PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JANUARY 2001

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE

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JANUARY 2001

HIGHLIGHTS AND PRACTICAL CLINICAL POINTS

1-1 GLYCATED HAEMOGLOBIN, DIABETES, AND MORTALITY IN MEN IN NORFOLK COHORT OF EUROPEAN PROSPECTIVE INVESTIGATION OF CANCER AND NUTRITION (EPIC-Norfolk)

Over 2 to 4 years, glycosylated hemoglobin concentration was a graded, continuous risk factor for death. Every increase of 1% in HbA1c above 5% was associated with a 29% increase in risk of all-cause death; a 38% increase in cardiovascular mortality; and 44% increase in ischemic heart disease mortality.

Adequate screening for impairments in glucose metabolism should include a HbA1c in addition to a fasting plasma glucose, at least if the glucose is over 110.

1-2 "NORMAL" BLOOD GLUCOSE AND CORONARY RISK:

Glycosylated hemoglobin provides a reliable estimate of usual glycemia and should be a more precise predictor of CHD risk. Glucose control for CHD prevention should begin in those with impaired glucose tolerance (110 to 125 mg/dL).

1-3 LONG-TERM WEIGHT LOSS AND CHANGES IN BLOOD PRESSURE: Results of the Trials of Hypertension Prevention, Phase II

Clinically significant long-term reductions in BP and reduced risk of hypertension can be achieved with even modest weight loss (5% to 10%).

1-4 OBESITY AND HYPERTENSION: What Should We Do?

Americans have intense interest in losing weight. Huge sums are spent in the effort. Physician's advice may produce some benefit, but weight-loss advice is frequently not given. Even in motivated persons, the motivation gradually wanes and few continue the recommended calorie restriction and the exercise program. Weight control is a major unsolved problem in clinical medicine. Primary care clinicians should set an example for weight control and physical activity, and relentlessly encourage overweight patients to lose and maintain the loss.

1-5 EFFECTS ON BLOOD PRESSURE OF REDUCED DIETARY SODIUM AND THE DIETARY APPROACHES TO STOP HYPERTENSION (DASH) DIET

The DASH diet is rich in vegetables, fruits, and low-fat dairy products; low in meat. Adherence to the diet will decrease BP significantly in hypertensive persons as well as in those without hypertension. Adding salt restriction lowers BP still more. This has important implications for both prevention and treatment of hypertension.

1-6 ANTIHYPERTENSIVE DRUG THERAPIES AND RISK OF ISCHEMIC STROKE.

The study suggests a particular benefit of thiazide diuretics in reducing the risk of ischemic stroke.

Compared with those using beta-blockers alone, calcium blockers alone, or ACE inhibitors alone, users of a thiazide diuretic alone experienced a much lower incidence of ischemic stroke.

Among users of 2 drugs, those patients who received 2 drugs other than a thiazide had a 1.3
greater relative risk than those receiving a thiazide as one of the two.

The most recent (1997) report of the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics as a first-line antihypertension agent. \

1-7 LONG-TERM EFFECTS OF GLUCOSAMINE SULPHATE ON OSTEOARTHRITIS PROGRESSION

Over 3 years, the combined structure-modifying and symptom-modifying effects of glucosamine sulphate suggest that it could be a *disease-modifying* agent in OA.

1-8 GLUCOSAMINE FOR OSTEOARTHRITIS: Dawn of a New Era?

Recent studies have shown that a pure form of oral glucosamine sulfate has anti-inflammatory and anabolic properties on arthritic joints. A robust mechanistic explanation is lacking.

The drug is widely available in the US as a nutritional supplement. Since it is generally self-prescribed, the results may not be generalizable due to the highly variable formulations of nutritional products bought off the counter.

1-9 EARLY STATIN TREATMENT FOLLOWING MYOCARDIAL INFARCTION AND 1-YEAR SURVIVAL.

Early initiation of statin treatment in patients with acute MI was associated with reduced 1-year mortality. "Initiation of statin treatment before or at the time of hospital discharge should be recommended for all acute MI survivors with total cholesterol or low density cholesterol levels above current guideline levels for statin treatment as secondary prevention."

1-10 REVIEW OF FIRST 5 YEARS OF SCREENING FOR FAMILIAL HYPERCHOLESTEROLAEMIA IN THE NETHERLANDS.

Primary care clinicians will inevitably encounter patients with FHC. It is common and leads to premature cardiovascular disease and death. When an unselected patient is identified with an unusually high cholesterol (eg, > 275) the family members should be screened.

Family screening of index individuals with FHC is highly effective in identifying family members with FHC, and leads to effective prophylactic therapy.

1-11 LOW-DOSE ASPIRIN AND VITAMIN E IN PEOPLE AT CARDIOVASCULAR RISK: A Randomised Trial in General Practice.

In women and men at risk of having a cardiovascular event because of the presence of at least one major risk factor, low-dose aspirin was effective when given as primary prevention.

Lack of effectiveness of vitamin E is consistent with other trials on secondary prevention.

1-12 TOLERATION OF HIGH DOSES OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN PATIENTS WITH CHRONIC HEART FAILURE.

ACE inhibitor therapy in most patients with HF can be successfully titrated to and maintained at high doses. More aggressive use is warranted. But start with a low dose (eg, 2.5 mg daily lisinopril) and gradually increase. Not all patients require the highest recommended dose.

1-13 CHLAMYDIA AND CERVICAL CANCER

C trachomatis is already known to be associated with pelvic inflammatory disease, infertility, and facilitation of transmission of HIV infection. Cervical cancer may be another complication.

1-14 THE RENAISSANCE OF C REACTIVE PROTEIN

Routine empirical measurement of CRP is a valuable aid to patient management across a broad range of clinical practice. Sensitive assay may become a new risk assessment marker for cardiovascular disease. A raised level in patients with active coronary disease identifies a high risk group likely to require interventions. "Possibly the more C reactive protein you produce, the sicker you get."

1-15 VIRAL HEPATITIS

A refresher course. See the abstract.

1-16 CARDIORESPIRATORY FITNESS AND THE PROGRESSION OF CAROTID ATHEROSCLEROSIS IN MIDDLE-AGED MEN.

Good cardiorespiratory fitness was associated with slower progression of early carotid atherosclerosis in middle-aged men.

1-17 INTAKE OF FISH AND OMEGA-3 FATTY ACIDS AND RISK OF STROKE IN WOMEN

Higher consumption of fish and omega-3 polyunsaturated fatty acids was associated with a reduced risk of thrombotic infarction, primarily among women who did not take aspirin regularly. No relation to hemorrhagic stroke.

1-18 PROPHYLACTIC TREATMENT OF MIGRAINE WITH ANGIOTENSIN CONVERTING ENZYME INHIBITOR (LISINOPRIL)

The ACE-inhibitor lisinopril had a clinically important prophylactic effect in migraine.

1-19 BIOETHICAL ASPECTS OF THE RECENT CHANGES IN THE POLICY OF REFUSAL OF BLOOD BY JEHOVAH'S WITNESSES

The commentator concludes that if the act of receiving blood is kept strictly confidential and not made known to the religious community, expulsion is unlikely. Under the ideal protection of medical confidentiality, decisions on blood transfusion made by a patient who is a Jehovah's Witness would be known only to the patient and the medical team, not the congregation.

Probably the most important advice to doctors at this time of flux in the policy of refusal of blood is to treat individual patients independently of the church's official policy. "Each case needs to be discussed and treated individually."

1-20 PUBMED CENTRAL: http://pubmedcentral.nih.gov

This new web based repository will archive, organize, and distribute peer reviewed reports from biomedical journals. It promises to archive the full texts and make them available in perpetuity. It is funded by the US National Institutes of Health and the National Library of Medicine.

But, too much information is the bane of a working clinician's existence. Physicians, and ultimately the public do not need more articles. Instead, they need better articles, preferably from a trusted source, that give new and useful information or help put knowledge into some sort of practical context.

RECOMMENDED READING

1-21 INTEGRATIVE MEDICINE: Orthodox Meets Alternative.

The January 20 issue of BMJ presented 8 articles on integrative (alternative; complementary) medicine. I abstracted a few highpoints. RTJ

1-22 AN IMPORTANT NEW SERVICE FROM JOHNS HOPKINS

Hopkins has launched an antibiotic database available to all free of charge. It offers diagnostic criteria and drug options on more than 160 drugs, and 140 diseases. It is continually updated and will immediately issue emergency alerts and drug recalls. **www.hopkins-abxguide.org**

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1-1 GLYCATED HAEMOGLOBIN, DIABETES, AND MORTALITY IN MEN IN NORFOLK COHORT OF EUROPEAN PROSPECTIVE INVESTIGATION OF CANCER AND NUTRITION (EPIC-Norfolk)

Glycated hemoglobin **(HbA1c),** an indicator of average plasma glucose over 3 months, has been suggested as a diagnostic or screening tool for diabetes.

This study examined the relation between HbA1c concentrations, diabetes, and subsequent mortality.

Conclusion: HbA1c seems to explain most of the excess mortality risk of diabetes. It appears to rise continuously after 5%

STUDY

1. Prospective population study entered over 4500 men (age 45-79). Measured HbA1c at baseline in 1995-97.

2. Follow-up to 1999 (2 to 4 years).
3. Determined mortality from all causes, cardiovascular disease, and ischemic disease.

RESULTS

1. 135 deaths occurred. As expected, men with known diabetes had increased mortality from all causes.
2. In men without known diabetes, increasing HbA1c levels were related to subsequent all-cause, cardiovascular, and ischemic mortality
3. Compared with a HbA1c under 5%, any increase of 1% in HbA1c above 5% was associated with a 29% increase in risk of all-cause death; a 38% increase in cardiovascular mortality; and 44% increase in ischemic heart disease mortality after adjustment for age, systolic BP, cholesterol, BMI, and smoking
4. All cause mortality — HbA1c %

	<5%	5-5.5%	5.5 to 7%	> 7%	Diabetes (self reported)
Rate / 100 persons	1.7	2.3	3.4	4.3	5.6
Relative risk of death	1.00	1.4	2.1	2.6	3.6

5. 82% of the excess mortality occurred in men with a HbA1c concentration of 5% to 7% (the majority of the population.)

DISCUSSION

1. HbA1c significantly predicted mortality. Risk increased as concentrations increased. The effect of HbA1c concentrations on mortality was evident even at the lower end of the population distribution. There was no apparent threshold effect.
2. "The predictive value of HbA1c for total mortality was stronger than that documented for cholesterol concentrations, BMI, and BP."
3. For established diabetes, mortality seems to be largely mediated through HbA1c levels.
4. HbA1c concentration is related to prevalent coronary disease and carotid intimal thickening in non-diabetic persons.
5. Clinical attention has focused on microvascular complications of diabetes. However, rates of myocardial infarction and stroke in diabetic persons are about twice the rates of microvascular events.
6. Control of other risk factors for cardiovascular disease is particularly beneficial in persons with HbA1c above 5% as well in those with overt diabetes. "Our data indicate that raised glycated haemoglobin concentration, even in men without diabetes, is a marker of greater absolute risk." Preventive treatment for hypertension and lipid control should be considered for such patients.
7. At a population level, lowering HbA1c by 0.1% of 0.2% would reduce prevalence of cardiovascular disease.

CONCLUSION

Glycosylated hemoglobin concentration seems to explain most of the excess mortality risk of diabetes in men, and to be a continuous risk factor over 5%.

BMJ January 6, 2001: 322; 15-18 Original investigation, first author Kay-Tee Khaw, University of Cambridge School of Clinical Medicine, UK **www.bmj.com.cgi/content/full/322/7277/15**

Comment:

The purpose of glycemic screening is to identify individuals at risk of complications and mortality.

When to label a patient as having "diabetes" is not a simple matter any more. Labeling an individual as having "diabetes" has downsides, both personal and societal

If the FPG is over 200 and typical symptoms are present, this should be no problem. If the FBG is consistently at 130 and the patient is asymptomatic, I believe considerable restraint should be used before informing the patient and his insurance company that he has "diabetes". Simply telling the patient he has some problem metabolizing sugar and convincing him to embark on a program of weight loss, diet, and exercise might be the most prudent course. Indeed, he might cease to be a "diabetic" after successful implementation of the program.

Adequate diagnostic screening should include a fasting plasma glucose and a HbA1c. Or at least a HbA1c for individuals with a FPG 110 and above. RTJ

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1-2 "NORMAL" BLOOD GLUCOSE AND CORONARY RISK:

Dose response effect seems consistent throughout the glycemic continuum

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

The association between glycemia within the "normal range" and coronary heart disease **(CHD)** has been controversial. Some studies have reported a continuum of risk. Other studies report a threshold effect, with risk observed only at glucose levels approaching or including current diagnostic criteria for diabetes. The study reports that glycosylated hemoglobin **(HbA1c)** is positively associated with the risk of future CHD in a linear stepwise fashion, with no evidence of a threshold effect, and independent of other common risk factors. "These are the most convincing data available that the association between glucose and coronary heart disease occurs throughout the normal range of glucose."

Glycosylated hemoglobin provides a more reliable estimate of usual glycemia and should be a more precise predictor of CHD risk.

This implies that glucose control for CHD prevention should begin in those with impaired glucose tolerance (110 to 125 mg/dL) , and points to the desirability of shifting the entire population glycemia curve to the left.

BMJ January 6, 2001; 322; 5-6 Editorial, first author Elizabeth Barrett-Connor, UCSD School of Medicine LaJolla, California **www.bmj.com/cgi/content/full/322/7277/5**

Comment:

Primary care clinicians should pay much more attention to fasting glucose levels between 110 and 125. A slightly elevated glucose might be a marker for other risk factors which require attention, in addition to being a causal risk factor for later development of diabetes. These individuals are more likely to have other risk factors such as overweight, sedentary life-style, abdominal obesity, and hypertension. Life-style changes are effective therapy.

A fasting glucose of 90 is preferable to one of 110. Certainly the ADA plasma glucose cut point of 126 mg/dL to define "diabetes" and 125 to rule out "diabetes" is falsely reassuring. RTJ

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1-3 LONG-TERM WEIGHT LOSS AND CHANGES IN BLOOD PRESSURE: Results of the Trials of Hypertension Prevention, Phase II

More than half the population has higher than *optimal BP* (defined as over 120/80). At present, drug therapy is usually not initiated until BP exceeds 140/90 (the diagnostic threshold for hypertension).

Lifestyle interventions for primary prevention and initial treatment of high BP remain a vital strategy.

This study investigated whether non-pharmacologic interventions can prevent hypertension over the long term.

Conclusion: Clinically significant long-term reductions in BP and reduced risk of hypertension can be achieved in overweight persons with modest weight loss.

STUDY

1. Multicenter randomized clinical trial entered over 1000 men and women age 30 to 54.
   Mean body mass index **(BMI)** was 31.
2. All had systolic BP under 140 and diastolic between 83-89. None were taking antihypertension drugs. Mean systolic = 127; mean diastolic = 86
3. At baseline, weights were 110% to 165% of ideal body weight.
4. Randomized to: 1) weight loss, and 2) usual care. Weight loss group included group meetings and individual counseling focused on dietary change, physical activity, and social support.
5. Follow-up = 3 to 4 years.

RESULTS

1. Mean weight change:	6 months	18 months	36 months
Intervention group	-4.4 kg	-2.0 kg	-0.2 kg
Usual care:	+0.1;	+ 0.7;	+1.8.

2. BP was significantly lower in the intervention group at all 3 periods. Participants in the quintile of greatest weight loss had reductions of 7/5 mm Hg. .
3. Risk ratio of hypertension (defined as at least 140/90, or prescription of antihypertension drugs) in the intervention group vs usual care was 0.58 at 6 months; 0.78 at 18 months; and 0.81 at 36 months.
4. Only 13% of participants were able to lose 4.5 kg and maintain the loss over 3 years. This subgroup had the greatest reduction in BP and a relative risk of hypertension of 0.35.

DISCUSSION

1. The pattern of weight loss suggests that weight loss alone, even if maintained, may not be sufficient to prevent an age-related increase in systolic pressure. Other determinants such as sodium restriction may be more important.
2. Only the individuals who maintained the weight loss over 36 months maintained significant lowering of BP. This applied to only 13% of the intervention participants.

CONCLUSION

Clinically significant long-term reductions in BP and reduced risk of hypertension can be achieved with even modest weight loss.

Annals Int Med January 2, 2001; 134: 1-11 Original investigation by the Trials of Hypertension Prevention Research Group, first author Victor J Stevens, Kaiser Permanente Center for Health Research, Portland, OR**. www.annals.org**

Comment

The investigators must have been disappointed at the weight loss outcome. (Weight regain by 36 months after a loss of 10 pounds during the first enthusiastic 6 months.) This is typical of weight loss programs.

At least the intervention group did not gain over 3 years.

"Clinically significant long-term reductions in BP and reduced risk of hypertension can be achieved with even modest weight loss." But realistically, weight loss is unlikely. RTJ

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1-4 OBESITY AND HYPERTENSION: What Should We Do?

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

"Even when blood pressure is adequately controlled by medication, hypertensive patients are still at substantially higher risk for cardiovascular morbidity than normotensive persons."

BP usually rises with age. This process, however, is not inevitable. Overweight is one major modifiable factor that magnifies the tendency to increases in BP with aging.

Hypertension is just one of the numerous consequences of overweight. "It has been shown that a person's medical care costs are directly proportional to his or her body mass index."

The problem with the study was the disappointing patient-adherence to the diet.

No doubt weight reduction is a worthwhile objective for people whose body weight is higher than ideal, whose BP is already high, or who are at risk for hypertension.

Americans have intense interest in losing weight. Huge sums are spent in the effort. Physician's advice may produce some benefit, but weight-loss advice is frequently not given. Even in motivated persons, the motivation gradually wanes and few continue the recommended calorie restriction and the exercise program.

Annals Int Med January 2, 2000; 134: 72-73 Editorial by Thomas G Pickering, Mount Sinai Medical Center, New York. **www.annals.org**

Comment:

Weight control is a major unsolved problem in clinical medicine.

Measurement of intra-abdominal fat accumulation by waist circumference adds to the predictive value of overweight. The 2 should be charted regularly on the medical record, just as is BP. RTJ

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1-5 EFFECTS ON BLOOD PRESSURE OF REDUCED DIETARY SODIUM AND THE DIETARY APPROACHES TO STOP HYPERTENSION (DASH) DIET

This study assessed the effect of different levels of sodium intake *in conjunction with* the Dietary Approaches to Stop Hypertension (DASH) diet. The DASH diet is rich in vegetables, fruits, and low-fat dairy products.

Conclusion: The DASH diet lowered BP. Adding salt restriction resulted in a further reduction in BP.

STUDY

1. Randomly assigned over 400 patients to: 1) DASH diet. or 2) a typical American diet. About half of

the subjects had hypertension (140-159/90-95); half were normotensive.

2. Within the assigned diets, participants in both groups ate foods with high (3.3 g/d) intermediate (2.5 g/d) , and low (1.5 g/d) levels of sodium for 30 days each. (This is equivalent to 8.3 g, 6.3 g, and 3.7 g NaCl.)
3. Assessed the effects of the DASH diet combined with varying levels of salt intake.

RESULTS

1. Reducing the sodium intake from a high to an intermediate level was associated with a lower systolic BP by 2.1 mm Hg in those on the typical American diet, and by 1.3 mm Hg in those on the DASH diet.
2. Reducing the sodium intake from an intermediate level to a low level was associated with an additional reduction in systolic BP by 4.6 mm Hg in those on the typical American diet and by 1.7 mm Hg in those on the DASH diet.
3. The effect was observed in subjects with hypertension, and in those without.
4. As compared with the typical diet with a high sodium content, the DASH diet combined with low sodium intake reduced mean systolic BP by 7.1 mm in patients without hypertension, and by 11.5 mm in those with hypertension.

DISCUSSION

1. The DASH diet lowered BP at all levels of sodium intake. The benefits of the diet apply throughout the range of sodium intake.
2. Reducing NaCl intake from the usual 8 grams daily to an intermediate level of 6 grams (the currently recommended level) in persons who continue a typical American diet was associated with a lowering of BP. Further decreases in sodium intake (to 4 grams per day) were associated with a still further lowering. "These results provide a scientific basis for a lower goal for dietary sodium than the level currently recommended."
3. The combined effects on BP of a low sodium intake + the DASH diet were greater than either intervention alone, and were substantial. "In participants with hypertension, the effects were equal or greater than those of single-drug therapy."
4. "The combination of the two interventions achieved the greatest effect on blood pressure, and therefore both — not just one— merit recommendation."
5. The BP lowering effect of sodium restriction was also evident in persons with normotension. "These results should settle the controversy over whether the reduction of sodium has a worth while effect on blood pressure in persons without hypertension."
6. The benefits of sodium restriction and the DASH diet were evident in blacks. "We speculate that a greater sensitivity to the deleterious effects of diet could contribute to the high prevalence of hypertension in blacks."
7. These results should be applicable to most people in the US. Adherence to the diet should blunt the rise in BP which normally occurs with age.

CONCLUSION

"Our results provide support for a more aggressive target for reduced sodium intake, in combination with use of the DASH diet, for the prevention and treatment of elevated blood pressure levels."

NEJM January 4, 2001; 344: 3-10 Original investigation, from the DASH-Sodium Collaborative Research Group. first author Frank M Sacks, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass**. www.nejm.com**
An editorial in this issue (p 53) comments: Benefits of BP reduction have a critical clinical importance. Nationwide, reductions in BP associated with dietary changes would reduce risk of coronary heart disease considerably. The reduction risk is in addition to those attained by other characteristics of a healthy lifestyle.

Comment:

See the DASH food pyramid on p 1 "This Week in NEJM":

Daily — low-fat dairy, olive oil, fruits, beans and nuts, vegetables, grains and starches, physical activity

Weekly — sweets, eggs, poultry, fish

Monthly — meat.

This is essentially a vegetarian diet with occasional fish and poultry and very restricted meat intake. An argument could be made for more frequent fish intake.

Lowering NaCl intake to below 6 g/d would be relatively easy for an enthusiastic adherent. Lowering to *below* 3g would be difficult.

The great problem is adherence in part due to ingrained dietary habits, and in part due to the high content of sodium in prepared foods. RTJ

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1-6 ANTIHYPERTENSIVE DRUG THERAPIES AND RISK OF ISCHEMIC STROKE.

Diuretics, beta-blockers, calcium channel blockers, and ACE inhibitors are the most widely used antihypertensive drugs. There are no major differences between them with regard to their BP-lowering effects. However, the drugs may have benefits and harms not related to their BP-lowering effect.

The relative effectiveness of various antihypertensives with regard to stroke incidence remains uncertain.

This study assessed the association between a first ischemic stroke and use of antihypertension drugs.

Conclusion: Drug regimens that included a thiazide diuretic were associated with a lower risk of ischemic stroke.

STUDY

1. Population-based case-control study among hypertensive patients using antihypertension drugs.

Case patients: Patients who sustained a first ischemic stroke. (N = 380)

Controls: Patients with drug-treated hypertension randomly sampled. None had a history of stroke. (N = 2700)

RESULTS

1. Among over 1200 single-drug users, compared with users of a thiazide diuretic alone, the adjusted risk of ischemic stroke was higher among those receiving beta-blockers alone (risk ratio = 2.0); calcium blockers alone (RR = 2.3); and ACE inhibitors alone (RR = 2.8).
2. Among users of 2 drugs, those patients who received 2 drugs other than a thiazide had a 1.3 greater relative risk than those receiving a thiazide as one of the two.
3. Patients taking 1 drug: Adjusted odds ratio of ischemic stroke

Thiazide 1.00 (referent)

No thiazide 1.40

4. Patients taking 2 drugs

Thiazide 1.00

No thiazide 1.33

DISCUSSION

1. In this case-control study patients with hypertension whose treatment included a thiazide diuretic had a lower risk of ischemic stroke compared with those taking any one other drug or two other drugs. The association persisted after adjustment for many potential confounders.
2. One possible explanation — systolic BP is more strongly associated with occurrence of stroke than diastolic. Thiazides may be more effective in lowering systolic BP. The effect of thiazides on diastolic is similar to other drugs.
3. The BP effect of antihypertension drugs may not be the only reason for their benefits.

CONCLUSION

The study suggests a particular benefit of thiazide diuretics in reducing the risk of ischemic stroke. Patients with previous cardiovascular disease as well as those without previous CVD received this benefit.

The most recent (1997) report of the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics and beta-blockers as first-line antihypertension agents.

Archives Int Med January 8, 2001; 161: 37-43 Original investigation, first author Olaf H Klungel, University of Seattle, Washington. **www.archinternmed.com**

Comment:

Systolic BP is the main risk factor, especially in the elderly. Lowering systolic to under 140 is the treatment goal. Benefits of antihypertension drugs may far outweigh those related to the effect on lowering BP .

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1-7 LONG-TERM EFFECTS OF GLUCOSAMINE SULPHATE ON OSTEOARTHRITIS PROGRESSION

Drugs for treatment of osteoarthritis **(OA)** have been classified as *structure* modifying if they are able to alter the joint structure favorably and actually interfere with the progression of the disease. Most anti-OA drugs (eg, NSAIDs) are simply *symptom*-modifying, and do not retard progression. Indeed, NSAIDs can worsen progression.

Glucosamine is a derivative of a natural constituent of glycosaminoglycans which occur in human cartilage matrix and synovial fluid. Several preliminary short-term studies have reported glucosamine improves symptoms of OA.

This trial assessed long-term effects on symptoms and on progression of the disease.

Conclusion: Combined symptom-modifying and structure-modifying effects of glucosamine suggest that it could improve symptoms and retard progression of OA over the long-term.

STUDY

1. Randomized, double-blind, placebo controlled trial entered 212 patients (mean age 66) with OA of the

knee. All had mild to moderate OA assessed by radiography and a symptom index.

2. Randomized to: 1) oral glucosamine (1500 mg daily), or 2) placebo.

3. Permitted use of analgesics including acetaminophen and NSAIDs.

4. Measured joint-space width at baseline and at 3 years.

5. Assessed change in symptoms with an OA index.

RESULTS

1. 355 patients were screened; 212 randomized; 139 (39% of those screened; 65% of those randomized) completed the 3 years.

2. Outcomes at 3 years	Glucosamine	Placebo
Joint space	Loss of 0.06 mm	Loss of 0.31 mm
Symptoms	Improved by 20-25%	Worsened slightly

(*See figure 2 p 254 for visual analogue scale of pain and function.)*

3. No difference between groups in use of NSAIDs.

4. No differences between groups in safety and reasons for early withdrawal. No substantial differences between groups in frequency or pattern of adverse effects. Withdrawals were equal in both groups (17% and 20%)— most because of GI complaints.

DISCUSSION

1. "We have reported that long-term administration of glucosamine sulphate over 3 years can prevent joint structure changes in patients with OA of the knee, with a significant improvement in symptoms."

2. Twice as many placebo patients had a striking joint-space narrowing as those receiving glucosamine.

3. Glucosamine is safer than standard NSAIDs.

4. Longer term studies are needed.

CONCLUSION

Over 3 years, the combined structure-modifying and symptom-modifying effects of glucosamine sulphate suggest that it could be a *disease-modifying* agent in OA.

Lancet January 27, 2001; 357: 251-56 Original investigation, first author Jean Yves Reginster, WHO Collaborating Center for Public Aspects of Osteoarticular Disorders, University of Liege, Belgium

www.thelancet.com

Comment:

The fact that only about 2 out of 3 randomized patients completed the 3 years is discouraging. In primary care practice, more would likely withdraw.

The crystalline glucosamine sulfate used in the trial is a pure substance derived from chitin. It is approved as a prescription drug in many countries in Europe for treatment of OA. (*My dictionary defines chitin as a horny polysaccharide that forms part of the hard outer integument of insects and crustaceans.)*

In the US, there is no standardization of "dietary supplements" bought off the shelf. Purity is not guaranteed. Purchasers do not know exactly what they are getting. Many "glucosamine" products are combined with "chondroitin". I have not read

any reports on efficacy and safety of chondroitin. (My dictionary defines chondroitin as a proteoglycan present in the matrix of connective tissue.)

Trial was supported by a grant from Rotta Research Group, Monza, Italy

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1-8 GLUCOSAMINE FOR OSTEOARTHRITIS: Dawn of a New Era?

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

"Scarce currency has been given to the notion that progression of OA could be retarded pharmacologically, let alone by a nutritional product. The report of this clinical trial . . . may radically change this situation. The quest for a disease-modifier in OA is long overdue, and this contender comes from an unexpected quarter."

Recent studies have shown that oral glucosamine sulfate is absorbed and distributed to joint tissues, and that it has anti-inflammatory and anabolic properties. Despite this, glucosamine remains a compound whose potential to influence cartilage destruction awaits a robust mechanistic explanation.

The drug is widely available in the US as a nutritional supplement. Since it is generally self-prescribed, the likely primary beneficiary of this trial will be the nutritional-product industry rather than the pharmaceutical company that sponsored the trial, even though the results may not be generalizable to the highly variable formulations of nutritional products.

Lancet January 27, 2001; 357: 247 Editorial by Tim McAlindon, Arthritis Center, Boston University Medical Center, Mass. **www.thelancet.com**

Comment:

My pharmacy quotes a "special" of $13 for 120 tablets, each containing 500 mg of glucosamine. Some other quotes are much higher. The usual disclaimer statement is on the label. RTJ

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1-9 EARLY STATIN TREATMENT FOLLOWING MYOCARDIAL INFARCTION AND 1-YEAR SURVIVAL.

Statins initiated 3 to 6 months after an acute myocardial infarction **(MI)** reduce mortality (secondary prevention). Among high risk persons without previous coronary events, statins reduce incidence of subsequent events (primary prevention).

This study of patients with acute MI evaluated the association between statin treatment initiated before or at the time of hospital discharge and 1-year mortality.

Conclusion: Early initiation of statins in patients with acute MI reduced 1-year mortality.

STUDY

1. Multicenter, prospective cohort study entered over 19 000 unselected consecutive patients with a first MI who were younger than age 80 and discharged alive from the hospital. No exclusions other than age.
2. The recommended indication for statin treatment was elevated cholesterol (> 200 mg/dL) or LDL-cholesterol (> 115).
3. Over 5500 patients received a statin drug at or before discharge; over 14 000 did not.
4. Median rate of statin prescription = 27%. Several different statins were used.
5. Obtained 1-year mortality in both groups.

RESULTS

1. At 1 year: Statin group No statins

Unadjusted mortality:	4.0%	9.3%
Adjustment for multiple covariates	3.7%	5.0%

2. After adjustment for confounding factors, early statin use was associated with a reduction in 1-year mortality. (Relative risk = 0.75).
3. The benefit extended to all subgroups — age, sex, baseline characteristics, diabetes, prior MI, congestive heart failure, and other medications.

DISCUSSION

1. Possible biological benefits of statins include improved endothelial function, plaque stabilization and regression, and reduction in inflammatory activity (decrease in C reactive protein).
2. The potential benefits seem substantial. Adverse effects were few.
3. "Initiation of statin treatment before or at the time of hospital discharge should be recommended for all acute MI survivors with total cholesterol or low density cholesterol levels above current guideline levels for statin treatment as secondary prevention."

CONCLUSION

Early initiation of statin treatment in patients with acute MI was associated with reduced 1-year mortality.

JAMA January 24/31, 2001; 285: 430-36 Original investigation by the Swedish Register of Cardiac Intensive Care (RIKS-HIA) first author Ulf Stenestrand, University of Linkoping, Sweden.

www.jama.com

Comment:

This is a clinically important application. I see no reason not to start a statin as early as possible. RTJ

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1-10 REVIEW OF FIRST 5 YEARS OF SCREENING FOR FAMILIAL HYPERCHOLESTEROLAEMIA IN THE NETHERLANDS.

Familial hyper-cholesterolemia **(FHC)** is caused by mutations in the LDL-receptor gene. In the heterozygous state, only 50% of these receptors are functional. This is enough to increase plasma cholesterol to between 288 mg/dL and 600 mg/dL (7.5 to 16 mmol/L). Characteristically FHC results in premature cardiovascular disease **(CVD)** and untimely death. The age and sex standardized mortality ratios are 4 to 5 times higher than in the general population.

Treatment will decrease morbidity and mortality, especially in those at highest risk. FHC is a common disorder. Most patients are not diagnosed.

This study asked whether screening relatives of patients with FHC would lead to discovery of more patients with FHC and to more active lipid-controlling treatment.

Conclusion: Many more individuals with FHC were identified. Most of the identified patients were successfully started on lipid-controlling treatment.

STUDY

1. Identified 237 index cases with FHC over a 5-year period:
2. Lipid clinic used a uniform diagnostic protocol including LDL-cholesterol levels, physical signs (tendon xanthomas, xanthelasmas, corneal arcus) and personal and family history as well as LDL-receptor gene analysis.

3. Family history was considered positive when there were signs of CVD before age 55 in men and 60 in women.
4. Performed screening tests in first degree relatives (n = over 5000) by measurement of cholesterol and DNA analysis for LDL-receptor gene mutations.

RESULTS

1. Of over 5000 first degree relatives screened, 2039 individuals were identified as heterozygous for FHC, slightly more women than men**.** Mean total cholesterol = 285 mg/dL; LDL-cholesterol = 216; HDL-cholesterol = 42 (In mmol/L = 7.4; 1.6; and 1.1)
2. 58% were under age 40; 27% 40 to 59
3. About 1/3 of these individuals were already on lipid-controlling treatment. At 1 year 0ver 90% were receiving treatment.

DISCUSSION

1. FHC is frequently underdiagnosed and inadequately treated.
2. Many of the family members identified were symptomless and quite young.
3. Public health interventions to identify and help individuals with FHC are feasible.

CONCLUSION

Family screening of index individuals with FHC was highly effective in identifying family members with FHC.

Lancet January 20, 2001; 357: 165-68 Original investigation, first author Marina A W Umans-Eckenhausen, Foundation for the Identification of Persons with Inherited Hypercholesterolemia. Amsterdam , Netherlands**. www.thelancet.com**

Comment:

Note how productive the screen was. This must be one of the most effective screening tests.

Primary care clinicians will inevitably encounter patients with FHC. We are often remiss in proceeding to check family members, including women.

DNA testing is not feasible at present in primary care practice. Lipid screening will uncover most family members with FHC.

Screening family members of patients with acute myocardial infarction (especially under age 60) would reveal some individuals with hyperlipidemia. I beleive this would also be a valid indication for screening.

Many screening tests lead to adverse effects and great expense and anxiety. (Eg, mammography; PSA testing.) Screening for FHC does not lead to biopsy or invasive follow-up. It must be very cost effective compared with many other screens. It may lead to decreased anxiety. RTJ

See also: "Outcome of Case Finding among Relatives of Patients with Known Heterozygous Familial Hypercholesterolemia" BMJ December 16, 2000; 321: 1497-500: **www.bmj.com/cgi/content/full/321/7275/1497**

"FHC is the most common (1 in 500 people in North America) potentially lethal genetic disorder." Lipid control with statin drugs is as effective in FHC as in other types of as in other types of coronary heart disease. (*These patients require removal of other risk factors as well.)* The study found almost 50% of relatives tested were heterozygous for FHC. Testing relatives of a proband with FHC is much more productive than mass screening. To be most effective, screening should discover individuals at an early age before clinical manifestations of CHD occur. Screening is considered cost-effective. Cost for a year of life saved is similar to that of patients treated after an acute myocardial infarction.

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1-11 LOW-DOSE ASPIRIN AND VITAMIN E IN PEOPLE AT CARDIOVASCULAR RISK: A Randomised Trial in General Practice.

General practice, where protocols closely reproduce the conditions of routine care, is the natural context for primary prevention strategies. Yet, rarely are randomized trials done in primary care.

This cooperative group for research in general practice planned a pragmatic trial to assess efficacy of antiplatelet and/or antioxidant strategies in *primary* prevention of cardiovascular events.

Conclusion: In individuals at risk of having a cardiovascular event because of the presence of at least one risk factor, low-dose aspirin, given in addition to treatment of risk factor(s), contributed an additional preventive effect. Vitamin E was ineffective.

STUDY

1. Randomized, controlled, open trial entered over 4500 persons (half female) to assess effect of long-term low-dose aspirin and vitamin E in prevention of cardiovascular events. None had prior history of cardiovascular events.
2. All had at least one risk factor for cardiovascular events (hypertension, hypercholesterolemia, diabetes, obesity, family history of premature myocardial infarction). All were over age 50 (mean = 64; both male and female). All risk factors are routinely identified in primary care practice.
3. Randomized to one of 4 groups: 1) aspirin alone 100 mg daily, 2) vitamin E alone 300 mg daily, 3) aspirin + vitamin E, and 4) neither.
4. Assessed frequency of major fatal and non-fatal cardiovascular events over 3.6 years.

RESULTS

1. After 3.6 years the trial was prematurely stopped on ethical grounds when newly available evidence from other trials on benefit of aspirin in primary prevention was consistent with the interim results of this study.
2. Aspirin significantly lowered cardiovascular death from 1.4% to 0.8% , and total cardiovascular events from 8.2% to 6.3%. [NNT(benefit 3.6 years)=166; and 53]
3. Incidence of non-fatal stroke, angina pectoris, transient ischemic attack, peripheral vascular disease, and revascularization procedures was lower in the aspirin group.
4. Adverse events: severe bleeding was more frequent in the aspirin group (1.1% vs 0.3%). [NNT(harm 3.6 years) = 125]
5. Vitamin E showed no effect on any prespecified endpoint.

DISCUSSION

1. Aspirin was beneficial with respect to all planned endpoints.
2. Effect of vitamin E appeared to be nil.
3. "The broad recruitment criteria for our study, and the corresponding population, form a more

realistic scenario of the population seen in general practice." The beneficial effect of aspirin on both fatal and non-fatal major cardiovascular events should further widen the category of candidates for aspirin prophylaxis.

4. Results also provide evidence of aspirin's preventive efficacy on angina pectoris, peripheral-artery disease, and TIA.
5. One bleeding complication among 8000 person-years of aspirin use was fatal. There was no suggestion of an excess risk for hemorrhagic cerebrovascular events.
6. "The non-conclusive evidence of our trial regarding vitamin E seems to reproduce the present state of knowledge well: there are no real reasons for including anti-oxidants among recommendable prevention strategies."

CONCLUSION

In women and men at risk of having a cardiovascular event because of the presence of at least one major risk factor, low-dose aspirin given as primary prevention, lowered risk of cardiovascular events.

Lack of effectiveness of vitamin E is consistent with other trials on secondary prevention.

Lancet January 13, 2001; 357: 89-95 Original investigation by the Primary Prevention Project Project Study Group, correspondence to Maria Carla Roncaglioni, Instituto di Recerche Farmacologiche, "Mario Negri", Milan, Italy **www.thelancet.com**

An editorial in this issue (p 84) comments: These results, together with other studies, should give general practitioners the confidence to recommend low doses of aspirin (80 to 100 mg daily) for primary prevention in individuals who have one or more risk factors, and whose blood pressure is contained within the normal range.

Comment:

Of course, aspirin in secondary prevention will benefit many more.

As noted, hypertension must be controlled before giving aspirin.

Pragmatic trials of subjects in the general population are more meaningful than trials limited because of many exclusion criteria. I welcomed the inclusion of women.

Would simply being over age 65 without any risk factors be sufficient indication for prophylactic aspirin? However, most of us over this age do have at least one additional risk factor. RTJ

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1-12 TOLERATION OF HIGH DOSES OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN PATIENTS WITH CHRONIC HEART FAILURE.

The efficacy of ACE-inhibitors **(ACE)** in patients with chronic heart failure **(HF),** as well as in those with left ventricular dysfunction *without* clinical HF, is established. Survival is prolonged, hospitalizations prevented, clinical status improved, and progression to worsening of left ventricular failure delayed.

A previous trial demonstrated that doses of lisinopril 32.5 to 35 mg once daily compared with 2.5 to 5 mg were associated with lower risk of death and hospitalization

A substantial number of appropriate patients remain untreated and undertreated. Many are receiving low doses that have never been demonstrated to be effective. Fear of excessive reductions in BP, adverse effects on renal function, and intolerance in the elderly has led to inadequate use.

This trial examined the safety and tolerability of high-dose compared with low-dose lisinopril (*Prinivil; Zestril*) in HF.

Conclusion: Most patients with HF can be successfully titrated to, and maintained at, high doses. More aggressive use is warranted.

STUDY

1. Multicenter, randomized, double-blind trial entered over 3500 patients. All had class II (15%); III (78%); and IV (7%) HF, and left ventricular ejection fractions no greater than 0.30.
2. Run in period (open label):
   Group A: One group of patients had never received ACE. These were started on lisinopril 2.5 mg daily for several weeks, and, if the low dose was tolerated, gradually increased to 5.0 mg for several weeks, then to 12.5 or 15 mg for several weeks.
   Group B: A second group had been taking ACE. They were stabilized on 12.5 to 15 mg daily
3. Both groups then randomized to a double-blind dose-titration period:
   Low dose group: to 2.5 or 5.0 mg daily + placebo. (Total dose = 2.5 or 5.0 mg daily) Ie, in some the dose was actually decreased for purposes of comparison.
   High dose group: gradually increased to as much as 35 mg daily.
4. Determined occurrence of adverse effects, and the need for discontinuation or dose reduction during follow-up with a focus on hypotension and renal function. .
5. Allowed continuation of other medications for HF (digitalis, beta-blockers, vasodilators)
6. Follow-up = median of 46 months.

RESULTS

1. Of those who had never received ACE, the beginning dose of 2.5 to 5 mg daily was well tolerated. Only 4% could not be titrated up to the next level because of symptoms related to hypotension (2%) or renal dysfunction or hypokalemia (2%).
2. In more than 90% of patients in both groups, doses were titrated to their assigned target — high as well as low dose.
3. Withdrawals:
   High dose — 27%
   Low dose — 31%.
4. Subgroups presumed to be at higher risk for ACE intolerance (systolic BP <120; creatinine > 132 umol/L; age over 70, patients with diabetes) generally tolerated the high dose.

DISCUSSION

1. More than a decade has passed since the first trials demonstrated that ACE inhibitors prolong survival and improve symptoms in patients with HF. Physicians continue to underuse them. Many patients are receiving doses that have never been shown to be effective in clinical trials.
2. Patients titrated up to 35 mg daily exhibited a trend toward improved survival, and highly significant reductions in hospitalizations.
3."High doses of lisinopril are generally well tolerated."
4. Although adverse events such as hypotension and renal dysfunction were more frequent in the high dose group, the differences between the high-dose group and the low-dose group were small for events classified as serious or leading to withdrawal.

5. Even for patients considered to be at a particularly high risk for adverse events, the occurrence of serious events was relatively low, and did not appear to be dose-related. Hypotension rarely required withdrawal of the drug, although dose reductions were frequent.
6. "Patients entering clinical trials often differ from the overall patient population in being more compliant and motivated and in having fewer comorbid conditions." Supervision during the trial may be closer that in ordinary practice. Similar degrees of tolerability may *not* be achieved in non-trial settings.
7. Not all patients will tolerate high doses. The study demonstrated that a strategy of titrating to and maintaining higher ACE doses than are used currently will be successful in most patients.
8. The lack of evidence that low doses of ACE improve mortality, and the additional reduction in the composite of death and hospitalizations at high doses, provide a clear message that higher ACE doses can and should be used in most patients.

CONCLUSION

ACE inhibitor therapy in most patients with HF can be successfully titrated to and maintained at high doses. More aggressive use is warranted. But start with a low dose (eg, 2.5 mg daily).

Archives Int Med January 22, 2001; 161: 165-71 Original investigation by the Assessment of Treatment with Lisinopril and Survival (ATLAS) Trial, first author Barry M Massie, VA Hospital , San Francisco, CA **www.archinternmed.com**

Comment:

The important point in treating long-term non-urgent HF is to start at a low dose and gradually increase as required. This will reduce incidence of adverse effects and withdrawals.

This clinical trial was not the gold standard of dosage optimum in primary care. Primary care clinicians must use their clinical judgement when titrating upward. Note that about 1 of every 3 could not tolerate the dose targeted, even if low. Even if a low dose was "Never demonstrated to be effective in clinical trials", this does not mean that they have "Been demonstrated to be ineffective" in individual patients. Indeed, I believe low doss will be of some benefit to individual patients.

ACE inhibitors are a valuable addition to the therapy of HF, and should be used routinely and titrated upward carefully as tolerated by the individual. The rule, "start low and go slow" is emphasized. RTJ

Trial supported by Zeneca Pharmaceuticals. RTJ

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1-13 CHLAMYDIA AND CERVICAL CANCER

The causal relationship between subtypes of human papilloma virus **(HPV)** and cervical cancer has been firmly established. This infection is common. In adolescent populations, infection rates as higher than 45% have been reported. The majority of patients with the infection spontaneously clear it without any specific medical interventions. Only a small minority will develop cervical dysplasia, and of these a minority will develop invasive cancer.

This issue of JAMA[1] presents an investigation using data from large serum banks (over 500 000 women) to determine IgG antibodies to 10 different *C trachomatis* serotypes. The serums were collected an average of 56 months before the diagnosis of cervical cancer. Serotype G was strongly associated with squamous cell carcinoma of the cervix. Increasing numbers of exposures to different *C trachomatis* serotypes increased risk.

The study strongly suggests an independent relationship between *C trachomatis* infection and cervical squamous cell carcinoma. Other studies report finding *C trachomatis* DNA in 5% of cases of cervical intraepithelial neoplasia.

Since the infection is curable, replication of this finding is important.

C trachomatis is already known to be associated with pelvic inflammatory disease, infertility, and facilitation of transmission of HIV infection. Cervical cancer may be another complication.

JAMA January 3, 2001; 285: 81-82 Editorial by Jonathan M Zenilman, Johns Hopkins University School of Medicine, Baltimore MD **www.jama.com**

1 JAMA January 3, 2001; 285: 47-51 "Serotypes of *Chlamydia Trachomatis* and Risk of Development of Cervical Squamous Carcinoma"

Comment

Not a practical point at this time, but a provocative public health concern. Prevention and treatment of *C trachomatis* may lower incidence of cervical cancer. A vaccine against human papilloma virus is in the offing. Perhaps also against *C trachomatis*?

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1-14 THE RENAISSANCE OF C REACTIVE PROTEIN

It may be a marker not only of acute illness, but also of future cardiovascular disease

(C reactive protein is a ß-globulin, a non-specific antibody. It was discovered in the era when pneumococcal pneumonia was treated with specific anti-pneumococcal serum. It precipitates in vitro with the C polysaccharide present in all types of pneumococci.)

C reactive protein **(CRP)** is a trace protein in healthy subjects. Normally, the median concentration is around 1 mg/L. Values can exceed 400 mg/L in the acute phase response. Interleukin-6 is the main cytokine mediator leading to increased CRP production. Routine applications in adult medicine require measurement above 5-10 mg/L, but development of high sensitivity assays has recently allowed clinicians to explore the role of CRP levels in atherosclerotic disease. Increased levels predict future cardiovascular disease.

CRP has traditionally been used as an acute phase marker of tissue injury, infection, and inflammation. The CRP response has no diagnostic specificity, but serial measurements can be helpful in clinical management. It is a powerful screening test for organic disease and is useful monitoring known infectious or inflammatory diseases and their response to treatment.

Although a high value is unequivocal evidence of tissue damage, CRP can be interpreted only when all other clinical and laboratory information is available. Nevertheless, serial measurements, added to the full clinical picture, contribute usefully to diagnosis, prognosis and treatment.

Predictor of coronary events:

Increased CRP values significantly predict coronary events in patients with stable and unstable angina, and predict outcome after coronary angioplasty. "Even in healthy asymptomatic people in the general population, individuals with baseline values in the top third of the distribution (mean of 2.4 mg/L) have twice the risk of future coronary events as those in the bottom third (mean of 1.0 mg/L). Similar relations exist for stroke and peripheral vascular disease.

Values increase with smoking and body mass index, but the association with coronary events remains after adjustment for these potential confounders. This suggests an association between inflammation and atherothrombosis. Inflammation is a central component of atherogenesis and is important in plaque instability and rupture.

A pathogenetic role?

CRP selectively binds to low density lipoprotein, particularly to the degraded LDL found within atherosclerotic plaques. Bound CRP activates complement, is proinflammatory, and may contribute to atherosclerosis. It also may increase production of tissue factor, the coagulation initiator responsible for occlusive thrombotic events.

It is of interest that statin drugs lower CRP values.

There is strong evidence that CRP production increases in all patients with myocardial infarction, peaking at about 50 hours. High values are associated with a poor prognosis.

All fatal acute infarcts contain CRP alongside activated complement. "It has now been confirmed that human C reactive protein, via its capacity to activate complement, greatly increases infarct size after experimental coronary artery ligation."

Routine empirical measurement of CRP is a valuable aid to patient management across a broad range of clinical practice. Sensitive assay may become a new risk assessment marker for cardiovascular disease. A raised level in patients with active coronary disease identifies a high risk group likely to require interventions. "Possibly the more C reactive protein you produce, the sicker you get."

Specific drugs to inhibit CRP may be developed.

BMJ January 6, 2001: 322; 4-5 Editorial by Mark B Pepys, Royal Free and University College Medical School, and Abi Berger, Science Editor, BMJ, London. **www.bmj.com/cgi/content/full/322/7277/4**

Comment:

CRP is replacing the sedimentation rate as a marker of inflammation.

The practical application in regard to atherothrombotic disease awaits further experience. I abstracted the paper because of its potential importance to primary care. RTJ

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A REFRESHER COURSE.

1-15 VIRAL HEPATITIS

(*This is one of series of reviews presented by BMJ — "ABC of Liver Pancreas, and Biliary System". I abstracted points of interest, — some I had forgotten, some I never knew. RTJ*)

Chronic viral hepatitis is often detected by finding abnormal liver blood chemistries in asymptomatic patients, or as a result of the complications of cirrhosis. The degree of rise in transaminase activity, however, has little relevance to the extent of underlying hepatic inflammation.

HEPATITIS B

Is one of the most common chronic viral infections in the world. Although not common in the US and UK, world-wide about 170 000 000 persons are infected. Vertical transmission (carrier mother to infant) is highly efficient. Almost all children born to infected mothers become infected and develop chronic infection.

In low endemicity countries, spread is mainly by sexual contact or by blood contact (eg, intravenous drug users). People living in institutions, especially those with learning disability are also at risk.

Most patients will be positive for the Hepatitis B surface antigen (HBsAg). The antigen is on the coat of the virus. Its presence implies that the patient is infected. Measurement of viral DNA in blood has replaced e antigen (HBeAg) as the most sensitive measure of viral activity.

The infection can be thought of as occurring in phases, dependent on the degree of immune response to the virus. In patients in whom the immune response is "immature", viral DNA concentrations in serum are very high and there is little or no response to the virus. Hepatocytes contain abundant viral particles, but there is little or no ongoing hepatocyte death.

As the immune response grows over the years, immune recognition increases, concentrations of DNA fall, and inflammation in the liver increases. Two outcomes are then possible: 1) the immune response is adequate and the virus is inactivated and removed, or 2) the attempt at removal results in extensive fibrosis, cirrhosis, and death.

Patients positive for hepatitis B surface antigen with no evidence of viral replication and with normal liver enzymes and normal liver ultrasonography require no further investigation. They are at low risk of cirrhosis and liver cancer. But, reactivation of viral replication can occur. Patients should have yearly serological and liver enzyme tests. Patients with repeatedly normal alanine transaminase activity and high concentrations of viral DNA are extremely unlikely to have developed advanced liver disease, and biopsy is not always required at this stage.

Interferon alfa remains the mainstay of treatment. The likelihood of stopping viral replication is about 40%. A few patients lose all markers of the infection. Surface antigen usually remains positive.

Lamivudine, a nucleoside analogue, is a potent inhibitor of viral replication. It has a good safety profile. It has been widely tested in patients with chronic hepatitis B in the Far East. Almost all patients show a sustained inhibition of viral replication. Combination with interferon alfa has not been found to have additional benefits.

HEPATITIS C

Hepatitis C is also common worldwide, in developed countries as well as developing countries. About 1 in 200 persons in the UK is infected where the virus is spread almost exclusively by blood contact (15% by transfusion; 70% by illicit use of intravenous drugs.) Spread by sexual contact is unusual as is vertical transmission.

The infection has a long course. Most patients are diagnosed in the presymptomatic stage, after history of an identifiable risk factor (transfusion, IV drug use, family history), or because of abnormal liver biochemistry. Screening for hepatitis C antibody is based on enzyme-linked immunosorbent assays (ELISA) using recombinant viral antigen and the patient's serum. Direct detection of viral DNA by polimerase chain reaction is regarded as the best test to determine infectivity and assess response to treatment.

Hepatitis C is usually slowly progressive, with an average time from infection to cirrhosis of around 30 years, albeit with a high level of variability. Age over 40 at infection and high alcohol consumption are main risk factors for progression.

Treatment is usually based on results of biopsy. Patients with mild changes are usually followed without treatment. Interferon combined with ribavirin is more effective than interferon alone.
With interferon alfa combined with ribavirin, about 30% attain a "cure" — ie, a sustained response.

BMJ January 27, 2001; 322: 219 - 21 Review article by S D Ryder and I J Beckingham, Queens Medical Centre, Nottingham UK **www.bmj.com/cgi/content.full/322/7280/219**

Comment:

Peginterferon (polyethylene glycol interferon) is an advance in treatment. The pharmacodynamics of peginterferon are more favorable. RTJ

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1-16 CARDIORESPIRATORY FITNESS AND THE PROGRESSION OF CAROTID ATHEROSCLEROSIS IN MIDDLE-AGED MEN.

Physical inactivity and poor cardiovascular fitness are major risk factors for atherosclerotic disease. The increased risk is similar to that seen in conventional modifiable risk factors (hypercholesterolemia, smoking, hypertension). Physical inactivity is related to an estimated 12% of all deaths in the US.

Physical activity alone, and physical activity combined with a low fat diet and comprehensive life-style modifications, together with improvement in cardiorespiratory fitness slows the progression of coronary atherosclerosis in patients with coronary heart disease **(CHD)** [secondary prevention].

This study asked — Is cardiorespiratory fitness **(CRF)** related to progression of carotid atherosclerosis?

Conclusion: CRF was related to slower progression of early carotid atherosclerosis.

STUDY

1. Followed a population-based sample of over 850 men age 42 to 60,
2. At baseline, determined the maximal O2 intake (VO_2 max; mLO_2/kg per minute) by cycle ergometer exercise test.
3. Assessed carotid atherosclerosis using B-mode ultrasound. Used four indicators of carotid atherosclerosis:
   - Maximal intimal-medical thickness **(IMT).** How deep the intima-media layer protruded into the lumen. (average of both sides).
   - Plaque height (average of the maximal and minimal IMT) an indicator of how steeply atherosclerotic lesions protrude into the lumen.
   - Surface roughness, and indicator to the variability of IMT.
   - Mean IMT, an overall indicator of atherosclerosis.
4. Determined physical activity by a detailed quantitative questionnaire.
5. Determined 4-year progression of intimal markers of carotid atherosclerosis.

RESULTS

1. After multiple adjustments for possible confounders, VO_2 max had a strong, graded, inverse association with 4-year increases in maximal IMT, surface roughness, plaque height, and mean IMT.
2. Increases in maximal IMT, surface roughness, and mean IMT (+23%; +31%, and +100%) were greater among men in the lowest quartile of VO_2 max than in those in the highest quartile.
3. Weight loss, by reducing the denometer of VO_2max, raises VO_2max. Thus combined aerobic exercise and weight loss in obese men and women increased VO2 max. "An important finding of this trial was that the combination of aerobic exercise and dietary energy restriction increased VO_2max more than either factor alone."

DISCUSSION

1. Carotid intima-media thickening — which is related to atherosclerotic risk and increased prevalence of coronary and peripheral atherosclerosis, and increased incidence of coronary heart disease and stroke — is regarded as a valid indicator of generalized atherosclerosis. These investigators previously found a strong association between higher levels of VO_2max and reduced risk of a first myocardial infarction.
2. Good CRF was related to slower progression of early atherosclerosis.
3." Low VO_2max was the strongest risk factor for the progression of carotid atherosclerosis in multivariate analyses, even compared with conventional risk factors."
4. Good CRF, as assessed by work capacity, exercise test duration, or heart rate response to exercise, has been related to greatly reduced premature cardiovascular mortality.

5. Ultrasonographically assessed IMT has been associated with risk of coronary disease and stroke.
6. "Our results suggest that good respiratory fitness is associated with slower progression of atherosclerosis and therefore could reduce the risk for clinical events of atherosclerotic vascular diseases."
7. The study did *not* find an association between ordinary physical activity and the 4-year change in IMT. The investigators speculate that the quantity and intensity of exercise in most middle-aged men is too low to improve cardiorespiratory fitness and to slow the progression of atherosclerosis. Only amounts of exercise intensive great enough to improve cardiorespiratory fitness may be related to lowering progression of atherosclerosis.
9. Effects on systolic BP, lipids, diabetes, and plasma fibrinogen levels partly explain the inverse associations of VO2 max with IMT. Physical activity and good cardiorespiratory fitness may also: 1) enhance endothelial function by increasing production of NO and prostacyclin, 2) reduce oxidation of LDL-cholesterol, 3) decrease the atherogenic activity of blood mononuclear cells by affecting production of cytokines, 4) decrease the number of atherosclerotic lesions by reducing heart rate and pulsatile stress, and 5) decrease accumulation of collagen in the arterial wall.

CONCLUSION

Good cardiorespiratory fitness was associated with slower progression of early atherosclerosis in middle-aged men. "These findings are important because they emphasize that middle-aged men can be evaluated for cardiorespiratory fitness to estimate their future risk for atherosclerotic vascular disease."

Annals Int Med January 2, 2001; 134: 12-20 Original investigation, first author Timo A Lakka, University of Kuipo, Finland. **www.annals.org**

Comment:

The point about benefit of weight loss in improving VO2 max is important. RTJ

Regular, moderate leisure-time physical activity, not fitness training, is a standard recommendation to lower risk of cardiovascular disease. It may be that attaining fitness is more protective than moderate activity. But, patients will be much more accepting of regular leisure time activities. RTJ

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1-17 INTAKE OF FISH AND OMEGA-3 FATTY ACIDS AND RISK OF STROKE IN WOMEN

Some prospective studies have shown an inverse (protective) association between increased fish intake and stroke. This study examined the association of fish and omega-3 polyunsaturated fatty acids with risk of specific stroke subtypes in women.

Conclusion: Higher fish consumption and higher omega-3 consumption were associated with a reduced risk of thrombotic infarction. No relation to hemorrhagic stroke.

STUDY

1. Prospective cohort study of women (age 34 to 59 at entry) in the Nurses' Health Study followed over 79 000 women for 14 years.
2. At baseline, all were free from prior diagnosis of cardiovascular disease, cancer, diabetes, and hypercholesterolemia.
3. Food frequency questionnaires determined consumption of fish and other frequently eaten foods.

RESULTS

1. Documented 574 incident strokes — 119 subarachnoid, 62 intraparenchymal hemorrhagic, and 313 ischemic (264 thrombotic; 62 embolic).
2. Among the thrombotic strokes — 142 lacunar infarctions and 90 large artery occlusive infarctions were identified.
3. Compared with women who ate fish less than once a month, those with higher intake had a lower risk of total stroke,

	Adjusted relative risks for fish intake
1 to 3 times monthly	0.93
Once a week	0.78
2 to 4 times a week	0.73
5 or more times a week	0.48

4. Among stroke subtypes, a significantly reduced risk of thrombotic stroke was found in women who ate fish 2 or more times a week. (RR = 0.49)
5. Women in the highest quintile of long chain omega-3 fatty acid intakes had a reduced risk of total stroke and thrombotic infarction. (RR = 0.72 and 0.67)
6. The dietary questionnaire segregated types of fish:

Dark meat fish: mackerel, salmon, sardines,	Content of omega-3 per serving
blue fish, and swordfish	1.5 g
Canned tuna	0.42 g
Other fish (flounder, whiting)	0.48 g
Shrimp. lobster, and scallops.	0.32 g

7. No association with hemorrhagic stroke.

DISCUSSION

1. There was a significant inverse association between fish intake and risk of stroke (protective effect), primarily thrombotic stroke. After adjustment for cardiovascular risk factors, risk of thrombotic stroke was reduced by 48% among women who ate fish 2 to 4 times weekly.
2. There was a reduced risk of stroke among women who had the highest quintile of omega-3 fatty acids. There may be other unknown components of fish which reduce risk of stroke.
3. Among the subgroup of women who took aspirin, the difference in risk of stroke in those who ate a lot of fish and those who did not eat much fish was blunted. (Ie, benefits of fish in preventing stroke was noted mainly in women who did not take aspirin. Aspirin reduced the risk of stroke. This obscured the benefit of fish.)

CONCLUSION

Higher consumption of fish and omega-3 polyunsaturated fatty acids was associated with a reduced risk of thrombotic infarction, primarily among women who did not take aspirin regularly. No relation to hemorrhagic stroke.

JAMA January 17, 2001; 285: 304-12 Original investigation, first author Hiroyasu Iso, Brigham and Women's Hospital and Harvard Medical School, Boston Mass. **www.jama.com**

Comment:

Omega-3 fatty acids have the first double bond at between the 3rd and 4th carbon atoms from the methyl end. H3C-C-C=C-C ....

Considering the large number of subjects (79 000) and the 14 years of follow-up, the absolute benefit would be small indeed and the number needed to treat per year to prevent one stroke would be very large.

Fish and omega-3 acids have protective effects against coronary disease as well as improving the lipid profile.

Possible mechanisms for the protective action of omega-3 acids include: inhibition of platelet aggregation, vasodilation, lowered blood viscosity, suppression of lipid mediators for neutrophil and macrophage aggregation, reduction of fibrinogen, lowering of BP, and reduction in insulin resistance.

The study concurs in the conclusion that aspirin is protective against stroke. It obscures the benefits of fish and omega-3 acids. RTJ

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1-18 PROPHYLACTIC TREATMENT OF MIGRAINE WITH ANGIOTENSIN CONVERTING ENZYME INHIBITOR (LISINOPRIL)

Drugs showing prophylactic effects against migraine include beta-blockers, sodium valproate, and several NSAIDs. Most cause adverse effects that preclude long-term prophylactic treatment.

These investigators observed an impressive improvement in migraine in a patient treated with lisinopril for hypertension. This study followed.

Conclusion: Lisinopril had a clinically important prophylactic efffect on migraine.

STUDY

1. Double-blind, placebo-controlled, cross-over study entered 60 patients with migraine. All had 2 to 6 episodes per month.
2. Randomized (cross-over) to: 1) lisinopril (*Prinivil*) 10 mg once daily for 1 week, then 10 mg twice daily for 11 weeks, or 2) placebo.

RESULTS

1. Complete data was obtained on 47 subjects.
2. Hours with headache, days with headache, and headache severity index were significantly reduced by about 20% with lisinopril compared with placebo. Use of triptans also decreased.
3. Days of migraine were fewer by at least 50% in 14 participants when taking lisinopril. Quality of life scores improved.
4. Lisinopril was well tolerated. Cough severe enough to cause withdrawal occurred in 3 patients.

DISCUSSION

1. ACE-inhibitors have actions in addition to blocking conversion of angiotensin I to angiotensin II. These include alterations in sympathetic activity, increases in prostacyclin synthesis, and blocking bradykinin degradation.
2. It has recently been shown that migraine without aura may be more frequent in people having the angiotensin converting enzyme DD gene. Migraineurs with this gene have higher angiotensin converting enzyme activity and a higher frequency of attacks.

CONCLUSION

The ACE-inhibitor lisinopril had a clinically important prophylactic effect in migraine.

BMJ January 6, 2001; 322: 19-22 Original investigation, first author Harald Schrader, Norwegian University of Science and Technology, Trondheim. **www.bmj.com/cgi/content/full/322/7277/19**

Comment:

The use of a genetic marker as noted in the article is an example of things to come. Individual therapy will be guided by the individual's genetic pattern.

Another example of an unexpected beneficial effect discovered serendipitously. Worth a try? RTJ

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RECOMMENDED READING.

1-19 BIOETHICAL ASPECTS OF THE RECENT CHANGES IN THE POLICY OF REFUSAL OF BLOOD BY JEHOVAH'S WITNESSES

(*This is a practical point. Sooner or later primary care clinicians will encounter one of these fine people. Their refusal to accept blood even at the cost of their lives has caused distress among their physicians. The recent changes in their policy may ease some of the distress.* RTJ)

Since 1961 the church has "disfellowshipped" any unrepentant member who willfully accepts prohibited blood components. Other members of the church have been instructed to ostracize and shun expelled members who then are considered outcasts.

This essayist analyzed recently publicized changes in this policy.

In June 2000 The Watchtower Society issued a directive that the *organization* would no longer initiate disfellowship of members who did not comply with the policy of refusing blood. "If a baptized member of the faith willfully and without regret accepts blood transfusions, he indicates *by his own actions* that he no longer wishes to be one of Jehovah's witnesses. The individual revokes his own membership by his own actions, *rather than the congregation* initiating this step." This represents a procedural change.

The commentator concludes that if the act of receiving blood is kept strictly confidential, dissociation is highly unlikely. Under the ideal protection of medical confidentiality, decisions on blood transfusion made by a patient who is a Jehovah's Witness would be known only to the patient and the medical team, not the congregation.

The patient would have almost full control over whether he or she dissociates from the religion by his or her treatment decision being made known to the congregation. He could remain silent and continue membership. Under previous policy, any suspicion of receiving blood would prompt a judicial committee, which could elicit an involuntary confession from the patient and result in disfellowship. Under the new policy, such a formal inquiry is unlikely to happen, and the treatment would not be verified unless medical confidentiality is breached.

Probably the most important advice to doctors at this time of flux in the policy of refusal of blood is to treat individual patients independently of the church's official policy. "Each case needs to be discussed and treated individually."

BMJ January 6, 2001; 322: 37-39 "Education and Debate" commentary by Osamu Muramoto Regional Ethics Council, Kaiser Permanente Interstate Medical Office, east, Portland OR. **www.bmj.com/cgi/content/full/322/7277/37**

Comment:

I do not believe the commentator considers this the final word. Members of the church may disagree on interpretation. Ongoing clarification is needed. The message is confidentiality and individualization. RTJ

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1-20 PUBMED CENTRAL: http://pubmedcentral.nih.gov

This new web based repository will archive, organize, and distribute peer reviewed reports from biomedical journals. It promises to archive the full texts and make them available in perpetuity. It is funded by the US National Institutes of Health and the National Library of Medicine.

The distinguishing characteristic is that it offers full texts of articles free of charge to anyone with a computer and access to the Internet. It is a logical extension of MEDLINE. It depends on publishers and societies transferring peer reviewed articles to Pub Med Central. At present PubMed Central is primarily interested in original research articles, although journals could also provide editorials, reviews, and perspectives if they choose to do so.

BMJ has joined because it agrees that "free access to the scientific literature would be a phenomenal advance in scientific publishing — the greatest in our lifetime."

PubMed Central is the first initiative really to take account of how fundamentally the world wide web has changed the landscape of scientific publishing.

BioMedcentral is a main supplier of electronic journals to PubMed Central. BioMedcentral is willing to publish any scientifically sound paper.

"Sooner or later, PubMed Central or something like it will flourish; the drivers are so strong. It will do the job of disseminating research better and more cheaply than it is done now."

The question is— What will happen then to the journals whose main contribution is peer review and distribution of research? Many leaders in clinical medicine are concerned about the stringency of peer review and the editing process. Some fear that when articles become freely available from the Internet, subscribers to journals will cancel their subscriptions. Others believe that it is more psychologically appealing to physicians to physically handle a journal than to read articles on a computer screen.

And what will be the effect on medical libraries.?

But, too much information is the bane of a working clinician's existence. Physicians, and ultimately the public do not need more articles. Instead, they need better articles, preferably from a trusted source, that give new and useful information or help put knowledge into some sort of practical context.[1]

BMJ January 6, 2001; 322: 1-2 Editorial by Tony Delamothe and Richard Smith, Editors, BMJ

www.bmj.com/cgi/content/full/322/7277/1

See also — Annals Int Med November 21, 2000; 133: 841-44 Editorial by Deborah Gesensway, Annals staff.

www.annals/org

1 Go to — **www.practicalpointers.org**

Comment:

I accessed **http://pubmedcentral.nih.gov** on February 27 2001. BJM is the only major journal listed which is of interest to primary care clinicians. The Canadian Medical Association Journal is promised. There is a link to BioMed Central (**http://www.biomedcentral.com**), which publishes, in its medicine section, peer-reviewed original research papers. . They present a long list of subsets of medicine ranging form Alternative Medicine to Women's Health. BioMedcentral in now the main supplier of electronic journals to PubMed Central.

This is the inception of what might be a revolution in medical publishing. RTJ

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RECOMMENDED READING

1-21 INTEGRATIVE MEDICINE: Orthodox Meets Alternative.

The January 20 issue of BMJ presented 8 articles on integrative (alternative; complementary) medicine. **(IM).** I abstracted a few highpoints.

The main message is that traditional Western medicine has focused on the technical management of disease. IM focuses on health and healing rather than disease and treatment. The patient is seen as a whole — complete with dreams, disappointments, stories, loved ones, and enemies — not just "a biochemical puzzle to be solved".

"As diseases become defined strictly in chemical or physical terms, so the spiritual side of medicine has been lost. Koch and Pasteur caused germs and vaccines to eclipse vitalism."

IM encourages individual responsibility for one's own health.

Most patients turn to complementary medicine out of frustration with conventional care. IM makes patients feel more in control of their illness. "Complementary medicine may largely be driven by medicine's main omission — the failure of holism." The art of good doctoring seems not to be addressed directly by mainstream medical curriculums.

"Yet the multiple options of complementary therapies range from the sensible and worth while to the ridiculous and even dangerous, and patients need physicians with the biomedical knowledge to distinguish between them."

Hopelessness accelerates disease and increases mortality. "We cannot ignore that human caring and interaction is a powerful, creative activity." Compassion, empathy, trust, and positive motivation are the basic skills of human interaction. They can improve outcomes directly in addition to any intervention used.

Yet, the question — "Where is the evidence?" is not answered, and will be most difficult to answer. How can primary care clinicians tap into the interaction of mind-body to benefit the patient?"

"It would be a tragic loss if traditional human caring had to move to the domain of complementary medicine."

BMJ issue for January 20, 2001; 322. **www.bmj.com**

Comment:

In traditional medicine, the responsibility of addressing the whole patient falls on the primary care clinician. The skills of specialists in Western medicine are awesome indeed. Surgeons performing coronary bypass or hip replacement apply their skill to a particular technology. But, they have little time and not much continuing care to enable a lasting empathetic relationship with patients.

Consider the shaman who visits a sick woman. He is elaborately dressed and performs time-consuming rituals. Surely, the woman must feel that she is very important and cared for to receive such attention. We Westerners may believe that the outcome of the illness would be the same with or without the Shaman's visit. Would it necessarily be so? Would not the psychological effect on the woman have some bearing on her recovery? Of course, it would depend on the type of illness the woman has. It would give her a sense of belonging, of importance, of being cared for, of hope. This is, I believe, the secret of some forms of alternative medicine.

Primary care clinicians have the greatest opportunity to act somewhat in the mode of the shaman. As it has often been said, the doctor's chief therapeutic intervention may at times be giving the patient "a dose of the doctor".

Conversely, TV advertisements of herbs to "Promote mental alertness", "Promote vein health", and "Improve prostate health" are pure chicanery. RTJ

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HISTORICAL NOTE

1-22 THE FIRST PATIENT TO UNDERGO CORONARY ANGIOPLASTY — 23 YEAR FOLLOW-UP

Coronary angioplasty was performed on a 38 year old man on September 14, 1977 by Dr. Andreas Gruentzig in Switzerland. The procedure successfully dilated a high grade, discrete stenosis of the proximal left anterior descending artery.

The patient then quit smoking. Twenty years later his physician convinced him to take aspirin and a statin drug. In 2000, at the age of 61, the patient had recurrent chest pain for the first time. Coronary angiography revealed that the previously restricted site had normal patency. There were only minor abnormalities elsewhere. Exercise test was essentially normal.

NEJM January 11, 2001: 144-45 Letter to the Editor by Bernhard Meier, Swiss Cardiovascular Center, Bern.
www.nejm.com

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1-23 AN IMPORTANT NEW SERVICE FROM JOHNS HOPKINS

Hopkins has launched an antibiotic database available to all free of charge. It offers diagnostic criteria and drug options on more than 160 drugs, and 140 diseases. It is continually updated and will immediately issue emergency alerts and drug recalls.
www.hopkins-abxguide.org

Cited from BMJ April 14, 2001; 322: 881