

**PRACTICAL POINTERS**  
**FOR**  
**PRIMARY CARE**  
**ABSTRACTED MONTHLY FROM THE JOURNALS**  
**MAY 1999**

**MANAGING LOW LEVELS OF HDL-CHOLESTEROL**  
**MACROVASCULAR RISKS AND BENEFITS OF THERAPY FOR DIABETES**  
**PREVENTION OF POST-HERPETIC NEURALGIA**  
**WHEN DOCTORS MIGHT KILL THEIR PATIENTS**  
**PALPABLE CYSTS — A RISK FACTOR FOR BREAST CANCER**  
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**PATIENT-PHYSICIAN RACIAL CONCORDANCE**  
**PROVIDING PALLIATIVE CARE FOR MENTALLY INCOMPETENT PATIENTS**  
**A NEW TREATMENT FOR RHINOVIRUS COLDS**

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## HIGHLIGHTS MAY 1999

### 5-1 NEW PERSPECTIVES ON THE MANAGEMENT OF LOW LEVELS OF HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

A low serum high-density lipoprotein cholesterol is a major, independent predictor of coronary heart disease. Existing evidence supports treatment of patients with isolated low HDL-cholesterol, a common abnormality. Charts such as the Framingham (Figure 5, p 1055) will aid in prediction of absolute risk over succeeding years. *Archives Int. Med.* May 24, 1999; 159: 1049-57

### 5-2 TYPE 2 DIABETES MELLITUS: Greater Cardiovascular Risks and Greater Benefits of Therapy

This brief editorial stresses an important clinical point. Diabetic persons are much more likely to suffer myocardial infarction and stroke than non-diabetics — and at a lower level of BP and at lower levels of LDL-cholesterol. Treatment of hypertension and lipids results in more benefit than in non-diabetics. Decisions to treat with drugs should start at lower cut points for BP and LDL-cholesterol. *Archives Int. Med.* May 24, 1999; 159: 1033-34

### 5-3 PREVENTION OF POSTHERPETIC NEURALGIA

This brief commentary calls attention to trials which suggested that addition of small daily doses of the antidepressant amitriptyline [Elavil] to antiviral drugs early in the course significantly reduced prevalence of post-herpetic neuralgia at 6 months. *Lancet* May 15, 1999; 353: 1636-37

### 5-4 WHEN DOCTORS MIGHT KILL THEIR PATIENTS: Foreseeing is Not Necessarily the Same as Intending

There is a practical test of the difference between foreseeing and intending:

A. If, having relieved the patient's pain and distress, one ceases to give morphine until and unless the pain or distress recur, then one's intention has clearly not been to kill the patient.

B. If, despite relieving the pain and distress, one goes on giving more morphine until the patient does die (or gives a much higher dose than one thinks necessary) then clearly one not only foresees the patient's death — one intends it.

According to the principle of "double effect", if the patient dies after A, the intervention can be considered a side effect of treatment. If the patient dies after B, death is intended and not a side effect, and not considered ethical under the principle of "double effect". *BMJ* May 29, 1999; 318: 1431-32

### 5-5 RISK OF BREAST CANCER IN WOMEN WITH PALPABLE BREAST CYSTS

Women with breast cysts were at increased risk of breast cancer, especially at ages below 45. This may be a reasonable indication for screening in age 40-49. *Lancet* May 22, 1999; 353: 1742-45

### 5-6 THE LONELINESS OF THE LONG-TERM CARE GIVER

Care givers want better communication with professionals, education and training, emotional support, and advocacy. They want help in negotiating the impenetrable thicket of financing mechanisms, and the inconsistent interpretations of

policies and eligibility. They want respite, too. They want professionals to appreciate how much fear and anxiety complicate the learning of new tasks. They need relief from their suffering. NEJM May 20, 1999; 340: 1587-90

#### 5-7 DIFFICULT PATIENT ENCOUNTERS IN THE AMBULATORY CLINIC

"Poor physician psychosocial attitude was strongly predictive of experiencing more encounters as difficult."

Archives Int. Med. May 24, 1999; 159: 1069-75

#### 5-8 ASSESSMENT OF PATIENTS' REPORTING OF PAIN: An Integrated Perspective

"Because of their inherent subjectivity, pain, suffering and disability are difficult to prove, disprove, or quantify. An individual's report of pain reflects multiple contributing factors, such as cultural conditioning, expectations, social contingencies, mood state, and perceptions of control. Disease or tissue injury is only one factor that contributes to the experience of pain. If one hopes to understand and treat a patient with pain, especially persistent pain, the patient who reports pain must be assessed, and not just his or her physical pathology and pain severity." Lancet May 22, 1999; 353: 1784-88

#### 5-9 DISCUSSING PALLIATIVE CARE WITH PATIENTS

"Uncovering painful emotions does not seem to increase short-term suffering. In the long-term, exploring such difficult issues may lessen feelings of aloneness and raise opportunities to find comfort and resolution."

As patients struggle to find closure to their lives, active listening and empathy have therapeutic value in and of themselves. Annals Int. Med. May 4, 1999; 130: 744-49

#### 5-10 META-ANALYSIS OF TRIALS COMPARING BETA-BLOCKERS, CALCIUM ANTAGONISTS, AND NITRATES FOR STABLE ANGINA

In this meta-analysis of randomized trials of patients who had stable angina, beta-blockers provided similar clinical outcomes — and they were associated with fewer adverse effects than calcium blockers. JAMA May 26, 1999; 281: 1927-36

#### 5-11 NON-ALCOHOLIC STEATOHEPATITIS: Another Disease of Affluence

Patients with persistent, commonly quite marked, abnormalities of liver function are increasingly being referred to gastroenterologists. Many are picked up by routine biochemical screening panels. In western countries, once hepatitis C has been excluded, and heavy alcohol consumption is unlikely, the diagnosis is probably non-alcoholic steatohepatitis (NASH). NASH is now the second or third commonest liver disease in outpatient hepatology practice in North America. Lancet May 15, 1999; 353: 1634-36

#### 5-12 THE DEFINITION OF ANEMIA IN OLDER PERSONS

Anemia (hemoglobin concentrations below 12 g/dL for women and below 13 g/dL for men) was associated with increased mortality in individuals over age 85. These criteria for diagnosing anemia are appropriate for older persons. A lower hemoglobin at old age signifies disease. JAMA May 12, 1999; 281: 1714-17

#### 5-13 INFlixIMAB FOR THE TREATMENT OF FISTULAS IN PATIENTS WITH CROHN'S DISEASE

Infliximab was efficacious in treatment of enterocutaneous fistulas complicating Crohn's disease. NEJM May 6, 1999; 340: 1398-1405

#### 5-14 BENEFIT OF ABCIXIMAB IN PATIENTS WITH REFRACTORY UNSTABLE ANGINA IN RELATION TO SERUM TROPONIN T LEVELS

Troponin T may serve as a surrogate marker of active thrombus formation. Patients with unstable angina and high levels are at high risk for cardiac events. They benefited from abciximab therapy. A new diagnostic test (troponin T) and a therapeutic advance (abciximab) can be combined to benefit patients with acute coronary syndromes. NEJM May 2, 1999; 340: 1623-29

#### 5-15 REDUCTION OF SERUM CHOLESTEROL WITH SITOSTANOL-ESTER MARGARINE IN MILDLY HYPERCHOLESTEROLEMIC POPULATIONS

Substituting sitostanol margarine (Benecol) for part of the daily fat intake in subjects with mild hypercholesterolemia effectively lowered serum total cholesterol and LDL-cholesterol NEJM November 16, 1995; 333: 1308-12

#### 5-16 ORAL HEALTH OF ELDERLY OCCUPANTS IN RESIDENTIAL HOMES

This study reports poor dental health was the standard in nursing homes. There was no systematic approach to arranging dental care. Care was arranged only when the resident or family complained of acute dental problems. Few had seen a dentist in the past 2 years.

Poor dental health may contribute to eating problems, and the low nutrient and vitamin C levels found in this group — and cause weight loss, dehydration, and debility Lancet May 23, 1999; 353: 1721

#### 5-17 DIETARY MANAGEMENT OF HEPATIC ENCEPHALOPATHY

The myth of protein restriction persists. Protein restriction continues to be advised. Perhaps more alarmingly, restriction therapy is used in patients with cirrhosis who have no neuropsychiatric impairment.

At the current state of knowledge it seems sensible to give enough protein (up to 1.5 g/kg/d) to maintain a good nutritional state. BMJ May 22, 1999; 318: 1364-65

#### 5-18 NATURAL HISTORY OF PROGRESSION AFTER PSA ELEVATION FOLLOWING RADICAL PROSTATECTOMY

Radical prostatectomy for PC provided excellent long-term cure rates at 15 years.

Many men who develop PSA elevations after radical prostatectomy remained free of metastatic disease for an extended period after initial biochemical recurrence — without other forms of therapy. "This has important implications in the selection of systemic therapies that are not curative and have no demonstrated impact on eventual outcome." JAMA May 5, 1999; 281: 1591-97

#### 5-19 MANAGEMENT OF PROSTATE CANCER AFTER PROSTATECTOMY: Treating the Patient, Not the PSA

What are the implications of the preceding study? The long interval between documentation of biochemical progression and clinical metastatic disease suggests that much of the testing currently performed at the time of biochemical relapse can be eliminated, particularly for patients who experience biochemical recurrence late. JAMA May 5, 1999; 281: 1642-44

#### 5-20 ULTRASOUND THERAPY FOR CALCIFIC TENDINITIS OF THE SHOULDER

Ultrasound helped resolved calcifications and was associated with short-term clinical improvement as compared with sham treatment. NEJM May 20 1999; 340: 1533-38

## 5-21 PATIENT-PHYSICIAN RACIAL CONCORDANCE AND THE PERCEIVED QUALITY AND USE OF HEALTH CARE

Black respondents with black physicians were more likely than those with non-black physicians to rate their physicians as excellent, to report receiving preventive care, and all needed care. Hispanics with Hispanic physicians were more likely than those with non-Hispanic physicians to be very satisfied with their care. Physicians who are able to overcome this lack of concordance are indeed expert clinicians. *Archives Int. Med.* May 10, 1999; 997-1004

## 5-22 A CONSENSUS-BASED APPROACH TO PROVIDING PALLIATIVE CARE TO PATIENTS WHO LACK DECISION-MAKING CAPACITY

The palliative care strategy described by the authors is grounded in the theory that decisions are the result of dialogue and consensus building. The physician's duty is to teach all participants that the patient has a chronic, irreversible, and ultimately fatal disease, at the same time learning from those who participate about the patient's values and quality of life.

This frames decisions about hospitalization, antibiotics, and enteral nutritional support as medical choices that ultimately shape the way the patient will live in the last phase of life. *Annals Int. Med.* May 18, 1999; 130 835-40

## 5-23 EFFICACY OF TREMACAMRA, A SOLUBLE INTERCELLULAR ADHESION MOLECULE 1, FOR EXPERIMENTAL RHINOVIRUS INFECTION

Tremacamra, a rhinovirus receptor blocker, reduced the frequency and severity of experimental rhinovirus colds. Clinical usefulness is not yet established. *JAMA* May 19, 1999; 281: 1797-1804

## RECOMMENDED READING

5-4 WHEN DOCTORS MIGHT KILL THEIR PATIENTS: Foreseeing is Not Necessarily the Same as Intending

5-6 THE LONELINESS OF THE LONG-TERM CARE GIVER

5-8 ASSESSMENT OF PATIENTS' REPORTING OF PAIN: An Integrated Perspective

5-9 DISCUSSING PALLIATIVE CARE WITH PATIENTS

5-22 A CONSENSUS-BASED APPROACH TO PROVIDING PALLIATIVE CARE TO PATIENTS WHO LACK DECISION-MAKING CAPACITY

## REFERENCE ARTICLES

5-1 NEW PERSPECTIVES ON THE MANAGEMENT OF LOW LEVELS OF HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

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## REFERENCE ARTICLE

5-1 NEW PERSPECTIVES ON THE MANAGEMENT OF LOW LEVELS OF HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

A low serum high-density lipoprotein cholesterol (HDL-c) is a major, independent predictor of coronary heart disease (CHD).

A high HDL-c is protective.

A high LDL-c is a major, independent predictor of CHD.

A low LDL-c is protective.

The most favorable combination is a low LDL-c with a high HDL-c

The most adverse combination is a high LDL-c and a low HDL-c

The higher the HDL-c / LDL-c ratio the more the benefit.

The adverse effect of a high LDL-c level is not completely removed by a high HDL-c, although a high HDL-c may offset some of the risk.

An estimated 11% of men in the US have low HDL-c levels.

Isolated low HDL-c (ILHDL-c) has been defined at levels below 35 mg/dL in persons with LDL-c levels below 160 mg/dL, and triglyceride levels below 250 mg/dL. Patients with ILHDL-c are quite common, yet are minimally addressed in guidelines. The prevalence of ILHDL-c in persons with CHD averages about 25%.

Clinical trial evidence suggests that raising HDL-c concentrations is beneficial. The Helsinki Heart Study 1 (using gemfibrozil therapy) reported that for every 1 mg/dL increase in HDL-c there was a 2% to 3% decrease in CHD, independent of changes in LDL-c. Individuals with both a low HDL-c and a high LDL-c were at highest risk.

Therapy of low HDL-c:

#### 1. Lifestyle measures:

Weight loss: Even if modest, can have a significant impact on raising HDL-c. Caloric restriction and weight loss are the most important considerations for raising HDL-c by diet.

Diet: Restriction of fat intake is important in lowering LDL-c. But, fat-restriction also lowers HDL-c.

Decreasing intake of trans fats (hydrogenated vegetable oils), polyunsaturated, and saturated fats will lower HDL-c. Monounsaturated fats are an exception. They are neutral, neither raising nor lowering HDL-c. Thus use of monounsaturated fats (olive and canola oil) is preferable, and will result in a more favorable HDL-c to LDL-c ratio.

Exercise: In sedentary men moderate exercise increases HDL-c. Vigorous exercise is no more beneficial. Much of this effect may be due to associated weight loss.

Smoking: Has a dose dependent negative effect on HDL-c.

Alcohol: Moderate use can increase HDL-c. This may in part explain the lower risk of CHD reported by many epidemiological studies in persons with moderate alcohol intakes.

#### 2. Drugs:

Niacin, statins, fibric acids, and estrogens all increase HDL-c levels.

Niacin in adequate dose benefits HDL-c, LDL-c, and triglycerides. Problems include adverse effects and compliance. Long-term secondary prevention studies report reduction in mortality following treatment with niacin in patients with CHD.

Fibrates: Effectively raise HDL-c and lower triglycerides; LDL-c is unchanged. Recent studies suggest that raising HDL-c by fibrate therapy in patients with ILHDL-c is beneficial

Hormone replacement therapy : Estrogen may benefit by raising HDL-c, lowering LDL-c, decreasing fibrinogen, and by effects on the arterial wall. Progestogens typically lower HDL-c levels (counteracting some of the beneficial LDL-c lowering effect of estrogen). Combined, a beneficial effect still occurs — increase in HDL-c and decrease in LDL-c.

After all these years, the benefit of estrogen on incidence of CHD is still problematic. There is biologic plausibility. Epidemiological studies report benefit. But the reported benefits may be due to bias — ie, the "healthy user" effect. Women who use HRT are healthier and have more favorable lifestyles.

Statins: Act predominantly by lowering LDL-c. They modestly raise HDL-c. Subset analysis of several landmark studies suggest that individuals with high LDL-c and low HDL-c benefit as much as those with high LDL-c and normal HDL-c. A recent Air Force study 2 (primary prevention) reported benefit in those with average LDL-c and low HDL-c..

#### 3. Who to treat:

For secondary prevention: Patients with LDL-c should be started on statins first. If the HDL-c remains low, a fibrate or niacin may be used.

For primary prevention: The absolute degree of risk over a period of years guides the decision to use drugs. (See figure 5 p 1055 for the Framingham Study risk prediction chart. This includes age, total cholesterol, HDL-c, systolic BP, smoking, diabetes, left ventricular hypertrophy as variables.)

## CONCLUSION

Existing evidence supports treatment of patients with isolated low HDL-cholesterol, a common abnormality. Charts such as the Framingham will aid in prediction of absolute risk over succeeding years.

Archives Int. Med. May 24, 1999; 159: 1049-57 Review article by Charles R Harper and Terry A Jacobson, Emory University, Atlanta, GA

Comment:

1. "Gemfibrozil for the Secondary Prevention of Coronary Heart Disease in Men with Low Levels of High-Density Lipoprotein Cholesterol" NEJM August 5, 1999; 341: 410-18)

2. "Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol levels the AFCAPS/TexCAPS study JAMA 1998; 279: 1615-22

All of this is well known and has been abstracted in previous issues of Practical Pointers. I do find it helpful to have the data presented as a review in condensed form.

Risk prediction charts such as the Framingham can be used as a guide for patient information, but cannot be used to decide therapy for an individual patient. The comprehensive benefit/harm-cost ratio of drug treatment (as accurate as possible based on current knowledge) should be presented to the individual who then autonomously decides to accept or reject. Benefit will, of course, be greater for secondary prevention. Those who accept drug therapy should be informed that it is a long-term commitment.

An editorial in this issue (p 1038-40) suggests that the cutpoint for HDL-c levels might be raised to 40 to 50 mg/dL instead of 35. This would expand the population who may benefit from HDL-c raising therapy.

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## 5-2 TYPE 2 DIABETES MELLITUS: Greater Cardiovascular Risks and Greater Benefits of Therapy

"Type 2 diabetes is associated with 2- to 3-fold increased risk of cardiovascular morbidity and mortality." The absolute risk reduction for all major cardiovascular events in adequately treated diabetic persons is twice as great as for non-diabetic persons

The risks of myocardial infarction (MI) and death from coronary disease in diabetic individuals without previous MI equals that of non-diabetic individuals with previous MI.

The risk of stroke in patients with diabetes is also 2- to 3-fold higher than the risk in non-diabetic persons. Diabetic patients are at risk at lower levels of BP. Those with systolic pressures 125 to 142 have twice as high a risk of stroke as those with lower systolic pressures. Reducing BP is more important than which particular agent is used. Benefits have been shown whether therapy is based on diuretics, beta-blockers, ACE inhibitors, or calcium blockers.

What is the evidence that treatment of risk factors such as hypertension and hyperlipidemia decreases morbidity and mortality? The author cites 4 excellent trials (see text for citations) reporting a reduction in relative risk of stroke by 22% to 73%. In one trial, target diastolic BP of 80 mmHg was more beneficial than targets of 85 or 90. (Two of the trials were based on calcium channel blockers.)

Adequate treatment of abnormal lipid levels in diabetic patients is associated with a marked reduction in cardiovascular mortality and morbidity — about 33% to 50% greater reductions than in non-diabetic persons. The editorialist suggests that a BP of 130/80 or less and an LDL-cholesterol level below 100 mg/dL should be the aim of treatment in diabetic persons.

Treatment of hyperglycemia has little, if any, effect on macrovascular disease. It does lower incidence of microvascular disease. In addition, diabetic persons with any evidence of cardiovascular disease should receive prophylactic aspirin.

Archives Int. Med. May 24, 1999; 159: 1033-34 Editorial, first author Timothy C Fagan, University of Arizona College of Medicine. Tucson.

Comment:

We should be just as concerned about lipid levels and BP in diabetic patients as we are about glucose levels.

See text for citations of the various trials. Practical Pointers has abstracted all of them in the past. RTJ

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### 5-3 PREVENTION OF POSTHERPETIC NEURALGIA

At present, antiviral drugs provide the greatest opportunity for reducing the likelihood of postherpetic neuralgia (PHN). They are recommended for herpes zoster (HZ) patients at high risk of PHN and other complications – the elderly, those who have moderate or severe rash, have moderate or severe pain, or have ophthalmic involvement.

Unfortunately, a substantial number of zoster patients will have chronic pain despite adequate antiviral therapy. Can supplements in addition to antiviral drugs help?

Recent trials have suggested that the addition of a corticosteroid does not shorten the duration of HZ, although it may hasten return of quality of life.

The well-established efficacy of tricyclic antidepressants in PHN and other neuropathic pain syndromes prompted a trial of very early treatment with an antidepressant in addition to the antiviral drug (acyclovir). Patients (all over age 60) were given amitriptyline [Elavil] 25 mg daily starting within 48 hours of onset of the rash, and continued for 90 days. Not all patients received antiviral drugs. The major analysis compared the percentage of patients free of pain at 6 months in the amitriptyline group vs placebo. Irrespective of acyclovir therapy – 84% on amitriptyline were free of pain vs 65% of placebo patients. (Absolute difference = 19%; NNT = 5 (benefit-3 months)

Among those receiving both amitriptyline and acyclovir only 11% had PHN pain at 6 months vs 47% receiving only acyclovir. (Absolute benefit = 36%; NNT= 3 (benefit-6 months)

Despite the small numbers in the trial, the data suggest that antidepressants may have an important role, when combined with antiviral drugs, in prevention of PHN.

Lancet May 15, 1999; 353: 1636-37 Commentary by Robert H Dworkin, University of Rochester School of Medicine and Dentistry, Rochester, NY

Comment:

Worth a try? Adverse effects would be minimal. RTJ

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Read the Original !

### 5-4 WHEN DOCTORS MIGHT KILL THEIR PATIENTS: Foreseeing is Not Necessarily the Same as Intending

This essay is one side of a debate by 2 ethicists following the trial and acquittal of an English doctor who had given a dying patient a lethal dose of morphine.

"Like him and many other doctors, I too have given a patient intravenous heroin intending to relieve his distress, but foreseeing that my action might hasten death. Yet some argue — often passionately — that there is no difference between a) my foreseeing that my action may kill the patient, and my patient then dying, and b) my intending my action to kill the patient and my patient then dying. If the court believed that there was no difference then I, as well as Dr Moor and countless other doctors would be murderers. I argue that a and b are different logically, experientially, conceptually, legally, and morally. "

"All this is true whether or not voluntary euthanasia is legalized, for voluntary euthanasia is a different issue."

"It is a logical truth that any two actions, the same in all respects including their outcomes but differing in the agent's intentions, are two different actions. Foreseeing is not intending death."

"The most important difference is that if you intend to do something you necessarily aim to make it happen. That is not necessarily true if you merely foresee its happening." There is a practical test of the difference. If, having relieved the patient's pain and

distress, one ceases to give morphine until and unless the pain or distress recur, then one's intention has clearly not been to kill the patient. If, despite relieving the pain and distress, one goes on giving more morphine until the patient does die (or gives a much higher dose than one thinks necessary) then clearly one not only foresees the patient's death — one intends it.

"If the difference between foreseeing and intending is rejected, doctors will no longer be able to give adequate pain relief to their dying patients — and we are all potentially dying patients."

BMJ May 29, 1999; 318: 1431-32 Essay by Raanan Gillon, Imperial College School of Medicine at St Mary's, London.

Comment:

I have continued to struggle between "foreseeing" and "intending". I appreciate the essayist's clarification by presenting a practical test. If the patient dies as a result of sedation given for the purpose of relieving suffering, the death can be accepted as a "side effect" of the treatment, not the purpose of the treatment.

The practical test of the difference mentioned in the article clarified my thinking. RTJ

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## 5-5 RISK OF BREAST CANCER IN WOMEN WITH PALPABLE BREAST CYSTS

Gross or palpable breast cysts are thought to be aberrations of the normal process of involution and not a disease. An estimated 7% of women in the western world develop palpable cysts. There are two clearly defined types:

1) Type I cysts are lined by apocrine epithelium and contain fluid with an electrolyte composition similar to that of intra-cellular fluid (high K and low Na with Na/K ratios below 3), and high concentrations of steroid hormones.

2) Type II are lined with flattened attenuated epithelium and contain fluid with an electrolyte composition similar to plasma (Na/K ratio over 3), and lower concentrations of steroid hormones.

Patients with type I cysts are more likely to develop additional cysts. Women with large numbers of cysts almost always have type I. It has been suggested that type I carries a higher risk of breast cancer (BC).

This study assessed risk of development of BC in women with palpable cysts and whether particular groups of women with cysts are at higher risk than others.

Conclusion: Women with cysts are at increased risk. The type of cyst did not alter the risk.

## STUDY

1. Prospectively followed over 1300 women (great majority age 40-49) with palpable cysts. All were aspirated and classified as type I or type II.

2. Follow-up from 1981-1989 to 1995.

3. Compared incidence of BC with the expected numbers of BC calculated from the age-specific incidence in Scotland in 1988.

## RESULTS

1. 65 cancers developed during follow-up.

2. Overall incidence rate of BC in patients with palpable cysts was 2.8 relative to the calculated incidence.

3. Relative incidence of BC in those younger than 45 was 5.9.

4. Relative incidence decreased with age to 1.7 in those older than 54.

5. Incidence rate was highest in the first year after aspiration (RR = 7), but was still high at 5 years (RR = 2.7).

6. Risk of BC did not differ with type of cyst (I vs II).

## DISCUSSION

1. Most pathological changes that comprise what was previously called fibrocystic disease are now known to be part of the normal involutionary process. Only gross or palpable cysts can be taken as abnormal, or more precisely, as aberrations of the involutionary process. Although palpable cysts occur in association with involution, the process is active and cysts may be a marker of epithelial activity.

2. Women with cysts seem to be at an almost 3-fold subsequent risk of BC compared with the general population.
3. Cancers rarely develop in cysts, but cysts may be a marker of generalized increased epithelial activity making BC more likely to occur.
4. Risk of BC was not related to the number of cysts present.
5. Age was a significant factor related to risk of BC — higher in younger women. Those under 45 had the highest risk. The majority of women with cysts develop them between age 40 – 50.
6. Since cysts are produced by an active process, increased epithelial activity combined with the presence of estrogen in the pre-menopausal period may increase risk.
7. "The risk of breast cancer in women younger than 45 years is of a magnitude that is clinically important and occurs in an age group in which breast screening is not generally available." The authors ask if women who develop cysts at a relatively young age should be offered regular mammographic screening.

## CONCLUSION

Women with breast cysts were at increased risk of breast cancer, especially at ages below 45.

Lancet May 22, 1999; 353: 1742-45 Original investigation first author J M Dixon, on behalf of the Edinburgh Breast Group. Western General Hospital, Edinburgh Scotland

Comment: Until confirmed or refuted by further observations, I believe clinicians can consider the presence of cysts in young women as an increased risk factor, and advise early mammography in this group. RTJ

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Read the Original !

### 5-6 THE LONELINESS OF THE LONG-TERM CARE GIVER

This is a true story. The author describes her 9-year struggle and distress in caring for, and advocating care of, her husband who suffered severe brain damage as a result of an automobile accident.

He is totally disabled and requires 24-hour care. He is quadriplegic — incontinent of bladder and bowel. His right forearm has been amputated as a result of an iatrogenic blood clot. His personality changed to extreme emotional lability alternating with unpredictable rages and periods of withdrawal.

Rehabilitation efforts have been extensive and prolonged.

"During my nine-year odyssey, I stopped being a wife and became a family care giver. In the anxious weeks when my husband was in the intensive care unit, I was still a wife. At some point however, when he was no longer in immediate danger of dying, and the specialists and superspecialists drifted out of the picture, I became invisible." "Friends and even family members fade away."

The narrator manages her husband's care and daily activities. She is his only advocate. No one advocates for her. "I feel abandoned by a health care system that commits resources and rewards to rescuing the injured and ill, but then consigns such patients and their families to the black hole of chronic 'custodial' care." The problem is that public policy looks to families to accept responsibility and then fails to support those who accept the responsibility.

Care givers want better communication with professionals, education and training, emotional support, and advocacy. They want help in negotiating the impenetrable thicket of financing mechanisms, and the inconsistent interpretations of policies and eligibility. They want respite, too. They want professionals to appreciate how much fear and anxiety complicate the learning of new tasks.

NEJM May 20, 1999; 340: 1587-90 "Sounding Board", essay by Carol Levine, United Hospital Fund, NY

Comment:

Ms. Levine is a co-author of "The Trouble with Families: Toward an Ethic of Accommodation" Annals Int Med 1999; 130: 148-52 abstracted in the January 1999 issue of Practical Pointers.

I abstracted this article as an excellent example of the power of narrative in medicine and ethics. Individuals' stories may have a more meaningful impact on practice than observational studies. A comparative example might be: A study reports that, of 1000 care-givers responding to a questionnaire, 69% found care giving stressful; 79% felt they needed more support; and 43% felt abandoned. Interesting to some clinicians, perhaps, but not as likely to be remembered as the powerful narrative, and not as likely to lead to a change in relation between clinician and care-giver.

Clinicians who care for the chronically ill should address the stress of care-givers. They need relief from their suffering. One way to start is simply to acknowledge the stress as a way of validating it. RTJ

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#### 5-7 DIFFICULT PATIENT ENCOUNTERS IN THE AMBULATORY CLINIC

One out of every 6 patient encounters is perceived by clinicians as "difficult".

These investigators report a series of 500 adult patients presenting to a primary care walk-in clinic. Their doctors rated fifteen percent "difficult". Several characteristics contribute to "difficulty"—mental illness, multiple somatic complaints, more severe symptoms, poorer functional status, unmet expectations, and higher use of health services.

But, on the other side of the coin, physicians with poorer psychosocial attitudes as reflected by higher scores on a "Physician's Belief Scale" (citation # 30) experienced more encounters as being difficult. (Odds ratio = 4.)

"Poor physician psychosocial attitude was strongly predictive of experiencing more encounters as difficult."

Archives Int. Med. May 24, 1999; 159: 1069-75 Original investigation, first author by Jeffrey L Jackson, Uniformed Services University of the Health Sciences, Bethesda, MD.

Comment: I shortened this abstract to emphasize the other side of the coin. The degree of "difficulty" depends on the physician's problems as well as the patient's RTJ

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#### REFERENCE ARTICLE

#### 5-8 ASSESSMENT OF PATIENTS' REPORTING OF PAIN: An Integrated Perspective

"A common assumption about pain is that it always results from the presence of underlying organic pathology. In the absence of objective pathology, an individual's report of pain may be ascribed to psychological causes. There is a wide variation in patients' experience of pain. Organic factors alone cannot explain individual differences in patients' reports. Assessment of patients who report pain requires attention to psychosocial, behavioral, and organic factors."

"We describe a comprehensive approach to the assessment of psychological and behavioral variables that affect patients' reports of pain. We counter the duality of the somatogenic versus psychogenic perspective and suggest a more integrated assessment that encompasses not only the severity of pain and related physical pathology, but also the person who is reporting the persistence of pain."

Physicians may assume that, in the absence of organic pathology, the report of pain must stem from psychological factors. This approach creates a duality – pain is either somatic or psychogenic. This view is inadequate and is not substantiated by available evidence or the current understanding of pain.

Assessment of pain leads to 3 central questions: 1) What is the extent of disease or injury? 2) What is the magnitude of the illness? — ie, to what extent is the patient suffering, disabled, or unable to enjoy activities?, 3) Does the patient's behavior during the interaction with the physician seem to reflect the nature and extent of the physical disease or injury, or is there evidence that symptoms are amplified by psychological or social reasons? (pain behaviors)

The authors go on to discuss measurement of pain, self-report of functional activities, physiological indicators, pain behaviors, and psychological contributions to pain and suffering.

"Because of their inherent subjectivity, pain, suffering and disability are difficult to prove, disprove, or quantify. An individual's report of pain reflects multiple contributing factors, such as cultural conditioning, expectations, social contingencies, mood state, and perceptions of control. Disease or tissue injury is only one factor that contributes to the experience of pain. If one hopes to understand and

treat a patient with pain, especially persistent pain, the patient who reports pain must be assessed, and not just his or her physical pathology and pain severity."

Lancet May 22, 1999; 353: 1784-88 Review article by Denis C Turk and Akiko Okifuji, University of Washington, Seattle.

Comment: This is one of a series on pain presented by Lancet. See also "Management of Cancer Pain" Lancet May 15, 1999; 353: 1695-1700

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## Recommended Reading

### 5-9 DISCUSSING PALLIATIVE CARE WITH PATIENTS

"Palliative care focuses on relief of suffering, psychosocial support, and closure near the end of life. Even experienced physicians often struggle when initiating complex, emotionally laden discussions about palliative care with seriously ill patients and their families."

The authors present two hypothetical case scenarios to illustrate how physicians can initiate these discussions. They emphasize several communication techniques.

Physicians can elicit a patient's concerns, goals, and values by using open-ended questions and following up on the patient's response before discussing specific clinical decisions. Physicians can acknowledge patients' emotions, explore the meaning of these emotions, and encourage patients to say more about difficult topics. Physicians should also screen for unaddressed spiritual and existential concerns.

Some patients may make statements or ask questions that are difficult for physicians to respond to. The authors give examples of responses that align the physician with patients' wishes without reinforcing unrealistic plans. "Physicians do not need to fix all identified problems. Being a 'fellow traveler' who understands and listens carefully to insoluble problems often is therapeutic. Patients no longer feel alone with their problems if they believe that their concerns have been heard."

"Uncovering painful emotions does not seem to increase short-term suffering. In the long-term, exploring such difficult issues may lessen feelings of aloneness and raise opportunities to find comfort and resolution."

As patients struggle to find closure to their lives, active listening and empathy have therapeutic value in and of themselves.

Annals Int. Med. May 4, 1999; 130: 744-49 Commentary from the ACP-ASIM End-of-Life Care Consensus Panel, first author Bernard Lo, University of California, San Francisco.

Comment:

Perfecting the art of listening and compassionately eliciting and understanding patient's concerns is a life-long quest.

Because people vary within every culture, each patient and family needs to be approached as individuals. RTJ

An editorial in this issue of Annals (pp 772-74) comments:

"Throughout the ages, people have sought a "good death" in which they are physically as comfortable as possible, are treated with compassion and respect, and find closure in their lives. In the United States at the end of the 20th century, this quest remains elusive."

Palliative care is commonly considered terminal care, separate from and mutually exclusive with treatments that attempt to cure the underlying disease. In this view, there is a sharp transition from disease-oriented therapy to palliative care.

Serious problems result when palliative care is considered only after disease-oriented care fails or becomes too burdensome, or when the patient reaches a clearly defined terminal phase. Hospice is often considered only in the final stages of disease. Patients often enter only in the last month or week of death. (This is a result of linking Hospice under Medicare.) Opportunities to relieve symptoms and achieve meaningful closure may be missed. It is difficult to identify likely duration of life in patients who are expected to die in the future for diseases other than cancer — eg, congestive heart failure. Discussing palliative care only with patients who are highly likely to die soon will miss many patients who may benefit from it. Physicians should take a "both/and" approach to palliative and disease-oriented instead of an "either/or" approach. Palliative care should co-exist with disease-oriented therapy throughout a patient's care rather than as a sharp transition before death.

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## 5-10 META-ANALYSIS OF TRIALS COMPARING BETA-BLOCKERS, CALCIUM ANTAGONISTS, AND NITRATES FOR STABLE ANGINA

"Stable angina affects more than 7 million people in the US, with an estimated 350 000 new cases annually." The choice of a first-line agent is controversial. Some advocate beta-blockers because they reduce mortality after a myocardial infarction. Some advocate calcium blockers because they are assumed to have equal efficacy in relieving symptoms and have fewer adverse effects. Some recommend nitrates, but concern about the need for nitrate-free periods has led many to use them as a second-line agent.

This study compared relative efficacy and tolerability of the 3 drugs.

Conclusion: Beta-blockers were judged first choice.

### STUDY

1. Meta-analysis identified 90 randomized or cross-over studies comparing the 3 classes of antianginal drugs.
2. Outcomes included cardiac death, myocardial infarction, adverse effects, nitroglycerin use, angina frequency, and exercise duration.

### RESULTS

1. Rates of cardiac death and myocardial infarction were not different for beta-blockers vs calcium blockers. (Odds ratio = 0.97)
2. There were 0.31 fewer episodes of angina per week with beta-blockers than with calcium blockers. But, angina relief, as measured by nitroglycerin use and exercise time did not differ significantly between the 2 drugs.
3. Beta-blockers were discontinued because of adverse events less often than calcium blockers. (Odds ratio = 0.72). This difference was most striking for nifedipine. The absolute difference in adverse event rate was 2 fewer events with beta-blockers per 100 patients treated.
4. Too few trials appeared comparing nitrates with the other 2 drugs to draw any firm conclusions about relative effects.

### DISCUSSION

1. Beta-blockers were associated with a fewer number of adverse events. (The authors comment that this observation was unexpected. Past reviews have recommended that calcium blockers be used because of their low adverse effect profile. Indeed, in the US, as compared with Europe, current treatment of stable angina frequently does not include beta-blockers.)
2. Beta-blockers are already used for patients post myocardial infarction. In this group they will be considered first-line therapy for patients with angina as well as those without.

### CONCLUSION

In this meta-analysis of randomized trials of patients who had stable angina, beta-blockers provided similar clinical outcomes. But they were associated with fewer adverse effects than calcium blockers.

JAMA May 26, 1999; 281: 1927-36 Original study, first author Paul A Heidenreich, Veterans Affairs Palo Alto Health Care System, CA

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## 5-11 NON-ALCOHOLIC STEATOHEPATITIS: Another Disease of Affluence

Patients with persistent, commonly quite marked, abnormalities of liver function are

increasingly being referred to gastroenterologists. Many are picked up by routine biochemical screening panels. In western countries, once hepatitis C has been excluded, and heavy alcohol consumption is unlikely, the diagnosis is probably non-alcoholic steatohepatitis (NASH). NASH is now the second or third commonest liver disease in outpatient hepatology practice in North America.

NASH is described as "the pathological and clinical features of non-alcoholic disease of the liver associated with the pathological features most commonly seen in alcoholic liver disease". Indeed, the finding that some obese individuals have a liver disease histologically indistinguishable from alcoholic liver disease itself has long been recognized.

More recently, different patterns of the disease have been recognized. Depending on definition, about 40% of these patients are obese, 20% have diabetes, and a further 20% are hyperlipidemic.

About half of patients have upper abdominal discomfort or fatigue, or both.

Histologically, in 15% to 50% of patients there is substantial fibrosis or cirrhosis. Some with obvious fibrosis develop cirrhosis after 10 years. A substantial proportion of cases of cryptogenic cirrhosis may be "burnt out" NASH since a high proportion of these patients have associated obesity, type 2 diabetes, or hyperlipidemia. The disease is not limited to adults. NASH is now the commonest liver disease among (generally overweight) adolescents in North America.

At the other end of the range, in patients with only fatty liver on biopsy, long-term follow-up suggests a benign, non-progressive course.

Other associations include NASH as a complication of jejunal-ileal bypass surgery for morbid obesity, and a reaction to a few drugs, eg, amiodarone.

At present, fatty changes alone should be described merely as non-alcoholic, simple steatosis.

Diagnosis rests on histopathology, rigorous exclusion of alcohol abuse, and exclusion of other forms of chronic liver disease. The ratio of alanine amino-transferase (ALT) to aspartate aminotransferase (AST) is almost always greater than 1 (and almost less than 1 in alcoholic liver disease). Biopsy is necessary for the diagnosis because the predictive value of clinical diagnosis is low.

The increased frequency of the disease is probably a combination of increased awareness and a rise of prevalence of obesity. Central obesity and weight cycling (sudden weight loss followed by weight gain) may predispose to NASH.

Two metabolic abnormalities are strongly associated with NASH – insulin resistance, and an increased supply of fatty acids to the liver mobilized from central (visceral) sources which drain directly to the liver through the portal vein.

Lancet May 15, 1999; 353: 1634-36 Commentary by Oliver James and Christopher Day, University of Newcastle, Newcastle upon Tyne, UK

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## 5-12 THE DEFINITION OF ANEMIA IN OLDER PERSONS

The WHO defines anemia as a hemoglobin (Hb) concentration below 120 g/L (12 g/dL) in women and below 130 g/L (13g/dL) in men. On average, Hb concentrations are lower in old people and could necessitate an adjustment of these criteria. On the other hand, the decline during aging is small and may not require unique criteria.

This study investigated the association between Hb concentrations and mortality in persons over age 85. The investigators postulated that a low concentration represents underlying disease and would necessitate evaluation of the patient for possible causes.

Conclusion: The WHO definition of anemia is valid for old persons as well as the young.

### STUDY

1. A community-based study entered and followed over 750 individuals, all over age 85 (median = 89) at baseline. Follow-up = 10 years.
2. Related 10 year survival to Hb levels at entry.

### RESULTS

1. Anemia was found at baseline in 17% of women and 28% of men. Mostly normocytic.

2. Some of those with anemia did have disease at baseline: malignancy – 13%; history of peptic ulcer – 2%; any infection – 2%. There were no differences between persons with anemia and those with a normal Hb for other diseases.
3. During 10 years of follow-up, 86% of those with anemia died (chiefly with malignancy and infections); 65% of those with normal Hb died (chiefly of respiratory disease).
4. Compared with those with a normal Hb, women with anemia had a relative risk of mortality of 1.6, and men a relative risk of 2.3. Risk increased with lower Hb levels.
5. In persons without self-reported clinical disease at baseline, the relative risk of mortality associated with anemia was 2.2.

## DISCUSSION

1. The mortality risk of elderly persons defined as anemic was increased 2-fold compared with persons with a normal Hb.
2. Anemia of old age is probably due to disease. Hb levels below normal are a reason for further investigation.
3. Conversely, the investigators also noted a small increase in mortality in individuals with high Hb, caused, for example by dehydration or chronic pulmonary disease.

## CONCLUSION

Anemia (hemoglobin concentrations below 12 g/dL for women and below 13 g/dL for men) was associated with increased mortality in individuals over age 85. These criteria for diagnosing anemia are appropriate for older persons. A lower hemoglobin at old age signifies disease.

JAMA May 12, 1999; 281: 1714-17 Original investigation, first author Gerbrand J Izaks, Leiden University, Netherlands

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## 5-13 INFLIXIMAB FOR THE TREATMENT OF FISTULAS IN PATIENTS WITH CROHN'S DISEASE

Fistulas in patients with Crohn's disease rarely heal spontaneously or as a result of drug therapy. They frequently require surgery.

Local production of tumor necrosis factor-alpha (TNF-alpha) is thought to have a key role in initiation and propagation of Crohn's disease.

Infliximab is a IgG murine-human monoclonal antibody that binds TNF-alpha and inhibits a broad range of its activities. It may also cause lysis of cells that produce TNF-alpha.

This study assessed effectiveness and safety of infliximab in treatment of patients with Crohn's disease who had developed draining fistulas.

Conclusion: Infliximab was efficacious.

## STUDY

1. Entered 94 adult patients (mean age = 40; duration of disease = 12 years). All had draining abdominal or perineal fistulas. The majority had chronically active disease, and had previously received several therapies.
2. Randomized to: 1) infliximab 5 or 10 mg per kg administered at 0, 2, and 6 weeks, or 2) placebo.
3. Primary end point – reduction of 50% or more in number of draining fistulas.
4. Patients could also receive concomitant therapy – aminosalicylates, oral corticosteroids, methotrexate, azathioprine, or mercaptopurine.

## RESULTS

1. 68% of those receiving 5 mg dose, and 56% of those receiving 10 mg achieved the primary endpoint vs 26% of control patients.

2. Complete closure occurred in 55% of those receiving 5 mg and 38% of those receiving 10 mg; vs 13% of controls. Complete closure occurred in those with multiple fistulas as well as those with single fistulas. (Illustration p 1402.)
3. Median time the fistulas remained closed = 3 months.
4. Adverse effects were common – headache, abscess formation, upper respiratory infection, and fatigue.  
There was a trend toward more adverse effects in the 10 mg group.

#### DISCUSSION

1. Closure of fistulas is rare in patients with Crohn's disease who are receiving standard therapy.
2. The effect of infliximab became evident early—in about 2 weeks.
3. Benefit did not appear to be dose-related. (No comment as to why 5 mg dose was superior to 10 mg.  
RTJ )

#### CONCLUSION

Infliximab was efficacious in treatment of enterocutaneous fistulas complicating Crohn's disease.

NEJM May 6, 1999; 340: 1398-1405 Original multicenter investigation, first author Daniel H Present, Mount Sinai Medical Center, New York NY

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#### 5-14 BENEFIT OF ABCIXIMAB IN PATIENTS WITH REFRACTORY UNSTABLE ANGINA IN RELATION TO SERUM TROPONIN T LEVELS

The underlying pathophysiologic mechanism of unstable angina involves rupture or erosion of an atherosclerotic plaque followed by local thrombus formation. If thrombotic material is transported downstream, focal cell necrosis results. This degree of myocardial injury (less extensive than with an acute myocardial infarct) is detected in about 1/3 of patients with unstable angina as measured by troponin levels, but rarely as measured by creatine kinase.

Patients with unstable angina are at increased risk of myocardial infarction and sudden death.

This study assessed efficacy of an anti-platelet drug (platelet glycoprotein IIb/IIIa-receptor antibody, abciximab), in reducing incidence of cardiac events in patients with unstable angina severe enough to have caused some myocardial damage as determined by elevated troponin T levels.

Conclusion: Patients with refractory unstable angina and elevated troponin levels benefited from abciximab therapy.

#### STUDY

1. Multicenter study recruited almost 900 patients with unstable angina. (See text p 1624 for definition.)  
None had acute myocardial infarction.
2. All underwent coronary angiography which demonstrated one culprit lesion. All received heparin and nitroglycerin.
3. Troponin T concentrations were recorded in all.
4. Randomized to 1) abciximab, or 2) placebo.

#### RESULTS

1. Troponin levels were elevated in 30% of patients.
2. The 6-month event rate was 24% for patients with elevated levels vs 8% without elevated levels.  
(Absolute difference = 16%.)
3. For patients with elevated troponin levels, abciximab treatment was associated with a highly significant reduction in the risk of death or non-fatal MI as compared with those treated with placebo. (Relative risk = 0.32)
4. In patients without elevated troponin, at 6 months there was no benefit of treatment

with abciximab.

## DISCUSSION

1. Troponin levels are potent, independent predictors of both short- and long-term risk of death and MI in patients with unstable angina.
2. This study indicated that patients with unstable angina and elevated troponin T levels may be treated effectively with antiplatelet agents of the glycoprotein IIb/IIIa-receptor blocker type. Treatment of 100 such patients is calculated to prevent 15 cardiac events.
3. High troponin levels reflect an active thrombotic process with distal embolization of platelet thrombi originating from the culprit lesion. Glycoprotein IIb/IIIa-receptor blockers will reduce thrombus formation at the culprit lesion and may facilitate the resolution of microthrombi which embolize distally, thus protecting the myocardium from further injury.
4. The protective effect of abciximab was not evident in patients without elevated troponin levels.
5. An undetectable troponin T level does not rule out the presence of coronary heart disease, but it does identify patients at lower risk for cardiac events.

## CONCLUSION

Troponin T may serve as a surrogate marker of active thrombus formation. Patients with unstable angina and high levels are at high risk for cardiac events. They benefited from abciximab therapy. A new diagnostic test (troponin T) and a therapeutic advance (abciximab) can be combined to benefit patients with acute coronary syndromes.

NEJM May 2, 1999; 340: 1623-29 Original investigation by the Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators, first author Christian W Hamm, University Hospital Eppendorf, Hamburg, Germany.

### Comment:

The CAPTURE study (Lancet 1997; 349: 1429-35) demonstrated that treatment with abciximab reduced the risk of MI preceding and after coronary angiography and balloon angioplasty in patients with unstable angina.

Tirofiban is another platelet glycoprotein IIb/IIIa-receptor blocker. It also benefits patients with unstable angina and elevated troponin levels. See "Troponin Concentrations for Stratification of Patients with Acute Coronary Syndromes in Relation to Therapeutic Efficacy of Tirofiban" NEJM November 20, 1999; 354: 1757-62 Next step is to compare the two. RTJ

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## 5-15 REDUCTION OF SERUM CHOLESTEROL WITH SITOSTANOL-ESTER MARGARINE IN MILDLY HYPERCHOLESTEROLEMIC POPULATIONS.

Dietary plant sterols, especially sitostanol (a sterol derived from wood), reduce serum cholesterol levels by inhibiting cholesterol absorption. Sitostanol is not absorbed.

This study assessed tolerability and efficacy of a margarine containing sitostanol (Benechol) in lowering serum cholesterol.

Conclusion: Substituting sitostanol margarine for part of daily fat intake lowered total-c and LDL-c.

## STUDY

1. Randomized, double-blind study followed 153 subjects for 1 year.
2. All had mild hypercholesterolemia (mean total-c = 235; LDL-c = 160). Dietary cholesterol intakes averaged about 300 mg.
3. Randomized to: 1) margarine with a total sitostanol content of 3 g daily, or 2) regular margarine containing rapeseed oil. (The margarines contained: 0.5% total trans acids; 47% mono-unsaturated fat; 17% polyunsaturated fat.

4. Each container held about 8 g of fat. Subjects used one container with each of 3 meals daily. (24 g of fat daily).

## RESULTS

1. Body weight did not increase in either group.
2. The sitostanol preparation was well tolerated. Compliance was good.
3. Mean change in total cholesterol in the treated group = -24 mg/dL; LDL-c = -21mg/dL
4. No significant change in controls. HDL-c and triglycerides unchanged.

## DISCUSSION

1. Plant sterols are present in the normal Western diet in an amount almost equal to dietary cholesterol intake. (160-300 mg/d). They are virtually unabsorbable.
2. The substituted margarine replaced almost 1/5 of daily dietary fat.
3. The taste of the two margarines differed, but subjects could not decide which tasted better.
4. Individuals consuming a low dietary intake of cholesterol may not benefit as much. (This group was consuming about 300 mg/d)

## CONCLUSION

Substituting sitostanol margarine for part of the daily fat intake in subjects with mild hypercholesterolemia effectively lowered serum total cholesterol and LDL-cholesterol

NEJM November 16, 1995; 333: 1308-12 Original investigation, first author Tatu A Miettinen, University of Helsinki, Finland.

### Comment:

I retrieved this 1995 article because the sitostanol margarine (Benecol) is now available in our grocery stores. Benecol should be part of a low saturated fat, low trans fat, low-cholesterol diet. Subjects in the study had only mild-moderate total cholesterol and LDL elevations. The next step would be a study adding Benecol to statins.

Benecol itself is fat. The dose used in this study provided over 200 k/cal per day. It is expensive compared with regular diet margarine. Acceptance of taste may vary. I have tried it and found the taste differs considerably from usual margarine and butter. More diverse applications are forthcoming — eg, in salad oils.

Some patients might be interested in trying it after being fully informed. RTJ

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## 5-16 ORAL HEALTH OF ELDERLY OCCUPANTS IN RESIDENTIAL HOMES

Elderly nursing home patients have poorer oral health than those living independently at home. This study assessed a random sample of the oral health of elderly occupants in 48 residential and nursing homes in the UK — about 250 men and 800 women.

Poor oral hygiene was significantly related to the presence of root caries. Plaque retention was a problem in elderly people who have difficulty in mechanically removing plaque due to diminishing manual dexterity, impaired vision, or illness.

A high degree of denture debris was present on the fitting surface of the upper dentures. This was related to the frequency (12%) of clinically diagnosed denture stomatitis; 13% had angular chielitis; 9% both stomatitis and chielitis; 3% oral ulcerations; 9% glossitis (sore or fissured tongue).

Two hundred and fifty had difficulty eating, 200 problems with taste, 260 found it difficult to care for their mouth. Few reported the staff had helped them with cleaning.

The majority received medications known to produce xerostomia. About 1/3 suffered from dry mouth. Many received syrups containing glucose.

There was no systematic approach to arranging dental care. Care was arranged only when the resident or family complained of acute dental problems. Few had seen a dentist in the past 2 years.

Poor dental health may contribute to eating problems, and the low nutrient and vitamin C levels found in this group — and cause weight loss, dehydration, and debility.

Lancet May 23, 1999; 353: 1721 Research letter, first author D Simons, Principal Health Centre, St Albans, Herts, UK

Comment: An often forgotten disability in the elderly. One relatively simple to address. RTJ

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Another change in the fashion of medicine

#### 5-17 DIETARY MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a syndrome of impaired mental status and abnormal neuromuscular function which results from major failure of liver function. Important factors contributing to the degree of hepatocellular failure include porto-systemic shunting and exogenous factors such as sepsis and variceal bleeding.

Pathogenesis is uncertain. Hypotheses include impaired detoxification of ammonia absorbed from the gut, and an increase in aromatic amines — precursors of some neurotransmitters. Increased expression of benzodiazepine receptors suggests that the gamma-aminobutyric acid-benzodiazepine system may be implicated.

Myths are difficult to dispel and may delay application of good evidence-based medicine.

Protein restriction in symptomatic patients with hepatic encephalopathy has been the cornerstone of treatment since the 1950s, yet there is no evidence that it has any clinical benefit. Protein restriction continues as a practice despite evidence showing that patients with stable cirrhosis have a higher protein requirement than normal (around 1.2 g/kg to remain in positive balance). Protein energy malnutrition is common in patients with cirrhosis — caused by anorexia, nausea, malabsorption, and a hypermetabolic state. Intake may be further reduced by use of unpalatable low protein diets.

In 1997 the European Society for Parenteral and Enteral Nutrition guidelines recommended that daily protein intake in patients with liver disease should be around 1.0 to 1.5 g/kg.

Aggressive enteral nutritional support of patients with alcoholic liver disease accelerates improvement without exacerbating hepatic encephalopathy. Taking smaller meals more often and eating a late evening meal also improve nitrogen balance without exacerbating the encephalopathy.

The dilemma for the clinician arises in patients with acute hepatic encephalopathy where increasing protein intake may worsen the condition. This may occur in 35% of patients. There is no consensus about the rate at which protein should be reintroduced for these patients, and at what clinical stage this is appropriate. (Thus, key points for the clinician are uncertain.)

The myth of protein restriction persists. Protein restriction continues to be advised. Perhaps more alarmingly, restriction therapy is used in patients with cirrhosis who have no neuropsychiatric impairment.

"At the current state of knowledge it seems sensible to give as much protein as needed (up to 1.5 g/kg/d) to maintain a good nutritional state."

BMJ May 22, 1999; 318: 1364-65 Editorial by Carol A Seymour and Kevin Whelan, St. George's Hospital Medical School, London.

A study "Dietary Management of Hepatic Encephalopathy in Cirrhotic Patients: Survey of Current Practice in United Kingdom" BMJ May 22, 1999; 318: 1391 reports:

In the early 1950s it was reported that some patients with cirrhosis given "nitrogenous" substances, including dietary protein, developed hepatic "precoma". These largely uncontrolled observations led to the introduction of protein restriction to treat hepatic encephalopathy. Recent research has shown, however, that protein requirements are increased in these patients, that high protein diets are well tolerated, and that their use, particularly in patients who are malnourished, is associated with sustained improvement.

The study reports that, despite clear recommendations to the contrary, most patients in the UK with cirrhosis and hepatic encephalopathy have their protein intake restricted, often for prolonged periods. Dietitians are less in favor of protein restriction, but their advice may not be heeded.

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## 5-18 NATURAL HISTORY OF PROGRESSION AFTER PSA ELEVATION FOLLOWING RADICAL PROSTATECTOMY

Radical prostatectomy provides excellent long-term cancer control in most men with clinically localized prostate cancer (PC). However, about 1/3 of men will experience a detectable serum prostate specific antigen (PSA) within 10 years following surgery. (Biochemical recurrence)

What is the prognosis in this subset? What is the time-course of progression to distant metastases or death due to PC?

This study characterized the time course of disease progression in men after radical prostatectomy.

Conclusion: Prognosis was generally good even though PSA rises after surgery.

### STUDY

1. Retrospective study followed almost 2000 men after radical prostatectomy for localized PC classified as:

- A. Organ confined
- B. Capsular penetration with Gleason score < 7
- C. Capsular penetration with Gleason score  $\geq 7$
- D. Involvement of seminal vesicles, negative lymph nodes. (Only 5% in this group.)
- E. Involvement of pelvic lymph nodes. (Only 6% in this group)

(The inclusion of D. and E. surprised me. I had thought these would not be classified as "localized

PC. Perhaps they were so classified before surgery and thus were included in the study. RTJ )

- 2. A detectable PSA of at least 0.2 ng/mL was considered evidence of biochemical recurrence.
- 3. None received neoadjuvant therapy.
- 4. Median follow-up = 5 years; about 20% for 10 or more years.
- 5. Distant metastases were diagnosed by radionuclide bone scan or other imaging.

### RESULTS

1. For the entire 2000-men group:

- A. The actuarial metastasis-free survival for all men was 82% at 15 years after surgery.
- B. No man with an undetectable PSA experienced a distant or local recurrence.
- C. The most predictive factors indicating an undetectable PSA level at 10 to 15 years were low pretreatment PSA level, low Gleason score (< 7), and more confined pathological stage.

2. For the group with biochemical recurrence (315 men; 16% of the entire group):

- A. Of these, 34% (103 men) developed metastatic disease within the study period.
- B. The median actuarial time from the time of PSA level elevation to metastases was 5 years.
- C. A higher Gleason score, shorter PSA doubling time and a shorter time to biochemical recurrence were predictive of a shorter time to metastases. Men with Gleason score < 8 had a 27% chance of progression to metastatic disease 5 years after biochemical recurrence. Those with scores 8 and above had a 40% chance of progression.
- D. After development of metastatic disease, the median actuarial time to death was 5 years;  
43% of the 103 men with metastatic disease died due to PC at a median time of 5 years after development of metastatic disease. Those with the shortest time from surgery to metastasis had the poorest prognosis.

E. Prognosis was poorer as stage of disease progressed from completely organ confined disease, to seminal vesicle disease, to involvement of pelvic lymph nodes.

## DISCUSSION

1. Between 50% and 75% of men undergoing radical prostatectomy will have undetectable PSA levels at 10 years following surgery. A small number will have an initial rise in PSA after 10 years.
2. Some men remain free of metastatic disease for an extended time after biochemical recurrence. The metastasis-free rate in this group was 63% at 5 years.

## CONCLUSION

Radical prostatectomy for PC provided excellent long-term cure rates at 15 years.

Many men who develop PSA elevations after radical prostatectomy remained free of metastatic disease for an extended period after initial biochemical recurrence without other forms of therapy. "This has important implications in the selection of systemic therapies that are not curative and have no demonstrated impact on eventual outcome."

JAMA May 5, 1999; 281: 1591-97 Original investigation, first author Charles R Pound, Johns Hopkins Medical Institutions, Baltimore, MD

Comment:

Remember, the outcomes are those of an institution with vast experience. Local outcomes may not be as favorable.

This is valuable information for primary care clinicians as well as for urologists. Primary care MDs can contribute to guidance and strive to help to develop a consensus about follow-up with the patient and the surgeon.

The benefit of prostatectomy may be great for some individuals. The excellent prognosis following surgery forms the benefit part of the benefit/harm-cost ratio.

The article did not concern the harms and costs. RTJ

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5-19 MANAGEMENT OF PROSTATE CANCER AFTER PROSTATECTOMY: Treating the Patient, Not the PSA  
(This editorial comments and expands on the preceding study).

Heated debate surrounds early detection and screening for prostate cancer (PC). Equally controversial is the use and interpretation of serial changes in prostate specific antigen (PSA) for assessing prognosis. After radical prostatectomy, a persisting PSA is a sign of residual disease. But, an undetectable value does not necessarily mean cure.

What if the PSA becomes undetectable after surgery and then becomes detectable and continues to increase? A rising PSA may predate other signs of progression by months or years. Misinterpretation of the significance of a change in PSA can create havoc for patients who are profoundly concerned with their PSA, and for physicians who must address the anxieties and fears of their patients. Unfortunately, documentation of a rising PSA often triggers a cascade of expensive testing that can prompt treatments that may not be necessary, and can perhaps be detrimental.

"The detection and later serial increases in PSA after surgery is not a death warrant for all patients. We recognize that, left untreated, the natural history of PC is to progress. However, we should not lose focus on the reasons for treating PC. We should concentrate on clinical objectives and not solely on the PSA." Not all patients with relapsing disease have an equal risk of death due to the PC. Only some will develop clinical metastatic disease or symptoms in their lifetime. Do all need immediate intervention? No. Do all need any treatment? No.

In patients whose PSA increases after surgery, we should distinguish between those whose only finding is a rising PSA, and those with established metastatic disease detected by imaging studies.

The study reported outcomes in almost 2000 men who underwent radical prostatectomy. After surgery, patients were not offered treatment solely on the basis of their rising PSA values. Treatment was offered only when metastases or symptoms of disease were

documented. "Adherence to such a policy is extremely difficult given the anxieties of patients and pressures on physicians to provide treatment of a cancer that is 'growing' ".

What are the implications of the study? The long interval between documentation of biochemical progression and clinical metastatic disease suggests that much of the testing currently performed at the time of biochemical relapse can be eliminated, particularly for patients who experience biochemical recurrence late.

Many factors influence the decision of a patient to accept treatment when he is not experiencing symptoms – age, general state of health, precision of the estimate of the rates of metastatic progression, and the benefit/risk ratio of the proposed intervention.

One of the great controversies in PC management is whether, and when, to initiate androgen ablation, the first-line therapy for a patient with metastatic disease. There is evidence that early administration of hormone therapy can delay the progression of disease. However, the overall survival benefit, and the overall PC-specific survival benefit are less clear. For most patients the long term adverse effects of hormone therapy — impotence, hot flashes, gynecomastia, anemia, weakness, fatigue, muscle wasting, and accelerated bone loss do not justify the uncertain level of benefit. The situation may be different for those at high risk for early development of metastatic disease.

JAMA May 5, 1999; 281: 1642-44 Editorial by Howard I Scher, Memorial Sloan-Kettering Cancer Center, New York, NY

Comment:

The study indicates that immediate chemical (hormonal) therapy is not necessary for the great majority. This may spare patients much grief.

What is the other side of the coin? A number of studies indicate a favorable prognosis without surgery. Decisions about screening and treatment of PC remain controversial. RTJ

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#### 5-20 ULTRASOUND THERAPY FOR CALCIFIC TENDINITIS OF THE SHOULDER

Approximately 50% of patients with calcific tendinitis have shoulder pain, restricted motion, and limitations of activities of daily living. Ultrasound has been used as treatment. Its efficacy has not been rigorously evaluated.

This study assessed efficacy by randomizing patients to ultrasound vs sham insonation.

Conclusion: Ultrasound was beneficial.

#### STUDY

1. Enrolled 63 consecutive patients (70 shoulders). Almost 90% completed the study.
2. Randomized to 24 fifteen minute sessions of: 1) ultrasound, or 2) indistinguishable sham treatments.

#### RESULTS

1. Outcomes:	Treated group	Placebo
At 6 weeks		
Calcium deposits resolved	19%	0
Calcium deposits reduced in size	50%	28%
At 9 months		
Calcium resolved	42%	8%
Calcium improved	23%	12%

2. At the end of treatment, ultrasound patients had greater decreases in pain and greater improvements in quality of life. But at 9 months, these differences between groups were no longer significant.

#### DISCUSSION

1. The course of calcific tendinitis may be cyclic, with spontaneous resorption and reconstitution of the tendon. This study included only patients with homogeneous and clearly circumscribed calcium deposits, for which spontaneous remission may be uncommon.
2. The disease commonly becomes chronic.
3. Surgery to remove the calcium deposits is highly successful, but carries the risk of operative complications. Percutaneous needle aspiration alleviates symptoms in up to 60% of patients and resolves the deposits in about 50%.
4. Ultrasound alleviates symptoms in the short term. "In the long term the symptoms may be self-limiting and improve independently from the resolution of the calcium."
5. The treatment schedule is time consuming and was the main reason for the drop-out.
6. The mechanism of ultrasound-associated stimulation of calcium resorption is unknown.

## CONCLUSION

Ultrasound helped resolve calcifications and was associated with short-term clinical improvement as compared with sham treatment.

NEJM May 20 1999; 340: 1533-38 Original investigation, first author Gerold R Ebenbichler, University Hospital of Vienna, Austria.

Comment:

Watchful waiting and time may resolve the calcifications and the symptoms. Short-term therapy will depend on the patient's assessment benefit/ harm-cost, and development of concurrence with the physician. RTJ

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## 5-21 PATIENT-PHYSICIAN RACIAL CONCORDANCE AND THE PERCEIVED QUALITY AND USE OF HEALTH CARE

Patients from racial and ethnic minority groups use fewer health care services and are less satisfied with their care than patients from the majority white population.

This study was designed to determine if racial concordance between patients and physicians affects patient satisfaction

Analyzed data from over 2000 respondents to a Minority Health Survey. All reported having a regular physician.

Black respondents with black physicians were more likely than those with non-black physicians to rate their physicians as excellent, to report receiving preventive care, and all needed care. Hispanics with Hispanic physicians were more likely than those with non-Hispanic physicians to be very satisfied with their care.

Archives Int. Med. May 10, 1999; 997-1004 Original investigation, first author Somnath Saha, Puget Sound Health Care System, Seattle, Washington.

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## 5-22 A CONSENSUS-BASED APPROACH TO PROVIDING PALLIATIVE CARE TO PATIENTS WHO LACK DECISION-MAKING CAPACITY

"Making palliative care decisions for a patient who lacks decision-making capacity presents several challenges. Other people, such as family and caregivers, must choose for the patient. The goals and values of these decision-makers may conflict with those of each other and with those of the patient, who now lacks the capacity to participate in the decision."

This paper presents a case study of a patient with severe Alzheimer disease who has two common clinical problems: neurogenic dysphagia, and aspiration pneumonia. It describes a consensus-based decision-making strategy that keeps what is known about the patient's wishes and values in the foreground. But it also expects guidance from the physician and elicits input from family members and others who care for, and have knowledge about the patient.

Even if a patient has completed an advanced directive, the preferences she expressed when competent may well have been indeterminate guides for managing her actual problems. Those close to her might have different views about what ought to be done. Despite lack of evidence, those who care for and care about her must make decisions.

The palliative care strategy described by the authors is grounded in the theory that decisions are the result of dialogue and consensus building. The physician's duty is to teach all participants that the patient has a chronic, irreversible, and ultimately fatal disease, at the same time learning from those who participate about the patient's values and quality of life. This frames decisions about hospitalization, antibiotics, and enteral nutritional support as medical choices that ultimately shape the way the patient will live in the last phase of life.

Physicians can guide a highly emotional and personal process in a structured manner that has meaning for the patient, family, physician and other caregivers.

Surrogates must try to represent the patient's voice. Differences should be explored through dialogue that focuses on the patient's best interests and seeks common ground. "Except when decisions seem to clearly violate the patient's best interests or prior wishes, the family has the final say in representing the patient in decision making. Families have to live with themselves and their role in these decisions long after the patient has died. "

"Through the process of repeatedly listening to the perspectives of each participant and involving the participants in a consensus-based interaction, decisions that respect the patient's dignity and quality of life can generally be achieved."

Annals Int. Med. May 18, 1999; 130 835-40 Commentary for the ACP-ASIM End-of Life Care Consensus Panel, first author Jason H T Karlawish.

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#### 5-23 EFFICACY OF TREMACAMRA, A SOLUBLE INTERCELLULAR ADHESION MOLECULE 1, FOR EXPERIMENTAL RHINOVIRUS INFECTION

Rhinoviruses are the most frequent causes of the common cold. Approaches to prevention have not been feasible because of the large number of serotypes.

Attachment of the majority of rhinovirus serotypes to cells is dependent on a single cellular receptor, termed "intercellular adhesion molecule-1 — ICAM-1". It is possible that blocking the receptor could prevent infection.

Now, a recombinant soluble ICAM-1 (termed tremacamra) has been prepared. It actually is a truncated form — the intracellular and transmembrane domains have been deleted. The extracellular portion of the ICAM-1 remains. It effectively inhibits rhinovirus replication in cell culture.

This study assessed the efficacy and safety of intranasal tremacamra in experimental rhinovirus colds.

Conclusion: Tremacamra reduced severity of colds.

#### STUDY

1. Randomized, double-blind, placebo-controlled trial entered almost 200 volunteers. All were in good health. None were immune to rhinovirus (antibody titers < 1:4 to the challenge virus).
2. Randomized to: 1) tremacamra inhalation at 7 hours before inoculation of rhinovirus type 39, 2) 12 hours after inoculation, and 3) placebo.

#### RESULTS:

1. Outcomes	Tremacamra	Placebo
Total symptom score	10	18
Clinical colds	44%	67%
Nasal mucus weight	15 g	33 g

2. Chilliness, nasal congestion, cough, headache, malaise, rhinorrhea, sneezing, and sore throat were less common in the tremacamra group.

3. No adverse effects or evidence of absorption. Tremacamra did not interfere with development of neutralizing antibody.
4. In untreated patients with colds there is a direct correlation between concentrations of inflammatory mediators and symptoms. Treatment with tremacamra was associated with a significant decrease in elaboration of interleukin-8

#### DISCUSSION

1. "These are the first human trials to test the effectiveness of receptor blockade with soluble ICAM-1 in rhinovirus infections."
  2. Many different rhinoviruses share the same cellular receptor.
  3. The efficacy of tremacamra on rhinovirus-induced illness was similar when the drug was given before or after virus challenge.
- "Thus, even when given after viral replication is established (within 12 hours) tremacamra reduced the amount of virus produced and had a beneficial effect on symptoms."

#### CONCLUSION

Tremacamra, a rhinovirus receptor blocker, reduced the frequency and severity of experimental rhinovirus colds. Clinical usefulness is not yet established.

JAMA May 19, 1999; 281: 1797-1804 Original investigation, first author Ronald B Turner, Medical University of South Carolina, Charleston.

Comment: Interesting cutting-edge technology. Not yet clinically applicable. Perhaps of considerable importance in the future. RTJ

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#### 5-24 CLOSER TO A CURE FOR THE COMMON COLD?

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

In most instances symptoms of colds appear when the immune response is already active and the virus is at, or even past, its peak. Symptoms are thought to be produced by a combination of viral replication and the immune response. In rhinovirus infections, which are responsible for about 70% of upper respiratory infections, actual damage by the virus appears to be minimal. The virus is probably the trigger for a cascade of locally released mediators which combine with the immune response to produce the familiar symptoms.

The preceding study presents a new concept in antiviral research — inhibition of viral spread through blockage of specific cellular receptors. Most of rhinovirus serotypes use a single receptor on cells of the respiratory tract — the intercellular adhesion molecule. Blocking this receptor is a route to successful prevention or treatment of rhinovirus colds. The investigators rightly call their post-inoculation application "prophylaxis" rather than "treatment", since symptoms have not yet appeared.

Not all colds are rhinovirus-induced. Despite the encouraging findings, it is clear that the "cure for the common cold" is still not at hand. Tremacamra appears to be a promising candidate.

JAMA MAY 19, 1999; 1844-45 Editorial by Kenneth McIntosh, Children's Hospital, Harvard Medical School School, Boston, Mass.



