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HIGHLIGHTS AND *EDITORIALCOMMENTS* OCTOBER 2004

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

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

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

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

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

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

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

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

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

10-2 QUESTIONNAIRE SURVEY ON USE OF PLACEBO

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10-3 POSTPRANDIAL GLUCOSE REGULATION AND DIABETIC COMPLICATIONS.

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

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

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

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

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

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

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

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

10-4 ASPARTAME AND ITS EFFECTS ON HEALTH

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

Is it harmful? The European Scientific Committee on Food was convinced in 1988 that aspartame was safe. The committee conducted a further review encompassing over 500 reports in 2002, It concluded from biochemical, clinical, and behavioral research that a daily intake of up to 40 mg/kg/day remained entirely safe—except for people with phenyketonuria.

Does aspartame embody a healthy way of life and reduce prevalence of obesity? In most Western countries, sugar provides about 10% of total calories (50 g daily, or about 200 kcal). If this were entirely replaced by a non-nutritive, non-caloric sweetner, "obesity could indeed be vanquished—assuming these calories were not replaced". However, evidence that aspartame prevents weight gain or obesity is generally inconclusive.

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

One rounded teaspoon of sucrose (5 g) contains 20 kcal. If I added a teaspoonful of sugar to each of my 3 cups of coffee daily in place of 3 packets of aspartime (and all other intake remained constant) my caloric intake would increase by 60 kcal each day. By my calculation, if I added this amount to my daily caloric intake, and assuming perfect metabolism and conversion into fat tissue, I would gain over 5 pounds a year.

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

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

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

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

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

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

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

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

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

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

My primary advice for a patient consulting me for back pain would be to keep on being as active as possible. Stay out of bed. Take acetaminophen or an NSAID temporarily. In most cases the pain will abate spontaneously.

For more protracted back pain, I would not hesitate to refer to a chiropractor well established in the community with whom I was personally acquainted. I would not refer for conditions other than back pain.

10-6 COXIBS AND CARDIOVASCULAR DISEASE

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

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

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

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

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

How should clinicians respond? Selective inhibitors of COX-2 remain a rational choice for patients at low cardiovascular risk who have had serious gastrointestinal events, especially while taking traditional NSAIDs.

"It would appear prudent to avoid coxibs in patients who have cardiovascular disease, or who are at risk for it."

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

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

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

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

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

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

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

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

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

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

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

10-8 ANTIOXIDANT SUPPLEMENTS OF PREVENTION OF GASTROINTESTINAL CANCERS

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

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

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

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

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

"Our systematic review contains several major findings." Beta-carotene, vitamin A, and vitamin E supplements given alone or in combination do not seem to have much effect on the prevention of gastrointestinal cancers. Further, they seem to *increase* overall mortality. However, 95% confidence intervals were large in the analysis of single cancer types and could be compatible with either beneficial or harmful effects.

Most trials have investigated the effects of antioxidant vitamins given at substantially higher doses than those usually found in a balanced diet, and some trials used dosages well above the recommended upper intake levels.

This might be a cause for the absence of the expected protective effect, and for the increase in mortality associated with high-dose antioxidant supplements.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

I believe other balance exercises may benefit: eg. standing still on one foot; walking in tandem heel to toe. The objective is to fatigue an old symptom and train a new one.

See the preceding abstract for description of the exercises. RTJ

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

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

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

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

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

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

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

ABSTRACTS OCTOBER 2004

Have A Greater Prevalence of Other Risk Factors.

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

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

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

Conclusion: They have a greater prevalence of other risk factors.

STUDY

1. Analyzed data from over 3400 adults obtained in 1999 and 2000 by the National Health and Nutrition Examination Survey.
2. Determined prevalence of risk factors: total cholesterol, diabetes, overweight, and obesity in addition to BP.
3. Compared the number or risk factors present in persons with normotension, prehypertension, and hypertension.

RESULTS

1. Overall, roughly 1/3 of adults had hypertension, 1/3 prehypertension, and 1/3 normotension.

2. Prevalence differed considerably with age:

	Normotension (%)	Prehypertension (%)	Hypertension (%)
20-39	59	33	8
40-59	35	35	30
60 and above	11	23	66

3. Men had a higher prevalence of prehypertension than women.

4. African Americans had a higher prevalence of prehypertension than Whites and Mexican Americans.

5. Risk factors varied with BP:

	Normotension (%)	Prehypertension (%)	Hypertension (%)
Cholesterol over 200	42	59	71
BMI > 25	53	64	79
BMI > 30	19	31	45
Diabetes	2	4	13

6. Persons with prehypertension were 1.7 times more likely to have at least one other risk factor compared with normotensives. Only about ¼ of adults with prehypertension had *none* of the major risk factors.

DISCUSSION

1. This highlights the need for early interventions to lower BP and other risk factors through lifestyle changes.

2. Overweight/obesity was the most prevalent risk factor.

3. The high prevalence of risk factors in persons with prehypertension (as well as hypertension) suggests opportunities for further preventive and public health efforts.

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

CONCLUSION

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

Archives Int Med October 25, 2004; 164: 2113-18 Original investigation, first author Kurt J Greenlund, Centers for Disease Control and Prevention, Atlanta, GA.

See also: "Effects of Prehypertension on Admissions and Deaths" *Archives Int Med October 25, 2004; 164: 2119-24,* first author Louise B Russell, Rutgers University, New Jersey. This original investigation reports that together, prehypertension and residual hypertension (defined as patients with hypertension who take drugs who do not achieve a systolic BP below 140) account for many hospital admissions, nursing home stays, and deaths.

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"Used Wisely, Placebos Might Have A Legitimate Place in Therapeutics."

10-2 QUESTIONNAIRE SURVEY ON USE OF PLACEBO

This small study from Israel asked—How commonly are placebos used in clinical practice?

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

This study concerned the frequency and circumstances of use of placebo in clinical practice, and attitudes towards its use among those who administer it.

Conclusion: Most practitioners used placebos. Placebos might have a legitimate place in therapeutics.

STUDY

1. A questionnaire in hospitals and clinics in Israel asked 31 senior hospital-based physicians, 31 head nurses, and 27 family physicians about placebo use.
2. Main outcome = self-report of frequency and circumstances of, and attitudes towards, use of placebo.

RESULTS

1. Among 89 respondents 60% used placebos. Among these:
   94% reported that they found placebos generally or occasionally effective.
   62% prescribed a placebo as often as once a month.
   68% told patients they were receiving actual medication. (*Deception*)
   28% considered placebo a diagnostic tool.
   17% said nothing at all.
2. Placebos were given in the form of saline infusions, intramuscular injections, or vitamin C tablets.
3. Placebos were used for anxiety, pain, agitation, vertigo, sleep problems, asthma, contractions in labor, withdrawal from recreational drugs.
4. Ethical issues: Only 5% thought use should be categorically prohibited. Most others considered use conditional on circumstances such as prior experience with use, notifying the patient that a placebo was given, or evidence from research that the placebo was effective.

DISCUSSION

1. Despite general disapproval in the medical literature, use of placebo in this population was widespread. Circumstances included a wide variety of clinical situations.
2. Only 5 in 100 respondents would prohibit use in all circumstances.
3, Most clinicians claimed effectiveness of the placebo. They believed placebos can have analgesic potency.
4. Many claimed that placebos were a diagnostic tool. But. . . "The physician who uses a placebo diagnostically is at risk of reaching unfounded conclusions, to the detriment of his or her patients."
5. Some clinicians advocate banning placebo use because of the deception involved and possible damage to the doctor-patient relationship.

CONCLUSION

Most practitioners in this study continued to use placebos. “Used wisely, placebos might have a legitimate place in therapeutics.”

BMJ October 23, 2004; 329: 944-46 Original investigation, first author Uriel Nitzan, Hadassah School of Medicine, Jerusalem, Israel.

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Control Postprandial Glucose to Prevent Vascular Complications.

10-3 POSTPRANDIAL GLUCOSE REGULATION AND DIABETIC COMPLICATIONS.

“Since the 2-hour postchallenge level of glucose increases with age, and that of fasting glucose does not, most cases of asymptomatic diabetes (*and glucose intolerance*) in the elderly have isolated postchallenge hyperglycemia.”

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

This article provides an up-to-date review of the hypothesis that controlling postprandial glucose levels is an important strategy in prevention of complications of diabetes.

The postprandial glucose level is determined by many factors: timing, quantity and composition of the meal; carbohydrate content of the meal; and the resulting secretion of insulin and inhibition of glucagon secretion. Because the absorption of food continues for 5 to 6 hours after a meal, the optimum time to measure postprandial blood glucose levels is an open question. (*I suspect it will vary between individuals. RTJ*) In general, measurement 2 hours after a meal is practical and provides a reasonable assessment.

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

The HbA1c level is a useful measure of the integrated metabolic control over the preceding 2 months. It does not reveal any information on the extent or frequency of blood glucose excursions. One can argue that HbA1c is not the best or most clinically useful glycemic indicator of risk of complications, particularly at the lower end of the HbA1c range. There is no threshold of HbA1c that will prevent vascular complications.

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

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

Archives Int Med October 25, 2004; 164: 2090-95 "Special article" review by the International Prandial Glucose (PGR) Study Group, first author Antonio Ceriello, University of Udine, Italy.

Comment:

a Would not small, frequent meals also relieve some of the burden of glycemia?

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10-4 ASPARTAME AND ITS EFFECTS ON HEALTH

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

Is it harmful? The internet contains a vast catalogue of frightening personal accounts attributing multiple health disasters to aspartame. Although no orchestrated public outcry has taken place, much sensationalist journalism has been published. People do resent interference with foods (eg, genetically modified foods) and regard synthetic components with suspicion.

In contrast, aspartame marketing implies that it embodies a healthy way of life and avoids obesity. Evidence does not support any link between aspartame and cancer, hair loss, depression, dementia, behavioral disturbances, or any of the other conditions appearing in websites. (But, proving negatives is difficult.) Randomized controlled trials of high doses in humans have not shown any behavioral or other adverse effects.

The European Scientific Committee on Food was convinced in 1988 that aspartame was safe. The committee conducted a further review encompassing over 500 reports in 2002, It concluded from biochemical, clinical, and behavioral research that a daily intake of up to 40 mg/kg/day remained entirely safe—except for people with phenyketonuria.

Does aspartame embody a healthy way of life and reduce prevalence of obesity? In most Western countries, sugar provides about 10% of total calories (50 g daily, or about 200 kcal). If this were entirely replaced by a non-nutritive, non-caloric sweetner, "obesity could indeed be vanquished—assuming these calories were not replaced". However, evidence that aspartame prevents weight gain or obesity is generally inconclusive. (Replacing fructose-containing soft drinks in children with "diet' [artificial sweetner] drinks is inversely related to weight gain.)

BMJ October 2, 2004; 329: 755-56 Editorial, first author Michael E J Lean, University of Glasgow, Scotland.

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Access to Chiropractic was Associated with Reduced Health Costs.

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

Back pain accounts for billions in annual health care costs. It is a leading cause of physician visits. It is associated with long-term disability, and is a common cause of restricted activity and use of prescription and non-prescription drugs.

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

This study assessed the effects of access to chiropractic care on the overall consumption of health care.

Conclusion: Access to chiropractic was associated with *reduced* health costs.

STUDY

1. Retrospective study analyzed claims data covering a 4 year period. It compared more than 700 000 health plan members who had additional chiropractic coverage *vs* over 1 million members without coverage.
2. Claims were primarily for lower back pain. Other neuromusculoskeletal disorders were also included: neck pain; thoracic spine and rib disorders; headache; upper and lower extremity myalgias and arthralgias.

RESULTS

1. Compared with those without coverage, members with chiropractic coverage had *lower* annual costs (by $200). They also had a *lower* average back-pain episode-related cost.
2, Having coverage was associated with a 1.6% decrease in total annual health care costs.
3. Patients with chiropractic coverage had lower utilization of plain radiographs and MRI; fewer hospitalizations; less surgery and inpatient care.

DISCUSSION

1. Back pain is a major public-health concern. There is growing evidence for the low risks associated with chiropractic spinal manipulation in most cases. And favorable evidence for its effectiveness in treating back pain.
2. Chiropractic care sought by members with insurance coverage was more often substituted for usual medical care. It was less often an add-on care.
3. Patients treated for back pain by chiropractors tend to be more satisfied than those treated by MDs.

CONCLUSON

Access to managed chiropractic care may reduce overall heath care expenditures. It may prove to be clinically beneficial.

Archives Int Med October 11, 2004; 164: 1985-92 Original investigation, first author Antonio P Legorreta, UCLA School of Public Health, Los Angeles.

An editorial in this issue of Archives (pp 1953-54), first author Jose Ness, University of Iowa, Iowa City comments:

Chiropractic is certainly one to the most popular therapeutic modalities encompassed by complementary and alternative medicine. Chiropractors are now recognized as qualified practitioners by a growing number of health insurance companies. They receive referrals from a considerable number of physicians practicing in other fields of expertise. Chiropractic is now…"A profession at the crossroads of mainstream and alternative medicine".

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

Some in the chiropractic profession argue for the right to be acknowledged as primary care providers, to diagnose and treat a myriad of problems, not restricting their practice to musculoskeletal conditions. Critical questions remain regarding which subsets of patients could derive the most benefit from chiropractic care. Careful scrutiny should be applied toward defining the subset of patients who would be at a higher risk for major complications from chiropractic and in whom intervention would cease to be appropriate. (*An important ill-defined decision primary care clinicians must make on a basis of anecdotal evidence and judgment RTJ*.)

On the other hand, chiropractic manipulation may prove to be a *safer* alternative when compared with the use of NSAIDs or opiates in frail patients.

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Serious Adverse Effects Uncovered After 5 Years Of General Use.

10-6 COXIBS AND CARDIOVASCULAR DISEASE

Cyclo-oxygenase 1:

COX-1 is an enzyme, *continuously* present, the action of which leads to *ongoing* formation of a prostaglandin in many cells, including the gastric epithelium. The prostaglandin so formed protects the gastric epithelium from ulcer formation. Inhibition of COX-1 reduces formation of the protective prostaglandin and leads to increased tendency for formation of gastric ulcers.

Cyclo-oxygenase 2:

COX-2 is an enzyme formed *intermittently* in response to inflammation. It leads to formation of a prostaglandin which mediates inflammation. (Ie, produces fever and aching.) Selective inhibition of COX-2 reduces symptoms of inflammation while retaining the protective prostaglandin effect on the stomach.

The traditional NSAIDs inhibit both COX-1 and COX-2. While they benefit fever and aching, they also are associated with an increased risk of stomach ulceration and bleeding.

Three COX-2 inhibitors: 1) rofe-coxib (*Vioxx*) , 2) cele-coxib (*Celebrex*) , and valde-coxib (*Bextra*) , termed "coxibs" have been available on prescription in the USA. They have been aggressively marketed directly to the public. Sales have been in the millions. Two more coxibs are under consideration. Coxibs are a subclass of

nonsteroidal anti-inflammatory drugs (NSAIDs) designed to selectively inhibit COX-2 (thus reducing symptoms of inflammation) while sparing the action of COX-1 (thus maintaining the protective effect on the stomach).

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

Prostaglandin I_2 is the predominant cyclo-oxygenase product in endothelium. It inhibits platelet aggregation, causes vasodilation and prevents proliferation of vascular smooth muscle. (Ie, a protective factor.) Suppression of I_2 may remove this protective effect and lead to adverse vascular events. It was previously assumed that prostaglandin I_2 was derived mainly by action of COX-1, and that selective COX-2 inhibitors would not lessen its formation. This is incorrect. Both *Celebrex* and *Vioxx*, as well as traditional NSAIDs suppress the formation of prostaglandin I_2.

The effects on prostaglandin I_2 contrast with those of thromboxane. Thromboxane causes platelet aggregation, vasoconstriction, and vascular proliferation. (I.E, a harmful factor). Aspirin and traditional NSAIDs inhibit *both* prostaglandin I_2 and thromboxane formation. (Ie, the adverse effects of thromboxane are diminished as the beneficial effects of prostaglandin I_2 are blunted, somewhat canceling each other out.) It is now suggested that suppression of COX-2, while blunting the protective effects of prostaglandin I_2, may leave the adverse effects of thromboxane intact, thus causing an increased tendency to thrombosis.

Thus, a single mechanism of COX-2 inhibitors (depressing I_2 while leaving thromboxane intact) might elevate BP, accelerate atherogenesis, and predispose to thrombosis. The higher the patient's intrinsic risk of cardiovascular disease, the more likely the manifestation of a clinically important adverse event.

Before the recent *Vioxx* study, the benefit of COX-2 inhibitors in protecting the stomach appeared to outweigh the adverse cardiovascular effects. However, the study has shifted the burden of proof. "We now have clear evidence of an increase in cardiovascular risk that revealed itself in a manner consistent with a mechanistic explanation that extends to *all* coxibs."

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

NEJM October 21, 2004; 351: 1709-11 "Perspective", editorial by Garret A FitzGerald, Institute for Translational Medicine and Therapeutics, University of Pennsylvania, Philadelphia.

See also an editorial *Failing Public Health—Rofecoxib, Merck, and the FDA* in this issue of NEJM (pp 1707-09) by Eric J Topol, Cleveland Clinic Foundation, Cleveland Ohio.

The editorial faults both the FDA and Merck for not heeding the many warning signs of adverse cardiovascular events which were reported along the way. Indeed, Merck issued a relentless series of publications reconfirming the favorable

cardiovascular safety of *Vioxx*. One study comparing naproxin with *Vioxx* reported an increase in cardiovascular events from *Vioxx* vs naproxin. But, the study suggested that the difference was due to a protective effect of naproxin, not an adverse effect of *Vioxx*.

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

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

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Significantly Ameliorates Diabetes, Hyperlipidemia, Hypertension, and Obstructive Sleep Apnea.

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

The world epidemic of overweight (BMI > 25) and obesity (BMI > 30) is estimated to encompass 1.7 billion individuals. About 2/3 of individuals living in the USA are overweight, and, of these, almost half are obese. An estimated 23 million individuals in the USA have a BMI over 35; 8 million have a BMI over 40.

The associated co-morbidities are legion and are responsible for over 2 million deaths per year and loss of life span of 12 years.

Diet therapy, with or without support organizations, is relatively ineffective long-term. Currently there are no truly effective pharmaceutical agents available to treat obesity, especially morbid obesity. Morbid obesity is defined as a BMI > 40 (or BMI > 35 in the presence of significant co-morbidities). The NIH has established guidelines for surgical treatment (bariatric surgery).

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

Conclusion: Surgery achieved effective weight loss and greatly reduced co-morbidity.

STUDY

1. Reviewed 136 bariatric surgery studies (total of over 20 000 patients; 73% women). Mean age = 39. Baseline BMI = 47, highest 69 (morbid obesity).
2. Analyzed effects of 4 different surgical interventions.

RESULTS

1. Mean absolute weight loss = 40 kg; mean BMI decrease = 14. Mean percentage of excess-weight loss was 61%. In most cases, the degree of weight loss remained the same 2 years after surgery as before.
2. Operative mortality depended on the complexity of the procedure, from 0.1% for gastric binding to 1% for bilio-pancreatic diversion and duodenal switch.
3. Diabetes was "completely resolved" in 77% (defined as ability to discontinue all diabetes-related drugs and maintain blood glucose within normal range).
4. Hyperlipidemia improved in 70%.

5. Hypertension resolved in 62%

6. Sleep apnea resolved in 86%. "Improvement in sleep apnea was dramatic."

DISCUSSION

1. "Bariatric surgery in morbidly obese individuals reverses, eliminates, or significantly ameliorates diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea." It benefits the majority of patients.
2. Resolution of diabetes often occurred in days following surgery, even before weight loss.
3. A recent randomized study from Sweden reported that, after 2 years, the incidence of hyperlipidemia was lower by 10-fold in the surgical group *vs* controls. Of subjects with diabetes, the annual mortality rate was decreased by 80%
4. Benefits in reducing the adverse social effects of obesity are considerable.

CONCLUSION

In addition to achieving effective weight loss, bariatric surgery led to resolution of diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea in a substantial majority of patients.

JAMA October 13, 2004; 292: 1724-37 Systematic review, first author Henry Buchwald, University of Minnesota, Minneapolis.

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The Bloom Seems to be Coming Off the "Antioxidant" Theory.

10-8 ANTIOXIDANT SUPPLEMENTS OF PREVENTION OF GASTROINTESTINAL CANCERS

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

This systematic review and meta-analysis aimed to establish whether high-dose antioxidant supplements reduce the incidence of GI cancer and mortality.

Conclusion: No evidence that high-dose supplements prevent cancer. Some evidence that they may *increase* overall mortality

STUDY

1. The review identified 14 randomized trials (n = 170 000 subjects) comparing antioxidants *vs* placebo for prevention of GI cancers. The quality of the trials was generally high.
2. Supplements were given daily by mouth.

	Doses	Usual daily supplement dose:
Beta-carotene	15 to 50 mg	6 mg
Vitamin A	1.5 to 15 mg	1 mg

Vitamin C	120 to 2000 mg	60 mg
Vitamin E	30 to 600 mg	15 mg
Selenium	50 to 228 ug.	70 ug

(The mean of these doses exceeded the recommended daily dose and the usual supplement dose.)

3. Outcome measures = incidence of GI cancers and overall mortality.

RESULTS

1. The meta-analysis did *not* show any significant benefits of supplementation with high-dose beta-carotene, vitamins A, C, and E (alone or in combination) *vs* placebo for esophageal, gastric, colorectal, pancreatic or liver cancer.
2. An analysis of 7 high-quality trials showed that antioxidants were associated with a significantly *increased* mortality.
3. Four trials (only one was high quality) reported that selenium showed significant *benefit* on incidence of GI cancers.

DISCUSSION

1. "Our systematic review contains several major findings." Beta-carotene, vitamin A, and vitamin E supplements given alone or in combination do not seem to have much effect on the prevention of gastrointestinal cancers. Further, they seem to *increase* overall mortality. However, 95% confidence intervals were large in the analysis of single cancer types and could be compatible with either beneficial or harmful effects.
2. Most trials have investigated the effects of antioxidant vitamins given at substantially higher doses than those usually found in a balanced diet, and some trials used dosages well above the recommended upper intake levels. This might be a cause for the absence of the expected protective effect, and for the increase in mortality associated with high-dose antioxidant supplements. "Our result for the detrimental effect of antioxidant supplements on mortality was unexpected."
3. A recent study suggested that beta-carotene might act as a co-carcinogen.
4. The study also identified seven randomized trials that assessed antioxidant supplements in the primary or secondary prevention of colo-rectal adenomas. The pooled effect of all trials was not statistically significant.
5. Use of antioxidant supplements in the USA has increased substantially. More than half of women in the Women's Health Initiative took antioxidant supplements in some form.
6. If the mortality findings are correct, the number needed to treat to harm one patient = 112. For every million people exposed, about 9000 premature deaths could have occurred.
7. The results should not be translated to the potential effects of vegetables and fruits, which are rich in antioxidants. Many substances they contain have been postulated to have anticarcinogenic properties. Data on the effect of fruits and vegetables on cancer have been conflicting.
8. The US Preventive Task Force considers that antioxidant supplements might *not* be beneficial for cancer prevention.

CONCLUSION

"We could not find evidence that antioxidant supplements prevent gastrointestinal cancers; on the contrary, they seem to increase overall mortality."

Lancet October 2, 2004; 1219-28 Original investigation, first author Goran Bjlakovic, Copenhagen University Hospital, Denmark.

Comment:

Vitamin A is a generic term for compounds that exhibit the biological properties of retinol (a chemical entity).

Beta-carotene is a plant pigment consisting of 2 molecules of retinol joined in a chain.

An editorial in this issue of Lancet (pp 1193-94), first author David Forman, University of Leeds, Leeds, UK comments on the study:

"Antioxidant supplements are not having a good press." Randomized trials set up to study prevention of lung cancer showed that beta-carotene actually *increased* the risk of disease.

A trial of patients at high-risk of cardiovascular disease showed *no* benefit after 5 years treatment with a supplement combination.

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

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

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A High Intake of cis Fatty Acids was Associated with a Reduced Risk Of Gallstone Disease

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

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

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

Conclusion: A high intake of cis unsaturated fats was associated with a reduced risk of gallstone disease in men.

STUDY

1. Beginning in 1986, the *Health Professionals Follow-up Study* followed over 45 000 men ages 40 to 75. All were free of gallstone disease at baseline.
2. Periodically determined intake of unsaturated fats as part of a 131-item semi-quantitative food-frequency questionnaire.
3. Main outcome = self-reported newly diagnosed symptomatic gallstone disease related to cis unsaturated fat intake. Follow-up = 14 years.

RESULTS

1. Documented 2323 new cases of gallstone disease over the follow-up period. Outcomes were restricted to men with cholecystectomy and diagnostically confirmed but unremoved symptomatic gallstones.
2. After adjustment for age and other potential confounding risk factors, the relative risk (RR) of gallstone disease among men in the highest quintile of cis unsaturated fats compared with the lowest quintile was 0.82.

   RR (highest quintile vs lowest) of intake of mono-unsaturated fats = 0.83

   RR (highest quintile vs lowest) of intake of poly-unsaturated fats = 0.84
3. Median intake:

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

   (Ie, the median intake varied by about 2-fold between lowest and highest.)

DISCUSSION

1. "In this large prospective study, a high intake of cis unsaturated fats was associated with a lower risk of gallstone disease in men." The inverse relationship was evident for both mono-and poly-unsaturated fat.
2. There was an inverse relationship between intakes of linoleic acid and oleic acid, the predominant cis unsaturated fats in the US diet. Addition of palmitic acid (a saturated fat) enhanced cholesterol gallstone formation.
3. In animal experiments, substitution of olive oil or corn oil for butter prevented gallstone formation. This may have been due to effects on stabilization of bile-excreted cholesterol.
4. In addition, intake of mono- and poly-unsaturated fatty acids can improve insulin sensitivity. Gallstone disease is thought to be one manifestation of the insulin-resistance syndrome. (The "metabolic syndrome".) Hyperinsulinemia has been linked to enhanced hepatic synthesis of new cholesterol and increased excretion of cholesterol in the bile and may enhance cholesterol gallstone formation.
5. Epidemiologic and clinical studies have reported a lower incidence of gallstones in populations consuming higher amounts of cis acids. (However, results have been somewhat conflicting.)
6. Silent gallstones were not included in the study. The results may underestimate the prevalence of gallstones.

CONCLUSION

A high intake of cis fatty acids was associated with a reduced risk of gallstone disease in men.

Annals Int Med October 5 2004; 141: 514-22 Original investigation, first author Chung-Jyi Tsai, Harvard Medical School, Boston, Mass.

The article included a glossary:

Cis (unsaturated) fatty acids:

1) Mono-unsaturated: At only one point along the carbon backbone, 2 carbon atoms are connected by a single double-bond. (Eg, olive oil, peanut oil, most nuts)

2) Poly-unsaturated: Two or more double bonds. (Eg, vegetable oils [safflower, corn, canola], fatty fish.)

Subdivided into: 1) n-3 and n-6 groups depending on the distance of the first double bond from the CH3 end.

Saturated fatty acids:

Completely saturated with hydrogen atoms. No double bonds. (Eg coconut oil, palm oil, meats, poultry, and dairy products.)

Trans fatty acids:

Formed through partial hydrogenation of unsaturated oils. This changes oils to solids.

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Vestibular Rehabilitation Exercises May Be an Effective Treatment for Dizziness

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

Dizziness is a very common symptom in the general population.. It is associated with falls, fear of falling, and loss of independence in older people. It may lead to substantial disability.

The most common cause of dizziness presenting to primary care is a peripheral vestibular disorder. Psychiatric factors are also common causes. Serious cardiovascular or neurological disease is not common. A multifactorial syndrome is common in older people.

No medication in current use has well-established curative or prophylactic value or is suitable for long-term palliative use.

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

This study evaluated the effectiveness of nurse-delivered VR for patients with chronic dizziness.

Conclusion: Vestibular rehabilitation improved symptoms, postural stability, and dizziness-related handicap.

STUDY

1. A single-blind randomized, controlled trial in 20 general practices entered 170 adult patients with chronic dizziness. Mean age = 62; duration of symptoms averaged 8 years. At baseline all patients had dizziness provoked by head movement.
2. The exercises served as a screening test to identify patients with movement-provoked dizziness which is typical of vestibular imbalance and therefore should respond to VR. The most common diagnoses recorded by the primary care clinician were dizziness of unknown cause and vertigo of unknown cause. Benign positional vertigo was reported in only 9 patients.[a]

3. Randomized to: 1) vestibular rehabilitation, or 2) usual medical care. At the end of 3 months, the usual-care group crossed over and received VR. Patients adapted the exercise program to suit their symptoms, capabilities, and lifestyle.
4. Each patient assigned to VR received one 30- to 40- minute appointment with a primary care nurse. The nurse taught the patient exercises to be carried out daily at home, with the support of a treatment booklet. The set of head and eye exercises consists of repeatedly moving the head as far and as fast as comfortably possible, first from left to right, and then up and down with eyes open, with fixation and then without fixation; and then with eyes closed. Exercises were repeated several times every day—beginning slowly while sitting and then progressing as individually possible to a more rapid rate while standing and walking. Continued for 3 months, or until dizziness was no longer provoked by any movement.
5. Measured outcomes at 3-months and 6-months by self-reported symptoms of dizziness, dizziness-related quality-of-life, and by objective measurement of postural stability.
6. Primary outcome = self-reported spontaneous and provoked symptoms of dizziness, dizziness-related quality-of-life, and objective measurements of postural stability Five outcome measures = vertigo symptom scale, movement-provoked dizziness, postural stability eyes open, postural stability eyes closed, and dizziness handicap inventory.

RESULTS

1. At baseline, all participants had symptoms provoked by head movement.
2. At 3 months, improvement occurred in all 5 primary outcome measures in the VR group. Of 83 treated patients, 67% reported clinically significant improvement compared with 38% of the usual care group; (NNT = 3). Improvement was maintained at 6 months.
3. At 3-months, 23% in the VR group had no provoked symptoms *vs* 6% in the usual care group. (NNT = 6)
4. Between 3 and 6 months, the VR group maintained their improvement. (No significant deterioration.)
5. The usual care group received VR during the second 3 months. They improved significantly during this time. No difference between groups at 6 months.
6. Self-reported adherence was fair—71% reported carrying out the exercises most days of the week. But only 55% continued with the exercises for at least 2 months or until the symptoms ceased.[b]
7. No serious medical problems related to the VR were reported.

DISCUSSION

1. VR introduced and supervised by nurses can reduce symptoms, disability, and handicap resulting from chronic dizziness.
2. Outcomes were based on subjective reports. Reported improvement could be due to nonspecific psychological effects. However, the results are consistent with a specific treatment effect.
3. The success of VR relies on the willingness of patients to practice daily movements that may make their symptoms worse initially. Patients should be informed of this and that recovery may be partial. Only those who are committed should be accepted into treatment.

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

Annals Int Med October 18, 2004; 141: 598-605 Original investigation, first author Lucy Yardley, University of Southampton, UK.

Comment:

a I believe benign positional vertigo is much more common in primary care. A different type of VR may be useful.

b I believe fewer patients in primary care will comply. This application requires an enthusiastic mentor and a willing patient. But, this is not a reason to refrain from recommending the procedure.

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Places the Onus on Primary Care Physicians to Put into Practice this Inexpensive, Simple-To-Perform Treatment.

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

(This editorial comments and expands on the preceding study.)

Dizziness and vertigo are related to many physiological and pathologic processes. There are many types: vestibular rotational vertigo syndromes with nausea and vomiting, visual vertigo, presyncopal light-headedness, hypoglycemia, drug intoxication, phobias, panic attacks, physiological motion sickness, and height vertigo. Although prophylaxis and treatments differ depending on cause, physical therapy for balance control is common to all.

Balance control is one of the key functions of the vestibular system. The vestibular system, together with the visual and somatosensory systems, promotes spatial orientation, locomotion, and control of posture.

Overlapping functions of different sensory systems allow one sense to substitute, at least in part, for deficiencies in the others.

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

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

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

Annals Int Med October 19, 2004; 141: 641-43 Editorial by Marianne Deiterich, Johannes-Gutenberg University, Mainz, Germany.

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

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

For effective management of upper gastrointestinal symptoms, the intragastric pH should be maintained above 4.0 for at least 18 hours daily. Acid suppression may lead to impaired elimination of pathogens and increased colonization.

The bacteria and viruses in a contaminated stomach have been identified as species from the oral cavity.

This study examined the association between use of acid-suppressing drugs **(ASD)** and community-acquired pneumonia. **(CAP)**

Conclusion: Current use of ASD was associated with an increased risk of CAP.

STUDY

1. Identified use of ASDs in about 150 primary care practices. This included over 350 000 individuals whose records over 8 years were availably electronically.
2. Determined use of proton pump inhibitors and H2 blockers, and duration of use. Determined the first occurrence of pneumonia.
3 Conducted a case-control analysis: 1) Cases = individuals with incident pneumonia during or after stopping use of ASD; 2) Controls = individuals not using ASD matched for each case of pneumonia.

RESULTS

1. Documented over 5500 first-occurrences of community-acquired pneumonia.
2. Rates of incident pneumonia: 1) no ASD use = 0.6 per 100 person-years; 2) ASD use = 2.45 per 100 person-years.
3. Relative risks for community-acquired pneumonia:

	Unexposed to ASD	Exposed to ASD
No. of patients	345 000	19 000
No. of cases of pneumonia	5366	185
Relative risk	1.00	4.5

4. About 0.5% of patients not taking ASDs developed pneumonia over one year *vs* about 2.4% of those taking ASDs for a year. Absolute difference = about 2% per year of administration.
5. Adjusted relative risk for pneumonia among current users of ASD compared with those who had stopped use = 1.63.
6. Risk was higher in those taking proton-pump inhibitors compared with H2-receptor blockers.
7. Current use was more risky than use over 30 days prior.
8. There was a clear dose-response relationship.

DISCUSSION

1. In this large cohort, current use of ASDs was associated with an increased risk of community-acquired pneumonia. This is likely a real biological effect.
2. As long ago as 1934, a study suggested that bacillary and amoebic dysentery occurred much more frequently in subjects with hypochlorhydria or achlorhydria.
3. Studies in mechanically ventilated patients support the results. In these patients use of ASDs is associated with colonization of the oral space via the stomach. The colonized microbes in the stomach gain access to the oral cavity and on to the lower airways causing lower respiratory infection. Backflow of gastric contents into the esophagus because of an incompetent barrier at the gastro-esophageal junction is common.
4. The investigators believe the results, although observational, are generalizable to the general population.
5. Elderly patients are likely to incur severe infection, partly due to an impaired immune response and the natural reduction of gastric acid secretion.

CONCLUSION

Acid-suppressive drugs were associated with an increased risk of community-acquired pneumonia. This is likely due to reduction of gastric acid leading to increased prevalence of microbial colonization of the stomach. Backflow into the oral cavity and then to the lungs follows.

JAMA October 2004; 292: 1955-60 Original investigation, first author Robert J F Laheij, University Medical Center St. Radboud, Nijmegen Netherlands.

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