PRACTICAL POINTERS

FOR

PRIMARY CARE

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HIGHLIGHTS JUNE 2001

6-1 "TELL ME ABOUT YOURSELF": The Patient-Centered Interview.

Physicians should focus more attention on patient's concerns, feelings, and ideas. Inattention to the person of the patient, to the patient's characteristics and concerns, leads to inadequate clinical data-gathering, non-adherence, and poor outcomes. Each patient's experience of illness is unique. "To know what kind of a person has a disease is as essential as knowing what kind of disease a person has." The art (of listening) is long; time is short.

Practical point: Primary care physicians must go beyond disease-centeredness in the clinical encounter. They must become expert at listening without interruption and with undivided attention, and then lead patients to disclose more about themselves. RTJ

6-2 OPTIMAL TREATMENT OF ACUTE CORONARY SYNDROMES — An Evolving Strategy

This article summarizes the latest recommendations. A reference algorithm is presented on p 1941.

Practical point: Primary care clinicians can serve their patients optimally by immediately beginning non-interventional measures (aspirin, heparin, oral beta-blocker, and medication for pain control). Primary care clinicians remote from emergency centers must keep up with the rapid changes in therapy in order to correlate urgent treatment with their cardiologist colleagues. Each minute of myocardial ischemia adds to risk. The new bolus agents will facilitate early fibrinolysis out of hospital.

6-3 THE EFFECT OF FRUIT AND VEGETABLE INTAKE ON RISK FOR CORONARY DISEASE

The data support a protective effect of greater consumption of fruits and vegetables, particularly green leafy vegetables and vitamin C rich fruits and vegetables, against CHD.

Practical point: Primary care clinicians should repeatedly advise patients about the benefits of a healthy diet.

6-4 MIDLIFE VASCULAR RISK FACTORS AND ALZHEIMER'S DISEASE IN LATER LIFE

Raised systolic BP and high cholesterol concentrations (and particularly the combination) in midlife were associated with increased risk of Alzheimer's disease later in life. This possible added benefit would be most welcome.

Practical point: Both factors should be controlled in mid-life regardless of any possible benefit on reducing risk of Alzheimer's. Control of both to reduce risk of cardiovascular disease is one of the great challenges and opportunities for primary care clinicians. Any possible reduction in incidence of Alzheimer's would be an additional benefit. .

6-5 EFFECT OF RAMIPRIL VS AMLODIPINE IN RENAL OUTCOMES IN HYPERTENSIVE NEPHROSCLEROSIS

Practical point: African Americans with hypertension are at high risk of renal dysfunction. Obviously, do not wait for renal dysfunction to be established before beginning effective anti-hypertension therapy. We should protect the kidney as well as the heart and brain. Identifying and treating patients at the stage of microalbuminuria (20 to

200 mg/d) would lead to greater benefit than waiting for renal dysfunction to become established. Angiotensin converting enzyme inhibitors are the drugs of choice.

6-6 DRUG TREATMENT FOR OBESITY

The editorialist comments on a recent study of sibutramine which reported benefit in reducing weight re-gain after a program of weight loss.

Practical point: Should primary care clinicians prescribe sibutramine, or any other weight-loss drug? I would vote against it. I believe use should be limited to special clinics where suitable candidates can be carefully screened and followed. The adverse effect on BP is a serious downside.

6-7 *HELICOBACTER PYLORI* AND SYMPTOMATIC RELAPSE OF GASTRO-ESOPHAGEAL REFLUX DISEASE

Eradication of the infection led to a benefit -- a longer asymptomatic period before relapse of symptoms.

Practical point: This study contradicts previous studies which suggested a harmful effect of eradication. Eradication therapy should be considered to reduce risk of stomach cancer, recurrence of peptic ulcer, and possibly for a slight reduction in severity of dyspepsia.

6-8 LONG-TERM OUTCOME OF MEDICAL AND SURGICAL THERAPIES FOR GASTROESOPHAGEAL REFLUX DISEASE

Antireflux surgery should *not* be advised with the expectation that patients will no longer take antisecretory drugs. It is clearly *not* a cancer-preventing procedure.

Practical point: Primary care clinicians should inform their patients with long term troublesome GERD about the long-term results of surgery vs medical treatment and allow them to decide.

6-9 NATURAL HISTORY OF CERVICAL HUMAN PAPILLOMAVIRUS INFECTION IN YOUNG WOMEN: A Longitudinal Cohort Study

In this cohort of young women, only limited inferences could be drawn from the characteristics of HPV status at a single point in time. Longer observation in older women is needed.

Attempts to exploit the association between HPV and cervical intraepithelial neoplasia (CIN) to improve effectiveness of screening is limited. Any lead time (time from detection of HPV to development of CIN) gained by detecting HPV is likely to be short.

6-10 NATURAL HISTORY OF HUMAN PAPILLOMA VIRUS INFECTIONS

"A positive HPV test, especially in young women, rarely represents disease that could, if unrecognized, progress to cervical cancer."

"Knowing more about the natural history of HPV infection, especially in young women, reinforces the view that testing should *not* be carried out among women under age 35."

6-11 WHY SHOULD WOMEN HAVE LOWER REFERENCE LIMITS FOR HAEMOGLOBIN AND FERRITIN CONCENTRATIONS THAN MEN?

"The data from humans point to the possibility that the current lower reference levels for red blood cell counts and hemoglobin and serum ferritin concentrations in women have been derived from sampling populations that are deficient in iron."

Reclassification of these parameters in women to the same values as for men would be expected to have fundamental and positive implications for women's health and welfare.

Practical point: Primary care clinicians should be aware of the near universal likelihood of iron deficiency in young women. Supplementation is reasonable.

6-12 DIAGNOSIS AND CARE OF PATIENTS WITH ANOREXIA NERVOSA IN PRIMARY CARE SETTINGS

Clinical diagnosis of AN is often obscure. Patients with mild cases usually seek help for non-specific symptoms such as asthenia, dizziness, and lack of energy. Presentation may be remarkable for its lack of complaints. Family members may bring patients to the physician because of concerns about amenorrhea or weight loss.

The primary care physician is often the first to consult and suspect AN. Early clinical suspicion and diagnosis is likely to lead to more effective treatment.

The primary care clinician is involved with arranging and coordinating a comprehensive and multidisciplinary treatment program.

Practical point: Suspect anorexia nervosa and bulimia in a thin young woman who exercises excessively and has amenorrhea.

6-13 RANDOMIZED TRIAL OF CRANBERRY-LIGONBERRY JUICE AND *LACTOBACILLUS* GG DRINK FOR THE PREVENTION OF URINARY TRACT INFECTION IN WOMEN.

Daily consumption of cranberry juice reduced the recurrence of urinary tract infections in young women. Lactobacillus did not.

Practical point: Primary care clinicians may suggest cranberry juice as a prophylactic measure in women with frequent recurrences.

6-14 SMOKING CESSATION AND THE COURSE OF MAJOR DEPRESSION

Smokers with a history of depression who abstained from smoking were at high risk of developing a new episode of major depression.

Practical point: How should primary care clinicians respond to this information? Which is worse -- continuing smoking or developing another episode of major depression? Is cigarette smoking always bad? Obviously, millions of persons choose to smoke fully knowing the risks. There must be some benefit. Relentlessly pushing some patients to stop smoking could drive them away. A frank discussion about pros and cons might lead to a trial of nicotine replacement.

6-15 TIME TO TAKE SOUNDINGS IN ACUTE RHEUMATIC FEVER.

Doppler echocardiographic demonstration of subclinical carditis represents definite heart disease. The criteria for confirmation require that the regurgitant jet must extend 1 cm back of the valve and be holosystolic (mitral) and holodiastolic (aortic).

Practical point: Although rheumatic fever is rare in the US, it still occurs. Primary care clinicians should be aware that echocardiography may be a valuable aid in early diagnosis and lead to more effective prophylaxis.

6-16 DO DOCTORS POSITION DEFIBRILLATION PADDLES CORRECTLY?

The International Liaison Committee of Resuscitation guidelines specify placement of the centers of the two paddles:

Sternal paddle — below the **right** clavicle in the mid-clavicular line

Apical paddle — to the left of the nipple with the center of the electrode in the mid-axillary line.

6-17 EFFICACY AND SAFETY OF INFLIXIMAB MONOTHERAPY FOR PLAQUE-TYPE PSORIASIS

Patients with moderate to severe psoriasis receiving infliximab (an antibody to tumor necrosis factor) experienced a high degree of clinical benefit and rapid time to response. Tumor necrosis factor has a pivotal role in the pathogenesis of psoriasis.

Practical point: Primary care clinicians should establish a referral relationship with dermatologists who will be able to offer new treatments which will more safely and effectively reduce the severe physical and psychological effects psoriasis brings to many individuals.

6-18 HIGH-DENSITY LIPOPROTEIN CHOLESTEROL AND ISCHEMIC STROKE IN THE ELDERLY: The Northern Manhattan Stroke Study

Increased HDL-c levels were associated with reduced risk of ischemic stroke in the elderly. This is possibly another benefit of statin drugs which raise HDL-c.

Practical point: Primary care clinicians should consider the entire lipid profile, not just the total cholesterol or the LDL-cholesterol, when advising patients about risks.

6-19 GLUCOSAMINE FOR OSTEOARTHRITIS: Magic, Hype, or Confusion?

"We conclude that there is more confusion and hype than magic about glucosamine. The rationale for its use in unclear; the best dose and route of administration are unknown, and the published trials do not allow any conclusion about its efficacy or cost effectiveness. However, it seems to be safe.

Practical point: When patients confront primary care clinicians about use of glucosamine, how should they respond? I would neither prescribe it nor dissuade patients who are convinced of its benefit from taking it since it appears to be safe.

6-20 GENE THERAPY FOR HEMOPHILIA

An article in this issue of NEJM reports results of introduction of a factor VIII gene into skin fibroblasts ex vivo and then implanting the cells into the peritoneal cavity of patients with hemophilia. Detectable levels of factor VIII appeared in the serum of patients who received such cells. Therapeutic levels persisted for several months.

Practical Point: None at present. I abstracted the article because of the promise of a great leap forward in therapy of a historically devastating disease.

6-21 FATTY FISH CONSUMPTION AND RISK OF PROSTATE CANCER.

Consumption of large amounts of fatty fish over years was associated with a decreased incidence of PC.

Practical point: Another possible benefit of fish. Primary care clinicians should recommend fish consumption in the healthy diet for protection against cardiovascular disease -- and now, possibly to protect against PC.

6-22 THUNDERSTORMS AND ASTHMA

During a thunderstorm, a downdraft of air sweeps up pollen and other particles and concentrates them in a shallow band of air at ground level. Patients with asthma should note any association with weather patterns, and take air-conditioned shelter if possible.

Practical point: In individual patients, primary care clinicians might determine the incidence of exacerbations of asthma related to weather. Recommendations to avoid outdoor air during storm times might be appropriate.

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RECOMMENDED READING

6-1 "TELL ME ABOUT YOURSELF": The Patient-Centered Interview.

This is the first of a series of articles on "Words That Make A Difference". It focuses on the language physicians use when they talk with patients. The authors have identified words and expressions that are powerful tools for understanding patients, and helping them manage their illnesses effectively.

Many patients wish that their physician would focus more attention on their concerns, feelings, and ideas. Inattention to the person of the patient, to the patient's characteristics and concerns, leads to inadequate clinical data-gathering, non-adherence, and poor outcomes. Each patient's experience of illness is unique. "To know what kind of a person has a disease is as essential as knowing what kind of disease a person has."

Primary care physicians must go beyond disease-centeredness in the clinical encounter.

The authors suggest language for conducting a patient-centered interview and offer words and phrases to help develop a more effective relationship with patients, and to communicate the fact that the patient is understood and valued. No one phrase works equally well for all physicians at all times. "A skilled interviewer will titrate the language to the patient and the circumstances."

Some suggestions:

1. Who is the patient? "*I'd like you to tell me a little about yourself as a person."*

2. What does the patient want from the physician? What does the patient hope to accomplish now and in the future? Unexpressed and conflicting expectations have torpedoed many a promising medical relationship. It's best to uncover them early and understand what the physician can and cannot accomplish. *"It would help me to understand what you're most hoping for in a relationship with a doctor."*

3. How does the patient experience the illness? *"What has this illness been like to you?" "I imagine the illness has been very hard for you." "Tell me more about it."* (Indeed, nothing beats *"tell me more about it")*

4. What are the patient's ideas about the illness? *"What do you think is causing your illness? What do you think is happening right now? What is most worrisome? What had you thought we ought to do about it?*

5. What are the patient's main feelings about the illness? *How does that make you feel?* (fear, distrust, anger, sadness, ambivalence?) *"I know I would feel angry (or frustrated, or depressed) under the same circumstances."*

Respectful attention builds long-lasting relationships. Non-verbal communication by attitude and feelings speaks as loud as what is said. Undivided attention is the strongest evidence of a desire to help the patient. Permit the patient to state all of her concerns without interruption. A skilled physician can obtain a useful sketch of the patient as a person in a short time. "Contrary to intuition, permitting patients to state all their concerns without interruption does not substantially add to the length of the interview."

Ask the patient to "Tell me about yourself", and then patiently wait for an answer.

"For physicians to be therapeutic they must connect with patients on at least some emotional level to motivate them toward healing."

Annals Int Med June 5, 2001; 134: 1079-85 "Medical Writings", commentary, first author Frederic W Platt, University of Colorado, Denver. **www.annals.org**

Comment:

1 Patients want to know: What is wrong with me? What is going to happen to me? What can be done about it?

Practical Pointers has emphasized articles regarding patient-centered medicine over the years. It lies at the heart of primary care. Primary care clinicians are privileged to care for many patients over a long-period. This gives us the time to "connect" and "concur".

The art (of listening) is long; time is short. Good listening involves not only listening to understand, but also responding in a way that encourages the patient to reveal more to listen to.

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REFERENCE ARTICLE

6-2 OPTIMAL TREATMENT OF ACUTE CORONARY SYNDROMES — An Evolving Strategy

*Acute coronary syndromes include… acute myocardial infarction (**MI**) with ST elevation; acute MI without ST elevation; and unstable angina. Some authorities do not include acute ST-elevation MI as an acute coronary syndrome. The distinction is important. Differences in treatment should be kept in mind.*

The management of acute coronary syndromes has evolved rapidly over the past decade and continues to do so. This article summarizes the latest recommendations. I attempt to outline a treatment plan especially for primary care clinicians who do not have immediate emergency department backup. RTJ

<u>Acute MI with ST-segment elevation, or new left bundle branch block.</u>

These patients are at high risk. They have chest pain at rest, evidence of injury on ECG, and elevated troponins.

A. Emergency hospital treatment immediately available. Catheterization laboratory is immediately available:

1) Aggressive therapy with iv nitroglycerin, beta-blocker, low-molecular-weight heparin, antiplatelet agent (aspirin, clopidogrel [*Plavix*]). As well as pain control.

2) Primary percutaneous revascularization

3) Stenting

4) Abciximab, a glycoprotein IIb/IIIa platelet inhibitor.

(In the past decade, there has been increasing evidence of the synergistic role of pharmacotherapy and primary percutaneous coronary revascularization. The concept of "facilitated primary coronary revascularization" has emerged. This combines early use of adjunctive agents with mechanical reperfusion. Stenting has emerged as the preferred approach to revascularization because the rate of restenosis is low, and because of the synergistic effect when combined with a glycoprotein IIb/IIIa platelet inhibitor.)

B. Emergency hospital treatment immediately available. Catheterization laboratory is <u>not</u> available:

1) Bolus infusion of fibrinolytic agent. [1]

2) With or without a GP IIb/IIIa platelet inhibitor.

C. Emergency hospitalization <u>not</u> immediately available:

Here primary care clinicians should determine the protocols of their consultant cardiologists and be able to administer early treatment:

1) As above

2) Bolus infusion of a fibrinolytic agent.[1]

3) With or without a glycoprotein IIb/IIIa platelet inhibitor.

(Since every passing minute adds to risk of death, the primary care clinician may have an opportunity to improve prognosis. Promptness of fibrinolysis is likely to be more important than the details of pharmacotherapy.)

<u>Acute coronary syndrome *without* ST-elevation:</u>

A. High risk: elevated troponins; ST depression; persistent angina:

Again, treatment depends on the immediate availability of a hospital emergency department and catheterization laboratory

Primary care clinicians should correlate their emergency treatment with their consultant cardiologists. They may immediately administer aspirin, low-molecular weight heparin, and a glycoprotein IIb/IIIa platelet inhibitor. (But not fibrinolysis.)

B. Those whose ST segment depression has stabilized and chest pain resolved may be transferred to the hospital for more definitive therapy.

Primary care clinicians are then often responsible to long-term monitoring of secondary prevention measures: aspirin, clopidogrel, beta-blocker, ACE-inhibitor, and a statin.

A reference algorithm is presented on p 1941.

NEJM June 21, 2001; 1939-42 Editorial by William E Boden and Raymond G McKay, Hartford Hospital Hartford Conn. **www.nejm.org**

1 Three bolus fibrinolytic agents are in phase 2 and phase 3 trials. They are derived from alteplase (tPA; *Activase*) by altering its molecular structure. Their duration of action is longer.

Reteplase

Lanoteplase

Tenecteplase

All produce benefits similar to alteplase. Ease of administration makes them more suitable for emergency administration out of hospital. All are administered with aspirin and heparin.

We await information on the doses and best combinations.

See "Bolus Fibrinolytic Therapy in Acute Myocardial Infarction" JAMA July 25, 2001; 286: 442-49

Comment:

Primary care clinicians can serve their patients optimally by immediately beginning non-interventional measures (aspirin, heparin, oral beta-blocker, and medication for pain control).

Primary care clinicians remote from emergency centers must keep up with the rapid changes in therapy. Each minute of myocardial ischemia adds to risk. If it is not possible to immediately transfer the patient to an ED, primary care clinicians should be able to administer the first diagnostic measures and non-invasive treatments (including bolus fibrinolysis), correlated with the regimens used by their local cardiologist colleagues. RTJ

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6-3 THE EFFECT OF FRUIT AND VEGETABLE INTAKE ON RISK FOR CORONARY DISEASE

Many constituents of fruits and vegetables may reduce risk of coronary disease. These authors recently reported that higher fruit and vegetable intakes were related to a decrease in risk of stroke. (JAMA 1999;282: 1233-39)

The current study evaluated the association between fruit and vegetable consumption and risk of coronary heart disease (**CHD**).

Conclusion: Consumption of fruits and vegetables appeared to have a protective effect.

STUDY

1. The Nurses' Health Study and the Health Professionals' Follow-up Study entered over 126 000 persons age 34 to 59. At baseline all were free of cardiovascular disease, cancer and diabetes.
2. Assessed diet by a food-frequency questionnaire on several occasions over the follow-up period.
3. Followed during 8 to 14 years.

RESULTS

1. After adjustment for standard cardiovascular risk factors, those in the highest quintile of fruit and vegetable intake had a relative risk of CHD of 0.8 vs those in the lowest quintile.
2. Each serving per day of a fruit or vegetable was associated with a 4% lower risk.
3. Green leafy vegetables and vitamin C rich fruits and vegetables contributed most to the apparent protective effect.

DISCUSSION

1. Intake of green leafy vegetables and vitamin C-rich fruits and vegetables was inversely related to risk of CHD.
2. The decrease in risk began at the level of 4 servings a day. Further reductions seemed to occur at up to 8 servings daily.
3. Previous studies reported a reduction in risk from nuts and whole grains.
4. The inverse association was slightly stronger in those taking supplements.

CONCLUSION

The data support a protective effect of greater consumption of fruits and vegetables, particularly green leafy vegetables and vitamin C rich fruits and vegetables, against CHD.

Annals Int Med June 19, 2001; 134: 1106-14 Original investigation, first author Kaumudi J Joshipura, Harvard School of Public Health , Boston, Mass. **www.annals.org**

Comment:

The benefits of a healthy diet are substantiated in several recent studies. Primary care clinicians should set the example in their own eating habits, and constantly encourage patients to do the same. RTJ

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6-4 MIDLIFE VASCULAR RISK FACTORS AND ALZHEIMER'S DISEASE IN LATER LIFE

Risk factors for vascular disease may also be risk factors for Alzheimer's disease. If so, it is important to identify them at an early age.

This study examined the relation of midlife raised blood pressure and cholesterol concentrations to Alzheimer's disease later in life.

Conclusion: Raised systolic BP and high serum cholesterol, and particularly the combination, in middle life were associated with increased risk of Alzheimer's later in life.

STUDY

1. Prospective, population-based study in two areas of Finland followed a total of over 1400 participants

studied in 1972, 1977, 1982, and 1987. After an average of 21 years, participants (then age 65-79) took part in a final examination in 1998.

2. Main outcome measures — midlife BP and cholesterol concentrations and development of Alzheimer's disease in late life.

RESULTS

1. A total of 57 participants were diagnosed as having dementia; 48 fulfilled the diagnostic criteria (DSM - IV) for probable or possible Alzheimer's.
2. All 48 showed generalized or temporal brain atrophy. None had appreciable vascular pathology on magnetic resonance scans.
3. After adjustment for possible confounders, those with raised systolic BP (> 160) or high cholesterol (> 250) had a significantly greater risk of Alzheimer's in later life. Odds ratio for raised systolic BP = 2.3; for raised cholesterol = 2.1; for the combination of both = 3.5.

DISCUSSION

1. Both raised systolic BP (but not diastolic) and high cholesterol in midlife were associated with later development of Alzheimer's disease. The combination of both increased risk to a greater degree.
2. Participants who developed Alzheimer's were more likely to have received antihypertensive drug treatment.
3. "Our findings are partly corroborated by the only drug trial to date showing that blood pressure control may prevent dementia, which was carried out in patients with isolated systolic blood pressure." ("Prevention of Dementia in Randomized, Double-blind, Placebo-controlled Systolic Hypertension in Europe (Syst-Eur) Trial" *Lancet 1998; 352: 1347-51*)
4. "Hypertension and hypercholesterolemia may increase the risk of dementia by inducing atherosclerosis and impairing blood flow, but they may also directly induce the neurodegeneration of Alzheimer's disease."

CONCLUSION

Raised systolic BP and high cholesterol concentrations, and particularly the combination, in midlife were associated with increased risk of Alzheimer's disease later in life.

BMJ June 16, 2001; 322: 1447-51 Original investigation, first author Miia Kivipelto, University of Kuipo, Finland. **www.bmj.com/cgi/content/full/322/7300/1447**

Comment:

More a hypothesis-suggesting study than a conclusive study. We should treat and control both abnormalities in midlife. It is possible that there is an important benefit in addition to that on cardiovascular disease. RTJ

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6-5 EFFECT OF RAMIPRIL VS AMLODIPINE IN RENAL OUTCOMES IN HYPERTENSIVE NEPHROSCLEROSIS

Mortality from hypertensive vascular disease has declined in the past 2 decades. At the same time, the incidence of end-stage renal disease (**ESRD**) due to hypertension has increased steadily, particularly among African Americans. In some age groups, risk of hypertensive ESRD is 20-fold greater than in whites. Might angiotensin-converting enzyme inhibitors (**ACEI**) be particularly beneficial in this segment of our population?

What is the optimal strategy for treatment of hypertension to prevent renal failure? Recent data in proteinuric patients with diabetic kidney disease as well as non-diabetic renal disease suggest a significant benefit from ACEI.

This article describes effects of the ACEI ramipril (*Altace*) vs the dihydropyridine calcium-channel blocker amlodipine (*Norvasc*) on progression of hypertensive renal disease.

Conclusion: Ramipril was more effective in slowing decline in renal function.

STUDY

1. Entered over 650 self-identified African Americans with hypertension. All had a reduced glomerular filtration rate. None had identified diabetes or causes of renal failure other than hypertension. Mean duration of hypertension = 14 years. Patients were taking a variety of drugs for hypertension.
2. Mean baseline characteristics:
   BP 151/86; age range 18-70; urine protein -- men 610 mg/d, women 400 mg/d; serum creatinine -- men 2.2 mg/dL, women 1.8 mg/dL; glomerular filtration rate (**GFR**) 20 to 65 mg/min per 1.73 m^2 of body surface. (Ie, at entry, all had long-standing hypertension, and significant renal dysfunction.)
3. Randomized to: 1) amlodipine, 5 to 10 mg daily; or 2) ramipril, 2.5 to 10 mg daily. Dosage was adjusted to achieve the BP goal of at least a mean arterial BP below 107 mm Hg. A variety of other drugs were added if the target BP was not achieved.
4. Primary outcome measure = rate of change in glomerular filtration rate.
5. Clinical endpoints included degree of proteinuria, and development of end stage renal disease and death. Follow-up = 3 years.

RESULTS

1. Among those with 24 h protein excretion over 300 mg, the ramipril group had a 36% slower decline in GFR over 3 years compared with the amlodipine group.
2. Over 3 years, compared with the amlodipine group, the ramipril group had a 36% slower decline in GFR, and a 48% reduced risk of end-stage renal disease and death.
3. The ramipril group also had a decline of 20% in protein excretion vs a 58% increase in the amlodipine group during the first 6 months of the study. Thereafter, moderate increases occurred. (Note -- ramipril slowed, but did not stop, the decline in renal function.)

DISCUSSION

1. Compared with amlodipine, treatment with ramipril offered greater benefits in patients with mild to moderate hypertensive, nephrosclerotic renal disease.
2. Ramipril was associated with a slowing in decline in GFR and slowed progression of proteinuria. Also lowered incidence of end-stage renal disease and death.
3. Patients with proteinuria of 300 mg/d or above at baseline received the greatest benefit.
4. CCBs may have a disadvantage because they dilate the glomerular afferent arteriole, leading to increased glomerular pressure and loss of renal autoregulation. Intraglomerular pressure rises even as systemic pressure falls. ACEI generally reduce intraglomerular pressure and do not interfere with autoregulation.
5. The authors suggest that the benefits of ramipril might extend to individuals without proteinuria.
6. These results are consistent with prior observations that ACEI have a renal protective effect in patients with non-diabetic as well as diabetic renal disease.
7. Measurement of urinary protein is recommended to guide initial therapy selection.

CONCLUSION

JAMA June 6, 2001; 285; 2719-28 Original investigation by the African American Study of Kidney Disease and Hypertension, first author Lawrence Y Agodoa, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. **www.jama.com**

Comment:

African Americans should be considered at high risk of renal dysfunction due to hypertension. Primary care clinicians obviously do not wait for renal dysfunction to be established before beginning effective anti-hypertension therapy. We should protect the kidney as well as the heart and brain.

Identifying and treating patients at the stage of microalbuminuria (20 to 200 mg/d) would lead to greater benefit than waiting for renal dysfunction to become established. I believe ACEI are the drugs of choice.

I had to refresh my memory about the normal reference ranges. According to Harrison's textbook of medicine:

Glomerular filtration rate

A. Inulin clearance -- Men 100-150 mL/min; women 105-130 mL/min

B. Creatinine clearance -- 91 to 130 mL/min

Serum creatinine -- < 1.5 mg/dL

Urine protein excretion -- men 0 to 60 mg/d; women 0 to 90 mg/d RTJ

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6-6 DRUG TREATMENT FOR OBESITY

"Obesity, especially abdominal obesity, is the commonest cause of complications such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease. Doctors most often use drugs to treat the complications rather than the underlying condition." This may be due to lack of recognition of obesity as an important causal factor, doctor's ignorance about the potential contribution of drugs to manage obesity, and lack of evidence that weight loss drugs can help maintain a reduced body weight.

A recent trial[1] provided good evidence of the long-term effectiveness of a weight loss drug. The objective of the trial was not to show that sibutramine (*Meridia*; a drug acting on the central nervous system to increase energy expenditure) could induce weight loss beyond that achieved by a reduced calorie diet or placebo. Rather, it tested whether sibutramine given after weight loss was achieved would prevent weight regain. Over 40% of patients maintained at least 80% of their weight loss compared with 16% in the placebo group. In addition, significant reductions in cardiovascular risk factors were noted — increased HDL-cholesterol; and reductions in triglycerides, total cholesterol/HDL cholesterol ratio, insulinemia, and abdominal circumference.

However, BP did not decline, as one would expect from the weight loss. "It is possible that sibutramine should be preferred for obese insulin-resistant dyslipidemic patients who are not hypertensive. Indeed, these high risk but normotensive obese patients represent a substantial proportion of the obese population."

Can the results of this trial be generalized? The study used specialized obesity clinics in an academic setting, a sophisticated approach, and frequent visits. Furthermore, only 75% of the subjects originally entered were followed for 18 months; 25% failed to lose weight initially.

The successful findings of the trial should pave the way to the design of long-term randomized trials in high-risk, abdominally obese patients.

BMJ June 9, 2001; 322: 1379-80 Editorial by Jean-Pierre Despres, Quebec Heart Institute, Sainte-Foy, Quebec, Canada. **www.bmj.com/cgi/content/full/322/7299/1379**

1 "Effect of Sibutramine on Weight Maintenance after Weight Loss" The STORM Trial Lancet 2000; 356: 2119-25. **www.thelancet.com**

See also: "Obesity — Extracts from "Clinical Evidence" BMJ June 9, 200; 322: 1406-09

The reviewers found 6 randomized, controlled trials which provided limited evidence that sibutramine was more effective than placebo in promoting weight loss. The weight loss was not sustained after the drug was stopped. There was limited evidence about short-term safety and no evidence of long-term safety. No evidence of effects on morbidity or mortality was reported. Common adverse effects were headache, dry mouth, anorexia, constipation, and insomnia. Increases in BP occurred — mean 1 to 3 mm Hg. Hypertension was the most common reason for withdrawal (5%). Heart rate increased by a mean of 5 beats / min.

The authors make the interesting comment that nearly 5 million US adults used prescription weight loss pills in 1996. A quarter of the users were not overweight. www.bmj.com/cgi/content/full/322/7299/1406

Comment:

Should primary care clinicians prescribe sibutramine, or any other weight-loss drug? I would vote against it. I believe use should be limited to special clinics where suitable candidates can be carefully screened and followed. The adverse effect on BP is a serious downside.

A drug approach which depends on increasing metabolism rate seems to me too risky. RTJ

6-7 *HELICOBACTER PYLORI* AND SYMPTOMATIC RELAPSE OF GASTRO-ESOPHAGEAL REFLUX DISEASE

The role of *H pylori* in the pathogenesis of GERD has been controversial. Some studies report a protective role; some report an increased risk of developing GERD when *H pylori* is eradicated. The pH of gastric content is a major determinant of damage to the distal esophagus. *H pylori* has divergent effects on gastric secretory function. This depends on the distribution of the infection and the severity of the gastritis. Gastritis predominantly in the antrum is associated with raised acid output. Gastritis in the body results in inhibition of acid secretion.

This study examined the effect of eradication in patients with established GERD.

Conclusion: Eradication could be protective against relapse.

STUDY

1. Double-blind, randomized trial entered 70 patients; 58 completed the trial All had symptoms of GERD. All had either endoscopically proven reflux esophagitis or a pathological reflux on 24-hour pH monitoring.
2. 29 patients had proven *H pylori* infections; 33 patients without infection served as *H pylori* controls.
3. All patients received lansoprazole (a proton pump inhibitor) therapy to reduce acid production for 8 weeks.
4. Randomized to one of 3 groups:
   1) *H pylori* positive:
      A. Received antibiotic therapy
      B. Served as *H pylori* positive controls
   2) *H pylori* negative controls
5. Follow-up = 6 months.

RESULTS

1. In 13 patients eradication was successful
   In 16 *H pylori* remained positive (3 treatment failures and 13 who were not treated)
   In 29 controls, *H pylori* was never present
2. In all patients in whom *H pylori* was successfully eradicated, the active component of gastritis (neutrophil granulocytes) disappeared
3. Among those who remained positive (untreated, failures, and controls) the GERD symptoms

relapsed earlier (Mean of 54 days). Among those in whom eradication was successful, relapse occurred at a mean of 100 days. Patients who remained positive and those who did not have the infection (controls) relapsed at the same time.

4. Time to relapse was also affected by severity of the esophagitis. When results were corrected for the effects of esophagitis grade, patients who remained positive still relapsed earlier.

5. No beneficial effect on patients with severe esophagitis (grade II and IV). These patients relapsed almost immediately.

DISCUSSION

1. Results of studies with duodenal ulcer patients have indicated that eradication of *H pylori* substantially raises the risk of GERD. (*H pylori*-positive ulcer patients may have a different pattern of acid secretion than those without ulcer disease.
2. But, other studies do not support the view that eradication in ulcer patients aggravates or precipitates GERD symptoms.
3. The presence of *H pylori* led to a shorter symptom free interval. Therefore . . . "eradication therapy should be considered in patients with GERD."

CONCLUSION

H pylori infection influenced the relapse rate of GERD. Eradication of the infection led to a benefit -- a longer asymptomatic period before relapse of symptoms.

Lancet June 2, 2001; 357: 1738-42 Original investigation, firs author W Schwizer, University Hospital, Zurich, Switzerland**. wwww.thelancet.com**

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6-8 LONG-TERM OUTCOME OF MEDICAL AND SURGICAL THERAPIES FOR GASTROESOPHAGEAL REFLUX DISEASE

About 20% of U.S. adults experience GERD symptoms such as heartburn and acid regurgitation at least once a week. Severe GERD is a lifelong problem, It can be complicated by peptic esophagitis, stricture, and Barrett esophagus (**BE**). BE has been considered a strong risk factor for esophageal carcinoma.

Medical treatment of GERD involves long-term administration of antacids and antisecretory agents, at high cost over years.

Surgical treatment (fundoplication) has become increasingly popular since minimally invasive (laparoscopic) surgical approaches have been developed.

Both medical and surgical antireflux therapies are effective in controlling symptoms. Some reports suggest that fundoplication might be more effective, and might obviate the inconvenience and expense of lifelong medical treatment.

In the late 1980s, the VA conducted a randomized trial of medical vs surgical therapies in over 225 patients with complicated GERD. Over a 2-year follow-up, surgery was found significantly better in controlling symptoms.

The present study conducted a long-term follow–up on this cohort of patients.

Conclusion: Antireflux surgery should not be advised with the expectation that patients with GERD will no longer need antisecretory medication or that the procedure will prevent esophageal cancer.

STUDY

1. At baseline (10 years previously), all had severe GERD, with a high proportion of esophageal ulcers, strictures, and BE. 52% of the original cohort participated in the follow-up.
2. Main outcome measures: use of antireflux medication, symptom scores, grade of esophagitis, frequency of treatment of esophageal structure, frequency of subsequent antireflux operations, general health scores, satisfaction with antireflux therapy, incidence of esophageal adenocarcinoma.]
3. Median follow-up = 10 years.

RESULTS

1. At follow-up:	Medical (n=91)	Surgical (n=38)
A. Regular use of antireflux medication	92%	62%

B. There were no significant differences in grade of esophagitis, frequency of treatment for esophageal stricture, subsequent antireflux operations, physical and mental scale scores, and overall satisfaction with therapy.

2. Patients with BE at baseline developed adenocarcinoma at a rate of 4/1000 per year. Adenocarcinomas developed in patients without Barrett esophagus at a rate of 0.7/1000 per year. Not a statistically significant difference.
3. Survival during the mean of 10 years of follow-up was less in the original surgical group due to a higher death rate from heart disease. The authors offer no explanation.

DISCUSSION

1. In this study of patients with severe GERD, Barrett esophagus developed into adenocarcinoma at a rate of 0.4% per year. This, and other studies have suggested that the cancer risk associated with BE has been overestimated. Acceptance of this low rate could have a profound influence on recommendations regarding endoscopic surveillance in patients with BE. The cancer incidence among patients with severe GERD who did not have BE was 0.07% per year).
2. GERD was an uncommon cause of mortality, even in elderly patients with severe GERD.
3. Almost all patients in the medical group continued to take antireflux medication (including proton

pump inhibitors), but 62% of surgical patients also continued to take antireflux medication on a regular basis. This suggests that antireflux surgery should not be advised with the expectation that medication will no longer be needed.

4. During follow up, a substantial number of patients in both groups had one or more antireflux operations (10% medical vs 16% surgical) and had treatment for esophageal stricture (8% vs 14%).
5. Most patients in both groups were satisfied with their therapy.

CONCLUSION

Antireflux surgery should not be advised with the expectation that patients will no longer take antisecretory drugs. Or that it is a clearly a cancer-preventing procedure.

JAMA May 9, 2001; 285: 2331-38 Original investigation, first author S J Spechler, VA Medical Center, Dallas TX **www.jama.com**

Comment:

An editorial in this issue by Peter J Kahrilas comments: "The basic tenants of the surgical argument -- permanence, cancer prevention, and freedom from use of antisecretory medications -- have all been seriously challenged by this report."

The message -- fundoplication is not the definitive therapy some believe it to be. Surgery does not relieve the burden of long-continued medical therapy. Proton-pump inhibitors have largely solved the problem of peptic esophagitis, although the drugs must be continued indefinitely.

When GERD symptoms are treated medically, severe complications are no more common than in those undergoing surgery

There is a significant complication rate (including death) from surgery, open and laparoscopic. Although the complication rate is low, it may equal or exceed the risk of development of adenocarcinoma and death in patients continuing on medical therapy. GERD has a remarkably low mortality rate.

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6-9 NATURAL HISTORY OF CERVICAL HUMAN PAPILLOMAVIRUS INFECTION IN YOUNG WOMEN: A Longitudinal Cohort Study

Case-control studies have consistently revealed a strong association between cervical neoplasia and detection of HPV DNA in exfoliated cervical cells.

What are the temporal relations between HPV and onset of cervical intraepithelial neoplasms (**CIN**)? How strong is the relationship between HPV and CIN? Only cohort studies that include women who are HPV negative and cytologically normal at enrollment can attempt to answer these questions.

This study describes the natural history of incident HPV infection and its temporal relationship to development of high-grade intraepithelial neoplasia (high-grade CIN).

Conclusion: The association between HPV and CIN is transient and tenuous in young women.

STUDY

1. Recruited 1075 women age 15-19 who were sexually active. All had normal cervical smears and were HPV negative at baseline.
2. Rechecked every 6 months for HPV and CIN. Mean follow-up = 3 years.
3. Determined HPV DNA by polymerase chain reaction.
4. When an abnormal smear was reported, patients were referred to a research clinic where a sample of colposcopically abnormal epithelium was removed for histological examination. Treatment was postponed until there was histological evidence of high-grade CIN (CIN 2 or 3). Once CIN 2 or CIN 3 developed, these individuals were excluded from the study. (Ie, the study supplied no information on development of carcinoma of the cervix.)

RESULTS

1. HPV infections:
    - What percentage of women became HPV positive?
        - Cumulative risk at 3 years was 44%; 60% at 5 years.
    - What types of HPV are most common?
        - HPV -16 was the most common. Seven other types were detected. Many women had unidentified types. Some women were positive for 2 to 4 different types during the follow-up period.
    - Once infection developed, how long did it remain present?
        - A median of 14 months. Infections were self-limited.

(*Comment: An extraordinary prevalence of infection. Infections waxed and waned*.)

2. Abnormal smears:
    - How many women developed abnormal smears?
        - Cumulative risk at 3 years of any abnormal smear was 28%. (Again, a high prevalence of cytologic abnormalities.
    - What stage CIN developed?
        - Borderline nuclear abnormality -- 43%.
        - Mild dyskaryosis -- 42%
        - Moderate or high grade dyskaryosis -- 15%. The majority -- CIN 2 or CIN 3
    - How long did the episodes of abnormality last?
        - Median duration = 9 months. (The dyskaryosis cleared itself. Some women had more than one episode of dyskaryosis. Duration in those with more

severe dyskaryosis was longer than those with milder dyskaryosis.

(*Comment: As with the infection, the abnormal cytology waxed and waned. The acquisition rate of CIN abnormalities was high.)*

3. Relation between HPV and abnormal smears:

How many women did <u>not</u> have HPV at time of appearance of abnormal smear?

40% tested negative for HPV up to and including the visit when the first abnormal smear was reported.

Although most episodes of cytological abnormality were associated with HPV, some women who developed abnormalities remained negative. Five women who remained negative developed high grade CIN. These five women tested negative on 16 occasions.

What was the risk of developing high grade CIN?

Overall, 2% of those who became positive for HPV progressed to high grade CIN. Risk was greatest in those testing positive for HIV 16

How long did the high grade CIN last?

Risk of developing high grade CIN was maximum between 6 to 12 months after first detection of HPV and declined rapidly thereafter. Relative risk of high-grade CIN at 18 months was 3 vs 19 at 6 to 12 months.

What was the temporal relationship between abnormal smears and identification of HPV?

HPV appeared before the abnormal smear -- 27%

Detected at the same time -- 33%

Compared with women who remained negative for HPV, those who became positive developed a higher grade of abnormality Risk was maximum at an average of 6 months, and declined rapidly thereafter.

Recurrent episodes of HPV-associated cytological abnormalities were usually associated with detection of a new HPV type.

What were the implications of viral load (high vs low)?

More women with a high viral load at their first HPV-positive sample had an abnormal smear than those with a low viral load. Some women developed a high viral load following a first determination of a low viral load. Cumulative risk = 45% at 3 years.

DISCUSSION

1. The risk of acquisition of HPV infection was very high in these young women. A similar risk has been reported in North American college students. Acquisition of HPV is apparently inevitable in this age group.
2. HPV infections, or at least the period during which the virus can be continuously detected, are usually of short duration. But infections may disappear and reappear. This could be due to:

Reactivation of endogenous infection

Low levels of HPV fluctuating around threshold of detectability

Inadequate sampling

New exposure.

The investigators could not distinguish between these possibilities. Th duration of infection cannot be measured with certainty.

3. High viral loads were associated with cytological abnormalities. But viral load seemed to wax and wane over time.
4. Cross sectional surveys reveal a high prevalence of cytological abnormalities in sexually active teenagers. Many of these abnormalities are transient, spontaneously regressing. Many women have more than one episode of CIN.
5. Most women who progressed to high grade CIN did so rapidly.
6. HPV infections often precede onset of CIN. The period between infection and CIN is frequently short.
7. There is a widely held view that persistent HPV infection is a prerequisite for the development of high grade CIN, a prolonged period of HPV exposure is not necessary for progression to take place. Ie, high grade CIN may be a surprisingly early manifestation of infection. Little lead time might be gained by detection of HPV.
8. Not all women who developed CIN were positive for HPV. A substantial number remained negative.
9. The International Biological Study on Cervical Cancers reported detection of HPV in 99.7% of cervical cancers. Thus, HPV negative high grade CIN, if it exists, has little malignant potential. However, the possible importance of HPV negative high grade CIN should not be discounted.
10 There is now understandable enthusiasm for exploiting the association between HPV and CIN to improve the efficiency of cervical screening programs. This would bring a risk of causing unnecessary anxiety and increasing management dilemmas.

CONCLUSION

In this cohort of young women, only limited inferences could be drawn from the characteristics of HPV status at a single point in time. Longer observation in older women is needed.

Attempts to exploit the association between HPV and cervical neoplasia to improve effectiveness of screening is limited. Any lead time (time from detection of HPV to development of CIN) gained by detecting HPV is likely to be short.

Lancet June 9, 2001; 357: 1831-36 Original investigation, first author Ciaran B J Woodman, University of Manchester, UK. **www.thelancet.com**

Comment

I congratulate the investigators on this fascinating study. It must have required enduring dedication on pat of patients as well as investigators. It raises more questions than it answers.

The data in the report was highly condensed and jumbled. I found abstracting it difficult and time consuming, but worthwhile. I believe in most aspects the abstract is accurate.

The extremely high acquisition rate of HPV astounded me. Certainly the infection is much more common than cervical cancer. This association reminded me of the *H pylori*-peptic ulcer story. HPV may be in many women necessary for the development of cervical cancer, but is not sufficient. It may be that repeated episodes of infection over years is needed for cancer to begin.

Some have speculated that a vaccine against HPV might be developed to prevent CIN. The large number of HPV types would make this more difficult.

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6-10 NATURAL HISTORY OF HUMAN PAPILLOMA VIRUS INFECTIONS

"One of the general principles governing the introduction of screening is that the natural history of the disorder should be known. A major difficulty is that, until screening is initiated, the natural history of the disorder is not known. The reason for this lack of knowledge is that the abnormality discovered by screening has not been recognized before in that particular phase of the disease's natural history. So the proportion of individuals that progress to clinically recognized disease and the rate of such progress will not have been described."

There is an additional difficulty. The introduction of highly sensitive screening tests may reveal disease that might never have been detected in the absence of screening ("overdiagnosis"). This is probably true for prostate cancer It is also true for cervical cancer because *low-grade intraepithelial neoplastic lesions* (low-grade CIN) rarely become invasive.

In the study cohort, of almost 250 women who had an abnormal smear, 40% tested negative for HPV. Another 33% tested HPV positive for the first time only at the same time as the abnormal smear. Thus, for only 21% of women was the positive HPV test predictive of abnormal cytology at a subsequent visit.

For the 28 women who developed high grade CIN during follow-up, 82% had become HPV positive. The risk of moderate to severe dyskaryosis was substantially greater in those who tested HPV positive.

The study confirms the transitory nature of most HPV infections. Cytology may identify dyskaryosis soon after the first evidence of HPV infection. The development of CIN in a woman who has a positive HPV test may be due more to the play of chance than most investigators have assumed.

"A positive HPV test, especially in young women, rarely represents disease that could, if unrecognized, progress to cervical cancer."

"Knowing more about the natural history of HPV infection, especially in young women, reinforces the view that testing should *not* be carried out among women under age 35."

"A radically new approach to screening is needed which recognizes that most cervical cancers are caused by specific subtypes of HPV." Screening for HPV, if done at the right age, may identify women with a low risk of cervical cancer if they test negative, but cannot help identify the minority who have a high risk of progression.

Lancet June 9 , 2001; 357: 1816 Commentary by Anthony B Miller, Deutsches Krebsforschungszentrum, Heidleburg, Germany **www.thelancet.com**

1 "Natural History of Cervical Human Papilloma Infection in Young Women" Lancet June 9, 2001; 357: 1831-36, first author C B J Woodman

Comment:

All clinical medicine is based on the natural history of disease. The study helps define the natural history of HPV. Much more observation will be needed to clarify the relationship with CIN and cervical cancer. Meanwhile, it is not likely that screening for HPV in young women will be rewarding. RTJ

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6-11 WHY SHOULD WOMEN HAVE LOWER REFERENCE LIMITS FOR HAEMOGLOBIN AND FERRITIN CONCENTRATIONS THAN MEN?

Before puberty, no major differences are found between the sexes in red blood cell count, hemoglobin, and ferritin concentrations. Only after the onset of menses does a difference emerge. Not until 10 years after the menopause does this situation reverse in women, when the hemoglobin concentration becomes similar to that of age matched men. At present women are deemed to be anemic if their hemoglobin is less than 11.5 g/L. For men the cut point is 13.0 g/L.

The situation is compounded now because modern women reach sexual maturity at an earlier age, have fewer pregnancies, and breast feed for shorter periods. Thus, they menstruate for more years.

Furthermore, up to 90% of females of childbearing age do not achieve the recommended daily intake of elemental iron (15 mg). Women worldwide are at risk of being in negative iron balance.

The mean upper limit for hemoglobin in primates that menstruate is significantly lower in females than in males, similar to humans. This is not the case for primates that do not menstruate. This suggests that menses are responsible for limiting the upper limit of hemoglobin, as in humans.

"The data from humans point to the possibility that the current lower reference levels for red blood cell counts and hemoglobin and serum ferritin concentrations in women have been derived from sampling populations that are deficient in iron."[1] "It would seem that a large number of women spend a major part of their lives with a negative iron balance." Indeed, iron deficiency is the most important nutritional problem affecting humans around the world.

Reclassification of these parameters in women to the same normal values as for men would be expected to have fundamental and positive implications for women's health and welfare.

BMJ June 2, 2001; 322: "Education and Debate", commentary, first author D Hugh Rushton, University of Portsmouth, UK **www.bmj.com./cgi/content/full/322/7298/322**

Comment:

1 This reminds me of the "traditional reference intervals for total cholesterol given several decades ago. The top normal was 300 mg/dL. This was because 2.5% of "normal", healthy persons had a total cholesterol above 300. The problem was later recognized. The "normal" population was not normal. It was loaded with individuals who were at high risk for cardiovascular disease.

An iron-deficient state is near-universal in menstruating women. Iron supplementation should be given to almost all. .

I reviewed the System International (SI) traditional reference intervals:

	Women	Men
Hemoglobin (g/dL)	11.5 - 15.5	14 - 18
Hematocrit (%)	33 - 43	39 - 49
Red cell count (10^6/cu mm)	3.5 - 5.0	4.3 - 5.9
Ferritin (ng/mL)	18 - 300	18 - 300
Iron (ug/dL)	60 - 160	80 -180

No age-differentiation mentioned. The reference values are not intended to be definitive. Each laboratory determines its own values.

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REFERENCE ARTICLE

6-12 DIAGNOSIS AND CARE OF PATIENTS WITH ANOREXIA NERVOSA IN PRIMARY CARE SETTINGS

Anorexia nervosa (**AN**) is a psychiatric disorder characterized by abnormal eating behaviors that results in weight loss and serious medical consequences. It is common, with a prevalence of 1% to 2%. Most of the complications are readily treatable if diagnosed and attended to early. The primary care physician plays a critical role in caring for these patients. Primary care clinicians should be vigilant in suspecting and recognizing the disorder. The young age of patients with AN simplifies the diagnosis of weight loss.

Could this patient have AN? Clinical diagnosis of AN is often obscure. Patients with mild cases usually seek help for non-specific symptoms such as asthenia, dizziness, and lack of energy. Presentation may be remarkable for its lack of complaints. Family members may bring patients to the physician because of concerns about amenorrhea or weight loss. Menstrual disorders are among the most common reasons for seeking medical attention. Hypothalamic-induced amenorrhea is a universal features of AN. It should be determined if the amenorrheic patient has a history of recent weight loss.

The criteria for AN:

Intense fear of weight gain

Undue emphasis on body shape

Body weight < 85% of predicted

Amenorrhea for 3 consecutive periods.

Young adults who strive for an unhealthy weight are more likely to engage in other harmful behaviors such as substance abuse.

Almost half of the patients with AN develop bulimia. (Actually, bulimia is more common than AN.)

Criteria for bulimia nervosa (BN):

Recurrent episodes of eating a larger amount than most persons, or a sense of not having control over eating.

Recurrent, inappropriate, compulsive behavior to prevent weight gain — self-induced vomiting, abuse of laxative, diuretics, or other medications. Excessive exercise.

Bingeing and purging at least twice a week for 3 months.

Self-evaluation unduly influenced by body weight and shape.

Both bulimic and anorectic patients frequently engage in excessive amounts of exercise. Compulsive exercise training is associated with weight obsession. Runners experience "withdrawal" symptoms if they cannot run, and are unable to stop running even if they are sick or injured. Excessive exercise often precedes development of the formal eating disorder.

The article goes on to discuss other aspects of AN and bulimia: criteria to suspect mild AN; appropriate initial course of treatment; referral to mental health specialist; concern about bradycardia; gastrointestinal symptoms; estrogen replacement. The primary care clinician is involved with arranging and coordinating a comprehensive and multidisciplinary program.

AN is often a protracted illness. It has become an increasingly important health concern. Many have poor outcomes from treatment. It is associated with substantial morbidity and mortality.

"The invaluable role of the primary care physician is to point out the reality and severity of this chronic illness, while diligently monitoring and assessing the patient's physical status."

Annals Int Med June 5, 2001; 134: 1048-59 Review article by Philip S Mehler, University of Colorado Health Sciences Center, Denver**. www.annals.org**

Comment:

The primary care physician is most often the first to consult and suspect AN. Early diagnosis or clinical suspicion is more likely to lead to effective treatment.

Excessive exercise by a thin young woman is a good hint leading primary care clinicians to suspect AN. Would it not be reasonable to suspect AN in some thin young women who are dedicated to anaerobic exercise training classes?

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6-13 RANDOMIZED TRIAL OF CRANBERRY-LIGONBERRY JUICE AND *LACTOBACILLUS* GG DRINK FOR THE PREVENTION OF URINARY TRACT INFECTION IN WOMEN.

Up to 60% of women have a urinary tract infection (**UTI**) at some point in their life. Many will experience a recurrence within the following years.

The bacteria causing UTI arise from the stool. Dietary changes (eg, products containing lactobacilli) can alter the balance of fecal bacteria. Locally administered lactobacilli have been reported to act against coliform bacteria.

Some berries act against the coliform bacteria that cause most UTIs. Cranberries contain tannins which, by preventing the expression of bacterial fimbriae, block the adhesion of *E coli*. Cranberry juice prevents bacteriuria in elderly women.

This study evaluated the effect of these products in preventing symptomatic recurrences of UTI.

Conclusion: Cranberry juice reduced recurrence rate of UTI; lactobacillus did not.

STUDY

1. Open, randomized trial entered 150 women (mean age 30) with UTI caused by *E coli* — a typical group at risk.
2. All had a recent UTI. None were taking antimicrobial prophylaxis.
3. Randomized to: 1) 50 mL of a cranberry-ligonberry juice (80% cranberry) concentrate daily for 6 months; 2) 100 mg of a lactobacillus drink 5 days a week for 1 year; or 3) no intervention control group.
4. Followed for UTI recurrence over 1 year.

RESULTS

1. At 6 months, 8 (16%) of women in the cranberry group, 19 (39%) in the lactobacillus group, and 18 (36%) in the control group had at least one recurrence.
2. Number needed to treat with cranberry for 6 months to prevent one UTI = 5.
3. Lactobacillus was not effective.

DISCUSSION

1. "Our study confirms the common belief that symptomatic recurrences of urinary tract infection can be prevented with cranberry juice."
2. Cranberry juice could reduce use of prophylactic antimicrobials.

CONCLUSION

Daily consumption of cranberry juice reduced the recurrence of urinary tract infections in young women. Lactobacillus did not.

BMJ June 30, 2001; 322: 1571-73 Original investigation, first author Tero Kontiokari, University of Oulu, Finland **www.bmj.com/cgi/content/full/322/7302/1571**

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6-14 SMOKING CESSATION AND THE COURSE OF MAJOR DEPRESSION

Previous investigations reported that smokers attending a cessation clinic had a much higher than average frequency of past episodes of major depression. Those who had a history of depression, but had been free of past episodes of depression for years, were twice as likely as those who had never been depressed to start smoking again.

Many epidemiological studies have shown associations between smoking and major depression, and between depression and inability to stop smoking. Is it likely that smoker's depressive symptoms return when they try to stop smoking?

This smoking-cessation investigation followed smokers who had a history of major depression to determine recurrence rate of depression.

Conclusion: Smokers who abstained had significantly higher risk of developing a new episode of depression.

STUDY

1. Enrolled 100 smokers in a cessation program. Followed 76 to completion of the study. All were smoking over 1 pack per day. All had a history of major depression, but were currently free of depression, and had not been on antidepression medication for at least 6 months.
2. Participants were self-selected. All wanted to stop smoking. All were at the mild-to-moderate end of the spectrum of depressive illness. They were more representative of patients seen in primary care than in a psychiatrist's office.
3. Assessed recurrence of depression at 3 and 6 months after cessation.

RESULTS

1. 76 of 100 (76%) were followed for 6 months. Many subjects failed to return for follow-up.
   A. 42 (55%) successfully maintained cessation. Of these abstainers, 14 (18%) had a recurrence of depression.
   B. 34 (45%) relapsed into smoking. Of these, 2 (6%) had a recurrence of depression.

DISCUSSION

1. Smokers with a history of major depression who stopped smoking were 7 times more likely to have a recurrence of depression than individuals who continued to smoke.
2. Unlike withdrawal symptoms, depression did not generally arise immediately after cessation, but was distributed across the entire study period.
3. "Some smokers with a history of depression undoubtedly sense that cessation provokes

depression, and they fear trying to stop." It is not known if antidepression medication would be a better alternative than continued smoking.

4. Data suggest that nicotine decreases vulnerability to depression. "Nicotine or nicotine-like drugs could be useful antidepressant treatments."

CONCLUSION

Smokers with a history of depression who abstained from smoking were at high risk of developing a new episode of major depression.

Lancet June 16, 2001; 357: 1929-32 Original investigation, first author Alexander H Glassman, New York State Psychiatric Institute, New York, NY **www.thelancet.com**

Comment:

Is cigarette smoking always bad? Are there no beneficial effects?

During world war II, cigarettes were available to service personnel at 50 cents a carton. Smoking was almost universal. Did smoking help us to win the war? Or at least make the stress more bearable. Would some individuals willingly accept the long-term risks of smoking in exchange for the short-term benefits? It is obvious that many do. There must be some short-term benefit. RTJ

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6-15 TIME TO TAKE SOUNDINGS IN ACUTE RHEUMATIC FEVER.

With the addition of Doppler and color-flow technology, echocardiography is particularly well suited for assessing rheumatic fever (**RF**). It provides more reliable hemodynamic and anatomical data than can be obtained with invasive studies.

Can a diagnosis of RF be made based solely on echo findings of mitral and aortic regurgitation in patients with "isolated" RF or "pure" chorea?

A recent report[1] adds to the evidence that echo demonstration of inaudible left-sided valvular incompetence is valid confirmation of rheumatic carditis.

The investigators evaluated 35 children with RF including Doppler echo. Aortic or mitral regurgitation was found in 20 patients who had no auscultatory evidence of carditis. Five years later, subclinical carditis was still present in 3 of 6 children, a proportion similar to that of audible regurgitant murmurs that persisted.

The investigators advocate that echo evidence of valvular incompetence be accepted as carditis in the Jones criteria.[2] The criteria for confirmation of subclinical rheumatic carditis require that the regurgitant jet must extend 1 cm back of the valve, and be holosystolic (mitral) or holodiastolic (aortic). \

Subcutaneous nodules and erythema marginatum almost never present as isolated manifestations of acute RF. Chorea alone establishes the diagnosis of RF without needing other major or minor criteria or confirmation of an antecedent streptococcal infection. The demonstration of subclinical carditis may be most helpful for

confirmation of the diagnosis in patients with polyarthritis in whom supportive minor manifestations may be equivocal.

"That the echocardiographic demonstration of subclinical carditis represents definite rheumatic heart disease can no longer be contested." The finding emphasizes the need for continuous penicillin prophylaxis. "Although hard data are scarce, logic would suggest that such patients receive prophylaxis against infective endocarditis.

No progression of the subclinical lesions occurred over the time of the study. The frequency of chronic heart disease, however, cannot be predicted. Establishing the extent of the lesions at baseline will allow recognition and confirmation of recurrences. Echo will increase the precision with which patients are managed.

Lancet June 23, 2001; 357: 1994-95 Commentary by L George Veasy, University of Utah School of Medicine, Salt Lake City. **www.thelancet.com**

1 "Prospective Comparison of Clinical and Echocardiographic Diagnosis of Rheumatic Carditis" Heart 2001; 85: 407-10

Comment:

Rheumatic fever and carditis were major problems in the US 50 years ago. Now, most clinicians have never seen a case. Surely, this is one of the major victories in health care in the past century.

If echo had been available 50 years ago, it would have been a great help in diagnosis.

I enjoyed this opportunity to refresh my memory of the Jones criteria — updated 1992:

Major criteria	Minor criteria
Carditis	Clinical
Migratory polyarthritis	Fever
Subcutaneous nodules	Arthralgia
Erythema marginatum	Laboratory
Chorea	Elevated acute phase reactants
	Prolonged PR interval

For the diagnosis, either 2 major criteria or one major + two minor criteria PLUS, supporting evidence of recent group A streptococcal infection -- eg. positive throat culture or rapid antigen test and/or increase in streptococcal antibody test.

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6-16 DO DOCTORS POSITION DEFIBRILLATION PADDLES CORRECTLY?

Every minute of delay in restoring sinus rhythm in patients with ventricular fibrillation increases mortality. Successful defibrillation requires depolarization of a critical mass of myocardium. This is most likely to be achieved if the defibrillation paddles are correctly placed.

The International Liaison Committee on Resuscitation guidelines specify placement of the centers of the two paddles:

Sternal paddle — below the **right** clavicle in the mid-clavicular line

Apical paddle — to the left of the nipple with the center of the electrode in the mid-axillary line.

This study comments on how 100 doctors placed the paddles when asked to demonstrate defibrillation on manikins. About 2/3 of the sternal paddles were placed within 5 cm of the recommended site. But, most apical paddles were placed too medially and too cranially. This reduces the degree of separation of the paddles.

Incorrect paddle placement will result in a greater percentage of current passing through non-cardiac tissue, and reduce chances of successful defibrillation.

BMJ June 9, 2001; 322: 1393-94 original investigation, first author Richard M Heames, Southampton General Hospital, UK **www.bmj.com/cgi/content/full/322/7299/1393**

Comment:

See diagram p 1393.

First responders may wish to review these recommendations.

An anecdote — Years ago, I failed to defibrillate a patient by what I considered the usual paddle placement (which may have been incorrect according to the above guidelines). I then placed the apical paddle on the back just below the left scapula. The patient converted. RTJ

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6-17 EFFICACY AND SAFETY OF INFLIXIMAB MONOTHERAPY FOR PLAQUE-TYPE PSORIASIS

Psoriasis can be psychologically and physically disabling. It affects 1% to 3% of the US population. About 25% of patients have moderate to severe disease.

Currently available treatments are either incompletely effective or associated with toxic effects. (Cyclosporine is the most effective.)

Tumor necrosis factor alpha (**TNF**) is thought to have a role in the pathogenesis of psoriasis. This study assessed the clinical benefit and safety of infliximab (*Remicade*), a monoclonal antibody against TNF.

Conclusion: Infliximab was beneficial and safe.

STUDY

1. Randomized 33 patients with moderate to severe psoriasis to: 1) intravenous infliximab 5 or 10 mg at weeks 0, 2, and 6; or 2) placebo.
2. Follow-up at 10 weeks for physician's global assessment of response.

RESULTS

1. Responders (good, excellent, or clear):

Infliximab 5 mg	82%
Infliximab 10 mg	91%
Placebo	18%

2. Median time to response was 4 weeks.
3. No serious adverse effects. Headache occurred more commonly in the active treatment groups.

DISCUSSION

1. There are 2 major pathological lesions seen in psoriasis: 1) epidermal hyperproliferation with abnormal differentiation, 2) and inflammatory infiltration of the epidermis and dermis.
2. These processes are driven mainly by activated T cells which release chemokines and cytokines that signal hyperproliferation and abnormal differentiation. TNF is one of the signal molecules involved. Increased concentrations have been found in psoriatic lesions.
3. Blockade of TNF should reduce inflammation, keratinocyte proliferation, and the differentiation abnormalities of psoriasis.
4. The response was similar to that of cyclosporine, and greater than that reported for the soluble TNF inhibitor etanercept.
5. The findings support the pivotal role of TNF in the pathogenesis of psoriasis.
6. Infliximab has been reported to benefit rheumatoid arthritis and Crohn's disease. It is FDA approved for these indications.

CONCLUSION

Patients with moderate to severe psoriasis receiving infliximab (an antibody against tumor necrosis factor) experienced a high degree of clinical benefit and rapid time to response. Tumor necrosis factor has a pivotal role in the pathogenesis of psoriasis.

Lancet June 9, 2001; 357: 1842-47 Original investigation, first author U Chaudhari, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ**. www.thelancet.com**

Comment:

Several other agents to treat psoriasis are in development. See " Treatment of Chronic Plaque Psoriasis by Selective Targeting of Memory Effector T Lymphocytes" NEJM July 26, 2001; 345: 248-55.

T-cells and inflammatory cytokines are involved in the pathogenesis of psoriasis. We await more information on efficacy and safety of these anti-cytokine and anti-T cell preparations. None is currently approved by the FDA.

We should establish contact with dermatologists who will be able to offer these treatments to reduce the adverse physical and psychological effects psoriasis brings to many individuals. RTJ

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6-18 HIGH-DENSITY LIPOPROTEIN CHOLESTEROL AND ISCHEMIC STROKE IN THE ELDERLY: The Northern Manhattan Stroke Study

Many studies have provided strong evidence linking lipids with risk of coronary artery disease. Specifically, elevated high-density cholesterol (**HDL-c**) is protective.

The relationship of lipids and specific lipid classes with ischemic stroke has not been clearly established.

This study evaluated the association between HDL-c and ischemic stroke in an elderly population.

Conclusion: Increased HDL-c was associated with a reduced risk of ischemic stroke.

STUDY

1. Population-based case-control study 1993 through 1997. About 2/3 were over age 65.
   Cases (n > 500) had a first ischemic stroke
   Controls (n > 900) without stroke, matched by age, sex, and ethnicity.
2. Determined lipid profiles in all.

RESULTS

1.	Cases (stroke)	Controls (no stroke)
HDL-c mg/dL (mean)	40	47
< 34	34%	20%
35-48	47%	42%
> 50	19%	37%

2. A protective effect was observed for HDL-c levels of at least 35 mg/dL. More controls than cases had HDL-c concentrations over 35.
3. A dose response relationship was present: adjusted odds ratio cases/controls = 0.31 for those with HDL-c > 50
4. The protective effect of HDL-c was significant in those age 65-70 and those over age 75; less so in those under age 65.
5. Protective effect occurred in all racial groups.

DISCUSSION

1. Compelling data from statin trials show impressive stroke reductions among persons with established coronary disease (secondary prevention). [Statins raise HDL-c] Efficacy of statins has been reported significantly greater among those with initially lower HDL-c levels.
2. This case-control study demonstrated a protective efffect for ischemic stroke of higher HDL-c levels in men, women, the elderly, blacks, and Hispanics.
3. The protective effect persisted after adjustment for total cholesterol, LDL-c, and triglyceride levels.
4. Ultrasound studies have reported higher HDL-c is related to lower degrees of carotid atherosclerosis.

5. The National Cholesterol Education Program recommends the addition of HDL-c to cholesterol testing, and changed the recommended lower level to 40 mg/dL

CONCLUSION

Increased HDL-c levels were associated with reduced risk of ischemic stroke in the elderly, and among different ethnic groups.

JAMA June 6, 2001; 285: 2729-35 Original investigation, first author Ralph L Sacco, College of Physicians and Surgeons, Columbia University, New York. **www.jama.com**

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6-19 GLUCOSAMINE FOR OSTEOARTHRITIS: Magic, Hype, or Confusion?

It's probably safe — but there's no good evidence that it works

Huge amounts of glucosamine are being consumed by persons with joint pain and osteoarthritis, fueled by recent media coverage.

Glucosamine is a sugar, a sulfated amino-mono-saccharide. It is one of the constituents of the proteoglycans present in articular cartilage. In *vitro*, it can alter chondrocyte metabolism. This is the rational given for its use in osteoarthritis.

However, it is unclear whether oral glucosamine can reach chondrocytes in vivo. The most appropriate and route of administration (oral; injectable?) remain unknown.

"We do not even seem to know how to classify it: is it a drug, a food supplement, a neutraceutical, or a complementary therapy?" Investigators have used several different patient-related outcomes and often mix up different domains of outcome.

Why should we expect an agent that affects articular cartilage to have an effect on symptoms? There are no nerves in articular cartilage.

A recent trial reported in Lancet did report benefit. (*Lancet 2001; 357: 251-56*)

But, the evidence that glucosamine alters either the symptomatic expression of osteoarthritis or its radiographic progression is not very good. "Glucosamine may become the first agent about which we have more published systematic reviews, editorials, meta-analyses and comments than we do primary research papers." Most primary studies are poor quality and are small. Much of the research is sponsored by companies making glucosamine. The editorialists identified 12 trials with a clear involvement by a company producing the product. All 12 gave positive results.[1] Of 3 trials that reported a negative effect, only 1 reported commercial funding.

Although much of research points to glucosamine being a safe and effective treatment, problems with bias and quality of studies mean that the results must be treated with caution.

"We conclude that there is more confusion and hype than magic about glucosamine. The rationale for its use in unclear; the best dose and route of administration are unknown, and the published trials do not allow any conclusion about its efficacy or cost effectiveness. However, it seems to be safe.

BMJ June 16, 2001; 322: 1439-40 Editorial by Jiri Chard and Paul Dieppe, University of Bristol, UK.

www.bmj.com/cgi/content/full/322/7300/1439

Comment:

1 We all know that positive "spin" often occurs in favor of drug products of the company funding the trial. This is not limited to studies of alternative medicines by any means; it occurs in trials of FDA approved drugs.

How should the primary care clinician respond when a patient asks about glucosamine, or discloses its use? I believe they should be told what the editorial says.

I doubt, however, patients will be dissuaded from its use, particularly if they report symptomatic benefit. The primary function of primary care clinicians regarding "alternative medicines" is to be knowledgeable about their safety and warn patients about preparations with reported adverse effects and those which have frequent adverse interaction with FDA approved drugs the patients may be taking. Since glucosamine is probably safe, I would not try to dissuade anyone who reports benefit from taking it. RTJ

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The Cutting Edge

6-20 GENE THERAPY FOR HEMOPHILIA

The current therapy of hemophilia consists of periodic replacement of the deficient factor (VIII or IX) with recombinant proteins. Ideally, there should be continuous endogenous production of these factors to protect against bleeding and minimize exposure to infectious agents that may be present in replacement therapies. Theoretically, this can be achieved with gene therapy.

Factors VIII and IX can be expressed by a wide variety of cells.

An article in this issue of NEJM[1] reports results of introduction of a factor VIII gene into skin fibroblasts ex vivo and then implanting the cells into the peritoneal cavity of patients with hemophilia. They found detectable levels of factor VIII in patients who received such cells. Therapeutic levels persisted for several months.

NEJM June 7, 2001; 344: 1735-42 Original investigation, first author David A Roth, Harvard Medical School, Boston, Mass. **www.nejm.org**

1 "Nonviral Transfer of the Gene Encoding Coagulation Factor VIII in Patients with Severe Hemophilia" NEJM June 7, 2001; 344: 1735-42

See also; "The Hemophilias — from Royal Genes to Gene Therapy" Review article NEJM June 7, 2001; 344: 1773-79 The review comments:

Of all the genetic disorders, the hemophilias represent a combination of features that makes a favorable response to gene-replacement treatment likely. The clinical manifestations are entirely attributable to the lack of a single gene product which circulates in minute amounts in plasma. Tightly controlled gene expression is not essential. A small increase in the plasma level of factor VIII markedly ameliorates the symptoms. Many different types of cells are capable of making coagulation factors. The site of synthesis is not critical to function.

"Hemophilia is likely to be the first common severe genetic condition to be cured by gene therapy." "We can confidently predict that the new millennium will see an end to this ancient scourge."

Comment:

I abstracted this article because of its cutting edge connotations. Watch for developments. RTJ

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6-21 FATTY FISH CONSUMPTION AND RISK OF PROSTATE CANCER.

Essential fatty acids contained in fish inhibit the growth of prostate cancer (**PC**) cells in vitro. A case-control study supported the protective effect of fatty acids from fish. Only fish high in omega-3 fatty acids are likely to lower risk.

This study examined the relationship between fish consumption and PC.

Conclusion: Consumption of fatty fish might reduce the risk of PC.

STUDY

1. Population-based study of twins followed over 6000 male twin pairs in Sweden for over 30 years. Sweden is a country with a traditionally high consumption of fatty fish from Northern waters (salmon, herring, mackerel) which contain large amounts of omega-3 acids.
2. In 1967, questionnaires were sent to twin pairs born between 1886 and 1925. (Sweden maintains a twin registry.)
3. The questionnaire investigated life-style factors, including fish consumption.
4. Followed the cohort to 1997, determining incidence of PC from a National Cancer Registry.

RESULTS

1. During the follow-up of up to 30 years (average = 21 years), there were 455 cases of PC diagnosed at a mean age of 77.
2. An increasing consumption of fish was associated with a decreasing frequency of PC. Men who ate no fish had a 2- to 3-fold higher frequency of PC than those who ate moderate to high amounts of fish.

DISCUSSION

1. The authors speculate on a possible mechanism for the protective effect of omega-3 acids. Consumption of fish high in omega-3 results in lower blood levels of tumor growth-enhancing prostaglandins.

CONCLUSION

Consumption of large amounts of fatty fish over years was associated with a decreased incidence of PC.

Lancet June 2, 2001; 357: 1764-66 Original investigation, first author Paul Terry, Karolinska Institutet, Stockholm Sweden. **www.thelancet.com**

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6-22 THUNDERSTORMS AND ASTHMA

"For many people with asthma, severe weather conditions may trigger an attack."

Australian researchers have found that the culprit is the airflow pattern of some thunderstorms. (Reported in June *Throrax*.) They identified epidemic asthma days that occurred in 6 towns in Australia and compared hospital admission rates with airflow patterns which occurred on those days. They included a random sample of control days.

Thunderstorms with outflows — downdrafts of cold air containing high concentrations of particles — occurred on 33% of epidemic days vs only 3% of control days. During a thunderstorm outflow, a downdraft of air sweeps up pollen grains and other particles and concentrates them in a shallow band of air at ground level — just where the hypersensitive airways of people with asthma are likely to encounter them .

The link was even stronger during spring and summer, when pollen counts were at their highest. Then, a thunderstorm outflow preceded nearly half of all asthma epidemics.

JAMA June 13, 2001; 285: 2847 "The World in Medicine" commentary by Joan Stephenson, JAMA staff.
www.jama.com

Comment:

I had not thought of this possible triggering factor before. It makes sense. We know that air pollution is strongly associated with asthma. Patients in the US with asthma should note any association with weather patterns, and take air conditioned shelter, if possible, for as long as the threat remains. It would be interesting to know how long the low lying air pollution lasts. Times must vary.

Unfortunately, they cannot avoid man-made pollution. RTJ

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