PRACTICAL POINTERS

FOR

PRIMARY CARE

JULY TO DECEMBER

2005

PRACTICAL POINTS FOR PRACTICE

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

JAMA, NEJM, BMJ, LANCET

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This document is divided into three parts:

1) "Practical Points"—one sentence statements of how the articles abstracted during this 6-months may influence primary care practice. Clicking on the bracket will link to the "Highlights-*Editorial Comments*"

2) Fifty four medical subject headings (MeSH) from "Acute Coronary Syndromes" to "Vitamin D".

3) A "Highlights-*Editorial Comments*" section, arranged alphabetically following the list of MeSH. This enables recall 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 also refer to the full abstract. For example, [9-2] refers to the 2nd abstract published in the September issue.

The indexes and each monthly issue for the past 5 years can be found on the website (www.practicalpointers.org).

I hope you find the publication useful and interesting.

Richard T. James Jr., M. D. Editor/publisher

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

PRACTICAL POINTS JULY-DECEMBER 2005

HOW THE ABSTRACTS INFLUENCED MAY INFLUENCE PRACTICE

Caution in primary care in prescribing warfarin and aspirin combined because of risk of bleeding [8-5]

Women with symptoms of urinary tract infection who have negative dipstick tests may benefit from antibiotics [7-1]

Advise adolescents and early age adults that being physically fit reduces risk of cardiovascular disease later in life. [12-1]

Testing for human papilloma virus is replacing the Pap smear for cervical cancer screening. Delaying screening until age 30 will reduce number of false positive tests [11-4] [11-5]

Lowering LDL-cholesterol reduces risk of cardiovascular events regardless of the initial LDL level. [10-4]

Avoid the "Oh, by the way doctor" syndrome by beginning the clinical interview by asking the patient to list all concerns [11-1]

Inhibiting gastric acid production may predispose to *Clostridium difficile* infection [12-7]

Echinacea is not effective treatment for the common cold [7-10]

Caution in using antipsychotic drugs in patients with dementia. [10-8]

Add a "help" question to the two classical questions to screening for depression [10-9]

Suggest inhaled insulin (with reservations) for patients as an alternative method of administration. [11-7]

Intensive treatment of type 1 diabetes protects against *macro*-vascular disease [12-9]

Many older women will experience recurrence of menopausal symptoms after hormone replacement therapy is discontinued. Decide—does symptomatic control trump the slight risk of adverse events? [7-2]

"White coat" hypertension a risk factor for hypertension [7-3]

Exercise reduces BP in patients with hypertension (19 points regarding benefits) [9-3]

New drugs of insomnia [8-2]

Consider the metabolic syndrome a risk factor for non-alcoholic fatty liver disease [12-5]

Abdominal obesity is more highly related to myocardial infarction than BMI [11-2]

Bariatric surgery is a reasonable intervention for morbid obesity [10—2]

Vitamin D supplements are necessary to maintain adequate blood levels in northern latitudes. [11-3]

Periodontal disease may be a risk factor for cardiovascular disease. Primary care clinicians should note it [12-2]

A new, safer, pertussis vaccine is available [10-7]

Right brain stroke is under-recognized. [7-7]

MEDICAL SUBJECT HEADINGS (MeSH)

JULY - DECEMBER 2005

HIGHLIGHTS AND *EDITORIAL COMMENTS*
BASED ON MEDICAL SUBJECT HEADINGS
JANUARY-JUNE 2005

ACUTE CORONARY SYNDROMES

Should Primary Care Clinicians Prescribe This Therapy?

8-5 WARFARIN PLUS ASPIRIN AFTER MYOCARDIAL INFARCTION OR ACUTE CORONARY SYNDROME: Meta-analysis with Estimates of Risk and Benefit.

After acute coronary events, a marked thrombin generation state persists for months. This suggests a role for anticoagulation beyond the initial use of low-molecular-weight heparin.

This study quantified the risks and benefits of warfarin + aspirin vs aspirin alone after acute coronary syndromes **(ACS).** Patients considered at high risk of major bleeding from warfarin therapy were excluded.

Outcomes per 1000 patients per year:

	Warfarin + aspirin	Aspirin alone	Absolute difference	NNT (2 y)
MI	22	41	19	53
Ischemic stroke	4	8	4	250
Major bleeding	1.5	0.6	0.9	1100
Death	No difference			

I included this abstract mainly to point out why many primary care clinicians will, with good reason, resist prescribing warfarin in addition to aspirin for patients with ACS . I believe primary care clinicians should rarely, if ever, prescribe warfarin for this indication..

1. The NNT to benefit one patient is high. No benefit for mortality. The cited risk of major bleeding (~ 1 in 1000 per year) is unrealistically low when applied to primary care. Non-major bleeding will commonly occur and create anxiety, inconvenience, and additional costs.

2. Patients in primary care differ substantially from those in trials: They will be at higher risk for bleeding. Exclusion criteria may not be strictly applied. Patients will be less adherent to laboratory control; they will be less carefully followed; they may use OTC drugs that are contraindicated when warfarin is used; they may be more likely to eat foods which can increase risk of bleeding. Costs and inconvenience may be too high.

3. Many patients in primary care are elderly, medically indigent, and medically illiterate. Warfarin therapy is not suitable for these groups.

Primary care clinicians will still apply the many other drug and lifestyle measures which reduce risk of recurrence of ACS

This is a good example of the "Catch 22" of interventions in primary care—benefits are often hidden, harms are evident. Physicians and patients would have no way of knowing which 19 patients of the 1000 treated are the

ones that avoided an MI. On the other hand, patient and physician alike would be painfully and dramatically aware of bleeding.

"No Single Element Of Chest Pain History Is A Powerful Enough Predictor Of Non-ACS To Allow the Clinician To Make Decisions According To It Alone."

11-6 VALUE AND LIMITATIONS OF CHEST PAIN HISTORY IN THE EVALUATION OF PATIENTS WITH SUSPECTED ACUTE CORONARY SYNDROMES: A Systematic Review

Despite diagnostic advances, missed acute coronary syndromes **(ACS)** and acute myocardial infarctions **(AMI)** remain problematic. The diagnosis is missed in 2% to 10% of patients.

Conversely, a large proportion of patients with chest pain who are admitted do *not* turn out to have an ACS. This has enormous economic implications.

Chest pain must be used in conjunction with other markers to determine disposition.

A. Low risk of ACS

Pain that is pleuritic, positional, stabbing, or reproducible with palpation.

B. Probable low risk

Pain not related to exertion or that occurs in a small inframammary area.

C. Probable high risk

Pain described as pressure, is similar to that of a prior MI, or worse than prior anginal pain.

D. High risk

Pain that radiates to one or both shoulders or arms,, or is related to exertion.

Despite limitations, the chest pain history allows the clinician to establish approximate probabilities for acute cardiac ischemia.

Overall, the likelihood ratios of positive tests (the presence of an individual descriptor of pain) varies from 0.2 to 4.7. That is, the discomfort described can be present in 2 out of 12 patients with ACS. Or can be present in 5 out of 6. This is not robust enough to be independently useful in establishing a diagnosis. There will always be patients without ACS who have discomfort similar to that of patients with ACS.

ANTIBIOTICS

Antibiotic Therapy Shortened The Time To Resolution Of Symptoms.

7-1 RESPONSE TO ANTIBIOTICS OF WOMEN WITH SYMPTOMS OF URINARY TRACT INFECTION BUT NEGATIVE DIPSTICK URINE TEST RESULTS.

A sizable group of women with urinary symptoms who subsequently have UTI established by culture are dipstick negative.

This pragmatic trial (as in primary care practice) compared the effectiveness of antibiotic treatment vs placebo in women with symptoms of UTI who had a negative dipstick.

Double-blind placebo-controlled study followed 59 women presenting to primary care with a history of dysuria and frequency. All had a negative dipstick for both leukocytes and nitrites.

All were treated with: 1) Trimethoprim 300 mg daily for 3 days, or 2) placebo.

The median time to resolution of dysuria: Trimethoprim—3 days; placebo—5 days.

Ongoing symptoms	At 3 days	At 7 days
Trimethoprim	24%	10%
Placebo	74%	41%

(Number needed to treat with trimethoprim to benefit one patient = 4.)

Only 5 women (of 59) had microbiological evidence of bacterial infection when standard criteria were used—a pure growth of 100 000 organisms per mL. Three were in the treatment group; 2 in the placebo group.

"These results indicate a bacterial or other infectious cause for the symptoms that was missed by dipstick testing and standard testing [*by culture*] in a diagnostic laboratory."

The resolution of symptoms that generally accompany infection would provide some support for an atypical or occult cause, implying that these women do not have "urethral syndrome", a diagnosis of exclusion.

A past history of UTI increases the risk of subsequent infection. Ninety % of the women in the study reported a history of similar symptoms.

Admittedly, this is a small trial. Confirmation with a larger number of subjects would be more convincing. Nevertheless, I believe it has clinical validity.

Many primary care clinicians treat symptoms of UTI empirically with antibiotics, rather than wait for bacterial confirmation. This would apply particularly to patients who have had a history of repeated UTI. Indeed, I believe some clinicians will prescribe an antibiotic to be reserved at home for patients to take at the onset of symptoms.

AROMATASE INHIBITOR (See BREAST CANCER)

BARIATRIC SURGERY (See OBESITY)

BOTULINUM TOXIN

An Important Therapeutic Agent With Widespread Applications.

12-6 THE MYRIAD USES OF BOTULINUM TOXIN

Botulinum toxin (**BTx**) is an important therapeutic agent with widespread applications. It is one of the most potent neurotoxins known. BTx derives its name from the Latin word *botulus*, "sausage". This refers to poisoning from badly preserved meat observed in the early 19th century. BTx is a protein produced by *Clostridium botulinum.*

BTx targets peripheral cholinergic systems and prevents the release of acetylcholine, blocking synaptic transmission.

Over the past 24 years, it has proved to be remarkably successful in relieving spasms, unwanted movements, abnormal postures, and pain associated with many disorders. It has made it possible to control some neurological conditions that once required systemic therapy. Double-blind placebo-controlled clinical trials have shown that it safely and effectively resolves excessive muscle contraction in dystonia (a condition characterized by sustained twisting and posturing movements); hemifacial spasm; and spasticity from stroke, cerebral palsy, brain trauma,

and multiple sclerosis. It has also been successful in patients with hyperhidrosis due to autonomic disorders. More recently, BTx has attracted interest in headache and pain disorders, and for cosmetic uses.

This issue of *Annals* reports effectiveness in treatment of the pain of lateral epicondylitis ("tennis elbow").

BREAST CANCER

10-6 DOES DIETARY FOLATE INTAKE MODIFY EFFECT OF ALCOHOL CONSUMPTION ON BREAST CANCER RISK: Prospective Cohort Study

High alcohol consumption is a known risk factor for breast cancer **(BC).** Although the association is modest, its adverse effect on BC is one of the most consistent findings among dietary risk factors.

Some studies report an inverse association between folate intake and risk of BC. This study asked: Is the association between alcohol consumption and risk of BC modified by intake of dietary folate?

This prospective cohort study recruited and followed over 17 000 women age 40-69 at baseline (mean = 55)

At baseline, obtained information about alcohol consumption. Calculated folate intake from a dietary questionnaire.

Hazard ratios for BC considering both alcohol and folate intake: For women who consumed 40 g alcohol per day and 400 ug of folate daily the rate of BC was half that of women who consumed 40 g alcohol per day and 200ug folate. (A suggestive protective effect.)

Women who had a high alcohol intake and a low folate intake had increased risk of BC. Women who had a high alcohol intake and a high folate intake were not at increase risk.

Value of a therapeutic intervention has been defined as the ratio between benefit/harm-cost.

Benefit depends on the absolute risk reduction (Number needed to treat to benefit one patient). It also depends on the type of benefit achieved. Preventing a BC may be considered a greater benefit than preventing a less ominous outcome.

Harm depends on the absolute number of adverse effects. (NNT to treat to harm one patient.) It also depends on the severity of the harm produced.

Cost is a basic consideration for primary care. It is seldom mentioned in scientific reports. Availability and accessibility are also cost considerations.

Folic acid has been reported to benefit (reduce risk of) neural tube defects, osteoporotic fractures, congestive heart failure, dementia and Alzheimer's disese. And now, BC in heavy alcohol consumers.

Consider the benefit/harm-cost ratio of a daily supplement of folic acid:

Benefit (except for reduction of risk of spina bifida) is not firmly established. Evidence of benefit is strongly suggestive.

Cost is nil. Harm is nil if B12 deficiency is not present. Availability and accessibility are high.

Because the absolute level of the denominator of the ratio (harm-cost) is so low, the benefit/harm-cost ratio may be very high.

I believe many primary care clinicians will prescribe daily folate (in a multivitamin capsule) for many patients on the basis of the high putative benefit and low harm-cost.

Letrozole Was Associated With Greater Reduction In Risk Of Recurrent Disease.

12-3 A COMPARISON OF LETROZOLE WITH TAMOXIFEN IN POST MENOPAUSAL WOMEN WITH EARLY BREAST CANCER

Tamoxifen inhibits activity of estrogen by competitively binding to the estrogen receptor. Aromatase inhibitors block the conversion of androgens to estrogen, and reduce estrogen levels in tissue and plasma.

Letrozole (*Femara)*, a third-generation aromatase inhibitor inhibits aromatase activity by over 99%.

This study compared letrozole with tamoxifen therapy in postmenopausal women with hormone-receptor-positive BC.

At five year follow-up	Letrozole (%)	Tamoxifen (%)
5-y Disease-free survival	84	81.4
Breast cancer recurrence	10.3	13.6
Node-positive BC survival	77.9	71.4
Node-negative BC survival	88.7	88.7
Distant recurrence	4.4	5.8

The absolute % differences in favor of letrozole ranged from 1.4% to 6.2%. The number needed to treat with letrozole vs tamoxifen to benefit one patient ranged from 15 to 71. Patients who were node positive benefited more from letrozole.

“Our study confirms the positive results reported in other trials of letrozole as adjuvant treatment for hormone-receptor positive breast cancer in postmenopausal women.”

Of particular interest was the finding of a significant reduction in the risk of recurrences at distant sites. (Difference = 1.4% favoring letrozole).

In postmenopausal women with endocrine-responsive BC, adjuvant treatment with letrozole, as compared with tamoxifen, reduced risk of recurrent disease, especially at distant sites

12-4 AROMATASE INHIBITORS—A TRIUMPH OF TRANSLATIONAL ONCOLOGY

“All evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes, and who are at substantial risk of recurrent disease. “

CARDIOVASCULAR DISEASE

“Low Cardiorespiratory Fitness Affects Approximately 1 Out Of 5 Persons Aged 12 Through 49 In The US”

12-1 PREVALENCE, AND CARDIOVASCULAR DISEASE CORRELATES, OF LOW CARDIORESPIRATORY FITNESS IN ADOLESCENTS AND ADULTS

The National Health and Nutrition Examination Survey (NHANES) is a continuous, cross-sectional, nationally representative sampling of the non-institutionalized civilian US population. This report covers years 1999-2002.

Participants were adolescents age 12-19, and adults age 20-49. All were free of CVD.

All underwent submaximal graded treadmill testing to achieve 75% to 90% of age-predicted maximum heart rate. Estimated maximal oxygen consumption (**VO2max**) by comparing heart rate response to reference levels of submaximal work. (Higher VO2max indicates more favorable fitness.) Cutpoints for fitness were defined as low (< 20th percentile); moderate (20th -59th percentiles); and high (60th and higher).

Thirty three % of adolescents and 14% of adults had low fitness. (This represents 7.5 million adolescents in the US, and 8.5 million adults.)

More than 25% of adults reported *no* moderate or vigorous physical activity in the past month.

Adults mean body mass index (**BMI**) = 27. About 20% had the metabolic syndrome.

Low fitness persons were 2 to 4 times more likely to be obese compared with those in the moderate-high fitness groups.

The strong association between obesity and CVD risk factors is the most striking indication of the health burden of low fitness. BMI and waist circumference demonstrated the most consistent association with fitness. Mean values decreased in a nearly graded fashion with increasing fitness. The association is already present in adolescents and young adults.

The relationship between low fitness and cardiovascular mortality is proposed to be mediated by the development of CVD risk factors including hypertension, diabetes, dyslipidemia, and the metabolic syndrome.

Physical activity training in efforts to improve fitness has been shown to lower the likelihood of developing risk factors, independent of changes in weight.

As primary care clinicians follow patients, they should watch for any increase in BMI and abdominal girth. A change may present an opportunity to ask about the patient's physical activity and to encourage intervention..

Clinician must first be able to point to their own fitness as an example.

CERVICAL CANCER

''Exercise Restraint and Prudence in Screening Initiation".

11-4 A 21-YEAR-OLD WOMAN WITH ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE

The decision to begin cervical cancer screening is of greater significance than clinicians often appreciate. Beginning too soon may set in motion a series of interventions and investigations that do not yield a beneficial health outcome.

Cervical-vaginal HPV prevalence is less than 2% before initiation of vaginal intercourse.

Prevalence of HPV: 71% in age 18-22; 31% in age older than 29; 29% in ages over 40.The decline is due to the immune response.

An abnormal cytology (ASC-US) occurs in up to 1 in 6 of sexually active young women.

Acute HPV infection causes cervical changes that can manifest as low-grade abnormal cytology, but such cytology does *not* indicate the presence of underlying cervical intraepithelial neoplasia **(CIN).**

HPV infections and ASC-US often regress spontaneously.

"Young women enthusiastic about cervical cancer screening need to be made aware of the projected benefits and potential harms of screening and treatment." Screening young women often elicits anxiety and a cascade of clinical interventions of no clinical value. We should . . . ''exercise restraint and prudence in screening initiation". "Just because we can test doesn't mean we should test. "

Patient's preferences and values should be integrated into clinical decision about screening. This requires explanation of risks, benefits, and burdens.

Women should be told that cigarette smoking increases risk of CC.

This and the following article would suggest delay in screening until age 30.

Why wait?

Prevalence of cervical cancer is very low in younger women

HPV and ASC-US are very common in sexually active women age 21. The burden of following, treating, and advising them would be considerable.

Between ages 21 and 30, many HPV infections and ASC-US will regress leading to avoidance of colposcopy and biopsy. Considerable anxiety will be avoided if screening were delayed.

. *It takes about 10 years for dysplasia to develop into cancer. The risk of developing cancer during the 20-30 decade is small.*

So. . .the benefit/harm-cost ratio of screening at age 21 is extremely low. The ratio increased by age 30.

There Is A Single Root Cause Of Cervical Cancer Is the Venerable PAP Test Outdated?

11-5 THE PROMISE OF GLOBAL-CERVICAL-CANCER PREVENTION

"Because there is a single root cause of cervical cancer, we can envision both primary prevention through vaccination against HPV in young women, and secondary preventive screening directly for carcinogenic HPV in older women."

"HPV DNA testing is more sensitive and the results more easily reproducible than cytologic screening and colposcopy for the detection of extant and incipient cervical precancerous conditions and cancer."

A negative test for carcinogenic HPV types provides a degree and duration of reassurance not achievable by any other diagnostic method.

We can target the optimal age at which screening should be performed; determine the most cost-effective testing intervals; which HPV types to screen for (strongly carcinogenic *vs* weakly carcinogenic); and the threshold of viral loads (very low loads only minimally raise the risk).

Because of the greater accuracy of HPV DNA testing, screening should be focused on reaching women at the time of the peak risk of treatable precancerous conditions, and before the average age at which incurable invasive CCs occur. Screening women once at age 35, or twice at ages 35 and 40 with current HPV DNA tests targeting 13 carcinogenic types can achieve more cost-effective reductions in cancer than can conventional cytological methods.

The peak prevalence of transient infections occurs among women during their teens and 20s, after the initiation of sexual activity. The peak prevalence of cervical pre-cancerous lesions occurs about 10 years later; the peak prevalence of invasive CC at age 40 to 50. The conventional model of CC prevention is based on repeated

rounds of cytological examinations and colposcopy. Alternative strategies include HPV vaccination of adolescents, or one or two rounds of HPV screening at the peak ages of treatable precancerous lesions and early cancer.

Would universal vaccination against HPV make cervical HPV testing unnecessary?

In regard to HPV we will soon have for primary care:

1) Early and more definitive screening.

2) Prophylaxis with vaccination.

Remarkable advances in immune therapy are in the offing:

HPV vaccine

Herpes Zoster vaccine

Improved TB vaccine

Malaria vaccine

Vaccine for H5N1 Flu

HIV is the holdout. Many persons still have high hopes.

CHOLESTEROL

The Proportional Reduction In The Event Rate Per Mmol/L Reduction In LDL-C Was Largely Independent Of The Pre-Treatment Level

10-4 EFFICACY AND SAFETY OF CHOLESTEROL-LOWERING TREATMENT: Prospective Meta-Analysis From 90 056 Participants In 14 Randomised Trials Of Statins

Observational studies indicate a continuous relationship between coronary heart disease (CHD) risk and low density lipoprotein cholesterol **(LDL-C**) concentrations. There is no definite threshold below which lowering LDL-c is not associated with lower risk.

This systematic meta-analysis was designed to remove uncertainty about over-estimating and under-estimating of effects of statin drugs on CHD, and other vascular or non-vascular outcomes.

Outcomes were reported as the effects per 39 mg/dl (1.0 mmol) reduction in LDL-c. Mean follow-up = 5 years.

Five-year absolute benefits per 39 mg/dL reduction in LDL-c:

A. Participants without previous CHD:

Outcomes avoided per 1000 participants:

Major coronary events	8
Coronary revascularizations	12
Stroke	5
Major vascular events	25

B. Participants with previous CHD:

Outcomes avoided per 1000 participants:

Major coronary events	30

Coronary revascularizations	27
Stroke	8
Major vascular events	48

Effects were evident during the first year. Benefits were greater in subsequent years. Absolute benefits increased with continuing treatment.

There was *no* evidence that lowering LDL-c by 39 mg/dL over 5 years increased the risk of non-vascular cause of death or any type of cancer. (*Statins remain among the safest of the major dugs used today. RTJ*)

The proportional reduction in the event rate per mmol/L reduction in LDL-c was largely *independent* of the pre-treatment level:

Lowering LDL-c from 156 to 117 reduces the risk of vascular events by about 23%

Lowering LDL-c from 117 to 78 also reduces (residual) risk by about 23%.

Treatment goals should aim chiefly to achieve substantial reductions in LDL-c (rather than to achieve particular target levels) since the risk reductions are proportional to the absolute LDL-c reduction.

LDL-c is only one of many risk factors for CVD. Even if LDL-c were controlled to the maximum, some risk would persist. The goal of therapy is to reduce all risk factors concomitantly I believe that benefits from lowering all factors to a modest degree (even if not reduced to "normal") would reduce risk more than lowering LDL-c maximally without concern for other risk factors.

CLINICAL INTERVIEW

How To Avoid The "Oh, By The Way, Doctor" Syndrome.

11-1 "WHAT ELSE" SETTING THE AGENDA FOR THE CLINICAL INTERVIEW

A too common ending of a medical interview:

Dr: "It looks like you have a bad virus cold and not a bacterial sinus infection. Antibiotics don't help. I will treat your symptoms and you can expect to get better. Let me know if you do not improve in a few days."

(Doctor then stands and gets ready to leave the room.)

Patient: "Before you go there is one more thing I would like to mention. I have been passing a little blood in my stool." "Should I do anything about it."?

Dr: "Why didn't you tell me this before"

Patient" "You didn't ask me."

The syndrome occurs at the end of the interview. "We believe it has its origin at the beginning."

If the physician jumps into an exploration of the first problem the patient mentions before knowing all of the patient's worries, he will often be confronted with these unvoiced concerns at the end of the interview. Open ended questions such as "What else?"; What other problems do you wish to attend to today?"; "What specific requests do you have today?" are most helpful in eliciting the patient's entire list of concerns.

We should not blame the patient for a defective interview process.

This article should be read in its entirety. See the abstract.

I believe some patients would respond if asked to list their agendas before coming to the office.

The same question "Is there anything else?" may also be asked at the end of the interview to reach completion.

This is important advice. I wish I had received it at the beginning of my medical career.

CLOSTRIDIUM DIFFICILE

C Difficile Infection Is Becoming An Important Public Health Issue. It May Occur Without Prior Antibiotic Use.

12-7 USE OF GASTRIC ACID-SUPPRESSIVE AGENTS AND THE RISK OF COMMUNITY-ACQUIRED *Clostridium difficile*- ASSOCIATED DISEASE

C difficile is an important cause of nosocomial diarrhea. *C difficile*-associated disease (**CDAD**) is also a cause of diarrhea in the community. It has been reported that it is the 3rd most common cause of infectious diarrhea in persons over age 75. The absolute number of CDAD cases in the community could be significant.

Gastric acid constitutes a major defense mechanism against ingested pathogens. Loss of stomach acid has been associated with colonization of the normally sterile upper gastrointestinal tract.

Suppression of stomach acid production by proton-pump inhibitors (**PPI**) and histamine2-receptor blockers (**H2RB)** may lead to increased likelihood of CDAD.

This case-control compared:

1) Cases of community-acquired CDAD (n = 1233; mean age 72—no hospitalization in the prior year), with

2) Ten matched controls without CDAD (n = 12 330—also not hospitalized in the prior year).

3) Determined current use of PPI and H2-RB in both groups.

Cases were 3 times more likely than controls to have received antibiotics; 3 times more likely to have received PPI; and 2 times more likely to have received H2RB.

Between 1994 and 2004, antibiotic prescriptions per outpatient per year declined by about 1/3 while prescriptions for PPI increased. Community cases of *C difficile* per year rose dramatically from less than 1 case per 100 000 patients to 22 per 100 000 patients.

Antibiotic exposure has, in the past, been considered almost a prerequisite for the diagnosis of CDAD. In this study, only 37% cases had received antibiotics within the preceding 90 days. "The belief that prior antibiotic exposure is practically a prerequisite for *C difficile* infection needs to be reevaluated."

"*C difficile* -associated disease is becoming an important public health issue."

Primary care clinicians should consider that C difficile infection can occur without prior antibiotic use. And that users of PPI, especially the elderly, may be at increased risk.

Case-control studies are not definitive. This requires confirmation.

A New Very Virulent Strain Resistant To Fluoroquinolones.

12-8 THE NEW *CLOSTRIDIUM DIFFICILE*

Old pathogens can emerge with increased virulence and challenge scientists to explain their rebirth, and clinicians to care for patients, and infection-control personnel to prevent their spread.

C difficile appears to illustrate these challenges. It already has some distinctive features. It causes disease almost exclusively in the presence of exposure to antibiotics.[1]

Two articles in this issue of NEJM describe new gene-variant strains of *C difficile* isolated from patients with *C difficile*-associated disease (**CDAD**). The variant types were resistant to fluoroquinolones. They produced up to 23 times more toxins A and B than some other strains. One of the studies reported hospital incidence of CDAD of 2 per 100 admissions and a high mortality rate, especially in the elderly. In the majority of cases, fluoroquinolones were the inducing agent.

"A more virulent strain of *C difficile* is causing epidemic disease."

Treatment consists of prompt discontinuation of the implicated offending agent, and administration of oral metronoidazole (*Flagyl*) Oral vancomycin should be considered in patients who do not have a prompt response.

"Particularly important is antibiotic stewardship, with restraint in the use of implicated antimicrobial agents."

1 *See the previous article. It suggests that community-acquired C difficile-associated disease may occur without prior antibiotic use.*

COFFEE

Increasing Consumption Associated With A Reduced Risk

7-11 COFFEE CONSUMPTION AND RISK OF TYPE 2 DIABETES: A Systematic Review

Epidemiological evidence has suggested that higher coffee consumption may reduce the risk of type 2 diabetes **(DM2).** Coffee contains numerous substances beside caffeine some of which have been shown to have an effect on glucose metabolism

This systematic review of cohort studies contained a total of over 199 000 subjects. And 8394 cases of DM2. Determined daily coffee consumption

Relative risk of DM2: coffee vs no coffee:	RR	Confidence interval
Six or more cups	0.54	0.54-0.78
4 to 5 cups	0.72	0.62-0.83
1 to 3 cups	0.94	0.88-1.01
All levels combined	0.65	

This supports a significant inverse association between coffee consumption and risk of DM2. Participants who drank 4 to 6 cups and over 6 cups daily had a 28% to 35% lower risk of DM2

Mechanisms? The authors speculate that various components of coffee other than caffeine may have beneficial effects by increasing insulin sensitivity, reducing hepatic glucose output, inhibiting glucose absorption, and enhancing insulin secretion. They suggest that caffeine is not the cause of the inverse association between

coffee and DM2. Indeed, some studies report that caffeine acutely *increases* post-load glucose concentrations and *lowers* insulin sensitivity.

I included this abstract because the conclusions of the study were provocative. I do not believe there is any clinical message at present, except that coffee is not harmful in this respect.

Another interesting connection between coffee and risk of dyslipidemia concerned the difference between pot-boiled coffee (once common in Finland) and filtered coffee. Some factor in pot-boiled lowered concentrations of LDL-cholesterol (increased risk). BMJ 1996; 313: 1362-66

COMMON COLD

No Beneficial Effect

7-10 AN EVALUATION OF *ECHINACEA ANGUSTIFOLIA* IN EXPERIMENTAL RHINOVIRUS INFECTIONS

This study extracted 3 different preparations of echinacea.

About 400 volunteers were randomized to either: 1) prophylaxis with echinacea beginning 7 days before viral challenge with rhinovirus), or 2) treatment of the experimental infection (beginning on the day of challenge), or 3) placebo.

There were no significant effects of echinacea extracts on severity of symptoms, volume of nasal secretions, polymorphonuclear leukocytes, interleukin-8 concentrations in nasal-lavage specimens, or on quantitative virus titers.

These extracts, either alone or in combination, do not have clinically significant effects on rhinovirus infection, or on the resultant clinical illness.

This brief abstract does not do justice to the meticulous methods in which this remarkable study was conducted. To gain the full flavor, read the article.

Even sophisticated, educated persons will remain convinced of the efficacy of echinacea for colds.

It is almost impossible to prove a negative. Advocates can cite numerous reasons why this study does not disprove effectiveness—they can avow that extracts from different varieties of plant, different parts of the plant, different preparations, different extraction procedures and manufacturing processes, location and season of cultivation will be effective. And treating cold viruses other than rhinovirus will also be effective.

The investigators are correct in stating that the burden of proof of effectiveness and safety should be placed on manufacturers of various alternative herbal preparations touted for a myriad of ills. I believe that the Congress made a serious error when it exempted these nostrums from surveillance by the FDA. There have been grave misapplications of these over-the-counter products: false advertising and egregious promotion, surreptitious addition with standard efficacious drugs, contamination with dangerous substances such as arsenic and mercury.

CORONARY HEART DISEASE

Primary Prevention Is Much More Rewarding

9-10 MODELLING THE DECLINE IN CORONARY HEART DISEASE DEATHS IN ENGLAND AND WALES 1981-2000: *Comparing Contributions From Primary Prevention And Secondary Prevention*

Since the 1980s, coronary heart disease **(CHD)** mortality rates have halved. Studies consistently suggest that 50% to 75% of the decrease in cardiac deaths can be attributed to population-wide improvements in the major risk factors, particularly smoking, cholesterol, and high blood pressure. Modern cardiological treatments for CHD generally explain the remaining 25% to 50% of the fall in mortality.

Fall in mortality from CHD attributable to changes in risk factors:

		Deaths prevented or postponed yearly (2000 vs 1981)		
	% changes *	Primary prevention	Secondary prevention	Total
Smoking	- 35%	24 000	5000	29 000
Cholesterol	- 4.2	4700	3100	7900
Blood pressure	-7.7	7200	500	7700
All 3		36 000	8700	45 000

(* % changes in the risk factor level in the population)

This article places our efforts to reduce risks (by enthusiastic prescription and by example) in concrete terms. This is a major public health achievement. Congratulations to all involved !

If weight reduction and physical activity were also considered, benefits would be larger.

We never know, however, which individuals in our practices and in the general population are benefited. This should not deter us.

I abstracted this article mainly to point out how important improvements in public health are. Certainly, primary care clinicians contributed a great deal .

DEMENTIA

Should Be Used Only When A Demented Patient Has An Identifiable Risk Of Harm To Themselves Or To Others.

10-8 ANTIPSYCHOTIC DRUGS IN DEMENTIA

Antipsychotic drugs are used to treat psychiatric and behavioral symptoms that affect the majority of persons with dementia. In nursing homes, where many residents have dementia, up to 25% of individuals receive such therapy.

In the 1990s, the introduction of atypical, or second-generation, antipsychotic drugs was met with enthusiasm because the rate of adverse effects (parkinsonism and tardive dyskinesia) was reported to be lower. However, in 2003 a study reported higher rates of cardiovascular adverse events and mortality in patients with dementia-associated agitation and psychosis who were treated with the newer antipsychotic risperidone (*Risperdal*) compared with placebo.

“Antipsychotic drugs should not be used when non-drug treatments are available and the risk of harm or significant distress is low.”

"Patients with hallucinations and delusions that are neither distressing nor placing themselves or others at risk or harm should not be treated with antipsychotic drugs."

At present, we cannot say that there is a "safe" antipsychotic drug. And we cannot say that one drug is safer than another.

Primary care clinicians who follow nursing home patients should ask themselves__"Am I prescribing this antipsychotic to benefit the patient, or to benefit the staff and the family?"

DEPRESSION

10-9 EFFECT OF THE ADDITION OF A "HELP" QUESTION TO TWO SCREENING QUESTIONS ON SPECIFICITY FOR DIAGNOSIS OF DEPRESSION IN GENERAL PRACTICE

Two questions have been used as a screening test for depression:

1) During the past month have you often been bothered by feeling down, depressed, or hopeless?

2) During the past month have you been bothered by little interest or pleasure in doing things?

The sensitivity of the screen is high. If the patient is indeed depressed, one or two questions will be answered "yes". (True positive rate = > 90%.)

The specificity however, is relatively low (~ 60% to 85%). Many persons who are not actually depressed will answer "yes". (False positive rate ~ 15% to 40%)

This study adds a 3rd question.

"Is there something for which you would like help? "

Adding the help question improved specificity (increased true negative responses from 78% to 89%, and reduced false positive responses from 22% to 11%. This increased the likelihood that a positive screen does indeed denote depression.

I believe screening for depression in some groups of primary care patients should be applied universally. (Almost any serious condition with a prevalence of 5% requires screening.)

The authors of the study suggest the questions be put in writing for the patient to answer.

Will adding the "help" question aid the diagnosis? The study says so. It is simple and takes little additional time and bother.

What to do if the questions are answered positively? Certainly, not reach immediately for the prescription pad. Further conversation will allow patients to ventilate (which in itself may be helpful), and may lead to a better understanding of their problem and more willingness to seek help..

10-10 SENSITIVITY, SPECIFICITY, POSITIVE LIKELIHOOD RATIO, NEGATIVE LIKELIHOOD RATIO OF SCREENING TESTS FOR DEPRESSION: Review by the Editor

Statistical analysis in now an essential component of studies presented by peer-reviewed journals. Primary care clinicians do not need to be expert statisticians, but they should know and be able to calculate several basic functions. Clinicians should be familiar with the meaning of sensitivity, specificity, positive

likelihood ratio, and negative likelihood ratio, and be able to calculate them from the data presented. This will enhance enjoyment of journal-reading and make it more meaningful.

Some articles present the opportunity to review these aspects of statistics as applied to general clinical practice. I enjoy calculating them.

Although I have calculated them many times from various studies, I still struggle to get them right, and then wonder if I did indeed get them right. A periodic refresher is required.

The preceding study allowed me to make these calculations from the data presented.

DIABETES

Increasing Consumption Associated With A Reduced Risk

7-11 COFFEE CONSUMPTION AND RISK OF TYPE 2 DIABETES: A Systematic Review

Epidemiological evidence has suggested that higher coffee consumption may reduce the risk of type 2 diabetes **(DM2).** Coffee contains numerous substances beside caffeine some of which have been shown to have an effect on glucose metabolism

This systematic review of cohort studies contained a total of over 199 000 subjects. And 8394 cases of DM2. Determined daily coffee consumption

Relative risk of DM2: coffee vs no coffee:	RR	Confidence interval
Six or more cups	0.54	0.54-0.78
4 to 5 cups	0.72	0.62-0.83
1 to 3 cups	0.94	0.88-1.01
All levels combined	0.65	

This supports a significant inverse association between coffee consumption and risk of DM2. Participants who drank 4 to 6 cups and over 6 cups daily had a 28% to 35% lower risk of DM2

Mechanisms? The authors speculate that various components of coffee other than caffeine may have beneficial effects by increasing insulin sensitivity, reducing hepatic glucose output, inhibiting glucose absorption, and enhancing insulin secretion. They suggest that caffeine is not the cause of the inverse association between coffee and DM2. Indeed, some studies report that caffeine acutely *increases* post-load glucose concentrations and *lowers* insulin sensitivity.

I included this abstract because the conclusions of the study were provocative. I do not believe there is any clinical message at present, except that coffee is not harmful in this respect.

Another interesting connection between coffee and risk of dyslipidemia concerned the difference between pot-boiled coffee (once common in Finland) and filtered coffee. Some factor in pot-boiled lowered concentrations of LDL-cholesterol (increased risk). BMJ 1996; 313: 1362-66

Coming Soon? Maybe

9-16 INTEREST IN INHALED INSULIN GROWS

The lungs provide a large surface area for drug absorption. Inhaled insulin is absorbed more rapidly than regular insulin given subcutaneously. The time to peak concentration of most inhaled insulins is nearly superimposable with the rapid-acting insulin analogues.

Controlled trials compared *Exubera* (one brand of inhaled insulin) + oral agents with injected insulin + oral agents. After 2 years, Exubera provided continuing glycemic control. HbA1c decreased 1.8%, compared with a 1.5% decrease in the injected insulin group.

Is it safe? Some studies have reported no adverse pulmonary events; some have reported cough as the most common side effect. A slight decline in carbon-monoxide-diffusing capacity occurred. Hypoglycemia, headache and dizziness have been reported. Patients with asthma absorbed lower amounts of insulin.

Longer term studies (a decade or more) are required to evaluate pulmonary function and insulin-binding antibodies, as well as use in children and smokers.

Should The "Normal" FPG Be Lowered?

10-5 NORMAL FASTING PLASMA GLUCOSE LEVELS AND TYPE 2 DIABETES IN YOUNG MEN

The normal fasting plasma glucose **(FPG)** is now defined as less than 100 mg/dL. An "impaired FPG" is now considered to range between 100 and 125.

Persons with impaired FPG are at increased risk for type two diabetes **(DM2).**

Do FPG levels below 100 (especially those in the 90s) independently predict DM2 in young adults? Better and earlier identification of young adults at risk of DM2 may lead to interventions aimed at delaying onset of DM2.

This study followed over 13 000 men age 26 to 45 (mean = 33) for 14 years. All had baseline FPG under 100. None had DM2.

Primary endpoint = incidence of DM2 defined as FPG of 126 or more. Mean follow-up = 6 years.

Compared with FPG less than 82, risk of DM2 progressively increased as FPG rose from 82 to 99.

Hazard ratios for DM2 according to quintiles of normal fasting glucose:

	Quintile 1	2	3	4	5
Fasting plasma glucose	50-81	82-86	87-90	91-94	95-99
Number of incident DM2	20	24	37	50	77

Risk of DM2 increased when other risk factors were associated with FPG:

Hazard ratios for DM2 when TG and FPG were combined:

FPG	< 87	88-90	91-99
TG < 150	1.00	1.76	2.65
TG > 150	2.42	5.26	8.23

Hazard ratios for DM2 when BMI and FPG were combined:

FPG	< 87	78-90	91-99
BMI 24 and less	1.00	0.75	1.79
BMI 25-29.9	1.99	2.75	4.77
BMI 30 and more	3.42	7.78	8.29

In apparently healthy young adults, risk of developing DM2 rose across quintiles of FPG levels usually considered to be within normal range. A FPG in the high "normal" range may predict DM2.

Risk increases when other factors are associated with a high "normal" FPG: higher BMI and triglyceride levels,; age; family history; sedentary lifestyle; abdominal girth.

When clinicians inform a patient that her blood test is "normal", this in no way indicates that risk of associated disease is absent—only that risk may be lower than in patients with an " abnormal" test.

Patients should realize that risk increases when risk factors are combined even if they are all "normal", especially if they are "high normal". There is a continuum, not an absolute cutpoint. "Normal" is not necessarily normal anymore. It is relative. A given level of a risk factor may be normal for one patient and abnormal for another. It is the combination of risk factors, not the level of one, which determines risk.

This advances the concept that lowering all risk factors (BP, lipids, BMI, abdominal girth, FPG) is beneficial even if they are not reduced to "normal".

The term "favorable" might replace "normal".

The term "requires intervention" should be used more frequently.

"Overall The Inhaled Insulin Approach Seems Effective And Safe."

11-7 INHALED INSULIN IMPROVES GLYCEMIC CONTROL WHEN SUBSTITUTED FOR OR ADDED TO ORAL COMBINATION THERAPY IN TYPE 2 DIABETES.

This study examined the effect of a preparation of inhaled, dry-powdered human insulin (*Exubera*) which is currently in development. The inhaled insulin delivers aerosolized powdered insulin to the small airways and alveoli. This enables rapid absorption. Its effect lasts 4 to 6 hours.

Does inhaled insulin improve glycemic control when taken alone, or when added to oral agents?

Open label parallel-group followed over 300 patients with DM2 (mean age 57; mean BMI = 30).
All were receiving two oral antidiabetes medications (predominantly a sulfonylurea and metformin). All had a HbA1c of 8% or greater (mean = 9.5%). All were considered to have failed on dual oral therapy.
None had significant respiratory disease. None were smokers.

Randomized to:

A. Inhaled insulin alone given 3 times daily before meals.

B. Inhaled insulin + continued oral agents

C. Oral agents alone.

HbA1c reduction compared with oral agents alone:

A. Inhaled insulin alone = -1.18 %

B. Inhaled insulin + continued oral agents = - 1.67 %

HbA1c levels less than 7%:

A. Inhaled insulin + continued oral agents = 32%

B. Oral agents alone = 1%.

In the insulin groups, fasting glucose and 2-hour postprandial glucose mean levels improved by up to 50 mg/dL and 75 mg/dL. Triglyceride levels improved by 40 to 54 mg/dL

Hypoglycemia occurred at a rate of 1.3 to 1.7 episodes per month in the insulin groups; 0.1 in the oral agents-alone group. No patient discontinued insulin due to hypoglycemia.

Cough was more common in the insulin groups. It was generally mild and decreased in incidence and prevalence during the trial. No patients discontinued for this cause.

Mean body weight increased in the insulin groups over 3 months (+ 6 pounds); did not change in the oral-alone group.

Withdrawals were similar in all 3 groups (about 6%--none due to adverse events).

Pulmonary function remained similar in all groups.

One would expect inhaled insulin to be more rapidly absorbed into the general circulation than subcutaneous insulin. It has a faster onset of action and thus a more rapid glucose-lowing effect. Its duration of action is longer than the short-acting insulin lispro and is similar to regular insulin. This makes it suitable for administration before meals.

I included this abstract to follow-up on this new technology, which I believe is of great interest to many patients with DM2. There is a long road ahead before inhaled insulin becomes freely available. I believe we will reach the end of the road.

Intensive Glycemic-Control Had Long-Term Beneficial Effects In Reducing Risk Of Cardiovascular Disease.

12-9 INTENSIVE DIABETES TREATMENT AND CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 1 DIABETES The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC)

This study assessed whether more intensive therapy, as compared with conventional therapy, would affect long-term incidence of *macro*-vascular complications (cardiovascular disease). Type 1 diabetes (**DM-1**) is associated with at least a 10-fold increase in cardiovascular disease.

The Diabetes Control and Complications Trial (**DCCT 1983-93**) randomized 1441 patients with DM-1 to: 1) intensive therapy, or 2) conventional therapy. Mean duration of 6.5 years. Mean baseline age = 27. At baseline, subjects had no, or minimal, microvascular disease; no hypertension; no hypercholesterolemia (by standards at the time); and no clinical evidence of cardiovascular disease.

At the end of 6 years, all participants were returned to their own health care providers and the Epidemiology of Diabetes Interventions and Complications study (**EDIC**) began. Ninety three % of the subjects were subsequently followed until 2005 (11 more years; total of 17 years). In the EDIC study, patients in both treatment group then received intensive therapy, During the subsequent 11 years, there were non-significant differences in the use of 3 or more daily injections of insulin.

(Ie, this report compares 6 years of intensive therapy + 11 years of continued intensive therapy with 6 years of conventional therapy + 11 years of intensive therapy.)

During the mean of 17 years, 46 cardiovascular events occurred in 31 patients in the 17-year intensive group vs 98 events in 52 patients in those originally assigned to conventional therapy. (0.38 vs 0.80 events per 100 patient-years.)

At baseline, mean HbA1c was 9.1 % in both groups. At the end of DCCT (6 years), it was 7.4% in the intensive group *vs* 9.1% in the conventional group. At the end of the 17 years, mean levels were about equal in both groups (7.9% vs 7.8%). The intensive group maintained HbA1c at a lower level; the HbA1c of those originally in the conventional group were subsequently treated intensively and their HbA1c fell to comparable levels.

Seventeen continuous years of intensive therapy resulted in greater sustained benefit on subsequent risk of cardiovascular event than the period of 6 years of conventional therapy followed by 11 years of intensive therapy. The original 6-years of intensive therapy, begun at a younger age, produced a sustained benefit.

The same glycemic mechanisms related to development of micro-vascular disease may also apply to the development of arteriosclerosis. Epidemiological evidence suggests that any elevation in glycemia, even within the subdiabetic range, increases risk of cardiovascular disease. This may be mediated by formation of advanced glycemic end-products

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The mean age at end of 17 years was 44. I would judge the benefits would continue to accrue over a more extended period of time.

The atherosclerotic process in patients with DM-1 begins at an early age. The earlier you start intensive treatment, the better.

The results could easily be extrapolated to patients with DM-2

The patients in the study did not meet the American Diabetes Association goal of a HbA1c 7.0% and under. Achieving this goal is difficult. Newer insulins would likely make achieving the goal easier.

Of course, treatment should include other interventions to reduce risk of cardiovascular disease (aspirin, statins, BP control, weight and abdominal girth control, increased physical activity, and especially tobacco cessation. (11% to 20% of subjects continued to smoke.)

FITNESS

10-3 REFINING THE EXERCISE PRESCRIPTION FOR HYPERTENSION

Guidelines for management of hypertension are likely to include advice to: “engage in regular aerobic activity such as brisk walking (at least 30 minutes a day) most days of the week”.

This article states that there is enough published work on exercise and hypertension to refine aspects of this advice.

The authors present 19 points regarding benefits of exercise.

I am sure the effects of exercise on BP differ a great deal between individuals.

I was not aware of many of these points.

Primary care patients may find them helpful. That moderate exercise 3 times a week is as beneficial as more frequent, prolonged, and strenuous exercise may be welcome news to many. The flexibility and benefits of accumulating exercise in 10-minute sessions may increase compliance. The helpfulness of exercise independent of weight loss might encourage some.

Physical exercise instructors may post these points to foster continuing compliance with exercise programs they offer their clients.

“Low Cardiorespiratory Fitness Affects Approximately 1 Out Of 5 Persons Aged 12 Through 49 In The US”

12-1 PREVALENCE, AND CARDIOVASCULAR DISEASE CORRELATES, OF LOW CARDIORESPIRATORY FITNESS IN ADOLESCENTS AND ADULTS

The National Health and Nutrition Examination Survey (NHANES) is a continuous, cross-sectional, nationally representative sampling of the non-institutionalized civilian US population. This report covers years 1999-2002.

Participants were adolescents age 12-19, and adults age 20-49. All were free of CVD.

All underwent submaximal graded treadmill testing to achieve 75% to 90% of age-predicted maximum heart rate. Estimated maximal oxygen consumption (**VO2max**) by comparing heart rate response to reference levels of submaximal work. (Higher VO2max indicates more favorable fitness.) Cutpoints for fitness were defined as low (< 20^{th} percentile); moderate (20^{th} -59^{th} percentiles); and high (60^{th} and higher).

Thirty three % of adolescents and 14% of adults had low fitness. (This represents 7.5 million adolescents in the US, and 8.5 million adults.)

More than 25% of adults reported *no* moderate or vigorous physical activity in the past month.

Adults mean body mass index (**BMI**) = 27. About 20% had the metabolic syndrome.

Low fitness persons were 2 to 4 times more likely to be obese compared with those in the moderate-high fitness groups.

The strong association between obesity and CVD risk factors is the most striking indication of the health burden of low fitness. BMI and waist circumference demonstrated the most consistent association with fitness. Mean values decreased in a nearly graded fashion with increasing fitness. The association is already present in adolescents and young adults.

The relationship between low fitness and cardiovascular mortality is proposed to be mediated by the development of CVD risk factors including hypertension, diabetes, dyslipidemia, and the metabolic syndrome.

Physical activity training in efforts to improve fitness has been shown to lower the likelihood of developing risk factors, independent of changes in weight.

As primary care clinicians follow patients, they should watch for any increase in BMI and abdominal girth. A change may present an opportunity to ask about the patient's physical activity and to encourage intervention..

Clinician must first be able to point to their own fitness as an example.

HEADACHE

"Suicide Headache"

9-9 CLUSTER HEADACHE

Cluster headache **(CH)** is one of the most severe pain syndromes. It is underdiagnosed and suboptimally managed in primary care. It has substantial effects on functioning, even when appropriate treatments are used.

Headaches often start about 1 to 2 hours after falling asleep, or in the early morning. Attacks can strike up to 8 times a day, are relatively short-lived (18 to 180 minutes) , and are characterized by very severe unilateral head pain localized in or around the eye. Attacks may occur daily for some weeks followed by a period of complete remission. (CH is cyclic.)

Patients with CH, unlike those with migraine, are restless and prefer to pace about or sit and rock back and forth. Some will isolate themselves or leave the house to get into cold air. Some become aggressive.

Unilateral autonomic symptoms ipsilateral to the pain occur only during attacks: ptosis and pupil constriction (a partial Horner's syndrome); as well as lacrimation, conjunctival injection, rhinorrhea, and nasal congestion. This indicates parasympathetic hyperactivity, and sympathetic impairment. Sweating and blood flow to the skin increase on the painful side.

The author presents a long list of suggested drugs for treatment and prevention. (The rather large number of choices suggests that none is "best" and individual trials are necessary. RTJ)

Primary care clinicians, if they practice long enough, will encounter a patient with CH. Recognition and treatment will provide most welcome relief, and may even be life-saving. (CH has been termed the "Suicide Headache" because the severe unremitting pain may drive some patients to take their own life.)

Therapy may be tried in primary care. Complicated cases require referral to a headache clinic.

HEART FAILURE

2-Hour PC Blood Glucose—A Risk Marker For CHF

7-9 INSULIN RESISTANCE AND RISK OF CONGESTIVE HEART FAILURE

Diabetes and obesity are established risk factors for congestive heart failure **(CHF).** Both are related to insulin resistance. In patients with established CHF, insulin resistance is associated with more severe disease and a worse prognosis.

This study explored if insulin resistance, determined by 2-hour blood glucose on the oral glucose tolerance test, as well as several other more sophisticated methods, might predict CHF and provide the link between obesity and CHF.

After adjusting for multiple established risk factors, an increase of 1 standard deviation in the *2-hour glucose value* was associated with an increased hazard ratio of 1.44 in incidence of CHF. After adjusting for diabetes, fasting glucose levels were not predictive.

Insulin resistance predicted incidence of CHF independently of diabetes, truncal and overall obesity, and other risk factors. The previously described association between obesity and CHF may be mediated, in part, by insulin resistance.

This sophisticated study presented more detailed methods of measuring insulin resistance than I have included. My purpose was to describe a simple risk marker (2-hour p.c. glucose) which is readily applicable to primary care practice.

I believe the 2-hour glucose should be a standard and important measure of risk. It is often neglected. The lower, the better. A level of 140 is much too high. A fasting glucose is less predictive.

HORMONE REPLACEMENT THERAPY

Many Elderly Women Experience Recurrence Of Symptoms

7-2 SYMPTOM EXPERIENCE AFTER DISCONTINUING USE OF ESTROGEN PLUS PROGESTIN

The publication of the Women Health Initiative **(WHI)** Trial led to a change in the clinical use of combined estrogen + progestin **(E + P)** in symptomatic post-menopausal women. Previous observational studies suggested a significant protective effect against cardiovascular disease. The WHI, a randomized, placebo-controlled trial, not only disproved any protective effect, but reported a slight increase in risks.

The present study, an extension of the WHI, determined the frequency of recurrence of symptoms after discontinuing E + P.

Over half of the women (now mean age 69) who had been taking CEE + MPA for 5 years reported recurrence of at least one moderate or severe symptom 8 to 12 months after discontinuing use.

Symptoms also recurred in women who had been taking placebo although to a lesser extent than women who had taken active hormones.

This study pointed out the high rate of recurrence of menopausal symptoms after discontinuation of both E + P and placebo—years after the menopause. Clinicians then must decide how to help patients with more severe symptoms. Women with severe recurring vasomotor symptoms after discontinuing active hormone therapy may be informed about the risk/benefit ratio and asked to express their personal preference. Judicious use of HRT at low doses for a limited time is reasonable. I would avoid use in patients with risk factors such as smoking, history of CVD, dyslipidemia, hypertension, and diabetes. Life-style changes may help these patients.

Note that the mean baseline age of subjects was 63 at the beginning of the WHI study. Many had a history of smoking, diabetes, hypertension, dyslipidemia, and cardiovascular disease. (Ie, they represented a cross section of women in this age group.) Risks of HRT would be much lower in women who start at a younger age, and in women who had none of the other risk factors. Risks are also much less in patients who take only estrogen.

Following publication of the WHI trial, the media proclaimed that hormones were dangerous. The study led many clinicians to advise women to discontinue HRT. The risks of E + P were exaggerated by patients and physicians alike. I believe that the risk of serious adverse events from aspirin and NSAIDs in a comparable group of 10 000 women is greater.

HUMANITIES

9-1 "THE MEDICAL HUMANITIES", For Lack Of A Better Term

So, what are "The medical humanities" anyway?

The commentator (an established poet and essayist) finds it very difficult to define.

We know intuitively that the way medicine is now taught and practiced is simply wrong—that the humane is being supplanted by unfeeling science and uncaring economics. The medical literature describes the practice of medicine in the modern era as increasingly dominated by economic constraints and technological hubris.

Medicine, in losing sight of how the arts and humanities inform and elevate the work of healing, is following the footsteps of larger societal trends.

"Distancing" is the process whereby physicians remove themselves from the particulars of patients' experiences of illness so that they may render accurate diagnosis and treatment. It imperils the work of doctoring, and has converted it from a sacred vocation, borne of a desire and duty to alleviate suffering, into a mere financially rewarded, technically challenging line of work.

The view of any kind of work as simply a means to the all-important paycheck is widespread nowadays. "Distancing" pervades most human interactions.

Perhaps it is expedient to blame the shortcomings of modern biomedicine on the stereotypically bespectacled, heartless philistine hiding behind his bleeping machines in his white coat, rather than to look more critically at the economic pressures that have so harshly changed medical practice. Can we really expect beleaguered clinicians and medical educators to teach ethical thinking or to nurture compassion in trainees who come to their prospective profession lacking in these fundamental personal virtues that more appropriately ought to have been instilled in them by their parents, or by immersion in what should be a healthier, more universally humane society?

Only with omnipresent and immediately accessible humanities resources for ourselves and our trainees can we nourish in our profession "the art of medicine' from which we have become so estranged.

I do not agree that medical care is being" dehumanized". I do not agree that unfeeling science and uncaring economics are supplanting the "humane" in medicine.

In my view, the editorialist's criticism is much too harsh. I do not believe that physicians are less "humane" (ie, less caring; less empathetic) than they were in the 18th, 19th and 20th centuries. Many health care practitioners simply do not have the opportunity to establish an empathetic relation with patients. It takes time to develop a "connection". They are much more involved in the difficult task of providing the best of evidence-based medicine and technology. (Little of evidence-based medicine and present day technology existed before the mid-1900s.) They nevertheless retain a desire and duty to alleviate suffering, and they do indeed alleviate suffering. They are "humane" in a new and different way.

Conscientiously applying the best of modern therapy and diagnosis to each patient is an expression of caring ("humaneness"). Expert use of a blinking machine, which will often benefit patients' health and increase longevity, is an important part of caring. I doubt many patients (including the editorialist) would be willing to exchange the miracles of modern medicine, surgery, imaging, and anesthesia in favor of a more consistent and personal "caring" connection with every health-care provider.

Caring and technology are not mutually exclusive. Primary care clinicians are blessed with the opportunity to combine the two. They care for patients and families over time. This provides opportunity to connect and give support to the cares and concerns of their patients; to elicit , understand, and respond to each patient's "story" in addition to attending the presenting complaint.

Has the practice of medicine been "converted into a mere financially rewarding line of work"? Not by a long shot. I do not believe young aspiring physicians enter the profession for the purpose of making money.

Nowadays, in contrast to the past, maintaining an office staff is costly. Technology is expensive. I doubt the income of the average physician, especially primary care clinicians, exceeds that of other professions. Few become "rich" as a result of their medical practice. But, it is important to earn enough to provide the family with a comfortable, safe home, a good education, and to save for retirement. This is also a form of "caring".

Many physicians give generously of their income to charitable organizations and church. Many express humaneness by pro-bono work, caring for the less fortunate in one of the many free clinics scattered throughout the country.

The healing professions do not lack humaneness. The way it is expressed has changed.

9-2 "THE MEDICAL HUMANITIES": Attempting A Definition

"A Humanity" is any product of human creativity and any human relationship which promotes understanding, kindness, good will, compassion, care, and caring.

"The Humanities" is the totality of all "A Humanity".

"A Medical Humanity" ("The Medical Humanities") does not differ from any other. However, medical professionals (nurses, therapists, dieticians, and physicians) may have more opportunity to express "A Humanity" because they care for others when the others are most vulnerable.

HYPERTENSION

. ***"Not A Totally Benign Condition."***

7-3 WHITE-COAT HYPERTENSION AS A RISK FACTOR OF THE DEVELOPMENT OF HOME HYPERTENSION

White-coat hypertension **(WCHT)** is characterized by an elevated BP in medical settings, and a normal BP when self-recorded at home, or determined by ambulatory recorders.

Sustained hypertension is the presence of an elevated BP regardless of the setting.

In this study, WCHT was defined as home BP < 135/85; and office BP > 140/90). Sustained normotension was defined as home BP < 135/85 and office BP < 140/90.

During the 8-year follow-up, 47% of the WCHT group progressed to home hypertension, vs 22% of the sustained normotension group. (Odds ratio= 2.9)

WCHT was a significant predictor of the development of sustained home hypertension, independent of other confounding factors and baseline home BP levels. "WCHT is not a totally benign condition."

This begs the questions: What should clinicians do about patients with WCHT? What can be done?

Patients with WCHT should be followed more closely. They should be treated judiciously, especially with lifestyle interventions, to lower all cardiovascular risk factors.

I believe home BP determinations are essential in primary care practice. This will lead to both an increase and a decrease in prescription of anti-hypertension drugs. The Japanese are well ahead of us in this respect.

"Doing It In The Doctor's Waiting Room May Be Better Than Doing It At Home."

9-3 SELF MONITORING OF HIGH BLOOD PRESSURE

This issue of BMJ reports a randomized trial on self monitoring BP *in the physician's office* The self measured and the professionally measured BPs were comparable. This suggests that hypertension guidelines are applicable to self monitoring.

Patients were welcomed into the BP measuring room of the practice and encouraged to measure their own BP at least once a month using an electronic BP machine. They received instructions on how to use the machine on their first visit. Patients were given an instruction card showing their BP target (140/85). Monthly BP readings were recorded on the card. Patients were asked to see the practitioner or nurse if BP exceeded target on successive months, or if it was very high. More than 90% of patients were seen by the medical staff during the year.

This is a switch from the usual studies on self monitoring BP at home.

I wonder if some primary care clinicians would be tempted to place a validated electronic device in an alcove of the waiting room allowing any patients who are waiting to measure their BP. I believe this would be more meaningful and accurate than self measuring in a drug store.

Note the "Spin"

9-11 PREVENTION OF CARDIOVASCULAR EVENTS WITH AN ANTIHYPERTENSIVE REGIMEN OF AMLODIPINE, ADDING PERINDOPRIL AS REQUIRED, VERSUS ATENOLOL, ADDING BENDROFLUMETHIAZIDE AS REQUIRED.

This study asked—Would a regimen based on a calcium channel blocker **(CCB)** + an angiotensin converting enzyme inhibitor **(ACE)** lead to more favorable outcomes than a regimen based on a beta-blocker **(BB)** + a **Thiazide** diuretic?

The study was stopped prematurely after a median of 5.5 years (over 106 000 patient-years) because fewer patients in the CCB-ACE group had the primary endpoint. *(Note: this did not reach statistical significance.)*

Outcomes over 5.5 years	ACE + CCB (n = 9639)	BB + Thiazide (n = 9618)	NNT*
Primary endpoint	429	474	208**
Stroke (fatal & non-fatal)	327	422	65
Total cardiovascular events & procedures	1362	1602	25
All-cause mortality	738	820	116
Incidence of diabetes	567	799	24***

(* NNT for 5.5 years to benefit one patient. ** Not statistically significant. The authors attributed this to under powering of the study. *** NNT to harm one patient (develop diabetes) (*My calculations. RTJ*)

"The findings of ASCOT-BPLA show that in hypertensive patients at moderate risk of developing cardiovascular events, an antihypertensive drug regimen starting with amlodipine adding perindopril, as required, is better than one starting with atenolol adding a thiazide, as required, in terms of reducing the incidence of all types of cardiovascular events and all-cause mortality, and in terms of risk of subsequent new-onset diabetes."

. "Pending further information, we believe the combination of a beta-blocker and a diuretic should not be recommended in preference to the comparator regimen used in ASCOT-BPLA for routine use, but only for specific circumstances."

This is an extraordinary (and expensive) study. I congratulate the investigators on their persistence. I feel they (and Pfizer) are disappointed with the outcome.

Benefits of antihypertension drug therapy would be much less when used for primary prevention.

But, there is an extraordinary degree of "spin" in this detailed 12-page article. As noted, the absolute differences between groups is small. And the NNT to benefit one patient over 5.5 years is large (25 to 208).

I believe these differences are of little clinical significance.

The number needed to treat <u>unnecessarily</u> for 5.5 years, with the amlodipine regimen as compared with the atenolol regimen, to achieve benefit for one patient is high, varying from 24 to 207.

I calculated the MNT (money needed to treat) for 5.5 years to benefit one patient. According to my pharmacy:

	Cost per day $	*Cost for 5.5 years $*	*Total $*
Atenolol 50 mg	*0.15*	*240*	
Hydrochlorothiazide 25 mg (I could not access cost of bendroflumethiazide)	*0.09*	*180*	*481*
Amlodipine (Norvasc 2.5 mg)	*1.45*	*2910*	
Perindopril (Aceon 2 mg)	*1.15*	*2308*	*5,218*

Money needed to treat (MNT) with CCB + ACE vs BB + thiazide (at minimal doses) to prevent one adverse outcome over 5.5 years:

To treat 208 patients for 5.5 years to prevent one MI or one cardiovascular death::

CCB + ACE = 5218 X 208 = $1,085,344

BB + thiazide = 481 X 208 = $100,048

Difference = $ $985,296

To treat 25 patients for 5.5 years to prevent total cardiovascular events and procedures = $130,450 and $ 12,025

Difference = $118,425

(My calculations RTJ)

Application of lifestyle interventions would be much more effective at no cost.

Study supported mainly by Pfizer.

See the following abstract for additional analysis.

More "Spin"

9-12 ROLE OF BLOOD PRESSURE AND OTHER VARIABLES IN THE DIFFERENTIAL CARDIOVASCULAR EVENT RATES NOTED IN THE ANGLO SCANDINAVIAN CARDIAC OUTCOMES TRIAL-BLOOD PRESSURE LOWERING ARM (ASCOT-BPLA)

(This article, by the same investigators, expands on the previous trial)

Differences between the groups included BP, HDL-cholesterol, triglycerides, potassium, fasting glucose, heart rate, and body mass index. All of these variables were significantly associated with rates of coronary events and stroke during the trial. (CCB-ACE, in addition to a slightly greater reduction in BP, was associated with reductions in other risk factors.) The investigators offer no explanation except . . ."That it remains possible that differential effects of the two treatment regimens on other variables also contributed to the different rates noted".

These factors influenced outcomes favoring the CCB-ACE group. After adjusting for these factors the investigators determined that they accounted for about half the reported difference in coronary events and about 40% of the differences in stroke noted between the two groups. (Ie, the reported benefits in the CCB-ACE group were attenuated because, overall, the differences in risk factors favored this group.)

Note—the "spin" continues. If there is any benefit of CCB - ACE over BB-Thiazide, it is certainly minimal. This additional analysis markedly increases the number of patients needed-to-treat to more clinically

insignificant levels. It also greatly increases the NNT(unnecessarily) and the "Money Needed to Treat" to benefit one patient.

It does not convince me to change first-line therapy away from BB- Thiazide. I would begin with a diuretic.

The Difference Between Relative Risk Reduction And Absolute Risk Reduction

9-13 EVIDENCE THAT NEW ANTIHYPERTENSIVES ARE SUPERIOR TO OLDER DRUGS

(This editorial comments, in generally favorable terms, on the preceding articles.)

"The amlodipine-based regimen in ASCOT . . . reduced major cardiovascular endpoints by 16%, stroke by 23%, and cardiovascular and total mortality by 24% and 11% respectively, compared with the beta-blocker atenolol, with or without bendroflumethiazide."

"On balance, the ASCOT results endorse the European guidelines for the treatment of hypertension, which leave the choice of drug class for antihypertensive treatment to the doctor."

Note again how misleading relative risk reductions can be. In absolute terms, the percentage reductions are by my calculation:

	Relative risk reduction (%)	*Absolute risk reduction (%)*
Major C-V endpoints	*16*	*0.5*
Stroke	*23*	*1.0*
Cardiovascular mortality	*24*	*0.5*
Total mortality	*11*	*0.9*

Absolute risk would be further reduced if the adjustments cited in the second study were considered.

Journal editors and investigators should not present relative risk reductions in their studies.

10-3 REFINING THE EXERCISE PRESCRIPTION FOR HYPERTENSION

Guidelines for management of hypertension are likely to include advice to: "engage in regular aerobic activity such as brisk walking (at least 30 minutes a day) most days of the week".

This article states that there is enough published work on exercise and hypertension to refine aspects of this advice.

The authors present 19 points regarding benefits of exercise.

I am sure the effects of exercise on BP differ a great deal between individuals.

I was not aware of many of these points.

Primary care patients may find them helpful. That moderate exercise 3 times a week is as beneficial as more frequent, prolonged, and strenuous exercise may be welcome news to many. The flexibility and benefits of accumulating exercise in 10-minute sessions may increase compliance. The helpfulness of exercise independent of weight loss might encourage some.

Physical exercise instructors may post these points to foster continuing compliance with exercise programs they offer their clients.

The Basic DASH Diet Modified By Increased Protein and Monounsaturated Fat Improved BP and Lipid Levels

11-10 MORE NOVEL EFFECTS OF DIET ON BLOOD PRESSURE AND LIPIDS: Results of the OmniHeart Randomized Trial "Effects of Protein, Monounsaturated fat, and Carbohydrate Intake on Blood Pressure and Serum Lipids"

This issue of JAMA presents the OmniHeart randomized trial which represents the latest effort by members of the DASH Trials group to examine the effect of varying protein, monounsaturated fat, and carbohydrate intakes on BP.

The Trial recruited subjects with BP 120-159/80-99. It used a complex crossover design which continued the basic DASH diet and modified it to contain:

A. 58% of kcal as carbohydrate, or

B. 25% of kcal as protein, or

C. 37% of kcal as monounsaturated fat (olive oil, canola oil, safflower oil).

Compared with the carbohydrate diet, the high protein decreased systolic by 3.5 in those with hypertension, decreased LDL-c by 3.3 mg/dL and decreased triglycerides by 15.7 mg/dL, but *decreased* HDL-c by 1.3 mg/dL

Compared with the carbohydrate diet, the high monounsaturated fat diet decreased systolic in those with hypertension by 2.9; had no significant effect on LDL-c; *increased* HDL-c by 1.1 mg/dL, and lowered triglycerides by 9.6 mg

Overall, the high monounsaturated diet seemed to produce the greatest benefit with the least adverse effects.

The authors suggest that a basic DASH diet modified by increased protein or monounsaturated fat content improved BP and lipid levels and reduced risk of estimated cardiovascular disease.

The investigators suggested that their results . . ."Should be widely applicable to the US population" But note that the subjects were relatively young and enthusiastic, the trial periods lasted only 6 weeks, the diets were prepared in research kitchens and under controlled circumstances. Nevertheless, about 10% to 15% dropped out of the study.

I applaud the noble effort, but I do not believe the results are applicable to primary care. Certainly, diet does play an important part in control of lipids and BP. For the latter, I believe salt restriction is the most important and achievable component.

Weight loss per se (calorie restriction + exercise) is more relevant to lowering BP than is the type of diet.

Most primary care clinicians, I believe, would emphasize treatment of lipid and BP disorders with drugs.

Coffee Lovers—Be Reassured. Cola Drinkers—Some Reason For Concern

11-11 HABITUAL CAFFEINE INTAKE AND THE RISK OF HYPERTENSION IN WOMEN

Much clinical lore about the possible association between caffeine intake and the risk of hypertension is available. Some have reported an increased risk. But studies have been limited by short observation periods. Information about prolonged, regular intake is not available.

This study prospectively examined the association between caffeine intake and incident hypertension in a large cohort of women over many years.

A. Caffeine consumption: Those in the third quintile had a 13 % increased risk of hypertension. Interestingly, those in the 4th and 5th quintiles were not at increased risk –an *inverse U-shaped* curve.) Trend was non-linear.

B. Caffeinated coffee consumption: No increase in the risk between quintiles. Actually, those in the 4th and 5th quintile had a lower risk than those in the 1st quintile.

C. Decaffeinated coffee: Similar to caffeinated.

D. Sugared caffeinated cola: There was a definite linear increase in incidence of hypertension with increasing intake between quartiles—highest quartiles had 28% to 44% higher risk.

E. Diet caffeinated cola: also a linear trend with increasing intake—highest quartiles had 16% to 19% greater risk.

Caffeine consumption does not appear to increase risk of incident hypertension.

Consumption of coffee (caffeinated and decaffeinated) does not appear to increase risk of developing hypertension.

Caffeinated soft drink (sugared and diet) appear to be associated with increased risk of hypertension. Whether the association is causal will require further study.

INFLUENZA

The Big Question—Will It Mutate To Facilitate Human-To-Human Transmission?

9-5 INFLUENZA A ("Bird Flu"; H5N1): *Will It Become The Next Pandemic Influenza? Are We Ready?*

Experts have predicted a next pandemic flu for many years. They believe that the question is not whether another pandemic will occur, but when. They fear an event like the Spanish flu of 1918-19 (H1N1) which rapidly caused death of millions and reduced the average life expectancy in the USA by 13 years. The 1918-19 pandemic affected mostly young, previously healthy adults. Death occurred within a week due to a hemorrhagic, necrotizing, viral (not bacterial) pneumonia.

Avian influenza (influenza A H5N1) appears to have a similar potential.

Most flu viruses occur in birds. Aquatic waterfowl are their natural reservoir. Only a few types of the virus have circulated widely in humans. "Bird flu" refers to both influenza in birds and to instances when the virus jumps the species barrier to cause human disease.

To cause a global pandemic the virus needs three properties: 1) ability to infect people, 2) substantially new antigenic properties to which humans are not immune, and 3) efficient person-to-person transmission. H5N1 has the first 2 properties, but there is only minimal evidence of 3).

Amantadine and rimantadine are not active against H5N1 even though it is a type A virus. Oseltamivir (*Tamiflu*; given orally) and zanamivir (*Relenza*; given by inhalation) are active in vitro and in animal models. Clinical utility for treatment and prevention of H5N1 has not been rigorously studied. The supply is inadequate for a global pandemic. Antiviral resistance does occur.

What about drug treatment and prophylaxis? Early administration of antiviral agents appears to be beneficial. Patients with suspected H5N1 should promptly receive a neuraminidase inhibitor pending diagnosis by laboratory

testing. The optimal dose and duration of treatment are uncertain. Currently approved regimens likely represent the minimum required. High levels of resistance to *Tamiflu* have been detected in several patients with H5N1. Amantadine and rimantadine are not effective for H5N1. For prophylaxis, *Tamiflu* is warranted for persons who have had a possible exposure to H5N1.

Current supplies of Tamiflu and Relenza are grossly insufficient for prophylaxis and treatment of H5N1. Those of us who are knowledgeable about H5N1 and affluent enough to afford Tamiflu may be tempted to purchase and hoard a supply for possible use. There are serious objections to this. The limited supply should be reserved for treatment of individuals who are infected with the flu virus. "Ring" prophylaxis may be a reasonable control measure. This involves quarantine and prophylactic drug therapy of individuals (eg, family; health care workers) in close contact with a patient with proven influenza. This may reduce likelihood of spread in the community.

The North Carolina Department of Health has issued a statement strongly discouraging personal stockpiling of Tamiflu. It points out: 1) There has been no sustained human-to-human transmission in Asia; 2) There is no H5N1 in the USA. No poultry have been infected; 3) Supplies are limited and should be reserved for people who will need it for prevention of regular influenza this season; 4) If a pandemic occurs, Tamiflu should be used by priority groups rather than for personal stockpiles; 5) Inappropriate use may led to resistance.

INSOMNIA

A Review of Newer Pharmacological Agents

8-2 CHRONIC INSOMNIA

	Duration of action	Half-life (hr)	Dose (mg)	Indications
1) *Restoril* (tamezepam)	Intermediate	8-15	7.5-30	Sleep maintenance

May be tried for insomnia associated with difficulty in maintaining sleep. The greatest effect is on total sleep time. May soon be supplanted by *Lunesta*. Tolerance, measured by deterioration in sleep measures over time, has not been noted after use for 8 weeks. Daytime sleepiness, dizziness, and incoordination may occur with the intermediate-acting agents, but are not common.

The FDA has approved use for up to 10 days

2) *Lunesta* (eszopiclone)	Intermediate	5-7	1-3	Sleep maintenance

A 6-month study of *Lunesta* showed a 50% reduction in sleep-latency (onset of sleep) and a 65% reduction in wake time after onset of sleep. The greatest effect was on total sleep time. After 6 months, a sustained beneficial effect without development of tolerance was reported. Daytime sleepiness, dizziness, and incoordination may occur with the intermediate-acting agents, but are not common.

(I was unable to find any limitations by the FDA for duration of use.)

3) *Ambien* (zolpidem)	Short	3	5-10	Sleep onset

Studies of *Ambien* used intermittently (3 to 5 times a week) report effectiveness in chronic insomnia,

with sustained benefits on nights the drug is taken, and sleep that is no worse than baseline on nights without medication. No rebound insomnia was reported after discontinuation. The greatest effect is on sleep latency. (Difficulty in going to sleep.) Short-term tolerance has not been noted after continuous use for 4 weeks, and intermittent use for 12 weeks. Amnesia, including that associated with sleep-related eating, has been described rarely. Adverse effects (drowsiness, dizziness, and incoordination) are less frequent with use of short-acting drugs and generally occur only after high dose.

The FDA has approved use for up to 10 days

4) *Sonata* (zaleplon) Ultra short 1 5-20 Sleep onset and maintenance.

Sonata may have effects in reducing the time to go to sleep, but may have no significant effect on total sleep time. Because of its very short half-life, it may be given on awakening during the night. Administered 3.5 hours after lights out, with 4 hour more sleep permitted, it did not result in any daytime drowsiness or cognitive impairment. No rebound insomnia reported. Use for 6 months showed a sustained benefit without development of tolerance. Adverse effects (drowsiness, dizziness, and incoordination) are less frequent with use of short-acting drugs and generally occur only after high dose.

The FDA has approved use for up to 10 days

I believe these newer sleep medications will be increasingly prescribed by primary care clinicians.

To fit the drug to the sleep difficulty, we should ask the patient whether they have difficulty in sleep onset, or difficulty in sleep maintenance. Sonata may be a useful first choice for the former, and Lunesta of the latter.

Several of the author's comments interested me: 1) Use for secondary insomnia when elimination of the cause is not achievable. 2) "Off label" use (over ten days) for Ambien and Sonata. 3) Many sleep specialists recommend long-term use of pharmacological therapy in a subgroup of patients who do not respond to cognitive behavioral therapy This would also include patients for whom cognitive behavioral therapy is simply not an available means of therapy—ie, most patients consulting primary care clinicians.

I believe many primary care clinicians prescribe "sleeping pills" freely and for periods longer than approved. Clinical judgment is required. Several different drugs may be prescribed on a trial-and-error basis. We can now fit the pill to the patient. Intermittent therapy is preferable. I wonder. .. Would switching periodically from one to another be advantageous?

INSULIN

Coming Soon? Maybe

9-16 INTEREST IN INHALED INSULIN GROWS

The lungs provide a large surface area for drug absorption. Inhaled insulin is absorbed more rapidly than regular insulin given subcutaneously. The time to peak concentration of most inhaled insulins is nearly superimposable with the rapid-acting insulin analogues.

Controlled trials compared *Exubera* (one brand of inhaled insulin) + oral agents with injected insulin + oral agents. After 2 years, Exubera provided continuing glycemic control. HbA1c decreased 1.8%, compared with a 1.5% decrease in the injected insulin group.

Is it safe? Some studies have reported no adverse pulmonary events; some have reported cough as the most common side effect. A slight decline in carbon-monoxide-diffusing capacity occurred. Hypoglycemia, headache and dizziness have been reported. Patients with asthma absorbed lower amounts of insulin.

Longer term studies (a decade or more) are required to evaluate pulmonary function and insulin-binding antibodies, as well as use in children and smokers.

"Overall The Inhaled Insulin Approach Seems Effective And Safe."

11-7 INHALED INSULIN IMPROVES GLYCEMIC CONTROL WHEN SUBSTITUTED FOR OR ADDED TO ORAL COMBINATION THERAPY IN TYPE 2 DIABETES.

This study examined the effect of a preparation of inhaled, dry-powdered human insulin (*Exubera*) which is currently in development. The inhaled insulin delivers aerosolized powdered insulin to the small airways and alveoli. This enables rapid absorption. Its effect lasts 4 to 6 hours.

Does inhaled insulin improve glycemic control when taken alone, or when added to oral agents?

Open label parallel-group followed over 300 patients with DM2 (mean age 57; mean BMI = 30).
All were receiving two oral antidiabetes medications (predominantly a sulfonylurea and metformin). All had a HbA1c of 8% or greater (mean = 9.5%). All were considered to have failed on dual oral therapy.
None had significant respiratory disease. None were smokers.

Randomized to:

A. Inhaled insulin alone given 3 times daily before meals.

B. Inhaled insulin + continued oral agents

C. Oral agents alone.

HbA1c reduction compared with oral agents alone:

A. Inhaled insulin alone = -1.18 %

B. Inhaled insulin + continued oral agents = - 1.67 %

HbA1c levels less than 7%:

A. Inhaled insulin + continued oral agents = 32%

B. Oral agents alone = 1%.

In the insulin groups, fasting glucose and 2-hour postprandial glucose mean levels improved by up to 50 mg/dL and 75 mg/dL. Triglyceride levels improved by 40 to 54 mg/dL

Hypoglycemia occurred at a rate of 1.3 to 1.7 episodes per month in the insulin groups; 0.1 in the oral agents-alone group. No patient discontinued insulin due to hypoglycemia.

Cough was more common in the insulin groups. It was generally mild and decreased in incidence and prevalence during the trial. No patients discontinued for this cause.

Mean body weight increased in the insulin groups over 3 months (+ 6 pounds); did not change in the oral-alone group.

Withdrawals were similar in all 3 groups (about 6%--none due to adverse events).

Pulmonary function remained similar in all groups.

One would expect inhaled insulin to be more rapidly absorbed into the general circulation than subcutaneous insulin. It has a faster onset of action and thus a more rapid glucose-lowing effect. Its duration of action is longer than the short-acting insulin lispro and is similar to regular insulin. This makes it suitable for administration before meals.

I included this abstract to follow-up on this new technology, which I believe is of great interest to many patients with DM2. There is a long road ahead before inhaled insulin becomes freely available. I believe we will reach the end of the road.

INSULIN RESISTANCE

2-Hour PC Blood Glucose—A Risk Marker For CHF

7-9 INSULIN RESISTANCE AND RISK OF CONGESTIVE HEART FAILURE

Diabetes and obesity are established risk factors for congestive heart failure **(CHF).** Both are related to insulin resistance. In patients with established CHF, insulin resistance is associated with more severe disease and a worse prognosis.

This study explored if insulin resistance, determined by 2-hour blood glucose on the oral glucose tolerance test, as well as several other more sophisticated methods, might predict CHF and provide the link between obesity and CHF.

After adjusting for multiple established risk factors, an increase of 1 standard deviation in the *2-hour glucose value* was associated with an increased hazard ratio of 1.44 in incidence of CHF. After adjusting for diabetes, fasting glucose levels were not predictive.

Insulin resistance predicted incidence of CHF independently of diabetes, truncal and overall obesity, and other risk factors. The previously described association between obesity and CHF may be mediated, in part, by insulin resistance.

This sophisticated study presented more detailed methods of measuring insulin resistance than I have included. My purpose was to describe a simple risk marker (2-hour p.c. glucose) which is readily applicable to primary care practice.

I believe the 2-hour glucose should be a standard and important measure of risk. It is often neglected. The lower, the better. A level of 140 is much too high. A fasting glucose is less predictive.

LIVER DISEASE

A Major Cause Of Liver-Related Morbidity And Mortality

12-5 THE METABOLIC SYNDROME AS A PREDICTOR OF NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease **(NAFLD)** is a major cause of liver-related morbidity and mortality. It has the potential to progress to cirrhosis and liver failure. Non-alcoholic steatohepatitis (**NASH)** is an intermediate

stage of NAFLD. NASH is characterized by hepatic steatosis, liver cell injury, hepatic inflammation, fibrosis, and necrosis.

NAFLD is often associated with obesity, type 2 diabetes, dyslipidemia, and hypertension. Each of these abnormalities carries a cardiovascular disease risk. Together they are often categorized as the insulin-resistance syndrome, or the metabolic syndrome (**The MS).** The MS is an emerging problem worldwide. Its prevalence is increasing.

This study characterized the longitudinal relationship between The MS and NAFLD.

Prospective observational study followed over 4400 apparently healthy Japanese men and women age 21 to 80 who attended routine medical checkups. None abused alcohol. None were taking drugs. None had hepatitis B or C.

The examination included an abdominal ultrasound. The diagnosis of NAFLD was based on ultrasound using hepato-renal contrast and liver brightness as markers.

At baseline, 18% of the 4000 participants had NAFLD.

NAFLD was more common in men than in women (25% vs 10%).

During a follow-up of 14 months, 241 men who did *not* have NAFLD at baseline developed NAFLD. These men had gained weight. About 10% of men who *had* NAFLD at baseline had normal ultrasound on follow-up. These men had lost weight.

The term NAFLD refers to a spectrum of liver disease in the absence of significant alcohol consumption. At the "benign" end of the spectrum, most patients with NAFLD have simple steatosis. About 10% have features of liver cell injury or fibrosis (non-alcoholic steatohepatitis—**NASH**).

The distinction between simple steatosis and NASH is important because their natural history differs. Patients with simple steatosis have a benign prognosis, at least from the standpoint of liver disease. Up to 20% of patients with NASH may ultimately develop advanced liver disease.

The prognosis of NASH-related cirrhosis is poor. About 1/3 develop liver failure or liver-related death. Hepatocellular cancer is a complication of NASH-related cirrhosis.

Although only a minority of patients with NAFLD develops advanced liver disease, it is causing alarm because of its high prevalence.

The adverse effects of The MS extend beyond the cardiovascular system.

An important recommendation to patients with NAFLD—even small amounts of weight loss (and loss of abdominal girth) can reverse NAFLD. Conversely, small gains in weight can induce NAFLD.

I believe abstinence from alcohol may also be an important recommendation. In patients with hepatitis C, abstinence has been recommended. In addition to possible toxic effects, the tendency of alcohol to increase caloric intake adds to risk of The MS.

If geese can be force-fed to produce fatty livers, why cannot humans? Why not call NAFLD the "Foie Gras syndrome"?

Abdominal obesity (more specifically intra-abdominal obesity) is emerging as a serious risk factor for cardiovascular disease. Abdominal girth, a marker of intra-abdominal obesity, had been considered the major

criterion (of the 5) for The MS. Is the lesser risk of NAFLD in women due to their tendency to add weight to the hips and lower extremities rather than the abdomen? .

The "Big Belly" syndrome is a major risk factor for both cardiovascular and liver disease.

MEDICAL HUMANITIES

9-1 "THE MEDICAL HUMANITIES", For Lack Of A Better Term

So, what are "The medical humanities" anyway?

The commentator (an established poet and essayist) finds it very difficult to define.

We know intuitively that the way medicine is now taught and practiced is simply wrong—that the humane is being supplanted by unfeeling science and uncaring economics. The medical literature describes the practice of medicine in the modern era as increasingly dominated by economic constraints and technological hubris.

Medicine, in losing sight of how the arts and humanities inform and elevate the work of healing, is following the footsteps of larger societal trends.

"Distancing" is the process whereby physicians remove themselves from the particulars of patients' experiences of illness so that they may render accurate diagnosis and treatment. It imperils the work of doctoring, and has converted it from a sacred vocation, borne of a desire and duty to alleviate suffering, into a mere financially rewarded, technically challenging line of work.

The view of any kind of work as simply a means to the all-important paycheck is widespread nowadays. "Distancing" pervades most human interactions.

Perhaps it is expedient to blame the shortcomings of modern biomedicine on the stereotypically bespectacled, heartless philistine hiding behind his bleeping machines in his white coat, rather than to look more critically at the economic pressures that have so harshly changed medical practice. Can we really expect beleaguered clinicians and medical educators to teach ethical thinking or to nurture compassion in trainees who come to their prospective profession lacking in these fundamental personal virtues that more appropriately ought to have been instilled in them by their parents, or by immersion in what should be a healthier, more universally humane society?

Only with omnipresent and immediately accessible humanities resources for ourselves and our trainees can we nourish in our profession "the art of medicine' from which we have become so estranged.

I do not agree that medical care is being" dehumanized". I do not agree that unfeeling science and uncaring economics are supplanting the "humane" in medicine.

In my view, the editorialist's criticism is much too harsh. I do not believe that physicians are less "humane" (ie, less caring; less empathetic) than they were in the 18th, 19th and 20th centuries. Many health care practitioners simply do not have the opportunity to establish an empathetic relation with patients. It takes time to develop a "connection". They are much more involved in the difficult task of providing the best of evidence-based medicine and technology. (Little of evidence-based medicine and present day technology existed before the mid-1900s.) They nevertheless retain a desire and duty to alleviate suffering, and they do indeed alleviate suffering. They are "humane" in a new and different way.

Conscientiously applying the best of modern therapy and diagnosis to each patient is an expression of caring ("humaneness"). Expert use of a blinking machine, which will often benefit patients' health and increase

longevity, is an important part of caring. I doubt many patients (including the editorialist) would be willing to exchange the miracles of modern medicine, surgery, imaging, and anesthesia in favor of a more consistent and personal "caring" connection with every health-care provider.

Caring and technology are not mutually exclusive. Primary care clinicians are blessed with the opportunity to combine the two. They care for patients and families over time. This provides opportunity to connect and give support to the cares and concerns of their patients; to elicit , understand, and respond to each patient's "story" in addition to attending the presenting complaint.

Has the practice of medicine been "converted into a mere financially rewarding line of work"? Not by a long shot. I do not believe young aspiring physicians enter the profession for the purpose of making money.

Nowadays, in contrast to the past, maintaining an office staff is costly. Technology is expensive. I doubt the income of the average physician, especially primary care clinicians, exceeds that of other professions. Few become "rich" as a result of their medical practice. But, it is important to earn enough to provide the family with a comfortable, safe home, a good education, and to save for retirement. This is also a form of "caring".

Many physicians give generously of their income to charitable organizations and church. Many express humaneness by pro-bono work, caring for the less fortunate in one of the many free clinics scattered throughout the country.

The healing professions do not lack humaneness. The way it is expressed has changed.

9-2 "THE MEDICAL HUMANITIES": Attempting A Definition

"A Humanity" is any product of human creativity and any human relationship which promotes understanding, kindness, good will, compassion, care, and caring.

"The Humanities" is the totality of all "A Humanity".

"A Medical Humanity" ("The Medical Humanities") does not differ from any other. However, medical professionals (nurses, therapists, dieticians, and physicians) may have more opportunity to express "A Humanity" because they care for others when the others are most vulnerable.

MENOPAUSE

Many Elderly Women Experience Recurrence Of Symptoms

7-2 SYMPTOM EXPERIENCE AFTER DISCONTINUING USE OF ESTROGEN PLUS PROGESTIN

The publication of the Women Health Initiative **(WHI)** Trial led to a change in the clinical use of combined estrogen + progestin **(E + P)** in symptomatic post-menopausal women. Previous observational studies suggested a significant protective effect against cardiovascular disease. The WHI, a randomized, placebo-controlled trial, not only disproved any protective effect, but reported a slight increase in risks.

The present study, an extension of the WHI, determined the frequency of recurrence of symptoms after discontinuing E + P.

Over half of the women (now mean age 69) who had been taking CEE + MPA for 5 years reported recurrence of at least one moderate or severe symptom 8 to 12 months after discontinuing use.

Symptoms also recurred in women who had been taking placebo although to a lesser extent than women who had taken active hormones.

This study pointed out the high rate of recurrence of menopausal symptoms after discontinuation of both E + P and placebo—years after the menopause. Clinicians then must decide how to help patients with more severe symptoms. Women with severe recurring vasomotor symptoms after discontinuing active hormone therapy may be informed about the risk/benefit ratio and asked to express their personal preference. Judicious use of HRT at low doses for a limited time is reasonable. I would avoid use in patients with risk factors such as smoking, history of CVD, dyslipidemia, hypertension, and diabetes. Life-style changes may help these patients.

Note that the mean baseline age of subjects was 63 at the beginning of the WHI study. Many had a history of smoking, diabetes, hypertension, dyslipidemia, and cardiovascular disease. (Ie, they represented a cross section of women in this age group.) Risks of HRT would be much lower in women who start at a younger age, and in women who had none of the other risk factors. Risks are also much less in patients who take only estrogen.

Following publication of the WHI trial, the media proclaimed that hormones were dangerous. The study led many clinicians to advise women to discontinue HRT. The risks of E + P were exaggerated by patients and physicians alike. I believe that the risk of serious adverse events from aspirin and NSAIDs in a comparable group of 10 000 women is greater.

A Helpful Overview

7-6 TREATMENT OF MENOPAUSAL SYMPTOMS: What Shall We Do Now?

Almost all women who reach the menopause will have symptoms at some point. Almost 80% have hot flashes and night sweats. About 20% of these find them intolerable. Many will request treatment. Hot flashes may continue for up to 5 years and, in some individuals, even longer.

During the past few years, a substantial number of women have discontinued hormone replacement therapy (**HRT**)—the most effective therapy, because of concerns about adverse effects.

This review article (based on a PubMed search of randomized controlled trials and observational studies) summarizes data from studies addressing the efficacy, risks, and benefits of frequently prescribed treatments.

I believe the risks of HRT have been grossly overemphasized. And that many women who would benefit greatly have been denied treatment because of fear of adverse effects.

Adverse effects would be essentially absent in women closer to the menopausal age, in those with no risk factors for cardiovascular disease, in those who use estrogen alone, and in those using low-dose for a shorter time.

METABOLIC SYNDROME

9-4 THE METABOLIC SYNDROME—A New Worldwide Definition

The ultimate importance of the MS is that it identifies individuals at high risk for type 2 diabetes **(DM2)** and cardiovascular disease **(CVD).**

The International Diabetes Federation (2004) felt there was a strong need for one practical definition that would be useful in any country for the identification of high risk of DM2 and CVD:

1) Central (abdominal) obesity is a prerequisite to the diagnosis of the MS.

Waist circumference 94 cm or more for white men of European origin; 80 cm or more for women. (The cut points for other ethnic groups have been changed (See

text) In the USA, cut points of 100 cm and 88 cm are likely to be retained in the definition.

Central obesity is related to each of the other components of the MS. If it is not present, the MS is not diagnosed.

Plus any two of the following four factors:

2) Triglycerides 150 mg/dL and above.

3) HDL-cholesterol under 40 mg/dL in man and under 50 mg in women.

Both 2) and 3) are commonly observed in patients with DM2 and insulin resistance. Both are risk factors for CVD.

4) BP 130 systolic and above; diastolic 85 and above, or previously treated hypertension.

5) Fasting blood glucose 100 and above, or previously diagnosed diabetes.

If above 100, a glucose tolerance test is strongly recommended.

Note that persons with 2), 3), 4) and 5) who do not have abdominal obesity are not defined as having the MS. Nevertheless, they are at increased risk. Not all 5 factors carry the same weight. But, the more factors present, the higher the risk. Of course, the other factors should be determined and treated.

I would wager that most men over age 50 in the USA have an abdominal girth over 100 cm (40 inches). And that men with obvious abdominal obesity have the MS.

It would be reasonable to immediately recommend life-style changes for them. Indeed, the need for lifestyle changes in the USA is universal.

I garnered some details from the web site of the IDF.

http://www.idf.org/webdata/docs/Metac_syndrome_def.pdf

A Major Cause Of Liver-Related Morbidity And Mortality

12-5 THE METABOLIC SYNDROME AS A PREDICTOR OF NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease **(NAFLD)** is a major cause of liver-related morbidity and mortality. It has the potential to progress to cirrhosis and liver failure. Non-alcoholic steatohepatitis (**NASH)** is an intermediate stage of NAFLD. NASH is characterized by hepatic steatosis, liver cell injury, hepatic inflammation, fibrosis, and necrosis.

NAFLD is often associated with obesity, type 2 diabetes, dyslipidemia, and hypertension. Each of these abnormalities carries a cardiovascular disease risk. Together they are often categorized as the insulin-resistance syndrome, or the metabolic syndrome (**The MS).** The MS is an emerging problem worldwide. Its prevalence is increasing.

This study characterized the longitudinal relationship between The MS and NAFLD.

Prospective observational study followed over 4400 apparently healthy Japanese men and women age 21 to 80 who attended routine medical checkups. None abused alcohol. None were taking drugs. None had hepatitis B or C.

The examination included an abdominal ultrasound. The diagnosis of NAFLD was based on ultrasound using

hepato-renal contrast and liver brightness as markers.

At baseline, 18% of the 4000 participants had NAFLD.

NAFLD was more common in men than in women (25% vs 10%).

During a follow-up of 14 months, 241 men who did *not* have NAFLD at baseline developed NAFLD. These men had gained weight. About 10% of men who *had* NAFLD at baseline had normal ultrasound on follow-up. These men had lost weight.

The term NAFLD refers to a spectrum of liver disease in the absence of significant alcohol consumption. At the "benign" end of the spectrum, most patients with NAFLD have simple steatosis. About 10% have features of liver cell injury or fibrosis (non-alcoholic steatohepatitis—**NASH**).

The distinction between simple steatosis and NASH is important because their natural history differs. Patients with simple steatosis have a benign prognosis, at least from the standpoint of liver disease. Up to 20% of patients with NASH may ultimately develop advanced liver disease.

The prognosis of NASH-related cirrhosis is poor. About 1/3 develop liver failure or liver-related death. Hepatocellular cancer is a complication of NASH-related cirrhosis.

Although only a minority of patients with NAFLD develops advanced liver disease, it is causing alarm because of its high prevalence.

The adverse effects of The MS extend beyond the cardiovascular system.

An important recommendation to patients with NAFLD—even small amounts of weight loss (and loss of abdominal girth) can reverse NAFLD. Conversely, small gains in weight can induce NAFLD.

I believe abstinence from alcohol may also be an important recommendation. In patients with hepatitis C, abstinence has been recommended. In addition to possible toxic effects, the tendency of alcohol to increase caloric intake adds to risk of The MS.

If geese can be force-fed to produce fatty livers, why cannot humans? Why not call NAFLD the "Foie Gras syndrome"?

Abdominal obesity (more specifically intra-abdominal obesity) is emerging as a serious risk factor for cardiovascular disease. Abdominal girth, a marker of intra-abdominal obesity, had been considered the major criterion (of the 5) for The MS. Is the lesser risk of NAFLD in women due to their tendency to add weight to the hips and lower extremities rather than the abdomen? .

The "Big Belly" syndrome is a major risk factor for both cardiovascular and liver disease.

MYOCARDIAL INFARCTION

Waist/Hip Ratio Showed A Graded And More Highly Significant Association With Risk Of MI Than BMI.

11-2 OBESITY AND THE RISK OF MYOCARDIAL INFARCTION IN 27 000 PARTICIPANTS FROM 52 COUNTRIES: The INTERHEART Study

This study postulated that markers of central obesity (especially the W/H ratio) are more strongly related to the risk of myocardial infarction **(MI)** than BMI.

Case-control study entered over 27 000 subjects world-wide.

A. Cases: Over 12 000 subjects with a first MI

B. Controls: Over 14 000 age and sex-matched subjects who did not have an MI.

Measured waist and hip circumferences and BMI

Results: Cases had a strikingly higher W/H ratio than controls. This observation was consistent for all regions of the world.

BMI: There was a modest and graded association with MI between quintiles (odds ratio top quintile compared with bottom quintile (1.44). However, when adjusted for other risk factors, odds ratio became insignificant (0.98)

W/H ratio: The odds ratios for MI for every successive quintile of the W/H ratio was significantly greater than that of the previous one:

1st	2nd	3rd	4th	5th
1.00	1.15	1.39	1.90	2.52

The population-attributable risk of MI in the two top quintiles of W/H ratio was 24%.

The population-attributable risk of MI in the top two quintiles of BMI was only 8%.

"The INTERHEART study clearly indicates that, of the various anthropometric measures commonly used, the waist-to-hip ratio shows the strongest relation with the risk of myocardial infarction."

"The global burden of obesity has been substantially *underestimated* by the reliance on BMI in previous studies." If a raised W/H ratio were to be used to assess the risk of cardiovascular disease, the proportion classified as obese would increase substantially.

The best anthropometric index of obesity as a predictor of MI is the W/H ratio. It shows a graded and highly significant association with MI risk.

Redefinition of obesity based on waist-to-hip ratio instead of BMI increases the estimate of MI attributable to obesity. For a rule of thumb, a cut point of a W/H ratio above 8.5/10 for women and 9/10 for men would be considered to increase risk.

This remarkable study was carried out by many investigators in all continents and supported by many drug companies and heart associations.

Being a case-control study, it is not definitive and requires confirmation.

Its important contribution is to point out that the danger of obesity is not due to fat in the extremities, but to intra-peritoneal fat which drains directly into the liver. This results in adverse metabolic effects which increase the risk of cardiovascular disease.

No Difference in Cardiovascular and All-Cause Mortality.

11-8 HIGH-DOSE ATORVASTATIN *VS* USUAL-DOSE SIMVASTATIN FOR SECONDARY PREVENTION AFTER MYOCARDIALINFARCTION The IDEAL Study

Statins are part of the standard treatment regimen after myocardial infarction **(MI).** Incremental benefits have been demonstrated with intensive lowering of LDL-cholesterol **(LDL-c)** among patients with the acute coronary syndrome **(ACS**). The National Cholesterol Education Program now recommends a LDL-c level less than 70 for patients at very high risk of ACS.

The IDEAL study hypothesized that intensive lowering of LDL-c with atorvastatin (*Lipitor*) at the highest recommended dose would yield incremental benefits compared with the usual recommended dose of simvastatin (*Zocor*).

Prospective, randomized, open label, multicenter trial enrolled over 8500 patients (mean age = 61). All had a history of acute MI. (*This is a secondary preventions study*.)

Subjects were randomized to 1) atorvastatin 80 mg daily, or 2) simvastatin 20 mg daily.

Over 4.8 years:	Atorvastatin (n = 4439)	Simvastatin (n = 4449)	Absolute difference	NNT*
LDL-c (mean mg/dL)	81	100		
Major cardiac event	9.3%	10.4%	1.1%	90**
Non-fatal acute MI	6.0 %	7.2%	1.2%	

(* Number needed to treat for 5 years to benefit one patient.)

(** not statistically significant)

Non-cardiovascular death	3.2%	3.5%		
Death from any cause	8.2%	8.4%		

Adverse effects: Adverse event resulting in permanent discontinuation were more common in the atorvastatin group (9.6% vs 4.2%). Transaminase elevation in 1% vs 0.1%. Serious myopathy and rhabdomyolyis were rare in both groups.

When standard and intensive LDL-c lowering were compared in patients at high risk (past MI), there was no statistically significant reduction in major coronary events. There was no difference in cardiovascular and all-cause mortality. There was a reduction in other composite secondary endpoints and non-fatal MI. (NNT for 5 years = 26 to 62.)

When I first noted the title of the investigation, I expected much more favorable results in the atorvastatin group.

Note that the recommended level of LDL-c of 70 was not reached in either group.

Lipitor therapy is more burdensome (more discontinuation; need to follow more closely for transaminase).

Note that at baseline, hypertension was present in 33% of subjects, mean body mass index was 27, and 20% were current smokers. I believe clinicians have focused too much on cholesterol lowering as a preventive measure and have neglected the other risk factors. This study did not mention any interventions for the other risk factors other than to state that subjects received dietary counseling.

I believe a primary prevention trial would report better results from atorvastatin. It is too late to gain much benefit after a severe cardiovascular event has occurred.

NUTRIENTS

Use Of High Doses Of Single Nutrients To Prevent Disease Has Been Disappointing

7-4 ESSENTIAL NUTRIENTS: FOOD OR SUPPLEMENTS. Where Should The Emphasis Be?

In the USA there has been a trend toward unregulated addition of nutrients to a wide range of foods that do not traditionally contain them. There have been recommendations that nutrient supplements be used by the general public.

However, instead of focusing on dietary patterns, most intervention trials have used high doses of single nutrients in an attempt to prevent disease. These results for the most part have been disappointing.

The American Heart Association now concludes that . . . "There is currently no basis for recommending that patients take vitamin C or E supplements or other antioxidants for the express purpose of preventing or treating coronary artery disese".

High dose beta-carotene does not reduce risk of lung cancer in smokers.

A recent meta-analysis of vitamin E supplements suggested that doses greater than 400 IU daily (10 times RDA) *increased* all-cause mortality.

Recent studies have reported that folic acid, B12, and B6 given to patients who had experienced a non-disabling stroke had no significant benefit on vascular outcomes.

Conclusion: "There are insufficient data to justify an alteration in public health policy from one that emphasizes food and diet to one that emphasizes nutrient supplements."

The vitamin E bubble has burst with a loud bang. High doses do not reduce risk of CHD or cancer. Indeed, they may slightly increase risk of congestive heart failure. Vitamin E does not reduce risk of progression of mild cognitive impairment to Alzheimer's disease (See Practical Pointers June 2005 [6-10])

It is estimated that an astounding 10% of Americans use high dose vitamin E (400 IU and higher).

I do not believe the authors of the article were talking about the daily use of supplements containing the RDAs of vitamins and minerals. I do not believe the authors infer that supplements which mimic daily requirements are harmful. Many of the individual components will be unnecessary, but I do not believe they are harmful.

OBESITY

Environmental Incivilities And Graffiti Have An Adverse Effect On Health

9-15 GRAFFITI, GREENERY, AND OBESITY

Independently of individual characteristics, the place of residence may be associated with health outcomes, including body size, and health-related behaviors such as the level of physical exercise. Perceived attractiveness of neighborhoods has been related to levels of physical activity. Incivilities, such as litter and graffiti, are associated with adverse effects on general wellbeing.

This study hypothesized that areas which are unpleasant, with many incivilities and few green areas, might discourage people from exercising, and thus influence the levels of obesity.

For individuals living in neighborhoods with high amounts of greenery, the likelihood of being more active was more than 3 times as high as that of those living in neighborhoods with low levels of greenery.

For respondents whose residential environment contained high levels of incivilities, the likelihood of being more physically active was about 50% less, and the likelihood of being overweight/obese was about 50% higher.

"In efforts to promote physical activity and reduce weight, attention should be paid to environmental facilitators and barriers as well as individual factors."

What does this have to do about primary care? A great deal. Economically disadvantaged patients are also medically disadvantaged. Those who live in dangerous neighborhoods will, with good reason, not walk the recommended mile or two daily. And they do not have the means to go to a spa.

I recall an article I abstracted in December 2004 "Economics of Obesity" (Practical Pointers December 2004 [12-6]). This suggests that economics plays a large part in the obesity epidemic. Foods high in fat and sugar have become less expensive as obesity rates have risen. The poor are more likely to depend on these foods. The economic situation of low-income people forces them to adopt "obesogenic" diets. "If you live in the inner city you aren't going to suddenly start eating mangos and playing tennis."

These articles should make us more understanding and compassionate, and less critical. "Non-adherence" and "non-compliance" are often not due to lack of motivation, but to poverty and lack of opportunity.

Of course, obesity also occurs more and more frequently in the affluent. Just observe the crowd in an upscale Mall.

The cause of obesity is multi-factorial. Down-graded neighborhoods and lack of economic advantages is an important factor.

The Only Effective Application To Correct It Morbid Obesity

10-2 WEIGHING IN ON BARIATRIC SURGERY: Procedure Use, Readmission Rates, And Mortality

An estimated 5% of the adult population in the USA has a BMI greater than 40. (*Morbid obesity*.) In recent years, as the prevalence of obesity has increased, use of bariatric surgery has increased dramatically.

Combinations of diet therapy, behavior modifications, prescribed exercise programs, and pharmacotherapy in various combinations are widely used. They generally accomplish some degree of weight loss, but unfortunately the loss is generally transient, particularly in persons with severe obesity. In contrast, over a 10-year period, bariatric surgery patients have demonstrated sustained weight loss which is sufficient to favorably affect obesity-related complications.

Despite the exponential increase in bariatric surgery, and despite surgery being the only effective application to correct morbid obesity, relatively few persons actually receive it.

The advent of laparoscopic surgical techniques and development of high-volume surgical centers has been associated with improved patient safety. Now, surgical capacity has increased and is no longer a limiting factor in some environments. Surgical techniques have improved and favorable outcomes occur in the majority. "Experience and technique count."

"On a practical level, patients who present to their primary care physician with a breast mass or symptomatic gallstones are routinely referred for surgical consultation. In contrast, patients who present with severe obesity are

routinely entered into medical treatment programs even if such programs have failed on multiple previous occasions."

"Morbid obesity is a significant health concern. Bariatric surgery offers a potentially effective and enduring treatment for weight reduction." It helps resolve co-morbidities of obesity, and provides a survival benefit. It has had increasing success.

The editorialist is an enthusiast.

When, if ever, should primary care clinicians consider advising bariatric surgery?

1) The patient is morbidly obese and is subject to medical complications and early death.

2) The patient should be relatively young and have little co-morbidity.

3) Repeated attempts to lose have failed miserably.

4) The clinician knows the consultant surgeons well, and understands that they have performed many procedures with long-term success, and little morbidity and mortality.

5) The patient wants desperately to lose weight, and is fully informed about outcomes, bad as well as good.

Would it be advisable to wait until the patient opens the subject? There may be good reason to do so. As with screening procedures, if the clinician opens the discussion he or she assumes greater responsibility for any adverse outcome. And yet, we do not wait for patients to open the possibility of surgery if they have gallbladder disease or a breast mass.

I suspect advice for bariatric surgery will be given with less reservation in the future.

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OSTEOPOROSIS

"All Women Should Have A Measurement Of Bone Mineral Density At The Age Of 65."

7-8 SCREENING FOR OSTEOPOROSIS

Clinicians should routinely recommend that patients have an adequate total intake of calcium (1200 mg per day), and of vitamin D (400 to 800 IU per day), and participate in weight bearing exercises. Many patients will not lose bone if they have an adequate intake of calcium and vitamin D and exercise regularly. Nevertheless, the rates of fractures remain high in individuals who receive these interventions.

It is important to identify high-risk persons by appropriate screening.

Dual x-ray absorptiometry at the lumbar spine and hip is a reliable and safe way of assessing fracture risk in postmenopausal women. Peripheral measurements (eg, ultrasonography) should not be used for decision making.

The 10-year risk of a fragility fracture in a postmenopausal woman with a T-score at -2.5 standard deviations or less (compared with a normal young woman), and no other risk factors is more than 20% at age 65.

"Low bone mass" (osteopenia) is defined by a T-score between -1.0 and -2.5. About half of fragility fractures occur in the osteopenic group.

Despite the recommendations for screening, there is little evidence of its effectiveness in enhancing prevention and treatment programs.

These screening efforts detect the disease after it has been present for several years. Treatment is then "catch up".

If a woman lives long enough, osteoporosis seems inevitable. I await a study which begins low-dose prophylactic drug therapy (in addition to calcium and vitamin D) at the time of menopause to prevent the disease or at least to delay it for decades.

Bone Turnover Increases with Teriparatide; Decreases with Alendronate. Both Lead to Increased BMD.

8-3 OPPOSITE BONE REMODELING EFFECTS OF TERIPARATIDE AND ALENDRONATE IN INCREASING BONE MASS

Imbalances in the bone remodeling process affect mechanical properties related to bone strength, including bone geometry and microarchitecture. When bone resorption exceeds bone formation, osteoporosis results, and the risk of fracture increases.

Therapies can preferentially modulate 1) bone resorption (eg, alendronate) or 2) bone formation (eg, teriparatide; human recombinant parathyroid hormone). Both correct the imbalances in the bone remodeling process.

This study compared the biochemical effects of both drugs and their effects on bone mineral density (**BMD).**

Alendronate *suppressed* bone turnover. It inhibited bone resorption after one month and inhibited formation at 3 months. A new steady state was achieved and persisted through 12 months. The effect on inhibition of resorption continued and more than compensated for the reduction in formation. As a result, BMD increased modestly in the spine and proximal femur.

Teriparatide *increased* bone turnover. It increased the formation of bone which persisted for at least 12 months. Bone resorption also increased modestly for up to 12 months. The increase in bone formation more than overcame the rate of resorption. As a result, BMD increased.

Why should we be concerned about the detailed metabolic effects of these drugs? Because, since they act differently, their beneficial effect in increasing BMD and bone strength may be additive. Would use of both drugs, concomitantly or in sequence, increase BMD and bone strength compared with use of either alone? See the following abstract.

One Year Of Parathyroid Hormone Followed By One Year Of Alendronate An Effective Means Of Increasing BMD

8-4 COMBINATION AND SEQUENTIAL THERAPY FOR OSTEOPOROSIS

Bisphosphonates produce a steady increase in bone mineral mass averaging about 1% a year for up to 8 to 10 years. And once-daily parathyroid hormone given subcutaneously increases central bone mass by 8% to 10% per year for up to 2 years.

Combinations of PTH + bisphosphonates appear to increase central bone mass, but to a lesser extent than with PTH alone.

When PTH is used alone, in the months after PTH is discontinued, some or all of the bone gained appears to be lost.

Administering bisphosphonates *after* a course of PTH appears to conserve the bone gained, and adds a further increase in its own right, roughly similar in magnitude to the short-term effect of bisphosphonates given to previously untreated patients.

The term “osteoporosis” denotes not only defects in bone mass, but also defects in “bone quality”. The latter may be as important as the former in promoting weakness of bone. Both drugs improve “bone quality”.

An accompanying article "One Year of Alendronate after One Year of Parathyroid Hormone (1-84) for Osteoporosis." NEJM August 1, 2005; 353: 555-65 reports:

1) One year of PTH followed by one year of placebo:

Patients receiving PTH for one year gained BMD. During the 2nd year, when receiving placebo, much of the gain was lost. (Apparently PTH must be continued to maintain the gain in BMD.)

2) One year of PTH followed by one year of alendronate:

Patients receiving PTH for one year gained BMD. During the 2nd year of alendronate-alone therapy, BMD continued to increase.

3) One year of alendronate + PTH followed by one year of alendronate alone:

During the first year of combined therapy, there was no advantage over PTH alone. Over 2 years, BMD increased, but at somewhat lower rate than those receiving PTH for one year followed by alendronate.

4) One year of alendronate followed by a second year of alendronate:

BMD increased over 2 years, but not as much as in the group receiving 1-year of PTH followed by 1-year of alendronate.

"Thus, from a clinical perspective, one year of parathyroid hormone followed by one year of alendronate would seem to be an effective means of increasing bone mineral density while minimizing the use of parathyroid hormone."

Note that 2-years of PTH was not used as a comparator.

More observation is required to determine the most favorable use of combinations. There seems to be some advantage.

Most of the studies of osteoporosis I have abstracted thus far concern treatment of the established disease. Prevention is much more important. Making sure that calcium and vitamin D intakes are adequate during all periods of life is a start. Would very low-dose bisphosphonate, given perhaps once monthly, starting at the time of menopause, and continued for years, prevent the disease.?

PARATHYROID HORMONE

Vitamin D Supplements Are Necessary For Adequate Vitamin D Status In Northern Climates.

11-3 RELATIONSHIP BETWEEN SERUM PARATHYROID HORMONE LEVELS, VITAMIN D SUFFICIENCY, AND CALCIUM INTAKE.

This study used the serum parathyroid hormone (**PTH)** level as a marker of sufficiency or insufficiency of vitamin D and calcium. (If vitamin D and calcium levels are insufficient, PTH will be high; if sufficient, PTH will be low.) The investigators examined calcium intake and serum levels of 25-hydroxyvitamin D (**25-OH-D**) with respect to optimal serum PTH levels in a healthy adult population living in a northern latitude where sunshine is limited.

The lowest PTH (most favorable) levels were observed in the group with the highest serum 25-OH-D (18 ng/mL and above) In this group, the intake of calcium made little difference in the PTH levels. (Ie, when comparing intake of less than 800 mg with over 1200 mg.)

The highest PTH (least favorable) was observed in the group with 25-OH-D less than 10 ng/mL. In this group, calcium did make a difference in PTH levels. PTH was higher when the calcium intake was less than 800

mg, and lower when intake was over 1200 gm. (Ie, calcium intake may be more important in persons with lower vitamin D intake.)

"The significance of our study was demonstrated by the strong negative association between sufficient serum levels of 25-hydroxyvitamin D and PTH with calcium intake varying between 800 mg/d, and to more than 1200 mg/d." Vitamin D sufficiency can ensure ideal serum PTH values even when the calcium intake level is less than 800 mg/d.

"There is already sufficient evidence from numerous studies for physicians to emphasize the importance of vitamin D status and to recommend vitamin D supplements for the general public when sun exposure and dietary sources are insufficient."

No vitamin D biosynthesis occurs during the winter months at latitudes of 42^{o} north (Boston) and 52^{o} north (Edmonton, Alberta). Iceland is 64^{o} north. Only subjects who took supplements maintained a serum level of 25-OH-D above 18 ng/mL during the winter.

The study does not suggest that intake of calcium should be limited even though vitamin D may compensate for modest intakes of calcium. I believe generous intakes are warranted (> 1000 mg daily). The study does suggest that vitamin D, not calcium, is the main determinate of bone health .

Vitamin D is the key to adequate bone metabolism. Higher dietary calcium intake can only partially compensate when vitamin D is not sufficient.

The main point of the study for primary care is that intake of vitamin D is often not sufficient for optimum metabolic needs. Supplementation is needed, not only in northern climates, but also for other circumstances. Individuals in nursing homes and those confined to indoors need supplements. Adolescents need all the bone in their bone-banks they can get to maintain best bone health in older age. I believe supplementation would be reasonable in this group as well as in the elderly.

A daily multivitamin supplement is convenient, safe, and inexpensive. It contains 400 IU vitamin D, which is likely to ensure adequate serum levels when added to the dietary intake.

PERIODONTAL DISEASES

"Could Have A Role In The Initiation Or Progression Of Coronary Artery Disease And Stroke."

12-2 PERIODONTAL DISEASES

The term periodontal disease usually refers to the common inflammatory disorders (gingivitis and periodontitis) that are caused by pathogenic microflora in the biofilm (dental plaque) that forms adjacent to the teeth every day.

Inflammation that extends deep into the tissues and causes loss of supporting connective tissue and alveolar bone is termed *periodontitis*. The result is formation of soft tissue pockets, or deepened crevices between the gum and the tooth root. Severe periodontitis results in loosening of teeth, occasional pain and discomfort, impaired mastication, and eventually tooth loss. An estimated 13% of US adults have moderate to severe periodontitis.

The clinical diagnosis is based on visual and radiographic assessment.

Causes include

1. Oral microorganisms:

The mouth contains hundreds of species of aerobic and anaerobic bacteria (many uncharacterized) living in symbiosis with a healthy host. These organisms grow on tooth surfaces in biofilms. They are attached to, and densely packed, against the tooth.

2. Tobacco:

Smokers are much more likely to develop periodontitis. Smokeless tobacco may also lead to gingivitis, loss of tooth support, and precancerous leucoplakia at the site of quid placement.

"In the USA, about half of the risk of periodontitis can be attributable to tobacco use.

3. Osteoporosis:

Osteoporosis raises susceptibility to periodontal break down. The risk could be attenuated by estrogen replacement therapy.

Association with cardiovascular disease and stroke:

Inflammation has been implicated in the cause and pathogenesis of atherosclerosis. "Periodontal disease could have a role in the initiation or progression of coronary artery disease and stroke."

Periodontitis is associated with raised systemic concentrations of C-reactive protein, fibrinogen, and cytokines, all of which have been causally linked to atherosclerotic-induced diseases. Periodontitis treatment has been shown to reduce serum inflammatory markers and C-reactive protein.

In animals, periodontal bacteria can promote platelet aggregation.

One study reported that severe periodontitis was associated with increased intima-media thickening. Severe periodontal bone loss was associated with a nearly four-fold increase in risk for presence of carotid artery plaques.

A meta-analysis concluded that periodontal disease was associated with a 19% increase in the risk of future cardiovascular disease. A 12-year study suggested that periodontal disease and fewer teeth could be associated with a raised risk of ischemic stroke.

Since periodontal disease is so common, even a modest increase in risk could have profound public-health effects.

I included this review mainly to comment on the putative relation of periodontitis with cardiovascular disease. Although tentative, I believe the relationship should be suspected.

Inspection of the teeth and gums should be routinely included in the physical examination. I believe many primary care clinicians do not regularly examine patients for periodontitis. They defer to the dentist.

Presence of periodontitis provides an opportunity to stress the importance of tobacco cessation.

Women may be told that osteoporosis may lead to tooth loss.

PERTUSSIS

10-7 EFFICACY OF AN ACELLULAR PERTUSSIS VACCINE AMONG ADOLESCENTS AND ADULTS

During the past 50 years, routine immunization of children has dramatically decreased the burden of childhood pertussis.

Immunization of children has *not* decreased the incidence of disease in older persons, nor has it eliminated the transmission of infections to unimmunized children.

Infections among adolescents and adults result from waning immunity. Neither immunization nor natural infection induces long-term immunity. Most adult cases are not suspected.

This trial, sponsored by the National Institute of Health, aimed to ascertain the protective efficacy of acellular pertussis vaccine among adolescents and adults

Double-blind multicenter trial randomized over 2700 healthy subjects mean age 35 to 1) a single dose of acellular pertussis vaccine used alone, or 2) a control vaccine (hepatitis A).

A total of 2672 illnesses with cough lasting over 5 days were evaluated.

Ten cases met the criteria for pertussis:

Nine in controls.

One in vaccine group

The incidence of pertussis in the control group = 9 cases per 2444 persons over 2 years. (390 cases per 100 000 person-years. ~ 4 per 1000 between ages 15 to 65.)

Overall efficacy of the vaccine = 92%

Vaccine safety: Serious adverse events occurred in 140 of 1391 subjects—equally in both groups. None were deemed to be vaccine-related.

Pertussis in adults is not uncommon. Extrapolating the rate of pertussis reported in this study would result in an estimated 1 million cases each year in the USA. This does not include asymptomatic or mild infections.

Pertussis is one of the least well controlled illnesses that are preventable by vaccine. Immunization of adolescents between ages 10 and 19 may be the most beneficial initial strategy in view of ease of administration and costs.

The purified acellular vaccine is associated with fewer local and systemic reactions than the whole-cell vaccine.

PLACEBO

This Is Fascinating!

10-1 PAIN STUDIES ILLUMINATE THE PLACEBO EFFECT

Recent studies based on MRI and PET scans of the brain provide the first direct evidence that the placebo effect is mediated by activation of the receptors in the endogenous opioid system. This demonstrates a mechanism through which patient's *expectation* of pain relief can alter their experience of pain and their emotional state.

This article cites a study in which a salt water solution was injected into the jaws of healthy male volunteers to maintain a steady state of pain. Brain imaging studies compared responses of 1) subjects received a placebo that was described as a medicine which might relieve pain, *vs* 2) subjects who did not receive the placebo. The images differed. In group 1) areas of the brain containing opioid receptors were activated. In group 2) they were not activated.

The mental events induced by placebo can activate mechanisms that are similar to those activated by drugs. There is a similarity between psychosocial and pharmacodynamic effects.

PRACTICE GUIDELINES

CPGs Give Little Guidance For Care Of Older Patients.

8-1 CLINICAL PRACTICE GUIDELINES AND QUALITY OF CARE FOR OLDER PATIENTS WITH MULTIPLE COMORBID DISEASES: Implications for Pay-for-Performance

As the population ages, the prevalence of patients with multiple chronic medical conditions increases. Previous studies reported that up to half of Medicare patients aged 65 and older have at least 3 chronic medical conditions. One fifth has 5 or more. Difficulties rise as the number of diseases increases.

Physicians who care for older adults with multiple diseases must strike a balance between following CPGs and adjusting recommendations for individual patients' circumstances.

This study evaluated the applicability of 9 CPGs to the care of older individuals. Only 4 of The 9 CPGs included in the study addressed older individuals with comorbidities. Many did not discuss the quality of evidence underlying the recommendations for older patients.

None of the CPGs discussed the burden of comprehensive treatments on patients and caregivers. None discussed balancing short- and long-term goals such as when short-term quality of life is better without a treatment even if that treatment might lengthen life.

The authors generated a possible treatment schedule that would result if all the recommendations of the CPGs were followed in patients with 5 or more comorbid conditions. Developing a treatment plan for a hypothetical patient in accordance with CPGs would result in treatment with multiple drugs with a high complexity of administration. This could increase risks of medication errors, adverse drug events, drug interactions, and hospitalizations. Independent self-management and adherence would be difficult. The treatment burden might be unsustainable.

"CPGs do not provide an appropriate, evidence-based foundation for assessing quality of care in older adults with several chronic diseases." Although they provide detailed guidance for managing a single disease, they fail to address the needs of older patients with complex comorbid illnesses. CPGs rarely address treatment of patients with 3 or more chronic diseases—a group that includes half of the population over the age of 65.

This is not to say that CPGs are not valuable—only that their value is restricted.

I believe that elderly patients take too many drugs. Many continue to take drugs which have outlived their benefit. As we get old and older, the benefit/harm-cost ratio of drugs and interventions changes. The probability of benefits falls; the probability of adverse effects increases; and costs may become more burdensome.

I believe that some elderly persons, especially the very elderly, who feel reasonably well and cherish each day of the "precious few" that remain, would opt to be left in peace, and not risk being subjected to tests, examinations, surgical interventions, and drugs and treatments with adverse effects that might undermine their present quality of life. There is a trade-off between maintaining the present quality-of-life by comfort care only versus interventions which may lengthen life at the risk of decreasing present quality of life. This is a personal decision.

Realizing that the remaining days of my life are limited, I would not trade one day of quality-life at age 85 for 50 days of poor health at age 95 likely to be associated with increasing dependency, dementia, and loss of dignity.

At present, much of daily medical practice addresses the indications for treatment of a single disease or symptom. Many older patients expect and request a "pill for every ill". They should understand that this may lessen their present quality of life. It may be preferable to bear some of the symptoms and go on with daily living.

Healthy life-styles should continue.

Primary care clinicians must understand the choices and goals of each individual patient. The goal is to extend days-of-quality-life, not days-of-life.

The "art" of medicine must continue unabated.

PROSTATE-SPECIFIC ANTIGEN

There Is No Cutpoint Of PSA With Simultaneous High Sensitivity And High Specificity

7-5 OPERATING CHARACTERISTICS OF PROSTATE-SPECIFIC ANTIGEN

PSA screening has become controversial. No studies have proven that it leads to a reduction in mortality from prostate cancer **(PC).** After 2 decades of screening, mortality from PC has decreased, but it is not known if this is due to screening or other factors such as treatment efficacy. PC mortality rates have also declined in countries where PSA screening is uncommon. In the USA, regions with different rates of PC screening and treatment have similar rates of disease-specific mortality.

A potential explanation for these observations may be due to the characteristics of PSA measurement as a screening test. In general, biopsy has not been recommended unless PSA levels exceed a threshold of 4.0 ng/mL. Other studies have reported that as many as 15% of men with a PSA less than 4.0 have PC, and that 15% of these are high grade.

This study estimated the relation between true positive PSA tests and true negative PSA tests over a range of PSA cutpoints. (Sensitivity vs specificity.)

Conclusion: For monitoring healthy men, there is *no cutpoint* of PSA with simultaneous high sensitivity and high specificity:

A. Setting the cutpoint high will result in:

More men <u>with</u> cancer being missed. (Many men with PC will have a PSA below the high cutpoint—

many false negative tests for PC.)

Fewer men without cancer being falsely considered positive for cancer and subject to biopsy. (Few men without PC will have a PSA above the high cutpoint—few false positive tests for PC.)

B. Setting the cutpoint low will result in:

More men with cancer being diagnosed. (Many more men with PC will have a PSA above the low cutpoint—more true positive tests for PC.)

More men without cancer being falsely considered positive for cancer and subject to biopsy. (More men without PC will have a PSA above the low cutpoint—more false positive tests for PC.)

I struggled to present this article in a clear, simple, meaningful manner. Teasing out sensitivities and specificities is always challenging and remains confusing at times even to individuals who frequently try to decipher them.

Even now, I remain uncertain at times as to whether I have presented the data correctly. The best approach is to begin with the classical 2 X 2 chart:

	Disease present	*Disease absent*
Test positive	*True positive (sensitivity)*	*False positive*
Test negative	*False negative*	*True negative (specificity)*

I am sure other similar studies would come up with different figures for cutpoints of sensitivity and specificity I believe, however, the principle is sound:

1) At low cutpoints, more men who actually have cancer will be diagnosed.

And more men who do not have cancer will be considered positive for PC.

2) At high cutpoints, fewer men who actually have cancer will be diagnosed,

And fewer men who do not have cancer will be considered positive for PC. .

There is an important corrrelary to these observations. Since more men screened with PSA do not have PC than men who have PC, PSA screening will necessarily lead to more false positives and unnecessary investigation as compared with those who are diagnosed as truly having cancer.

Consider screening a group of 100 000 men. Assume that:

20 % (n = 20 000) actually have PC, and

80% (n = 80 000) do not have PC.

According to this study:

1) Of the 20 000 with cancer, 20% will have a PSA level 4.1 and above. Thus using 4.1 as a cutpoint, 4000 will be diagnosed. The great majority will be missed.

2) Of the 80 000 without cancer, 6% will have a PSA level of 4.1 and above. Thus 4800 will be considered falsely to have PC, and be subject to unneeded biopsy,.

3) If the PSA cutpoint is set at 2.1, the numbers will be 1) 8000 vs 2) 15 200.

In addition, of the 4000 men with PC, many will have indolent cancers and many more will have co-morbidity which will cause their deaths before PC might cause death. Thus, prostatectomy will cause many adverse effects, and relatively few years of quality-life will be gained. One recent study reported that men over age 65 with PC did not benefit from prostatectomy as compared with watchful waiting.

(NEJM May 12,2005; 352: 1977-84 See Practical Pointers May 2005 [5-9])

ROCKY MOUNTAIN SPOTTED FEVER

Describing a New Dog Vector for One of the Most Virulent Human Infections Ever Identified.

8-6 ROCKY MOUNTAIN SPOTTED FEVER – Changing Ecology And Persisting Virulence

Rocky mountain spotted fever **(RMSF)** is one of the most virulent human infections ever identified. Up to 10% of persons infected will die. Many more will require intensive care, and have sequelae such as amputation and permanent learning impairment. This is despite the availability of a simple and highly effective treatment (doxycycline).

Diagnosis is difficult because of the non-specific presentation of the disease. Symptoms include fever, headache, myalgia, and (usually after 3 to 5 days) rash. The rash evolves from macular to macro-papular, to petechial. Organ-specific symptoms (nausea, vomiting, abdominal pain, and cough) confound diagnosis by distracting attention from systemic manifestations. Serologic analysis is not useful during an active infection.

Early clinical suspicion and empirical therapy are essential. Severe illness and death are associated with a delayed diagnosis, which may occur because of absence of a rash or presentation during a season with a low level of tick activity.

An accompanying study describes a new vector for RMSF—the brown dog tick which differs from the American dog tick. The brown dog tick is intimately related to households.

"No longer can we consider RMSF a disease of only rural and southern venues; it has emerged and re-emerged again. "

This is a caution aimed mainly at primary care clinicians. They should maintain a high degree of suspicion about the possibility of RMSF. On consultation by an acutely and seriously ill, previously well patient (especially a young patient with a rash), asking about ticks in the environment and tick bites should be routine.

As a public health measure, if ticks are prevalent, measures to eliminate them should be taken.

Since there is no confirmatory test immediately available, empiric treatment with antibiotic (doxycycline) is justifiable because the stakes are high. The outcome of unrecognized RMSF may be disastrous.

RMSF is defined as an infection caused by R rickettsii. But R rickettsii is not the only rickettsia carried by arthropods which can cause disease. Correspondence in this issue (NEJM August 1, 2005 pp 626-27) lists 6 different species. More unnamed species may exist.

SCABIES

9-8 SCABIES: *Diagnosis And Treatment*

Eight clinical points.

STATIN DRUGS

No Difference in Cardiovascular and All-Cause Mortality.

11-8 HIGH-DOSE ATORVASTATIN *VS* USUAL-DOSE SIMVASTATIN FOR SECONDARY PREVENTION AFTER MYOCARDIALINFARCTION The IDEAL Study

Statins are part of the standard treatment regimen after myocardial infarction **(MI).** Incremental benefits have been demonstrated with intensive lowering of LDL-cholesterol **(LDL-c)** among patients with the acute coronary syndrome **(ACS**). The National Cholesterol Education Program now recommends a LDL-c level less than 70 for patients at very high risk of ACS.

The IDEAL study hypothesized that intensive lowering of LDL-c with atorvastatin (*Lipitor*) at the highest recommended dose would yield incremental benefits compared with the usual recommended dose of simvastatin (*Zocor*).

Prospective, randomized, open label, multicenter trial enrolled over 8500 patients (mean age = 61). All had a history of acute MI. (*This is a secondary preventions study*.)

Subjects were randomized to 1) atorvastatin 80 mg daily, or 2) simvastatin 20 mg daily.

Over 4.8 years:	Atorvastatin (n = 4439)	Simvastatin (n = 4449)	Absolute difference	NNT*
LDL-c (mean mg/dL)	81	100		
Major cardiac event	9.3%	10.4%	1.1%	90**
Non-fatal acute MI	6.0 %	7.2%	1.2%	

(* Number needed to treat for 5 years to benefit one patient.)

(** not statistically significant)

Non-cardiovascular death	3.2%	3.5%		
Death from any cause	8.2%	8.4%		

Adverse effects: Adverse event resulting in permanent discontinuation were more common in the atorvastatin group (9.6% vs 4.2%). Transaminase elevation in 1% vs 0.1%. Serious myopathy and rhabdomyolyis were rare in both groups.

When standard and intensive LDL-c lowering were compared in patients at high risk (past MI), there was no statistically significant reduction in major coronary events. There was no difference in cardiovascular and all-cause mortality. There was a reduction in other composite secondary endpoints and non-fatal MI. (NNT for 5 years = 26 to 62.)

When I first noted the title of the investigation, I expected much more favorable results in the atorvastatin group.

Note that the recommended level of LDL-c of 70 was not reached in either group.

Lipitor therapy is more burdensome (more discontinuation; need to follow more closely for transaminase).

Note that at baseline, hypertension was present in 33% of subjects, mean body mass index was 27, and 20% were current smokers. I believe clinicians have focused too much on cholesterol lowering as a preventive measure and have neglected the other risk factors. This study did not mention any interventions for the other risk factors other than to state that subjects received dietary counseling.

I believe a primary prevention trial would report better results from atorvastatin. It is too late to gain much benefit after a severe cardiovascular event has occurred.

STROKE

Right-Sided Stroke Or TIA May Be "Silent", At Least As Far As Recognition Goes.

7-7 UNDERDIAGNOSIS OF RIGHT-BRAIN STROKE

A study in the July 30, 2005 issue of Lancet included over 20 000 patients with stroke or TIA. It reported a striking difference in the rate of diagnosis of left-sided and right-sided ischemic events. Symptoms of cerebrovascular events due to anterior (carotid) circulation deficits differ depending on the hemisphere involved.

The major difference between hemispheres is the lateralization of cognitive functions, particularly the left-hemisphere dominance of language. Patients, families, and physicians might be more likely to recognize a disturbance of speech or language, and apraxia of the right hand due to left-hemisphere ischemia than more difficult-to-define cognitive deficits (sudden confusion) or apraxia of the non-dominate left hand from a corresponding lesion in the right hemisphere. Neglect (defined as a reduction in awareness of neurological deficits) is associated with right-hemisphere lesions.

Assuming that right- and left-sided strokes have equal frequency, the German study suggested that, for every eight patients currently hospitalized for anterior-circulation stroke or TIA, one patient with right-sided ischemia will be overlooked. These patients are unlikely to receive the same standard of management for secondary prevention.

The authors stress that the difficulty in recognizing right hemisphere lesions pertains only to minor stroke or TIA. Major stroke, especially hemorrhagic, is more easily recognized.

I believe this difficulty in recognizing right hemisphere lesions is clinically important.

The major differences in presentation:

Right hemisphere lesion	*Left hemisphere lesion*
No aphasia	*Aphasia*
Less awareness of neurological deficits	*More awareness of neurological deficits*
(Symptoms less readily recognized	*(Symptoms more readily recognized.*
Neglect in recognizing confusion	*Less neglect. Aphasia and apraxia of,*
and apraxia of the left hand)	*the right hand more readily recognized.*

SYPHILIS

Equivalent Efficacy For Treating Early and Latent Syphilis, but Resistance May Occur

9-14 SINGLE-DOSE AZITHROMYCIN VERSUS PENICILLIN G BENZATHINE FOR THE TREATMENT OF EARLY SYPHILIS

A single intramuscular dose of 2.4 million units of penicillin G benzathine (*Bicillin LA*) is the recommended therapy for early syphilis. It is low cost. Adherence is no problem. Disadvantages include pain, the relatively high prevalence of self-reported penicillin allergy, and the need for injection equipment and trained personnel. In addition, there is some risk of transmission of blood-borne infections if the injection equipment is reused.

Azithromycin (*Zithromax*), a macrolide antibiotic with a long half-life (68 hours), would overcome some of these disadvantages. Efficacy against *Chlamydia trachomatis, Neisseria gonorrhoeae, and Haemophilus ducreyi* has been established. (Penicillin is not indicated and is ineffective against these organisms.)

Azithromycin is a promising candidate for treatment of primary and latent syphilis. [Latent syphilis is defined by 1) a positive serological test, 2) a normal CSF, and 3) no clinical manifestations.]

This study compared effectiveness of oral azithromycin vs intramuscular penicillin G benzathine in Tanzania. Cure rates at 9 months were 98% in the azithromycin group and 95% in the penicillin group.

There have been reports of azithromycin-resistant strains *T pallidum* in the USA and in Ireland. There was no evidence of resistance in Tanzania.

An accompanying editorial comments on two important reasons for caution: 1) The sustained success (50 years) of penicillin G benzathine. 2) The recent emergence of resistance to azithromycin.

Penicillin G benzathine is marketed as Bicillin LA. Bicillin LA is composed of one molecule of dibenzylethylene diamine + two molecules of penicillin G. Given intramuscularly, it maintains blood levels for 2 weeks or more.

It has been confused with Bicillin C-R, a combination of penicillin G benzathine and penicillin procaine G which produces blood levels more rapidly and of shorter duration. It is not indicated for treatment of syphilis.

Not too long ago, syphilis was considered a major stand-alone course in medical school. I remember well giving treatment with arsphenamine and neo-arsphenamine intravenously. The miracle of penicillin changed all that. The problem of syphilis remains, but is less a problem, at least in the USA.

TOBACCO

"Cutting Down" Reduces Risk Of Lung Cancer, But Not Risk Of Myocardial Infarction And COPD.

9-6 EFFECT OF SMOKING REDUCTION ON LUNG CANCER RISK

This study asks—Would "cutting down" reduce risk of LC?

Divided into 6 groups according to smoking habits:

1) Continued heavy smokers (> 15 cigarettes daily; mean = 20).

2) Reducers reduced smoking from > 15 per day by a minimum of 50% without quitting.

3) Continued light smokers (1-14 per day).

4) Quitters (stopped between 1st and 2nd examinations).

5) Stable ex-smokers.

6) Never smokers.

Groups:	1)	2)	3)	4)	5)	6)
Number	7351	832	3199	1355	2881	4066
Pack years at baseline	31	27	14	19	14	
Number of LCs	576	52	104	52	52	28
% with LC	7.8	6.3	3.3	3.6	1,8	0.7
Adjusted hazard ratio for LC:	1.00	0.73	0.44	0.50	0.17	0.09

Absolute difference, continued heavy smokers vs those who reduced consumption

by 50% = 7.8% - 6.3% = 1.5%. Sixty two smokers would have to cut consumption by 50% to prevent one LC. Twenty four would have to quit completely to prevent one LC.

The authors previously investigated the all-cause mortality, fatal and non-fatal myocardial infarction, and hospitalization for COPD in smokers. They found no reduction in risk associated with smoking reduction. "Cutting down" does not reduce these risks. LC is more likely to demonstrate a dose-response to cutting down.

See the following report on snuff. RTJ

Would You Advise Snuff For Nicotine Replacement?

9-7 MIXED FEELINGS ON SNUS

The British American Tobacco **(BAT)** company markets "snus" in Sweden. "Snus" is a finely ground snuff that is pasteurized to diminish the carcinogenic nitrosamines sometime found in high levels in snuff as well as in cigarettes. (The sale of snus is illegal in the European Union except in Sweden.)

BAT is trying to . . ."extend the appeal of snus to more adults smokers who have not heard of snus to try it." BAT claims that the move is part of their "continuing efforts in harm reduction". They claimed that the biggest group of quitters in Sweden used snus as "the main aid in quitting".

Is it true that snus is a harm-reduction product? It certainly is much less harmful than cigarettes. It has not been associated with any increase in lung cancer. But, it is classified as a carcinogen by the International Agency for Research on Cancer. A recent study reported an increased risk of pancreatic cancer. Snus is not harmless.

Is it effective as an aid to quitting cigarettes? Evidence is inadequate, but suggests that it may be effective for some smokers. Many nicotine users favor it over tobacco smoke. The fact that more Swedes choose snus rather than therapeutic nicotine replacement for routine use suggests that it offers a better "fix".

Is it addictive? This is controversial. Nicotine replacement therapy is relatively non-addictive, but there is a view that, if such therapy is to replace cigarettes it needs to be more competitive, and this means more addictive.

It is possible (however reluctantly) to agree that snus is a harm-reduction product, but only when compared with cigarettes.

In view of the ban on cigarettes in many restaurants and bars, tobacco companies are encouraging smokers to try snuff as an alternative where smoking is forbidden. Is this ethical?

I abstracted this article to ask myself—if my patient stated he had absolutely no intention of quitting, or was unable to quit after many tries, would I suggest his switching to snuff? (Snuff in the USA is probably more carcinogenic than snus.) Would I suggest snuff as a drug (nicotine replacement) hoping to enable cessation, or at least a reduction in cigarette smoking?

We accept risk with every drug we prescribe. With preventive therapy, (eg, aspirin, statin drugs; antihypertension drugs) patients seem quite willing to accept the risks. I abstracted this article to ask—should we consider snuff a preventive drug (ie, one that reduces risk)? Would the patient sue if he developed oral cancer after being informed of the risk and accepting it?

I would merely point this article out to the patient and let him decide on his own. I would not prescribe snuff. Indeed, I would place in the record that I advise cessation of all tobacco products.

A Public Health Intervention Producing Remarkable Benefits.

11-9 LEGISLATION FOR SMOKE-FREE WORKPLACES AND HEALTH OF BAR WORKERS IN IRELAND: Before And After Study

In March 2004, The Republic of Ireland introduced a comprehensive smoke-free law covering all indoor workplaces. This created a natural experiment for identifying effects of the ban.

This study compared exposure to secondhand smoke and respiratory health in bar staffs before and after the law was passed.

Enrolled staff working in pubs in the Republic (n = 111) six months before the smoking ban went into effect.

The study considered non-smokers only.

Followed the cohort for one year after to assess changes in exposure to secondhand smoke and symptoms.

Salivary cotinine concentrations fell by 71%. Levels fell in 106 of 111 subjects

Self reported exposure to secondhand smoke was high before the ban, with smoke at work accounting for by far the greatest exposure. Exposure fell from 40 hours a week to zero.

At baseline, 65% reported one or more respiratory symptoms. This dropped to 49% on follow-up. Fewer reported cough and production of phlegm, red eyes, and sore throat.

I included this article because it illustrates an important public health intervention. It certainly can be more widely applied.

URINARY TRACT INFECTION

Antibiotic Therapy Shortened The Time To Resolution Of Symptoms.

7-1 RESPONSE TO ANTIBIOTICS OF WOMEN WITH SYMPTOMS OF URINARY TRACT INFECTION BUT NEGATIVE DIPSTICK URINE TEST RESULTS.

A sizable group of women with urinary symptoms who subsequently have UTI established by culture are dipstick negative.

This pragmatic trial (as in primary care practice) compared the effectiveness of antibiotic treatment vs placebo in women with symptoms of UTI who had a negative dipstick.

Double-blind placebo-controlled study followed 59 women presenting to primary care with a history of dysuria and frequency. All had a negative dipstick for both leukocytes and nitrites.

All were treated with: 1) Trimethoprim 300 mg daily for 3 days, or 2) placebo.

The median time to resolution of dysuria: Trimethoprim—3 days; placebo—5 days.

Ongoing symptoms	At 3 days	At 7 days
Trimethoprim	24%	10%
Placebo	74%	41%

(Number needed to treat with trimethoprim to benefit one patient = 4.)

Only 5 women (of 59) had microbiological evidence of bacterial infection when standard criteria were used—a pure growth of 100 000 organisms per mL. Three were in the treatment group; 2 in the placebo group.

"These results indicate a bacterial or other infectious cause for the symptoms that was missed by dipstick testing and standard testing [*by culture*] in a diagnostic laboratory."

The resolution of symptoms that generally accompany infection would provide some support for an atypical or occult cause, implying that these women do not have "urethral syndrome", a diagnosis of exclusion.

A past history of UTI increases the risk of subsequent infection. Ninety % of the women in the study reported a history of similar symptoms.

Admittedly, this is a small trial. Confirmation with a larger number of subjects would be more convincing. Nevertheless, I believe it has clinical validity.

Many primary care clinicians treat symptoms of UTI empirically with antibiotics, rather than wait for bacterial confirmation. This would apply particularly to patients who have had a history of repeated UTI. Indeed, I believe some clinicians will prescribe an antibiotic to be reserved at home for patients to take at the onset of symptoms.

VITAMIN D

Vitamin D Supplements Are Necessary For Adequate Vitamin D Status In Northern Climates.

11-3 RELATIONSHIP BETWEEN SERUM PARATHYROID HORMONE LEVELS, VITAMIN D SUFFICIENCY, AND CALCIUM INTAKE.

This study used the serum parathyroid hormone (**PTH)** level as a marker of sufficiency or insufficiency of vitamin D and calcium. (If vitamin D and calcium levels are insufficient, PTH will be high; if sufficient, PTH will be low.) The investigators examined calcium intake and serum levels of 25-hydroxyvitamin D (**25-OH-D**) with respect to optimal serum PTH levels in a healthy adult population living in a northern latitude where sunshine is limited.

The lowest PTH (most favorable) levels were observed in the group with the highest serum 25-OH-D (18 ng/mL and above) In this group, the intake of calcium made little difference in the PTH levels. (Ie, when comparing intake of less than 800 mg with over 1200 mg.)

The highest PTH (least favorable) was observed in the group with 25-OH-D less than 10 ng/mL. In this group, calcium did make a difference in PTH levels. PTH was higher when the calcium intake was less than 800 mg, and lower when intake was over 1200 gm. (Ie, calcium intake may be more important in persons with lower vitamin D intake.)

"The significance of our study was demonstrated by the strong negative association between sufficient serum levels of 25-hydroxyvitamin D and PTH with calcium intake varying between 800 mg/d, and to more than 1200 mg/d." Vitamin D sufficiency can ensure ideal serum PTH values even when the calcium intake level is less than 800 mg/d.

"There is already sufficient evidence from numerous studies for physicians to emphasize the importance of vitamin D status and to recommend vitamin D supplements for the general public when sun exposure and dietary sources are insufficient."

No vitamin D biosynthesis occurs during the winter months at latitudes of 42^{o} north (Boston) and 52^{o} north (Edmonton, Alberta). Iceland is 64^{o} north. Only subjects who took supplements maintained a serum level of 25-OH-D above 18 ng/mL during the winter.

The study does not suggest that intake of calcium should be limited even though vitamin D may compensate for modest intakes of calcium. I believe generous intakes are warranted (> 1000 mg daily). The study does suggest that vitamin D, not calcium, is the main determinate of bone health .

Vitamin D is the key to adequate bone metabolism. Higher dietary calcium intake can only partially compensate when vitamin D is not sufficient.

The main point of the study for primary care is that intake of vitamin D is often not sufficient for optimum metabolic needs. Supplementation is needed, not only in northern climates, but also for other circumstances. Individuals in nursing homes and those confined to indoors need supplements. Adolescents need all the bone in their bone-banks they can get to maintain best bone health in older age. I believe supplementation would be reasonable in this group as well as in the elderly.

A daily multivitamin supplement is convenient, safe, and inexpensive. It contains 400 IU vitamin D, which is likely to ensure adequate serum levels when added to the dietary intake.