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HIGHLIGHTS NOVEMBER 2003

11-1 HOMOCYSTEINE AND CARDIOVASCULAR DISEASE

"A raised serum homocysteine concentration is a cause of cardiovascular disease." Risk can be reduced by folic acid supplementation.

11-2 NUT AND PEANUT BUTTER CONSUMPTION AND RISK OF TYPE 2 DIABETES IN WOMEN

Higher nut and peanut butter intake was related to a reduced risk of DM-2

Regular nut consumption can be recommended as a replacement for consumption of refined grains and red or processed meats.

11-3 A CONTROLLED TRIAL OF A HUMAN PAPILLOMA VIRUS TYPE 16 VIRUS

A HPV-16 vaccine given to young women reduced incidence of HPV-16 infection and cervical intraepithelial neoplasia. The vaccine may prevent cervical cancer.

11-4 TRANSIENT ISCHEMIC ATTACK – PROPOSAL FOR A NEW DEFINITION

A TIA is a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction.

With the new definition, the difference between a TIA and a stroke becomes similar to the distinction between an episode of angina pectoris and a myocardial infarction. Angina is a symptom of ischemia, which is usually brief, but can be prolonged, without myocardial infarction. If there is evidence of myocardial damage, myocardial infarction is diagnosed.

11-5 TRANSIENT ISCHEMIC ATTACK: Review Article

The high short-term risk of stroke after a TIA supports an approach involving rapid evaluation and initiation of treatment. Initial evaluation should include electrocardiography, imaging studies of the head, and Doppler ultrasonography of the carotids. Brain imaging may reveal a non-ischemic cause – eg, brain tumor or subdural hematoma.

11-6 OSTEOPOROSIS AND FRACTURES IN POSTMENOPAUSAL WOMEN USING ESTROGEN

Estrogen replacement increases bone density and lowers probability of fractures. However, risk of osteoporosis and fractures is still high in older women even if they use estrogens for years after menopause.

Other interventions are required to prevent osteoporosis.

11-7 EXERCISE TO REDUCE CARDIOVASCULAR RISK – HOW MUCH IS ENOUGH?

Exercise is associated with a graded response in a number of different lipoprotein variables. The ensemble of changes is likely to be beneficial. The study documented an effect of exercise on lipoproteins with only minimal changes in body weight and provides a ray of hope for those who find it easier to exercise than lose weight.

11-8 USE OF POSTMENOPAUSAL HORMONES, ALCOHOL, AND RISK FOR INVASIVE BREAST CANCER

Women who use PMH and consume an average of *over* one alcoholic drink daily had a significantly increased risk of BC, independent of the risk of using PMH alone. "Women who are currently using PMH may wish to consider the added risks of regular alcohol consumption."

11-9 EFFECTS OF COGNITIVE TRAINING INTERVENTIONS WITH OLDER ADULTS

Cognitive training interventions improved targeted cognitive abilities. Effects were of a magnitude equivalent to prevention of the usual amount of decline expected over 7- to 14-year intervals.

11-10 HORMONE REPLACEMENT THERAPY AND INCIDENCE OF ALZHEIMER DISEASE IN OLDER WOMEN.

Prior HRT use was associated with reduced risk of AD. There was no apparent benefit with current use unless such use exceeded 10 years.

11-11 TREATING ACUTE GOUTY ARTHRITIS WITH SELECTIVE COX 2 INHIBITORS

Work just as well as other NSAIDs, but no better. Is the added cost worthwhile?

11-12 DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

In adults with acute bacterial meningitis, dexamethasone given before initiation of antibiotic therapy improved outcomes and reduced rate of death. Dexamethasone should be given before the first dose of antibiotic.

11-13 PARATHYROID HORMONE FOR TREATMENT OF OSTEOPOROSIS

PTH increases BMD in the spine in a dose-dependent manner. But fracture reduction data are not robust, especially at non-vertebral sites. PTH may have detrimental effects on the radius BMD.

It protects against vertebral fractures, regardless of time since menopause. Approximately the same degree of fracture reduction resulted from PTH as from the bisphosphonate, alendronate (*Fosamax*), and the selective estrogen receptor modulator raloxifene (*Evista*)

11-14 THE MULTICENTER ANEURYSM SCREENING STUDY (MASS) INTO THE EFFECT OF ABDOMINAL ANEURYSM SCREENING OF MORTALITY IN MEN.

Substantial reductions in AAA-related mortality could be achieved by the implementation of a population-screening program for older men. Screening and following surgery was not associated with any decrease in quality-of-life.

11-15 META-ANALYSIS OF EFFECTS AND SIDE-EFFECTS OF LOW DOSAGE TRICYCLIC ANTIDEPRESSANTS IN DEPRESSION

Treatment of depression with low dose tricyclics is effective ion many patients. Adverse effects and withdrawals are lees frequent than with “standard” doses. .

11-16 WALKING AND LEISURE-TIME ACTIVITY AND RISK OF HIP FRACTURE IN POSTMENOPAUSAL WOMEN

More leisure-time activity was associated with a lower risk of hip fractures in postmenopausal women. Moderate levels of activity, including walking, were associated with substantially lower risk.

11-17 COMPARISON OF C-REACTIVE PROTEIN AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS IN PREDICTION OF FIRST CARDIOVASCULAR EVENT.

CRP is a stronger predictor of cardiovascular risk than LDL-c. It adds to prognostic information to that conveyed by the Framingham risk score.

A Marker Of Increased Risk – Simply, Cheaply, And Safely Treated.

11-1 HOMOCYSTEINE AND CARDIOVASCULAR DISEASE: Evidence On Causality From A Meta-Analysis

The higher the level of serum homocysteine (a sulfur-containing amino acid), the greater the risk of ischemic heart disease, deep vein thrombosis, and stroke. Large increases in serum homocysteine, as seen in the rare disorder, homocystinuria[1], are associated with premature cardiovascular disease. Moderate increases in homocysteine occur as a result of a mutation in the gene coding for methylene-tetra-hydro folate reductase, (MTHFR, an enzyme involved in folate metabolism). When this gene mutation occurs, the activity of the enzyme decreases and serum homocysteine concentrations rise by about 20%.

The increase in homocysteine is small in persons with MTHFR mutation. Increased levels of homocysteine also occur in the general population of persons without the mutation. Since elevations of homocysteine are relatively small in both cohorts, large numbers of patients (as in a meta-analysis) need to be included in studies to show any adverse effect.

The investigators conducted two separate meta-analyses (one a study of genetic mutation patients, the other of the general population) comparing risk of cardiovascular disease in persons with increased levels of homocysteine vs those with lower levels. The investigators stated that the 2 cohorts of patients did not share the same potential sources of error. Thus, if they yielded similar highly significant results, this would be strong evidence of causality in the association between homocysteine and cardiovascular disease.

This new meta-analysis also quantified the effect of homocysteine reduction in preventing cardiovascular disease. Resolving this question is important because homocysteine levels can be lowered by the simple and safe administration of folic acid.

Conclusion: There was highly significant evidence of causality. Lowering homocysteine levels with folic acid significantly reduced risk of cardiovascular disease.

STUDY

1. Meta-analysis of two studies of the above 3 diseases:
   A. 72 case-control studies in which persons with the mutation of the MTHFR gene (and its resultant increase in homocysteine) were compared with controls. MTHFR mutation studies included:
      A. Homozygous gene (TT) patients, and B. "normal" gene (CC) patients. Mean difference in serum concentration of homocysteine between TT and CC was 2.7 umol/L. (Higher in the TT group.)
   B. 20 prospective studies comparing homocysteine levels with risk of disease.
2. Main outcome = odds ratio of the 3 diseases associated with a 5 umol/L increase in serum homocysteine.

RESULTS

1. There were significant associations between increased homocysteine and the 3 diseases.

2. The odds ratio for a 5 umol/L increase in serum homocysteine:

	Ischemic heart disease	Deep vein thrombosis	Stroke
Genetic studies	1.4	1.6	1.7
Prospective studies	1.3	No study	1.6

3. Evidence of risk reduction:

A previous randomized trial *("Decreased Rate of Coronary restenosis after Lowering Plasma Homocysteine Levels" NEJM 2002; 345: 1593*) reported lowering homocysteine with folic acid, B12, and B6 in patients with ischemic heart disease reduced risk of coronary restenosis.

The maximum reduction in homocysteine achieved by 800 ug folic acid is about 3 umol/L.

4. In this study, a reduction by 3 umol/L of homocysteine was associated with a reduction in risk of:

Ischemic heart disease	Deep vein thrombosis	Stroke
16%	25%	24%

DISCUSSION

1. "On the basis that the association is causal and reversible, we estimate that folic acid could reduce the risk of ischemic heart disease by 16%, deep vein thrombosis by 25%, and stroke by 24%."
2. The causal association is based on these observations:
   A. The genetic studies showed a moderate increase in risk for a moderate increase in homocysteine. The genetic linkage to some unknown risk factor might be the explanation, although no such linkage is known.
   B. The prospective studies showed an association between homocysteine and cardiovascular disease after allowance for confounding.
   C. These two types of study are susceptible to different sources of error, but show quantitatively similar associations, a result that is unlikely to have occurred through different potential sources of confounding acting independently.
   D. The homocystinurias[1] cause high serum levels and high risks of premature cardiovascular disease.
   E. Lowering homocysteine reduces risk.
   F. "In the light of these five observations, we could not have concluded otherwise."

CONCLUSION

"A raised serum homocysteine concentration is a cause of cardiovascular disease." Risk can be reduced by folic acid supplementation.

BMJ November 23, 2002; 325: 1202-06 First author David S Wald, Southampton General Hospital, Southampton, UK www.bmj.com/cgi/content/full/325/7374/1202

Comment:

There has been a fascinating sea change in therapy with nutritional supplements over the years. Old teaching recommended vitamins only if the diet was insufficient to protect against specific vitamin-deficient disease (eg, rickets; megaloblastic anemia). Now supplements are recommended to reduce risk of non-deficiency diseases (eg, osteoporosis; cardiovascular disease and spina bifida; and possibly macular degeneration). The benefit/harm-cost ratio of these therapies is very high. Indeed, we are becoming a nation of drug takers for primary prevention – eg, a small daily portion of alcohol with our statins, low-dose aspirin, and folic acid.

1 A. Homocystine and B. homocysteine are simple sulfur-containing amino acids. A is a di-sulfide; B is a mono-sulfide. Since their metabolism is similar, they are frequently considered an entity. RTJ

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Eat More Nuts, Less Red Meat

11-2 NUT AND PEANUT BUTTER CONSUMPTION AND RISK OF TYPE 2 DIABETES IN WOMEN

Diet modification is important in preventing type 2 diabetes (**DM-2**). Specific types of fat, rather than total fat intake, predict risk of DM-2

Nuts contain 70% to 80% of fat. Most fatty acids in nuts are unsaturated (polyunsaturated and monounsaturated). These fatty acids may be beneficial for glucose and insulin homeostasis. Several studies reported that a higher intake of polyunsaturated and monounsaturated fatty acids improves insulin sensitivity.

A higher intake of saturated and *trans*-fat adversely affects glucose metabolism and risk of DM-2.

Other components of nuts (fiber, magnesium) decrease insulin demand and resistance. They have been inversely associated with risk of DM-2. Nuts are also a rich source of many vitamins, minerals, anti-oxidants, and plant protein, which could also be beneficial.

This prospective study examined the association between nut and peanut butter consumption and risk of DM-2 in a large cohort of women.

Conclusion: Higher nut and peanut butter consumption was associated with a lower risk of DM-2.

STUDY

1. Prospectively followed over 83 000 women (age 34 to 59 at baseline). None had history of diabetes, cardiovascular disease, or cancer.
2. Dietary questionnaire at baseline, and periodically thereafter, determined consumption of nuts and peanut butter. (How often, on average, do you consume nuts (average size 1 oz) or peanut butter (1 tablespoon)?
3. Main outcome = incident DM-2
4. Follow-up = 16 years.

RESULTS

1. Documented over 3600 new cases of DM-2

2. After adjustment for multiple other risk factors, nut consumption was inversely associated with risk of DM-2.

Relative risks:

Almost never	< once / wk	1-4 times/wk	5 or more times /wk (5% of cohort)
1.0	0.92	0.84	0.73

(*By my calculation from their tables, comparing consumers of nuts with non-consumers, 800 women would have to consume nuts daily for one year to benefit one person; and 1400 would have to consume peanut butter daily to benefit one. These probabilities could be meaningful on a population basis. RTJ*)

3. Consumption of peanut butter was also inversely associated with risk of DM-2. Relative risk = 0.79 in those consuming peanut butter 5 times per week compared with those rarely consuming peanut butter.
4. Further adjustment for intakes of fat, cereal fiber, and other dietary factors did not appreciably change results.
5. Of interest – women who consumed more nuts:

Generally weighed *less*.

Were less likely to smoke, and more likely to exercise

Consumed more polyunsaturated fat, dietary fiber, alcohol, and multivitamin supplements.

Consumed a lower glycemic load and less *trans* fat.

Consumed less meat and refined grain.

(Nevertheless, the authors believed they had resolved any confounding effects.)

DISCUSSION

1. Consumption of nuts and peanut butter was inversely associated with risk of DM-2, independent of known risk factors for DM-2.
2. Recent studies suggest that specific types of fat, rather than total fat as percentage of energy play an important role in development of DM-2. (Eg, high saturated fat diet is associated with decreased insulin sensitivity compared with high monounsaturated fat diet.) Women in the highest quintile of vegetable fat had a 40% lower risk of DM-2 compared with those in the lowest quintile. Higher intake of oils, consisting mostly of polyunsaturated fat, was associated with lower fasting glucose.
3. Nuts are rich in fiber and magnesium and have a relatively low glycemic index. Some studies reported a decrease in demand for insulin.
4. There have been concerns that nut consumption may result in weight gain. In this cohort there was no association between weight gain and nut consumption.
5. Other studies have reported a beneficial effect of nuts on blood lipids and a reduced risk of coronary heart disease.
6. “It is advisable to recommend regular nut consumption as a replacement for refined grain products or red or processed meats, which would avoid increasing caloric intake.”

CONCLUSION

Higher nut and peanut butter intake was related to a reduced risk of DM-2

Regular nut consumption can be recommended as a replacement for consumption of refined grains and red or processed meats.

JAMA November 27, 2003; 288: 2554-60 Original investigation, first author Rui Jiang, Harvard School of Public Health, Boston, Mass www.jama.com

Comment:

The authors comment that, although peanuts botanically are classified as legumes, their fatty acid and nutrient profiles are very similar to nuts. It seems fortuitous that peanuts are termed "nuts".

The authors made no distinction between intake of hydrogenated peanut butter (high in *trans* fat) and unsaturated (natural) peanut butter. The latter are much to be preferred. I suspect at the time of the study that peanut butter was generally hydrogenated.

I find a portion of nuts with raisins or dates to be a satisfying snack.

Should we recommend nut consumption and peanut butter for established DM-2? I believe so, if other dietary intakes and lifestyles can be adjusted concomitantly. RTJ

Hope For Very Effective Vaccine

11-3 A CONTROLLED TRIAL OF A HUMAN PAPILLOMA VIRUS TYPE 16 VACCINE

Human papilloma virus (HPV) infection is a common sexually transmitted disease. Approximately 20% of adults become infected. Most infections are benign. Persistent infection (repeated detection of an oncogenic type) is associated with development of cervical and anogenital cancers. Of the more than 30 types, HPV 16 is the most commonly linked to cancer. It is present in 50% of cervical cancers and high grade cervical intraepithelial neoplasms. A vaccine that prevents persistent infections could substantially reduce the incidence of cervical cancer.

Now a vaccine type 16 vaccine is being tested. It is synthesized in yeast with the use of cellular expression systems. The vaccine is composed of "L1 protein", empty viral capsids termed "virus-like particles". Vaccination with L1 virus-like particles derived from specific papilloma viruses leads to high levels of antibodies.

This study determined whether such a vaccine could protect HPV 16 in women.

Conclusion: The vaccine reduced incidence of both HPV-16 infection and related cervical intraepithelial neoplasms.

STUDY

1. Double-blind study entered over 2300 young women (age 16 – 23). Women with evidence of HPV-16 infection at enrollment were excluded.
2. Randomized to:
   1) HPV-16 virus-like particle vaccine 3 doses at 0 month, month 2, and month 6 or
   2) Placebo vaccine.
3. Tested genital samples for HPV DNA at enrollment, one month after the third vaccination, and

every 6 months thereafter.

4. Obtained biopsy tissue to evaluate for cervical intraepithelial neoplasia and HPV-16 DNA by polymerase chain reaction.
5. Primary end point = persistent HPV-16 infection, defined as the detection of HPV-16 DNA in samples obtained at two or more visits.

RESULTS

1. Over 1500 women were followed for a median of 17 months after completing the vaccination regimen.
2. 99.7% of women receiving the vaccine seroconverted. Mean titer of HPV-16 antibodies: 1510 mMU/mL among those receiving vaccine vs less than 6 mMU/mL in the placebo group. (*For reference, the mean titer of HPV-16 antibodies in patients with HPV-16 infection at baseline was 26 mMU/L.*)
3. Incidence of persistent HPV-16 infection:
   Placebo group -- 4 per 100 women-years at risk
   Vaccine group – 0 per 100 woman-years at risk.
4. All 41 cases of HPV-16 infection occurred in the placebo group (31 were persistent). Vaccine efficacy = 100%
5. Nine women contracted HPV-16 related cervical intraepithelial neoplasia, all in the placebo group.
6. An additional 44 cases of cervical intraepithelial neoplasia that were not associated with HPV-16 infection were detected, equally distributed between groups.
7. Adverse events were similar in the 2 groups, the most frequent was pain at the injection site.

DISCUSSION

1. The data provide evidence of a highly efficacious prophylactic vaccine against HPV-16 infection.
2. All 41 cases of new HPV-16 infection and all 9 cases of cervical intraepithelial neoplasia occurred in the placebo group.
3. Only 6 cases in which tests were positive at a single visit occurred among vaccine recipients; vs 26 cases were expected on the basis of the observed rate in the placebo group, “Assuming that all women with a single positive had a new infection, the data support the possibility that sterilizing immunity developed in some women.”
4. There was no evidence that the vaccine provided post-infection protection against either persistent infection or lesions.
5. Some women who received the vaccine were infected with other types of HPV. Cross-protection is either minimal or absent.
6. The primary reason to vaccinate is to prevent cervical cancer. Persistent HPV-16 infection is a reasonable surrogate end point, since approximately 50% of cervical cancers are associated with

HPV-16 infection. (HPV-16 is a potent carcinogen.) A broad spectrum vaccine of HPV types would be more advantageous. Multivalent vaccines are being tested.

CONCLUSION

A HPV-16 vaccine given to young women reduced incidence of HPV-16 infection and cervical intraepithelial neoplasia. The vaccine may prevent cervical cancer.

NEJM November 21, 2002; 347: 1645-51 Original investigation, first author Laura A Koutsky, University of Washington, Seattle. www.nejm.org

An editorial by Christopher P Crum, Brigham and Women's Hospital, Boston Mass comments:

The importance of the Papanicolaou smear remains under dispute. Tens of thousands of dollars are spent in the USA each year to manage minor cytological abnormalities. Over 90% of cervical papillomavirus infections resolve spontaneously. Cervical cancer develops in a minority. Screening appears to benefit only a small fraction of women. Many more endure inconvenience and anxiety of the smear.

The vaccine particles are devoid of DNA and therefore are not infectious. However, they generate a potent immune response. The vaccine not only prevents disease from developing, but also provides its causative agent from residing in the genital tract where it can infect new sexual partners.

The vaccine cannot be expected to reverse infection or cervical neoplasia.

HPV-16 and HPV-18 are the most common culprits. Immunizing for both would likely lower the death rate from cervical cancer by 95%

"Oncogenic genital HPVs produce neoplasms in the vulva, penis, larynx, nasopharynx, nail bed, conjunctiva, and perhaps other sites, so a case can be made for vaccinating everyone." Vaccination would also prevent most cases of genital warts.

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Transient Symptoms Without Any Evidence Of Brain Infarction

11-4 TRANSIENT ISCHEMIC ATTACK – PROPOSAL FOR A NEW DEFINITION

"The definition of transient ischemic attack (**TIA**) and the assumptions underlying the definition have been out of date for some time, and are no longer consistent with current concepts of brain ischemia."

Both health care professionals and the public tend to consider TIAs as benign; strokes as serious.

The *classic* definition of TIA:— "A sudden, focal neurological deficit that lasts for less than 24 hours, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery." A variety of symptoms may occur. TIAs are often referred to as ministrokes, warning strokes, or transient strokes because they resolve quickly. The definition has been based on the assumption that TIAs are associated with *complete* resolution of the brain ischemia which occurs rapidly enough to cause only transient symptoms, and no permanent brain injury. The definition was based arbitrarily on the duration of symptoms. (If symptoms last over 24 hours, an injury to brain parenchyma should be detected by microscopy.)

Computed tomography (**CT**) and magnetic resonance imaging (**MRI**) have changed these concepts. Imaging studies (especially MRI) have made it clear that a substantial percentage of patients with TIA are left with ischemic brain injury. Many have evidence of infarction on follow-up imaging. Small foci of permanent brain injury may occur with relatively brief episodes of focal ischemia. “Permanent brain injury is not an all-or-none phenomenon after transient brain ischemia. There is a continuum ranging from transient mild episodes of ischemia that do not cause neuronal death, to moderate episodes that cause loss of isolated neurons, to severe episodes that cause brain infarction.”

TIAs offer a greater opportunity to initiate treatment that can forestall brain infarction. After a first TIA, up to 20% of patients have a stroke within the next 90 days – about 10% within the first 2 days. TIAs are underrecognized, and underrated. “The development of symptoms of acute brain injury constitutes a medical emergency.”

Physicians need to focus on the cause of the ischemia rather than the duration of symptoms. Cardiologists have leaned that, whether a patient has angina or a myocardial infarction, the most important criteria for determining prognosis and treatment are the nature, location, and severity of the coronary artery disease that causes the cardiac ischemia. Similarly, the cause of brain ischemia (whether cardiac, extracranial arteriopathy, intracranial large- or small-artery disease, or a coagulopathy) determines its outcome and treatment. “The focus of diagnosis and treatment should be on the causative processes.”

“In view of these changes, we propose a redefinition of TIA and outline a new understanding of its pathophysiology and management.”

Proposed new definition:

> *A TIA is a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and <u>without evidence of acute infarction</u>.*

The new definition is based on the supposition that patients who have TIAs have no objective evidence of infarction in the affected region. Patients with acute symptoms who, on diagnostic evaluation, are found to have acute infarction would no longer be classified as TIA, regardless of the duration of symptoms. The arbitrary time limit defining TIA (eg, less than 24 hours, or less than one hour) no longer applies to the definition.

A corollary is that persistent clinical signs or characteristic imaging abnormalities define infarction – that is, stroke.

With the new definition, the difference between a TIA and a stroke becomes similar to the distinction between an episode of angina pectoris and a myocardial infarction. Angina is a symptom of ischemia, which is usually brief, but can be prolonged, without myocardial infarction. If there is evidence of myocardial damage, myocardial infarction is diagnosed.

As advances in neurodiagnostic techniques continue to be made and become more widely available, diagnostic accuracy will improve.

The authors advocate urgent brain imaging for patients with symptoms suggestive of acute cerebral ischemia. We need to be aware of the serious implications of TIA. The development of acute brain ischemia constitutes a medical emergency. Transient symptoms do not rule out the possibility of infarction.

NEJM November 21, 2002; 347: 1713-16 Sounding Board", commentary, first author Gregory W Alpers, Stanford University School of Medicine, Palo Alto, CA www.nejm.org

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Short Duration of Symptoms Does Not Rule out Infarction.

11-5 TRANSIENT ISCHEMIC ATTACK

(*This is a companion article to the preceding. It emphasizes some points, including treatment*.)

Brain infarcts can occur without neurological deficits. Evidence of acute infarction is identified in up to 50% of patients who meet the old criteria for definition of TIA. Short duration (< 1 hour) of TIA symptoms reduces the likelihood of infarction. Conversely, infarction may not occur even if symptoms last longer.

The causes of TIA – atrial fibrillation, carotid artery disease, and large- and small-artery disease are identical to those of stroke. Strategies for prevention are similar.

Treatment:

Aspirin reduces the long-term risk of cardiovascular events after a TIA (as well as stroke). The risk of brain hemorrhage is probably less in patients with TIA, so the net benefit is likely to be greater. Start immediately.

Anticoagulation

Warfarin has not been evaluated in patients with atrial fibrillation who have a TIA. In view of the benefit in stroke prevention, patients with TIA are also likely to benefit. In patients without AF, anticoagulation is no better than aspirin. What about heparin? Given the high risk of stroke after a TIA, in patients with AF and a relatively low risk of brain hemorrhage, heparin is probably justified until warfarin has produced effective anticoagulation.

Carotid endarterectomy is beneficial in patients with internal carotid stenosis of 70% to 99% who have had a TIA attributed to the stenosis. It is marginally beneficial in those with stenosis 50% to 69%. Benefits are highly dependent on surgical experience. Optimum timing of surgery is unknown. However, interventions need to be rapid to be effective. When infarction is absent, urgent surgery is probably indicated for patients who can undergo surgery with a low risk of complications.

Treatment of risk factors is likely to reduce risk of stroke after a TIA:

Statin drugs (even in patients with "normal" lipids).

Treatment of hypertension. One recent study suggested the ACE inhibitor losartan (Cozaar) might be more beneficial in reducing risk of stroke than the beta-blocker, atenolol BP should not be lowered if the cause of TIA is likely to be due to narrowing of an artery.

Lifestyle changes – smoking cessation, exercise, weight control, moderate alcohol consumption

The high short-term risk of stroke after a TIA supports an approach involving rapid evaluation and initiation of treatment. Initial evaluation should include electrocardiography, imaging studies of the head, and

Doppler ultrasonography of the carotids. Brain imaging may reveal a non-ischemic cause – eg, brain tumor or subdural hematoma.

"Clinical Practice" NEJM November 21, 2002; 347: 1687-92, review article by S Clairborne Johnston, University of California, San Francisco. www.nejm.org

Comment:

So what should the primary care clinician do when a patients presents with a presumed TIA?

A. If the patient presents with an acute neurological deficit which is persistent, hospitalize immediately for definitive study. Is a brain infarct present? In enthusiastic centers, treatment might include thrombolysis if the patient has an infarct.

B. If symptoms have cleared at the time of presentation:

Give one aspirin immediately

Listen for carotid bruit

Check heart rhythm for atrial fibrillation.

Start antihypertension treatment if BP is high and no carotid bruit.

Arrange for definitive study as soon as possible.

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Estrogen Helps A Bit, But Leaves Most Vulnerable For Fracture.

11-6 OSTEOPOROSIS AND FRACTURES IN POSTMENOPAUSAL WOMEN USING ESTROGEN

"Half of all postmenopausal women will have an osteoporosis-related fracture during their lives." Twenty five percent will develop a vertebral fracture; 15% a hip fracture. "The evidence linking estrogen deficiency and accelerated bone loss is unequivocal." Bone loss in the early postmenopausal period undoubtedly contributes to the increase in fractures later in life.

Estrogen replacement improves or stabilizes bone density. Estrogen replacement therapy reduces fracture risk. But, those using estrogen supplementation may still be at substantial risk as they age.

This study asks – to what extent do estrogen users remain at risk for osteoporosis and fractures?

Conclusion: Osteoporotic fractures remain common in women who use estrogen continuously since menopause.

STUDY

1. Followed over 8500 women over age 65 (mean = 70) from community settings in the USA.
2. Determined type of estrogen use and incidence of fractures.
3. Main outcomes = hip, vertebral, and other fractures. Follow-up over 10 years.

RESULTS

1. At baseline, 40% of continuous estrogen users (n = 373 used estrogen over a mean of 24 years until baseline) were osteopenic; 13% osteoporotic according to WHO criteria.

2. Women who currently used estrogen lost less bone than past users or never-users.
3. During 10 years of observation, the probability of non-vertebral fractures was 19% for continuous users, similar to current partial users 22%), and lower than never-users 31%). These comparisons were similar for hip and vertebral fractures.
4. Probability of an incident fracture over 4 years was 2.5% in continuous users, and 4% in never-users.

DISCUSSION

1. A substantial number of women who used estrogen continuously were osteoporotic or osteopenic. Most (80%) lost bone density.
2. Results are consistent with previous findings that women who use estrogen have a lower risk of fractures than never- or past-users, particularly if initiated early after the menopause. But, about 1 in 5 of these women experienced a fracture within 10 years. "A substantial health burden persists among women using estrogen."
3. Other causes of fracture that are not estrogen-dependent such as falls, become more frequent with age, and may become more important than the estrogen effect.
4. Estrogen users should be considered in screening and treatment guidelines. The National Osteoporosis Foundation recommendations include the need for bone density assessments in estrogen users.
5. Other preventive measures could be added: vitamin D and calcium; exercise; bisphosphonate; raloxifene; and now, parathyroid hormone.

CONCLUSION

Estrogen replacement increases bone density and lowers probability of fractures. However, risk of osteoporosis and fractures is still high in older women who have used estrogen for years.

Other interventions are required to prevent osteoporosis.

Archives Int Med November 11, 2002; 162: 2278-84 Original investigation, first author Heidi D Nelson, Oregon Health Sciences University, Portland www.archinternmed.com

Comment:

Certainly vitamin D and calcium should be universally prescribed.

I wonder if it would not be reasonable to prescribe another anti-resorptive drug in addition to estrogen and calcium/vitamin D for all women to prevent this almost inevitable disease. Bone density screening would then not be needed.

The place of parathyroid hormone requires additional observation. RTJ

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Exercise Benefits Even If Weight Does Not Decline Much

11-7 EXERCISE TO REDUCE CARDIOVASCULAR RISK – HOW MUCH IS ENOUGH?

Increasing levels of physical activity are associated with a decrease in cardiovascular events Exercise improves mood, blood pressure, insulin sensitivity, and lipoprotein levels. The amount and intensity of exercise required to attain these goals, and the underlying mechanisms are poorly understood. Exercise-associated changes in lipoproteins may be an explanation.

A randomized trial in this issue of NEJM[1] reported changes in plasma lipoprotein levels and particle size involving different amounts and intensities of exercise among overweight men and women with dyslipidemia.

Low amounts of exercise at moderate or high intensity (eg, walking or jogging 12 miles per week) were associated with beneficial changes in plasma lipoproteins.

Higher levels of high-intensity exercise (equivalent to 20 miles per week) resulted in more pronounced benefits. Higher levels were required to produce elevations of HDL-cholesterol. The effects of exercise on HDL were most clearly seen in overweight persons with high triglyceride levels and low HDL levels.

"The graded response of the plasma lipoprotein levels to increasing amounts of exercise may help explain the progressive decrease in cardiovascular risk associated with increasing levels of exercise".

As compared with non-exercising groups, all exercise groups had potentially beneficial changes in lipoproteins: decreases in total and very-low-density lipoproteins; decreases in triglycerides; and increases in the size of LDL particles; and a trend toward decreased numbers of LDL particles. The largest effect on LDL occurred in the high-intensity group. An increase in HDL-cholesterol was observed only in the high-intensity exercise group.

The changes in lipoproteins were observed in patients who experienced only small decreases in weight (a mean of about 3 to 4 pounds).

Many of the improvements in lipoprotein variables and insulin sensitivity are seen after a single session of exercise.

"In summery, exercise is associated with a graded response in a number of different lipoprotein variables. The ensemble of changes is likely to be beneficial. The study documents an effect of exercise on lipoproteins with only minimal changes in body weight and provides ray of hope for those who find it easier to exercise than lose weight."

NEJM November 7, 2002; 347: 1522-24 Editorial by Alan R Tall, Columbia University, New York.
www.nejm.org

1 "Effects of the amount and intensity of exercise on plasma lipoproteins" NEJM November 7, 2002; 347: 1483-92 Original investigation, first author William E Kraus, Duke University Medical Center, Durham, NC

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PMH + 2 Drinks Per Day = A Bad Combination

11-8 USE OF POSTMENOPAUSAL HORMONES, ALCOHOL, AND RISK FOR INVASIVE BREAST CANCER

Alcohol increases risk of breast cancer (**BC**), at least in part by altering circulating steroid hormones. In premenopausal women, alcohol increases both plasma and urinary levels of estradiol and estrone. In postmenopausal women taking postmenopausal hormones (**PMH**), acute ingestion of alcohol increases estradiol levels a mean of 300% compared with placebo.

Compared with never-users of PMH, the relative risk of BC in PMH users is about 1.3.

Alcohol intake is also associated with increased risk of BC. RR = 1.16 in women consuming 15 to 30 g alcohol daily compared with abstainers. And 1.4 for those drinking more.

This study examined the relation between concurrent use of PMH and alcohol and invasive BC.

Conclusion: Both alcohol and PMH were associated with increased incidence of BC.

STUDY

1. Prospective cohort study (The Nurses' Health Study) followed over 44 000 women. (Median age = 60)
2. Repeatedly determined self-reported data on PMH use and alcohol consumption from 1980 to 1990.
3. Calculated risk of developing BC according to use.

RESULTS

1. During over 550 000 person-years of follow-up, 1722 women developed BC over the 10 years.
2. Relative risks of BC compared with non-users:

Current PMH use; no alcohol	1.3
Current use of alcohol (1.5 to 2 drinks daily): no PMH	1.3
Current use of both PMH (5 years or more) and alcohol	2.0

3. "A hypothetical woman whose lifetime risk of breast cancer is 4% could increase her risk to 8% with 5 or more years of current PMH use and consumption of more than one alcoholic drink daily."

DISCUSSION

1. Average alcohol intake of less than 10 g did not significantly increase the risk.
2. Current users of PMH for 5 or more years who also consumed 1.5 to 2 drinks of alcoholic had almost twice the risk of BC compared with those who did not drink alcohol and did not use PMH.
3. A hypothetical woman with a lifetime risk of BC of 4% in the absence of alcohol or PMH use would increase her risk to 6% with current PMH use for at least 5 years, and to 8% with current use of PMH for more than 5 years, and current consumption of more than one drink per day.
4. Women who used both would theoretically increase risk from 4% to 8% compared with those who used neither.
5. The effects of PMH use is most closely tied to current use. Risk decreases to baseline with past use.

For alcohol the same seems to hold true.

CONCLUSION

Women who use PMH and consume an average of over one alcoholic drink daily had a significantly increased risk of BC, independent of the risk of using PMH alone. “Women who are currently using PMH may wish to consider the added risks of regular alcohol consumption.”

Annals Int Med November 19, 2002; 137: 798-804 Original investigation, first author Wendy Y Chen, Brigham and Women’s Hospital and Harvard Medical School, Boston , Mass. www.annals.org

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“Use It Or Lose It”

11-9 EFFECTS OF COGNITIVE TRAINING INTERVENTIONS WITH OLDER ADULTS.

The Advanced Cognitive Training for Independent and Vital Elderly Trial (ACTIVE)

Nearly half of community-dwelling persons over age 60 express concern about declining mental abilities. A growing body of research supports the protective effects of late-life intellectual stimulation on incident dementia. Human neural plasticity endures across the lifespan. Cognitive stimulation is an important predictor of enhancement and maintenance of cognitive function. A sizable body of literature documents that different types of cognitive training programs have large and durable effects on the cognitive functioning of older adults, even in advanced old age.

This study tested the effectiveness and durability of 3 distinct cognitive training interventions in improving the performance of elderly persons on basic measures of cognition and on measures of cognitively demanding daily activities.

Conclusion: Cognitive training interventions improved targeted cognitive abilities.

STUDY

1. Randomized, controlled trial entered a diverse sample of over 2800 volunteers age 65 to 94 (mean = 74) recruited from senior housing, community centers, and hospitals/clinics in 6 metropolitan areas. None had substantial cognitive or functional decline at baseline.
2. Randomized to one of four groups:
   1) Memory training (Mneumonic strategies and exercises for remembering).
   2) Inductive reasoning -- ability to solve problems that follow a serial pattern. (Understanding the pattern in every day activity and abstract reasoning tasks.).
   3) Speed of processing (Visual search skills and ability to identify and locate visual information quickly).
   4) No contact group.

   [*See text for details*]

3. Each intervention group received a 10-session intervention by certified trainers.
4. For the 3 treatment groups, 4-session booster training was offered to 60% of subjects 11 months later.
5. Main outcome = cognitive function and cognitively demanding every-day functioning. (Eg, food preparation, driving, medication use, financial management).
6. Follow-up = 2 years.

RESULTS

1. Each intervention improved the targeted cognitive ability as compared with baseline. 26% of the memory group, 74% of the reasoning group, and 26% of the memory group demonstrated cognitive improvement immediately after the intervention.
2. Booster training enhanced gains in speed and reasoning. The benefits were maintained at a 2-year follow-up.
3. However, no training effects on everyday functioning were detected at 2 years.

DISCUSSION

1. The study "demonstrated that cognitive interventions helped normal elderly individuals to perform better on multiple measures of the specific cognitive ability for which they were trained".
2. It did not, however, demonstrate the generalization of such interventions in everyday performance in the initial 2 years. (Most of the subjects were functioning at high levels at baseline, leaving little room for improvement. In addition, the control group had little functional decline over 2 years.)
3. Age-related decline occurs later for everyday functioning. Declines in basic abilities such as reasoning and memory typically occur earlier in life. Because of minimal functional decline across all groups, longer follow-up is likely required to observe training effects on everyday function.
4. These interventions may have the potential to reverse age-related decline.

CONCLUSION

Cognitive training interventions improved targeted cognitive abilities. Effects were of a magnitude equivalent to prevention of the usual amount of decline expected over 7- to 14-year intervals.

JAMA November 13, 2002; 288: 2271-81 Original investigation, first author Karlene Ball, University of Alabama, Birmingham. www.jama.com

Comment:

Maintaining cognitive function apparently involves interventions in several modalities. And continued training. The effects on daily activity functioning will await further study.

I believe elders can do a great deal now to help maintain their cognitive function and ability to perform daily living tasks: maintain physical function by regular walking; stay socially involved; protect the brain as well as the heart by

interventions to reduce risk of atherosclerotic damage; perform cognitive tasks daily to help maintain memory and reasoning power. RTJ

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Suggestion Of Benefit If Taken For Over 10 Years, And Nearer To The Time Of Menopause.

11-10 HORMONE REPLACEMENT THERAPY AND INCIDENCE OF ALZHEIMER DISEASE IN OLDER WOMEN.

Compared with men, women over age 80 appear to be at increased risk of Alzheimer disease (**AD**). Does postmenopausal depletion of endogenous estrogens contribute to the risk? Will hormone replacement therapy (**HRT**) reduce risk? Early case-control study of the association between AD and HRT were inconclusive.

This prospective study examined the relationship.

Conclusion: Prior HRT use was associated with reduced risk of AD. Current use was beneficial only if use exceeded 10 years.

STUDY

1. Prospective study of incident dementia entered over 1300 men and over 1800 women (mean age = 73) residing in a single county in Utah. (This is a generally healthy and long-lived population.)
2. First assessed in 1995-1997 by the Mini-Mental State examination. Followed up in 1998-2000. (Mean = 3 years)
3. Obtained history of current and former HRT use (the majority estrogen-alone), as well as calcium and vitamin D supplementation.
4. Determined association between HRT use and AD.
5. Main outcome = diagnosis of incident AD.

RESULTS

1. Thirty five men (2.6%) and 88 women (4.7%) developed AD between the time of the first interview and a 3-year follow-up.
2. The annual hazard for AD appeared similar for men and women before age 80. It diverged rapidly afterward with an excess risk found in women. (Adjusted hazard ratio women over 80 vs men over age 80 = 2.)
3. Among women completing the study, those who used HRT at any time had a reduced risk of AD (26 of 1066 – 2.4%) compared with non-users (58 of 800 – 7.3%). Adjusted hazard ratios were 0.4 for HRT users compared with non-users, and 0.77 compared with men. (*Ie, HRT use reversed the female/male risk ratio*.)
4. Risk varied with duration of HRT use. Women's sex-specific increase in risk of AD (vs men) disappeared entirely with more than 10 years of use.
5. Almost all the HRT-related reduction in incidence reflected former use of HRT. There was no effect

with current use unless duration of treatment exceeded 10 years.

6. No similar effect was seen with calcium and multivitamin use. (The authors considered this use an indicator or a healthy life-style. They therefore concluded the effect of HRT was not biased by a healthy lifestyle.)

DISCUSSION

1. The study provides new evidence to suggest a protective effect of HRT. The adjusted risk of incident AD among women who used HRT during their lifetime was reduced to more than half that among non-users.
2. Considerably stronger effects were observed with longer usage. Compared with never-users, women who had used HRT for more than 10 years experienced a 2.5-fold lower incidence compared with the risk observed in men.
3. "Taken to their logical conclusion, our findings suggest that if women were to use long-term HRT, their excess risk of AD over that of men in late old age might disappear."
4. There is an apparent limited time window during which sustained HRT exposure seems to reduce risk of AD. In contrast with earlier use, HRT exposure within 10 years of AD onset yielded little, if any, apparent benefit. This in accord with prior findings of reduced cognitive decline in elderly women who initiated HRT at menopause, but not in those with more recent exposures. This and all prior observational studies are consonant with no benefit of HRT begun near the onset of dementia. (This finding is similar to those reported by use of NSAIDs in reducing risk of AD.) This suggests that HRT, to be protective, may be useful only if taken in the latent pathogenic stages of AD. There is also no evidence of benefit from HRT in patients with established AD.
5. The study attempted to control for "healthy user" biases. However, the investigators state that all observational studies are subject to unsuspected confounding, and do not suggest that these results are generalizable to other populations.
6. "Benefits of HRT, if any, may take years to appear, and a considerable latency period may intervene between treatment and perceptible effects."

CONCLUSION

Prior HRT use was associated with reduced risk of AD. There was no apparent benefit with current use unless such use exceeded 10 years.

JAMA November 6, 2002; 288: 2123-29 Original investigation, first author Peter P Zandi, Johns Hopkins University, Baltimore, MD www.jama.com

An editorial in this issue of JAMA by Susan Resnick and Victor Henderson (pp 2170-72) from the National Institute of Aging, Baltimore MD, comments:

Human imaging studies provide evidence that estrogen-containing hormone therapy influences the pattern of brain activation during memory processing, increases regional cerebral blood flow and metabolism in temporal lobe structures, and modulates brain activity in specific brain regions affected by early stages of AD. The protective effect of ever-use therapy suggests the possibility of a critical period during climacteric years which are characterized by relatively rapid estrogen depletion. It will be critical to examine prior use of HRT, especially during the menopausal transition, as a modulator of later effects of treatment in these critical years.

Comment:

We continue to struggle with uncertainty surrounding benefits/harms of progestin/estrogen and estrogen alone replacement therapy. Any benefit in reducing risk of AD must be associated with long-term use. I believe this provocative study presents some hope, but no more than hope. We can be sure that HRT does not *increase* incidence of AD. We are a long-way from an answer definitive enough to allow recommendation of therapy for benefits on reduction of risk of AD.

What should primary care clinicians advise in this regard? I believe strongly that, despite the recent down-grading of benefits from HRT, we should continue to prescribe HRT for women at the menopausal period to relieve estrogen-withdrawal symptoms and greatly improve their quality of life. RTJ

Just as Effective: Does The Added Safety Justify The Added Cost?

11-11 TREATING ACUTE GOUTY ARTHRITIS WITH SELECTIVE COX 2 INHIBITORS

Successful treatment of acute microcrystalline events depends on early use of an effective and safe anti-inflammatory drug in full doses. The sooner treatment is started, the more rapid and complete the response.

Treatment options include colchicines, NSAIDs, corticosteroids, and corticotrophin (ACTH). Although colchicine is traditionally rooted in the treatment of acute gout, in recent years its use has declined. Drawbacks include slow onset of action, a narrow ratio of benefit to toxicity, and reduced efficacy when used more than 24 hours after an attack begins.

Valuable and effective drugs include:

Intra-articular corticosteroids (methyl prednisolone 5 – 24 mg per joint)

Oral corticosteroids (prednisone 20 mg/d tapered over 4 to 10 days)

Parenteral corticosteroid (intramuscular triamcinolone 60 mg/d, repeated in 1 -4 days)

ACTH 40 – 80 units (intramuscular every 6 – 24 hours)

These drugs are especially useful in patients who should not take NSAIDs: the elderly, patients with cardiac failure, hypertension, liver dysfunction, peptic ulcer disease, and hypersensitivity.

What about NSAIDs? "Non-salicylate NSAIDs are the drugs of choice for acute crystal induced arthritis." Compared with colchicine, they are generally better tolerated and have more predictable therapeutic effects. Patients are usually supplied with the appropriate NSAID, preferably carried with the person. This allows self-treatment at the first "twinge" of an attack. (Gout often strikes when the patient is far from home.) There is no clear advantage of one NSAID over another. Large initial doses are recommended: indomethacin (*Generic* 25 & 50 mg tablets) 150-200 mg/d; naproxin (*Generic* 250; 375; & 500 mg tablets) 1000 mg/d; diclofenac (Diclofenac; *Voltarin*) 50 mg prescription only) 150 mg/d. Duration of therapy is usually 4 to 8 days. Serious toxicity at this dosage is rare.

Cyclo-oxygenase-2 (**COX-2**) is highly inducible. It has a role in inflammation and infection. In crystal and other inflammatory arthritides, cytokines increase production of prostaglandins via COX-2 induction (and prostaglandin E) in synoviocytes and macrophages. Conventional NSAIDs inhibit both COX-1 and COX-2. Their anti-inflammatory effect is largely due to suppression of COX-2. Most toxic effects (particularly GI toxicity) result from inhibition of the protective COX-1. The newer NSAIDs are highly selective in inhibiting COX-2. They reduce GI toxicity by about 50%. (*Note – they are not without GI toxicity*.)

A recent randomized, double-blind trial of the COX-2 inhibitor, etoricoxib (150 mg three times daily over 8 days, compared with indomethacin in acute gout showed equal efficacy.

COX-2 inhibitors (as well as dual COX-1, COX-2 inhibitors) should be used with caution in patients with cardiac failure, renal insufficiency, hypertension, peptic ulcer, and in users of anti-coagulants.

Selective COX-2 inhibitors may be of particular benefit in patients who are intolerant to non-selective NSAIDs, and in patients presenting with an acute attack of gout of several days duration, since a longer course of treatment is likely to be required.

BMJ November 2, 2002; 325: 980-81 Editorial by Adel G Fam, University of Toronto, Canada.
www.bmj.cpm/cgi/content/full/325/xxxx/980

Comment:

The advice for caution when prescribing NSAIDs for patients with renal disease, hypertension, congestive heart failure, peptic ulcer disease, and liver disease is clinically important. COX-2 inhibitors are modestly protective against only peptic ulcer. They are more expensive.

Costs quoted by my pharmacy:

Prednisone 20 mg daily for 7 days	Less than $5
Indomethacin 150 mg daily for 7 days	~ $9
Naproxin 1000 mg daily for 7 days	~ $4
Diclofenac 150 mg daily for 7 days	~ $9
Celebrex 200 mg	$2.50 each
Vioxx 25 mg	$2.50 each

I doubt the excess cost is justified, considering the short term treatment of acute gout. Would not prednisone be a good first choice? RTJ

Medical Emergency!! Give Antibiotic Immediately Along With Dexamethasone -- Before Hospitalization

11-12 DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

Mortality and neurological sequelae among adults with bacterial meningitis are high, especially among those with pneumococcal meningitis. Bacterial lysis induced by antibiotic therapy leads to release of pro-inflammatory mediators into the subarachnoid space. This may contribute to unfavorable outcomes. Adjuvant treatment with anti-inflammatory agents such as dexamethasone may reduce spinal fluid inflammation and neurologic sequelae.

This study determined whether adjunctive dexamethasone improves the outcome in adults with bacterial meningitis.

Conclusion; Early treatment with dexamethasone improved outcomes.

STUDY

1. Prospective, randomized, double-blind study entered over 300 patients (mean age 45) with acute bacterial meningitis.
2. Organisms included: *Streptococcus pneumoniae* (35%) ; *Neisseria meningitides* (33%); other bacteria (10%); and negative culture (22%).
3. Randomized to:
   1) Dexamethasone 10 mg up to 20 minutes before first dose of antibiotic and every 6 hours thereafter for 4 days, or
   2) Placebo.
4. Primary outcome = score on the Glasgow Outcome Scale at 8 weeks.

   Glasgow Outcome scale score:

Death	1
Vegetative state	2
Unable to be independent	3
Living independently, but unable to return to work	4
Mild or no disability able to return to work	5

RESULTS

1. Dexamethasone was associated with a reduction in risk: (Relative risk -- dexamethasone vs placebo):

   Unfavorable outcomes (1,2,3 and 4 on the scale)

Strep pneumoniae	0.5 (Statistically significant)
N. meningitidis	0.75
Other bacteria	2.8
Negative culture	0.4

   Death

Strep pneumoniae	0.5 (Statistically significant)
N. meningitidis	0.75
Other bacteria	2.8
Negative culture	0.4

2. Focal neurological abnormalities and hearing loss were less frequent in the dexamethasone group, but not at a statistically significant level.
3. Among those with pneumococcal meningitis, unfavorable outcomes were 26% in the dexamethasone group vs 52% in the placebo group.

DISCUSSSION

1. Early treatment with dexamethasone improved outcomes in some adults with acute bacterial

meningitis, reducing rate of death and unfavorable outcomes.

2. The benefit was most evident in patients with pneumococcal meningitis. A beneficial effect in those with meningococcal meningitis could not be ruled out.
3. The investigators recommend dexamethasone treatment for all patients with acute bacterial meningitis.
4. The delay in initiation antibiotic therapy in this cohort was a matter of concern. In the setting of suspected acute bacterial meningitis, antibiotic therapy should be started empirically immediately. Don't wait for a CT scan or lumbar puncture before starting treatment when meningitis is suspected.
5. Dexamethasone has been shown to be beneficial in children only if given before the first dose of antibiotic.
6. Monotherapy with amoxicillin was the initial treatment. Resistance of the pneumococcus and meningococcus to amoxicillin is very low.

CONCLUSION

In adults with acute bacterial meningitis, dexamethasone given before initiation of antibiotic therapy improved outcomes and reduced rate of death. Dexamethasone should be given before the first dose of antibiotic.

NEJM November 14, 2002; 347: 1549-56 Original investigation by the European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators, first author Jan De Gans, Academic Medical Center, Amsterdam, Netherlands. www.nejm.org

An editorial in this issue of NEJM (*November 14, 2002; 347: 1613-14*), first author Allan Tunkel, Drexel University College of Medicine, Philadelphia, PA, comments:

> "We believe that routine use of adjunctive dexamethasone is warranted in most adults with suspected pneumococcal meningitis." It should be given with or just before the first dose of antibiotic.
>
> Use in patients who have already received an antibiotic is not recommended. If the meningitis is found not to be pneumococcal, dexamethasone should be discontinued.

Comment:

Primary care clinicians should be prepared to administer empiric amoxicillin immediately in the office to sick patients with suspected meningitis. This is a genuine medical emergency. Dexamethasone should be administered at the same time. The unavoidable delays due to hospital admission and triage should not be tolerated. I believe any harms will be overshadowed by potential benefits (including preservation of life and lessening of complications). RTJ

The Only Agent To Induce Bone Formation

11-13 PARATHYROID HORMONE FOR TREATMENT OF OSTEOPOROSIS

To date, all approved osteoporosis treatments are agents which block resorption of bone. They do not induce bone formation. Parathyroid hormone (**PTH**) is a potential inducer of bone formation. It may be useful alone, or in conjunction with treatments which reduce bone resorption.

This broad review discusses evidence for efficacy and safety of PTH.

Conclusion: PTH increases spine bone density and decreases vertebral fractures in postmenopausal women. This is at the expense of a *decrease* in bone density of the radius.

STUDY

1. Systematic review found 20 randomized trials involving PTH and postmenopausal osteoporosis. Trials were heterogeneous. Treatment duration and the dose of PTH varied. PTH was usually given subcutaneously daily. Almost all trials used human PHT (1-34). Most subjects also took supplemental calcium/vitamin D.

RESULTS (*Since trials differed in many respects, results differed*.)

1. In the range of 50 to 100 ug/d, effects were dose-related. Increases in BMD of the lumbar spine ranged from 4% to 9%. Some increase in BMD also occurred in the total hip, femoral neck, and femoral trochanter. Effects were evident within 9 to 12 months.
2. PTH decreased the incidence of radiographically detected spinal fractures. It also reduces the corollary – pain.
3. One trial comparing PTH alone vs PTH + estrogen reported combination therapy was superior in increasing BMD of the spine and total hip.
4. Trials suggested *detrimental* effects on BMD of the radius. Some studies, however, reported that PTH recipients were less likely to experience non-vertebral fractures as compared with the placebo group, but results were conflicting.
5. Benefit was also demonstrated in patients with glucocorticoid-induced osteoporosis.
6. Some patients found compliance with the injections difficult. Withdrawals were more frequent in the PTH groups.
7. No serious adverse effects were reported. Mild hypercalcemia was occasionally reported. It was dose-dependent, but remaining within the normal range. Levels decreased with lowering of calcium intake.
8. An increase in cancer was not reported.

CONCLUSION

PTH increases BMD in the spine in a dose-dependent manner. But fracture reduction data are not robust, especially at non-vertebral sites. PTH may have detrimental effects on the radius BMD.

It protects against vertebral fractures, regardless of time since menopause. Approximately the same degree of fracture reduction resulted from PTH as from the bisphosphonate, alendronate (*Fosamax*), and the selective estrogen receptor modulator raloxifene (*Evista*)

Maximal anabolic effects may require 12 months therapy.

Injection therapy was associated with decreased compliance.

PTH induces hypercalcemia in a small percentage of patients.

Archives Int Med November 11, 2002; 162: 2297-99 Original investigation, review article by Carolyn Crandell, University of California, Los Angeles www.archinternmed.com

Comment:

I suspect PTH will be used primarily in combination with anti-resorptive agents.

PTH (teriparatide – recombinant DNA origin) had been approved by the FDA for treatment of osteoporosis. Trade name *Forteo*, Eli Lilly . It will be supplied in a multiple-dose pen for injection of 20 micrograms daily. RTJ

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Screening Leads To A Significant Reduction In Mortality

11-14 THE MULTICENTER ANEURYSM SCREENING STUDY (MASS) INTO THE EFFECT OF ABDOMINAL ANEURYSM SCREENING OF MORTALITY IN MEN.

Most deaths from ruptured abdominal aortic aneurysms (**AAA**) occur in men. In men over age 65 in the UK, ruptured AAA accounts for 2% of all deaths. About half of these deaths take place before the patient reaches the hospital. For those who arrive at the hospital alive, the mortality rate is 30% to 70% The overall mortality rate is 65% to 85%.

Ultrasound (**US**) reliably visualizes AAA. It is relatively cheap and non-invasive.

Elective early surgery can reduce the frequency of rupture. However, surgical mortality at this stage is 2% to 6%.

This trial was designed to assess whether screening with US would lead to a reduction in mortality from ruptured AAA. .

Conclusion: The study provided reliable evidence of benefit from screening.

STUDY

1. Entered a population-based sample of men (over 68 000 -- age 65-74).
2. Randomized to:
   1) US to detect possible AAA (n = over 27 000)
   2) Control group
3. Determined maximum transverse diameter and maximum anterior-posterior diameters. Men with aortas less than 3 cm were not rescanned.
4. Men in whom AAA was over 3 cm in diameter were followed with repeat US for a mean of 4 years.
5. Surgery was considered if: 1) diameter was 5.5 cm or more, 2) expansion over 1 cm per year, or 3) symptoms occurred.
6. Obtained mortality data and assessed quality-of-life scores.
7. Primary outcome = mortality related to AAA.

RESULTS

1. In over 27 000 men screened, 1333 AAAs were detected. (*5% of men age 65-74 had AAA*):

2. Operations:

Screened group = 354

Controls = 146

3. AAA related deaths over 4 years:

Screened group – 65 (absolute risk = 0.19%)

Controls – 113 (absolute risk = 0.33%)

Absolute benefit in reducing death = 0.14%. [NNT to benefit one patient = 714]

4. Thirty day mortality after elective surgery = 6%; after emergency surgery = 37%.

5. Quality-of-life assessments at all times and across all groups were within age-matched population norms. Those who underwent surgery rated their health equal to those who screened negative.

DISCUSSION

1. "Screening can significantly reduce mortality rates associated with abdominal aortic aneurysms."

2. Because many aneurysms were detected in the screened group and required treatment in the first 1-2 years, the investigators anticipated that the mortality in the invited groups might exceed that of the control group over this period due to surgical mortality. However, this did not occur. The postoperative mortality was low

3. For men age 65-74, over 700 would need to be screened to prevent one death.

4. Screening was not associated with any adverse effects on the emotional state of men who had an AAA detected.

5. Few new AAAs will develop and proceed to rupture within an interval of less than 10 years. A national screening program could logically consist of a single screen at age 65.

CONCLUSION

Substantial reductions in AAA-related mortality could be achieved by the implementation of a population-screening program for older men. Screening and following surgery was not associated with any decrease in quality-of-life.

Lancet November 16, 2002; 360: 1531-39 Original investigation by the Multicentre Aneurysm Screening Study Group (MASS) Trial supported by the UK Medical Research Council www.thelancet.com

Comment:

What should primary care clinicians in the USA do in this regard? Should we advise screening for a serious disease with a prevalence of 5%? Health conscious men may be informed about results of this trial and may consider if they wish to be screened.

Men who are screen positive and their primary care doctors have a serious decision to make. Should they undergo immediate surgery, risking a surgical mortality, albeit low. Or should they delay while the AAA inevitably increases in diameter? The decision depends greatly on the skill and experience of the surgical team.

I believe some medical measures will reduce rate of expansion: BP control, lipid control, cessation of smoking, beta-blocker to reduce rate of systolic expansion of the aorta. RTJ

Low Dose May be Effective and Cause Less Withdrawals.

11-15 META-ANALYSIS OF EFFECTS AND SIDE-EFFECTS OF LOW DOSAGE TRICYCLIC ANTIDEPRESSANTS IN DEPRESSION

Despite growing popularity of selective serotonin reuptake inhibitors (**SSRI**), tricyclic antidepressants (**TC**) are still widely prescribed. Evidence for dosage is poor. Many guidelines recommend over 100 mg/d. but there is lack of convincing evidence that lower dosages are not effective. "This uncertainty casts doubt on the widely held view that depression is undertreated in primary care."

It also questions whether SRIs should be preferred over tricyclics when convincing trials fail to find differences in effectiveness between the two.

This study assessed the effects and side-effects of low dosage tricyclic antidepressants compared with placebo, and with standard dosage tricyclics in acute phase treatment of depression.

Conclusion: Treatment of depressed adults with low dose tricyclics is justified.

STUDY

1. Conducted a systematic review of randomized trials comparing low dosage of tricyclics with placebo, and with standard dose the same tricyclic for adults in treatment of the acute phase of depression. Low dose defined as 100 mg or less per day of amitriptyline (*Elavil*), clomipramine (*Generic*), or desipramine (*Norpramin; generic*) and others. Standard dose defined as over 100 mg/d.
2. Main outcome = response in depression according to the author's definition (usually defined as greater than 50% reduction in severity of depression).
3. Also determined relative risks of overall dropouts and dropouts due to side-effects.

RESULTS

1. Thirty five studies (over 2000 participants) compared low-dose TC with placebo:
   Low dose (usually 75 to 100 mg/d) was 1.7 times more effective than placebo in bringing about response at 4 weeks, and 1.5 times more effective at 6 to 8 weeks.
2. Six studies (551 participants) compared low-dose TC with standard dose:
   Standard doses failed to bring about more response, but produced more dropouts due to side-effects than low-dose. (Standard dose users were 55% more likely than low-dose users to drop out due to side-effects.)

DISCUSSION

1. Compared with placebo, low dose TC (75 to 100 mg/d) and possibly below this dose, brought

about more reduction in depression at 4 to 8 weeks and beyond. However, there were more side effects and more dropouts. The number needed to treat to bring about response in depression was between 4 and 6 at 1-6 months of treatment. The NNT to harm or produce one dropout due of side-effects was about 24.

2. Standard dosage TC may or may not be able to bring about more reduction in depression than low-dosage, although they cause more dropouts due to side-effects than placebo. (NNT to harm = about 11.)
3. "These sensitivity analyses greatly strengthen the inference that in the treatment of depression, tricyclics at dosages lower than the usually recommended range, are more effective than placebo, but possibly a little bit less effective than standard dosage of tricyclics, although with fewer side effects."

CONCLSION

Treatment of depression with low dose tricyclics is justified.

BMJ November 2, 2002; 325: 991-95 Original investigation, first author Toshi A Furukawa, Nagoya City University Medical School, Nagoya, Japan. www.bmj.com/cgi/content/full/325/7371/991

Comment:

I believe this observation is of clinical importance for primary care. Most primary care clinicians switch responsibility of treatment of severe depression to their psychiatrist colleagues. Higher doses are much more difficult to maintain.

During my clinical years, I often prescribed low dose TC, usually amitriptyline (*Elavil*) Sometimes patients would report improvement in depression with a dose of 25 mg at bedtime. RTJ

Keep Walking As Long As You Can. Every Little Bit Helps

11-16 WALKING AND LEISURE-TIME ACTIVITY AND RISK OF HIP FRACTURE IN POSTMENOPAUSAL WOMEN

Several studies have demonstrated that regular activity can reduce risk of falls and fractures through improvements in muscle strength and balance. Physical activity (weight bearing and resistance exercise) can also reduce risk of fractures by increasing bone remodeling and bone density.

This study examined the association between exercise and leisure-time activities and the risk of hip fracture among postmenopausal women.

Conclusion: Moderate levels of activity, including walking, reduced risk of hip fracture.

STUDY

1. Nurse's Health Study followed over 61 000 postmenopausal women for 12 years. None had diagnosis of cancer, stroke, heart disease, or osteoporosis at baseline.
2. Repeated questionnaires determined intensity and duration of leisure-time activity and time spent walking, sitting, and standing.
3. Determined rate of hip fracture resulting from low or moderate trauma.

RESULTS

1. Identified 415 incident hip fractures. Median age at fracture was 67 years.
2. After controlling for age, bone mass index, use of postmenopausal hormones, smoking, and dietary intakes, risk of hip fracture was lowered by 6% for each increase in 3 metabolic equivalent-hours (MET-hours per week) of activity (equivalent to 1 h/ week of walking at an average pace).
4. Active women with at least 24 MET-hours/week had a 55% lower risk (RR = 0.45) compared with sedentary women with less than 3 MET-hours/week.
5. Even women at lower risk of hip fracture due to a higher body weight experienced a decrease in hip fracture with higher levels of activity.
6. Risk of hip fracture decreased linearly with increasing levels of activity among women who were not taking postmenopausal hormones, but not among women taking hormones.
7. Among women who did no other exercise, walking for at least 4 hours/week was associated with a 41% lower risk of hip fracture, compared with those with less than 1 hour/week.
8. More time spent standing was also independently associated with lower risk.

DISCUSSION

1. Total physical activity from exercise and leisure-time activity was associated with significantly lowered risk of hip fracture. A faster pace was also associated with a lower risk, perhaps because of a greater impact on bone.
2. Incidence of hip fracture decreased by 6% for each hour per week of walking an average pace.
3. Activity must be maintained to preserve the benefit.
4. In clinical studies, a combination of HRT plus exercise has been reported to increase bone mineral density more than exercise alone. In this study, active women not taking HRT had similar protection against hip fracture as that provided by HRT.
5. Activities that promote balance and flexibility are also important in reducing risk of falling. Weight bearing and resistance exercises can increase muscle size and strength, and lead to higher bone density.
6. Standing was also associated with a lower risk of hip fracture, independent of body-weight and time spent in leisure-time activities.. As a weight bearing activity, standing could confer benefits to balance and muscle that may translate into improved bone strength and protection against hip fracture.

CONCLUSION

More leisure-time activity was associated with a lower risk of hip fractures in postmenopausal women. Moderate levels of activity, including walking, were associated with substantially lower risk.

JAMA November 13, 2002; 288: 2300-2306 Original investigation, first author Diane Fesanich, Brigham and Women's Hospital and Harvard Medical School, Boston Mass. www.jama.com

Comment:

One MET = the energy spent when sitting quietly. Walking at an average pace expends about 3 METs. MET-hours combine duration and intensity of activity. The more MET-hours per week, the lower the risk of hip fracture.

There was a trend toward benefit in women who took HRT and also exercised. Don't rely on HRT alone.

Some of the benefit must have been due to improvements in strength and balance, reducing the risk of falling. RTJ

A Stronger Predictor Of Future Cardiovascular Events Than LDL-Cholesterol

11-17 COMPARISON OF C-REACTIVE PROTEIN AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS IN PREDICTION OF FIRST CARDIOVASCULAR EVENT.

LDL-cholesterol is presently the focus of current guidelines for determination of risk of cardiovascular disease. However, atherothrombosis often occurs in the absence of hyperlipidemia. The National Heart, Lung, and Blood Institute has concluded that populating-based data on other risk factors are urgently needed.

C-reactive protein (**CRP**) is a marker of inflammation. It has been shown to be associated with increased risk of myocardial infarction (**MI**), stroke, sudden death, and peripheral arterial disease. Population-based cut points remain uncertain. There is insufficient data to directly compare the predictive value of CRP with that of LDL-cholesterol. (**LDL-c**)

This study compared the value of CRP in predicting a first cardiovascular event compared with LDL-c.

Conclusion: CRP was the stronger predictor.

STUDY

1. At baseline, the Woman's Health Study measured both CRP and LDL-c in a representative sample of over 27 000 apparently healthy women.
2. Followed for a mean of 8 years for occurrence of MI, ischemic stroke, coronary revascularization, or death from cardiovascular disease.
3. Evaluated whether CRP provided prognostic information on risk after adjustment for all components of the Framingham risk score.

RESULTS

1. The median CRP value was 1.52 mg/dL; median LDL-c was 124 mg/dL: Overall, 77% of all events occurred in women with LDL-c below 160 mg/dL. 46% occurred among those with LDL-c below 130 mg/dL.
2. CRP and LDL-c were minimally correlated. (Ie, rose independently of each other. They identify different high-risk groups.)
3. Baseline levels of both CRP and LDL-c had a strong linear relationship with the incidence

of cardiovascular events. After adjustment for other risk factors, the risk of a first cardiovascular event rose according to increasing quintiles of CRP and LDL-c.

Relative risks	1 (lowest level)	2	3	4	5 (highest level)
CRP	1.00	1.4	1.6	2.0	2.3
LDL-c	1.00	0.9	1.1	1.3	1.5

4. Similar effects were observed in separate analyses of each component of the composite end-point.
5. Screening with both biologic markers provided better prognostic information than screening with either alone. Relative risks of an event according to both CRP and LDL-c levels:

Relative risk of event		Events per 1000 person-years
1) Low-CRP and a low LDH-c,	-- 1.0 (referent)	1.3
2) Low CRP; high LDL-c	-- 1.5	2.0
3) High CRP; low LDL-c	– 1.5	2.6
4) High CRP; high LDL-c	– 2.1	3.0

6. CRP remained a strong, independent predictor of risk, rising with each quintile.
7. Increasing CRP levels were associated with increased risk of events at LDL-levels below 130, 130 to 160, and above 160 mg/dL.
8. Independent effects were observed for CRP in analyses adjusted for all components of the Framingham risk score. (*Ie, added to prognostic value of the score.)*

DISCUSSION

1. CRP, a marker of systemic inflammation, is a stronger predictor of future cardiovascular events in women than LDL-c.
2. CRP was superior to LDL-c in predicting risk at all study end-points: MI, stroke, revascularization, and death.
3. CRP and LDL-c were minimally correlated in predicting events. The combined elevation of both CRP and LDL-c was superior as a method of risk detection.
4. Since a large proportion of a first cardiovascular event occurs in individuals with “normal” LDL-c levels, and below the threshold values for intervention and treatment according to the current guidelines, addition of CRP increases prognostic value.
5. Women with low-LDL-c but with high CRP were at higher absolute risk than those with a low CRP and a high LDL-c. Statin therapy may have clinical value for primary prevention among persons with low LDL-c and high CRP.
6. CRP is stable over long periods, has no diurnal variation, and can be measured inexpensively.

CONCLUSION

CRP is a stronger predictor of cardiovascular risk than LDL-c. It adds to prognostic information to that conveyed by the Framingham risk score.

NEJM November 14, 2002; 347: 1557-65 Original investigation, first author Paul M Ridker, Brigham and Woman's Hospital, Boston, Mass. www.nejm.org

Comment:

I await further experience. Will CRP replace LDL-c? Or will we measure both? RTJ
