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This document is divided into two parts:

1) The *Highlights* section contains brief comments patterned after the "abstract" placed on the first page of many studies reported in journals. *Highlights* condenses the content of studies, and allows a quick review of pertinent points of each article.

   The *Editorial Comments* are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of *Practical Pointers*.

2) The main *Abstracts* section is designed as a reference. It presents structured summaries of the content of articles in much more detail.

An *Index* containing all the Highlights is published twice a year. In an evening or two, the reader can refresh memory of the entire content of practical points abstracted from 6 major journals over the 6-month period.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 years can be accessed at www.practicalpointers.org

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

HIGHLIGHTS AND *EDITORIAL COMMENTS* JULY 2005

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.

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.

"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.

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.

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 <u>without</u> 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 <u>with</u> cancer being diagnosed. (Many more men with PC will have a PSA above the low cutpoint—more true positive tests for PC.)

More men <u>without</u> 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 <u>not</u> 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])

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.

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.*

"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.

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.

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.

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

ABSTRACTS JULY 2005

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.

Urine is commonly tested by dipstick for the presence of leukocytes and nitrites to predict a subsequent diagnosis of urinary tract infection **(UTI)** confirmed by culture.

In primary care practice, the presence of leukocytes or nitrites in a turbid urine has a positive predictive value[1] of about 66% of finding a pure growth on subsequent culture. Conversely, a negative dipstick for both leukocytes and nitrites has a negative predictive value of finding a pure growth on subsequent culture of 80% to 98%.

One approach to women with symptoms of uncomplicated UTI who have a positive dipstick is to give antibiotics empirically.

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.

Conclusion: Antibiotic therapy significantly shortened the time to resolution of symptoms.

STUDY

1. 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. The urine was sent for culture.
2. All were treated with: 1) Trimethoprim 300 mg daily for 3 days, or 2) placebo.
3. Main outcome = resolution of symptoms at 3 and 7 days. And median time to resolution.

RESULTS

1. The median time to resolution of dysuria: Trimethoprim—3 days; placebo—5 days.
2. 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.)

3. The median duration of constitutional symptoms (feverishness, shivers) was reduced by 4 days in the trimethoprim group.
4. What did the cultures show? Only 5 (of 59) women 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.

DISCUSSION

1. "These results indicate a bacterial or other infectious cause for the symptoms that was missed by dipstick testing, and standard testing in a diagnostic laboratory."
2. 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.
3. A past history of UTI increases the risk of subsequent infection. Ninety % of the women in the study reported a history of similar symptoms. This high rate is consistent with other studies of women presenting in primary care with UTI. An alternative, but less likely hypothesis is that trimethoprim has an effect other than its bactericidal one in reducing symptoms.
4. *Chlamydia trachomatis* has been implicated as a cause of UTI and dysuria. It does not respond to trimethoprim and would not have contributed to the observed effect.
5. The pragmatic design (ie, of typical patients seen in primary care) is its strength.
6. Implications for clinical practice: "If these finding are confirmed, empirical treatment with antibiotics of (dipstick positive or dipstick negative) patients presenting in primary care is justified irrespective of dipstick findings."
7. An infectious cause which is not being diagnosed by using the current approach is likely. This further highlights the tension between relieving symptoms expeditiously with the desire to minimize unnecessary antibiotic use.

CONCLUSION

Although a negative dipstick test accurately predicted absence of infection, confirmed by a negative culture, it did not predict response to antibiotic treatment.

Three days treatment with trimethoprim significantly reduced dysuria in women whose dipstick test was negative. This supports empirical use of antibiotics, guided by symptoms.

BMJ July 16, 2005; 331: 143-46 original investigation, first author Dee Richards, Christchurch School of Medicine had Health Sciences, New Zealand.

1 Positive predictive value:

Number of true positive tests divided by the total number of positive tests

True positive plus sum of true positive + false positive = 66 divided by (66 + 34) = 66 divided by 100 = 66%.

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 [1] 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. This randomized, placebo-controlled trial not only disproved any protective effect, but reported a slight increase in risks. The trial was discontinued early because the overall health risks exceeded the benefits.

Women frequently cite relief of vasomotor symptoms (hot flashes and night sweats), vaginal dryness, and improvement in well-being as reasons for continuing menopausal hormone therapy. This study asks: What is the effect of discontinuing E + P therapy and placebo on older women who have taken it for considerable time?

Conclusion: More than half of the women who discontinued use reported return of some symptoms.

STUDY

1. This study began after the WHI study was terminated in July 2002.Women had been taking conjugated equine estrogens (0.625 mg) + medroxyprogesterone acetate (2.5 mg),or placebo, **(CEE + MPA)** for a mean of 5.6 years. All discontinued use at a mean age of 69.
2. Eight to 12 months after termination of the WHI study, and both E + P and placebo were suddenly stopped, a survey asked the subjects (n = 8400) to describe any recurrence of symptoms.

RESULTS

1. Over half of the women who had been taking CEE + MPA reported recurrence of at least one moderate or severe symptom 8 to 12 months after discontinuing use. Many who had been taking placebo also reported symptoms:

	CEE + MPA (%)	Placebo (%)
Hot flashes and night sweats	21	5
Pain and stiffness (joint, general, low back)	37	22
Feeling tired	21	12
Difficulty sleeping	18	8
Mood swings	8	3
Vaginal dryness	10	5

(Would not the recurrence of menopausal symptoms after discontinuing placebo indicate a powerful placebo effect? RTJ)

2. After discontinuation, women who developed symptoms adopted a wide variety of management strategies, both lifestyle (eg, drinking more fluids, exercising, changing diet) and medical (talking to their clinician, vitamin E, alternative medical techniques). The majority believed these were helpful.
(*Perhaps another indication of a placebo effect. RTJ*)
3. Recurrence of vasomotor symptoms was more common in women who reported these symptoms at baseline (1993 to 1998) in the WHI trial.
4. Recurrence of vasomotor symptoms diminished with age of subjects who had previously taken CEE + MPA: 55-59 age group (35%); 60-69 group (28%); 70 and over (12%).

DISCUSSION

1. The study provides insights about symptom experience after postmenopausal women discontinue CEE + MPA after taking it for a number of years.

2. The mean age (63) of women who began the WHI study in 1993 to 1998 was considerably older than the age at which women typically begin menopausal hormone treatment.. The present study judged symptom recurrence at mean age 69.
3. Women in this study who discontinued CEE + MPA therapy after 5 to 6 years of use were more likely to report recurrence of symptoms than women who discontinued placebo. However, a significant number of women who had been taking placebo also reported symptoms.
4. Troublesome recurrent symptoms were more common in women in the WHI trial who had been experiencing vasomotor symptoms in the past compared with those who had not. Few women who did not have vasomotor symptoms before they started therapy developed symptoms after discontinuing.
5. The higher prevalence of pain and stiffness in respondents who were formerly taking CEE + MPA suggest an additional benefit. This withdrawal symptom had not been documented in the past. This warrants further investigation.
6. After treatment was discontinued women used a wide variety of lifestyle and medical strategies to manage symptoms. They were considered helpful.

CONCLUSION

Many participants (now mean age 69) who terminated use of CEE + MPA after using it for 5-years experienced recurrence of a range of symptoms.

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

JAMA July 13, 2005; 294: 183-93 Original investigation, first author Judith K Ockene, University of Massachusetts Medical School, Worcester.

1 The Women's Heath Initiative trial determined the "Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women" JAMA July17, 2002; 288: 321-33.

The study enrolled women between 1993 and 1998. It was designed to determine if estrogen + progesterone given to a cross section of postmenopausal women mean age 63 would reduce risk of cardiovascular events or protect against them. It was not designed to determine effects on postmenopausal symptoms.

The harms over 5 years slightly outweighed the benefits:

For 10 000 women over one year:

CHD events	+ 7 (harm)
Stroke	+ 8 (harm)
Pulmonary embolism	+ 8 (harm)
Invasive breast cancer	+ 8 (harm)
Colorectal cancer	- 6 (benefit)
Hip fracture	- 5 (benefit)
Global index	+ 19 (harm)

The main conclusion was that E + P did *not* protect against cardiovascular disease. The increased risk of breast cancer was confirmed.

"Not A Totally Benign Condition."

7-3 WHITE-COAT HYPERTENSION AS A RISK FACTOR OF TE 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.

Is WCHT related to later development of sustained (home) hypertension? Studies have been contradictory.

This present study was designed to quantitatively determine the risk of transition from WCHT to sustained hypertension.

Conclusion: WCHT is a transitional condition which proceeds to sustained hypertension.

STUDY

1. This longitudinal observation study from Japan compared subjects with:
   WCHT (defined as home BP < 135/85; and office BP > 140/90) . N = 128
   Sustained normotension (defined as home BP < 135/85 and office BP < 140/90). N = 777
   (Home BP determined by the HEM401C Omron Health-Care company device.)
2. At baseline, subjects were mean age 56.
3. Mean baseline BP

	Home	Office
WCHT	124/74	150/84
Sustained normotension	115/70	121/70

4. Follow-up for 8 years, compared risk of progression of WCHT to sustained (home) hypertension.

RESULTS

1. 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)
2. In both groups, rates of development of sustained home hypertension was greater as the baseline home BP increased. (Ie, a baseline home BP of 110/70 was less likely to progress to sustained hypertension than a baseline home BP of 120/80.)
3. Older age, obesity, and male sex predicted development of home hypertension.

DISCUSSION

1. 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."
2. Home BP measurements are now widely used in clinical settings. The Japanese are particularly keen on home BP determinations. Over 30 million devices for self-determination of BP have been distributed in Japan.
3. Some studies have reported that home BP better predicts cardiovascular events. WCHT may carry a poor cardiovascular prognosis.

CONCLUSION

Over 8-years, WCHT often progressed to sustained home hypertension. Progression was about twice the rate compared with subjects with normal office BP.

Archives Int Med July 11, 2005; 165: 1541-46 Original investigation, first author Takashi Ugajin, Tohoku University, Sendai, Japan.

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?

Advance in our understanding of essential nutrients has led to the ability to quickly and inexpensively treat nutritional deficiencies. But it has allowed the possibility that the proper balance of purified vitamins could supplant the need for a varied diet. We must determine how best to advise the public in developed countries with respect to nutrient supplements in an era which nutrient deficiencies are rare, chronic disease rates are high, and overweight and obesity have reached epidemic levels.

The government has issued recommended dietary allowances (RDAs) ever since 1943. They have been revised periodically. A new system establishes dietary reference intakes (DRIs) for each nutrient. This includes the RDAs and estimated average requirements, along with tolerable upper intake levels. As scientific evidence accumulates, recommendations have changed.

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.

Single-nutrient interventions; Disappointing results.

Low fat and sodium diets which are high in fruits and vegetables are associated with a decrease in BP and risk of cardiovascular diseases. However, instead of focusing on dietary patterns, most intervention trials have used high doses of single nutrients, or nutrient cocktails, in an attempt to prevent disease. These results for the most part have been disappointing.

Vitamin E, vitamin C, and beta carotene:

Recommendations for use were supported by in-vitro studies in which addition of these vitamins reduced the susceptibility of isolated LDL-cholesterol to oxidation. As with other examples of observational studies, subsequent intervention studies did not support the putative benefits. 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".

Another example of discordance between the observational associations and single-nutrient intervention by beta-carotene dispelled the notion that high-dose supplements would 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.

Folic acid:

In 1991, a large-scale study concluded that folate supplements do indeed reduce risk of neural tube defects in newborns. This led to fortification of flour and other dietary grains. A general reduction of homocysteine levels and an increase in folate levels resulted.

Epidemiological and clinical data suggest that elevated plasma homocysteine levels are associated with increased risk of cardiovascular disease. Folic acid reduces homocysteine levels. In 1999, authors concluded that... "Higher folic acid intake, by reducing homocysteine levels promises to prevent atherosclerotic vascular disease". However, the relationship between diet and plasma homocysteine is complex, and does not rely solely on folate status.

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. Others studies have warned that high does of folate may interfere with B12 metabolism and thus increase cognitive decline. Supplemental folic acid can precipitate vitamin B12 dementia in patients who have minimal B12 levels.

"A final assessment . . . awaits the results of ongoing placebo-controlled intervention trials."

Although observational data are valuable in identifying areas in which to conduct intervention studies, they should not be used to draw premature conclusions.

Good data suggest that certain dietary and lifestyle patterns are associated with decreased risk of chronic disease. However, providing nutrient supplementation to mimic these effects has failed to result in the efficacy that was originally anticipated.

There remain, however, some strong reasons to make targeted recommendations for use of specific supplements:

1) Folic acid to prevent neural tube defects.
2) Vitamin B12 (high dose) in the elderly who often have atrophic gastritis and do not absorb food B12 adequately.
3) Vitamin D and calcium intakes are often deficient in Americans of all ages, especially in older persons. Supplements are the most practical way to meet the RDAs.

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

JAMA July 20, 2005; 294: 351-58 "Special Communication", first author Alice J Lichenstein, Tufts University, Boston, Mass

Comment:

Our pharmacy shelves are replete with stocks of individual vitamins. Vitamin E is a favorite.

Some examples from my cursory examination:

	Content PER tablet	Times RDA
Vitamin A	8000 IU	2

Vitamin E	1000 IU	25
Vitamin B1	100 mg	66
Vitamin B2	100 mg	59
Vitamin C	500 mg	8
Vitamin B6	50 mg	25
Vitamin D	400 IU	1
Vitamin B12	500 mcg	83
Folic acid	800 mcg	2

Although the costs are generally modest, costs will far exceed that of a daily multivitamin supplement containing up to 100% of the RDAs of all. Not only are the above a waste of money, but some of them may be toxic.

I do not believe the authors were talking about the daily use of supplements containing the RDAs of vitamins and minerals. I do not believe the authors of the article 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.

Note the possible benefits of daily low-dose supplements—containing up to 100% of RDA:

1) Vitamin D 400 IU: Many persons are deficient. In low dose, daily use is very safe. This, I believe should be supplemented by added calcium.
2) Folic acid 400 mcg: Already is considered essential to prevent neural tube defects. I would not yet discount studies relating lowering of homocysteine levels to benefit by reducing risk of cardiovascular disease.
3) Vitamin B12 6 mcg: Crystalline B12 is absorbed in elderly persons with atrophic gastritis who lack ability to absorb food B12. This would negate the possible harmful effects of folate in obscuring neurological effects of B12 deficiency. However, a dose of 6 mcg is not sufficient since only about 1% of cyanocobalamin is absorbed. This may be one instance where a much higher dose (eg 1000 mcg) will be beneficial. The 6 mcg dose adds nothing except to look good on the label.

No one argues against a balanced diet. The problem is—most Americans simply will not change to, or maintain, a more healthful diet to ensure adequate nutrient intakes.

I believe daily supplements containing the RDAs of vitamin D and folic acid are helpful because the diets of many Americans are deficient. I am not willing to give up on the putative benefits of folic acid on lessening risk of cardiovascular disease by decreasing levels of homocysteine.

Vitamin B12 as an individual supplement is an exception in some circumstances. Some elderly persons who lack the ability to absorb B12 from food will absorb enough from high doses of crystalline cyanocobalamin (1 mg) to maintain a normal blood level. The RDA amount is not sufficient in these individuals.

Admittedly, most of the contents of the daily supplement are a waste. The RDAs of Vitamin D and folic acid are likely to be beneficial.

At a cost of 3 cents a day, I will continue to take my supplement in addition to trying to maintain a healthy diet.

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

7-5 OPERATING CHARACTERISTICS OF PROSTATE-SPECIFIC ANTIGEN

In 2001, approximately 75% of men in the USA reported they had previously undergone PSA screening; 54% reported regular screening.

Currently men in the USA have a 17% lifetime chance of PC diagnosis, while the lifetime risk of prostate cancer death is 3%.

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 with cancer being missed.

Fewer men without cancer being falsely considered positive for cancer and subject to biopsy.

B. Setting the cutpoint low will result in:

More men with cancer being diagnosed.

More men without cancer being falsely considered as having cancer and subject to biopsy.

STUDY

1. This present study is an extension of the Prostate Cancer Prevention Trial which entered over 18 000 healthy men age 55 and older (mean age = 62) in 1994-2003.
    A. At baseline, no one was considered to have PC. All had normal digital rectal examinations. All had a PSA under 3.0
    B. Subjects were followed for up to 7 years with annual PSA determinations and rectal examinations. If the PSA exceeded 4.0 and/or the digital rectal examination was abnormal, a biopsy was recommended.
    C. After 7 years, an end-of-study biopsy was recommended in all cancer-free subjects regardless of PSA values and results of digital rectal examination.
2. At the end of the study, the authors calculated the sensitivities and specificities of 9 PSA levels arbitrarily set at increasing cutpoints from 1.1 to 10.1. From these they plotted a receiver operating characteristic **(ROC)** curve.
3. Main outcome measures = operating characteristics of PSA for PC detection, including sensitivity, specificity, and the ROC curve.

RESULTS

1. Of the participants who underwent biopsy (n = 5587), 22% (n = 1225) had PC.

2. Of the 1213 PCs with Gleason scores recorded, 21% were Gleason grade 7 or greater, and 5% were Gleason grade 8 or greater.

3. Determining a clear-cut rule for prostate biopsy from these results would be challenging.

A. *Sensitivities*: various cutpoints of PSA in men who have PC

PSAs for men *with* PC	True + %	False negative %
1.1	83	17
2.6	40	60
4.1	20	80
10.1	1	99

According to these figures, for every 1000 men *with* prostate cancer:

830 (83%) had a PSA 1.1 and above; and 170 (17%) had a PSA less than 1.1

400 (40%) had a PSA 2.6 and above; and 600 (60%) had a PSA less than 2.6

200 (20%) had a PSA 4.1 and above; and 800 (80%) had a PSA less than 4.1

10 (1%) had a PSA 10.1 and above; and 990 (99%) had a PSA less than 10.1

B. *Specificities* of various cutpoints of PSA in men who do *not* have PC

PSAs for men *without* PC	True negative %	False positive %
1.1	40	60
2.6	81	19
4.1	94	6
10.1	99	1

According to these figures, for every 1000 men *without* prostate cancer:

600 (60%) had a PSA 1.1 and above; and 400 (40%) had a PSA less than 1.1

190 (19%) had a PSA 2.6 and above; and 810 (81%) had a PSA less than 2.6

60 (6%) had a PSA 4.1 and above; and 940 (94%) had a PSA less than 4.1

10 (1%) had a PSA 10.1 and above; and 990 (99%) had a PSA less than 10.1

3. The area under the ROC curve for prostate cancer vs no prostate cancer (true positive rate on the vertical axis vs false positive rate on the horizontal axis charted at all cut-points) was 0.678. (*Not very discriminating. An area of 0.500 would indicate no ability to diagnose PC. As many subjects with PC would have a positive test as those without PC. The test would be useless. RTJ .)*

DISCUSSION

1. Use of PSA for detection of early PC with the commonly recommended cut-point of 4.0 may result in delayed detection of PC. “It will be a challenge to the medical community to change the long-held notion that there is a ‘normal’ PSA.” There is a continuum of risk and no clearly defined PSA cut-point at which to advise biopsy.

2. Many PCs, even those with high-grade, are missed even at low levels of PSA. This . . .”Could explain the discrepancy between the rate of PSA screening and the [*lack of*] change in prostate mortality over the past 15 years”.

3. The delay in diagnosis of high-grade tumors until PSA levels exceed the current threshold of "normal" values could also explain why there is a 35% risk of subsequent treatment after radical prostatectomy, presumably due to disease recurrence.
4. Lowering the PSA threshold would have 2 consequences: 1) increased biopsy rates; and 2) the possibility of increased detection of biologically inconsequential cancers.
5. An inherent property of all screening tests is that they disproportionately enhance the detection of slower-growing cancers because more-aggressive tumors have a greater likelihood of becoming clinically apparent between screenings. While lowering the PSA threshold is likely to increase the detection of such aggressive tumors at an earlier stage, the unavoidable tradeoff is the increased detection of biologically inconsequential cancers.
6. Patients, in concert with their physicians will ultimately have to weigh the sensitivity-specificity trade-offs, in combination with the uncertain natural history of the disease, to determine whether further evaluation with a biopsy is appropriate.

JAMA July 6, 2005; 294: 66-70 Original investigation, first author Ian M Thompson, University of Texas Health Sciences Center, San Antonio

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A Helpful Overview

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

In the past few years, many studies have reported on the benefit/harm-cost ratio of hormone replacement therapy and other interventions for treatment of menopausal symptoms. Confusion remains. This article permits us to step back and gain an overlook. RTJ

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. Effective long-term as well as short-term safe and effective therapy is needed.

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.

Numerous alternatives have been suggested. But, assessment of the quality of evidence about the safety and effectiveness of different treatments has been difficult.

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.

Hormone replacement therapy (HRT):

Evidence-based guidelines for HRT for menopausal symptoms:

Indications:

Systemic HRT for moderate to severe vasomotor symptoms (hot flashes).

Systematic HRT for night sweats, insomnia, poor sleep quality (indirectly improving wellbeing and symptoms of depression).

Urogenital symptoms (vaginal estrogen if systemic HRT is not taken).

General advice:

Benefits should be offset against risks. For otherwise healthy women, benefits of short term HRT are likely to outweigh risks. Women who take HRT for longer than 5 years should be told about potential risks

Advice should be individualized.

Lifestyle and alternative therapies should be discussed.

Treatment should be at the lowest effective dose.

Potential risks:

Breast cancer:

The absolute risk of breast cancer is small, but it is the greatest concern. Risk probably increases after use of combined E + P after 5 years. There may be no risk for estrogen-alone. Women with a history of breast cancer should not take HRT.

Coronary heart disease:

No evidence of benefit in reducing risk. HRT should not be given for primary or secondary prevention. It should generally be avoided in women at increased risk for CVD. There may be a slight *increase* in risk in women taking combined E + P (7 per 10 000 per year). There may be a slight *reduction* in risk in women taking estrogen alone (5 per 10 000 per year).

Stroke

HRT may be associated with increased risk of ischemic stroke. (8 per 10 000 women taking E + P vs 12 in those taking estrogen alone).

Venous thromboembolism

VTE is the major risk factor in the first 5 years of use of both estrogen-alone and E + P. Oral HRT increases risk. (18 per 10 000 women per year for combined E + P; 7 per 10 000 per year for estrogen alone).

Osteoporosis

HRT is not recommended as first line therapy. When used for treatment of menopausal symptoms, there may be an added benefit in reducing risk of osteoporotic fractures.

Although the beneficial effects of estrogen therapy on the skeleton are not reduced by increasing age, once treatment stops, bone loss resumes.

Endometrial cancer

Estrogen alone increases risk. Combined HRT should be used in women with a uterus.

Dementia

No role for HRT

Selective serotonin reuptake inhibitors

Slow-release venlafaxine [*Effexor*] might be effective in the short term (<12 week).

Life style changes

Increased exercise, achieving a normal body mass index, and discontinuing smoking are reasonable, since these changes will benefit long-term health.

Alternative and complimentary therapies

There is not enough evidence that any of the complimentary therapies available are any better than placebo for vasomotor symptoms. Few safety data exist.

Lancet July 30, 2005; 366: 409-21 Review article, first author Martha Hickley, University of Western Australia, Subiaco.

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

7-7 UNDERDIAGNOSIS OF RIGHT-BRAIN STROKE

"Recognizing a stroke should be relatively simple, right? Wrong!"

A study in this issue of Lancet[1] 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.

Right-sided stroke was often overlooked. Why?—The perceived severity or significance of symptoms is the dominant factor.

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.

There are deficiencies in knowledge about the signs and symptoms of stroke. Non-language deficits in particular may get little mention. Even complex clinical severity rating scales, such as the National Institutes of Health Stroke Scale systematically emphasize deficits associated with left-hemisphere lesions. Imaging studies show that patients with right hemisphere stroke can have a low NIHSS score despite substantial infarct volume.

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. Patients with right-hemisphere events are underrepresented in major trials of endarterectomy for symptomatic carotid stenosis.

The effect on cognitive impairment due to right-hemisphere dysfunction on day-to-day living is no less than that of left-hemisphere dysfunction. Important unrecognized consequences include: influences on relationships, maintenance of employment, appropriate advice about driving, and access to rehabilitation.

Imaging by MRI is valuable when the clinical picture is uncertain. Up to half of patients with clinical TIA will have positive images.

Lancet July 30, 2005; 366: 349-50 Commentary by John N Fink, Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand.

1 "Difference In Recognition Of Right And Left Hemispheric Stroke" Lancet July 30, 2005; 366: 392-93, first author Christian Foerch, Johan Wolfgang Goethe University, Frankford am Main, Germany. This study points out:

Cerebrovascular events are frequently accompanied by characteristic, but different, neuropsychological deficits, depending on the side of the lesion—aphasia due to lesions in the left hemisphere, and neglect (diminished awareness) associated with lesions in the right hemisphere. Self-recognition of symptoms is especially important in patients with TIA.

Most stroke scales emphasize deficits associated with lesions in the left hemisphere. In this study, left-hemisphere TIAs were recorded in over 2100 patients vs 1300 right-hemisphere TIAs

The probable explanation is that symptoms attributable to cerebral ischemia are more noticeable if language or right hand function is affected. Both of these functions are controlled by the left hemisphere.

In contrast, right-hemisphere lesions are associated with a reduction in awareness of neurological deficits (neglect). They are therefore perceived by patient and physician as being less severe, or are not identified at all as stroke symptoms.

The asymmetry of symptoms and awareness (right vs left hemisphere) is most striking in individuals with mild-to-moderate defects. This lends support to the effect of awareness-related factors. The asymmetry does not apply to cerebral hemorrhage, which causes more severe symptoms.

Selection effects might lead to fewer prophylactic interventions in patients with right-hemisphere lesions.

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

7-8 SCREENING FOR OSTEOPOROSIS

Osteoporosis is a favored subject in the current literature. This article presents details about recommendations for screening. I abstracted a few highlights. RTJ

Fewer than 1/3 of patients who have had fragility fractures are appropriately evaluated and treated for osteoporosis. The rates of diagnosis are even lower for those who have not yet had a fracture.

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.

Factors other than T-score which indicate elevated risk include: a previous fragility fracture, family history of fracture, low body weight, loss of 5% or more of baseline weight and loss of height, silent vertebral fracture, discontinuation of postmenopausal estrogen therapy, increased tendency to fall, and drugs such as corticosteroids

which increase bone resorption. Indeed, “Any fracture in a postmenopausal woman should prompt consideration of bone-density measurement”.

“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.

“All women should have a measurement of bone mineral density at the age of 65.”

The possibility of osteoporosis *in men* who have a fragility fracture or other risk factors should not be forgotten.

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

NEJM July 14, 2005; 353: 164-71 “Clinical Practice”, review article by Lawrence G Raisz, University of Connecticut Heath Center, Farmington.

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 might predict CHF and provide the link between obesity and CHF.

Conclusion: Insulin resistance (recorded in a number of ways, including the 2-hour glucose level measured on an oral glucose tolerance test) predicted incidence of CHF independently of established risk factors.

STUDY

1. The Uppsala Longitudinal Study of Adult Men, a prospective, community-based observational study, followed 1187 men for a mean of 9 years. All were over age 70 at baseline. All were free of CHF and valvular disease.
2. Analyzed a number of variables reflecting insulin sensitivity together with established risk factors.
3. Main outcome measure = first hospitalization for CHF.

RESULTS

1. One hundred and four men of 1187 developed CHF over 9 years. As expected, prior myocardial infarction, hypertension, diabetes, left ventricular hypertrophy, and current cigarette smoking were significant risk factors for CHF.
2. After adjusting for presence of diabetes at baseline, 5 indicators of insulin resistance remained significant predictors of subsequent CHF: clamp glucose disposal rate; fasting insulin levels; fasting proinsulin levels; BMI; waist circumference: and *2-hour glucose level.*
3. 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.
4. After adjusting for diabetes, fasting glucose levels were not predictive.

DISCUSSION

1. Insulin resistance, measured by the 2-hour glucose level on the oral glucose tolerance test, predicted incidence of CHF independently of diabetes, truncal and overall obesity, and other risk factors.
2. The previously described association between obesity and CHF may be mediated, in part, by insulin resistance.
3. The authors cite a number of possible mechanisms for the association. (page 339).

CONCLUSION

Insulin resistance (as determined by the 2-hour glucose levels) independently predicted incidence of CHF in this group of elderly men.

JAMA July 20 2005; 334-41 Original investigation, first author Erik Ingelson, Uppsala University, Sweden

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No Beneficial Effect

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

Echinacea is widely used as a herbal remedy for the common cold. It was recently endorsed by the WHO for treatment of the common cold. Efficacy studies have produced conflicting results.

A variety of Echinacea products are on the market. This study concerned *E angustifolia* roots. *E angustifolia* is the species originally used by Native Americans in the Midwest.

This study produced 3 different preparations with distinct phytochemical profiles by extraction.

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.

Results: 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.

Conclusion: The results indicate that these extracts, either alone or in combination, do not have clinically significant effects on rhinovirus infection, or on the resultant clinical illness.

The investigators conclude that the burden of proof of effectiveness should now lie with those who advocate this treatment.

NEJM July 28, 2005; 353: 341-48 Original investigation, first author Ronald B Turner, University of Virginia School of Medicine, Charlottesville. (The study was supported by a grant from the National Center for Complementary and Alternative Medicine of the National Institutes of Health)

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. Not until recently has a relation to risk of DM2 been studied. A Dutch study reported that higher consumption of coffee was associated with a lower risk of DM2. [1]

This systematic review examined the association between habitual coffee consumption and risk of DM2.

Conclusion: The review supports the hypothesis that habitual coffee consumption is associated with a substantially lower risk of DM2.

STUDY

1. MEDLINE search through January 2005 identified 9 cohort studies of habitual coffee consumption associated with and risk of DM2. DM1 was excluded.
2. Extracted data on study design, participant characteristics, measurements of coffee consumption, and outcomes adjusted for confounders.
3. Distinguished 4 levels of daily consumption:
   1) Six or more cups
   2) 4 to 5 cups
   3) 1 to 3 cups
   4) No coffee consumption (Reference category)

RESULTS

1. Cohort studies contained a total of over 199 000 subjects. And 8394 cases of DM2.

A. Relative risk of DM2: coffee vs no coffee:	RR	Confidence interval
Level 1)	0.54	0.54-0.78
Level 2)	0.72	0.62-0.83
Level 3)	0.94	0.88-1.01
All levels combined	0.65	

B. One study reported an inverse association between coffee consumption of 6 or more cups daily vs 2 or fewer cups and incidence of *impaired glucose tolerance*. (RR = 0.37)

C. No study reported an association with *impaired fasting glucose.*

D. Two US studies assessed decaffeinated coffee. Consumption of 4 or more cups vs 0 cups was also associated with a reduction in RR of DM2 (0.74 for men and 0.85 for women).

E. Adding sugar and/or cream made no difference.

DISCUSSION

1. These cohort studies support 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 285 to 35% lower risk of DM2.

2. 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.
3. Residual confounding cannot be fully excluded as a potential explanation of findings in observational studies. Observational studies cannot prove causality
4. It is premature to recommend increasing coffee consumption as a public health strategy.

CONCLUSION

This systematic review supports the hypothesis that habitual coffee consumption is associated with a substantially lower risk of DM2.

JAMA July 6, 2005; 294: 97-104 Original investigation, first author Rob M van Dam, Vrije Universiteit, Amsterdam, Netherlands.

1 Lancet 2002; 360: 1477-78