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HIGHLIGHTS JULY 1999

7-1 AGGRESSIVE LIPID-LOWERING THERAPY COMPARED WITH ANGIOPLASTY IN STABLE CORONARY ARTERY DISEASE

In low-risk patients with stable coronary artery disease, aggressive lipid lowering is at least as effective as angioplasty and usual care in reducing incidence of ischemic events. NEJM July 8, 1999; 341:70-76

7-2 WALKING TO WORK AND RISK FOR HYPERTENSION IN MEN: The Osaka Health Survey

Walking to work and other types of physical activity decreased the risk for hypertension in Japanese men. Annals Int Med July 6, 1999; 130: 21-26

7-3 RANDOMISED CONTROLLED TRIAL OF LONG TERM EFFICACY OF CAPTOPRIL ON PRESERVATION OF KIDNEY FUNCTION IN NORMOTENSIVE PATIENTS WITH INSULIN DEPENDENT DIABETES AND MICROALBUMINURIA

The effect of ACE inhibition in preserving renal function in patients with NIDDM lasts at least 8 years. BMJ July 3, 1999; 319: 24-25

7-4 EFFECTIVENESS OF LIVE, ATTENUATED INTRANASAL INFLUENZA VACCINE IN HEALTHY, WORKING ADULTS

Intranasal LAIV safely and effectively reduced severity of illness, absenteeism, and use of health care. This despite poor correlation between the strain used and the strain which appeared during the year . JAMA July 14, 1999; 282: 137-44

7-5 INTRANASAL INFLUENZA VACCINE: Adding to the Armamentarium for Influenza Control.

The major advantage of LAIV is the ease of self-administration. It is painless and can be administered when convenient. It might be made available over the counter and be less costly.

"The Institute of Medicine has placed the administration of influenza vaccines to the general population on its list of most beneficial vaccines and strategies for the 21st century."
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7-6 ZANAMIVIR IN THE PREVENTION OF INFLUENZA AMONG HEALTHY ADULTS.

The neuraminidase inhibitor, zanamivir, administered by inhalation once daily for 4 weeks was efficacious and well tolerated in prevention of influenza JAMA July 7, 1999; 282: 31-35

7-7 NEW OPTIONS FOR PREVENTION AND CONTROL OF INFLUENZA.

Even under ideal circumstances, in which there is a close match between vaccine and epidemic strains, inactivated (intramuscular) vaccine effectiveness is typically in the range of 30% to 50% in the elderly. Large gaps in immunity must be filled by other means. JAMA July 7, 1999; 282: 75-76

7-8 RANDOMIZED, PLACEBO CONTROLLED TRIAL OF EFFECT OF LEUKOTRIENE RECEPTOR ANTAGONIST, MONTELUKAST, ON TAPERING INHALED CORTICOSTEROIDS IN ASTHMATIC PATIENTS.

Montelukast reduced the need for inhaled corticosteroids among patients with chronic asthma who required moderate to high doses of corticosteroids.

Leukotriene receptor antagonists such as montelukast may be useful for long term treatment. BMJ July 10, 1999; 319: 87-90

7-9 ALCOHOL INTAKE AND THE RISK OF CORONARY HEART DISEASE MORTALITY IN PERSONS WITH OLDER-ONSET DIABETES MELLITUS

This study suggests an overall beneficial effect of alcohol consumption on decreasing risk of death from CHD in people with older-onset diabetes. JAMA July 21, 1999; 282: 239-46

7-10 SHOULD PATIENTS WITH DIABETES DRINK TO THEIR HEALTH?

What is true for most patients with diabetes is true for other patients at high risk for CHD — light to moderate alcohol consumption likely provides benefit, but is contraindicated in anyone who, for whatever reason, cannot restrict his or her drinking to light or moderate levels. Judicious recommendations can be made in individual cases when the patient is well known to the clinician. But, the recommendation to drink should not be generalized. JAMA July 21, 1999; 282: 279-80

7-11 RANDOMISED CONTROLLED TRIAL OF EXERCISE FOR LOW BACK PAIN

For subacute and recurrent low back pain, exercise class was more clinically effective than traditional general practitioner management and was cost effective. BMJ July 31, 1999; 319: 279-83

7-12 SYSTEMATIC REVIEW OF TOPICAL TREATMENTS FOR FUNGAL INFECTIONS OF THE SKIN AND NAILS OF THE FEET.

There is little evidence to differentiate between popular over-the-counter topical treatments for fungal skin infections. The most effective strategy is to initially use an over-the-counter drug and save the prescription drug to treat failures. BMJ July 10, 1999; 319: 79-82

7-13 SKIN AND NAIL FUNGI — Almost Beaten

The editorialist believes "that the most effective treatment for a topical dermatophyte infection is topical terbinafine, and for onychomycosis is oral terbinafine." BMJ July 10, 1999; 319: 71-72

7-14 HAEMODYNAMIC ANALYSIS OF EFFICACY OF COMPRESSION HOSIERY IN ELDERLY FALLERS WITH ORTHOSTATIC HYPOTENSION

The investigators concluded that compression hosiery effectively reduced OH. Whether falls will be prevented in the long term remains to be studied. Lancet July 3, 1999; 354: 45-46

7-15 EARLY LUNG CANCER ACTION PROJECT: Overall Design and Findings from Baseline Screening

Low-dose CT can greatly improve detection of small non-calcified modules, and lung cancer at an earlier and potentially more curable stage. Lancet July 10,1999; 354: 99-105

7-16 SCREENING FOR LUNG CANCER: Time To Think Positive

The prevalence rate of lung cancer in the study was 2.7%. This was 4 times higher than the 0.7% detected by chest X-ray. "And incidentally about five-fold higher than for first-round breast-cancer screening."

CT scanning detected cancers when they were small. It would be strange if cancers detected at this stage did not prove to have a high cure rate. Lancet July 10, 1999; 354: 86

7-17 GENERAL PRACTITIONERS' BELIEFS AND ATTITUDES ABOUT HOW TO RESPOND TO DEATH AND BEREAVEMENT: Qualitative Study

GPs need support and learning methods to manage their own and their patients' bereavement. BMJ July 31, 1999; 319: 293-96

7-18 USE OF ALTERNATIVE MEDICINE BY WOMEN WITH EARLY-STAGE BREAST CANCER

Among women with newly diagnosed early-stage breast cancer who had been treated with standard therapies, new-use of alternative medicine was a marker of greater psychosocial distress and worse quality of life. NEJM June 3, 1999; 340: 1733-39

7-19 PREDICTED IMPACT OF INTRAVENOUS THROMBOLYSIS ON PROGNOSIS OF GENERAL POPULATION OF STROKE PATIENTS: Simulation Model

"Treatment with alteplace may benefit single patients but will have no impact on the general prognosis of stroke." Alteplace therapy requires a specialist setting. It would require large investments and reorganization of the care of stroke patients. This marginally effective treatment, which is also potentially harmful, requires more study before being widely offered. BMJ July 31, 1999; 319: 288-89

7-20 GASTROINTESTINAL TOXICITY OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Billions are spent on these drugs every year (including over-the-counter). Billions more are spent on complications — dyspepsia, gastroduodenal ulcers, gi bleeding, perforation. "It has been estimated conservatively that 16 500 NSAID-related deaths occur among patients with rheumatoid arthritis or osteoarthritis every year in the United States." Almost equal to the number of deaths due to AIDS. NEJM June 17, 1999; 340: 1888-1899

7-21 STORIES AT WORK: Reflective Writing for Practitioners

Reflective writing is part of a deep and valuable tradition of stories in medicine. Doctors temporarily become co-authors of their patients' life-narrative. They may become a central character, and sometimes help patients write the last chapter of their narrative. Lancet July 17, 1999; 354: 243-45

7-22 FUNCTIONAL FOODS: Health Boon or Quackery?

"The dividing line between foods and drugs is becoming increasingly blurred, In the United States a canned split pea soup features the herb St.John's Wort to 'give your mood a natural lift' and a chewing gum with phosphatidyl serine claims it 'improves concentration'. In Japan a soft drink named VegitaBeta is fortified with beta-carotene 'to support a healthy lifestyle'. And in the United Kingdom MD Foods claimed that its butter-like spread made with fish oil would benefit the heart. What is our food supply turning to?"BMJ July 24, 1999; 319: 205-06

7-23 HORMONE REPLACEMENT THERAPY

In June 1999, the European Institute of Oncology met at Milan Italy with the aim of synthesizing clinical data on hormone replacement therapy (HRT). Much of the data came from women who used conjugated equine estrogens or estradiol, often given with a progestagen.

Users tend to be healthier, better educated, more physically active, leaner, and to more often drink moderate amounts of alcohol than other women in the same region. Thus, data must be interpreted with caution. Bias probably influences results of studies. Lancet July 19, 1999; 354: 152-55

7-24 PREVALENCE AND CLINICAL OUTCOME ON MITRAL VALVE PROLAPSE

In a large community-based sample of the population. The prevalence of MVP was lower than previously reported. The prevalence of adverse sequelae commonly associated with MVP was also low. NEJM July 1, 1999; 341; 1-7

7-25 PERSPECTIVES ON MITRAL-VALVE PROLAPSE

Now MVP is understood, not as a single entity, but as a spectrum of abnormalities with varied clinical,echo-cardiographic, and pathological features. At one end of the spectrum are patients with leaflet redundancy as a result of marked myxomatous proliferation of the spongiosa, and elongation of the chordal apparatus. At the other end are those with morphologically normal appearing leaflets that bulge into the left atrium.

The prevalence of MVP in the general population is low. NEJM July 1, 1999; 341: 48-50

7-26 FREUD'S PHYSICIAN-ASSISTED DEATH

"Freud's choice of physician-assisted suicide was not merely an interesting historical event, but one of paramount rationality, and one that is relevant to our contentious contemporary debates concerning euthanasia and physician-assisted suicide. Archives Int Med July 26, 1999; 159: 1521-23

7-27 COELIAC DISEASE

This reviews symptoms and signs, epidemiology, pathogenesis, diagnosis, treatment, prognosis, and complications. BMJ July 24, 1999; 319:236-40

RECOMMENDED READING

7-17 GENERAL PRACTITIONERS' BELIEFS AND ATTITUDES ABOUT HOW TO RESPOND TO DEATH AND BEREAVEMENT
7-21 STORIES AT WORK: Reflective Writing for Practitioners
7-26 FREUD'S PHYSICIAN-ASSISTED DEATH

REFERENCE ARTICLES

7-20 GASTROINTESTINAL TOXICITY OF NSAIDs
7-23 HORMONE REPLACEMENT THERAPY
7-27 COELIAC DISEASE

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7-1 AGGRESSIVE LIPID-LOWERING THERAPY COMPARED WITH ANGIOPLASTY IN STABLE CORONARY ARTERY DISEASE

Percutaneous transluminal coronary angioplasty (PTCA) is widely used to treat patients with stable angina. This study assessed efficacy of medical treatment (compared with PTCA) by aggressive lipid-lowering for low-risk patients with stable coronary artery disease (CAD).

Conclusion: Medical treatment was at least as effective as PTCA.

STUDY

1. Multicenter trial entered 341 patients (mean age 59) with stable coronary artery disease.
2. All had one or two vessel disease, relatively normal left ventricular ejection fractions, and no severe symptoms of angina. About 16% were asymptomatic, the rest had angina class I or II. All had been referred for PTCA
3. All had a serum LDL-cholesterol over 115 mg/dL.
4. Randomized to: 1) medical treatment with atorvastatin (Lipitor) 80 mg daily, or 2) PTCA
5. Patients in both groups received usual care (which could include lipid-lowering treatment in the PTCA group).
6. Follow-up = 18 months.

RESULTS

1. Outcomes:	Atorvastatin (n = 164)	PTCA (N = 177)
LDL-c baseline	145 mg/dL	146 mg/dL
LDL-c at 18 months	77 mg/dL	119mg/dL
HDL cholesterol increase from baseline	+ 8%	+11%
Incident ischemic events	13%	21%

2. The reduction in events in the atorvastatin group was due to a smaller number of angioplasty procedures, coronary by-passes, and hospitalizations for worsening angina or myocardial infarction (11 vs 25).

3.The atorvastatin group also had a significantly longer time to first ischemic event.

DISCUSSION

1. In this study, aggressive lowering of LDL cholesterol with atorvastatin was at least as effective as angioplasty.
2. The authors postulate that aggressive lowering of LDL cholesterol was more likely than PTCA to prevent further progression of coronary atherosclerosis.
3. The authors anticipated that aggressive lowering of LDL cholesterol would complement angioplasty in patients with more severe angina.
4. Treatment with aggressive lipid-lowering therapy might be first choice in patients similar to those in the study. If at any time symptoms worsen patients may elect to undergo revascularization without any penalty for their initial decision.

CONCLUSION

In low-risk patients with stable coronary artery disease, aggressive lipid lowering was at least as effective as angioplasty and usual care in reducing incidence of ischemic events.

NEJM July 8, 1999; 341:70-76 Original investigation, first author Bertram Pitt, University of Michigan School of Medicine, Ann Arbor.

Comment:

This reinforces the benefits of lipid control in treatment of CAD (secondary prevention). Benefits of interventions are greater for patients at higher risk for an outcome than for those at lower risk (secondary prevention vs primary prevention).

Nevertheless, the study has implications for lipid control for patients at lower risk for CAD, including asymptomatic patients (primary prevention).

Study supported by Parke-Davis RTJ

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7-2 WALKING TO WORK AND RISK FOR HYPERTENSION IN MEN: The Osaka Health Survey

It is not known whether mild physical activity, especially walking, reduces risk of hypertension.

Physicians in Japan usually advise patients to walk to work as often as they can. In many men this may be the main source of exercise.

This study prospectively examined the relation between walking to work and risk for hypertension over 6 to 16 years of observation.

Conclusion: Walking to work decreased risk for hypertension.

STUDY

1. Prospective cohort study entered over 6000 Japanese men (age 35-60; mean 42)

2. All had BP < 140/90. (Mean = 122/67)
3. None had history of diabetes or hypertension at baseline.
4. Data on physical activity were obtained by questionnaire.

RESULTS

1. During almost 60 000 person-years of observation, confirmed 626 cases of hypertension (> 160/95)
2. Duration of walk to work was associated with a reduction in risk for hypertension:

	10 min or less	11-20 min	21 min or more
Relative risk	1.0	0.88	0.71

3. For every 26 men who walked more than 20 minutes, one case of hypertension was prevented.

DISCUSSION

1. Duration of walking to work was associated with a decreased risk for incident hypertension, even after adjustment for age, BMI, alcohol consumption, leisure-time activity, smoking status, BP at baseline, and fasting glucose.
2. Other regular physical exercise at least once weekly was also inversely related to incident hypertension.

CONCLUSION

Walking to work and other types of physical activity decreased the risk for hypertension in Japanese men.

Annals Int Med July 6, 1999; 130: 21-26 Original investigation, first author Tomoshige Hayashi, Osaka City University Medical School . Japan.

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7-3 RANDOMISED CONTROLLED TRIAL OF LONG TERM EFFICACY OF CAPTOPRIL ON PRESERVATION OF KIDNEY FUNCTION IN NORMOTENSIVE PATIENTS WITH INSULIN DEPENDENT DIABETES AND MICROALBUMINURIA

In patients with insulin dependent diabetes mellitus (IDDM) angiotensin converting enzyme (ACE) inhibitors delay the progression from microalbuminuria to diabetic nephropathy. Previous studies have been too short to show a preservation of kidney function.

This study assessed long-term effectiveness of an ACE inhibitor Captopril (generic) for preservation of kidney function.

Conclusion: Benefit of captopril was long-lasting.

STUDY

1. Followed 44 normotensive patients with IDDM. All had persistent microalbuminuria (30 – 300 mg/d).
2. Randomized to: 1) captopril (100 mg/24 h) + bendrofluazide (2.5 mg/24h), or 2) no treatment — controls.
3. Diabetic nephropathy was defined as persisting albuminuria greater than 300 mg/d.
4. Follow-up = 8 years.

RESULTS

1. At 8 years, 40% in the control group had progressed to diabetic nephropathy vs 10% in the captopril group.
2. Decline in glomerular filtration rate (GFR) in the treatment group during 8 years was 1.2 mL/min vs
12 mL/min in the control group.

3. Two patients in the control group developed diabetic nephropathy vs 8 in the treatment group.
4. Hemoglobin A1c and BP did not differ between groups .

DISCUSSION

1.The beneficial effect of captopril in prevention of diabetic nephropathy was long-lasting and associated with preservation of normal glomerular filtration rate.
2. The clinically significant effect of ACE inhibition on preservation of normal GFR was related to prevention of progression from microalbuminuria to diabetic nephropathy in patients with IDDM.

CONCLUSION

The effect of ACE inhibition in preserving renal function in patients with NIDDM lasts at least 8 years.

BMJ July 3, 1999; 319: 24-25 Original investigation, first author Elizabeth R Mathiesen, Steno Diabetes Centre, University Hospital of Copenhagen, Denmark.

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7-4 EFFECTIVENESS OF LIVE, ATTENUATED INTRANASAL INFLUENZA VACCINE IN HEALTHY, WORKING ADULTS

Live, attenuated influenza virus (LAIV) vaccines offer a new option for prevention and control of influenza. Intranasal administration results in infection with the attenuated strains. It may more effectively stimulate mucosal and cell-mediated immune responses.

This study assessed safety and effectiveness of intranasal trivalent, live, attenuated vaccine among healthy working adults.

Conclusion: The vaccine was safe and effective.

STUDY

1. Randomized, double-blind, placebo controlled multicenter, trial entered over 4500 healthy, working adults (mean age 38).
2. Randomized to: 1) single-dose intranasal trivalent LAIV, or 2) placebo.
3. Both were self-administered under direct supervision.

RESULTS

1. Vaccine was associated with a 19% reduction of severe febrile illnesses, and a 24% reduction in febrile upper respiratory tract infections.
2. Vaccine was associated with fewer days of illness, fewer days of work lost for severe febrile illness, fewer visits to health care providers, and less use of prescription (including antibiotics) and over-the- counter medications.
3. Averse effects: Vaccine recipients were more likely to experience runny nose or sore throat for 1 week after vaccination. Serious adverse events did not differ between groups.
4. The match between vaccine and the predominant circulating strain of influenza virus during the season was poor. This suggests substantial cross-protection.

DISCUSSION

1. The trial did not compare LAIV with inactivated vaccine.
2. The vaccine was generally safe and well tolerated.

CONCLUSION

Intranasal LAIV safely and effectively reduced severity of illness, absenteeism, and use of health care. This despite poor correlation between the strain used and the strain which appeared during the year .

JAMA July 14, 1999; 282: 137-44 Original investigation, first author Kristin L Nichol, University of Minnesota, Minneapolis.

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7-5 INTRANASAL INFLUENZA VACCINE: Adding to the Armamentarium for Influenza Control

(This editorial comments and expands on the preceding study)

The investigators concede that a direct comparison between LAIV and inactivated vaccine would be required to determine whether LAIV is more protective. They imply that enhanced protection might be expected from the live vaccine.

The major advantage of LAIV is the ease of self-administration. It is painless and can be administered when convenient. It might be made available over the counter and be less costly.

"The Institute of Medicine has placed the administration of influenza vaccines to the general population on its list of most beneficial vaccines and strategies for the 21st century."

JAMA July 14, 1999; 282: 182-83 Editorial, first author Gregory A Poland Mayo Medical School and Foundation, Rochester Minn.

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7-6 ZANAMIVIR IN THE PREVENTION OF INFLUENZA AMONG HEALTHY ADULTS.

A new class of antivirals has been designed to specifically inhibit the action of viral neuraminidase. Both influenza A and B are inhibited. "The sites affected are conserved; thus, the anitviral action is independent of antigenic change."

This study examined the efficacy of zanamivir in prevention of influenza infection and disease.

Conclusion: Zanamivir was efficacious.

STUDY

1. Double-blind, randomized, controlled trial entered over 1000 healthy adults (mean age 29) recruited before the flu season.
2. At the start of the flu outbreak, randomized to: 1) zanamivir, or 2) placebo daily for 4 weeks.
3. Micronized powdered zanamivir (10 mg) was given by inhalation once daily using a Diskhaler device.

RESULTS

1. Zanamivir was 67% efficacious in preventing laboratory-confirmed clinical flu, and 84% efficacious in preventing illness with fever.
2. Adverse effects did not differ from placebo.

DISCUSSION

1. Zanamivir may be more efficacious for preventing disease, particularly more severe disease, than for preventing infection.
2. Because asymptomatic infection still occurs, antibodies will be produced and could protect against later infection.
3. Viral resistance to zanamivir has been sought, but not as yet found.
4. The advantages are safety and once a day use.
5. Antiviral prophylaxis is considered an adjunct to vaccination.

CONCLUSION

The neuraminidase inhibitor, zanamivir, administered by inhalation once daily for 4 weeks was efficacious and well tolerated in prevention of influenza

JAMA July 7, 1999; 282: 31-35 Original investigation, first author Arnold S Monto, University of Michigan, Ann Arbor.

Comment:

How to encourage use of daily inhalations of a costly preparation for patients who are asymptomatic and healthy? This would, I believe, be difficult in a population. Use will probably be selective.

Another neuraminidase inhibitor is now available on prescription (oseltamivir; Tamiflu). It has the advantage of oral administration by capsule twice daily. And can be effective when given within two days of onset of flu. Treatment for 5 days is recommended RTJ

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7-7 NEW OPTIONS FOR PREVENTION AND CONTROL OF INFLUENZA.

"Mandatory vaccination programs for enlisted personnel have virtually eliminated influenza outbreaks in military installations." Annual vaccination may be cost-beneficial for working adults.
Live attenuated intranasally administered flu virus vaccine may enhance local and systemic antibody response in elderly recipients when given simultaneously with inactivated vaccine.

The intranasal vaccine has similar incidence of adverse events as placebo.

Even under ideal circumstances, in which there is a close match between vaccine and epidemic strains, inactivated (intramuscular) vaccine effectiveness is typically in the range of 30% to 50% in the elderly. Large gaps in immunity must be filled by other means.

The new age of crystallographic studies and computer-assisted drug design has yielded zanamirvir, a selective inhibitor of neuraminidase. (Neuraminidase is an enzyme which enables release of the flu virus from infected cells and promotes spread of the virus.) The downside is cost, inconvenience, and compliance.

JAMA July 7, 1999; 282: 75-76 Editorial by Peter A Patriarca, U S Food and Drug Administration, Bethesda. MD.

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7-8 RANDOMIZED, PLACEBO CONTROLLED TRIAL OF EFFECT OF LEUKOTRIENE RECEPTOR ANTAGONIST, MONTELUKAST, ON TAPERING INHALED CORTICOSTEROIDS IN ASTHMATIC PATIENTS.

Persons with persistent asthma often require daily treatment to control symptoms, usually with inhaled corticosteroids. When asthma is not completely controlled, adding a second drug, rather than increasing the dose of corticosteroid, achieves better control.

This study determined the ability of montelukast [Singulair] a leukotriene receptor antagonist, to allow tapering of inhaled corticosteroids for patients with clinically stable asthma.

Conclusion: Montelukast reduced amount of inhaled corticosteroids needed.

STUDY

1. Double-blind, randomized, placebo-controlled trial entered 226 patients with clinically stable asthma (mean age 40; mean duration of asthma = 14 years). Prior to entry, patients were followed to determine the minimum dose of inhaled corticosteroids needed to achieve stability. Most received high doses — range of 300 to 3000 ug/d.
2. Randomized to: 1) montelukast (10 mg) daily, or 2) placebo.
3. Inhaled corticosteroids were increased or decreased every 2 weeks as needed to maintain clinical stability.
4. Follow-up = 12 weeks.

RESULTS

1. Montelukast was associated with a significant reduction in corticosteroid use:

	Montelukast	Placebo
% reduction in inhaled steroid	-47%	-18%
Tapered off inhaled steroid completely	40%	29%
Unable to taper at all	28%	36%
Required increased doses of steroids	16%	30%

DISCUSSION

1. Compared with placebo, montelukast allowed reduction in inhaled corticosteroids for patients with clinically stable chronic asthma who were taking moderate to high doses of steroid while maintaining clinical stability.
2. Given the potential limitations of prolonged exposure to high doses of inhaled corticosteroids, using the lowest dose of would be advisable.
3. The authors comment that patients often receive higher doses of inhaled corticosteriods than required. In the run in period of the study (before starting montelukast), patients reduced the dose by about 1/3.
4. Montelukast was generally well tolerated.

CONCLUSION

Montelukast reduced the need for inhaled corticosteroids among patients with chronic asthma who required moderate to high doses of corticosteroids.
Leukotriene receptor antagonists such as montelukast may be useful for long term treatment.

BMJ July 10, 1999; 319: 87-90 Original investigation, first author Claes-Goran Lofdahl, University Hospital, Lund, Sweden.

Comment:

Study funded by Merck. RTJ

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7-9 ALCOHOL INTAKE AND THE RISK OF CORONARY HEART DISEASE MORTALITY IN PERSONS WITH OLDER-ONSET DIABETES MELLITUS

"Numerous prospective epidemiological studies . . . have reported a nearly consistent pattern of a beneficial effect of modest levels of alcohol consumption, with reductions in the risk of coronary heart disease (CHD) or death ranging from 20% to 60%."

Does this apply to persons with non-insulin dependent diabetes? (NIDDM)

This long-term study assessed use of alcohol in persons with NIDDM and risk of death.

Conclusion: Alcohol consumption was associated with a decrease in risk of death.

STUDY

1. Population-based prospective cohort study followed almost 1000 persons (mean age 67) with diabetes. Follow-up for up to 12 years.
2. Information on alcohol intake was obtained at baseline in 1985-86.
3. Main outcome — time to death from CHD by category of alcohol intake.

RESULTS

1. Alcohol use was inversely associated with risk of CHD mortality. CHD mortality per 1000 person years:

Never drinkers	Former drinkers	Less than 2 drinks/wk	2 to 14/wk	> 14/wk

44	38	25	21	10

2. After controlling for multiple other risk factors, relative risk of death:

Never drinkers	Former drinkers	Less than 1 drink per wk	2 to 13 /wk	> 14 / wk
1.0	0.7	0.54	0.44	0.21

DISCUSSION

1. In this cohort, older-onset diabetic persons who drank higher amounts of alcohol had a considerably reduced risk of death from CHD compared with never drinkers.
2. There was a significant positive correlation between alcohol intake and HDL-cholesterol levels.
3. Only 2% of the cohort drank more than 3 drinks daily. Most were either non-drinkers or infrequent drinkers. Nevertheless… "We were able to consistently find a protective, graded association from infrequent drinkers to regular drinker of about 1 drink or more per day." This in persons largely known to have more advanced atherosclerotic disease.
4. "The consistency of our results with those of others who studied healthier populations, showing an apparent protective effect on moderate alcohol consumption on the risks of coronary events is notable.".
5. The results are not inconsistent with current guidelines of the American Diabetes Association. "The same precautions regarding the use of alcohol that apply to the general public also apply to people with diabetes." Daily intakes of no more than 1 drink for women and 2 drinks for men have been recommended.
6. Long-term prospective studies are needed to assess risks of alcohol consumption.

CONCLUSION

This study suggest an overall beneficial effect of alcohol consumption on decreasing risk of death from CHD in people with older-onset diabetes.

JAMA July 21, 1999; 282: 239-46 Original investigation, first author Charles T Valmadrid, University of Wisconsin-Madison Medical School

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7-10 SHOULD PATIENTS WITH DIABETES DRINK TO THEIR HEALTH?

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

The reductions in risk for CHD and total mortality reported in the preceding study exceed those in most prior studies. "A greater absolute benefit actually would be expected in older patients with diabetes compared with unselected populations because they are at higher baseline risk of disease1 — comparable with subjects with known cardiac disease. By contrast, no benefit from alcohol consumption at any level has been identified in men younger than 40 years or premenopausal women."

What does this mean for the clinician caring for persons with diabetes?

Evidence is mounting that light to moderate alcohol consumption lowers CHD risk. But there are serious problems extrapolating these findings to treatment recommendations:

A. Abstainers often resist drinking for a reason — family or personal history of alcohol abuse, medical contraindications, or other problems potentiated by alcohol. "It would seem folly to recommend alcohol to such individuals. Clearly, those who avoid alcohol include an overpresentation of persons destined for a less favorable risk-benefit ratio were they to drink."

B. Alcohol may induce and mask potentially severe hypoglycemic effects caused by other therapy. "Even at relatively low doses, alcohol may induce hypoglycemia."

C. Heavy alcohol intake may worsen neuropathy and produce insulin resistance.

D. Overall mortality does not adequately address the spectrum of morbidity from alcohol — increased risk of cancer, liver disease, drug interactions, depression, unintentional injuries, and social discord. "50% of drinkers will experience some alcohol-related problem in their lifetime."

Discussion and recommendation regarding alcohol intake fall on the shoulders of treating physicians, who have less time than ever to discuss lifestyle issues.

"But, what is true for most patients with diabetes is true for other patients at high risk for CHD — light to moderate alcohol consumption likely provides benefit, but is contraindicated in anyone who, for whatever reason, cannot restrict his or her drinking to light or moderate levels. For some patients, 1 drink is plenty, 2 is too many, and 3 is not half enough."

Judicious recommendations can be made in individual cases when the patient is well known to the clinician. But, the recommendation to drink should not be generalized.

JAMA July 21, 1999; 282: 279-80 Editorial by Michael H Criqui and Beatrice A Golumb, University of California, San Diego

Comment:

1. This re-emphasizes a generalization — interventions are more beneficial in persons at high risk than for those at moderate or low risk. Certainly, patients with diabetes are at high risk.

A reasonable approach would be to discuss alcohol only with those older patients who already drink. Then a modest daily consumption of 1 glass of wine with dinner would be reasonable and likely beneficial. RTJ

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7-11 RANDOMISED CONTROLLED TRIAL OF EXERCISE FOR LOW BACK PAIN: Clinical Outcomes, Costs, and Preferences

Although low back pain may settle quickly, it often recurs within the following 12 months. Recent guidelines encourage early return to physical activities. But patients are often afraid of movement after acute onset of back pain.

There is evidence that an exercise program which aims to increase individuals' confidence in use of their spine and overcome the fear of physical activity can be effective for patients with chronic back pain (more than 6 months duration).

This community setting study evaluated effectiveness of exercise for patients with low back pain with the aim of encouraging return to normal activity.

Conclusion: Exercise was more clinically effective than traditional general practitioner management.

STUDY

1. Randomized, controlled trial entered 187 patients with subacute mechanical back pain of 1 to 6 months duration. All had subacute or recurrent back pain and were referred by general practitioners.
2. Randomized to : 1) progressive exercise program, or 2) usual primary care management
3. Exercise classes were conducted by a physiotherapist. Included strengthening exercises for all main muscle groups, stretching exercises, relaxing session, and brief education on back care. A cognitive-behavioral approach was used.
4. Program was spread out over 4 weeks with the aim of encouraging normal movement of the spine. (See text p 280 for details.)

RESULTS

1. At 6 weeks, the intervention group reported less distressing pain and improved marginally more than the control group on the disability questionnaire.

2. At 6 months and 1 year, the intervention group showed significantly greater improvement in the disability questionnaire.
3. At 1 year, the intervention group showed greater improvement in a back pain scale and reported about 1/2 as many days off work as the control group.
4. The intervention group used fewer healthcare resources.
5. Outcome was not influenced by patients' baseline preferences. (Ie, whether or not before randomization they would prefer exercise or regular care.)

DISCUSSION

1. Simple exercise class can lead to long-term improvement for back pain.
2. The program showed patients how they can safely start moving again and increase their levels of physical activity.
3. Patients with back pain who use coping strategies that do not avoid movement and pain have less disability.
4. Patient preference before allocation to control or intervention groups in a study such as this can be an important determination of outcome. However, this study demonstrated no effect of prior preference on outcomes. Exercise classes can be effective even in patients who are not highly motivated.

CONCLUISION

For subacute and recurrent low back pain, exercise class was more clinically effective than traditional general practitioner management and was cost effective.

BMJ July 31, 1999; 319: 279-83 Original investigation, first author Jennifer Klaber Moffett, , University of York, UK

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7-12 SYSTEMATIC REVIEW OF TOPICAL TREATMENTS FOR FUNGAL INFECTIONS OF THE SKIN AND NAILS OF THE FEET.

About 15% of the population of the UK have fungal infections of the feet. The main treatments are topical fungistatic or fungicidal preparations, some of which are available over the counter.

This review identified and synthesized evidence for efficacy and cost of topical treatments for superficial fungal infections.

Conclusion: The most cost-effective strategy for skin infections (not nail infections) is to use over-the-counter topicals first and use prescription topicals only if that fails.

STUDY

1. Systematic review compared 3 groups of drugs used topically for superficial fungal infections of the skin and nails:
   A. Azoles — eg, chlortrimazole (Lotrimin); itraconazole (Sporanox) is not available for topical use on skin.
   B. Undecenoic acid — eg, Desenex; Cruex.
   C. Allylamines —eg, naftidine (Nafton); terbinafine (Lamasil).
2. A and B are available over the counter; C by prescription.
3. Main outcome measure — cure defined by culture and microscopy.

RESULTS

1. 72 trials met inclusion criteria.
2. Pooled relative risks of failure to cure skin infections (drug vs placebo):
   Azoles — 0.54 (Ie, 46% cured vs 0 for placebo)
   Undecenoic acid — 0.28 (72% cured vs 0)

Allylamines — 0.30 (70% cured vs 0)

3. Meta-analysis of 11 trials comparing allylamines with azoles showed a relative cure rate slightly in favor of allylamines.
4. Allylamines (by prescription only) cost more than the over-the-counter undecenoic acid and azoles. Undecenoic acid costs less than azoles.
5. Neither trial of nail infections showed significant differences between alternative topicals. But, information about efficacy of topical treatment of nails is very sparse. Little can be concluded about cure for infected toenails. 1

DISCUSSION

1. Good evidence shows that all 3 classes of drugs are efficacious compared with placebo.
2. Allylamines are generally more efficacious than azoles. They are available only on prescription at greater cost.
3. The most cost-effective strategy is to treat first with an azole or undecenoic acid and to reserve allylamines for treatment failures.

CONCLUSION

There is little evidence to differentiate between popular over-the-counter topical treatments for fungal skin infections. Allylamines cure slightly more infections than azoles but are more expensive. The most effective strategy is to initially use an over-the-counter drug and save the prescription drug to treat failures.

BMJ July 10, 1999; 319: 79-82 Original systematic review, first author Rachel Hart, University of Wales, Cardiff.

Comment:

It required several hours to abstract this short article. I had to look up the various individual drugs in the PDR and PDR Nonprescription Drugs (Azoles? Allylamines? Undecenoic acid?)

The list of preparations for topical use for fungal infections is long and confusing. Some are available both in over-the-counter and prescription strength.

Primary care physicians have the happy option of simply telling the patient to pick up a tube of a topical from the shelf. Desenex (Undecenoic acid) might be a suggestion if the patient requests one. Treatment may have to be continued for several weeks to obtain cure.

1. Treatment of nail infections is an entirely different matter. The study does not help with these patients. See following article RTJ

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7-13 SKIN AND NAIL FUNGI — Almost Beaten

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

It is now possible to eradicate most of the dermatophyte (between toes and in nails) infections, and more widespread infections with antifungal agents.

The editorialist comments that topical terbinafine [Lamisil] , a fungicidal allylamine, requires fewer applications (over about 1 week) to achieve cure. Fungistatic drugs require up to 4 weeks.

Nail infections are another matter. They require systemic therapy. A recent study reported in BMJ 1 convincingly demonstrated the superiority of oral terbinafine over oral itraconazole and recommended it as first choice therapy.

The editorialist believes "that the most effective treatment for a topical dermatophyte infection is topical terbinafine, and for onychomycosis is oral terbinafine."

There are risks from oral agents— including idiosyncratic liver damage.

BMJ July 10, 1999; 319: 71-72 Editorial by Andrew Y Finlay, University of Wales College of Medicine, Cardiff.

1. BMJ April 17, 1999; 318: 1031-35 "Double-Blind, Randomised Study of Continuous Terbinafine Compared with Intermittent Itraconazole in Treatment of Toenail Onychomycosis."

Comment:

Terbinafine (Lamisil) is fungicidal.

Itraconazole (Sporanox) is fungistatic. In addition it inhibits the liver cytochrome P450 enzyme system and may raise plasma concentrations of drugs metabolized by this system. RTJ

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7-14 HAEMODYNAMIC ANALYSIS OF EFFICACY OF COMPRESSION HOSIERY IN ELDERLY FALLERS WITH ORTHOSTATIC HYPOTENSION

Orthostatic hypotension (OH) is a common and important independent risk factor for falls in elderly people. It is defined as a sustained drop in systolic BP of more than 20 mm Hg when the patient rises from a supine to upright. Etiology is diverse, multifactorial, and commonly iatrogenic. Pharmacological treatment is unpredictable and unsatisfactory.

Symptoms can be attenuated by non-pharmacological measures: head up tilt during sleep, small frequent meals1, increased salt intake, and appropriate exercise.

Graduated elastic hosiery may be an effective treatment by enhancing venous return and cardiac output when the patient stands.

This study assessed efficacy of compression hosiery in elderly people with persistent symptomatic OH and a history of falls. The investigators gathered 10 patients attending a geriatric falls clinic (mean age 77). All had reproducible, symptomatic OH.

BP was recorded continuously on an automatic recording machine while the patients were supine for 3 minutes. The patients were then tilted to the 900 upright and BP recorded for another 3 minutes. OH was confirmed.

After elastic compression tights fitted to the individual were applied a second identical test was made. In 9 patients there were highly significant reductions in the orthostatic fall in systolic BP averaging over 20 mm Hg on the second examination. At 2 minutes upright before hosiery the fall averaged 32 mm Hg; with stockings, less than 1 mm Hg.

Orthostatic dizziness was abolished in 7.

The investigators concluded that compression hosiery effectively reduced OH. Whether falls will be prevented in the long term remains to be studied.

Lancet July 3, 1999; 354: 45-46 Original investigation, first author R Henry, University of Birmingham UK.

Comment:

1. Previous studies reported that OH is much more common in elderly persons after meals. This is because of the shift in blood volume to the intestinal tract which occurs in response to digestive needs. Patients with a history of OH should not immediately rise after eating. RTJ

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7-15 EARLY LUNG CANCER ACTION PROJECT: Overall Design and Findings from Baseline Screening

The cure rate for lung cancer is 12%. The 5-year survival is only slightly higher.
When stage 1 cancer is resected, the 5-year survival can be as high as 70%.

This trial was designed to evaluate screening by computed tomography (CT) scanning in people at high risk for lung cancer.

Conclusion: CT screening greatly improved detection of lung cancers at an earlier and potentially curable stage.

STUDY

1. Enrolled 1000 symptom-free volunteers, age 60 and older (mean = 67). All had at least 10 pack-years of cigarette smoking. None had a history of cancer. All were medically fit to undergo thoracic surgery if needed.
2. All received chest radiographs and low-dose chest CT at baseline.
3. A diagnostic CT with high resolution was performed when a non-calcified nodule was detected on low-dose CT.
4. If high-resolution CT showed calcifications not identified on low-dose CT in a nodule with smooth edges and size less than 20 mm, the nodule was considered benign.
5. The non-calcified nodules were classified by size. Follow-up depended on size. (See text for details.RTJ)
   A. Large non-calcified nodules received immediate biopsy by guided fine-needle.
   B. Smaller nodules were followed periodically by repeat high resolution CT to determine growth. If no growth occurred over 2 years, the nodule was considered benign.

RESULTS

1. Low-dose CT detected non-calcified nodules in 233 (23%) patients; radiography detected non-calcified nodules in 68 (7%).
2. Biopsies done in 28 patients, only 1 was benign. (Only 1 false positive)
3.

	High resolution CT/biopsy	Radiography/biopsy
Malignant	27 patients	7 patients
Resectable cancer	26	
Stage 1 cancer	23	4
Less than 10 cm diameter	57%	

4. No participant had thoracotomy for a benign nodule.

DISCUSSION

1. Compared with radiography, CT greatly increased the likelihood of detection of small non-calcified nodules.
2. Cancers detected by CT were substantially smaller and at an earlier and potentially more curable stage than those detected by radiography. (Size significantly influences survival.)
3. The likelihood of malignant disease in patients with 2 to 6 non-calcified nodules was not appreciably less than that of solitary nodules. The presence of multiple nodules should not lessen search for malignancy.
4. Screening by annual repeat low-dose CT is suggested for those originally negative for non-calcified nodules. The investigators would then expect to discover at the rate of 5 per 1000 patients on each annual screen. The majority would be under 10 cm in diameter.
5. Low-dose CT takes 20 seconds and does not require contrast injection. Cost is lower than a standard CT is only slightly higher than chest radiography.

CONCLUSION

Low-dose CT can greatly improve detection of small non-calcified modules, and lung cancer at an earlier and potentially more curable stage.

Lancet July 10,1999; 354: 99-105 Original investigation by the Early Lung Cancer Action Project (ELCAP), first author Claudia I Henschke, Weill Medical College of Cornell University, New York.

Comment:

Resectability is not synonymous with cure. We must await follow-up for cure, the ultimate goal of the study. RTJ

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7-16 SCREENING FOR LUNG CANCER: Time To Think Positive

(This editorial comments and expands on the preceding.)

"Lung-cancer screening ought to work" The disease is common. At its earliest stages up to 70% of cases can be cured by surgery. Despite this the prognosis is so dismal that the incidence exceeds prevalence.

Dogma states that screening is ineffective.

The prevalence rate of lung cancer in the study was 2.7%. This was 4 times higher than the 0.7% detected by chest X-ray. "And incidentally about five-fold higher than for first-round breast-cancer screening."

CT scanning detected cancers when they were small. It would be strange if cancers detected at this stage did not prove to have a high cure rate.

What about cost and radiation dose? Each scan takes less than 20 seconds. The investigators state that costs and radiation dose are only slightly higher than for a standard chest X-ray.

What about over diagnosis? In breast cancer screening it is accepted that a significant number of in-situ cancers would never have become clinically significant. In lung cancer this possibility seems unlikely. The 5-year survival of screen detected stage 1 cancer falls from around 70% to less than 20% if left unresected.

Lancet July 10, 1999; 354: 86 Editorial by Ian E Smith, Institute of Cancer Research, London, UK

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Recommended Reading

7-17 GENERAL PRACTITIONERS' BELIEFS AND ATTITUDES ABOUT HOW TO RESPOND TO DEATH AND BEREAVEMENT: Qualitative Study

Bereavement carries appreciable morbidity and mortality. Some studies suggest that bereaved persons benefit from involvement of family doctors. But there is a lack of research evidence about the efficacy of bereavement management, and the role of the general practitioner (GP) There is no definition of good bereavement practice.

What are the beliefs and attitudes of GPs about death and bereavement? What do they do when a death occurs in their practice? How do they explain their actions? How do they manage themselves and bereaved patients?

The study conducted semi-structured interviews of 25 GPs in a borough of London. A qualitative analysis followed.

Conclusion: GPs need support and learning methods to manage their own and their patients' bereavement.

RESULTS

1. Almost all GPs felt guilty about issues relating to the death of patients in the family of the bereaved.
2. Their feelings were based on: 1) their expectations of their diagnostic precision and 2) not making mistakes. When the clinical course of illness differed from that expected, GPs described fears of making mistakes and guilt and self blame. Medical school education, with its expectation of not making a mistake, with its emphasis on the biomedical model and appearing to "get it right", left some with a feeling of inadequacy.
3. In the absence of useful teaching on bereavement, many GPs devised strategies which relied more on their personal experiences and those obtained from their family and culture.

4. They used various methods of relating to bereaved patients, especially if the GP had been involved in the terminal care of the loved one, or if the death was particularly shocking.

5. The GPs also experienced a sense of their own loss and were bereaved by the death of a well known patient. And sometime needed to grieve and express emotion because of a process of identification with the patient.

6. Most described a difference they perceived between general practice and hospital medicine.

7. Most felt that they had a responsibility to make some sort of contact with bereaved patients. Some expressed the view that if there was a perceived error it was especially important to make contact in order to seem to be taking responsibility.

BMJ July 31, 1999; 319: 293-96 Original investigation, first author Eric M Saunderson North Street Medical Care, Romford, Essex, UK

Comment:

"Bereaved people need to separate from the memory of the diseased, readjust to the environment in which the deceased is missing, and form new relationships." Can the primary care physician help families make this adjustment? RTJ

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7-18 USE OF ALTERNATIVE MEDICINE BY WOMEN WITH EARLY-STAGE BREAST CANCER

The failure of standard health care, changes in the health care delivery system, patients' need for autonomy, a preference for "holisitic" or "natural" therapy, and chronic health problems have all been suggested as contributing factors motivating people to use alternative medicine (AM)

Collectively, higher levels of income, amount of education, and age are strongly (positively) predictive of rate of use of AM.

This study analyzed new-use of AM by women who had received standard therapy for early-stage breast cancer (BC).

Conclusion: New-use of AM was a marker of greater psychological distress and worse quality of life.

STUDY

1. Recruited a cohort of almost 500 women. All had early-stage BC.
2. Studied how women choose treatment for BC — use of AM and conventional therapies.
3. Assessed health-related quality of life.

RESULTS

1. New use of AM was reported by 28%.
2. Use of AM was not associated with choices about standard medical treatment.
3. Women who initiated use of AM after surgery reported a worse quality of life than women who had never used AM.
4. Three months after surgery use of AM was independently associated with depression, fear of recurrence, lower scores for mental health and sexual satisfaction.
5. Physical symptoms were more frequent in this group, and symptoms were of greater intensity.
6. At one year after surgery, all groups reported improving quality of life.

DISCUSSION

1. Anxiety, marital stress, depression, increased symptoms, and lower levels of sexual satisfaction are common among patients with BC in the year after diagnosis.
2. Use of AM was common in women with early stage BC. Many began use of AM early in the wake of diagnosis.
3. Use was not related to type of standard therapy — surgery, radiation, or chemotherapy.

4. Women who newly-used AM reported more depression, worse general health, and greater fear of recurrence.
5. Use of adjuvant therapy was not associated with the decision to use AM. Patients who used AM considered it as a complement, not a substitute for standard therapy.
6. New-use may have clinical significance as a marker of psychosocial distress after surgery for BC.
7. Women who did not use AM had stable or improving mental health scores. By one year both groups had improved considerably.
8. It is possible that women may start using AM in response to psychosocial symptoms or distress. Use of AM may alert clinicians to inquire about anxiety, depression, or physical symptoms. "Vulnerable patients identified by new use of AM might benefit from programs tailored to their psychosocial and physical needs."

CONCLUSION

Among women with newly diagnosed early-stage breast cancer who had been treated with standard therapies, new-use of alternative medicine was a marker of greater psychosocial distress and worse quality of life.

NEJM June 3, 1999; 340: 1733-39 Original investigation, first author, Harold J Burstein, Dana-Farber Cancer Institute and Harvard Medical School, Boston Mass

An editorial in this issue (pp 1758-59) comments:

The results of the study contrast starkly with the widely held image of the woman who seeks help from alternative medicine as self-assertive, psychologically strong, and well adjusted — a woman who likes the sense of control and empowerment she gains from finding products used in alternative medicine on the internet, on on-line chat rooms, and in health food stores. These new data call into question the stereotype of the seeker of alternative medicine. Women in the study turned to alternative medicine to alleviate their distress.

There was one hopeful finding — most women who used AM informed their doctors about it. There was a dialogue about it. It is important for clinicians to routinely ask about use of AM because so many people use it and because use may complicate conventional therapy. In addition, now it appears a positive answer should prompt questions about distress and coping with the illness, fears, and depression.

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7-19 PREDICTED IMPACT OF INTRAVENOUS THROMBOLYSIS ON PROGNOSIS OF GENERAL POPULATION OF STROKE PATIENTS: Simulation Model

Alteplace (recombinant tissue plasminogen activator— tPA) was approved by the US FDA for stroke patients to be used within 3 hours of onset. This followed a study reporting a 32% relative increase in proportion of patients with full recovery, but with no effect on overall mortality.

Conversely, European trials have reported no significant positive effects.

The trials were performed in highly selected patients.

The Copenhagen Stroke Study (COST) comprised 1197 patients with acute stroke. These patients represented 88% of stroke patients in the area.

The authors started out with the 1197 patients and progressed to exclude those who did not meet inclusion criteria. (See table p 288.)

Results: Only five of the 1197 would have benefited from alteplace therapy. Even assuming all patients were admitted in due time, only 48 (4% of total population) would have benefited.

The authors comment that even these estimates may be too generous since those with rapidly improving symptoms could not be excluded.

"Treatment with alteplace may benefit single patients but will have no impact on the general prognosis of stroke." Alteplace therapy requires a specialist setting. It would require large investments

and reorganization of the care of stroke patients. This marginally effective treatment, which is also potentially harmful, requires more study before being widely offered.

BMJ July 31, 1999; 319: 288-89 Original analysis, first author Henrik Stig Jorgensen, Bispebjerg Hospital, Copenhagen, Denmark.

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REFERENCE ARTICLE

7-20 GASTROINTESTINAL TOXICITY OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

This long review article comments on the often unappreciated seriousness of toxicity of NSAIDs, a "silent epidemic".

Epidemiology:

Billions are spent on these drugs every year (including over-the-counter). Billions more are spent on complications — dyspepsia, gastroduodenal ulcers, gi bleeding, perforation. "It has been estimated conservatively that 16 500 NSAID-related deaths occur among patients with rheumatoid arthritis or osteoarthritis every year in the United States." Almost equal to the number of deaths due to AIDS.

Risk factors:

Gastric and duodenal ulcers occur in 10% to 25% of patients treated chronically with NSAIDs. Some patients are at more risk for NSAID-associated gastroduodenal ulcers: advanced age, history of ulcer, higher doses and use of multiple NSAIDs, concomitant anticoagulation.

What about concomitant H pylori infection? "Infection with H pylori increases the risk of gastrointestinal injury associated with NSAID use only minimally if at all."

Pathogenesis of NSAID-induced mucosal injury

Gastroduodenal mucosal injury develops when the deleterious effect of gastric acid overwhelms the normal defensive properties of the mucosa. The systemic effects of NSAIDs (the predominant factor) are largely due to decrease in protective prostaglandins. This in turn leads to decreases in: 1)epithelial mucus, 2) secretion of bicarbonate, 3) mucosal blood flow, 4) epithelial proliferation, and 5) mucosal resistance to injury. Indeed, doses of aspirin as low as 30 mg are sufficient to suppress prostaglandin synthesis in the gastric mucosa

In addition, topical mucosal injury is due to the acidic properties of NSAIDs. However, enteric coated preparations do not retard mucosal injury. The systemic effects persist. Cyclo-oxygenase-1 (constantly present) appears to function as a "house keeping" enzyme, maintaining homeostasis in the stomach, kidney, and platelets. Cyclo-oxygenase-2 is an enzyme induced by inflammation (not constantly present). Inhibition of Cyclo-oxygenase-2 blunts the inflammatory properties of its resultant prostaglandins. (Presumably a beneficial effect.)

Inhibition of cyclo-oxygenase-1 decreases the protective effects of prostaglandins on the gi mucosa. Ulceration may result.

NSAID-related dyspepsia:

At least 10% to 20% of patients taking NSAIDs have dyspepsia. However, the symptoms are poorly correlated with the endoscopic appearance and severity of mucosal injury. Many with endoscopically visualized injury have no symptoms. Conversely, many with symptoms have a normal appearing mucosa.

"Although H2-receptor antagonists are effective in reducing NSAID-related dyspepsia, their routine use in asymptomatic patients taking NSAIDs cannot be recommended."

Proton pump inhibitors (eg, omeprazole) appear to provide a safe and effective form of therapy for NSAID dyspepsia.

Misoprostol [Cytotec] use was not associated with any improvement in dyspeptic symptoms.

Prevention of NSAID-related ulcers:

Concomitant therapy with H2-receptor antagonists have been effective in preventing duodenal ulcers, but not gastric ulcers. They are not recommended
Proton pump inhibitors are superior to H2 receptor blockers in preventing both gastric and duodenal ulcers.

Misoprostol is also effective in preventing ulcers during continued use of the NSAID. However, use was not associated with any improvement in dyspeptic symptoms. Diarrhea and abdominal pain occurs in many patients. Uterine contractions can lead to abortion.

Highly selective COX-2 inhibitors have been shown to have a markedly reduced capacity to cause injury to the mucosa to a rate not significantly different from placebo. However, ultimate benefit and safety profile is to be determined.

Treatment of NSAID-related gastroduodenal ulcers:

Both omeprazole and misoprostol (a prostaglandin substitute) have been shown to lead to healing of ulcers whether or not the NSAIDs are continued. H2 receptors also have been reported to be associated with healing, but not as effectively as omeprazole.

Obviously the NSAID should be discontinued if possible when ulceration occurs.

NEJM June 17, 1999; 340: 1888-1899 Review article, "Medical Progress", first author M Michael Wolfe, Boston University School of Medicine, Mass.

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Recommended Reading

7-21 STORIES AT WORK: Reflective Writing for Practitioners

Reflective writing courses for general practitioners have been offered in various settings in the UK for the past 10 years. This essay comments. I gleaned some quotes. RTJ

Every triumph, disaster, or joy of our lives is a story waiting to be written. We create this dynamic literature about ourselves and patients, patients create it about us, and colleagues give us principal or walk-on parts in their own drama.

Stories and poems appear regularly in the flagship journals. Why? Such stories are the data-banks of experience, knowledge, and skill; they are embedded in practice. Reading or hearing stories makes skilled experience and knowledge available not only to colleagues, trainees and students, but also to the writers themselves. Reflective writers can study their own decision-making processes, relationships with colleagues, and responses to patients; analyse their hesitations and gaps in skill and knowledge; and face difficult and painful episodes.

Writing an ‘emotional diary’ is a framework allowing doctors to reflect on, and evaluate, their emotional responses to everyday practice.

Writing has power that thinking and talking do not have.It can have a far deeper reflective and educative function. Writing enables the writer to express and clarify experiences, thoughts, and ideas that are problematic, troublesome, hard to grasp, or hard to share. It enables exploration of issues, memories, and feeling not previously acknowledged. Unlike thinking and talking, writing can be re-organized and clarified at a later stage.

Reflective writing is part of a deep and valuable tradition of stories in medicine. Doctors temporarily become co-authors of their patients’ life-narrative. They may become a central character, and sometimes help patients write the last chapter of their narrative.

Expressive, explorative, and reflective writing relieves stress and fosters understanding. Poems profoundly alter the man or woman who writes them.

We are our stories. Writing and rewriting them keeps us alert, alive and flexible.

Lancet July 17, 1999; 354: 243-45 "Literature and Medicine" essay by Gillie Bolton, Sheffield University, UK.

Comment:

Well said!. Every patient has a story to tell. We are fortunate when we have time and take time to listen. We must listen before we can write. RTJ

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7-22 FUNCTIONAL FOODS: Health Boon or Quackery?

"Functional foods may prove a major health boon or result in a new generation of quackery"

"The dividing line between foods and drugs is becoming increasingly blurred, In the United States a canned split pea soup features the herb St.John's Wort to 'give your mood a natural lift' and a chewing gum with phosphatidyl serine claims it 'improves concentration'. In Japan a soft drink named VegitaBeta is fortified with beta-carotene 'to support a healthy lifestyle'. And in the United Kingdom MD Foods claimed that its butter-like spread made with fish oil would benefit the heart. What is our food supply turning to?"

The public's great interest in alternative health remedies and weak government regulation couple in attracting marketers who see big profits in 'functional foods'.

In some cases adding substances to foods offers real benefits (iodine to salt, orange juice fortified with calcium, folate enriched flour).

The editorialist suggests that governments should be involved to ensure that foods are safe, nutritious, and honestly labeled.

Providers continue to successfully market their products as food "supplements" to evade government rules that apply to foods. Government regulations can be by-passed.
Instead of making direct health claims, companies simply publicize the presence of ingredients that many consumers identify, rightly or wrongly, with health benefits.

The potential for defrauding and sickening consumers is illustrated by the unbridled marketing in the US — $12 billion worth annually.

BMJ July 24, 1999; 319: 205-06 Editorial by Michael F Jacobson and Bruce Silverglade, Center for Science in the Public Interest, Washington DC

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REFERENCE ARTICLE

7-23 HORMONE REPLACEMENT THERAPY

In June 1999, the European Institute of Oncology met at Milan Italy with the aim of synthesizing clinical data on hormone replacement therapy (HRT). Much of the data came from women who used conjugated equine estrogens or estradiol, often given with a progestagen.

Users tend to be healthier, better educated, more physically active, leaner, and to more often drink moderate amounts of alcohol than other women in the same region. Thus, data must be interpreted with caution. Bias probably influences results of studies. A few highlights:

The menopause:

Symptoms of vasomotor instability have substantially different prevalence across countries and regions. HRT is highly effective for women with typical menopausal symptoms and may improve less specific symptoms, with substantial improvement in quality of life. Early menopause usually produces more serious symptoms, and special attention to use of HRT should be considered in this group. Some women will not tolerate HRT.

Osteoporosis:

HRT is effective for prevention and treatment of osteoporosis for the duration of its use. Current use is associated with a 30-50% reduction in hip, spine, and wrist fractures. Benefits decline rapidly after treatment stops. Thus HRT would have to be continued for women in their 70s. Addition of calcium and vitamin D may be beneficial. "The combination of HRT with another antiresorptive drug (such as a bisphosphonate) or a bone forming agent is an interesting possibility that should be explored."

Cardiovascular disease:

Cause and effect relation is not proved. But, evidence that HRT lowers risk of coronary disease in women without a history of this disease (primary prevention) is sufficiently strong to consider this potential benefit.

HRT raises risk of venous thromboembolism, but the absolute risk is small in women without predisposing conditions.[2]

Added progestagen attenuates the benefits of estrogen on lipids. But evidence suggests that benefit for primary prevention remains when the combination is given.

For secondary prevention in women with coronary disease, combined therapy substantially increased risk of recurrent disease in the first 4 months of therapy.[3] There was a decline in risk with longer duration in the final 2 years. This raises concern about prescribing HRT for women with prior myocardial infarction, but does suggest a long-term benefit.

Risks regarding stroke are uncertain.

HRT and risk of cancer:

HRT is associated with a slight increase in risk of breast cancer (BC). Risk is restricted to current and recent users, and increases with duration of use. The effect wears off after 5 years of stopping. Use for 1 to 2 years is not associated with appreciable risk. The breast cancers that develop in HRT users may be less aggressive and associated with longer survival than in non-users. In absolute terms, the cumulative excess incidence in 1000 women using HRT for 5 to 10 years starting at age 50 is 2 to 6 cases.

Observational studies report a protective effect of HRT on colo-rectal cancer (RR for current use = 0.7)

Until recently, a prior history of BC was widely considered an absolute contraindication to HRT. Few data support or refute this thesis. Reducing or blocking naturally occurring estrogen by selective estrogen receptor modulators (eg, tamoxifen) delays recurrence and improves survival in women with BC. A symptomatic woman may cautiously consider HRT. (Fully informing the woman about risks and benefits is essential.)

Dementia:

HRT has been suggested to protect cognitive function and delay Alzheimer disease. Data are insufficient to use HRT solely for this purpose. There may be a beneficial effect in reducing risk of vascular dementia.

Conclusion:

Use of HRT for a few years at around the time of menopause will relieve symptoms, but will not lead to substantial increase or decrease in cancer, cardiovascular disease, or osteoporosis. Recommendations about long-term use are more difficult. "On average, the balance between risks and benefits is not overwhelming in either direction."[4]

"The use of HRT has to be tailored to the needs and desires of the individual." In the face of uncertainty, decision-making should be shared after establishing sensitive communication and fully informing the patient. The objective for starting HRT should be clearly identified to the patient.

Lancet July 19, 1999; 354: 152-55 Clinical Synthesis Conference funded by the European Institute of Oncology

Comment:

1. I have been waiting for such a study.

2. It is evident that persons with inborn derangements of the clotting process form a group at considerably higher risk.

3. The "Heart and Estrogen/progestin Replacement Study (HERS)— 1998

4. A minority of members of the panel disagreed with the statement in the conclusion that evidence does not overwhelmingly favor risk or benefit. These members felt that evidence on long-term use unequivocally shows net benefit.

This does not produce any unexpected conclusions. All the points have been considered in previous studies of HRT, results of which have been reported in Practical Pointers. Review articles such as this, which gather and condense data, and refresh our memories are helpful. RTJ

==========**7-24 PREVALENCE AND CLINICAL OUTCOME ON MITRAL VALVE PROLAPSE**

Mitral valve prolapse (MVP) has been described as a common disorder. And often portrayed as a disease with frequent and serious complications: stroke, atrial fibrillation, bacterial endocarditis, heart failure, and mitral regurgitation requiring surgery.

The prevalence and epidemiology of MVP heretofore has been based on use of hospital based samples which included those likely to have clinical complications.

This study determined prevalence in the general population.

Conclusion: In a community-based sample, prevalence was low.

STUDY

1. Defined MVP, assessed by echocardiography, in 2 ways:
   A. Classical MVP – superior displacement of the valve leaflets of more than 2 mm during systole and a maximal leaflet thickness of at least 5mm.
   B. Non-classical – displacement of more than 2 mm, with a maximal thickness of less than 5 mm. (*Note – no mention of mitral regurgitation in the definition. RTJ)*
2. Framingham Heart Study studied 3500 subjects (mean age = 55) selected from the community. All underwent two-dimensional echocardiography.

RESULTS

1. Total of 2.4% had MVP
   A. Classical MVP – 1.3%
   B. Non-classical MVP – 1.1%
2. Age and sex distributions were similar to subjects without prolapse.
3. No subject had history of heart failure; one had atrial fibrillation; one had cerebrovascular disease; three had syncope. Prevalence in subjects without MVP was similar.
4. Chest pain, dyspnea, and ECG abnormalities were similar between those with and those without MVP.

5.	Classical MVP	Non-classical MVP	No MVP
Mitral regurgitation	23%	10%	4%
Systolic click 11%	8%	1.5%	
Left atrial enlargement	4%	2%	1%
Left ventricular hypertrophy	2%	2%	1%

DISCUSSION

1. Prevalence of MVP in this unselected group of ambulatory subjects was substantially lower than that previously reported.
2. Rates of heart failure, atrial fibrillation, syncope, and cerebrovascular disease were no more common than in those without MVP.
3. Subjects with MVP were more likely to have mitral regurgitation than those without MVP. The degree of regurgitation on average was mild.1
4. The clinical profile of MVP is more benign than previously indicated.

5. Previous studies indicate that serious ventricular arrhythmias and sudden death are more common in patients with MVP who have severe mitral regurgitation and left ventricular dysfunction. This study did not address long-term outcomes in this subset.

CONCLUSION

In a large community-based sample of the population, the prevalence of MVP was lower than previously reported. The prevalence of adverse sequelae commonly associated with MVP was also low.

NEJM July 1, 1999; 341; 1-7 Original investigation by the Framingham Heart Study first author Lisa A Freed, Massachusetts General Hospital, Boston.

Comment:

1. Note the minority of those with MVP had regurgitation. Clinically, MVP has been diagnosed on the presence of regurgitation and clicks. This subset would be an entirely different cohort of patients on which to base epidemiological study.

Clinicians have screened for MVP by auscultation, on a basis of murmur and click, not by echo. I do not believe this study is helpful clinically. We need a study on long-term outcomes in patients with MVP severe enough to cause regurgitation. RTJ

See an accompanying article (NEJM July 1, 1999; 341:8-13 "Lack of Evidence of an Association between Mitral valve Prolapse and Stroke in Young Patients" This case-control study reports a low prevalence of MVP (2%) in a cohort of young patients (mean age = 26) with stroke or TIA. Prevalence of MVP was no more common in the cases than in the controls. The case patients were defined by echo, as in the preceding study.

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7-25 PERSPECTIVES ON MITRAL-VALVE PROLAPSE

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

The original description of MVP (over 30 years ago) was based on a constellation of clinical findings: non-ejection systolic clicks, late systolic murmur, T-wave abnormalities, and systolic billowing of the posterior mitral leaflet into the left atrium on ventriculograpy.

Though it is predominantly a benign condition, devastating complications have been described.

The contradiction of benign-malignant has led to confusion on the part of clinicians. Perhaps the most confusing aspect is the lack of universally accepted, standardized methods of diagnosis.

Now MVP is understood, not as a single entity, but as a spectrum of abnormalities with varied clinical, echocardiographic, and pathological features. At one end of the spectrum are patients with leaflet redundancy as a result of marked myxomatous proliferation of the spongiosa, and elongation of the chordal apparatus. At the other end are those with morphologically normal appearing leaflets that bulge into the left atrium.

The prevalence of MVP in the general population is low.

Patients with thickened leaflets should be described as having a primary form of MVP. The outcomes in those with mild bowing and normal leaflets probably do not differ from the general population. (Ie, a normal variant.)

The true primary form generally occurs in patients with connective tissue disorders or in older men.

Screening with echo to rule out MVP is warranted for patients with a midsystolic click or characteristic murmur. The use of echo to look for MVP in patients with atypical chest pain, palpitations, anxiety disorders, or other non-cardiac symptoms that are occasionally attributed to MVP is not indicated.

Patients with primary MVP require prophylaxis against infective endocarditis. "For patients with normal-variant prolapse and no murmur, prophylaxis is optional and probably unnecessary."1

If substantial mitral regurgitation is present, long standing volume overload may lead to left ventricular dysfunction even in asymptomatic patients with a normal ejection fraction. Mitral valve repair may be necessary.

NEJM July 1, 1999; 341: 48-50 Editorial by Risk A Nishimura and Michael D McGoon, Mayo Clinic, Rochester MN

1. This leaves a number of patients in between — those with murmur and bulging, but without valve thickening. I believe most clinicians would opt for prophylaxis against endocarditis in this group. RTJ

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Recommended Reading

7-26 FREUD'S PHYSICIAN-ASSISTED DEATH

At age 83, Freud had endured terrible suffering from a malignant epithelioma for many years. He had to use crude prostheses simply to talk and eat, had undergone more than 30 surgical procedures, repeated courses of primitive X-ray and radium therapy, and disruptions to his life from Nazi persecution.

When his pain no was no longer bearable, he asked his physician to honor a long-standing agreement to assist him in preemption of certain death from cancer.

The authors conclude that Freud's choice would be what now would be termed voluntary active euthanasia. "Freud's choice of physician-assisted suicide was not merely an interesting historical event, but one of paramount rationality, and one that is relevant to our contentious contemporary debates concerning euthanasia and physician-assisted suicide."

Archives Int Med July 26, 1999; 159: 1521-23 "Commentary" by Jack D McCue, St Mary's Medical Center, San Francisco, and Lewis M Cohen, Springfield Mass.

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REFERENCE ARTICLE

7-27 COELIAC DISEASE

This reviews symptoms and signs, epidemiology, pathogenesis, diagnosis, treatment, prognosis, and complications.

"Coeliac disease is an inflammatory disease of the upper small intestine and results from gluten ingestion in genetically susceptible individuals."

Symptoms and signs are caused by intestinal features and malabsorption of important nutrients. "It should be emphasized that many patients —especially those presenting in adulthood — have minimal or atypical symptoms."

Prevalence is estimated at 1 in 200 individuals. A minority has clinically recognized disease. The majority has "silent" coeliac disease, which may remain undiagnosed because the condition has no symptoms.

The test for endomysial1 auto-antibody has advanced the diagnosis owing to its specificity and sensitivity. The antigliadin antibody test is also used.

Complete withdrawal of gluten from the diet results in complete remission.

BMJ July 24, 1999; 319:236-40 "Clinical Review" by Conleth Feighery, St James's Hospital, Dublin Ireland.

Comment:

1. My dictionary defines endomysium as "The sheath of delicate reticular fibrils which surrounds each muscle fiber." I do not know how this relates to celiac disease. RTJ

Symptoms in adults may be non-specific — dyspepsia, fatigue, neuropsychiatric symptoms, weakness. Should celiac disease be ruled out when we encounter a patient with "somatization" ? It can be successfully treated.

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