

PRACTICAL POINTERS

FOR PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JANUARY 2006

FINAL QUESTION—ARE YOU AT PEACE?

YOUR PATIENT WITH ATRIAL FIBRILLATION HAD MASSIVE BLEEDING WHILE ON WARFARIN. WOULD YOU BE RELUCTANT TO PRESCRIBE WARFARIN FOR A SECOND PATIENT PRESENTING WITH AF?

THE PROMISE OF NEW ROTAVIRUS VACCINES

HIGH MIDLIFE BMI INCREASES RISK OF HOSPITALIZATION AND MORTALITY IN OLDER AGE

WATCHFUL WAITING VS REPAIR OF INGUINAL HERNIA IN MINIMALLY SYMPTOMATIC MEN

VITAMIN D INSUFFICIENCY STATE DURING PREGNANCY IMPACTS BONE DENSITY IN THE CHILD

ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN WOMEN AND MEN

HIGH FRUIT AND VEGETABLE CONSUMPTION ASSOCIATED WITH REDUCED STROKE

POPULATION-WISE, METABOLIC SYNDROME IS A MUCH GREATER RISK FACTOR FOR STROKE THAN DIABETES

HELICOBACTER ERADICATION marginally REDUCES PREVALENCE OF DYSPEPSIA

CDC RECOMMENDS NEW TUBERCULOSIS BLOOD TEST. QuantiFERON-TB Gold

MAGNET THERAPY—NO EVIDENCE OF VALUE

VENOUS THROMBOEMBOLISM—18 CLINICAL POINTS

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This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

***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 contents of articles in much more detail.

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

JANUARY 2006

One Simple Non-Threatening Question To Probe Spiritual Concerns At The End Of Life.

1-1 ARE YOU AT PEACE?

Acknowledging the importance of emotional and spiritual issues at the end of life is an important component of compassionate and comprehensive palliative care. Some physicians may question the appropriateness of their role in probing patients' spiritual distress, as well as the practicality of addressing such issues in the time-limited setting of usual practice. Yet, a patient's spirituality often influences treatment choices, and endows personal resources during serious illness.

Respondents (n = 248) completed several questionnaires which assessed quality-of-life at the end of life. All had advanced cancer, severe heart failure, severe COPD, or renal failure.

Examined distributions of several religious and non-religious alternative wordings—"at peace with God"; "at peace with my personal relationships"; "at peace with myself". To promote inclusiveness, the final wording was the simple question--"Are you at peace?"

Ninety % agreed with the importance of "coming to peace with God". Ranked equally, and as most important, "freedom from pain" and "being at peace with God". Items measuring peacefulness correlated highly with having a chance to say goodbye; with making a positive difference in the lives of others; giving others gifts and wisdom; sharing deepest thoughts; and having a sense of meaning in life.

Feeling at peace was strongly correlated with emotional and spiritual well-being.

"The results of this study suggest that the concept of patients' sense of being at peace may be a point in which to initiate a conversation about emotional and spiritual concerns in a non-threatening manner."

Spirituality has been defined as the search for the ultimate meaning and purpose of life. This often involves a relationship with the transcendent. Emotional and spiritual well-being underpin the broadly worded construct of "being at peace".

Patients' end-of-life experiences are constructed by multidimensional layers of relationships of physiological and biochemical processes, cognitive understandings, interpersonal connections, and bonds to the transcendent.

Asking patients about the extent to which they are at peace may offer a gateway to assessing spiritual concerns. Although these issues may be heightened at the end of life, it may influence medical decisions throughout a lifetime of care.

Read the original!

Being at peace is important at all phases of life. Asking a non-terminal 30-year old if he is at peace may lead to introspection and benefit.

Once Burned; Twice Shy

1-2 IMPACT OF ADVERSE EVENTS ON PRESCRIBING WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

This study quantified the influence of physicians' experiences of adverse events in patients for whom they had prescribed warfarin on their subsequent prescribing practices.

Considered patients who experienced severe gastrointestinal bleeding or hemorrhagic stroke while taking warfarin during the 120 days before admission to the hospital. Determined likelihood that the doctor who prescribed the warfarin would prescribe it to the next patient presenting with AF. (If a physician treated a patient with warfarin and the patient had serious bleeding, would this experience influence prescribing warfarin for a second patient who has AF?)

Also considered patients with AF who experienced an ischemic stroke during the preceding 120 days for whom the doctor had *not* prescribed warfarin. Determined the likelihood that the doctor would prescribe warfarin to the next patient with AF who consults him.

Over 500 physicians treated a patient with AF who had major bleeding while on warfarin, and then treated another patient with AF within the next 90 days.

The odds that a physician would prescribe warfarin for a second patient were 21% lower after a first patient experienced bleeding. (Some physicians were reluctant to again prescribe warfarin.)

Conversely, there were no significant changes in warfarin prescribing after a patient had a stroke while *not* taking warfarin. (Physicians were *no more likely* to prescribe warfarin for a second patient with AF despite this adverse outcome.)

“Doctors are neither passive recipients of, nor simple conduits of, clinical evidence.” We conduct an “inner consultation” with evidence, analyzing it in both a logical and intuitive way. In doing so, we are more likely to recall events which are more easily recalled. And the “chagrin factor” tends to make doctors avoid actions that cause them hassle.

Patients conduct similar internal consultations, adding the experience of a consultation to their previous intellectual and emotional understanding of illness.

“Statistical experience” and “clinical experience” guide consultations. These are not enough to clarify the dynamic interaction between patient and doctor. A third dimension is “personal significance”, a concept that captures the reciprocity of the evaluation and interpretation of a new idea by a doctor and patient together. At stake here is something quite profound, and poorly accepted within the medical community—the personal participation of the knower in all acts of understanding. Comprehension is neither an arbitrary nor passive act. It requires tacit skills of judgment.

“In medical consultations there are two participants, both personally knowing, both passionately participating, but from different perspectives, different “somewheres”. The outcome of their interaction in the form of clinical decision is an emergent property of two ways of knowing: biomedical and biographical.

The study illuminates this murky area and provides convincing evidence that within each doctor, these two ways of knowing compete for influence.

Patient's prior experience plays a major role in acceptance and compliance with therapy. This study points out that doctors respond to prior experience as well.

Patients and doctors consider adverse events due to commission more seriously than adverse events due to omission. When a patient with AF bleeds while he is taking warfarin, warfarin and the doctor who prescribes it get the blame (whether at fault or not). When the patient experiences an ischemic stroke, there is doubt about whether warfarin would have prevented it. (It may not have prevented it.) Warfarin and the doctor would less likely be blamed.

Prior experiences and "personal knowledge" do indeed influence subsequent practice.

Do not patients' "personal beliefs" have a much greater influence on their acceptance and compliance with treatments? Eg, belief in a placebo; belief in many "alternative medications"; belief in the advertisements of drug companies; beliefs based on ethnicity and family lore, belief in anecdotal experiences and advice of family and friends; belief in health advice given in the press, on TV, and in the Internet.

Do not physicians' "personal beliefs" influence the treatments they advise to a greater extent than evidence-based therapy? Eg, belief in the latest advertised drug; belief in the suggestions of colleagues given in curbside consultations; belief based on their educational experiences and past training which have become outdated; belief in anecdotal evidence from small, unsubstantiated observational studies, and even "alternative medicine".

"The Time For A Rotavirus Vaccine May Have Finally Arrived."

1-3 THE PROMISE OF NEW ROTAVIRUS VACCINES

This issue of NEJM, reports promising results from large clinical trials of two new oral vaccines:

- 1) *Rotateq* (Merck) is a penta-valent vaccine based on a bovine strain that contains 5 human-bovine viruses. It is naturally attenuated for humans. The bovine virus grows less well in the human intestine, so the aggregate titer required to immunize is greater. Three oral doses are required, with at least a month between doses. The vaccine strains are infrequently shed in the stool. It is not broadly cross-protective against other serotypes.
- 2) *Rotarix* (Glaxco Smith-Kline) is an attenuated, mono-valent vaccine derived from the most common human retrovirus strain. It is given in two doses one month apart.. It replicates well in the gut, and is frequently shed (like natural infections) in the stool. It cross-protects against most other serotypes.

Both vaccines demonstrate impressive efficacy against severe disease (85% to 98%) .

Both vaccines demonstrated a reassuring safety profile. There was no significant difference in the rate of intussusception between the vaccine and placebo

This may be a giant step forward.

I do not understand the pathophysiology of the increased risk of intussusception reported in studies of the old vaccine (1999). Anyone out there who can suggest a connection?

Obesity Per Se In Middle Age Is A Risk Factor For CVD And Diabetes In Older Age

1-4 MIDLIFE BODY MASS INDEX AND HOSPITALIZATION AND MORTALITY IN OLDER AGE

Does excess weight in middle life confer higher risk of cardiovascular disease (CVD) and diabetes in older age? Does a high body mass index (BMI) *per se* confer risks over time independent of its effect on BP and lipids?

This prospective study, begun in 1967-73, entered over 17 000 subjects age 31 to 64 (mean age = 45). All were free of coronary heart disease (CHD), diabetes, and major electrocardiography abnormalities.

At baseline, classified CVD risk as: 1) Low risk: BP < 120/80; total cholesterol < 200; and non smoking. 2) Moderate risk: BP 121-139/81-89; total cholesterol 200-239; non smoking; 3) Higher risk groups included subjects with any 1, 2, or 3 risk factors (BP > 140/90; total cholesterol > 240; and current smoking.

BMI categories: normal 18.5-24.9; overweight 25-29.9; obese 30 and over.

At baseline, only 7% of the entire cohort over 17 000 were at low risk. And only 4% were at both low risk and normal BMI.

Low risk group: (normal BP, normal cholesterol, and non-smoking)

Rate after age 65 per 1000 persons	CHD mortality	Hospitalization for CHD	Diabetes
Normal BMI	30	40	44
Overweight	42	49	110
Obese	44	112	265

Moderate risk group: (moderately elevated BP and cholesterol, non-smoking)

Rate after age 65 per 1000 persons	CHD mortality	Hospitalization for CHD	Diabetes
Normal BMI	42	53	60
Overweight	49	95	122
Obese	89	104	240

In higher risk groups (including smokers) as BMIs rose, outcomes rose in a similarly graded fashion. Within each risk stratum, the risk was higher for overweight and obese persons than for normal weight persons.

Non-smoking individuals with normal BP and normal total cholesterol who are obese in middle age have a higher risk of hospitalization and mortality from CHD and diabetes in older age than those whose weight is normal in middle age. This risk relationship extends to those with higher cholesterol and BP and to those who smoke.

Is Watchful Waiting A Safe And Acceptable Option?

1-5 WATCHFUL WAITING VS REPAIR OF INGUINAL HERNIA IN MINIMAL SYMPTOMATIC MEN

Patients often delay hernia repair until pain or discomfort occurs.

Surgical repair, while generally safe and effective, carries a long-term risks of recurrence, pain, and discomfort.

For minimally symptomatic men, the usual basis for recommending surgery is prevention of incarceration and strangulation. These are rare events.

Is deferring surgical repair a safe and acceptable option for men with minimally symptomatic inguinal hernias?

This study entered 724 men with inguinal hernias. (mean age = 57.) All were asymptomatic or had minimal symptoms. (No discomfort which limited usual activity. No difficulty in reducing the hernia.)

Randomized to: 1) watchful waiting, or 2) tension-free repair surgery.

What happened to the surgery group? 1) Intraoperative complications in 3 patients: wound hematoma requiring return to operating room; postanesthetic hypotension; and ilioinguinal nerve injury. 2) Postoperative complications in 22%: hematomas; urinary tract infections; wound infections; orchitis; urinary retention; postoperative bradycardia; deep venous thrombosis; postoperative hypertension. 3) Overall, at 2 years, discomfort was reduced slightly, but pain limited usual activities in 2%. 4) 3% of hernias recurred. 5) More than 97% were satisfied with the treatment they received.

What happened to the watchful waiting group? 1) Pain limiting usual activities occurred in 5% 2) Cross-over to surgery 23% at 2 years, 33% at 5 years (mainly due to increased pain) 3) Complications: incarceration, bowel obstruction rare, ~ 2 in 1000 patient-years. 4) More than 97% were satisfied with the treatment they received. Overall, they experienced a slight lessening of discomfort over 2 years.

A strategy of watchful waiting (over 2 years) is a safe and acceptable option for men with minimally symptomatic inguinal hernias.

The study does not include symptomatic hernias.

Natural history studies are valuable for informing patients when they ask—“What is going to happen to me?” “What should I do about it?” This study gives some indication of the outcomes of surgery vs WW. However, the observation period lasted a relatively short time in the life of a hernia.

Discussions between physician and patient about likely outcomes will aid negotiations between the two and enable the patient to make informed decisions. Whether to have a non-troublesome hernia repaired is an intensely personal decision. The decision will depend on many factors, two of which are 1) the duration of the hernia. 2) the age of the patient.

I believe patients whose hernias have been present for a long time and have remained non-troublesome will be more likely to avoid surgery. Recently developed hernias may cause more alarm and would lead the patient to seek a surgical consultation and tilt toward surgery.

A young man, because of his long life span, may be more accepting of surgery. He may be less willing to accept worry, bother, and anxiety over years. His hernia will be more likely to enlarge with time, and he will be more likely to develop pain and complications. (Note the study lasted only 2 to 4 years.)

An old man may be less willing to accept surgery because his life span is shorter. He is more likely to have co-morbidity and increased risk of surgical complications.

Another important consideration: Availability of an experienced surgeon with a proven track record of fewer perioperative complications and recurrence of the hernia.

The main message of this study is to point out to middle-aged men with asymptomatic hernias that they may safely defer surgery at least for several years.

Vitamin D Deficiency During Pregnancy Is Associated With A Deficit In Bone-Mineral Accrual In The Children

1-6 MATERNAL VITAMIN D STATUS DURING PREGNANCY, AND CHILDHOOD BONE MASS AT AGE 9 YEARS

This study tested the hypothesis that low vitamin D levels in women during pregnancy have persisting effects on bone mass in their children.

Measured serum 25(OH)-vitamin D at a mean of 34 weeks of pregnancy. Classified vitamin D levels as being deficient if the serum level was under 11 ug/L and as insufficient if level was 11-20. Normal > 20.

Nine years later, measured children's' bone mineral content (**BMC**) and areal bone mineral density (**BMD**) by dual energy X-ray absorptiometry.

Eighteen % of women had insufficient vitamin D levels, and 31% had deficient levels. (Half of all women.)

At age 9, children of mothers with reduced concentrations of vitamin D had reduced whole-body and lumbar spine bone mass compared with children of mothers with normal serum vitamin D.

Maternal UV exposure during late pregnancy varied by season and predicted serum concentrations of D. (Mean levels in winter = 14 ug/dL; summer = 30 ug/dL). Children of mothers whose third trimester occurred in summer had higher BMD than those whose third trimester occurred in winter.

Use of vitamin D supplements predicted maternal concentrations of vitamin D. (In this cohort, only 15% of mothers took supplements containing vitamin D.) Their children at age 9 had significantly greater whole-body BMD than children of non-users.

“Our results suggest that vitamin D insufficiency (or deficiency) during late pregnancy is associated with a deficit in bone-mineral accrual in their children which persists to age 9.”

Vitamin D deficiency and insufficiency were common in these pregnant women. Supplementation could lead to enhanced peak bone mineral accrual in their children, and lead to reduced risk of fragility fracture later in life.

Can these deficient children catch up as they grow older? I believe good nutrition including adequate calcium intake and vitamin supplementation (especially D) will allow catch up.

Vitamin D deficiency is highly prevalent in developed countries in northern latitudes in the winter. I believe it is by far the most common vitamin deficiency. Supplements are required life long.

Prevents Stroke In Women; MI In Men

1-7 ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN WOMEN AND MEN A Sex-Specific Meta-Analysis Of Randomized Controlled Trials

The American Heart Association has reported aspirin therapy is effective in *primary* prevention of coronary heart disease in adults of both sexes who are at increased risk. The AHA guidelines on primary prevention recommend low-dose aspirin in women whose 10-year risk of a first coronary event exceeds 20%, and consideration for those with a 10-year risk of 10% to 20%.

This meta-analysis determined if benefits and risks of aspirin therapy in primary prevention differed between men and women.

In absolute terms:

A. Women: Aspirin for an average of 6 years resulted in a benefit of approximately 3 cardiovascular events and 2 strokes prevented per 1000 women. No effect on MI or cardiovascular mortality.

B. Men: Aspirin for an average of 6 years resulted in a benefit of approximately 4 cardiovascular events prevented per 1000 men. MI was significantly reduced (absolute benefit of 1 MI per 125 men treated). No statistically significant reduction in stroke.

Major bleeding (mainly GI) occurred over 6 years in 1 of every 400 women and 1 in 300 men.

(2.5 major bleeds per 1000 women and 3 per 1000 men.)

The benefits of aspirin for primary prevention do not approach the substantial benefits in secondary prevention.

When negotiating a treatment plan with women who may be interested in aspirin for primary prevention of CVD, clinicians may tell them the benefit over 6 years in preventing ischemic stroke is 1 in 500. The risk of major bleeding is 1 in 400 .

Men may be told the benefit over 6 years in preventing MI is 1 in 150. And the risk of major bleeding is 1 in 300.

Note that these benefit and harm effects in this study occurred in persons considered healthy.

Do the benefits outweigh the harms? In this study, benefits and harms balanced about equally.

Individuals may decide for themselves after being fully informed. It depends on an estimation of the risk of CVD in each individual. In individuals at higher risk, aspirin for primary prevention may be associated with greater benefit.

Caution when prescribing primary prevention aspirin in patients with hypertension. Hypertension is the major risk for hemorrhagic stroke. Aspirin may be more dangerous in patients with hypertension because of its association with hemorrhagic stroke. BP should be well-controlled before aspirin is prescribed for primary prevention.

“A Major Modifiable Risk Factor” Eat Five or More Fruits and Vegetables Daily

1-8 FRUIT AND VEGETABLE CONSUMPTION AND STROKE

Epidemiological studies suggest that increased consumption of fruits and vegetables may be associated with reduced risk of stroke. The extent of the association is uncertain.

This meta-analysis assessed the relation quantitatively.

. Literature search entered 8 studies which met inclusion criteria. (Over 257 000 individuals)

Determined frequency of fruit and vegetable intake and correlated it with frequency of incident stroke.

Grouped consumption into 3 categories: 1) less than 3 servings daily; 2) 3 to 5 servings daily, and 3) more than 5 servings daily. The standard serving was 0.5 cup.

Average follow-up = 13 years

Relative risk of stroke:

Less than 3 servings	1.00
3 to 5 servings	0.89
More than 5	0.74

Fruit and vegetables had a protective effect on both ischemic and hemorrhagic stroke.

Increased fruit and vegetable intake in the range commonly consumed (over 5 servings daily) was associated with reduced risk of stroke.

The Population Impact Of The MetS Is Much Greater.

1-9 METABOLIC SYNDROME COMPARED WITH TYPE 2 DIABETES AS A RISK FACTOR FOR STROKE. *The Framingham Offspring Study*

This study compared the risk of stroke in patients with DM2-alone, and with MetS-alone. Estimated the population-attributable risk of stroke associated with each.

Over 10 years, the relative risk (RR) of stroke of persons with MetS-alone (compared to those without either DM2 or the MetS) = 2.10. The RR of stroke in persons with DM2-alone was 2.5.

The prevalence of the MetS-alone in the general population was much greater than prevalence of DM2-alone. Consequently, the population-attributable risk of stroke associated with the MetS-alone was larger than the risk of stroke associated with DM2. This was despite the higher RR of stroke associated with DM2-alone

Hyperinsulinemia and insulin resistance are accepted as prominent features of MetS. This suggests that, like impaired glucose tolerance and impaired fasting glucose, MetS may signal a prediabetic state. In the Framingham Heart Study cohort, those with MetS had a 5-fold risk of developing diabetes.

Because MetS is much more prevalent than diabetes, the population impact of the syndrome is greater.

There is a great potential for substantial reductions in stroke risk in people with MetS by treatment of its components.

MetS-alone per 100 000 population Risk of stroke over 10 years Absolute number experiencing stroke
 $22\% \times 100\,000 = 22\,000$ $37/461 = 0.08$ or 8% $22\,000 \times 0.08 = 1765$

DM2 per 100 000 population Risk of stroke over 14 years Absolute number experiencing stroke
 $5\% \times 100\,000 = 5000$ $12/99 = 0.121$ or 12.1% $5000 \times 0.121 = 606$

Thus, stroke occurred more than 3 times as frequently in persons with MetS-alone as with DM2-alone.

One in four adult Americans has MetS. This is a national disgrace. And a massive Public Health problem.

Primary care clinicians bear a great responsibility for guiding patients for prevention, and for treatment once it is established. Clinicians should take the lead by preventing themselves from developing MetS.

Practical Pointers has reported many studies regarding the MetS. To refresh memory, the diagnosis requires 3 of 5 criteria to be present:

- 1) Elevated fasting Blood glucose -- 100-125 mg/dL*
- 2) BP 130/85 or over, or treatment with antihypertension medication*

3) Triglycerides 150 and over

4) HDL-c < 40 in men and < 50 in women

5) Waist circumference > 88 cm in women and > 102 cm in men.

Not all 5 criteria carry equal weight in their association with risk. It is becoming more evident that abdominal obesity may be the greatest culprit. It may carry the greatest potential for development of insulin resistance and hyperinsulinemia.

Eradication Results in Modest Improvements in Patients with Dyspepsia

1-10 IMPACT OF HELICOBACTER ERADICATION ON DYSPEPSIA, HEALTH RESOURCE USE, AND QUALITY OF LIFE; The Bristol Helicobacter Project.

This study determined the impact of a community-based *H pylori* screening and eradication program on incidence of dyspepsia.

A program in 7 general practices screened over 10 500 unselected individuals for *H pylori*. About 25% had dyspepsia. All were screened by a ¹³C urea breath test. 15% were positive. Of these, 1558 were randomized to a 2 week course of 1) eradication treatment with ranitidine bismuth citrate and clarithromycin, or 2) placebo.

Followed for up to 2 years for rates of primary care consultations for dyspepsia to determine if eradication influenced subsequent dyspepsia.

Treatment eradicated 91% of the infections.

Subsequently consulted for dyspepsia over the subsequent 2 years:

Treated group 55/787 = 7/100

Placebo group 78/771 = 10/100

Number needed to treat to avoid one subsequent consultation for dyspepsia = 33.

As the investigators suggest, a trial entering only patients with dyspepsia (rather than patients selected from the general population) would likely yield a greater benefit from treatment. .

*In general, treatment of the infection in patients with functional dyspepsia associated with *H pylori* will relieve the symptom in about 5% to 10%. Whether to test and treat depends on negotiations between patient with dyspepsia and physician. The patient may be told that eradication will cure and prevent peptic ulcer, and prevent some gastric cancers. The downside would be the cost and possible adverse effects of eradication treatment. And the likely increase in resistance of the organism to clarithromycin.*

The study presents a good estimate of the percentage of free-living persons in the community who have the infection (~5% to 10%). I suspect the percentage is similar in the USA.

I suspect that, patients presenting to primary care with prolonged and troublesome dyspepsia will most likely be asked to consider endoscopy first. This would relieve anxiety and lead to more definitive therapy. If the outcome were functional dyspepsia, a “test and treat” approach would lead to reduction in symptoms in a minority of patients.

Fewer False Negative and False Positive Tests

1-11 CDC RECOMMENDS NEW TUBERCULOSIS BLOOD TEST. QuantiFERON-TB Gold

The QuantiFERON-TB Gold in vitro test replaces the older QuantiFERON-TB test which is no longer available. The CDC believes it is more accurate and represents a considerable advance over the original QuantiFERON-TB test. (MMWR December 16, 2005)

The test detects the release of interferon-gamma in fresh heparinized whole blood from sensitized persons when it is incubated with two synthetic peptides which simulate two proteins present in *M tuberculosis*.

No Proved Benefits

1-12 MAGNET THERAPY

Magnetic bracelets, insoles, wrist and knee bands are claimed to be therapeutic. They have been advertised to cure a vast array of ills, particularly pain. A Google search yielded over 20 000 pages, most of which tout healing properties.

Many “controlled” experiments are suspect because it is difficult to blind subjects.

Published research, both theoretical and experimental, is weighted heavily against any therapeutic benefit.

“Patients should be advised that magnet therapy has no proved benefits.” If they insist on using a magnetic device, they could be advised to buy the cheapest. This will at least alleviate the pain in their wallet.”

The powerful placebo effect undoubtedly influences patients’ perception of benefit.

How should primary care clinicians advise magnet-use for their patients? I believe it depends on the circumstances:

1) If patients ask beforehand if magnets provide any benefit, they can be advised that there is no scientific evidence that they benefit. Then let the patients decide.

2) If patients are already using magnets and claim they receive benefit, I would be reluctant to dissuade them. I would let the placebo effect lie unrestrained. There is no associated harm.

1-13 VENOUS THROMBOEMBOLISM—18 POINTS

(Review articles appear frequently. They are interesting and informative, but long and difficult to abstract. This is an experiment. These few points emphasize the important and serve as a memory-jogger. Is it helpful? I would appreciate feed-back. Is it helpful? RTJ)

ABSTRACTS JANUARY 2006

One Simple Non-Threatening Question To Probe Spiritual Concerns At The End Of Life.

1-1 ARE YOU AT PEACE?

Acknowledging the importance of emotional and spiritual issues at the end of life constitutes compassionate and comprehensive palliative care. Some physicians may question the appropriateness of their role in probing patients' spiritual distress, as well as the practicality of addressing such issues in the time-limited setting of usual practice. Yet, a patient's spirituality often influences treatment choices, and endows personal resources during serious illness.

A practical and evidence-based approach to discussing spiritual concerns, such as this investigation presents, may improve quality of care at the end of life.

Previous investigations reported that a positive end-of-life experience is associated with "coming to peace", or "being at peace". For many persons, this sense of peacefulness is related to a religious notion of "being at peace with God"; for others it is a non-theological sense of tranquility. A sense of peacefulness may result from a clear decision about whether to continue chemotherapy, or assurance that pain and symptoms will be managed. In some circumstances, peacefulness may lie in resolving conflicts with a loved one or within oneself; or in the relationship with God. Spiritual reflection on the meaning of illness may precede the subjective experience of peacefulness.

Resolution within the biomedical, psychosocial, and spiritual domains of life often precedes the experience of peacefulness. For some patients at the end of life, attention to issues of peacefulness is related to an antecedent, broader theme of life-closure, or "completion".

This study explored the applicability of the concept of peacefulness, and translated qualitative attributes of what is important at the end of life into quantitative terms.

Conclusion: Asking patients about the extent to which they are at peace offers a brief gateway to assessing spiritual concerns.

STUDY

1. Respondents (n = 248) completed several questionnaires which assessed quality-of-life at the end of life. All had advanced cancer, severe heart failure, severe COPD, or renal failure.
2. Examined distributions of several religious and non-religious alternative wordings "at peace with God"; "at peace with my personal relationships"; "at peace with myself".
3. To promote inclusiveness, the final wording was the simple question--"Are you at peace?"

RESULTS

1. Ninety % agreed with the importance of "coming to peace with God".
2. Ranked equally, and as most important, "freedom from pain" and "being at peace with God".
3. Items measuring peacefulness correlated highly with having a chance to say goodbye; with making a positive

difference in the lives of others; giving others gifts and wisdom; sharing deepest thoughts; and having a sense of meaning in life.

4. Variations in patient responses were not explained by demographic categories, or diagnosis. There was a broad applicability across patients
5. Feeling at peace was strongly correlated with emotional and spiritual well-being.
6. Older patients with advanced illness reported greater levels of peacefulness.

DISCUSSION

1. Dying patients confront complex spiritual concerns that influence the course of their illness, treatments chosen, relationships with loved ones, and overall quality of life.
2. These fundamental issues may not be readily elicited in the usual clinical encounter. Clinicians may struggle to initiate such a discussion in a non-threatening, inclusive manner. How the question is asked is important. “What are your religious or spiritual beliefs?” may evoke mistrust and intrude on personal boundaries, causing patients to question physicians’ motivations.
3. “The results of this study suggest that the concept of patients’ sense of being at peace may be a point in which to initiate a conversation about emotional and spiritual concerns in a non-threatening manner.”
4. Spirituality has been defined as the search for the ultimate meaning and purpose of life. This often involves a relationship with the transcendent. Emotional and spiritual well-being underpin the broadly worded construct of “being at peace”.
5. The concept of asking about peace may be a gateway to larger discussions about values, preferences, and life experiences.
6. Patients’ end-of-life experiences are constructed by multidimensional layers of relationships of physiological and biochemical processes, cognitive understandings, interpersonal connections, and bonds to the transcendent. Asking patients about the extent to which they are at peace may initiate discussions that relieve suffering in all of these dimensions.
7. Indeed, spiritual concerns affect patients’ choices throughout life, not only at end-of-life.

CONCLUSION

Asking patients about the extent to which they are at peace may offer a gateway to assessing spiritual concerns. Although these issues may be heightened at the end of life, it may influence medical decisions throughout a lifetime of care.

Archives Int Med January 9, 2006; 166: 101-105 Original investigation, first author Karen F Seinhauer, V A Medical Center, Durham, NC.

Once Burned; Twice Shy

1-2 IMPACT OF ADVERSE EVENTS ON PRESCRIBING WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

Long-term anticoagulation with warfarin reduces the risk of stroke associated with atrial fibrillation (AF). Only 30%-60% of appropriate patients receive warfarin. Physicians' overestimation the risks of anticoagulation is the most consistently cited explanation for the observed patterns of use.

This study quantified the influence of physicians' experiences of adverse events in patients for whom they had prescribed warfarin on their subsequent prescribing practices.

Conclusion: Physicians' experience with bleeding events can influence their subsequent prescribing habits. Conversely, ischemic stroke occurring in patients with AF who were *not* treated with anticoagulation may *not* affect subsequent prescribing.

STUDY

1. Retrospective cohort study included all patients with AF admitted to the hospital for 1) major hemorrhage while taking warfarin, and 2) patients with AF who experienced an embolic stroke while *not* taking warfarin.
2. Considered patients who experienced severe gastrointestinal bleeding or hemorrhagic stroke while taking warfarin during the 120 days before admission to the hospital. Determined likelihood that the doctor who prescribed the warfarin would prescribe it to the next patient presenting with AF. If a physician treated a patient with warfarin and the patient had serious bleeding, would this experience influence prescribing warfarin for a second patient who has AF?
3. Considered patients with AF who experienced an ischemic stroke during the preceding 120 days for whom the doctor had *not* prescribed warfarin. Determined the likelihood that the doctor would prescribe warfarin to the next patient with AF who consults him.

RESULTS

1. Over 500 physicians treated a patient with AF who had major bleeding while on warfarin, and then treated another patient with AF within the next 90 days.
2. The odds that a physician would prescribe warfarin for a second patient were 21% lower after a first patient experienced bleeding. (Ie, some physicians were reluctant to again prescribe warfarin.)
3. Conversely, there were no significant changes in warfarin prescribing after a patient had a stroke while *not* taking warfarin. (Ie, the physician was *no more likely* to prescribe warfarin for a second patient with AF despite this adverse outcome.)

DISCUSSION

1. "Our findings provide further insight about reasons for underuse of warfarin in the treatment of atrial fibrillation."
2. And more generally, about patterns of care for other similar conditions.

An editorial in this issue of BMJ (p 129-130) by Kieran Sweeney, Peninsula Medical School, Exeter, UK, comments and expands on the study:

The study is a brave attempt to quantify the under-recognized notion of personal knowledge in clinical practice. The researchers wanted to know if a previous adverse event affected subsequent prescribing.

“Doctors are neither passive recipients of, nor simple conduits of, clinical evidence.” We conduct an “inner consultation” with evidence, analyzing it in both a logical and intuitive way. In doing so, we are more likely to recall events which are more easily recalled. And the “chagrin factor” tends to make doctors avoid actions that cause them hassle.

Patients conduct similar internal consultations, adding the experience of a consultation to their previous intellectual and emotional understanding of illness.

“Statistical experience” and “clinical experience” guide consultations. These are not enough to clarify the dynamic interaction between patient and doctor. A third dimension is “personal significance”, a concept that captures the reciprocity of the evaluation and interpretation of a new idea by a doctor and patient together. At stake here is something quite profound, and poorly accepted within the medical community—the personal participation of the knower in all acts of understanding. Comprehension is neither an arbitrary nor passive act. It requires tacit skills of judgment.

“In medical consultations there are two participants, both personally knowing, both passionately participating, but from different perspectives, different “somewheres”. The outcome of their interaction in the form of clinical decision is an emergent property of two ways of knowing: biomedical and biographical.

The study illuminates this murky area and provides convincing evidence that within each doctor, these two ways of knowing compete for influence.

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“The Time For A Rotavirus Vaccine May Have Finally Arrived.”

1-3 THE PROMISE OF NEW ROTAVIRUS VACCINES

Rotavirus disease is the second most common disease in children. It kills approximately half a million children annually in developing countries.

In 1999, the first licensed rotavirus vaccine was withdrawn from the market because of an association with intussusception at an estimated rate of 1 in 10 000. Debate ensued over the possible use of this vaccine in developing countries, where the health benefits, particularly a reduction in deaths from rotavirus clearly exceeded the potential risks of the vaccine. It became evident that the introduction of a vaccine that had been withdrawn from the market in the US was untenable in developing countries. Hope was lost for a vaccine that could have prevented severe diarrhea in children around the world.

This issue of NEJM, reports promising results from large clinical trials of two new oral vaccines:

- 1) *Rotateq* (Merck) is a penta-valent vaccine based on a bovine strain that contains 5 human-bovine viruses. It is naturally attenuated for humans. The bovine virus grows less well in the human intestine, so the aggregate titer required to immunize is greater. Three oral doses are required, with at least a

month between doses. The vaccine strains are infrequently shed in the stool. It is not broadly cross-protective against other serotypes.

2) *Rotarix* (Glaxco Smith-Kline) is an attenuated, mono-valent vaccine derived from the most common human rotavirus strain. It is given in two doses one month apart. It replicates well in the gut, and is frequently shed (like natural infections) in the stool. It cross-protects against most other serotypes.

Both vaccines demonstrate impressive efficacy against severe disease (85% to 98%).

A particularly exciting finding of importance to public health (and to the economic burden of the disease) was the magnitude of reductions in hospitalizations for diarrhea of any cause, a decrease that was greater than the expected, given the number of diagnosed cases of rotavirus. (More of the severe cases of diarrhea leading to hospitalization are probably caused by rotavirus than had been estimated.) The vaccine could translate directly to improved child survival. It would also lower the number of work-days lost by parents caring for their sick children.

A point of great importance—both vaccines demonstrated a reassuring safety profile. There was no significant difference in the rate of intussusception between the vaccine and placebo. Nevertheless, a system of surveillance should be in place after licensure to monitor this complication since hundreds of thousands of infants will need to be immunized before a clean bill of health can be given.

Live oral vaccines must replicate and be processed in the infant's gut in order to induce a good immune response and be protective. Replication is highly dependent on the dose administered and host factors that might neutralize the virus.

“The time for a rotavirus vaccine may have finally arrived.”

1 NEJM January 5, 2006; 354: 11-22 “Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis”, first author Guillermo M Ruiz-Palcacios, Instituto National de Ciencias Medicas y Nutricion, Mexico. Study funded by Glaxco.

2 NEJM January 5, 2006; 354: 23-33 “Safety and Efficacy of a Pentavalent Human-Bovine Reassortant Rotavirus Vaccine”, first author Timo Vesikari, University of Tampere Medical School, Finland. Study funded by Merck.

Obesity Per Se In Middle Age Is A Risk Factor For CVD And Diabetes In Older Age

1-4 MIDLIFE BODY MASS INDEX AND HOSPITALIZATION AND MORTALITY IN OLDER AGE

Obesity adversely affects a large array of health outcomes. It is associated with cardiovascular risk factors, particularly diabetes, hypertension, and dyslipidemia.

Does excess weight in middle life confer higher risk of cardiovascular disease (CVD) and diabetes in older age? Does a high body mass index (BMI) *per se* confer risks over time independent of its effect on BP and lipids?

Conclusion: Obese middle-aged persons who have no other risk factors are at higher risk when they get older than non-obese persons. Obese middle-aged persons who have other risk factors are at greater risk than non-obese persons who have the same risk factors.

STUDY

1. This prospective study, begun in 1967-73, entered over 17 000 subjects age 31 to 64 (mean age = 45).
All were free of coronary heart disease (**CHD**), diabetes, and major electrocardiography abnormalities.
2. At baseline, classified CVD risk as:
 - 1) Low risk: BP < 120/80; total cholesterol < 200; and non smoking.
 - 2) Moderate risk: BP 121-139/81-89; total cholesterol 200-239; non smoking.
 - 3) Higher risk groups included subjects with any 1, 2, or 3 risk factors (BP > 140/90; total cholesterol > 240; and current smoking.
3. BMI categories: normal 18.5-24.9; overweight 25-29.9; obese 30 and over.
4. Determined hospitalizations and mortality from coronary heart disease, cardiovascular disease, or diabetes, starting at age 65.

RESULTS

1. At baseline, only 7% of the entire cohort over 17 000 were at low risk. And only 4% were at both low risk and normal BMI.
2. Low risk group: (normal BP, normal cholesterol, and non-smoking)

Rate after age 65 per 1000 persons	CHD mortality	Hospitalization for CHD	Diabetes
Normal BMI	30	40	44
Overweight	42	49	110
Obese	44	112	265

3. Moderate risk group: (moderately elevated BP and cholesterol, non-smoking)

Rate after age 65 per 1000 persons	CHD mortality	Hospitalization for CHD	Diabetes
Normal BMI	42	53	60
Overweight	49	95	122
Obese	89	104	240

4. In higher risk groups (including smokers) as BMIs rose, outcomes rose in a similarly graded fashion. Within each risk stratum, the risk was higher for overweight and obese persons than for normal weight persons.

DISCUSSION

1. In this cohort, persons who were overweight and obese earlier in life (mean age 45) had significantly higher risks of developing cardiovascular disease and diabetes after age 65 than persons with normal weight who had similar cardiovascular risk factors at baseline.
2. The Framingham Risk Score does not include obesity. This is based on the argument that its effects are “too a large extent through the major risk factors”, and its “unique contribution to CHD prediction can be difficult to quantify”.
3. “Having a normal BMI in young adulthood and middle-age confers significant health benefits at all levels of traditional risk factors.”

4. "Our results underscore the importance of including BMI earlier in life in comprehensive risk assessment."
5. The fact that elevated BMI has additional effects in each risk category has significant public health implications.

CONCLUSION

Non-smoking individuals with normal BP and normal total cholesterol who are obese in middle age have a higher risk of hospitalization and mortality from CHD and diabetes in older age than those whose weight is normal in middle age.

This risk relationship extends to those with higher cholesterol and BP and to those who smoke.

JAMA January 11, 2005; 295: 190-98 Original investigation, first author Lijing L. Yan, Feinberg School of Medicine, Northwestern University, Chicago, IL

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Watchful Waiting (Over 2 Years) Is A Safe And Acceptable Option.

1-5 WATCHFUL WAITING VS REPAIR OF INGUINAL HERNIA IN MINIMAL SYMPTOMATIC MEN

Patients often delay hernia repair until pain or discomfort occurs.

Surgical repair, while generally safe and effective, carries a long-term risks of recurrence, pain, and discomfort.

For minimally symptomatic men, the usual basis for recommending surgery is prevention of incarceration and strangulation. This is a rare event.

This study asked: Is deferring surgical repair a safe and acceptable option for men with minimally symptomatic inguinal hernias?

Conclusion; Watchful waiting (*over 3 to 4 years*) was a safe and acceptable option.

STUDY

1. Entered over 700 men with inguinal hernias. (mean age = 57.) All were asymptomatic or had minimal symptoms. (No discomfort which limited usual activity. No difficulty in reducing the hernia.)
2. At baseline, most hernias were unilateral (13% bilateral); a few extended into the scrotum. (Indirect 53%; direct 41%; recurrent 6%.)
3. Randomized to: 1) watchful waiting (n = 365), or 2) tension-free repair surgery (n = 364)
4. Main outcome measures = pain and discomfort interfering with usual activities at 2 years. And change in physical symptoms from baseline to 2 years.
5. Follow-up = 2 to 4.5 years. Outcomes calculated by intention-to-treat at 2 years.

RESULTS

1. What happened to the surgery group?

- 1) Intraoperative complications = 3: wound hematoma requiring return to operating room; postanesthetic hypotension; and ilioinguinal nerve injury.
- 2) Postoperative complications in 22%: hematomas; urinary tract infections; wound infections; orchitis; urinary retention; postoperative bradycardia; deep venous thrombosis; postoperative hypertension.
- 3) At 2 years, overall, discomfort was reduced slightly, but pain limited usual activities in 2%
- 4) 3% of hernias recurred.
- 5) More than 97% were satisfied with the treatment they received.

2. What happened to the watchful waiting group?

- 1) At 2 years, pain limiting usual activities occurred in 5%
- 2) Cross-over to surgery: 23% at 2 years; 33% at 5 years (Mainly due to increased pain)
- 3) Complications: Incarceration, bowel obstruction rare ~ 2 in 1000 patient-years.
- 4) More than 97% were satisfied with the treatment they received. Overall, they experienced a slight lessening of discomfort over 2 years.

DISCUSSION

1. "Watchful waiting is a reasonable option for men whose inguinal hernia is minimally symptomatic."

At 2 years after randomization, similar proportions of patients in the WW and surgical groups had pain sufficient to limit usual activities (5% and 2%)

2. Most patients assigned to the WW group who crossed over to surgery did so because of increased pain. Surgery then relieved the pain with no more complications and no more recurrence of pain than in those undergoing immediate surgery.
3. The older the patient, the more likely the likelihood of hernia emergencies. The rate is still low.
4. Minimally symptomatic men who choose to defer surgery also defer the risk of adverse consequences of surgery: 1) short term complications 22%; 2) longer term consequences including chronic pain 1% to 2%; and 3) recurrence of hernia 1% to 2%.
5. The median length of this study was slightly over 3 years. Because the risk of complications from hernias increase with the time, a longer follow-up may be needed to ascertain the long-term risks and benefits.

CONCLUSION

A strategy of watchful waiting (over 3 to 4 years) is a safe and acceptable option for men with minimally symptomatic inguinal hernias.

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Vitamin D Deficiency During Pregnancy Is Associated With A Deficit In Bone-Mineral Accrual In The Children

1-6 MATERNAL VITAMIN D STATUS DURING PREGNANCY, AND CHILDHOOD BONE MASS AT AGE 9 YEARS

Vitamin D insufficiency is common in otherwise healthy pregnant women.

This study tested the hypothesis that low vitamin D levels in women during pregnancy have persisting effects on bone mass in their children.

Conclusion: Maternal vitamin D deficiency was associated with reduced bone-mineral accrual in the offspring during childhood.

STUDY

1. Studied 160 mothers and children born to them in the UK in 1991-92. Determined mothers' nutritional and vitamin D status during the pregnancy..
2. Measured serum 25(OH)-vitamin D at a mean of 34 weeks of pregnancy. Classified vitamin D levels as being deficient if the serum level was under 11 ug/L and as insufficient if level was 11-20. Normal > 20.
3. Nine years later, measured children's' bone mineral content (**BMC**) and areal bone mineral density (**BMD**) by dual energy X-ray absorptiometry.
4. Related maternal characteristics to the children's' bone mass.

RESULTS

1. Eighteen % of women had insufficient vitamin D levels, and 31% had deficient levels. (Half of all women.)
2. At age 9, children of mothers with reduced concentrations of vitamin D had reduced whole-body and lumbar spine bone mass compared with children of mothers with normal serum vitamin D.

	Mothers deficient in D	Mothers insufficient in D	Vitamin D replete
Whole body BMC	1.04 kg	1.14	1.16 kg
3. Maternal vitamin D status was also significantly associated with areal BMD.
4. Maternal UV exposure during late pregnancy varied by season and predicted serum concentrations of D (Mean levels in winter = 14 ug/dL; summer = 30 ug/dL). Children of mothers whose third trimester occurred in summer had higher BMD than those whose third trimester occurred in winter.
5. Use of vitamin D supplements predicted maternal concentrations of vitamin D. (In this cohort, only 15% of mothers took supplements containing vitamin D.) Their children at age 9 had significantly greater whole-body BMD than children of non-users.
6. Reduced concentrations of umbilical venous blood calcium also predicted reduced childhood bone mass.

DISCUSSION

1. "Our results suggest that vitamin D insufficiency (or deficiency) during late pregnancy is associated

with a deficit in bone-mineral accrual in their children which persists to age 9.”

2. The deficit manifests as a reduction in both bone size and BMC in the children without effects on childhood height or lean mass.
3. The study provides direct evidence that the intrauterine environment correlates with bone mineral accrual at age 9.
4. The fetus accumulates about 30 g of calcium from the mother in utero; 80% occurs in the last trimester. The maternal capacity to supply the fetus with calcium is dependent on many factors, including maternal calcium intake and vitamin D status; intestinal calcium absorption; maternal bone turnover; maternal renal function; and placental calcium transfer.
5. Modification of peak bone mass in childhood and adolescence may have relevant effects on skeletal fragility in old age.

CONCLUSION

The vitamin D status of mothers in late pregnancy predicts the bone mass of their offspring some 9 years later.

Vitamin D deficiency and insufficiency were common in these pregnant women. Supplementation could lead to enhanced peak bone mineral accrual in their children, and lead to reduced risk of fragility fracture later in life.

Lancet January 7, 2006; 367: 36-43 Original investigation, first author M K Javaid, University of Southampton, UK

Prevents Stroke In Women; MI In Men

1-7 ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN WOMEN AND MEN *A Sex-Specific Meta-Analysis Of Randomized Controlled Trials*

The benefits of aspirin for reducing risk of myocardial infarction (**MI**), stroke, and vascular death among both men and women with *preexisting* cardiovascular events are established. (*Secondary* prevention.)

The role in *primary* prevention is less clear.

The American Heart Association has reported aspirin therapy is effective in *primary* prevention of coronary heart disease in adults of both sexes who are at increased risk. The AHA guidelines on primary prevention recommend low-dose aspirin in women whose 10-year risk of a first coronary event exceeds 20%, and consideration for those with a 10-year risk of 10% to 20%.

The first primary prevention trial in women¹ reported a decrease in risk of stroke, but no reduction in risk of MI or vascular death. This varied from studies reporting benefits of primary prevention in men.

A differential beneficial effect may exist between men and women.

This meta-analysis determined if benefits and risks of aspirin therapy in primary prevention differed between men and women.

Conclusion: There was a difference. In women, risk of ischemic stroke was reduced. In men, risk of myocardial infarction was reduced. Major bleeding occurred equally in both sexes.

STUDY

1. Extensive search found 6 randomized controlled *primary* prevention trial totaling over 95 000 individuals. (Mean age ~ 60) None had documented cardiovascular disease at baseline. The majority of the population studied had a relatively low risk of cardiovascular events. However, a substantial minority was hypertensive or was considered at high risk for CVD
2. This meta-analysis determined incidence of non-fatal MI, non-fatal stroke, and cardiovascular mortality; and major bleeding.

RESULTS

1. Women: Among over 51 000 women, aspirin was associated with a statistically significant 17% reduction in ischemic stroke. There was no statistically significant effect on myocardial infarction or cardiovascular mortality.
2. Men: In over 44 000 men, aspirin was associated with a statistically significant 32% reduction in MI. There was no statistically significant effect on stroke or cardiovascular mortality.
3. Aspirin increased risk of major bleeding in both men and women (Odds ratio = 1.7)

DISCUSSION

1. In absolute terms:
 - A. Women: Aspirin for an average of 6 years resulted in an absolute benefit of approximately 3 cardiovascular events and 2 strokes prevented per 1000 women. No effect on MI or cardiovascular mortality.
 - B. Men: Aspirin for an average of 6 years resulted in a benefit of approximately 4 cardiovascular events prevented per 1000 men. MI was significantly reduced corresponding to an absolute benefit of 1 MI per 125 men treated. No statistically significant reduction in stroke.
2. Major bleeding (mainly GI) occurred over 6 years in 1 of every 400 women and 1 in 300 men.
3. Current guidelines recommend 75 and 162 mg aspirin daily for primary prevention. Higher doses (eg 500 mg) are just as effective in inhibiting thromboxane (antithrombotic) but are more effective in potentiating prostacycline (tending to promote clotting).

CONCLUSION

Aspirin given for primary prevention over 6 years reduced incidence of stroke in women, but did not lower risk of myocardial infarction or cardiovascular deaths.

Aspirin given of primary prevention in men lowered risk of myocardial infarction, but did not lower risk of stroke or cardiovascular death.

Aspirin is associated with a risk of bleeding to an equal degree in men and women. Harm (major bleeding) approximates the benefits in reducing risk of MI and stroke.

JAMA January 18, 2006; 295: 306-13 Original investigation, first author Jeffrey S Berger, Duke University Durham, NC

1 “Randomized Trial of Low-dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women” NEJM March 31, 2005; 352: 1293-1304. The Women’ Health Study reported a reduction in risk of stroke among over 39 000 women taking low-dose aspirin. The NNT for 10 years to prevent one ischemic stroke was between 500 and 1000. Women taking aspirin experienced a 1.4 increase in relative risk of GI hemorrhage. See *Practical Pointers [3-6 2005]*

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“A Major Modifiable Risk Factor” Eat Five or More Daily

1-8 FRUIT AND VEGETABLE CONSUMPTION AND STROKE

Epidemiological studies suggest that increased consumption of fruits and vegetables may be associated with reduced risk of stroke. The extent of the association is uncertain.

This meta-analysis assessed the relation quantitatively.

Conclusion: Increased consumption was related to reduced risk.

STUDY

1. Literature search entered 8 studies which met inclusion criteria. (Over 257 000 individuals)
2. Determined frequency of fruit and vegetable intake and correlated it with frequency of incident stroke.
3. Grouped consumption into 3 categories: 1) less than 3 servings daily; 2) 3 to 5 servings daily, and 3) more than 5 servings daily. The standard serving was 0.5 cup.
4. Average follow-up = 13 years.

RESULTS

1. Relative risk of stroke:

Less than 3 servings	1.00
3 to 5 servings	0.89
More than 5	0.74

2. Fruit and vegetables had a protective effect on both ischemic and hemorrhagic stroke.

DISCUSSION

1. An increased consumption of fruit and vegetables (over 5 servings daily) was associated with a reduced risk of stroke.
2. Do some types of fruit and vegetables provide better protection than others? This is not known.
3. The investigators admit that observational studies are subject to bias. Persons who consume more fruit and

vegetables may lead more healthful lifestyles. “A meta-analysis is not able to solve problems with confounding factors that could be inherent in the included studies.”

4. Fruit and vegetables increase potassium intake and 24-hour urinary excretion. Increasing potassium has a BP-lowering effect. Dietary folate may reduce risk of stroke by lowering homocysteine levels.

CONCLUSION

Increased fruit and vegetable intake in the range commonly consumed (over 5 servings daily) was associated with reduced risk of stroke.

Lancet January 28, 2006; 367: 320-26 Original investigation, first author Feng J He, St George’s University of London, UK

An editorial in this issue of Lancet (pp 278-79) by Lyn M Steffen, University of Minnesota School of Public Health, Minneapolis, comments and expands:

Fruit and vegetables contain many health-promoting nutrients such as vitamin C, folate, potassium, fiber, and plant proteins that have been inversely related to high BP. It is likely that the combination of nutrients and compounds in foods has greater health benefits than the individual nutrients alone.

Fewer than a quarter of adults in the US eat 5 or more servings per day. This is despite the 1991 “5 A Day for Better Health” program which attempted to increase awareness of benefits.

On average, American adults eat 3.75 servings (1.75 to 2 cups of 400 – 455 g daily). This is considerably less than the 3.5 to 5 cups (800 to 1150 g) which the 2005 US Dietary Guidelines recommend.

Present advertising practices target young people and promote foods and drinks high in fat and sugar. Food habits develop in childhood, We must provide young people with the structure and means for developing healthy eating habits.

“Intake of fruit and vegetables is a major modifiable risk factor.”

The Population Impact Of The MetS Is Much Greater.

1-9 METABOLIC SYNDROME COMPARED WITH TYPE 2 DIABETES AS A RISK FACTOR FOR STROKE. *The Framingham Offspring Study*

Type 2 diabetes (**DM2**) is a risk factor for stroke equivalent to the risk of stroke associated with coronary heart disease.

The atherothrombotic risk imposed by DM2 appears to antedate its overt appearance, lurking in a prediabetic state of insulin resistance termed the metabolic syndrome (**MetS**).

The cardiovascular risk factors that make up the MetS predict occurrence of DM2. This pre-diabetic state may be considered an independent risk factor for cardiovascular disease and stroke.

This study compared the risk of stroke in patients with DM2-alone, and with MetS-alone. Estimated the population-attributable risk of stroke associated with each.

Conclusion: Persons with the MetS have an increased risk of stroke. The risk for stroke in each person with MetS is less than that of DM2. But because MetS is much more common in the general population, more strokes were be associated with MetS-alone than with DM2-alone.

STUDY

1. Determined the prevalence of the MetS-alone, DM2-alone in over 2000 subjects age 50-81 (mean age = 59). All were free of stroke at baseline. 22% were smokers; 12% had a history of cardiovascular disease.
2. Evaluated the risk of stroke associated with the MetS-alone and compared it with risk of stroke in persons with DM2-alone
3. Estimated the population-attributable risks of each risk factor over a 10-year period.

RESULTS

1. Twenty two % of subjects had the MetS-alone (n = 461); 5% had DM2-alone (n = 99); 7% had both (n = 117); 68% had neither (1421
2. Over 14 years of follow-up, 130 individuals developed a first stroke: (All but 4 ischemic)

		Rate per 1000 subjects	%
MetS alone	37 of 461*	80	8%
DM2 alone	12 of 99	121	12%
No Dm2; no MetS	65 of 1421	45	4.5%
Both	16 of 117	136	13.6%

(* absolute numbers kindly supplied by Dr. Philip A Wolf.)

3. The estimated population-attributable risk was much greater for the MetS-alone than for DM2-alone due to the greater prevalence of MetS-alone.
4. Over 10 years, the relative risk (RR) of stroke of persons with MetS-alone (compared to those without either DM2 or the MetS) = 2.10. The RR of stroke in persons with DM2-alone was 2.5.
5. The prevalence of the MetS-alone in the general population was much greater than prevalence of DM2-alone. Consequently, the population-attributable risk of stroke associated with the MetS-alone was larger than the risk of stroke associated with DM2. This was despite the higher RR of stroke associated with DM2-alone. (See below for calculation of population-attributable risk in absolute numbers per 100 000 population. RTJ.)

DISCUSSION

1. Hyperinsulinemia and insulin resistance are accepted as prominent features of MetS. This suggests that, like impaired glucose tolerance and impaired fasting glucose, MetS may signal a prediabetic state. In the Framingham Heart Study cohort, those with MetS had a 5-fold risk of developing diabetes
2. Because MetS is much more prevalent than diabetes, the population impact of the syndrome is greater.
3. There is a great potential for substantial reductions in stroke risk in people with MetS by treatment of its components.

4. Evidence supports antiatherosclerotic management for both diabetes and MetS.
5. MetS should be considered an especially important CHD risk factor because of its prevalence in the population
6. MetS probably signals a prediabetic state. Its identification and treatment likely will prevent occurrence of overt DM2. "Health professionals are well advised to institute vigorous preventive measures in prediabetic persons with evidence of MetS before the advent of overt diabetes."
7. There is an emerging epidemic of *macro*-vascular sequelae of diabetes. Primary care physicians appear not to have adopted sufficient aggressive management strategies. Too many physicians cling to the traditional approach to treatment that emphasizes glycemic control which may benefit micro-vascular disease more than macro-vascular disease.

CONCLUSION

MetS is much more prevalent than DM2. It is a significant and independent risk factor for stroke. Prevention and control of the MetS and its components will likely reduce incidence of stroke.

Archives Intern Med January 9, 2006; 166; 106-111 Original investigation, first author Robert N Najarian, Boston University School of Medicine, Boston Mass.

Eradication Results in Modest Improvements in Patients with Dyspepsia

1-10 IMPACT OF HELICOBACTER ERADICATION ON DYSPEPSIA, HEALTH RESOURCE USE, AND QUALITY OF LIFE; The Bristol Helicobacter Project.

Dyspepsia is defined simply as epigastric pain. It affects a high percentage of the population. It accounts for many primary care consultations, and results in billions in costs.

Previous investigations reported that *H pylori* eradication in patients with dyspepsia may benefit some patients.

This study determined the impact of a community-based *H pylori* screening and eradication program on incidence of dyspepsia.

Conclusion: Eradication of *H pylori* in the community resulted in modest reductions in subsequent consultations for dyspepsia over the next 2 years.

STUDY

1. A program in 7 general practices screened over 10 500 unselected individuals for *H pylori*. Subjects were age 20-59. About 25% had dyspepsia.
2. All were screened by a ¹³C urea breath test. 15% were positive. Of these, 1558 were randomized to a 2 week course of 1) eradication treatment with ranitidine bismuth citrate and clarithromycin, or 2) placebo.
3. Assessed eradication by repeat urea breath test.
3. Followed for up to 2 years for rates of primary care consultations for dyspepsia to determine if eradication influenced subsequent dyspepsia.

RESULTS

1. Treatment eradicated 91% of the infections.
2. Subsequently consulted for dyspepsia over the subsequent 2 years:
 - Treated group $55/787 = 7/100$
 - Placebo group $78/771 = 10/100$
 - Number needed to treat to avoid one subsequent consultation for dyspepsia = 33.
3. No difference in quality of life.

DISCUSSION

1. The study entered a large number of subjects over a wide age range. There were few exclusions.
 - This would increase generalizability of the findings.
2. The *H pylori* prevalence (15%) in the general population was comparable to findings of a Danish study.
3. Similar reductions in dyspepsia were observed in three other population-based eradication studies.

BMJ January 28, 2006; 332: 199-202 Original investigation, first author J Athene Lane, University of Bristol, UK

An editorial in this issue of BMJ by Brendan C Delaney, University of Birmingham, UK comments and expands on the study:

Dyspepsia has recently been defined as predominant epigastric pain present for at least 4 weeks, with or without heartburn. By implication gastro-esophageal reflux disease (GERD) refers to predominant heartburn.

Patients who have had endoscopy can be categorized according to the cause found—peptic ulcer, esophagitis, or functional dyspepsia or functional heartburn.

Eradication of *H pylori* is most effective in preventing recurrence of duodenal ulcer (NNT = 2 to prevent recurrence at one year.)

“It now seems naive to have expected such effectiveness of eradication in other conditions related to dyspepsia.” After peptic ulcer and esophagitis have been excluded by endoscopy, the NNT of eradication in functional dyspepsia is 15. “Nothing else is more effective in this condition. A reduction in the incidence of recurrent symptoms from 70% to 63% has been considered both as “insignificant” and as “of great value”.

Past observations suggested that eradication of *H pylori* increases risk of GERD. We now know it does not increase this risk.

A strategy of “test and treat” for dyspepsia is marginally less effective than management based on endoscopy, but is still cost effective because of the excess cost of endoscopy.

The evidence-based UK guidelines recommend eradication as first choice in endoscopically proved functional dyspepsia and as a treatment option in uninvestigated dyspepsia.

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Fewer False Negative and False Positive Tests

1-11 CDC RECOMMENDS NEW TUBERCULOSIS BLOOD TEST. QuantiFERON-TB Gold

QuantiFERON-TB Gold is a test produced by Cellestis, Victoria, Australia.

This in vitro test replaces the older QuantiFERON-TB test which is no longer available. The CDC believes it is more accurate and represents a considerable advance over the original QuantiFERON-TB test. (MMWR December 16, 2005)

The test detects the release of interferon-gamma in fresh heparinized whole blood from sensitized persons when it is incubated with two synthetic peptides which simulate two proteins present in *M tuberculosis*.

The San Francisco Department of Public Health states it is “one of the first [tuberculosis] advancements since the discovery of antibiotics”. The new test has higher sensitivity and specificity (fewer false negative and false positive tests) than the old TB PPD skin test and the former QuantiFERON-TB test. which used PPD (purified protein derivative) as the incubating agent.

The peptide sensitizing agents used in the test are absent from all BCG vaccine strains and most commonly encountered non-tuberculosis mycobacteria.

The patient needs to attend only once for the test.

The FDA approved the test in May 2005.

BMJ January 7, 2006; 332: 9 “News Roundup’ commentary by Fred Charatan, BMJ correspondent in Florida.

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No Proved Benefits

1-12 MAGNET THERAPY

Magnetic bracelets, insoles, wrist and knee bands are claimed to be therapeutic. They have been advertised to cure a vast array of ills, particularly pain. A Google search yielded over 20 000 pages, most of which tout healing properties.

Annual sales in the USA are about \$300 million.

Many “controlled” experiments are suspect because it is difficult to blind subjects.

A double blind study, designed so that treatments could not be identified, was carried out for carpal tunnel syndrome pain using magnet therapy. There was no statistical difference between groups. Another study of back pain reported no effect. This was despite tendency to report positive results.

Published research, both theoretical and experimental, is weighted heavily against any therapeutic benefit.

“Money spent for expensive and unproved magnet therapy might be better spent on evidence-based medicine.” More importantly, self treatment with magnets may result in undertreatment of an underlying condition. Some advertisers even claim magnets are effective for cancer treatment and for increasing longevity. “Extraordinary claims demand extraordinary evidence.”

Theoretically, magnet therapy seems unrealistic. If human tissue were affected by magnets, one would expect the massive fields generated by MRI imaging would have profound effects. But MRI shows neither ill nor healing effects.

“Patients should be advised that magnet therapy has no proved benefits.” If they insist on using a magnetic device, they could be advised to buy the cheapest. This will at least alleviate the pain in their wallet.”

BMJ January 7, 2006; 332: 4 Editorial, first author Leonard Finegold, Drexel University, Philadelphia, PA

1-13 VENOUS THROMBOEMBOLISM—18 POINTS

(Review articles appear frequently. They are interesting and informative, but long and difficult to abstract. This is an experiment. These few points emphasize the important and serve as a memory-jogger. Is it helpful? I would appreciate feed-back. Is it helpful? RTJ)

1. VTE comprises both deep vein thrombosis (**DVT**) and pulmonary embolism (**PE**).
2. A risk factor for VTE can be identified in the great majority of patients. Usually more than one factor is present (age; hospitalization; recent surgery (especially orthopedic); cancer; and thrombophilia). Risk factors often interact. The risk of VTE in users of oral contraceptives and hormone replacement is compounded by the presence of factor V Leiden.
3. Only a minority of patients (less than one third) with suspected VTE of a lower limb actually have the disease.
4. Compression ultrasound remains the non-invasive test of choice.
5. D-dimer (a fibrin degradation product) adds to diagnostic accuracy of non-invasive testing. Levels are > 500 ng/mL in nearly all patients with VTE.
6. A low pretest probability of VTE + a low or normal d-dimer makes a diagnosis of VTE and PE unlikely.
7. Most patients with PE have no leg symptoms at diagnosis. In patients with symptomatic VTE 50-80% have asymptomatic PE.
8. Sinus tachycardia is the most common ECG abnormality in PE. Atrial fibrillation, right bundle-branch block, and features of right heart strain are less common.
9. Normal perfusion on the ventilation-perfusion scan virtually excludes PE.
10. Mortality from PE increases with age > 65.
11. Despite anticoagulation, VTE frequently recurs in the first few months after the initial event.
12. Many of the classical risk factors for arterial thrombosis (diabetes, smoking) also are risk factor for VTE.
13. Idiopathic VTE on presentation often reveals occult cancers on follow-up.
14. Duration of anticoagulation treatment may last only as long as a (transient) risk factor persists.
Idiopathic VTE is usually treated for 6 months. Patients with recurrent VTE due to hypercoagulation states (acquired and inherited) and cancer should remain on anticoagulation for a minimum of one year, and perhaps indefinitely.
15. Low molecular weight heparin (LMWH) is more effective than warfarin in preventing VTE after major orthopedic surgery, with no greater risk of hemorrhage. Use of LMWH in patients with uncomplicated VTE allows patients to be treated at home, saving days of hospitalization.

16. Current recommendations advocate anticoagulation for at least 6 months for the first presentation of idiopathic VTE.
17. Fondaparinux (a factor Xa inhibitor lacking activity against thrombin) is at least as effective as LMWH in preventing VTE after orthopedic surgery, and may be associated with lower costs.
18. Direct thrombin inhibitors (eg hirudin; ximelagratan) are beginning to find a place in situations where heparin use is limited. Some may eventually replace warfarin.

BMJ January 28, 2006; 332: 215-19 "Clinical Review" first author Andrew D Blann, City Hospital, Birmingham UK.

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