PRACTICAL POINTERS

FOR

PRIMARY CARE

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HIGHLIGHTS AND PRACTICAL POINTS

3-1 CLINICAL REALITY OF CORONARY PREVENTION GUIDELINES: A Comparison Of EUROASPIRE I And II In Nine Countries.

There is a collective failure of medical practice in applying secondary prevention measures for CHD. Adverse lifestyles persist, BP remains uncontrolled, and most patients do not achieve adequate lipid control.

Practical point: The primary care clinician must be implacable in continuing advice and supervision of secondary prevention measures for CHD.

3-2 ABCs OF SECONDARY PREVENTION OF CHD: Easier Said Than Done

The author presents a simple A,B,C mnemonic for secondary prevention

A Aspirin; ACE inhibitors

B Beta-blockers

C Cholesterol lowering drugs (especially statins)

D Diet; Don't smoke

E Exercise.

Many physicians still do not understand the benefits of secondary prevention. A systematic approach, which should be started at the time of diagnosis, is not implemented in many hospitals.

Practical point: The burden should be on health-care providers to initiate appropriate preventive measures at the time of diagnosis. Good communication is essential.

3-3 TREATMENT OF OBESITY: Need to Focus on High Risk Abdominally Obese Patients

Epidemiologic and metabolic studies have emphasized the notion that complications commonly found in obese persons are more closely related to *where the excess fat is* rather than the excess weight per se. In men, a high accumulation of intra-abdominal fat is a major risk factor for glucose intolerance, hyperinsulinism, type 2 diabetes, CHD, and related mortality. Viscerally obese persons have an atherogenic plasma lipoprotein profile.

These individuals also tend to have hypertriglyceridemia and low concentrations of HDL-cholesterol, resulting in a high total-cholesterol/HDL-cholesterol ratio. This is a powerful predictor of CHD.

The authors describe a triad of "new" atherogenic metabolic risk factors in these individuals.

1. Fasting hyperinsulinemia
2. Increased apolipoprotein B concentrations
3. Increased proportion of small, dense, lipoprotein particles

The triad has been reported to increase risk of CHD 20-fold over a 5-year period.

Practical point: Simply measuring a fasting triglyceride level and waist circumference identifies high risk, viscerally obese men who are carriers of the triad.

3-4 ABDOMINAL OBESITY AND THE "HYPERTRIGLYCERIDEMIC WAIST" PHENOTYPE

Practical point: Measuring waist circumference in addition to BMI will enhance assessment of risk.

A large waist circumference combined with an elevated triglyceride calls attention to increased risk, and can be a long-term marker of progress in improving risk.

3-5 WHAT IS THE OPTIMAL WEIGHT FOR CARDIOVASCULAR HEALTH?

An estimated 10-year risk of CHD increased significantly in a dose-response fashion as BMI increased from <20 to >30.

This supports previous observations of a direct linear association between BMI and CHD mortality and morbidity. Adverse metabolic consequences of adiposity may exist as a continuum. Even small increases in BMI to the lower and middle range (<25) may translate into important increases in long term risk.

Although BMI is an imperfect surrogate for adiposity, and does not provide information about regional fat distribution, it is a simple and reliable measure of overall obesity that has been independently and consistently associated with several clinical endpoints.

Adding waist circumference (a measure of intra-abdominal fat) to BMI improves risk assessment.

Practical point: It is not necessary to gain a BMI of 22 to improve health. Loss of 5 to 10 pounds will reduce risk.

3-6 AMERICANS' VIEWS ON THE USE AND REGULATION OF DIETARY SUPPLEMENTS

Many feel so strongly about the potential benefits of some products that they would continue to take them even if scientifically conducted studies demonstrate they are ineffective.

The majority of users believe the claims of supplement manufacturers are generally true.

Practical point: Physicians should encourage patients to disclose their use of dietary supplements. But to do so in a non-judgmental way. Physicians should become aware of those that are indeed harmful as well as those which adversely interact with prescription drugs.

3-7 SHOULD ALL PATIENTS WITH TYPE 1 DIABETES MELLITUS AND MICROALBUMINURIA RECEIVE ANGIOTENSIN-CONVERTING ENZYME INHIBITORS?

In normotensive patients with type 1 diabetes and microalbuminuria, ACE significantly reduced progression to macroalbuminuria, and increased chances of regression.

Changes in BP did not explain the benefits.

Practical point: All patients with type 1 diabetes should take ACE inhibitors.

3-8 SEVERE SEPSIS — A NEW TREATMENT WITH BOTH ANTICOAGULANT AND ANTI-INFLAMMATORY PROPERTIES.

Recombinant human activated protein C is now available therapy This is a component of the natural anticoagulant system. It is a potent anti-thrombotic protease with substantial anti-inflammatory properties.

A trial in this issue of NEJM reported clinically significant reductions in mortality in patients with sepsis.

Practical point: "On the basis of this trial, activated protein C should be given to patients who meet all the inclusion criteria, including evidence of end-organ dysfunction with shock, acidosis, oliguria, or hypoxemia."

3-9 PHYSICAL ACTIVITY AND CORONARY HEART DISEASE IN WOMEN: Is "No Pain, No Gain" Passe?

Walking need not be fast-paced for benefit. Time spent walking was more important than walking pace. Physical activity, easily within the ability of almost all women, was associated with lower CHD risk. At least one hour of purposeful walking per week, regardless of pace, was associated with lower CHD risk among relatively sedentary women.

Practical point: A conservative approach is to endorse current guidelines recommending moderate-intensity physical activity for 30 minutes per day on most days of the week. This will reduce risk even in women who smoke, are overweight, and have elevated cholesterol levels. Duration of the walk, not the speed, is the beneficial factor.

3-10 RELATIONSHIP BETWEEN PLASMA ASCORBIC ACID AND MORTALITY IN MEN AND WOMEN IN EPIC-NORFOLK PROSPECTIVE STUDY: A Prospective Population Study.

"Our findings suggest that an increase in dietary intake of foods rich in ascorbic acid might have benefits for cardiovascular disease and all-cause mortality in men and women and add to the large amount of evidence that lends support to the health benefits of fruit and vegetable intake. Small and feasible changes within the normal population range of intake could have a large effect."

"Whether ascorbic acid supplements are beneficial remains to be seen."

Practical point: Another recommendation to increase intake of fruit and vegetables.

3-11 URINARY SODIUM EXCRETION AND CARDIOVASCULAR MORTALITY IN FINLAND: A Prospective Study

High sodium intake predicted mortality and risk of coronary heart disease independently of other risk factors, including blood pressure. "These results provide direct evidence of the harmful effects of high salt intake in the adult population."

Practical point: Another recommendation to decrease salt intake.

3-12 ASSOCIATION BETWEEN TRANS FATTY INTAKE AND 10-YEAR RISK OF CORONARY HEART DISEASE IN THE ZUTPHEN ELDERLY STUDY : A Prospective Population-Based Study

A high intake of TFA contributes to the risk of CHD. Over the years, a decrease in energy intake from TFA was associated with a substantial reduction in risk.

Practical point: Trans fatty acids should be removed from the healthy diet. With due care this can be done without reducing acceptability of the diet.

3-13 IMPROVEMENT IN ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA IN PATIENTS IN WHOM *HELICOBACTER PYLORI* WAS ERADICATED.

In the year after successful eradication of *H pylori*, atrophic gastritis and intestinal metaplasia (precursors of gastric carcinoma) improved in most patients.

Practical point: A reasonable indication to treat the infection.

3-14 PREVENTING RECURRENT UPPER GASTROINTESTINAL BLEEDING IN PATIENTS WITH *HELICOBACTER PYLORI* INFECTION WHO ARE TAKING LOW-DOSE ASPIRIN OR NAPROXEN

In patients infected with *H pylori*, eradication of the infection greatly lowered risk of recurrent GI bleeding when low-dose aspirin was continued. Omeprazole also lowered risk.

In patients infected with *H pylori* , eradication of the infection did not lower risk of recurrent GI bleeding when naproxin was continued. Omeprazole lowered risk

Practical point: *H pylori* infection and low-dose aspirin may have synergistic effects to increase risk of bleeding. The protective effect of omeprazole is an important clinical point.

3-15 THERAPY FOR *HELICOBACTER PYLORI* IN PATIENTS WITH NONULCER DYSPEPSIA; A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

This meta-analysis provides little support for the use of *H pylori* eradication therapy in patients with nonulcer dyspepsia.

Practical point: This does not preclude treatment. An occasional dyspeptic patient will be reassured, and may improve.

3-16 HORMONE REPLACEMENT THERAPY AND COGNITION: Systemic Review and Meta-Analysis

In women with menopausal symptoms, HRT may have specific cognitive effects. A meta-analysis found an improvement in some aspects of cognition, and a decreased risk of dementia in HRT users,
but most studies had important methodological limitations.

Practical point: Primary care clinicians and their symptomatic menopausal patients should consider that the benefits of HRT may include some cognitive improvement, regardless of whether the benefits are specific or non-specific.

3-17 ESTROGEN REPLACEMENT THERAPY AND OVARIAN CANCER MORTALITY IN A LARGE PROSPECTIVE STUDY OF US WOMEN

Women who used postmenopausal estrogen for 10 or more years were at increased risk of fatal ovarian cancer. Estrogen use for less than 10 years was not associated. The increased risk persisted for up to 29 years after cessation of use. These women were likely taking unopposed estrogen.

Practical point: Would it not be prudent to now add progestin on an empirical basis in women whose ovaries remain intact after a hysterectomy?

3-18 HISTAMINE POISONING ASSOCIATED WITH EATING TUNA BURGERS.

Histamine poisoning occurs when persons ingest fish in which bacteria have converted the amino acid histidine into histamine. (Previously termed "scombroid fish" poisoning.)

Reported symptoms include: facial flushing, vomiting, diarrhea, dyspnea, rash, itching, tight feeling in the throat, headache, and a metallic or peppery taste in the mouth. Symptoms occur within 2 hours of ingestion.

Practical clinical point: The syndrome should be recognized. It should be differentiated from fish and food allergy. Treatment with anti-histamines is effective.

3-19 MONOCLONAL MILESTONE

Scientists at Cambridge University, England have found a way to use human cells to produce fully human monoclonal antibodies. (Human B cells fused to human myeloma cells as contrasted with the present monoclonal antibodies which fuse human B cells with mouse myeloma cells.)

The technique promises a variety of clinical applications.

3-20 TREATMENT OF CIGUATERA POISONING WITH GABAPENTIN

Ciguatera poisoning is caused by ingestion of tropical carnivorous reef fish. Ciguatoxin is a neurotoxin origination in a protozoa, and transferred up the food chain. It is not inactivated by cooking, cold or gastric juice.

This is an anecdotal report of 2 cases treated successfully with gabapentin.

Practical point: A possibly effective treatment for a disabling poisoning.

3-21 VACCINE AGAINST CERVICAL CANCER VIRUS PASSES PHASE 1 TRIALS

A vaccine against HPV16, the most prevalent strain found in cervical cancer, has passed phase 1 clinical trials.

"Women may soon be able to take a vaccine to protect themselves against cervical cancer."

3-1 CLINICAL REALITY OF CORONARY PREVENTION GUIDELINES: A Comparison Of EUROASPIRE I And II In Nine Countries.

The objective for patients with coronary heart disease **(CHD)** is to reduce risk of atherosclerotic events, to improve quality of life, and to increase survival. Patients with established CHD have the highest priority for preventive measures.

Secondary prevention measures — discontinue smoking, healthy food choices, physical activity, body mass index less than 25, BP under 140/90, total cholesterol under 200 mg/dL (5 mmol/L), and an LDL-cholesterol under 100 mg/dL (3.0 mmol/L). And use of appropriate prophylactic drugs — aspirin and other platelet modifying drugs, beta blockers, ACE inhibitors, and anticoagulants.

The first EUROASPIRE study (1995-96) showed substantial potential for increasing secondary prevention measures.

The second EUROASPIRE survey (1999-2000) was done to see whether preventive measures had improved over the years.

This study compared the proportion of patients in both studies who achieved the life-style, risk factor, and therapeutic goals recommended.

Conclusion: Goals were not reached.

STUDY

1. Both studies were done in the same selected geographical areas. Identified over 6500 consecutive patients (men and women) under age 70 who had established coronary heart disease (CHD). All had undergone coronary bypass, percutaneous coronary angioplasty, or hospital admission for acute myocardial infarction, or myocardial ischemia.
2. All were interviewed in the first and second surveys to determine any changes in lifestyle or medications.
3. Most did not participate in any form of a professional cardiac rehabilitation program.

RESULTS

1. Comparison	Survey I	Survey II
Smoking	19%	21%
Obesity (BMI > 30)	25%	31%
High BP (>140/90)	55%	54%

Cholesterol > 200 mg/dL	82%	59%
Aspirin use	84%	84%

2. Use of beta-blockers, ACE inhibitors, and especially lipid lowering drugs increased.

DISCUSSION

1. Over the 3 to 5 years, after establishing presence of coronary heart disease, secondary prevention measures largely failed to be implemented.
2. Adverse lifestyle led to an increase in obesity and smoking.
3. There was virtually no change in the proportion of patients (55%) who maintained BP over 140/90. Indeed, in both surveys, more than a quarter patients maintained a BP over 160/95. "For so many patients with established vascular disease to have such high blood pressure in not acceptable in modern medical practice."
4. To comply with lifelong treatments, patients must have a clear understanding of the progressive nature of atherosclerotic disease, their level of risk, and the need to take drugs for the rest of their lives.
5. In contrast with BP, and despite the rising prevalence of obesity, there was improvement in the goal of less than 200 mg/dL of total cholesterol. This was likely due to a large increase in use of statin drugs. Nevertheless, over half of the patients did not achieve this goal.
6. Prevalence of diabetes increased.
7. Use of aspirin (and in selected patients, anticoagulants), beta-blockers, and ACE inhibitors also increased. Use of calcium antagonists decreased.
8. A high prevalence of modifiable risk factors continued over 3 to 5 years after diagnosis of coronary heart disease. Adverse trends in obesity and smoking (especially in younger patients) emphasize the overarching importance of a societal approach to prevention. However, without professional support, it will be difficult for patients with CHD to resist the lifestyle trends in society.
9. Almost all patients with CHD could be prescribed an antiplatelet drug, an ACE inhibitor, and a statin.

CONCLUSION

There was a collective failure of medical practice in applying secondary prevention measures for CHD. Adverse lifestyles persisted, BP remained uncontrolled, and most patients did not achieve adequate lipid control.

Lancet March 31, 2001; 357: 995-1001 Original investigation by the EUROASPIRE I and II Groups

www.thelancet.com

Comment:

Lancet considered this study important enough to fast-track publication.

The program of secondary prevention of CHD is exceedingly complex and expensive. How can it be simplified and made less costly? RTJ

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3-2 ABCs OF SECONDARY PREVENTION OF CHD: Easier Said Than Done

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

The past few decades have seen extraordinary progress in reduction of morbidity and mortality associated with CHD. Taken together, the data are the foundation for the simplistic, but important, advice for secondary prevention – the ABCs, an alphabetic mnemonic:

A Aspirin ; ACE inhibitors

B Beta-blockers

C Cholesterol lowering drugs (especially statins)

D Diet; Don't smoke

E Exercise.

The preceding study sadly reports that these measures are not widely implemented. Why this large gap between our knowledge and clinical reality?

Many physicians still do not understand the benefits of secondary prevention. A systematic approach, which should be started at the time of diagnosis, is not implemented in many hospitals.

The burden should be on health-care providers to initiate appropriate preventive measures at the time of diagnosis. Quality-assurance procedures should be implemented to assess practice patterns. Good communication is essential.

Poor compliance by patients is the second part of the problem. "It is the patient who must bear the ultimate responsibility for success or failure in lifestyle change." It is difficult to change behavior, but patients with clinical CHD may be more receptive to lifestyle advice when it is offered as part of a coordinated program.

To paraphrase Mark Twain, we may be on the right track, but it is not good enough. We will still be run over if we just sit there.

Lancet March 31, 2001: 357: 972-73 Editorial by Jerome D Cohen, St Louis University School of Medicine, St Louis, MO **www.thelancet.com**

Comment:

The primary care clinician bears much of the responsibility for assessing and encouraging patient's compliance with secondary prevention care. For many patients, drugs are too expensive; lifestyle changes difficult; life-long applications tedious; reminders irritating; benefits obscure.

The primary care clinician must be implacable in continuing advice and supervision.

Cost: Aspirin, generic thiazides, and generic beta-blockers are not expensive. ACE inhibitors are moderately expensive. Statins are still costly — can run over $100 a month. RTJ

3-3 TREATMENT OF OBESITY: Need to Focus on High Risk Abdominally Obese Patients

The body mass index (BMI = weight in kg ÷ height in meters^2) has been used to define obesity.[1] As BMI increases, prevalence of hypertension, diabetes, and coronary heart disease increases. However, there is

remarkable heterogeneity found in obese persons. Despite the presence of obesity, some individuals have a relatively normal metabolic risk factor profile; others who are only moderately overweight have a cluster of abnormalities.

In the past 15 years, epidemiologic and metabolic studies have emphasized the notion that complications commonly found in obese persons are more closely related to *where the excess fat is* rather than the excess weight per se.[2] In men, a high accumulation of intra-abdominal fat is a major risk factor for glucose intolerance,
hyperinsulinism, type 2 diabetes, CHD, and related mortality. Viscerally obese persons have an atherogenic plasma lipoprotein profile. Conversely, a high accumulation of fat in the gluteal and femoral regions (more common in women) is not a major risk factor.

CT and MRI can distinguish *intra*-abdominal (visceral) fat from subcutaneous abdominal fat. A simple measurement of waist circumference has been found to be an excellent correlate with the amount of visceral fat.

Viscerally obese persons represent a subgroup of obese persons with the highest glycemic and insulinemic responses to an oral glucose challenge. In addition, these individuals tend to have hypertriglyceridemia and low concentrations of HDL-cholesterol, resulting in a high total-cholesterol/HDL-cholesterol ratio. This is a powerful predictor of CHD.

Some viscerally obese persons have normal concentrations of LDL-cholesterol. But they have an increased concentration of apolipoprotein B, a marker of small, dense lipoprotein particles which are atherogenic.

Middle-aged men with visceral abdominal obesity have a cluster of risk factors even in the absence of the classic risk factors (hypertension, type 2 diabetes, and hypercholesterolemia). The authors describe a triad of "new" atherogenic metabolic risk factors in these individuals.

1. Fasting hyperinsulinemia
2. Increased apolipoprotein B concentrations
3. Increased proportion of small, dense, lipoprotein particles

The triad has been reported to increase risk of CHD 20-fold over a 5-year period.

Fasting plasma triglyceride is the variable closest to the presence of atherogenic small, dense lipoprotein particles. Simply measuring a fasting triglyceride level and waist circumference identifies high risk, viscerally obese carriers of the triad. In men age 30 to 65 a waist circumference of 40 inches provides discriminative ability to distinguish men with hyperinsulinemia and increased apolipoprotein B concentrations. A triglyceride level of 175 mg/dL provides a cut off point to identify men with the small, dense lipoprotein phenotype. These 2 cut off points identified more than 80% of white men with the triad. "These results emphasize the importance of the measurement of waist circumference and of fasting triglyceride concentration in the assessment of risk of coronary heart disease."

(The values may not apply to women and to other age and ethnic groups.)

Waist circumference is a simple marker of abdominal fat. It moves the focus from weight to the high risk form of obesity – intra-abdominal obesity. Weight girth should be considered as a "vital sign" and recorded in the

medical record of every patient. This approach may help physicians identify obese patients who may require pharmacotherapy aimed at the waist rather than at the weight.

Moderate weight loss (5% to 10%) can improve these major metabolic abnormalities

BMJ March 24, 2001; 322: 716-20 "Clinical Review", first author Jean-Piere Despres, Quebec Heart Institute, Canada **www.bmj.com/cgi/content/full/322/7287/716**

1 First proposed by Quetelet in 1869

2 First proposed by a French physician, Dr. Jean Vague in the mid-1940s

Comment:

The waist-hip ratio has also been used as a measure of risk. The authors prefer simple measurement of abdominal circumference because with weight gain both waist and hip circumference can increase in proportion. Thus the ratio might remain the same.

The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) recognizes a clinical identification of the "Metabolic Syndrome". [JAMA May 16, 2001 p 2493] This includes abdominal obesity (waist circumference > 40 inches in males, and > 35 inches in females. The risk of CHD can be reduced beyond LDL-cholesterol lowering therapy by modification of this syndrome.

A walk through shopping malls will reveal how common abdominal obesity is — the "Mall Syndrome".

I am sure that as a risk factor, waist circumference is a continuum just as other risk factors. Most of us male elders could improve risk by slimming the waist even if it is not over 40 inches in circumference.

I believe some males with a high girth would benefit if this risk was pointed out to them. It could be a simply measured goal which might improve compliance and health. RTJ

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3-4 ABDOMINAL OBESITY AND THE "HYPERTRIGLYCERIDEMIC WAIST" PHENOTYPE

(*This editorial comments and expands on the preceding article.)*

"Abdominal obesity . . . predicts subsequent coronary artery disease **(CAD)** better than body mass index." It is associated with insulin resistance, and predicts the development of type 2 diabetes.

High waist circumference and fasting triglycerides — the "hypertriglyceridemic waist" — is a marker for the "metabolic syndrome". It is associated with non-traditional risk factors — insulin resistance, raised apolipoprotein B, and small dense low density LDL cholesterol, as well as traditional risk factors — hypertension, hyperglycemia, low high density cholesterol.

The "metabolic syndrome" triad of high apolipoprotein B, hyperinsulinemia, and small dense LDL cholesterol strongly predicts CAD even after controlling for traditional risk factors.

In patients with high triglyceride and low HDL-cholesterol, fibrates provide effective secondary prevention even when LDL-cholesterol is low.

BMJ March 24, 2001; 322: 687-89 Editorial by Paul Little, Southampton University, UK.

www.bmj.com/cgi/content/full/322/7288/687

Comment:

Do we need any more risk factors? We have plenty now. The major problem is to act more effectively on those we have. However, I believe risk factors should be added if they lead to more effective prevention. High waist circumference for some individuals can be a simple measure to call attention to increased risk and can be a long-term marker of progress in lessening risk.

The editorialist argues that the reliability of waist measurement, including the optimal position of the tape measure, is not clear. Nevertheless, I believe if the same method of measurement is used consistently, change in circumference will readily be determined. RTJ

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3-5 WHAT IS THE OPTIMAL WEIGHT FOR CARDIOVASCULAR HEALTH?

Where does healthy weight end, and unhealthy weight begin?

A recent study in the European Heart Journal investigated the relation between body mass index (weight in kg ÷ height in meters[2)] and several established risk factors for coronary heart disease **(CHD).** The cross sectional study of over 14 000 women found that as BMI increased from < 20 to > 30 — BP, total cholesterol, LDL-cholesterol, triglycerides, and fasting blood glucose rose. HDL-cholesterol decreased.

An estimated 10-year risk of CHD increased significantly in a dose-response fashion as BMI increased from under 20 to over 30.

This provides support to previous observations of a direct linear association between BMI and CHD mortality and morbidity. Adverse metabolic consequences of adiposity may exist as a continuum. Even small increases in BMI to the lower and middle range (<25) may translate into important increases in long term risk. More than 50% of adults in the US are overweight. They are at increased risk of hypertension, dyslipidemia, type 2 diabetes, CHD, stroke, and other chronic diseases.

Several analyses of morbidity have found a direct association between the typical 5 to 10 kg gain that occurs during adulthood within the "normal" BMI range (18.5 to 25) and increased risk of hypertension, type 2 diabetes, and myocardial infarction.

A US study of over 100 000 nurses aged 30 to 55 compared the relative risk of CHD in women with BMI under 21 to those with higher BMI:

	Relative risk
BMI < 21	1.00 (referent)
21 to 23	1.19
23 to 25	1.46
25 to 29	2.06

Furthermore, among women with a BMI < 25, the amount of weight gained after age of 18 remained a strong predictor of risk of CHD and type 2 diabetes. Women with BMI 23 to 24 had almost a 4-fold increase in risk compared with women with a BMI < 22.

What then is the optimal BMI range? The recent data suggest that for middle aged women a healthy BMI is < 22. However, the investigators would not recommend a BMI cut-off point of 22 when trying to prevent coronary heart disease because BMI does not discriminate between muscle and fat mass. BMI alone is not a good indicator of fat distribution. Given that abdominal fat may increase risk of CHD and type 2 diabetes more than fat in the hip or thighs, the addition of abdominal circumference to BMI might improve prediction.

"Still, although BMI is an imperfect surrogate for adiposity, and does not provide information about regional fat distribution, it is a simple and reliable measure of overall obesity that has been independently and consistently associated with several clinical endpoints."

BMI should not be the sole indicator of weight-related health. Some individuals with a BMI < 25 may be considered overweight. Other indicators such as abdominal adiposity and metabolic factors must be assessed.

From a public health prospective, a population based approach must target the entire population — from young people to older adults— by educational programs that promote caloric balance through exercise and proper diet. An anti-obesity initiative using the US National Cholesterol Education Program as a blueprint could begin to quell the current worldwide epidemic of excess weight.

BMJ March 17, 2001; 322: 631-32 Editorial by Simin Liu and JoAnn E Manson, Brigham and Women's Hospital, Boston Mass **www.bmj.com/cgi/content/full/322/7287/631**

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RECOMMENDED READING

3-6 AMERICANS' VIEWS ON THE USE AND REGULATION OF DIETARY SUPPLEMENTS

"One of the most striking changes in Americans' health behaviors in the 1990s was the widespread and growing use of dietary supplements. Some of these products are taken regularly by millions of Americans." Dietary supplements have become a "big business".

These products are mostly untested and unregulated, raising concerns about potentially serious health risks. Use of dietary supplements may lead some ill persons to forgo proven conventional medical treatments.

The products are being increasingly advertised in the media and sold in drug stores and supermarkets. This may give the public a false sense of security. Many people may believe that dietary supplements are subject to existing government regulations similar to those applicable to over-the-counter medications sold without a prescription. "In fact, dietary supplements are subject to less stringent government standards of safety testing than other over-the-counter medications."

In 1994 Congress passed the Dietary Supplement Health and Education Act. This freed dietary supplement manufacturers from many existing FDA regulations. Now the burden of proof concerning the safety of dietary supplements has shifted. Instead of the manufacturers having to show that the product is safe, the FDA must

prove that it is unsafe. Manufacturers have been able to make general health claims about products as long as they do not contain references to preventing or curing specific diseases. (*Thus the universal disclaimer on the product labels.)*

These supplements are now sold under the same oversight standard as vitamins and are categorized under a separate category as "foods".

This study asked — What are the views of the American public about these products? These investigators conducted a public opinion survey. Some conclusions:

1. A substantial percentage of Americans reported they regularly use dietary supplements as part of their routine health regimen. Many give them to their children.
2. They do not discuss the use with their physicians because they believe that the physicians know little or nothing about these products, and may be biased against them. The medical community may not be aware of the benefits.
3. Many felt so strongly about the potential benefits of some products that they would continue to take them even if scientifically conducted clinical studies showed the products to be ineffective.
4. Nevertheless, there was broad public support for increased government regulation. The majority supported a requirement that the FDA review the safety on new dietary supplements prior to their sale; to provide increased authority to remove products shown to be unsafe; to increase government regulation to ensure that advertising claims about benefits are true.
5. The majority of users thought the claims of supplement manufacturers are generally true.

Archives Int Med March 26, 2001; 161: 805-10 Original investigation, first author Robert J Blendon, Harvard School of Public Health, Boston Mass. **www.archinternmed.com**

Comment:

Physicians should encourage patients to disclose their use of dietary supplements. But do so in a non-judgmental way. Physicians should become aware of those that are harmful as well as those which adversely interact with prescription drugs.

I doubt that users will accept advice to discontinue the supplements for which no adverse effects are known.

The long historical use of plant materials in pharmacotherapy is the basis of belief in supplements. Indeed, scientific studies have found some supplements beneficial (eg, glucosamine, St Johns wort). This encourages us to maintain an open mind set. RTJ

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3-7 SHOULD ALL PATIENTS WITH TYPE 1 DIABETES MELLITUS AND MICROALBUMINURIA RECEIVE ANGIOTENSIN-CONVERTING ENZYME INHIBITORS?

"Angiotensin-converting enzyme inhibitors **(ACE)** are recommended for all patients with type 1 diabetes and *micro*-albuminuria, regardless of blood pressure."

Because microalbuminuria often occurs in the first 5 years after diagnosis, relatively young people may begin therapy with ACE inhibitors on the basis of this indication alone, and would be expected to continue to take these drugs indefinitely.

This meta-analysis determined whether the response of albumin excretion rate to ACE has a threshold in patients with type 1 diabetes and microalbuminuria. It asked which subgroup, if any, is more likely to benefit from therapy. It explored the effects of covariates such as change in BP on treatment effect.

Conclusion: All patients with type 1 diabetes should receive ACE.

STUDY

1. Obtained data from 646 patients identified in 12 trials. All were normotensive.
   All had microalbuminuria. (20 ug/min to 200 ug/min.)
2. All studies were randomized to ACE or placebo. Follow-up at least 2 years.
3. A variety of ACE drugs was included.

RESULTS

1. In patients receiving ACE, progression to *macro*-albuminuria (greater than 200 ug/min) was reduced. (Odds ratio = 0.38).
2. The odds ratio for regression to normoalbuminuria (less than 20 ug/min) was 3.07.
3. At 2 years, albumin excretion was 50% lower in treated patients than in placebo.
4. Benefits were lower in those at the lower end of albuminuria (@ 20 ug/min) vs those at the higher end.

DISCUSSION

1. ACE inhibitors have a clear beneficial effect on albumin excretion rate in normotensive patients with type 1 diabetes and microalbuminuria.
2. Progression to macroalbuminuria decreased to approximately 1/3 of that in the placebo group.
3. Regression to normoalbuminuria increased threefold. "ACE inhibitors may prevent or even reverse renal dysfunction."
4. Adjustment for BP levels had little effect on the albumin excretion rate, indicating that the beneficial effect must operate through other pathways.
5. *Treatment* effect was strongly influenced by baseline albumin excretion rates; patients with highest levels of microalbuminuria had the greatest opportunity for improvement. There was, nevertheless, some benefit on patients with the lowest levels of microalbuminuria.
6. "ACE inhibitors will benefit people with type 1 diabetes regardless of age, diabetes duration, glycemic control, or baseline blood pressure." (Note these results may apply only to adults.)
7. ACE may help reverse renal disease.

CONCLUSION

In normotensive patients with type 1 diabetes and microalbuminuria, ACE significantly reduced progression to macroalbuminuria, and increased chances of regression. Changes in BP did not explain the benefits.

Annals Int Med March 6, 2001; 134: 370-379 Original investigation by The ACE Inhibitors in Diabetic Nephropathy Trialist Group, a multicountry meta-analysis**. www.annals.org**

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3-8 SEVERE SEPSIS — A NEW TREATMENT WITH BOTH ANTICOAGULANT AND ANTI-INFLAMMATORY PROPERTIES.

Despite antibiotic therapy, mortality remains high when an acute bacterial infection induces sepsis with shock, metabolic acidosis, oliguria, and hypoxemia.

About 500 000 episodes of sepsis occur annually in the US, with a 30% - 50% mortality despite intensive medical care.

Recombinant human activated protein C is now becoming available as therapy. This is a component of the natural anticoagulant system. It is a potent anti-thrombotic protease with substantial anti-inflammatory properties.

The initial response to infection (eg, intraabdominal abscess) is a release of a variety of endotoxins and exotoxins into the circulation which induce tissue macrophages to generate inflammatory cytokines. (Eg, tumor necrosis factor and interleukins.) The early-response cytokines play an important part in host defense by attracting activated neutrophils to the site of infection. However, the entry of these cytokines and bacterial products into the systemic circulation can bring about widespread microvascular injury, leading to multiorgan failure.

An extensive search for clinically active antagonists to the causes of sepsis has thus far failed, in part because the importance of the coagulation cascade in sepsis was not recognized. Several pro-coagulant mechanisms have been associated with decreased survival from sepsis. This includes a decrease in the natural circulating anti-coagulants antithrombin III and protein C. Endotoxins and early-response cytokines generate an environment that favors coagulation by activating the extrinsic coagulation pathway.

Thus, there are several synergistic pathways by which inflammatory and pro-coagulant mechanisms can initiate and perpetuate organ injury in patients with sepsis.

There are several compelling reasons why activated protein C might be an effective therapy for sepsis. Most patients with sepsis have diminished levels of activated protein C. Activated protein C inhibits activated factors V and VIII, thereby decreasing formation of thrombin; stimulates fibrinolysis by reducing concentrations of plasminogen activator. In animals with gram negative sepsis, activated protein C may reverse the procoagulant and inflammatory effects of sepsis and improve survival. Recent evidence suggests that activated protein C may improve outcomes in severe meningococcemia.

The study in this issue of NEJM[1] reported that administration of activated protein C was associated with a reduction in plasma D-dimer levels , evidence of a lowering of the procoagulant effect of sepsis. There was also a reduction in levels of interleukin-6, indicating attenuation of the inflammatory cascade. Also evidence that activated protein C reduces production of tumor necrosis factor. Thus several mechanisms may account for the combined anti-coagulant and anti-inflammatory effects of this new drug.

"On the basis of this trial, activated protein C should be given to patients who meet all the inclusion criteria, including evidence of end-organ dysfunction with shock, acidosis, oliguria, or hypoxemia."

NEJM March 8, 2001; 344: 759-62 Editorial by Michael A Matthay, University of California, San Francisco
www.nejm.com

1 "Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis" NEJM March 8, 2001; 344: 699-709 Original Investigation by the Recombinant Human Activated Protein C Worldwide Evaluation in Severe sepsis (PROWESS) Study Group, fist author Gordon R Bernard, Vanderbilt University School of Medicine, Nashville Tenn.

The generic name of activated protein C is drotrecogin alfa (activated) It has both anti-inflammatory, anti-coagulant, and profibrinolytic properties. In patients with severe sepsis. It reduces the levels of markers of coagulation and inflammation in a dose-dependent manner.

The randomized, double-blind, placebo-controlled trial entered over 1600 patients with systemic infection and organ failure. Mortality rates: placebo = 30.8% vs 24.7% in the activated protein C group. Absolute reduction = 6.1% [NNT(benefit) = 16].

The incidence of serious bleeding was higher in the activated protein C group — 3.5% vs 2.0%. Absolute increase of 1.5% [NNT(harm) = 66].

The drug will be very expensive at least at first.

The NEJM considered this study important enough to fast-track it on the Internet.

All of the old guard of primary care physicians will remember how helpless we felt when treating patients with what was often called "Disseminated Vascular Coagulation" No effective therapy to reverse the course was available. RTJ

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3-9 PHYSICAL ACTIVITY AND CORONARY HEART DISEASE IN WOMEN: Is "No Pain, No Gain" Passe?

Physical inactivity is a major risk factor for coronary heart disease **(CHD).** Active women experience lower CHD rates than inactive women.

What are the kinds and intensity of physical activities that are associated with lower risk? Recent recommendations call for at least 30 minutes of moderate-intensity activity (eg, brisk walking) most days of the week. (Previously, more vigorous activity had been recommended.) The latter recommendation posed a barrier to usually sedentary persons.

Another issue is whether physical activity is inversely related to risk of CHD among healthy women at high risk for CHD (eg, smokers).

This study examined the relationship between light-to-moderate activity and CHD among women, including those at high risk.

Conclusion: Even light-to-moderate activity was associated with lower CHD rates in women, including those at high risk.

STUDY

1. Cohort study enrolled over 39 000 healthy female professionals age 45 and older between 1992 and 1995.
2. Assessed physical activity by questionnaire — from inactivity to vigorous activity.
3. Follow-up for 4 to 7 years (average = 5 years) , correlating CHD incidence with recreational activity and stair climbing.

RESULTS

1. 244 cases of CHD occurred in follow-up.
2. Relative risk (RR) of CHD after adjusting for potential confounders:

Less than 200 kcal/wk	1.00 (Referent)
200-599	0.79
600-1499	0.56
1500 or more	0.75

3. Vigorous activity was associated with lower risk (RR = 0.63)
4. Walking (compared with no walking) without vigorous activities also predicted lower risk:

	Relative Risk
No walking	1.0
1 to 59 min per wk	0.86
1.0 to 1.5 min per wk	0.49
2 or more hours per wk	0.48

5. RR related to walking paces:

No regular walking	1.00
Less than 2 miles per hour	0.56
2.0 to 3.9 mph	0.71
3.0 mph or more	0.52

6. When analyzed simultaneously, time spent walking, but not walking pace, predicted lower risk
7. The inverse association between physical activity and CHD risk did not differ by weight or cholesterol levels.

8. Physical activity was inversely related to risk in current smokers. But not in hypertensive women.

DISCUSSION

1. "It is encouraging to observe that vigorous activities were not necessary for lower CHD rates."
2. Walking need not be fast-paced for benefit. Time spent walking was more important than walking pace.
3. Benefits of walking also occurred among those who were overweight, smokers, and women with elevated cholesterol levels.
4. This supports guidelines recommending moderate-intensity physical activity for at least 30 minutes most days of the week (generating energy expenditure of about 1000 kcal per week).
5. It is possible that even lesser degrees of activity may decrease CHD risk. A pace of walking slower than 3 miles per hour may be beneficial. Women who walked at least 1 hour per week had about half the CHD rates of women who did not walk regularly.
6. The questionnaire used probably measured purposeful walking rather than all walking (eg, walking around the home). If all walking were included, women who reported 1 hour of purposeful walking would have spent a total of about 3 hours/wk walking.
7. Among persons with little activity, institution of even light-to-moderate activity is beneficial. Among persons who are active and fit, more vigorous activity is needed for additional health benefits.

CONCLUSION

Physical activity, easily within the ability of almost all women, was associated with lower CHD risk. At least one hour of purposeful walking per week, regardless of pace, was associated with lower CHD risk among relatively sedentary women.

A conservative approach is to endorse current guidelines recommending moderate-intensity physical activity for 30 minutes per day on most days of the week. This will reduce risk even in women who smoke, are overweight, and have elevated cholesterol levels.

JAMA March 21, 2001; 285: 1447-54 Original investigation, first author I-Min Lee, Brigham and Women's Hospital, Harvard Medical School, Boston Mass. **www.jama.com**

Comment:

Several points to emphasize:

1. All of us could benefit from upping our physical activity by a notch. If you are sedentary, begin walking at least 15 minutes per day. The pace is not critical. If you already do this, up the time by 5 minutes a day. If you are already walking at a moderate time and pace, you will benefit from an increase in aerobic exercise which results in a training effect.

2. The word "purposeful" is a key.

3. Individuals with established risk factors can be informed that they will benefit from physical activity even if they do not stop smoking, do not lose weight, or do not lower their cholesterol levels. (Although physical activity may help them gain these objectives as well.) RTJ

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3-10 RELATIONSHIP BETWEEN PLASMA ASCORBIC ACID AND MORTALITY IN MEN AND WOMEN IN EPIC-NORFOLK PROSPECTIVE STUDY: A Prospective Population Study.

The role of antioxidants in chronic diseases such as cardiovascular disease and cancer is controversial. Trials have not been conclusive.

This study presented data from a prospective population study which examined the relation between plasma ascorbic acid and subsequent mortality.

Conclusion: Small increases in fruit and vegetable intake of about one serving daily were associated with increased plasma ascorbic acid levels and had encouraging prospects for possible prevention of disease.

STUDY

1. Prospective study examined the relation between plasma ascorbic acid and mortality due to all-causes, cardiovascular disease, ischemic heart disease, and cancer.
2. Followed about 20 000 men and women (age 45-79 at baseline) for 4 years.
3. Participants completed a dietary, health, and lifestyle questionnaire.
4. Determined sex-specific quintiles of plasma ascorbic acid.

RESULTS

1. Only fruit and vegetable intake correlated consistently and more substantially with plasma ascorbic acid levels.
2. Only fruit and vegetable intake correlated with mortality due to all-causes, cardiovascular disease, and ischemic heart disease in both men and women.
3. Risk in the highest quintile of plasma ascorbic acid was about half the risk on the lowest quintile.
4. Ascorbic acid was inversely related to cancer mortality in men but not in women.
5. The relation with mortality was continuous throughout the whole distribution of ascorbic acid concentrations. A 20 umol/L rise in ascorbic acid (equivalent to about 50 g per day increase in fruit or vegetable intake) was associated with about a 20% reduction in risk, independent of many other possible confounding factors.
6. For men

	Ascorbic acid quintile				
	1	2	3	4	5
Plasma ascorbic acid (umol/L)	21	38	48	57	73
All cause mortality (per 100)	5.1	4.0	3.0	2.4	2.4
Dietary ascorbic acid (mg/d)	51	77	83	92	109

Fruit intake (g/d)	75	120	147	164	192
Vegetable intake (g/d)	70	96	96	102	117

7. Women had similar outcomes, although mortality rates were less in all quintiles.
8. About 1/4 of men in the lowest quintile of ascorbic acid took supplements; about half in the highest quintile. But interestingly, the relative risk of all-cause mortality in supplement users was not associated with mortality.

DISCUSSION

1. "In this population of men and women aged between 45 and 79 years, increasing plasma ascorbic acid concentration was strongly and independently associated with reduction in risk of mortality from all causes, cardiovascular disease, and ischemic heart disease."
2. The authors admit that bias and residual confounding may be present and confound the results.
3. "Whether ascorbic acid supplements are beneficial remains to be seen. However, our findings suggest that an increase in dietary intake of foods rich in ascorbic acid might have benefits for cardiovascular disease and all-cause mortality in men and women and add to the large amount of evidence that lends support to the health benefits of fruit and vegetable intake. Small and feasible changes within the normal population range of intake could have a large effect."

CONCLUSION

Small increases in fruit and vegetable intake of about one serving daily has encouraging prospects for possible prevention of disease.

Lancet March 3, 2001: 357: 657-63 Original investigation, first author Kay-Tee Khaw, University of Cambridge, School of Clinical Medicine, UK **www.thelancet.com**

Comment:

I abstracted the article, which comes from a prestigious source, because the conclusions are provocative Most studies claiming large benefits from minor interventions will ultimately be disproved — the "too good to be true" law. RTJ

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3-11 URINARY SODIUM EXCRETION AND CARDIOVASCULAR MORTALITY IN FINLAND: A Prospective Study

There is substantial evidence that high salt intake can increase risk of cardiovascular disease **(CVD),** especially in obese people. Some have argued that the association is not well established.

This study aimed to find out if salt intake, measured by 24-hour urinary sodium excretion is an independent risk factor for CVD and mortality.

The 24-hour urinary sodium excretion is the best way to measure salt intake.

Conclusion: High sodium intake predicted mortality and risk of coronary heart disease independent of other risk factors, including BP.

STUDY

1. Prospectively followed over 2500 Finish men and women age 25-64 (mean = 45) at baseline. Obtained complete data on 24-hour sodium excretion and cardiovascular risk factors.
2. The baseline mean 24 hour excretion of sodium was high in this group of Finns. In terms of NaCl, equal to about 13 g/d in men and 9 g/d in women.
3. Followed for 8 to 13 years. Obtained mortality data, and non-fatal coronary and stroke events.

RESULTS

1. Hazard ration associated with a 100 mmol sodium (2.3 g Na; 5.7 g NaCl) increase in urinary sodium:

Coronary heart disease	1.5
Cardiovascular disease	1.5
All cause mortality	1.3

2. Frequency of acute coronary events, but not acute stroke increased significantly with increasing Na excretion.
3. There was a significant interaction between body mass index, urinary sodium, and mortality in men.

DISCUSSION

1. Coronary heart disease, cardiovascular mortality and all-cause mortality all rose significantly with increasing 24-hour sodium excretion. This was independent of other cardiac risk factors including BP, smoking, cholesterol, and body mass index.
2. A positive relation between body mass index, obesity, urinary sodium excretion, and BP has been consistently reported. Some studies have suggested that people who are overweight are more sensitive to effect of sodium on BP. Body mass index and sodium could act independently on blood pressure. A high sodium intake could have some direct effect on cardiovascular risk not mediated by blood pressure.

CONCLUSION

High sodium intake predicted mortality and risk of coronary heart disease independently of other risk factors, including blood pressure. "These results provide direct evidence of the harmful effects of high salt intake in the adult population."

Lancet March 17, 2001; 357: 848-52 Original investigation , first author Jaakko Toumilehto, National Public Health Institute, Helsinki, Finland. **www.thelancet.com**

Comment:

The baseline median intake of sodium (mostly NaCl) was high — about 13 g / d in men and 9 g/d in women. This is somewhat higher than average intakes in the US. Some individuals however, may exceed these levels.

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3-12 ASSOCIATION BETWEEN TRANS FATTY INTAKE AND 10-YEAR RISK OF CORONARY HEART DISEASE IN THE ZUTPHEN ELDERLY STUDY : A Prospective Population-Based Study

Trans fatty acids **(TFA)** have detrimental effects on both LDL-cholesterol and HDL-cholesterol (lowering HDL and raising LDL). Population-based studies have demonstrated increased risk of coronary heart disease **(CHD**) associated with higher intakes of TFA.

TFA are present mainly in solid fats produced by hydrogenation of oils. (In the US, mainly hydrogenated vegetable oils). Currently TFA contributes about 2% of energy intake in the US.

In the Netherlands, because of adverse publicity, intake of TFA has decreased substantially.

This prospective study investigated the association between change in TFA intake and risk of CHD in a population with high TFA intake at baseline.

Conclusion: A high intake of TFA contributed to the risk of CHD. A substantial decrease in TFA intake over the years led to lowered risk.

STUDY

1. Prospectively studied 667 men age 64-84 (mean = 71) at baseline in 1985. All were free of CHD.
2. Used dietary surveys in 1985, 1990, and 1995 to establish the participants' food consumption patterns.
3. During the next 10 years (to 1995) mean energy intake of TFA fell from 4.3% to 1.9%
4. Determined incidence of CHD over 10 years. (N = 98)

RESULTS

1. In 1985 average TFA intake was 4.3% of energy; in 1995, 1.9%. (*A remarkable population public health change*.)
2. After adjustment for age, body mass index, smoking, and dietary co-variates at baseline, TFA intake was positively associated with the 10-year risk of CHD.
3. The decrease of 2% or more in mean intake of TFA over the years was associated with a substantial decrease in risk.

DISCUSSION

1. High intake of TFA at baseline was strongly associated with risk of CHD in these elderly men.
2. The TFA intake at baseline in the Netherlands was much higher than the 2% reported in the US. However, in the US, the intake has remained stable. The decrease in TFA from margarines has been counterbalanced by an increase in TFA from commercially baked products and fast foods.
3. Evidence suggests that a decrease in TFA intake has a role in lowering CHD mortality. The number

of CHD deaths in the US due to TFA is thought to be considerable. In this study, the decrease of 2.4% energy intake from TFA could have contributed to about 23% fewer coronary deaths.

4. TFA content of bakery products and fast foods should be reduced. Substituting with saturated fats should be limited.

CONCLUSION

A high intake of TFA contributed to the risk of CHD. A substantial decrease in intake due to lowering of TFA content in the Dutch diet led to a substantial benefit on public health.

Lancet March 10,2001; 357: 746-51 Original investigation, first author Claudia M Oomen, National Institute of Public Health and the Environment, Bilthoven, The Netherlands **www.thelancet.com**

Comment:

See also "Trans Fatty acids and Coronary Heart Disease" NEJM June 24, 1999; 340: 1994-98:

The adverse effect of TFA on LDL-cholesterol/HDL-cholesterol ratio is significant. The average intake of 2% of calories as TFA in the US diet would predict a substantial increase in deaths from CHD.

2% of a 2000 cal diet = 40 calories = about 4 grams of fat. One doughnut contains 3.2 grams; one large French fries contains 10 grams.

TFA are a no-no in the healthy diet. With some care, we can avoid them almost entirely. RTJ

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Discovery of the link between Helicobacter pylori and peptic ulcer disease was one of the most startling turn-arounds in modern gastroenterology. Old time gastroenterologists were skeptical at first, and then were astounded. Eradication of the infection is now standard treatment to prevent relapse of peptic ulcer.

Debate continues about eradication in non-ulcer conditions. Does eradication prevent gastric cancer? Does the infection increase likelihood of gastric ulceration associated with aspirin and NSAIDs? Will eradication lessen the risk of ulceration associated with aspirin and NSAIDs? Will eradication benefit the many patients with non-ulcer dyspepsia? Should all patients with established infection be treated?

The following 3 studies shed some light. RTJ

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3-13 IMPROVEMENT IN ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA IN PATIENTS IN WHOM *HELICOBACTER PYLORI* WAS ERADICATED.

Few long-term studies of chronic gastritis associated with *H pylori* have been published. Two studies have reported progression (in about 1/3 of patients) to glandular atrophy and intestinal metaplasia at 10 to 30 years. These may be precancerous lesions.

This study asked whether eradication of *H pylori* would lead to improvement in the atrophic gastritis and metaplasia.

Conclusion: In the year after eradication, these precancerous lesions improved in most patients.

STUDY

1. Prospective study entered 163 consecutive patients with dyspepsia and *H pylori* infection.
2. All were treated with antibiotic therapy and a proton-pump inhibitor.
3. Performed endoscopy and antral biopsy at baseline, 1, 3, and 1 year.

RESULTS

1. *H pylori* was eradicated in 115 patients (70%).
2. Inflammation and mean neutrophil activity decreased at 1 to 3 months.
3. Glandular atrophy of the corpus and intestinal metaplasia in the antrum decreased at 1 year.
   A. Glandular atrophy in the corpus improved in 89% of those with atrophy before treatment.
   B. Intestinal metaplasia improved in 61% of those who had metaplasia at baseline.
4. In the 30% of patients in whom eradication was not successful, no significant histological changes were observed.

DISCUSSION

1. "Our results suggest that eradication of *H pylori* is associated with modification of the natural course of atrophic gastritis and intestinal metaplasia."
2. Intestinal metaplasia may be a precursor of intestinal-type gastric carcinoma.

CONCLUSION

In the year after successful eradication of *H pylori*, atrophic gastritis (a possible precursor of gastric carcinoma) and intestinal metaplasia (a precursor of intestinal-type gastric carcinoma) improved in most patients.

Annals Int Med March 6, 2001; 134: 380-86 Original investigation, first author Toshifumi Ohkusa, School of Medicine, Tokyo Medical and Dental University, Japan. **www.annals.org**

Comment:

I believe we should tilt toward treating patients with *H pylori* infection — for several reasons:

1. Possibly reducing risk of gastric cancer.
2. Possibly reducing risk of undiagnosed peptic ulcer disease. Of course, if the patient has diagnosed peptic ulcer disease, treatment is standard.
3. Possibly improving non-ulcer dyspeptic symptoms in a few patients
4. Giving the patient some reassurance. RTJ

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3-14 PREVENTING RECURRENT UPPER GASTROINTESTINAL BLEEDING IN PATIENTS WITH *HELICOBACTER PYLORI* INFECTION WHO ARE TAKING LOW-DOSE ASPIRIN OR NAPROXEN

This study assessed the risk of recurrent upper GI bleeding in patients who had a previous history of GI bleeding. Will eradication of *H pylori* lessen risk of recurrence if the drugs are continued? (Secondary prevention)

Conclusion: In patients who are infected with *H pylori* and had previous GI bleeding while taking aspirin or naproxen, eradication of *H pylori* reduced risk of bleeding in those continuing to take aspirin, but had no benefit for those continuing to take naproxen.

STUDY

1. Enrolled 400 patients who had *H pylori* infection and a history of upper GI bleeding confirmed

by endoscopy — 250 taking low-dose aspirin; 150 taking NSAIDs.

2. Their ulcers were healed by daily omeprazole for 8 weeks.

3. Then, for the next 6 months, those who had been taking aspirin were placed on 80 mg/d; those who had been taking NSAIDs were placed on naproxen 500 mg twice daily. (*Naprosyn; generic*)

4. The patients in each group were randomized to 1) 20 mg omeprazole [a proton pump inhibitor] daily, or 2) eradication therapy (bismuth subcitrate, tetracycline, and metronidazole) for one week followed by placebo for 6 months.

RESULTS

1. Aspirin patients	Recurrent bleeding over 6 months
A. *H pylori* eradicated	1.9%
B. Omeprazole — *H pylori* not eradicated	0.9%
2. Other NSAIDs	
C. *H pylori* eradicated	19%
D. Omeprazole — *H pylori* not eradicated	4.4%

DISCUSSION

1. In this study of secondary prevention of upper GI bleeding, in the group of patients who continued to take low-dose aspirin, eradication of *H pylori* was as effective as maintenance therapy with omeprazole in preventing recurrent GI bleeding. (There was no clinical important difference between recurrent bleeding in the 2 groups — 1.9% vs 0.9%).

2. In contrast, eradication of *H pylori* was much less beneficial compared with omeprazole in preventing recurrent bleeding for those continuing to take naproxen.

3.*H pylori* infection and low-dose aspirin may have synergistic effects to increase risk of bleeding.

CONCLUSION

In patients infected with *H pylori*, eradication of the infection greatly lowered risk of recurrent GI bleeding when low-dose aspirin was continued. Omeprazole also lowered risk.

In patients infected with *H pylori* , eradication of the infection did not lower risk of recurrent GI bleeding when naproxin was continued. Omeprazole lowered risk.

NEJM March 29, 2001: 344: 967-73 Original investigation, first author Francis K L Chan, Prince of Wales Hospital, Chinese University of Hong Kong **www.nejm.com**

Comment:

This was not a direct comparison of risk of ulceration in patients with *H pylori* infection given aspirin or NSAIDs, vs those without *H pylori* infection given aspirin or NSAIDs. The question — does *H pylori* infection increase risk of drug-induced ulceration is not answered. However, 19% of those in the study in whom *H pylori* was eradicated and continued to receive NSAIDs, had recurrent bleeding. This would indicate that eradication does not significantly protect against ulceration. The question — will those with infection be more likely to develop ulceration when given NSAIDs than those without infection is not answered.

The investigators suggest that patients with infection, when given aspirin, are more likely to develop ulceration than those without infection. This could be an important clinical point. However, still no direct comparison.

The protective effect of omeprazole is an important clinical point.

Clinicians in the US would be most reluctant to prescribe continued aspirin or NSAIDs to patients with history of bleeding. If strongly indicated, the prescription would be for Cox-2 inhibiting;Cox-1 sparing drugs + omeprazole or misoprostol.

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3-15 THERAPY FOR HELICOBACTER PYLORI IN PATIENTS WITH NONULCER DYSPEPSIA; A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

Dyspepsia is defined simply as pain or discomfort centered in the upper abdomen. It is extremely common. Predominant symptoms of heartburn (burning retrosternal pain) suggest gastroesophageal reflux disease, and excludes a diagnosis of dyspepsia.

The most common cause of dyspepsia is nonulcer dyspepsia. This is diagnosed when no structural or biochemical explanation is found after appropriate investigation.

Nonulcer dyspepsia is commonly chronic, interferes with the patient's quality of life, and places an additional burden on health care services.

Is *Helicobacter pylori* infection related to chronic nonulcer dyspepsia? Will eradication of the infection reduce symptoms of dyspepsia?

Conclusion: This meta-analysis provides little support for the treatment of chronic dyspepsia by eradication of *H pylori*.

STUDY

1. Included 10 studies of patients with nonulcer dyspepsia and *H pylori* infection eradicated with antibiotic therapy vs control dyspeptic patients not treated with antibiotics.

RESULTS

1. Odds ratio for treatment success in relieving nonulcer dyspepsia with eradication therapy vs control therapy = 1.3 (not statistically significant)
2. Significant heterogeneity called into question the validity of aggregating the data in question.
3. Antibiotic therapy for *H pylori* did not confer significant benefit when patients in whom the infection was cured were compared with those in whom it persisted.
4. The decrease in mean symptom score with therapy was generally similar to the decrease with control therapy.

DISCUSSION

1. "Our results do not support the use of *H pylori* eradication therapy in the treatment of nonulcer dyspepsia."
2. Documentation of the role of *H pylori* in peptic ulcer disease is based on studies showing that eradication significantly reduces the recurrence rate of ulcer, rather than on studies demonstrating direct induction of ulcers by *H pylori* infection.
3. Mechanisms other than *H pylori* infection are likely to be responsible for most cases of nonulcer dyspepsia.
4. It is important to differentiate management recommendations for patients who initially present

with symptoms of dyspepsia from recommendations for patients who have been evaluated and have received a diagnosis of nonulcer dyspepsia. Nonendoscopic testing for *H pylori* with subsequent treatment of infected patients (test and treat) is a reasonable strategy for management of patients who present with dyspepsia and no alarm symptoms. This strategy can decrease costs by decreasing the number of endoscopies performed while resulting in no change or a small improvement in symptoms. "However. after the diagnosis of nonulcer dyspepsia is established by full diagnostic evaluation, including endoscopy, our results suggest that *H pylori* therapy is not likely to result in benefit."

5. The benefit of "test and treat" in patients with dyspepsia is presumably caused by the cure of *H pylori* in the minority of patients who have ulcer disease.

CONCLUSION

This meta-analysis provides little support for the use of *H pylori* eradication therapy in patients with nonulcer dyspepsia.

Annals Int Med March 6, 2001; 134: 361-69 Original investigation, first author Loren Laine, University of Southern California School of Medicine, Los Angeles. **www.annals.org**

Comment:

What is the best approach to a patient with chronic dyspepsia? Treat empirically without further investigation, or proceed with investigation including endoscopy and determination of *H pylori* infection? I believe many clinicians would treat empirically without diagnostic testing for *H pylori.* Others would proceed to non-invasive testing for *H pylori* and treat if the infection is present. Still others would proceed to endoscopy to rule out peptic ulcer and other disease, to establish presence of *H pylori* infection,

I believe the decision depends on the severity and persistence of dyspepsia, and the informed-patient's personal decision.

If non-ulcer dyspepsia is confirmed:

With presence of *H pylori,* I believe treatment of the infection is reasonable to reassure the patient and to possibly lessen symptoms, at least in some individuals.

Without presence of infection, the patient may be reassured and symptomatic treatment continued.

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3-16 HORMONE REPLACEMENT THERAPY AND COGNITION: Systemic Review and Meta-Analysis

Some observational data suggest that hormone replacement therapy **(HRT)** may reduce risk of cognitive decline and dementia.

This study reviewed and evaluated studies of HRT for preventing cognitive decline in healthy postmenopausal women. [HRT included estrogen alone or estrogen + progestin.] Cognition includes a variety of processes (eg — memory, attention, motor speed) each mediated by different brain systems. Estrogen receptors are not distributed uniformly throughout the brain. Thus different cognitive processes may be affected differently.

Conclusion: In women with menopausal symptoms, HRT may have specific cognitive effects, and may decrease dementia.

STUDY

1. Large literature search included 29 observational and randomized, controlled trials of effects of HRT on cognitive decline, and observational studies on effects on risk of dementia.

RESULTS

1. Women symptomatic from menopause had improvements in verbal memory, vigilance, reasoning, and motor speed, but no enhancement of other cognitive functions.
2. Generally, no benefits were observed in asymptomatic women.
3. A meta-analysis of observational studies suggested that HRT was associated with a decreased risk of dementia. (Odds ratio = 0.6) However, there were possible biases and potential confounders which limited interpretation.
4. Studies did not contain enough data to assess effects of progestin, various estrogen preparations, doses, or duration of use.

DISCUSSION

1. The review offers provisional conclusions:
   - There were no deleterious effects of HRT on cognition.
   - Estrogen does not appear to enhance asymptomatic women's performance.
   - In symptomatic women, postmenopausal estrogen improved cognitive performance, especially in tests of verbal memory, vigilance, reasoning, and motor speed.
   - Symptomatic women taking estrogen might perform better on cognitive testing because they have fewer hot flashes, sleep better, and have improved mood.
   - Only some cognitive functions were affected by estrogen.
2. Previous studies suggested that HRT users have a significant decreased risk of Alzheimer's disease. However, the studies had limitations. It may be that the benefits were biased by the "healthy user effect", or variables such as education.
3. There was no evidence that estrogen improved cognitive function in women who already have dementia.
4. From a clinical prospective, the most important conclusion is that HRT improves some cognitive functions in symptomatic women. Not all functions are affected equally.

CONCLUSION

In women with menopausal symptoms, HRT may have specific cognitive effects. A meta-analysis found an improvement in some aspects of cognition, and a decreased risk of dementia in HRT users, but most studies had important methodological limitations.

JAMA March 31, 2001; 285: 1489-99 Original investigation, first author Erin S LeBlanc, Oregon Health Sciences University, Portland. **www.jama.com**

Comment:

Primary care clinicians and their symptomatic menopausal patients should consider that the benefits of HRT may include some cognitive improvement, regardless of whether the benefits are specific or non-specific. RTJ

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3-17 ESTROGEN REPLACEMENT THERAPY AND OVARIAN CANCER MORTALITY IN A LARGE PROSPECTIVE STUDY OF US WOMEN

Postmenopausal estrogen use is associated with increased risk of hormone-related cancers. Endometrial cancer incidence increases rapidly with use of unopposed estrogen. Breast cancer incidence increases only after long-duration of use. Epidemiologic studies of association of estrogen with ovarian cancer have been inconsistent.

This study examined the relation between use of estrogen replacement therapy **(ERT)** and ovarian cancer mortality.

Conclusion: ERT for 10 years or more was associated with increased risk of ovarian cancer.

STUDY

1. A prospective study (American Cancer Society's Cancer Prevention Study II) followed over 200 000 postmenopausal women from 1982 to 1996. None had history of cancer, hysterectomy, or ovarian surgery at baseline.
2. Determine incidence of ovarian cancer mortality between never-users, users at baseline, and former users as well as total years of ERT.

RESULTS

1. Over 14 years, 944 ovarian cancer deaths were recorded.
2. Women using ERT at baseline had higher death rates than never-users (Relative risk = 1.5)
3. Among former users RR = 1.2.
4. Duration of use was associated with increased risk among both baseline and former users. (The relative risk of cancer was higher in those using estrogen at baseline vs those who had used estrogen in the past. RR 2.2 vs 1.6.)
5. Annual age-adjusted ovarian cancer death rates for 10 or more years of use per 100 000 women = 64 for baseline users; 38 for former users; 26 for never users.
6. Risk declined with time since last reported use reported at study entry.

DISCUSSION

1. "This large prospective study supports the hypothesis that ERT increases the risk of ovarian cancer. The risk was associated with duration and recency of hormone use."
2. A possible mechanism is the negative feedback of estrogen on the pituitary. Decreased secretion of gonadotropins may significantly increase risk of ovarian cancer. Or possibly by a direct effect of estrogen on ovarian cells.
3. The majority of women in 1982 were likely taking unopposed estrogens. Therefore, the findings may or may not be relevant to hormone replacement therapy today if the addition of progesterone protects against ovarian cancer.
4. The increased risk of ovarian cancer must be considered in the context of the overall benefits of hormone replacement therapy.

CONCLUSION

Women who used postmenopausal estrogen for 10 or more years were at increased risk of fatal ovarian cancer. Estrogen use for less than 10 years was not associated. The increased risk persisted for up to 29 years after cessation of use.

JAMA March 21, 2001; 285: 1460-65 Original investigation, first author Carmen Rodriguez, American Cancer Society, Atlanta, GA. **www.jama.com**

Comment:

Would it not be prudent to now add progestin on an empirical basis in women whose ovaries remain intact after a hysterectomy? RTJ

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3-18 HISTAMINE POISONING ASSOCIATED WITH EATING TUNA BURGERS.

Histamine poisoning occurs when persons ingest fish in which bacteria have converted the amino acid histidine into histamine. This is often due to improper refrigeration.

The increasingly health-conscious US public is eating less red meat and more seafood.

This brief report describes 22 cases of histamine poisoning which occurred in North Carolina from July 1998 to February 1999.

Reported symptoms include: facial flushing, vomiting, diarrhea, dyspnea, rash, itching, tight feeling in the throat, headache, or a metallic or peppery taste in the mouth. Symptoms occur within 2 hours of ingestion.

Symptoms are self-limiting in most persons, but can be life-threatening in patients with asthma and heart disease. Patients taking monoamine oxidase inhibitors may suffer prolonged attacks.

Antihistamines such as diphenhydramine (*Benadryl*) and cimetidine (*Tagamet*) often relieve symptoms. Severe cases may require the same aggressive management as acute anaphylaxis.

In the NC series, all had ingested tuna. (mostly tuna burgers). Almost all patients sought emergency medical care.

The tuna samples available for analysis had histamine levels above FDA regulatory level (50 ppm). Levels reached as high as 3200 ppm. In most cases the tuna had been frozen and thawed more than once before serving. Violations in recommended temperature controls were identified. The fish might appear and smell normal. The consumer is unlikely to identify a problem.

Once the bacteria (usually Enterobacteriaceae) have formed the enzyme histidine decarboxylase, histamine production can continue even if the bacteria are killed. The toxic factors produced are heat stable, and once formed, are not destroyed by cooking, freezing, or smoking.

Histamine poisoning is the only form of fish poisoning caused by bacterial contamination. Spoiled fish of the family Scombridae (tuna, mackerel, and bonito) are commonly implicated. (Hence the former term scombroid fish poisoning.) However, other types of fish are often implicated. Thus "histamine fish poisoning" is more appropriate.

The poisoning may be underreported and classified as "seafood allergy".

JAMA March 14, 2001; 285: 1327-30 Original investigation , first author Karen Becker, Center for Disease Control and Prevention, Raleigh, NC. **www.jama.com**

Comment:

This syndrome is so distinctive, it should be easily recognized. Treatment is effective. It should be promptly reported. RTJ

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THE CUTTING EDGE

3-19 MONOCLONAL MILESTONE

For more than 2 decades Abraham Karpas and colleagues, Cambridge University, England have worked to find a way to use human cells to produce monoclonal antibodies.

These highly specific antibodies are produced by hybridomas — hybrid cells created by fusing an antibody-secreting B cell with a myeloma cell which can grow indefinitely in culture, churning out the antibody produced by the original B cell. Heretofore, the myeloma cells came from mice. This reduced the usefulness in humans.

Now these investigators have produced a line of human myeloma cells making it possible to produce fully human hybridomas. (Human B cells fused to human myeloma cells.)

The human hybridomas are stable and continuously secrete large amounts of human immunoglobulins. The technique promises a variety of clinical applications.

JAMA March 14, 2001; 1283 "The World in Medicine" Commentary by Joan Stephenson, JAMA staff. **www.jama.com**

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3-20 TREATMENT OF CIGUATERA POISONING WITH GABAPENTIN

Ciguatera poisoning is caused by ingestion of tropical carnivorous reef fish. Ciguatoxin is a neurotoxin origination in a protozoa, and transferred up the food chain. It is not inactivated by cooking, cold or gastric juice.

Gastrointestinal and a wide variety of neurologic symptoms occur. The latter may last for months. Treatments have varied, but are not usually effective.

This is an anecdotal report of 2 cases treated with gabapentin which was given one month after onset of disabling symptoms. The drug (400 mg orally 3 times daily) resulted in rapid improvement of symptoms. After 20 days the drug was stopped. Symptoms recurred within a few hours. Gabapentin was resumed, again with immediate relief of symptoms. After another 3 weeks of therapy the drug was stopped. Some lesser symptoms recurred.

Gabapentin (*Neurontin*) is an anticonvulsant drug used to treat epilepsy. It is structurally related to the neurotransmitter gamma-amino-butyric acid. It has been used successfully to treat neuropathic pain.

NEJM March 1, 2001; 344: 692-93 Letter to the Editor, first correspondent Carlos M Perez, Hospital Clinico Universidad Catolica de Chile, Santiago. **www.nejm.com**

Comment:

Several therapeutic drugs have been suggested, including IV infusion of mannitol.

This is a good example of our continuing reliance on anecdotal reports. For many conditions encountered by primary care clinicians, "evidence-based" therapy is simply not available. RTJ

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THE CUTTING EDGE

3-21 VACCINE AGAINST CERVICAL CANCER VIRUS PASSES PHASE 1 TRIALS

"Women may soon be able to take a vaccine to protect themselves against cervical cancer."

Human papillomavirus **(HPV)** is sexually transmitted. Up to 25% of sexually active women in the US are infected.

A vaccine against HPV16, the most prevalent strain found in cervical cancer, has passed phase 1 clinical trials. Researchers at Johns Hopkins and the NIH inoculated 72 volunteers (58 women) age 18-29 with a prototype vaccine. They were inoculated intramuscularly with either placebo or HPV16 virus-like particles 3 times within 3 months. The vaccine was constructed around a viral protein responsible for assembling the viral capsid. (An "empty" virus.) Thus there was no risk of causing cancer.

The vaccine elicited a strong immune response with antibody titers 40 times that seen in natural infections. Both IgG and IgM were increased.

The vaccine was well tolerated. It remains to be seen if such vaccines will actually protect against naturally acquired genital infections.

BMJ March 3, 2001; 322: 510 BMJ.com news roundup
www.bmj.com/content/vol 322/issue7285/#NEWS_ROUNDUP