the patient to come to the office fasting.

See Practical Pointers September 2004 9-3 and 9-4 for articles on relationship between glucose control and cardiovascular disease.

11-8 PREVENTING MICROALBUMINURIA IN TYPE 2 DIABETES.

This study was designed to assess whether an angiotensin-converting-enzyme inhibitor or a non-dihydropyridine calcium-channel blocker, or the combination, would *prevent* microalbuminuria in patients with DM2 who had hypertension and *normal* urinary albumin excretion.

Mean trough BP attained:		Development of microalbuminuria (%):	
Trandolapril alone	139/81	Trandolapril alone	6
Verapamil alone	141/82	Verapamil alone	11.9
Both	139/80	Both	5.7
Placebo	142/83	Placebo	10

Trandolapril alone significantly reduced the incidence of microalbuminuria in patients with DM2.

(NNT 4 years = 25)

In subjects with DM2 and hypertension, normoalbuminuria, and normal renal function, ACE-inhibitor therapy with trandolapril prevented the onset of microalbuminuria. A calcium blocker did not.

Should all patients with DM2 receive an ACE inhibitor regardless of BP or microalbuminuria? This study would tilt toward this application. Patients with DM2 who have hypertension (systolic > 130) will likely develop microalbuminuria eventually.

COST; Drug store.com quotes telmisartan (Mavix 2 mg) about $1 per day

Enalapril (Generic 20 mg) about 20 cents.

Note that the target BP was not reached. ACE inhibitors have effects on the vasculature of the kidney and other endothelium exceeding their effect on BP.

What about angiotensin II blockers? A companion study in this issue of NEJM (pp 1952-61), first author Anthony H Barnett, University of Birmingham, Alabama, reports that the angiotensin II blocker telmisartan was as effective (but not more effective) than the ACE inhibitor enalapril (Generic) in providing long-term renoprotection in DM2. At present, ACE inhibitors are first-line therapy. Angiotensin II inhibitors are reserved for those who cannot tolerate ACE.

12-3 HEPATOBILIARY DISEASE IN TYPE 2 DIABETES: A Narrative Review

This article discusses the spectrum of liver disease in DM2: non-alcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, hepatitis C, acute liver failure, and cholelithiasis.

The insulin resistance and relative insulin deficiency in patients with DM2 affects lipid as well as carbohydrate metabolism. Insulin resistance decreases glucose uptake in the skeletal muscle and increases lipolysis from adipocytes. Lipolysis increases circulating free fatty acids. This in turn may lead to more insulin resistance and more lipolysis. Thus a vicious cycle is started. The net effect is increased storage of fat in the liver.

"Non-alcoholic fatty liver disease is the most prevalent liver disease in the USA." NAFLD is a broad spectrum. It ranges from steatosis (bland fatty infiltration of hepatocytes), to non-alcoholic steatohepatitis (steatosis plus inflammation, necrosis, and fibrosis) and, in some patients, to end-stage liver disease and hepatocellular carcinoma. Prevalence of NAFLD is as high as 50% in patients with DM2 and obesity. (Of these, up to 50% have steatohepatitis; 19% cirrhosis).

The diagnosis is suspected in persons who do not use alcohol and have mildly elevated aminotransferase levels (AST and ALT; AST/ALT ratio greater than 1). Clinical features are non-descript. Some patients report malaise and a sense of fullness. Hepatomegaly may be present.

Imaging studies reveal a diffuse increase in echogenicity ("bright liver"). But only liver biopsy can assess the severity of damage and prognosis.

Treatment: Good metabolic control; caloric restriction (low glycemic index foods may be especially important); weight loss; exercise. Alcohol should be avoided. It is recommended that drug therapy begin with a secretogogue (a sulfonylurea) with rapid advancement to insulin therapy if control is not established. Insulin-sensitizing agents such as pioglitazone and rosiglitazone may be especially useful. The alpha-glucosidase inhibitors are also useful.

Cirrhosis, hepatocellular carcinoma, hepatitis C, acute liver failure, and cholelithiasis are also more common in patients with diabetes.

I was not aware of the frequency of NAFLD associated with DM2

Biochemical profiles sometimes unexpectedly report mildly increased liver enzymes. In the past, if I did not know of any clinical indication for the elevations, I would ignore the report. This article changes my approach. They may be indicating a significant illness which can be treated. Glucose tolerance should be checked in these patients.

12-5 ASPIRIN USE AMONG PATIENTS WITH DIABETES

Adults with diabetes, but with *no clinical cardiovascular disease*, may have risk of CVD events similar to non-diabetic adults *with established CVD.*

Strategies to prevent CVD events in persons with diabetes are underused. Aspirin effectively reduces risk of first and subsequent myocardial infarction in patients with diabetes as well as in those without. Many adults with diabetes do not use it.

This study assessed regular aspirin use among adults with diabetes between 1997 and 2001.

Use remained less than ideal for patients with CVD. One quarter of diabetic patients with established heart disease or stroke did not use aspirin. Among those with risk factors for CVD (hypertension, dyslipidemia, smoking) 60% did not use aspirin. Almost 2/3 of those without CVD did not use aspirin.

Overall use by women was lower than by men.

Although aspirin use in patients with diabetes is increasing, use is suboptimal, especially in women, younger patients, and in those with major CVD risk factors.

The benefit/harm-cost ratio of aspirin is among the highest of any drug.

Should all patients with diabetes take aspirin? I believe in the great majority the benefits outweigh risks. Risks of aspirin in younger persons with no other risk factors for CVD may outweigh benefits. But even in younger persons the duration of diabetes should be considered.

I believe at times primary care clinicians simply forget to recommend aspirin.

DIET

9-5 MEDITERRANEAN DIET, LIFESTYLE FACTORS, AND 10-YEAR MORTALITY IN ELDERLY EUROPEAN MEN AND WOMEN

Because of the cumulative effect of adverse factors throughout life, it is particularly important for older persons to adopt diet and lifestyle practices that minimize their risk of death and morbidity and maximize their prospects for healthful aging.

This study investigated the association of dietary patterns and lifestyle factors with mortality in elderly men and women in 11 European countries.

Followed a cohort of over 1500 apparently healthy men and over 800 apparently healthy women age 70-90 (mean = 75) at baseline.

Investigated the single and combined effect of 4 factors (Mediterranean diet, being physically active, moderate alcohol use, and non-smoking) on mortality.

Each of the 4 factors was individually associated with lower mortality rates from CHD, CVD, cancer, and all causes.

Individuals with 2, 3, or 4 low-risk factors had a significantly and progressively lower mortality compared with individuals with 0 or 1 low-risk factors.

Among individuals age 70 to 90, adherence to a MD and healthful lifestyles was associated with a more than 50% lower risk of mortality over 10 years.

There was no indication of the life-style habits in these persons during their earlier life. I suspect the habits were the same when they were young as when they aged.

Have we finally found the Fountain of Youth, or at least taken a sip from it? RTJ

DIZZINESS

10-10 EFFECTIVENESS OF PRIMARY CARE-BASED VESTIBULAR REHABILITATION FOR CHRONIC DIZZINESS

The central element of vestibular rehabilitation **(VR)** is a program of graded exercises that consists of eye, head, and body movements designed to stimulate the vestibular systems. The simulation promotes central compensation—neurologic adaptation to the altered input from the damaged labyrinth. The exercises also help patients overcome fear, and to regain skill and confidence in balance. Vestibular rehabilitation may be an effective treatment for dizziness resulting from many causes. It is a simple therapy with no requirement for equipment. It is highly suitable for primary care.

It is applicable only to patients with dizziness associated with head movement.

The study reported that, at 3 months, improvement occurred in all 5 primary outcome measures in the VR group. Of 83 treated patients, 67% reported clinically significant improvement compared with 38% of the usual care group; (NNT = 3). Improvement was maintained at 6 months.

The success of VR relies on the willingness of patients to practice daily movements that may make their symptoms worse initially. Patients should be informed of this and that recovery may be partial. Only those who are committed should be accepted into treatment.

"Our study provides substantive demonstration that it is feasible to offer an effective, inexpensive treatment to patients with dizziness in primary care." A single brief session with a nurse was sufficient.

This application requires an enthusiastic mentor and a willing patient. But, this is not a reason to refrain from recommending the procedure. RTJ

10-11 VESTIBULAR EXERCISES FOR BALANCE CONTROL: Easy, Inexpensive, and Effective

Movement-provoked dizziness is a typical sign of vestibular origin and therefore should respond to vestibular rehabilitation. The response mechanism seems to be central nervous system plasticity, a specific sensorio-motor rearrangement which can compensate for peripheral and central neurological defects.

To facilitate control capacities, we should expose patients to increasingly unstable body positions. Exercise rehabilitation should begin as early as possible, ideally immediately after symptom onset.

"This important study strikingly demonstrates that daily vestibular exercises in the aging population reduce symptoms, postural instability, handicaps, and falls due to dizziness." "These findings place the onus on primary care physicians to put into practice such an inexpensive, simple-to-perform treatment."

I believe other balance exercises may benefit: eg. standing still on one foot; walking in tandem heel to toe.

The objective is to fatigue an old symptom and train a new one.

See the preceding abstract for description of the exercises. RTJ

FAMILY HISTORY

11-2 THE FAMILY HISTORY—More Important Than Ever

"Today, with medicine poised at the dawn of the genomic era, it is seductive to believe that such high-tech options have already become the most important genomic tools in health care." However, as so often happens in medicine, new developments do not eclipse the tried-and-true method; instead, they give it new meaning and power.

Most diseases are the result of the interactions of multiple genes and environmental factors.

Almost every patient today has access to a free, well-proven, personalized genomic tool that captures many of these interactions and can serve as the cornerstone for individualized disease prevention. This valuable tool is the family history **(FH).** It will remain highly relevant for years to come.

Government agencies are now spearheading a national campaign to encourage families to record their health histories. Thanksgiving Day, when families traditionally gather, has been designated as the *National Family History Day*. This will serve to remind us about the value of the FH.

The government has launched a web site which allows families to collect, organize, and maintain the family history.

The article cites several web sites. One: www.hhs.gov/familyhistory

Most elderly patients will not have detailed information about their forebears. Individuals now age 70 and above may not have accurate information about their grandparents, but they can accurately add their own accounts and that of their cousins to the FH.

FIBROMYALGIA SYNDROME

11-12 MANAGEMENT OF FIBROMYALGIA SYNDROME

The diagnosis of the fibromyalgia syndrome **(FMS)** is based on a history of widespread chronic, bilateral upper body, lower body, and spine pain, and the presence of excessive tenderness on applying pressure to 11 or more of 18 specific muscle-tendon sites. FMS has not been traced to any specific structural or inflammatory cause.

FMS is the second most common disorder observed by rheumatologists (after osteoarthritis). It has a prevalence of 2% in the US. It is much more common in women. Chronic pain syndromes such as FMS are defined by subjective symptoms. No discrete boundary separates FMS from chronic fatigue syndrome, irritable bowel syndrome, and chronic muscular headache. Mood disturbances are comorbid with all.

This article summarizes the findings of a report (based on a detailed literature search) commissioned by the American Pain Society to provide evidence-based guidelines for the optimal management of FMS. There are major limitations to the literature. Many treatment trials are of short duration and lack masking. No medical therapies have been specifically approved by the FDA.

Despite the chronicity and complexity of FMS, there are interventions that may have clinical benefit in primary care practice. Several drugs and non-medical therapies are suggested.

FISH CONSUMPTION

12-8 BALANCING THE RISKS AND BENEFITS OF FISH CONSUMPTION

Studies from the past 2 decades have repeatedly linked consumption of fish—especially fish high in omega-3 fatty acids—with healthier hearts in the aging population. A reduced risk of stroke, dementia, kidney disease, asthma, and diabetes has also been reported.

There are risks stemming from 2 toxins—mercury and polychlorinatedbiphenyls **(PCBs)** which are found in fish living in polluted waters and in some farmed fish.

Mercury exposure and the role of the internist:

The only important source of organic mercury (methylmercury) is contaminated fish. Methylmercury reaches its highest levels in large predatory species such as shark, tilefish, swordfish king mackerel, and tuna; and in bottom feeders such as crab. A single serving of highly contaminated fish can contain more than 200 ug of mercury. Five of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, salmon, pollock, and catfish.

Fish sticks and “fast food” sandwiches are commonly made from fish low in mercury.

PCB exposure and the role of the internist:

PolyChlorinated Biphenyls (eg, dioxin) are a mixture of individual chemicals which are no longer produced in the USA. Prior to 1979 their use was widespread in industry. There are no known natural sources of PCBs. They do not break down in the environment, and may remain there for very long periods.

Fish are the main sources of concentrated PCB exposure. The highest levels have been found in farmed salmon. (90% of salmon consumed in the USA are farmed.) In the past they were fed PCB-contaminated ground-up fish. The fishing industry has started to change the way it feeds farmed fish. Contamination levels in salmon have declined by 90%. As of March 2004, the FDA maintained that the level of PCBs in farm-raised salmon is well below the safety standard.

The FDA emphasizes that the benefits of eating salmon on cardiovascular health outweigh the risk from PCBs, especially for those at highest risk.

I consider this a legitimate point for primary care clinicians to address. Patients may be asking about it.

I have wondered about the omega-3 content of fish, especially farm-fed fish. The natural content of omega-3 in fish comes up in the food chain beginning with plankton. How much omega-3 is contained in the food fed to farmed fish?

The relation between PCBs and cancer is very tenuous. The article cites a risk of one additional case of cancer in 100 000 people over a 70-year lifetime.

It is impossible for individual consumers to know the mercury and PCB content of the fish they consume.

I believe it reasonable for primary care clinicians to advise pregnant women and children against eating large predatory fish. For elders, the benefits of any fish far outweigh any risk. The good news is that older adults are the most likely to benefit from fish consumption. I will continue to eat fish at least twice a week,

The recent furor over the outrageous dioxin poisoning of the now President of Ukraine will allow us to follow the adverse effects of mega-doses in one individual.

The Internet is packed with information about contamination of fish. Go to Google and access salmon and mercury; and polychlorinatedbiphenyls. I included a few points from the Internet in the abstract.

FRAILTY

9-6 FRAILTY—AND ITS DANGEROUS EFFECTS—MIGHT BE PREVENTABLE.

The differences between a 70-year-old who is robust and one who is frail are easily detectable Frail old people are more vulnerable, withdrawn, unsteady, and weak. "In short, doctors know frailty when they see it." The newer view moves away from the common view that frailty is an inevitable part of old age toward a new view of frailty as an avoidable condition. Some experts believe that frailty may some day be an official coded disease, replete with FDA-approved treatments. It is likely that the diagnosis will be based on both laboratory tests and physical findings.

A recent study defined frailty as having at least 3 of 5 attributes: unintentional weight loss; muscle weakness; slow walking speed; exhaustion; and low physical activity. These findings persist in some old persons despite exclusion of the most common chronic illnesses. About 7% of persons older than 65, and 20% of those over age 80 may fit the definition of frailty. A screening tool for frailty has been described—gait speed, chair stands, and tandem balance.

"There is a biology of frailty that may be independent of age and specific disease states."

I enjoyed abstracting this article. Although somewhat "far out", it focused on a concept I had not thought about beforehand. We continue to search for the Fountain of Youth.

Can we die of "old age"? Do we require a more definitive cause of death on the death certificate?

I believe that, despite identical beneficial life-styles, some individuals become frailer at a younger age than others. There is something different between them. This is especially evident to residents of retirement communities and nursing homes.

As many studies have demonstrated, healthful lifestyles can delay the onset of frailty and prolong a productive and enjoyable life span. RTJ

GALLSTONES

10-9 THE EFFECT OF LONG-TERM INTAKE OF CIS UNSATURATED FATS ON THE RISK OF GALLSTONE DISEASE IN MEN

Cholesterol gallstones have many causes. One of the most important is hypersecretion of cholesterol into the biliary tract. Studies report that diets high in poly-unsaturated and mono-unsaturated fatty acids (both cis unsaturated fats) can inhibit cholesterol excretion in the bile, and may protect against cholesterol gallstone disease.

This study examined long-term dietary intakes of cis unsaturated fatty acids in relation to occurrence of gallstone disease.

After adjustment for age and other potential confounding risk factors, the relative risk (RR) of gallstone disease among men in the highest quintile of cis unsaturated fats compared with the lowest quintile was 0.82.

Median intake:	Poly-unsaturated		Mono-unsaturated	
	Lowest quintile	Highest quintile	Lowest quintile	Highest quintile
Grams per day	9.0	18	19	36

"In this large prospective study, a high intake of cis unsaturated fats was associated with a lower risk of gallstone disease in men. " The inverse relationship was evident for both mono-and poly-unsaturated fat.

Cis fatty acids have a protective effect on risk of atherosclerotic disease. Reduction in gallstone formation may be an added attraction.

A US population study reports 800 000 hospitalizations / year due to gallstone disease. A 20% reduction would be a major public health advance.

GLYCEMIC INDEX; GLYCEMIC LOAD **(See also DIABETES)**

11-1 EFFECTS OF A LOW-GLYCEMIC LOAD DIET ON RESTING ENERGY EXPENDITURE AND HEART DISEASE RISK FACTORS DURING WEIGHT LOSS.

This study determined whether dietary composition can influence the physiological adaptations of a weight-reducing diet as assessed by resting energy expenditure. It also determined if cardiovascular risk factors would be reduced on a low GL diet.

Randomized 39 overweight and obese adults (BMI at least 27; age 18 to 40) to low calorie diets. All subjects were in generally good health. Follow-up on diet = about 10 weeks.

The higher GL diet (lower-fat) was generally consistent with National Cholesterol Education Program guidelines for a heart-healthy diet.

Composition of the diets:	Run-in diet	Low-GL diet (higher fat)	Higher GL diet (lower fat)
% of energy needs	100	60	60
Kcal/d	2600	1500	1500
Glycemic load	287	82	205
Carbohydrate % of total kcal	49	43	65
Fat % total kcal	37	30	18

Outcomes at 10 weeks	Low GL diet	Higher GL diet
A. Resting energy expenditure	-96 kcal/d (- 6%)	-176 kcal/d (-11%)

(*Although absolute resting energy expenditure decreased in both groups, subjects on the low GL diet continued to burn more calories per day than those on the higher GL diet. This would lead to more efficient and continuing weight loss, estimated to be in the range of several pounds per year.)*

B. Perception of hunger was less in the low GL diet subjects.

C. Insulin resistance, triglycerides, C-reactive protein, and BP improved more in the low GL diet group than in the higher GL diet.

"Incorporation of glycemic load principles into current dietary guidelines may aid in the treatment of obesity and prevention of cardiovascular disease and diabetes."

This represents a continuing sea change in our thinking about benefits and risks of diets. What is the most beneficial diet? Are foods with a high glycemic load, which lead to continuing elevations in blood glucose, just as harmful as foods containing a high load of unsaturated fats?

Our US diets are high in sugar. I believe that a healthy diet should contain smaller amounts of sugar. This would suggest diets similar to the Mediterranean diet which is established as beneficial.

In the future, food manufacturers may be inclined to list the glycemic load of their products (especially if they are low).

HEADACHE

9-7 PREVALENCE OF MIGRAINE IN PATIENTS WITH A HISTORY OF SELF-REPORTED OR PHYSICIAN-DIAGNOSED "SINUS" HEADACHE.

"Sinus" headache may constitute one of the most common and misdiagnosed clinical presentations of migraine. Symptoms referable to the sinus areas are frequently reported during migraine attacks. They are not recognized as diagnostic criteria for migraine.

This study determined the presence of migraine-type headache (defined by the International Headache Society **(IHS)** classification of migraine) in patients with "sinus" headaches. The IHS states that chronic sinusitis is *not* validated as a cause of HA or facial pain unless it relapses into an acute phase.

The great majority of patients with a history of "sinus" HA were determined to have migraine-type HA. The referral of pain to the sinus-area may be a part of the migraine process. Overdiagnosis of "sinus" HA contributes to under-recognition of migraine. And undertreatment.

Certainly a clinical point worth considering. RTJ

HEART FAILURE

11-9 COMBINATION OF ISOSORBIDE AND HYDRALAZINE IN BLACKS WITH HEART FAILURE

Endothelial dysfunction, impaired bioavailability of nitric oxide, and increased oxidant stress occur in HF. Augmentation of nitric oxide (by the nitric oxide donor, isosorbide) may be an alternative or supplemental

approach to treatment of HF. Hydralazine may confer protection against degradation of nitric oxide induced by oxidative stress.

Studies have suggested that persons who identify themselves as black may have a less active renin-angiotensin system, and lower bioavailability of nitric oxide than those self-identified as white.

This study examined whether a fixed dose of isosorbide/hydralazine would provide additional benefits in blacks with advanced HF.

Black patients with grade III & IV HF were randomized to: 1) A fixed dose of isosorbide/hydralazine given by mouth daily, or 2) Placebo. Dose = 37.5 mg hydralazine + 20 mg isosorbide dinitrate three times daily. Dose could be increased to a total of 225/120 mg daily depending on absence of drug-induced side effects.

The study was terminated early owing to a significantly higher mortality in the placebo group. (10% vs 6%; absolute difference = 4%; NNT for 10 months = 25)

There was an absolute reduction in first hospitalization for HF of 10%; and improvement in the quality-of-life score *vs* placebo of 2 points in a scale of 0 to 105.

Would not white persons also benefit?

This remarkable study was facilitated by the Association of Black Cardiologists. It included patients from 161 centers. It needs independent confirmation. The study was supported by NitroMed. I wondered why a drug company would sponsor a study of drugs which can be readily obtained in generic form.

There is a substantial problem in classifying individuals in the USA as "black", and lumping them together as African-American. See the following commentary.

HUMAN PAPILLOMA VIRUS

11-7 EFFICACY OF BIVALENT L1 VIRUS-LIKE PARTICLE VACCINE IN PREVENTION OF INFECTION WITH HUMAN PAPILLOMA VIRUS TYPES 16 AND 18 IN YOUNG WOMEN.

"Persistent infection with high-risk HPV types is the necessary cause of cervical cancer." HPV-18 and HPV-16 are the most prevalent types.

This study determined if vaccination against the common oncogenic types of HPV (16 and 18) could prevent development of cervical infection.

Double-blind trial randomized over 1100 healthy women between ages 15 and 25. All were initially cytologically negative and seronegative for 16 and 18, and negative for HPV-DNA by PCR.

Randomized to: Three injections of: 1) HPV 16/18 vaccine formulated with an adjuvant, or 2) Placebo injections at months 0, 1, and 6.

Vaccine efficacy against incident infection with 16/18 was 92%. Efficacy against persistent infection was 100%. It was 93% effective against cytological abnormalities associated with 16/18. Three episodes of atypical squamous cells of undetermined significance occurred in the vaccinated group; 33 in the placebo group.

The vaccine was generally safe, well tolerated, and highly immunogenic.

Other HPV types also cause cervical cancer. The final composition of the vaccine remains to be determined.

The long-term protective effect is still not clear.

This is very exciting—likely to be the first vaccine to prevent cancer, and the first licensed vaccine to prevent a sexually transmitted disease.

World-wide implementation might be an impossible task.

HYPERTENSION

7-10 SERUM ALDOSTERONE AND THE INCIDENCE OF HYPERTENSION IN NON-HYPERTENSIVE PATIENTS

"All known monogenic forms of hypertension in humans can be traced to defects in renal sodium handling." The potential role of aldosterone in the pathogenesis of essential hypertension is of great interest. No studies have prospectively evaluated the effect of serum aldosterone on the incidence of hypertension.

Do aldosterone levels within the *physiological range* influence the risk of hypertension?

Higher aldosterone levels *within the normal physiologic range* predispose to hypertension. For each quartile increment of serum aldosterone there was a 16% increase in the risk of an increase of an elevation of BP category, and a 17% increase in risk of developing hypertension.

Relative to the lowest quartile of aldosterone, the highest quartile was associated with a 1.6-fold risk of an elevation in BP category and a 1.6-fold risk of developing hypertension. There was a linear increase with each quartile.

"Increasing aldosterone levels within the physiologic range may predispose to hypertension through promotion of sodium retention, potentiation of action of angiotensin II, and impairment of endothelial function."

I abstracted this article as a matter of interest. It has no practical importance at this time. Watch for follow-up studies. Are we beginning to take "essential" out of essential hypertension? RTJ

9-1 SYSTOLIC HYPERTENSION IN OLDER PERSONS

Systolic hypertension **(*SH*, *or preferably isolated systolic hypertension* *ISH*)** is defined as a systolic BP of 140 and above and a diastolic BP less than 90. Stage one ISH is defined as systolic 140-159, and diastolic less than 90.

It is the most common form of hypertension in elderly persons. It is a major public health issue. In persons over age 60, SH is a much more important cardiovascular risk factor than diastolic hypertension.

Guidance for treatment comes primarily from observational data which document increased risks in patients with ISH. The Framingham study reported a greater risk of development of cardiovascular disease; coronary heart disease; stroke; and heart failure in patients with stage one ISH (RRs = 1.47; 1.40; 1.42; and 1.60) compared with normotensive patients. (*Would it then be reasonable to assume that lowering BP would reduce risks? But the study did not consider effect of treatment. RTJ*)

In one trial, the benefit of active treatment compared with placebo reached its maximum at age 80. The RR for stroke in the oldest age group was 0.53 vs 0.74 in age 60-69. "Evidence suggests that older patients do benefit from treatment."

While there is strong evidence of benefit to guide treatment of ISH at a systolic BP of 160 and above, the evidence for treating BP between 140 and 159 is less strong. JNC 7 states that a BP higher than 140/90 warrants drug therapy, irrespective of age. But— " No randomized clinical trial evidence is available to demonstrate that reducing a BP of 140 to 159 in older persons (to under 140) reduces morbidity or mortality." Although JNC 7 states that patients should be treated to targets of less than 140 in most cases, and less than 130 for diabetes or chronic renal disease, there are no clinical trial data to support this recommendation.[a]

However, treatment should not be withheld solely according to advanced age. This group has especially high cardiovascular risk. Therapy should be determined by balancing potential benefits of treatment with individual patient preference and tolerance to therapy.

a *This does not suggest that there is evidence that reducing systolic BP below 140 does not reduce risk of cardiovascular complications. I believe there is a linear relationship between BP and risk, extending to the lower systolic levels. The problem is to judge how vigorously and rapidly drug treatment should be applied.*

This is an important clinical consideration for primary care. I believe many elders with ISH are overtreated. Some articles suggest that clinicians are not doing a good job of controlling hypertension if target levels are not reached.

Caution in using drastic BP-reduction in elderly patients! Go slow and go low. They are sensitive to adverse effects of drugs as well as to rapid reduction of BP. I believe many patients with ISH (especially the very elderly) are over-treated. A home BP monitoring device would be helpful in guiding treatment. Home BP may be lower than office BP and allow reduction in dose of drugs. I believe slight differences in the BP response reported between different dugs are not as meaningful as adverse effects. I would choose the lowest dose(s) of the least expensive drug and very gradually adjust as tolerated. I would try to get the systolic below 160, and would be content at this level if pushing the dose higher were not well tolerated.

The cause of elevation of systolic BP in older persons is increased stiffness and lack of compliance of their arterial system. Reducing the systolic BP does not remove the cause. It may reduce incidence of CVD by lessening stress and shear forces on the arteries. RTJ

12-2 ASSOCIATION BETWEEN CARDIOVASCULAR OUTCOMES AND ANTIHYPERTENSIVE DRUG TREATMENT IN OLDER WOMEN

This study, limited to postmenopausal women with hypertension, asked—1) What single drug is most effective in lowering risk of cardiovascular events? 2) What 2-drug combination is most effective?

Over a 6-year follow-up determined relationship between incidence of CVD and baseline use of 1) Diuretics, 2) ACE inhibitors, 3) Beta-blockers, 4) Calcium channel blockers, as *mono*therapy; and 5) *dual* therapy (combinations of two).

Used as monotherapy, the hazard ratio of CVD death calcium blocker *vs* diuretic = 1.55 (Ie, calcium blocker was more hazardous than diuretic, a statistically significant difference.) Neither of the other two drugs had statistically significant differences in risk as compared with diuretics.

In the subset of patients receiving dual therapy at baseline, those taking a calcium blocker + diuretic had an 85% *greater* risk of CVD death as compared with beta-blocker + diuretic.

There were no statistically significant differences between other combinations and risk of CVD.

In prevention of CVD in women with hypertension (and no history of cardiovascular disease) monotherapy with diuretics was equal or superior to monotherapy beta-blockers, ACE inhibitors or calcium blockers in preventing CVD complications.

Dual combination therapy with a calcium blocker + a diuretic was associated with *higher* CVD mortality than ACE inhibitors + diuretics and beta-blocker + diuretics.

The practical point for primary care clinicians: The less expensive diuretics and beta-blockers, and the combination, are in no way inferior to any other antihypertension drugs. Unless there is a strong indication for ACE inhibitors or calcium blockers, or unless there is intolerance to diuretics or beta-blockers, a diuretic or a beta-blocker or the combination should be first-line therapy.

I would use relatively low-dose of thiazide (not over 25 mg hydrochlorothiazide), and then add a beta-blockerh.

INFLUENZA

11-3 DOSE SPARING WITH INTRADERMAL INJECTION OF INFLUENZA VACCINE

This randomized trial compared the immunogenicity and safety of intradermal *vs* standard intramuscular vaccine.

Healthy young adults were randomized to a single dose of: 1) Intramuscular injection of the standard 0.5 mL of trivalent vaccine containing at least 15 ug of hemagglutinin per strain, or 2) Intradermal injection of 0.1 mL containing at least 3 ug of hemagglutinin per strain. Injections were made in the deltoid region.

Subjects who received the intradermal injections (1/5 the standard dose) had increases in hemagglutination-inhibition antibody (HAI) titers by a factor of 12 to 19 for the three strains. This was similar to the intramuscular response (factors of 7 to 15).

On day 21, seroconversion and seroprotection rates were similar between groups.

The data clearly show that *intradermal* injection of 1/5 the dose the standard dose of commercial vaccine elicits immune responses that are similar or superior to those elicited by a full dose of vaccine given intramuscularly to healthy young adults. It is generally accepted that the HAI response represents a fair surrogate marker for protection.

In times of vaccine shortage, we must decide whether to vaccinate a relatively few intramuscularly and induce a known response, or vaccinate many more intradermally with the hope of inducing a protective

response in the majority. At present, I would be inclined to use the full intramuscular dose in elderly infirm persons, nursing home residents, and in those with impaired immunity and chronic diseases such as asthma, heart and lung disease. If the supply were greatly impaired, and I had no other choice, I would give the ID dose. Combined half-dose IM and ID doses would save some vaccine.(And perhaps lead to greater immunity.)

The possibility of a pandemic of flu (predicted by many authorities as inevitable) would make ID vaccination more applicable.

Obviously the ID dose is preferable to no dose. I believe smaller doses, both IM and ID, will produce an adequate response in many persons.

Make sure the injection is not made into fat tissue. Immune response will be inadequate. In very obese persons, an intradermal injection may be preferable. The standard needle might not reach muscle.

I remember a vaccine shortage in the late 1950s or early 60s. We opted to give (on an empirical basis) intradermal vaccine to many more recipients than would have received it if the vaccine were given IM at full dose. We had no data on the response. Now it seems this was not such a bad idea.

IRRITABLE BOWEL SYNDROME.

9-9 CLINICAL DETERMINANTS OF HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME.

Patients with IBS have a health-related quality of life **(HRQOL)** that may be significantly worse than some other chronic diseases such as diabetes and end-stage kidney disease.

This study identified a concise set of mental and physical factors in patients with IBS that might lead to physician's gaining better insight into these patients.

Seven factors independently predicted *physical* HRQOL: 1) more than 5 physician visits per year; 2) tiring easily; 3) low in energy; 4) severe symptoms; 5) predominantly pain symptoms; 6) feeling that there is something seriously wrong with body; 7) symptom flares longer than 24 hours.

Other factors independently predicted *mental* HRQOL: 1) feeling tense; 2) feeling nervous; 3) feeling hopeless; 4) difficulty sleeping; 5) tiring easily; 6) low sexual interest; 7) IBS symptoms interfere with sexual interest.

HRQOL in patients with IBS is primarily lowered by *extraintestinal* symptoms rather than traditional gastrointestinal symptoms. By screening for predictors of HRQOL, physicians may be in a position to initiate effective, timely, and self-empowering therapy. Addressing HRQOL allows clinicians to better understand patient's needs and modify care-seeking patterns.

Instead of focusing on physiological epiphenomena (stool frequency, stool characteristics, and subtype of IBS) physicians might better serve the patient by gauging *global* symptom severity, addressing anxiety, and identifying and helping the patient to eliminate factors contributing to chronic stress.

This begs the question – Exactly how should the busy primary care clinician respond to these suggestions?

A basic function of primary care is to get to know the patient as a person. Merely allowing the patient to recognize and ventilate these HRQOL problems and validating them may in itself be therapeutic. It does not

follow necessarily that improving the patient's HRQOL will reduce symptoms of IBS. Improving HRQOL in itself is beneficial.

While we continue to seek a pathophysiogical basis for IBS and assess various new drug treatments, we already have a meaningful therapeutic approach. RTJ

LEFT VENTRICULAR HYPERTROPHY

11-11 LEFT VENTRICULAR HYPERTROPHY: The Next Silent Killer?

Even mild increases in BP are associated with increased left ventricular mass **(LV mass).**

Left ventricular hypertrophy **(LVH)** is a risk factor for premature death and cardiovascular events. The Framingham study has reported that LVH, as confirmed by ECG, is associated with a mortality rate as high as that associated with a Q-wave myocardial infarction.

LVH associated with hypertension appears to be reversible. A long-term reduction in BP is associated with reductions LV mass.

Two articles in this issue of JAMA report that reductions in left ventricular mass in the setting of treatment for hypertension correlate with long-term cardiovascular outcomes. The first trial of hypertensive patients with LVH documented by ECG criteria, reported the greater the treatment-decrease in ECG markers of LVH, the greater the reduction in cardiovascular events. The second trial reported data obtained by echocardiography. Over time, reductions in LV mass with treatment of hypertension were associated with reduced risk of cardiovascular events.

"Active efforts to reduce left ventricular mass may have important clinical benefits." Treatment to reduce LV mass may follow a course similar to reductions in cholesterol and BP.

I believe this is a clinically important point. Many primary care clinicians will have ECG available. If LVH is present, extra efforts should be taken to treat hypertension. A more careful follow-up is warranted.

MACULAR DEGENERATION

12-9 PEGAPTANIB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Extensive evidence has suggested a causal role of *vascular endothelial growth factor* **(VEGF)** in diseases of the eye in which neovascularization and increased vascular permeability occur.

Neovascularization in ARMD is dependent on VEGF. It is characterized by choroidal neovascularization that involves the subretinal space, often leading to exudation and hemorrhage, followed by a fibrovascular scar. Loss of central vision results.

Now a specific antagonist to VEGF (Peg-aptanib) is being tested in the treatment of neovascular ARMD. Peg-aptanib binds to and blocks activity of extracellular VEGF.

Results favored peg-aptanib. Fewer patients lost more than 15 letters. Fewer patients had severe visual loss. Some maintained or gained visual acuity.

This, of course, is not a practical point at this time. I considered the ray of hope to be interesting enough to include.

MENOPAUSE

8-7 SHORT-TERM MENOPAUSAL HORMONE THERAPY FOR SYMPTOM RELIEF

Hormone therapy **(HT)** provides the most effective relief of menopausal symptoms. Recently caution has been recommended because of an associated increase in risks of coronary heart disease **(CHD**), stroke, breast cancer **(BC),** and pulmonary embolism **(PE).** However, the average risk is very low—7 additional cases of CHD events, 8 more strokes, 8 more PEs, and 8 more BCs per 10 000 women each year. (3 chances per 1000/year.)

HT is associated with small losses in life expectancy. It is inappropriate for *primary prevention* of chronic disease. There is no place for its use in asymptomatic women.

This study identified women who would benefit from short-term HT by exploring the trade-off between relief of menopausal symptoms and risks of inducing disease.

Among women at low risk for CHD (no risk factors) , HT extended quality-adjusted life expectancy **(QALE)** even if menopausal symptoms were mild (reducing quality of life by as little as 4%). Among women at high CHD risk (3 risk factors), HT extended QALE if symptoms lowered quality of life by 12% or more.

"Whether short-term is beneficial or harmful depends primarily on a woman's treatment goals, the severity of her estrogen-responsive symptoms, and her cardiovascular disease risk." Each woman's values must be incorporated into the HT decision. Is she willing to accept a very small risk of breast cancer; coronary events; stroke; in order to be free of menopausal symptoms?

If the goal is to maximize QALE, HT can be beneficial, especially among women at low CVD risk, even when menopausal symptoms are mild.

The decision to use HT depends on its efficacy in alleviating symptoms. Not all symptoms during perimenopause are due to declining estrogen levels. Not all respond to HT. There is a large placebo effect. Clinical trials examining the impact of HT on symptoms suggest that a 1-month trial is sufficient to determine response. If response is not satisfactory, HT may be withdrawn.

I have found results of simulating "models" unhelpful in primary care practice. They cannot readily be applied to individuals. However, they may tilt clinicians toward or against using certain interventions, especially if there are other studies indicating a balance of benefit to harm.

A 12% reduction in quality of life seems to me to be a relatively small reduction. I believe if HT improved symptoms and QOL in women with such a moderate reduction of QOL, it would be much more strongly indicated in women with severe symptoms (eg, a 50% reduction in QOL.)

Treatment-associated risks increase with duration of HT. American College of Obstetricians and Gynecologists is considering advising short-term HT (less than 5 years) for control of menopausal symptoms.

Estrogen-alone therapy (in hysterectomized women) is much safer than combined estrogen/progestin.

I believe most primary care clinicians are generous in prescribing HT. The dose of HT should be kept as low as possible to relieve symptoms, and continued for as short a time as is necessary.

I would be more hesitant to prescribe HT for a woman who smokes, has high BP, diabetes or glucose intolerance, uncontrolled lipids, a strong family history of BC, is a carrier of the breast cancer gene, or has a past history of BC or CVD. RTJ

MULTIPLE CONDITIONS; MULTIPLE MEDICATIONS

12-1 POTENTIAL PITFALLS OF DISEASE-SPECIFIC GUIDELINES FOR PATIENTS WITH MULTIPLE CONDITIONS

Primary care clinicians are encouraged to adhere to evidence-based guidelines for the management of specific diseases. The goal is to maximize benefits, including prevention of disease-specific outcomes, deaths, and hospitalizations.

For patients with several coexisting health conditions, the long-term net benefits and harms of the combination of all medications taken in adherence to disease-specific guidelines is less clear. Twenty percent of Medicare beneficiaries have 5 or more chronic conditions, and 50% are receiving 5 or more drugs. Take, for instance, a 70-year old woman who has hypertension, a past myocardial infarction, depression, diabetes, and osteoporosis. According to guidelines she should be receiving aspirin, a beta-blocker, and ACE inhibitor, a bisphosphonate, calcium, a diuretic, a SSRI, a statin, a sulfonylurea, and perhaps a thiazolidinedione and vitamin D.

What added benefit (and added harm) does the 7^{th}, 8^{th}, or 9^{th} medication provide over the 2^{nd} or 3^{rd}? The risk of adverse effects increases as the number of medications (*and the length of time they are taken*) increases.

The prevalence of problems associated with multiple medications is probably underestimated. The broader physical, cognitive, psychological, and other effects remain unknown and unexplored. Patients, especially the elderly, and those with multiple complaints, vary in regard to the importance they place on health outcomes such as longer survival, the prevention of specific disease events, physical and cognitive functioning, and the amount of inconvenience and risk of adverse effects (*and costs*) they are willing to tolerate.

Elderly patients with multiple health problems who are receiving long-term, multiple-drug therapy present an important clinical problem. I believe older patients take too much medicine.

We have no way of knowing the benefits or adverse effects of multiple-drug combinations. No randomized trial has considered (or can consider) effects of a particular combination of 10 drugs with another 10 drugs, or with placebo. For example, an elderly patient takes 10 different drugs. [1, 2, 3, 4, 5, 6, 7, 8, 9,10]. Does drug 4 (even though medically indicated) add to her quality and length of life? We have no way of determining this. No conclusive randomized trial will, or can, be conducted comparing: 1) a group taking 9 drugs (omitting drug 4) with 2) a group taking all 10 drugs. I believe the benefit obtained from each of the 10 drugs would be much less for a patient taking 10 drugs than for a patient taking only one drug for one indication. I also believe that taking all 10 would be associated with more adverse effects than taking 9.

Clinicians (including myself), when presented with a new complaint by an elderly patient often automatically prescribe a drug for which the basis of benefit is established when prescribed for a lone condition. Multiple conditions and multiple drugs confuse the clinical picture. We should think twice.

Will adding a new drug really increase length and quality of life? Will it provide additional comfort? By how much? At what cost? Certainly many drugs given to younger patients for a specific condition do effectively prolong quality and length of life. But for elderly patients receiving multiple drugs little may be gained and much lost. Consider an elderly patient with limited life expectancy who is receiving multiple drugs, all with established benefits when used as lone therapy for a younger person. Will lowering her LDL-cholesterol from 130 to 100 enhance her length and quality of life? Will lowering his systolic BP from 170 to 140? Will increasing her bone density by 3%? Will lowering her HbA1c from 8% to 7%?

Periodically, I read in the newspaper of an elderly, economically disadvantaged, couple who must choose between paying for their medications or paying the rent. I feel compassion. I also think—How necessary are the drugs they are struggling to pay for? Do all of them add length and quality to their lives?

How should clinicians respond to this problem? There is no "scientific" answer. It depends on "clinical judgment" by the clinician and the informed preference of the patient. Patients should be able to judge for themselves the risks vs costs and harms. (Although at the practical clinical level this maybe impossible.) I believe short-term symptom-relieving drugs are more likely to improve quality-of-life in an elder than long-term risk-reducing medication. Regarding the illustrative patient, the SSRI may be the most important drug she receives.

When consulting with an elderly patient with multiple complaints who is receiving multiple medications ask--How do you feel? If "poorly", perhaps it might best to remove a drug instead of adding one.

What is the primary care clinician to do when consulting with 80-year-old Mrs. Jones who is already receiving multiple medications and presents with a new complaint which may lead to her receiving yet another long-term drug? "Mrs. Jones, I can prescribe a drug for your condition, but I do not know if, when added to the other drugs your are taking, you will be benefited or harmed. If you do wish to take an added drug, it is very important that you let me know soon whether it really makes you feel better."

OBESITY

8-1 SUGAR-SWEETENED BEVERAGES, WEIGHT GAIN, AND INCIDENCE OF TYPE 2 DIABETES IN YOUNG AND MIDDLE-AGED WOMEN

This study examined the relationships between sugar-sweetened beverage consumption (especially soft drinks), weight gain, and risk of diabetes in a large cohort of young and middle-aged women.

Over the entire 10 year period, women who *increased* their sugar-sweetened soft drink **(S-SSD)** intake from low to high had larger increases in weight compared with women who maintained a low intake, or substantially reduced their intake.

In contrast, women who *decreased* their S-SSD reduced their total energy consumption by 319 kcal/d. Women who *decreased* their intake during the first 5 years and maintained a low level gained less weight than those who increased their intake (2.8 kg. vs 4.4 kg).

Participants whose consumption of *diet* soft drinks *increased* from one drink or less per week to more than one drink per day gained significantly *less* weight (1.6 kg) than women who *decreased* their intake from one

or more drinks daily to 1 drink or less per week (4.2 kg). [*Ie, consumption of calorie free drinks apparently to some extent, blunts ingestion of calorie-containing foods.*]

Greater S-SSD consumption was strongly associated with progressively higher risk of type 2 diabetes. (RR = 1.9 in women consuming one or more drinks per day *vs* those consuming less than one per month.)

Sugar-sweetened fruit punch was also associated with increased risk of diabetes. (RR = 2.0)

"Pure" fruit juice was *not* associated with risk of diabetes.

Over 8 years, there were positive associations between sugar-sweetened beverage consumption and both greater weight gain and risk of type 2 diabetes, independent of other known risk factors.

Energy provided by sugar-sweetened beverages does not affect subsequent food and energy intake. (Ie, little or no compensation by reduction in intake of other foods.) Weight gain and obesity result from the positive energy balance.

Fruit juice was *not* associated with diabetes risk in this study. This suggests that naturally occurring sugars in beverages may have different metabolic effects than added sugars.

This is an important life-style consideration.. It convinces me to ask a screening question, especially for overweight patients and patients with type 2 diabetes—"How many Cokes and how many Diet Cokes do you drink every week?"

Grocery stores offer a wide range of fruit flavored drinks (fruit punches). Some contain high amounts of fructose and sucrose. Some contain an artificial sweetener. Look at the "Nutrition Facts" label.

A 12-oz can of Coke contains 42 gm of sugar (high fructose corn syrup or sucrose).

A 12-oz can of Diet Coke contains zero calories. (Aspartame).

My "pure" orange juice contains 36 grams of sugar per 12 oz, almost as much as 12 oz of Coke. What is the metabolic difference?

Note also that many other foods (especially breakfast cereals) contain a high concentration of sugar. Do these foods, in contrast to S-SSD, have a higher satiety value? Moral: "Give your pancreas a break". RTJ

8-2 SUGAR-SWEETENED SOFT DRINKS, OBESITY, AND TYPE 2 DIABETES.

When individuals include liquid carbohydrate consumption in their diet, they do *not* reduce their solid food consumption. An increase in liquid carbohydrates leads, perversely, to even greater caloric consumption of other foods.

"A better mechanism for weight gain could not have developed than introducing a liquid carbohydrate with calories that are not fully compensated for by increasing satiety."

Conversely, intake of *diet* (non-sugar containing) sodas is associated with a *lowering* of risk of childhood obesity.

"Reducing sugar-sweetened beverage consumption may be the best single opportunity to curb the obesity epidemic."

This convinces me to ask a routine screening question, especially for overweight patients and patients with type 2 diabetes. How many Cokes and how many Diet Cokes do you drink every week?" RTJ

10-7 BARIATRIC SURGERY: A Systematic Review and Meta-Analysis

This systematic review determined the impact of bariatric surgery on weight loss, the effect on co-morbidities of obesity, and operative mortality.

Mean absolute weight loss = 40 kg; mean BMI decrease = 14. Mean percentage of excess-weight loss was 61%. In most cases, the degree of weight loss remained the same 2 years after surgery as before.

Operative mortality depended on the complexity of the procedure, from 0.1% for gastric binding to 1% for bilio-pancreatic diversion and duodenal switch.

"Bariatric surgery in morbidly obese individuals reverses, eliminates, or significantly ameliorates diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea." It benefits the majority of patients.

I have read that there are now more obese individuals in the world than malnourished.

Certainly the approach to this universal problem is not surgery. How could 8 million persons in the USA undergo surgery? The USA needs concerted efforts to reduce obesity, This requires co-operation between educators, food manufacturers, public health officials, and primary care clinicians. I believe we are making some progress. It is slow.

The mean life-expectancy had increased dramatically in the USA over the past 80 years. What an even more remarkable change would have occurred if the obesity epidemic had been prevented! RTJ

12-6 ECONOMICS OF OBESITY

Traditional health promotion efforts have focused on the individual, relying on education, skills training, and building social support to help people change behavior. In the case of obesity, these approaches are failing. Public health officials are wondering—Why do people not listen?

This essay suggests that economics plays a large part in the obesity epidemic. Food, especially foods high in fat and sugar, have become cheaper as obesity rates have risen. Obesity rates among the poor are substantially higher than among those in higher income groups. The poor are more likely to depend on high fat, high sugar, less expensive foods As income drops, choice of foods contracts. From economists' perspective, people are rational beings who try to attain the maximum happiness within the constraints of their circumstances such as their income, available time, and other resources. The economic situation of low-income people forces them to adopt "obesogenic" diets. Economists say if you want to change behavior, change costs.

Obesity is a low-income problem, yet we offer middle-class solutions. "We say you need to eat more fresh fruits and vegetables and to exercise more. Well, if you live in the inner city you aren't going to suddenly start eating mangos and playing tennis."

Another important factor affecting diet is time. In order to prepare so called "thrifty" diets you need 20 hours a week for food preparation. The typical working mother spends 5 hours a week on this task. The poor often work long hours and have long commutes. They are "time poor" as well as cash poor.

Ultimately the solution to the problem of obesity is to improve the socioeconomic situation of the poor by providing better jobs, wages, and social services. “Obesity is, profoundly, a socioeconomic issue, and medical approaches will not work.”

I enjoyed this perspective. I believe it contains much truth. But it is certainly not the whole truth. Many economically advantaged persons are obese. Observe in any upscale mall. (I wonder what the poor/rich ratio is regarding obesity.)

The article will make me more compassionate and less critical when discussing the “overweight problem” of the majority of my patients. Some have great limitations regarding their choices of foods, convenience of shopping, and time to prepare. For many, eating fat and sweets is one of the pleasures of their lives. They do not want to give it up. Cultural influences remain strong.

Disadvantaged persons are also greatly limited in their choices of exercise. Walking through the neighborhood may be unsafe, unpleasant, and stressful. Sidewalks may be broken and uneven. Walkers may be harassed.

The just-published changes in the food pyramid call for more of the same expensive foods and for more exercise. Costs, time, and opportunity have become more limiting. Three daily glasses of skim milk are recommended. A gallon of milk now costs me over $3. For a family of 4 or 5, this adds up.

Obviously the root causes of the obesity epidemic have not been addressed.

A note about children: There is an effective means of limiting fat and sweets from their diet through changes in the school meal programs. I believe we are making headway in this regard.

PAIN CONTROL

8-8 APPROPRIATE USE OF OPIOIDS FOR PERSISTENT NON-CANCER PAIN

Primary care clinicians have been torn between opposing perspectives on use of opioids for severe non-cancer pain. Risks and benefits continue to be debated.

Beginning in the mid-1980s, the consensus view of pain specialists rapidly shifted toward less restrictive use. By 1997, opioid therapy for chronic pain was described as an “extension of the basic principles of good medical practice”. Data highlighted the variability of the population with chronic pain and showed highly favorable outcomes in some patients who received opioid therapy. Many patients with chronic pain who were treated with opioids for months or years had constant pain relief, no significant toxicity, and stable or improved function. Data confirmed that patients could handle these drugs responsibly, without the problematic behaviors of abuse and addiction.

Unfortunately, increased medical use was associated with heightened abuse. The burgeoning non-medical use of oxycodone and other drugs, combined with media stories of abuse-related tragedies, seemed to threaten medical practice with a regulatory backlash. Pain specialists perceived that championing this therapy could not continue without a clear focus on the risks of abuse, addiction in predisposed persons, and diversion to an

illicit market. This evolution brought the concept of balance to the level of the individual practitioner. Safe and effective prescribing requires skills in pharmacotherapy and in risk assessment and management.

Current recommendations for appropriate use for persistent non-cancer pain aim for a balance. The primary goal is comfort. Opioid therapy is just one tool among many to manage pain.

I believe most primary care clinicians would refer these patients to a pain center, if available. Occasionally the burden of prescription will fall on the generalist. I would suggest that the single main consideration for long-term opioid use would be—"Know the patient well". Know his personal history as well as his medical history.

If the sufferer lives in the community and he and his family have been known to you for years, the risk of abuse would be minimized. RTJ

See the abstract for web sites. RTJ

PERIPHERAL ARTERIAL DISEASE

7-7 FUNCTIONAL DECLINE IN PERIPHERAL ARTERIAL DISEASE

Currently, many medical textbooks and review articles report that most persons with peripheral arterial disease **(PAD)** and intermittent claudication experience stabilization or improvement in their symptoms over time. However, symptoms may not correlate with objective measurement of functional decline. It is possible that patients with PAD reduce their activity to keep leg symptoms in check. Patient-reported improvement or stabilization of leg symptoms may mask PAD-associated functional decline.

This study assessed whether PAD, ankle-brachial index **(ABI),** and specific leg symptoms predict functional decline over 2 years.

Lower baseline ABI values were associated with greater *mean annual* decline in 6-minute walk performance:

Patients with *asymptomatic* PAD at baseline (compared with patients without PAD), had a greater mean annual decline in 6-minute walk performance, and an increased odds ratio for becoming unable to walk continuously for 6 minutes.

Patients with PAD who experienced leg pain at baseline (compared to patients without PAD) had a greater decline in 6-minute walk, and a decrease in usual-pace 4-meter walking velocity.

This challenges standard thinking about the natural history of leg functioning in patients with PAD. In previous studies, most patients with intermittent claudication reported improvement or stabilization of leg symptoms over 5 years, implying a benign course. However, stabilization or improvement of symptoms does not necessarily indicate stabilization or improvement of leg performance.

Clinicians should consider patients with PAD to be at increased risk of functional decline.

The prevalence of PAD among older persons is high and often unrecognized.

PAD is a serious, progressive, and deadly disease. It requires the same primary and secondary prevention measures as for coronary disease.. Smokers may be told "You will not get better until you stop smoking".

PHYSICAL ACTIVITY

9-8 PHYSICAL ACTIVITY, INCLUDING WALKING, AND COGNITIVE FUNCTION IN OLDER WOMEN

This study examined the relation of long-term regular physical activity, including walking, to cognitive function in a large cohort of women. Higher levels of activity were associated with better cognitive performance. On a global score combining results of all cognitive tests, women in the second through the fifth quintile of energy expenditures scored an average of 0.06, 0.06, 0.09, and 0.1 standard units higher than women in the lowest quintile

Compared with women in the lowest physical activity quintile, those in the highest quintile had a 20% lower risk of cognitive impairment.

"In this large prospective study of older women, higher levels of long-term regular physical activity were strongly associated with higher levels of cognitive function and less cognitive decline. This benefit was similar in extent to being about 3 years younger in age." The association was not restricted to women engaging in vigorous activity. Walking the equivalent of at least 1.5 hours per week at a 20 to 30 minute per mile pace was also associated with better cognitive performance.

This is an interesting, provocative study. It is not proof of any relationship between physical activity and cognition. Observational studies cannot prove cause and effect. But I believe patients should be reminded of the many benefits of physical fitness. There is now suggestive evidence of improved cognitive function.

A companion article in this issue of JAMA (pp 1447-52) "Walking and Dementia in Physically Capable Elderly Men", first author Robert D Abbott, University of Virginia School of Medicine, Charlottesville, comes to the same conclusion. RTJ

PLACEBO

10-2 QUESTIONNAIRE SURVEY ON USE OF PLACEBO

One might surmise that clinical use of placebos is rare. The deception involved in administering a placebo raises ethical questions. There is a dearth of discussion about placebos in the medical literature. Almost all citations in Medline refer to a research context. Informal discussions with clinicians indicate that use still occurs.

This study from Israel concerned the frequency and circumstances of use of placebo in clinical practice, and attitudes towards its use among those who administer it. Placebos were given in the form of saline infusions, intramuscular injections, or vitamin C tablets. They were used for anxiety, pain, agitation, vertigo, sleep problems, asthma, contractions in labor, withdrawal from recreational drugs.

The majority of health care workers used placebos, some as often as once a month. Most found them to be generally or occasionally effective.

Ethical issues: Only 5% thought use should be categorically prohibited. Most others considered use conditional on circumstances such as prior experience with use, notifying the patient that a placebo was given, or evidence from research that the placebo was effective.

"Used wisely, placebos might have a legitimate place in therapeutics."

Placebos are fascinating. Over the ages, myriads of humankind have received interventions which possess no possible pharmacological benefits.

Placebos do not cure anything. Although, by definition, a placebo pill has no more pharmacological action than a teaspoon of water, it may have profound psychological effects in relieving distress. I believe relief of symptoms and lessening of anxiety in some patients may lead to faster resolution of the illness.

We do not use placebos to treat anemia, hypertension, or diabetes or any specific disease for which there is established treatment. We may use them in hope of providing relief of symptoms. Indeed, a simple (placebo) statement from the doctor may relieve considerable anxiety and bring peace. "You will be fine, Mr. Jones."

Response depends on the culture in which it is presented and the enthusiasm and beliefs of the practitioner, as well as the confidence of the recipient that it will help.

Are placebos ethical? Is their use deceptive? Does the end justify the means? This depends on whether the practitioner believes that there truly are benefits. It is true that placebos have no pharmacological action. But, they may relieve symptoms even though we do not know the mechanism. I believe placebos are a legitimate intervention in special circumstances. They may act by providing relief and comfort while the patient recovers naturally.

Should clinicians disclose that they are prescribing a placebo? Would this negate benefit? We do not explain to patients how penicillin works. Indeed, clinicians may not know the mechanism of action of many drugs they prescribe, and certainly do not so inform the patient. For some beneficial drugs, an exact mechanism of action may not be established. Use may depend solely on an empirical basis. Their use is nevertheless ethical.

I do not believe clinicians should routinely inform the patient. If she asks, however, I would not hesitate to disclose. I believe fully informing the patient about possible benefits will be an adequate defense. Indeed there is evidence that placebos initiate release of endorphins.

Should clinicians charge for placebos? This may be a more difficult decision. I believe most clinicians would be able to include a placebo without increasing the charge for a consultation.

Although extent of use may vary between individual clinicians, I believe use of placebos is much more prevalent than acknowledged. We use the placebo effect every day of practice. We use vast quantities of drugs for which there is no possible benefit. This may be the most common use of placebos in modern clinical practice. Consider the widespread use of antibiotics prescribed for viral infections. Would not this be considered a placebo intervention? The prescription is given to console the patient. Such use of drugs is becoming much more common now that advertising is directed specifically to patients.

Should placebos be used as a diagnostic tool? This could lead to erroneous and harmful conclusions. If the patient obtains relief, some would say that their symptoms are not due to organic disease. This is not true.

Do you believe the "nocebo" effect? Ie, are some interventions which have no possible pharmacological effects associated with onset and worsening of symptoms? ("That flu shot gave me the flu.") If you believe the nocebo effect, you must believe in the placebo effect.

PNEUMONIA

10-12 RISK OF COMMUNITY-ACQUIRED PNEUMONIA AND USE OF GASTRIC ACID-SUPPRESSIVE DRUGS.

Intragastric acid constitutes a major non-specific defense mechanism against ingested pathogens. When the pH is under 4.0, most pathogens are promptly killed. They survive in hypochlorhydric or achlorhydric states.

The bacteria and viruses in a contaminated stomach in persons receiving acid-suppressing drugs (ASD) have been identified as species from the oral cavity. This is likely due to reduction of gastric acid leading to increased prevalence of microbial colonization of the stomach. Microbes then backflow from the stomach to the oral cavity, and then infect the lungs.

This study examined the association between use of ASD and community-acquired pneumonia.

Rates of incident pneumonia: 1) no ASD use = 0.6 per 100 person-years; 2) ASD use = 2.45 per 100 person-years. About 0.5% of patients not taking ASDs developed pneumonia over one year *vs* about 2.4% of those taking ASDs for a year. Absolute difference = about 2% per year of administration. NNT (harm one person each year) = 50

Acid-suppressive drugs were associated with an increased risk of community-acquired pneumonia. This is likely a real biological effect.

I believe this is an important clinical point especially for elderly patients, considering the large numbers of patients taking ASDs. Primary care clinicians should be attuned to early suspicion of pneumonia in patients taking ASDs who develop lower respiratory symptoms.

POLYMEAL

12-4 THE POLYMEAL: A More Natural, Safer, and Tastier Strategy to Reduce Cardiovascular Disease by More than 75%

The concept of the Polypill was introduced in 2003**.** It was based on the premise that everyone in Western societies is at risk for cardiovascular disease. The investigators suggested it would immeasurably benefit if it were taken by everyone over age 50. The pill contained 6 individual drugs: a statin drug; 2) folic acid 800 micrograms; 3) aspirin 75 mg; 4), 5), 6) three antihypertension drugs at half dose (choose from a thiazide, beta-blocker, ACE inhibitor or angiotensin II blocker, and a calcium blocker).

The objective of the present study was to define a safer non-pharmacological and tastier alternative to the Polypill (a Polymeal) for use by the general population. The foods to be ingested daily: Wine, fish, dark chocolate, fruit and vegetables, garlic, and almonds.

Combining all ingredients of the Polymeal was calculated to reduce CVD in men by 76% and increase life expectancy free of cardiovascular disease by 9 years. In patients with CVD, life would be extended by 2.4 years.

The FDA would not approve any combination of drugs to be given to the general population without determination of individual risk. The Polymeal, although somewhat fanciful, is much more acceptable. Indeed,

it has merit in reminding us of the benefits of diet in reducing risk of CVD. Except for garlic and dark chocolate, I believe the ingredients would be acceptable to many persons on a daily basis.

Note that wine is the most beneficial component of the diet. Some epidemiologists are so convinced of its benefits that they consider abstinence to be a risk factor.

PRE-HYPERTENSION

10-1 PREVALENCE OF HEART DISEASE AND STROKE RISK FACTORS IN PERSONS WITH PRE-HYPERTENSION

Pre-hypertension is defined as a BP of 120-139/80-89. This is considered to be above-*optimal* BP. Optimal or "normal" BP is defined as under 120/80. Persons with prehypertension have a greater risk of developing hypertension later in life than those with lower BP.

Are persons with prehypertension more likely to have other risk factors for stroke and heart disease?

Compared to patients with "normal" BP, those with prehypertension were more likely to have an elevated cholesterol, to be overweight, and have diabetes. They were 1.7 times more likely to have at least one other risk factor compared with normotensives. Only about ¼ of adults with prehypertension had *none* of the major risk factors.

The relation between BP and cardiovascular disease risk is graded and continuous. Appropriate prevention efforts can be initiated in persons at any level of BP to avert development of risk factors. This extends to persons with prehypertension.

The greater prevalence of cardiovascular risk factors in persons with prehypertension *vs* normotension suggests the need for early clinical detection and intervention. It calls for comprehensive preventive and public health efforts.

This is an important clinical point for primary care. It presents an opportunity for earlier intervention and application of the most effective preventive measures (especially lifestyle).

Primary care clinicians should check patients with prehypertension for other risk factors: overweight/obesity, dyslipidemia, glucose intolerance and diabetes. It is evident that attaining "normal" BP, weight, and LDL-cholesterol does not assure the most favorable reductions in risk. Risk is graded and continuous for all these factors. Risk may be lowered by achieving levels below the usually quoted "normal" levels. What are the most favorable low levels? Still to be determined.

A host of persons in the USA who have hypertension are not aware of it. This lack of awareness must be much higher in those with prehypertension.

PROSTATE CANCER

7-4 PREOPERATIVE PSA VELOCITY AND RISK OF DEATH FROM PROSTATE CANCER AFTER RADICAL PROSTATECTOMY

This study assessed whether the PSA velocity during the year before the diagnosis of PC could identify those at higher risk for death from PC after radical prostatectomy.

Men whose PSA increased by more than 2.0 ng per mL (*vs* an increase of less than 2.0) during the year preceding the diagnosis of PC had a higher relative risk of dying from PC despite undergoing radical prostatectomy. (RR = 25)

An annual velocity over 2.0 was significantly associated with advanced pathological stage, and high-grade disease. Five % of men with an annual velocity over 2.0 had positive lymph nodes, as compared with 0.7% in men with velocity 2.0 or less.

"Watchful waiting may not be the best option" in men with higher velocities. However, whether these men would have a higher and faster rate of death from PC if they were treated with watchful waiting rather than with radical prostatectomy is not known. This awaits a randomized trial.

The initial Gleason score, clinical tumor stage, and PSA level at diagnosis also are important determinants of risk of death from PC.

PSA may fluctuate over time. This may be due to a "natural" variation, or to differences in and between laboratories. We must be assured that the laboratory produces reliable and reproducible results. It would be well to repeat an outlying PSA.

How can we apply the information from this essentially retrospective study to practicalities of primary care? This is not easy. Primary care patients are rarely followed by PSA determinations made every 6 months. The "length time" between determinations is usually much longer. Still, I believe, it would be well to consider a possible developing PC in a man whose PSA is rapidly rising. The cut point of 2.0 ng per mL/year is arbitrary.

A high initial PSA (confirmed) would also lead to consideration for biopsy. (The cut points are also debatable.) The usually stated cut point of 4.0 ng/mL is not reassuring. A cut point of 2.5 has been recommended for younger men. The Mayo Clinic cites an increase in "normal" range as age progresses. See the internet connection cited below.

"Few issues are as controversial" as screening for PC. All men considered for screening should be fully informed about risks as well as benefits of screening and then asked to make up their own minds. It is a mistake for primary care clinicians to add a PSA determination to the routine battery of screening chemical tests without informing the patient.

The U.S. Preventive Services Task Force concludes:

> *The evidence is insufficient to recommend for or against routine PSA screening. There is good evidence that PSA can detect early-stage PC. There is mixed and inconclusive evidence that early detection improves health outcomes Screening is associated with important harms.*

I believe older men and men with co-morbidity which would limit life span to 10 years or less should not be screened.

Many younger men do opt for screening. The object is to detect localized PC at a time when cure is possible. In younger men who have no nodules and who are screened periodically, an increased PSA velocity (or doubling time) as well as a high (and confirmed) initial PSA level would be a consideration for biopsy. There is still no precise answer to the implied question—"When both the patient and the physician agree that the potential adverse effects of treatment exceed the benefits, watchful waiting is an option for managing localized prostate cancer." The track record of the consultant surgeon who will do the radical prostatectomy is an important consideration. RTJ

7-5 PROGRESS TOWARD IDENTIFYING AGGRESSIVE PROSTATE CANCER

A substantial proportion of men in the age group most affected by PC die of other causes. Yet the rate of death from PC remains high. (In the USA, 82 men die of PC every day.) Evidence of tumor outside the gland and biochemical relapse may be indicative of incurable disease, but are *not* necessarily predictors of death from PC.

A considerable proportion of cancers diagnosed by screening are indolent and non-lethal, and otherwise would not have been detected during the patient's lifetime. In such men, treatment-related complications could exceed disease-related complications.

The rapidly growing body of information regarding the predictive value of PSA velocity (and PSA doubling time) suggests that this approach will become critical in predicting PC-specific survival. In the editorialist's experience, patients with biochemical relapse after prostatectomy, the Gleason score, the time to relapse, and the PSA doubling time all independently predict the probability of distant metastases, and might be an indication for early adjunctive treatment. The PSA doubling time overrides the other variables. The 10-year cancer-specific survival was 93% among patients with a PSA doubling time of more than 10 months, and 58% among those with a doubling time of less than 10 months.

I have tried to think through some guidelines for PSA screening applicable to primary care. This is a personal appraisal. Urologists and other experts may have a different approach.

I believe clinicians may legitimately ask suitable patients if they wish to be screened, while deterring others who might seek a PSA screening, and not even mentioning screening to others.

A. Who should we <u>not</u> screen with PSA

Men who are not beforehand fully informed about ultimate risks as well as possible benefits. (PSA should not routinely be included in the biochemical screen in men who come for a "check up".)

Older men and men with co-morbidity whose life expectancy is less than 10 years.

Men who would not be willing to undergo radical prostatectomy or radiation if indicated.

B. Who should we screen with PSA?

Only men who are fully informed about ultimate risks as well as benefits of screening

Only men with a quality life expectancy over 10 years. (This would tilt screening toward younger, healthier men.)

Only men who would be willing to undergo a radical prostatectomy or radiation if indicated.

C. How often should we screen?

This depends on the patient's degree of concern, and the doctor's willingness to comply with the concerns.

Once a year could be considered reasonable unless an upward trend is suspicious.

D. When should we advise prostate biopsy?

When initial PSA is high for patient's age.

When the PSA velocity over time is increasing rapidly.

When a suspicious nodule is discovered on DRE. (This now becomes a diagnostic procedure, not a screen.)

E. If cancer cells are found, when should radical prostatectomy be advised?

Gleason score 6 and over.

High initial PSA level.

High PSA velocity or short-time doubling

Nodule present

For younger men. In younger men, I believe definitive therapy is almost always indicated.

They are more at risk because they have more time to develop extension of PC. And a greater risk of developing a more aggressive tumor later in life.

F. If cancer cells are found, when should prostatectomy <u>not</u> be advised? (In favor of "watchful waiting"[a].)

In older men:

With significant co-morbidity and a limited life expectancy

With a Gleason score under 6

With a low PSA

No nodule present

Slow PSA velocity

*(**a** I am not sure what "watchful waiting" means. Watch for what? Perhaps advising early adjuvant therapy if extension occurs.)*

I believe the opening statement of the preceding study is a key determinant. "When both the patient and the physician agree that the potential adverse effects of treatment exceed the benefits, watchful waiting is an option for managing localized prostate cancer." This is a judgment call by both. Patient preference is important.

The purpose is to detect and treat while cure is possible and to extend quality life. RTJ

11-5 IS PSA TESTING STILL USEFUL?

Dr. Thomas A. Stamey (Stanford University School of Medicine), who is considered to be the "father" of PSA testing, says it is no longer a useful tool for screening for PC. In fact, it may be causing unwarranted treatment for a typically slow-growing tumor. Dr. Stamey drew his conclusions after studying over 1300 consecutive radical prostatectomies. Over time, there was a linear decrease in most parameters associated with PC. During the first 5 years of screening, 91% of cancers were palpable, the mean PSA was 25 ng/mL, the mean age was 64, and cancer volume was over 5 cm^3. During the last 5-years of screening, 17% were palpable, the mean PSA was 8 ug/mL, the mean age was 59, and the cancer volume was 2.4 cm^3. When PSA screening was first introduced, high levels were associated with a 50% chance of having a large PC for which

treatment was warranted. Over the past 5 years, the chance of having a large PC has fallen to 2%, presumably due to over screening. “Most prostate cancers we (*now*) remove need not be removed.”

An estimated 230 000 men in the USA will be diagnosed as having PC this year; 30 000 are expected to die of PC. Dr. Stamey says the fear of dying of PC may be disproportionate to the odds of death. One study reported that the prevalence of PC was 8% in men in their 20s, and the percentage grew linearly to 80% in men over 70. “It’s a cancer we all get if we live long enough.”

There is ambivalence in the prostate-treatment community regarding screening. Some researchers remain convinced that screening effectively detects clinically significant PC and leads to a reduced mortality.

“Physicians continue to be concerned about diagnosing prostate cancer at the earliest stage when it is most treatable, while at the same time avoiding unneeded biopsies and treatment for prostate cancers that might not become clinically meaningful.”

The mortality rate from the disease is low. But the reality is that some patients may benefit from early detection. Thus, PSA has lost some value, but it still may have some clinical relevance.

Patients at risk of overtreatment have a low, stable PSA with low-grade, low-volume cancers. We are detecting many low volume cancers that may not require treatment.

No doubt many men are now undergoing unnecessary treatments for PC. Undoubtedly some lives are saved. Where to draw the line?

I believe PSA should not be considered a “routine” screen (as is BP, blood glucose, and cholesterol). Patients should be fully informed about risks and benefits beforehand. I believe primary care clinicians should not even broach the subject when consulting with elderly men. Digital rectal examination is a more reasonable screen.

There are some guidelines when results of PSA are obtained in younger men. If the PSA is high, and if the rate of increase is rapid (eg, doubling time, or an increase of over 2.0 ug/year), biopsy is warranted. Surgery then depends on the grade of PC determined by biopsy.

When I was a child, almost all children and many adults underwent tonsillectomy. It seemed to be the mode. When we would consult with our European colleagues, they would admonish—“Hold onto your tonsils”. I believe many man in the USA should “Hold onto your prostate”.

RACE

11-10 A RATIONAL BASIS FOR RACE

Humans are not divided along clear color-based lines which are traditionally used in anthropological records. Some ask—Does race exist at all?

The problem occurs when society and the medical community generalizes findings to an entire group. Prostate cancer has a higher prevalence among African-American men. This does not mean that all African-American men have similar risks for prostate cancer.

The connection between self-identified race and genetic variation is very blurry. Culture, lifestyle, and social stress may play a greater role in disparity.

Black "African Americans" are an extremely diverse group.

We often choose subsets of individuals for screening—race may be one. I believe divisions according to 'race" still has some clinical validity. The disparity between races in the USA is gradually disappearing.

RISK OF DISEASE

7-9 CALCULATING THE RISK OF DISEASE www.yourdiseaserisk.harvard.edu

A review note in BMJ July 24, 2004; 329: 237 calls attention to an online tool for determining an individual's risk for five of the most important disease groups in the USA (cancer, diabetes, heart disease, stroke, and osteoporosis). It is presented by The Harvard Center for Cancer Prevention, part of the Harvard School of Public Health. It is an expanded version of the center's cancer risk assessment website.

The site is an interactive educational tool that seeks to encourage healthy lifestyles. It questions the inquirer's eating habits, drinking, and exercise, and offers personalized tips for disease prevention.

I accessed this site on August 13, 2004 and completed the heart disease risk evaluation. Individuals can easily and quickly complete the 21 or more questions asked. It includes all components of the Framingham Risk Score except HDL-cholesterol.

In addition it asks for past history of heart disease, family history, waist size, diabetes, 7 different questions about diet and alcohol, vitamin supplements, and exercise.

On completion it presents a colored risk scale (low to high) and places the individual's estimated risk compared with average.

A useful addition is a list of tips on how you can reduce your individual risk. I received 5 different tips to reduce my risk. RTJ

SHARED MEDICAL DECISION MAKING

11-6 SHARED MEDICAL DECISION MAKING: Problems, Process, Progress

"Sharing with a patient who faces *tough* choices when he or she is ill is one of the true gifts of being in the medical profession." The patient-physician relationship is the sacrosanct epitome of professionalism with the goals of ensuring that patients receive the treatment best for them (science) and that the best treatment is carried out in the most efficient and compassionate manner (quality and safety).

"Physicians should never make a choice for a patient—even if the patient wants the physician to do so ." Instead, physicians should ensure that the information used in the patient's decision-making is reasonable for the individual patient and that the patient understands the ramifications of choice. "The physician should be a navigator, not a pilot."

The consequences of a patient's choice cannot be shared with anyone else. Only the patient will suffer or enjoy the probabilistic outcomes associated with choosing one option over another. Only the patient will know how he or she feels about experiencing an adverse effect of a treatment or a reduced chance of an adverse outcome that a treatment is designed to alter. Patients must have time to reflect.

A decision that appropriately involves a patient requires viable options, and choosing one option over another must engender some element of risk. There has to be a definable trade-off of harm and benefit.

Some actions, however, are not really decisions to be made by the patient and do not require a patient's input. Patients need not decide if antibiotics are required for bacterial pneumonia. Sick patients should not be allowed to make decisions about treatments that are of clear value and that do not create significant levels of harm. If the significance of an adverse effect or harm is so minor compared with the benefit, no decision is required.

The conceptional framework for making a choice is understandable as a balance between harms and benefits weighed by the patient's values for gains and losses. Only the patient can do it. "Physicians cannot deny patients the opportunity and means to make their own choices."

I enjoyed this thought-provoking commentary.

The demise of physician's paternalism and authoritarianism has transferred some decision-making to the patient. In some circumstances, the physician's responsibility must be to fully inform patients of the best evidence about harms as well as benefits of treatment. This enables patients to choose based on their individual circumstances. How strictly should primary *care clinicians apply this principle?*

Shared decision-making is applicable when the choices are "tough". I believe the process needs to be applied to relatively few patients seen in daily primary care practice. If this process were applied to every patient, practice would grind to a halt. The process would be more applicable to patients seen in specialty care (eg, oncology, surgery).

The comment about no need for patient- decision making in clear cut situations such as antibiotics for pneumonia may not be so simple for an elderly, infirm patient who does not wish to receive therapy. If the patients is competent and wishes to avoid therapy, this is his decision.

There are many obstacles to application of "shared decision" in the real world of primary care:

The patient may be incompetent.

What about decisions for children?

Patients are often medically illiterate.

There may be cultural and language barriers. In some cultures, patients may rely on family and will refuse to make their own choice. Some patients may defer to the physician asking "What would you do?" and may refuse to choose.

Estimates of benefit/harm may not apply to individual "real world" patients. The true benefit/harm ratio may not be well established. It may be subject to change as more information becomes available.

The patient's best choice is often not available The patient may not be able to pay for the choice he makes. Insurance may not cover the costs.

How should the clinician respond when the patient chooses a course the physician considers futile?

I believe medical paternalism and authoritarianism is not dead yet.

STATIN DRUGS

7-12 ARE OTC STATINS READY FOR PRIME TIME?

This month, the 10 mg dose of simvastatin (*Zocor*) is expected to become available to the general public in the UK without a prescription. The UK government hopes this will make it easier for individuals to acquire a low-cost statin, and will increase use and reduce cardiovascular morbidity and mortality

There are opponents and proponents, both with good reasons.

Four years ago, a similar attempt in the USA failed to achieve OTC status. The FDA did not believe evidence was sufficient that a 10 mg statin could be used safely. However, the FDA is considering reversing this course. The National Lipid Association has received a grant from Johnson and Johnson-Merck to explore the pros and cons of OTC statin availability in the USA.

I wonder if a compromise would be feasible. The doctor writes a note (not a prescription) informing the pharmacy staff that Mr X is a candidate for OTC statin. This would give the clinician and the pharmacist an opportunity to educate the patient about risks as well as benefits. And also to give the clinician the opportunity to check on adverse effects and effectiveness at future consultations.

The note could be presented at time of each purchase. The statin is not displayed on the shelf. It is available and paid for at the pharmacy check-out, not at the check-out for general purchases and other OTC drugs.

I believe a good argument could be made that statins are safer than some drugs now freely available OTC—eg, NSAIDS, aspirin, and all sorts and conditions of "natural" and "alternative" nostrums. RTJ

I would vote in favor of OTC status. RTJ

8-6 PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE WITH ATORVASTATIN IN TYPE 2 DIABETES

Current prescription rates for lipid lowering drugs in patients with DM2 remain low, even in patients with established cardiovascular disease **(CVD).**

This study assessed the effectiveness of a 10 mg dose of atorvastatin (*Lipitor*) *vs* placebo in *primary* prevention of CVD in patients with DM2. None had high concentrations of LDL-c. The trial was stopped 2 years early because of demonstration of significant benefit.

None had documented history of CVD. All had at least one risk factor: retinopathy, macro- or micro-albuminuria, current smoking, or hypertension. The risk of a major cardiovascular event in these patients was 10% over 4 years.

Incidence of major cardiovascular events was 25 per 1000 person-years at risk in the placebo group vs 15 per 1000 person-years at risk in the atorvastatin group. Therefore, allocation of 1000 patients to atorvastatin would avoid 37 first major events over a 4-year follow-up. 27 patients would need to be treated for 4 years to prevent one event. [NNT (for 4 years to benefit one) = 27]

"The debate about whether *all* patients with DM2 warrant statin therapy should now focus on whether any patients can reliably be identified as being at sufficiently low risk for this safe and effective treatment to be withheld."

These data challenge the use of a particular threshold level of LDL-c as the sole arbiter of which patients with DM2 should receive statin therapy (as in the case of most current guidelines). Target levels of LDL-c (100 mg/dL) could be lowered.

An editorialist comments: The conclusions of the study—"Seems too far-fetched in view of the available clinical trials and epidemiological data". He cites 4 large studies of lipid control which contained many patients with DM2. Two of the four did not report a statistically significant reduction in coronary disease. Two did.

Clinical trials enroll carefully selected patients. The results cannot necessarily be extrapolated to primary care practice. Many patients may be at low risk and the benefit/ harm-cost ratio may be too low to warrant long-term treatment. Some may be at higher risk of adverse effects from statins. As always, individualization is required.

I believe the majority of patients with DM2 will benefit from statin therapy for primary prevention.. Most will have one or more additional risk factors. There would be no question regarding secondary prevention.

Authors and publishers persist in presenting relative benefits (rather than absolute differences). Thus, they reiterate that treatment with atorvastatin was related to a 37% reduction in major coronary events; a 31% reduction in coronary revascularizations; a 48% reduction in stroke; and a 27% reduction in deaths.

This can be very misleading. I believe statements of relative benefits should be eliminated from published reports.

SUGAR-SWEETENED BEVERAGES

8-1 SUGAR-SWEETENED BEVERAGES, WEIGHT GAIN, AND INCIDENCE OF TYPE 2 DIABETES IN YOUNG AND MIDDLE-AGED WOMEN

This study examined the relationships between sugar-sweetened beverage consumption (especially soft drinks), weight gain, and risk of diabetes in a large cohort of young and middle-aged women.

Over the entire 10 year period, women who *increased* their sugar-sweetened soft drink **(S-SSD)** intake from low to high had larger increases in weight compared with women who maintained a low intake, or substantially reduced their intake.

In contrast, women who *decreased* their S-SSD reduced their total energy consumption by 319 kcal/d. Women who *decreased* their intake during the first 5 years and maintained a low level gained less weight than those who increased their intake (2.8 kg. vs 4.4 kg).

Participants whose consumption of *diet* soft drinks *increased* from one drink or less per week to more than one drink per day gained significantly *less* weight (1.6 kg) than women who *decreased* their intake from one or more drinks daily to 1 drink or less per week (4.2 kg). [*Ie, consumption of calorie free drinks apparently to some extent, blunts ingestion of calorie-containing foods.*]

Greater S-SSD consumption was strongly associated with progressively higher risk of type 2 diabetes. (RR = 1.9 in women consuming one or more drinks per day *vs* those consuming less than one per month.)

Sugar-sweetened fruit punch was also associated with increased risk of diabetes. (RR = 2.0)

"Pure" fruit juice was *not* associated with risk of diabetes.

Over 8 years, there were positive associations between sugar-sweetened beverage consumption and both greater weight gain and risk of type 2 diabetes, independent of other known risk factors.

Energy provided by sugar-sweetened beverages does not affect subsequent food and energy intake. (Ie, little or no compensation by reduction in intake of other foods.) Weight gain and obesity result from the positive energy balance.

Fruit juice was *not* associated with diabetes risk in this study. This suggests that naturally occurring sugars in beverages may have different metabolic effects than added sugars.

This is an important life-style consideration.. It convinces me to ask a screening question, especially for overweight patients and patients with type 2 diabetes—"How many Cokes and how many Diet Cokes do you drink every week?"

Grocery stores offer a wide range of fruit flavored drinks (fruit punches). Some contain high amounts of fructose and sucrose. Some contain an artificial sweetener. Look at the "Nutrition Facts" label.

A 12-oz can of Coke contains 42 gm of sugar (high fructose corn syrup or sucrose).

A 12-oz can of Diet Coke contains zero calories. (Aspartame).

My "pure" orange juice contains 36 grams of sugar per 12 oz, almost as much as 12 oz of Coke. What is the metabolic difference?

Note also that many other foods (especially breakfast cereals) contain a high concentration of sugar. Do these foods, in contrast to S-SSD, have a higher satiety value? Moral: "Give your pancreas a break". RTJ

8-2 SUGAR-SWEETENED SOFT DRINKS, OBESITY, AND TYPE 2 DIABETES.

When individuals include liquid carbohydrate consumption in their diet, they do *not* reduce their solid food consumption. An increase in liquid carbohydrates leads, perversely, to even greater caloric consumption of other foods.

"A better mechanism for weight gain could not have developed than introducing a liquid carbohydrate with calories that are not fully compensated for by increasing satiety."

Conversely, intake of *diet* (non-sugar containing) sodas is associated with a *lowering* of risk of childhood obesity.

"Reducing sugar-sweetened beverage consumption may be the best single opportunity to curb the obesity epidemic."

This convinces me to ask a routine screening question, especially for overweight patients and patients with type 2 diabetes. How many Cokes and how many Diet Cokes do you drink every week?" RTJ

TELEVISION VIEWING

7-1 ASSOCIATION BETWEEN CHILD AND ADOLESCENT TELEVISION VIEWING AND ADULT HEALTH.

Watching TV in childhood and adolescence has been linked to adverse health outcomes.

This study explored the long-term health effects of childhood TV viewing.

Mean weekday viewing hours varied between 1.9 hours at age 5 to 3.9 hours at age 13. Ages 5-15

61% of subjects averaged more than 2 hours of TV on weekdays.

Adolescent TV watching correlated with lower childhood socio-economic status, increased parental smoking, higher maternal and paternal BMI, and higher BMI at age 5.

Childhood and adolescent TV viewing predicted (at age 26) a higher BMI, lower VO2 max, higher cholesterol, and increased smoking:

Several childhood behaviors could explain the relation between TV viewing and health. The most obvious are physical activity and diet. Watching TV could affect fitness and obesity by displacing time which would be spent on more active pursuits. TV viewing may influence cigarette smoking.

Viewing habits established in childhood may persist into early adulthood.

"We believe that reducing television viewing should become a population health problem."

Excessive viewing might have long-lasting adverse effects on health.

What else can I say? RTJ

TERMINAL SEDATION

8-9 TERMINAL SEDATION: An Acceptable Exit Strategy?

Terminal sedation is used by the physician to sedate a terminally ill patient until coma develops in order to alleviate intolerable suffering refractory to conventional palliative measures. It is controversial. It is illegal except in Oregon.

It has been condemned by some as euthanasia in disguise. Others, such as the U.S. Supreme Court Justice O'Connor, have endorsed the practice arguing that "a patient who is suffering from a terminal illness and who is experiencing great pain has no legal barrier to obtaining medication from qualified physicians to alleviate that suffering, even to the point of causing unconsciousness and hastening death".

One of the major objections to terminal sedation is that its intent may be to kill the patient in order to alleviate suffering. The intent of palliative care, by contrast, is to relieve suffering, even if the treatment, such as opioids, shortens life. "Intent matters"—in law and in ethics. The rule of "double effect" states that foreseeable adverse consequences of treatment (*ie, side-effects*) are acceptable only if they are *not* intended. A second objection is that terminal sedation could take place without the patient's consent, a process indistinguishable from involuntary euthanasia.

In America, we worry that patients who lack access to care, or whose values differ from those of their physicians, might be euthananized without their consent. And that the rate of terminal sedation might be high in the U.S. because physician-assisted suicide is largely unavailable.

"We need to control the use of terminal sedation by developing and implementing practice guidelines." We must confirm the diagnosis, consider alternative approaches, and obtain informed consent.

Is the patient conscious and competent to make his own decisions when nearing death? Then possible approaches to end-of-life care would include:

1) Request palliative, comfort care until death.

2) Request withdrawal of life-sustaining treatment.

3) Decide to cease intake of food and fluids

4) Request administration of a state of coma, or near coma, to be sustained until death.

5) Request a prescription of barbiturates to have on hand if the patient wishes at some time to take them.

(Although this is not legal in almost all states, I believe physicians invoke the practice in many cases by subterfuge.)

*If the patient is not competent to make his own decisions, or if his directions before loss of competency were not clearly stated, the problem becomes more difficult. A surrogate must then decide what is in the best interest of the patient. Options would include only 1), 2) and 3). R*TJ

VESTIBULAR NEURITIS

7-11 METHYLPREDNISOLONE, VALACYCLOVIR, OR THE COMBINATION FOR VESTIBULAR NEURITIS

This study was performed to determine if anti-viral therapy with valacyclovir (*Valtrex* which is rapidly converted to acyclovir) and/or corticosteroids would benefit.

Methylprednisolone alone significantly improved the long-term outcome of peripheral vestibular function. Antiviral therapy did not benefit any more than placebo.

There is good evidence that the major damage in VN is caused by swelling and mechanical compression of the vestibular nerve within the temporal bone. (As is assumed with the facial nerve in Bell's palsy.)

A reduction in swelling due to the anti-inflammatory effect of corticosteroid may explain why these drugs result in improvement.

Some patients (placebo group) apparently improved spontaneously, and about 4 out of 10 treated with methylprednisolone did not improve. Residual symptoms of VN may persist for years.

During their careers, primary care clinicians will likely encounter at least one case of VN. Incidence is about one case per 30 000 population.

Benign paroxysmal positional vertigo is common. Although the pathogenesis is vastly different. I wonder if a trial of short-term corticosteroids might help. RTJ