PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

AUGUST 1999

JAMA, NEJM, LANCET
BRITISH MEDICAL JOURNAL
ARCHIVES OF INTERNAL MEDICINE
ANNALS OF INTERNAL MEDICINE
ODDS AND ENDS

PUBLISHED BY PRACTICAL POINTERS INC.
EDITED BY RICHARD T. JAMES JR., M.D.
FIRST CHARLOTFE PHYSICIANS
300 BILLINGSLEY ROA
CHARLOTTE NC 28211 USA

A public service publication. Copies on file in Charlotte AHEC library.

==========

HIGHLIGHTS – INDEX AUGUST 1999

8-1 POPULATION BASED STUDY ON SOCIAL AND PRODUCTIVE ACTIVITIES AS PREDICTORS OF SURVIVAL AMONG ELDERLY AMERICANS

Social and productive activities that involve little or no enhancement of fitness lowered the risk of all cause mortality as much as physical fitness. Activities other than physical (which increases cardiopulmonary fitness) may confer survival benefits through psychosocial pathways. Social and productive activities that require less physical exertion may constitute alternative interventions for frail elderly people. An exclusive emphasis on physical fitness activity may be overly narrow. BMJ August 21, 1999; 319: 478-83

8-2 SOCIAL DISENGAGEMENT AND INCIDENT COGNITIVE DECLINE IN COMMUNITY-DWELLING ELDERLY PERSONS

At 12 years, the odds ratio of experiencing cognitive decline was approximately twice as great in the most disengaged group as in the most engaged group. Continued mental stimulation staves off cognitive deterioration in old age possibly by maintaining a critical density of neocortical synapses. Annals Int Med August 3, 1999; 131: 165-73

8-3 REDUCTION OF VERTEBRAL FRACTURE RISK IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS TREATED WITH RALOXIFENE

In postmenopausal women with osteoporosis, raloxifene increased BMD and reduced risk of vertebral fracture in postmenopausal women with osteoporosis. (Secondary prevention) JAMA August 18, 1999; 282: 637-45

8-4 THERAPY FOR FRACTURE PREVENTION

"It may no longer be ethical to subject patients with previous fractures, whose risk of a new spine fracture is more than 5% per year to a 3- to 5-year interval of treatment with calcium and cholecalciferol alone." JAMA August 18, 1999; 282: 687-89

8-5 GLUCOSE TOLERANCE AND MORTALITY: Comparison of WHO and American Diabetes Association Diagnostic Criteria

Fasting glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycemia. An oral glucose tolerance test, measuring the 2-hour glucose, enables detection of individuals with impaired glucose tolerance, as well as diabetes, who have the greatest attributable risk of death. Lancet August 21, 1999; 354: 617-21

8-6 CARDIOVASCULAR DISEASE IN OLDER ADULTS WITH GLUCOSE DISORDERS: Comparison of American Diabetes Association Criteria for Diabetes Mellitus with WHO Criteria

"If the purpose of screening for diabetes mellitus is to identify the maximum number of people at risk of cardiovascular disease events or death when glucose is slightly raised, then it would seem that the WHO criteria are superior to the fasting ADA criteria." Lancet August 21, 1999; 354: 622-25

8-7 NEW DIAGNOSTIC CRITERIA FOR DIABETES—Are They Doing What They Should?

The ADA and the WHO criteria do not identify the same groups of individuals. Among people with diabetes according to the ADA criteria, only 46% had a 2 hour post-glucose concentration that met the WHO criterion. And impaired fasting glucose by ADA (glucose of 110-125) was present in only 48% of individuals classified as having impaired glucose tolerance by WHO (140-199).

The ADA criteria were much less sensitive than the WHO criteria in predicting CVD mortality (sensitivity 28% vs 54%). Lancet August 21, 1999; 354: 610-11

8-8 EFFECTS OF METFORMIN IN PATIENTS WITH POORLY CONTROLLED INSULIN-TREATED TYPE 2 DIABETES.

The addition of metformin to insulin in type 2 diabetics who were poorly controlled by insulin alone resulted in better glycemic control, with a substantial decrease in HbA1c. The combination allowed insulin dose to be reduced with no weight gain.

"Metformin is an effective adjunct to insulin therapy in patients with type 2 diabetes. Annals Int Med August 3, 1999;131: 182-188

8-9 HAZARDOUS AND HARMFUL ALCOHOL CONSUMPTION IN PRIMARY CARE

The article defines hazardous and harmful drinking which are recognized as common, distinct entities. And do not yet reach the definition of abuse or dependence. Routine screening is recommended. Brief physician counseling is effective therapy Archives Int Med August 9/23, 1999; 159: 1681-89

8-10 GEMFIBROZIL FOR THE SECONDARY PREVENTION OF CORONARY HEART DISEASE IN MEN WITH LOW LEVELS OF HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

For secondary prevention in patient with demonstrated coronary heart disease whose primary lipid abnormality is a low HDL-c level (a finding commonly occurring in the context of central obesity, diabetes, and other features of the metabolic syndrome), gemfibrozil effectively prevented recurrence of myocardial infarction and death from coronary heart disease. NEJM August 5, 1999; 410-18

8-11 CHOLESTEROL LOWERING IN THE ELDERLY POPULATION

The National Cholesterol Education Program emphasizes the need to include the elderly (age 75-80+) in clinical management of high cholesterol. The elderly carry the highest risk for CHD and the highest burden of atherosclerotic heart disease. Archives Int Med August 9/23 1999; 159: 1670-78

8-12 A PROSPECTIVE STUDY OF WALKING AS COMPARED WITH VIGOROUS EXERCISE IN THE PREVENTION OF CORONARY HEART DISEASE IN WOMEN

Both walking and vigorous exercise were associated with substantial reductions in the risk of coronary events. There was a strong, graded inverse relation between energy expenditure, either walking or vigorous exercise and the incidence of coronary events. Risk was reduced equally in women who walked briskly for at least 3 hours per week and women who exercised vigorously for 1.5 hours per week.

Enormous public health benefits would accrue from the adoption of moderate intensity exercise by those who are currently sedentary. NEJM August 26, 1999; 650-58

8-13 HEARTBURN TREATMENT IN PRIMARY CARE

Omeprazole, a proton pump inhibitor, should be considered as first choice in treating patients with heartburn in primary care. Cisapride was not effective. BMJ August 28, 1999; 319: 550-53

8-14 DIETARY SUPPLEMENTATION WITH N-3 POLYUNSATURATED FATTY ACIDS AND VITAMIN E AFTER MYOCARDIAL INFARCTION

Dietary supplementation with n-3 PUFA led to a clinically important and statistically significant benefit in patients who recently had a myocardial infarction. (Secondary prevention) The benefit occurred in patients already receiving up to date pharmacological interventions.

Vitamin E had no benefit. Lancet August 7, 1999; 354: 447-55

8-15 BRIEF ENCOUNTERS: Speaking With Patients

"The foundation of good medical care . . . is a comfortable, evolving relationship between patient and physician." For new physicians, learning this art requires a prolonged relationship with a role-model, then adapting the art to their own personalities and practices.

The editorialist recommends 4 books to aid in learning the art. Annals Int Med August 3, 1999; 131: 231-34

8-16 HYPOGLYCEMIA AND THE DECISION TO DRIVE A MOTOR VEHICLE BY PERSONS WITH DIABETES.

Persons with type 1 diabetes may not judge correctly when their blood glucose levels are too low to permit safe driving. Many continue to drive when they are aware of low levels. Health care workers should be aware of the possible dangers and so counsel patients. JAMA August 25,1999; 282: 750-54

8-17 AZITHROMYCIN IN CONTROL OF TRACHOMA

Community-wide treatment with oral azithromycin markedly reduced C trachomatis infection and clinical trachoma in endemic areas. Oral treatment may have advantages over topical ointment. Lancet August 21, 1999; 345: 630-35

8-18 ORAL CORTICOSTEROIDS IN PATIENTS ADMITTED TO HOSPITAL WITH EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

The data support the current practice of prescribing low-dose oral corticosteroids to all patients with non-acidotic exacerbations of COPD who require hospitalization. Lancet August 7, 1999; 354: 456-60

8-19 LONG-TERM CLINICAL EFFECTIVENESS OF GRASS-POLLEN IMMUNOTHERAPY

Immunotherapy for grass-pollen allergy induced prolonged clinical remission which continued for at least 3 years after discontinuation of therapy. NEJM August 12, 1999; 341: 468-75

8-20 IMMUNOTHERAPY FOR ALLERGIC RHINITIS

Immunotherapy continues to be an attractive therapeutic option for selected patients because it provides benefits that cannot be achieved with pharmacotherapy. NEJM August 12, 1999; 341: 522-24

8-21 DRUG TREATMENT OF LIPID DISORDERS

This review discusses mechanisms of atherogenesis; target serum lipoprotein concentrations above which diet and drug therapy should be initiated; dietary treatment; drug treatment (statins, bile-acid-binding resins, nicotinic acid, fibrates); and other therapies (fiber, sitostanol, n-3 fatty acids, estrogen). NEJM August 12, 1999; 341: 498- 511

8-22 AN INTRODUCTION TO BAYESIAN METHODS IN HEALTH TECHNOLOGY ASSESSMENT.

The authors suggest a definition of the Bayesian method: "The explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation, and reporting of a health technology assessment." BMJ August 21, 1999; 508-12

8-23 DISSEMINATED INTRAVASCULAR COAGULATION

This article reviews incidence, associated causal clinical conditions, pathogenesis, diagnosis, clinical relevance, prognosis, and management. NEJM August 19, 1999; 341: 586-92

8-24 PARTNERSHIP FOR GOOD DYING

A 52-year old woman facing death from metastatic adenocarcinoma of the lung wrote this editorial. After receiving the usual surgery, chemo, and radiation, and had been offered a complementary health regimen, she decided not to try any longer "to beat cancer and live". It didn't work.

She now comments on her acceptance of death and physicians' role in the dying process of their patients. JAMA August 18, 1999; 282: 615-16

8-25 PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

For those who would enjoy a comprehensive view of therapy. Annals Int Med August 17, 1999; 131: 281-303

8-26 PATIENTS' PERCEPTIONS OF INTENSIVE CARE

Reflections of patients surviving intensive care. Lancet August 14, 1999; 354: 571-72

REFERENCE ARTICLES

RECOMMENDED READING

==========

8-1 POPULATION BASED STUDY ON SOCIAL AND PRODUCTIVE ACTIVITIES AS PREDICTORS OF SURVIVAL AMONG ELDERLY AMERICANS

Some studies have shown a link between activity levels and survival, presumably due to improved cardio-pulmonary fitness. The authors of this study suggested that, while physical fitness is important and clearly related to health and survival, an exclusive focus on physical activity obscures health benefits which may be associated with non-physical activities. They examined the relation between three types of activity on survival: 1) social, 2) productive, and 3) fitness.

Conclusion: Social engagement and productive activities which may involve little enhancement of fitness lowered risk of all cause mortality.

STUDY

1. Prospective cohort study collected data by structured interviews on over 2700 men and women (all over age 65) selected randomly beginning in 1982 and repeated annually for 8 years.

2. Assessed 3 types of activity: 1) Social — church attendance, visits to theater, dining out, sporting events, trips, playing games and cards, participation in social groups. 2) Productive — gardening, cooking, shopping, community service. 3) Fitness — active sports or swimming, walking, physical exercise.

3. Determined mortality from all causes over 13 years of follow-up.

RESULTS

1. All 3 types of activity were *independently* associated with survival
2. The 3 activity types were only modestly correlated with each other. This suggests that they are relatively independent domains of activity.
3. Of the entire cohort, 62% died during follow-up. There was a clear mortality gradient across levels of activity for each type. The most active quarter socially and productively enjoyed the strongest survival advantage. The least active quarters were less likely to survive. Compared with the least active quarters, those in the most active quarters had the best prognosis:
    A. Productive activities — 35% less likely to die.
    B. Social activities — 20% less likely to die.
    C. Fitness activity — 19% less likely to die.
4. The effect of social and productive activities on mortality was strongest among the least physically active.

DISCUSSION

1. Social engagement and productive activity are essential features of successful aging.

2. More active elderly people were less likely to die than those who were less active. Social and productive activities conferred equivalent survival advantages compared with physical fitness activities. Activities that entail little or no physical exertion may be beneficial.

3. The investigators noted the possibility that activity levels measured at baseline were actually measuring health status in ways not otherwise controlled for. However, on further analysis, after elimination of those who died within the first 5 years of follow up the protective effects of social and productive activities remained consistent and significant.

4. Social contacts reduce the deleterious effects of psychological stress through enhancement of both cellular and humoral immune responses.

5. Clinicians might recommend a broader range of activity options for older people. For patients with chronic conditions such as arthritis, social acitivity may promote wellbeing more effectively than physical activity.

CONCLUSION

Social and productive activities that involve little or no enhancement of fitness lowered the risk of all cause mortality as much as physical fitness. Activities other than physical (which increases cardiopulmonary fitness) may confer survival benefits through psychosocial pathways. Social and productive activities that require less physical exertion may constitute alternative interventions for frail elderly people. An exclusive emphasis on physical fitness activity may be overly narrow.

BMJ August 21, 1999; 319: 478-83 Original investigation, first author Thomas A Glass, Harvard University School of Public Health and Social Behavior, Boston, Mass.

Comment:

This confirms the empirical observation many have made. Ie, "Use it or lose it". More involved persons remain healthier, and I suspect less subject to cognitive deterioration

Some elderly who are outgoing and involved at a younger age find it easy to continue social activities as they grow older. I suspect these individuals do have a survival advantage. The question is — will it be possible for the elderly who have been retiring, quiet, and introspective when they were younger to change to a more outgoing lifestyle? And would it provide a survival benefit if they successfully did so? I suspect it would be possible, and beneficial in a few. RTJ

==========

8-2 SOCIAL DISENGAGEMENT AND INCIDENT COGNITIVE DECLINE IN COMMUNITY-DWELLING ELDERLY PERSONS

(I abstracted this as a companion study to the preceding article. It carries the same message. — Editor)

This study followed over 2500 community-dwelling persons over age 65. At baseline determined the social engagement of the subjects, including presence of a spouse, monthly visual contact with 3 or more relatives or friends, yearly non-visual contact with 10 or more relatives or friends, attendance at religious services, group memberships, and regular social activities. These activities imply an active reciprocal connection between persons and their communities.

Assessed cognitive function at baseline by a Mental Status Questionnaire.

Followed for 12 years.

Compared with persons who had 5 or 6 social ties, those with no social ties were at increased risk for incident cognitive decline after adjustment for many possible confounding factors, including initial cognitive function and physical activity. At 12 years, the odds ratio of experiencing cognitive decline was approximately twice as great in the most disengaged group as in the most engaged group. No particular type of social connections or activities was essential for preserving cognition.

A hypothesis postulates that continued mental stimulation staves off cognitive deterioration in old age possibly by maintaining a critical density of neocortical synapses.

Annals Int Med August 3, 1999; 131: 165-73 Original investigation, first author Shari S Bassuk, Harvard School of Public Health, Boston Mass.

8-3 REDUCTION OF VERTEBRAL FRACTURE RISK IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS TREATED WITH RALOXIFENE

Raloxifene [*Evista*] binds to estrogen receptors and inhibits bone resorption. It is a selective estrogen receptor modulator **(SERM) —** an agonist possessing estrogen-like effects on bone and on serum lipids, but not on endometrium or breast.

This study assessed the effect of raloxifene on risk of fracture in postmenopausal women with established osteoporosis. (Secondary prevention.)

Conclusion: Over 3 years raloxifene increased bone mineral density and reduced risk of vertebral fractures.

STUDY

1. Multicenter trial entered over 7 500 women (mean age 67). All were at least 2 years post-menopause.
2. All met the WHO criteria for having osteoporosis according to their bone mineral density **(BMD),** or had vertebral fractures regardless of the BMD.
3. Randomized to: 1) 60 mg/d of raloxifene, 2) 120 mg /d of raloxifene, or 3) placebo.
4. In addition all received supplemental calcium and vitamin D.
5. Follow-up = 3 years.

RESULTS

6. Compared with placebo, raloxifene increased BMD of the spine by 2.6%.

7. At 3 years:

	Placebo	60 mg/d	120 mg/d
At least one new vertebral fracture	10.6%	6.6%	5.4%

3. Frequency of vertebral fracture was reduced in women who had no previous fractures, as well as those with fracture present at baseline:

A. Women with no fracture at baseline who developed a new fracture over 3 years:

Placebo	Raloxifene 60mg	Relative risk	NNT(benefit-3years)
4.5%	2.3%	0.5	46

B. Women who had fracture at baseline and developed a new fracture over 3 years:

21%	15%	0.7	16

(*Note the high risk of fracture over 3 years in untreated patients. Ed.*)

8. Adverse effects:

A. 10% withdrew from raloxifene treatment vs 9% of the placebo patients; only 0.6% withdrew because of hot flashes.

B. Venous thrombosis (raloxifene 1%; placebo 0.3%).

9. Benefit: Breast cancer (relative risk = 0.3). No excess risk of endometrial cancer or vaginal bleeding or breast tenderness.

DISCUSSION

1. Risk of vertebral fractures decreased by 50% treated by raloxifene for 3 years. This is comparable to results of treatment with alendronate [*Fosamax*] and transdermal estrogen.
2. Effect of BMD was about half that reported with alendronate therapy, although the reduction in vertebral fractures was similar.
3. Venous thrombosis was more common; breast cancer less common.

CONCLUSION

In postmenopausal women with osteoporosis, raloxifene increased BMD and reduced risk of vertebral fracture in postmenopausal women with osteoporosis. (Secondary prevention)

JAMA August 18, 1999; 282: 637-45 Original investigation by the Multiple Outcomes of Raloxifene Evaluation (MORE) study, first author Bruce Ettinger, Kaiser Permanente Medical Care Program, Oakland CA

Comment:

Preventive treatment, or at least delaying treatment, for osteoporosis has been a major advance in therapy over the past decade. It will enable older women to live more comfortably for a decade or more.

Choice between the several drugs available will depend on further comparisons, and the woman's preference after considering adverse effects and associated benefits. I believe, such therapy should be offered to all postmenopausal women. RTJ

==========

8-4 THERAPY FOR FRACTURE PREVENTION

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

The risk of new vertebral fractures was substantially reduced by raloxifene therapy.

"It may no longer be ethical to subject patients with previous fractures, whose risk of a new spine fracture is more than 5% per year to a 3- to 5-year interval of treatment with calcium and cholecalciferol alone."

Raloxifene seems a less potent anti-resorptive drug than estrogen or low-dose alendronate [*Fosamax*]. Despite the difference in BMD response, the absolute reductions in spine fracture frequency appear similar for alendronate and raloxifene.

Raloxifene was not more effective than calcium alone in reducing incidence of hip fractures. The editorialist believes that, until more definite comparisons are available, estrogen and bisphosphonates should remain the preferred therapy for patients deemed at risk of non-spine fractures.

The ultimate role of these drugs will depend on effects on heart disease and breast cancer.

JAMA August 18, 1999;282: 687-89 Editorial by Michael R McClung, Oregon Osteoporosis Center, Portland

==========

8-5 GLUCOSE TOLERANCE AND MORTALITY: Comparison of Who and American Diabetes Association Diagnostic Criteria

To review the criteria:

ADA (By fasting plasma glucose levels)

	mg/dL
Normal (fasting)	<110
"Diabetes" (fasting)	≥126

	WHO (By a 75 g oral glucose tolerance test)
	mg/dL
Normal (fasting)	< 140
Normal (2 hour)	<140
"Diabetes" 2-hour	≥200

(To convert to mmol/L multiply by 0.0555)

A. The ADA recommends a fasting plasma glucose **(FPG)** of 126 as the cut point to define "diabetes". The glucose tolerance test **(GTT)** is not required.

B. The WHO requires use of a 75 g oral GTT with a cut point of 200 mg/dL at 2 hours to define "diabetes".

The purpose of the diagnostic criteria is to identify individuals who have no symptoms of diabetes, but who have hyperglycemia and are, therefore, at increased risk of subsequent complications and mortality.

This study compared mortality associated with hyperglycemia in patients with diabetes defined by 1) the ADA cut point of fasting plasma glucose of 126 mg/dL vs 2) the WHO cut point of 200 2 hours after a 75 g glucose challenge.

Conclusion: Fasting glucose of 126 alone did not identify individuals at increased risk of death. The oral glucose tolerance test provided additional prognostic information and identified individuals who have a greater risk of death.

STUDY

1. Retrospectively assessed outcomes of over 25 000 persons (13 studies). All had received a standard 2-hour oral GTT at baseline.
2. Over a median follow-up of 7 years, compared rates of death of: 1) individuals with a FPG ≥ 126 with 2) those with a cutpoint of ≥200 at 2 hours post-glucose challenge, and 3) those with a normal FPG.

RESULTS

1. Hazard ratio of death by ADA criteria for "diabetes" (Fasting plasma glucose):

<110	1.00 (Reference)
≥ 126	1.8

2. Hazard ratio of death according to WHO criteria for "diabetes" (2-hour glucose tolerance):

< 140 fasting and < 140 2-hour	1.0 (Reference)
> 200 at 2-hour	2.02 for men
	2.77 for women

1. 3. Lesser degrees of glucose intolerance were also associated with increased risk of death.

A. By ADA criteria:	Hazard ratio compared with normal
Impaired fasting glucose (110-125)	1.21 for men
	1.08 for women

B. By WHO criteria: Hazard ratio compared with normal

Impaired glucose tolerance (2-hour 140-199) 1.53

4. Hazard ratios for death increased significantly with increasing 2 hour glucose concentrations.

DISCUSSION

1. The main reason to test for high glucose concentrations in persons who have no symptoms of diabetes is to prevent late complications of hyperglycemia.
2. A high glucose concentration 2 hours after a glucose load is associated with increased risk of death, independently of the fasting glucose.
3. Conversely, mortality associated with fasting glucose concentrations depends on the 2 hour glucose in all categories of fasting glucose.
4. Diagnostic criteria based solely on the fasting glucose are not the most appropriate to predict outcomes.
5. About 30% of persons with 2 hour post glucose-load concentrations >200 mg/dL have a normal fasting glucose; and 20% have fasting glucose levels of 110-125 (classified as impaired fasting glucose). These individual have increased risk of premature death.
6. Persons normoglycemic by both criteria have the best prognosis.
7. "The high number of excess deaths in the impaired glucose tolerance group (2 hour post load glucose 140-199) for whom preventive strategies are a possibility, provides further evidence for the usefulness of screening by the oral glucose tolerance test."
8. Many persons who are at increased risk cannot be identified by the fasting glucose alone. It is important to measure the postprandial glucose when screening.

CONCLUSION

Fasting glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycemia. An oral glucose tolerance test, measuring the 2-hour glucose, enables detection of individuals with impaired glucose tolerance, as well as diabetes, who have the greatest attributable risk of death.

Lancet August 21, 1999; 354: 617-21 original investigation by the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study group, correspondence to Jakko Tuomilehto National Public Health Institute, Helsinki, Finland.

Comment:

Fasting and post-prandial glucose concentrations measure different things:

Fasting glucose measures the metabolic state some 12 hours or so after the last glucose challenge. This enables return toward normal even in persons with abnormal glucose metabolism.

Post-prandial glucose concentrations measure levels within an hour or two after challenge, before glucose (in persons with abnormal glucose metabolism) can adequately dispose of the glucose.

HbA1c levels reflect the average 24-hour glucose concentrations. Therefore, the HbA1c levels may be higher in persons with abnormal 2-hour glucose concentrations than in persons with a normal fasting glucose who have abnormal tolerance. I believe measuring an after-meal glucose at about 2 hours is a reasonable and certainly more convenient screen. (*I read recently that 28 jelly beans supply about 75 g of glucose. Ed.*)

Adding measurement of HBA1c to glucose determinations will give a more accurate assessment of risk. If the HbA1c is within the reference range, risk of long-term complications is low.

The increased risk associated with *lesser* degrees of glucose intolerance gives clinicians and patients a golden opportunity to intervene at an earlier stage. Lifestyle measures will then be more effective in preventing future complications.

The benefit/risk-cost of glucose screening is high — one of the most productive screening applications. Benefits may be very high. Risks and costs are nil. RTJ

8-6 CARDIOVASCULAR DISEASE IN OLDER ADULTS WITH GLUCOSE DISORDERS: Comparison of American Diabetes Association Criteria for Diabetes Mellitus with WHO Criteria

(*This is a companion study to the preceding article. Editor*)

A cross-sectional prospective analysis of over 4500 participants was designed to identify factors related to the onset and course of cardiovascular disease in adults over age 64.

Calculated the prevalence of cardiovascular disease among individuals with impaired glucose concentrations or newly diagnosed diabetes by both ADA and WHO criteria.

There was only a modest correlation between the 2 sets of criteria:

	ADA	WHO
Normoglycemic	78%	53%
Impaired fasting glucose	14%	
Impaired glucose tolerance		32%
Newly diagnosed diabetes	8%	15%

About a third of those defined as normoglycemic by ADA had impaired glucose tolerance.

Six percent of those defined as normoglycemic by ADA had newly diagnosed diabetes by WHO.

One purpose for diagnostic criteria is to improve the ability to detect risks for disease complications, especially cardiovascular diseases. Which criteria are more appropriate for identification of glucose disturbances in the elderly?

The number of cases of cardiovascular disease attributable to abnormal glucose states by the ADA criteria was a third of that attributable to the WHO criteria (53 vs 159 cases per 10 000 over 6 years). Those classified as normal by ADA criteria were at higher risk of cardiovascular disease than those classified as normal by WHO. (Ie, the ADA criteria were less sensitive in predicting cardiovascular events than the WHO criteria.)

"If the purpose of screening for diabetes mellitus is to identify the maximum number of people at risk of cardiovascular disease events or death when glucose is slightly raised, then it would seem that the WHO criteria are superior to the fasting ADA criteria."

Lancet August 21, 1999; 354: 622-25 Original investigation, first author Joshua I Barzilay, Emory University School of Medicine, Atlanta, GA

8-7 NEW DIAGNOSTIC CRITERIA FOR DIABETES—Are They Doing What They Should?

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

The ADA and the WHO criteria do not identify the same groups of individuals. Among people with diabetes according to the ADA criteria, only 46% had a 2 hour post-glucose concentration that met the WHO criterion. And impaired fasting

glucose by ADA (glucose of 110-125) was present in only 48% of individuals classified as having impaired glucose tolerance by WHO (140-199).

The ADA criteria were much less sensitive than the WHO criteria in predicting CVD mortality (sensitivity 28% vs 54%).

The groups seem to differ phenotypically, with the impaired fasting glucose by ADA (110-125) more likely in the middle aged and obese.

Impaired fasting glucose by ADA (110-129) is not as sensitive as impaired glucose tolerance by WHO (140-199) in measuring lesser degrees of glucose intolerance.

"For people who advocate a switch towards the exclusive use of fasting glucose concentrations to define glucose tolerance, the findings of the DECODE study make worrying reading."

Macrovascular disease (cardiovascular disease) accounts for most of the excess mortality associated with type 2 diabetes. The relation between hyperglycemia and mortality from cardiovascular disease is complex. Glucose intolerance, defined as fasting or postprandial concentrations at the upper end of the normal distribution in population based studies is accompanied by increased prevalence of, and mortality from, cardiovascular disease. Postprandial, rather than fasting glucose, is a better prognostic indicator.

In the DECODE study, people with a normal fasting glucose (< 110) formed the group with the largest number of excess deaths. This group makes up a third of all men and half of all women with any degree of glucose intolerance. It should not be ignored.

Lancet August 21, 1999; 354: 610-11 Editorial by Melanie Davies, Leicester Royal Infirmary, Leicester, UK

Comment:

Many individuals with a normal fasting glucose level do indeed have glucose intolerance. I suspect that those with lower fasting levels (eg, 90) will be less likely to have glucose intolerance than those with fasting levels 105-110. We should be aware of the possible risks in patients with high normal levels.

==========

8-8 EFFECTS OF METFORMIN IN PATIENTS WITH POORLY CONTROLLED INSULIN-TREATED TYPE 2 DIABETES.

Because many persons with type 2 diabetes are overweight and insulin resistant, high doses of insulin are often required to achieve adequate glycemic control. Insulin is associated with weight gain which attenuates the expected improvement in glycemic control. It is now common to combine therapeutic agents that have complementary mechanisms of action for therapy of type 2 diabetes.

Metformin [*Glucophage*] , a biguanide, is approved for use alone or in combination with sulfonylureas. Its main mechanisms of action are: 1) to decrease hepatic glucose output, and 2) to improve peripheral insulin sensitivity. Some authorities recommend metformin as the drug of first choice in patients with type 2 diabetes who are obese.

Combining metformin with insulin may improve glycemic control and insulin sensitivity while avoiding weight gain. This study evaluated the efficacy of combined metformin/insulin in patients with type 2 diabetes who were poorly controlled by insulin alone.

Conclusion: The combination lowered HbA1c levels and reduced insulin requirements.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered 43 patients (mean age 54) with poorly controlled type 2 diabetes. All were already on insulin.
2. Randomized to: 1) metformin or 2) placebo. Insulin was continued.
3. Metformin dose was gradually increased up to 2000 mg/d
4. Insulin dosage was adjusted by an algorithm according to glucose monitoring, and reported hypoglycemia. Dose was decreased if fasting glucose was consistently less than 100 mg/dL, or if hypoglycemia less than 50 g/dL occurred.
5. Follow-up = 6 months.

RESULTS

1. Outcomes at 6 months	Metformin group (n=21)		Placebo group (n=22)	
	Baseline	Change from baseline	Baseline	Change
Weight in Kg	104	+0.5	107	+3
Insulin dose U/d	96	-4.5	97	+23
HbA1c	9%		9%	
Final mean HbA1c		6.5%		7.6%
Final insulin dose		92 U/d		120 U/d

DISCUSSION

1 The combination of insulin/metformin has been approved by the FDA.
2. HbA1c levels fell in the placebo group over 6 months. (Ie, increasing insulin dose resulted in better control although the regimen became more complex and resulted in weight gain.)
3. The target level for HbA1c was 5.6%. Neither group achieved the target. Metformin group came the closest. (*6.5% is a respectable goal. Ed.*)
4. Insulin requirements did not change in the metformin group.
5. The metformin group avoided weight gain.
6. Adverse effects of metformin related to the gi tract. They were usually transient and occurred at initiation and with an increase in dose. Gi side effects were also reported by the placebo group at about the same rate.
7. Hypoglycemic episodes were similar in both groups.

CONCLUSION

The addition of metformin to insulin in type 2 diabetics who were poorly controlled by insulin alone resulted in better glycemic control, with a substantial decrease in HbA1c. The combination allowed insulin dose to be reduced with no weight gain.

"Metformin is an effective adjunct to insulin therapy in patients with type 2 diabetes."

Annals Int Med August 3, 1999;131: 182-188 Original investigation, first author Larissa Aviles-Santa, University of Texas Southwestern Medical Center, Dallas.

Comment:

Type 2 diabetes is a progressive disease. As time goes on, requirements for insulin and oral drugs increase. Concomitant use of several oral drugs, withor without insulin is required for better control. RTJ

==========

REFERENCE ARTICLE

8-9 HAZARDOUS AND HARMFUL ALCOHOL CONSUMPTION IN PRIMARY CARE.

This review article defines alcohol use disorders ranging from heavy drinking, to hazardous drinking, to harmful drinking, to abuse, and on to dependence.

The authors recommend the *Alcohol Use Disorders Identification Test* **(AUDIT)** as currently the only instrument specifically designed to identify hazardous and harmful drinking. (*The 10-item AUDIT is reproduced on page 1686.*)

Hazardous drinking is defined as a pattern of alcohol consumption that places the individual at risk for adverse health out comes. The WHO recognizes it as a distinct disorder. The AUDIT defines an average consumption of 21 drinks a week, or more than 6 drinks per occasion at least 3 times a week for men; for women, 14 or more drinks per week or more than 4 drinks per occasion at least 3 times a week.

Harmful drinking is defined as alcohol consumption that results in physical or psychological harm, but does not meet the criteria for alcohol dependence.

Less severe drinking disorders, especially hazardous drinking, are common in the population.

Routine screening for hazardous and harmful drinking is recommended for all primary care patients.

The authors reiterate the effectiveness of brief physician counseling sessions. These can be administered over multiple visits.

Archives Int Med August 9/23, 1999; 159: 1681-89 Review Article, first author M Carrington Reid, V A Connecticut Healthcare System, West Haven.

==========

8-10 GEMFIBROZIL FOR THE SECONDARY PREVENTION OF CORONARY HEART DISEASE IN MEN WITH LOW LEVELS OF HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

About 40% of patients with coronary heart disease **(CHD)** have LDL-cholesterol **(LDL-c)** levels below 130 mg/dL (3.4 mmol/L). Most of these people also have low levels of HDL-cholesterol **(HDL-c)** , with or without increased levels of triglycerides.

Overall, low levels of HDL-c without high levels of LDL-c characterize up to 30% of patients with CHD.

Low HDL-c levels are strongly and independently associated with risk of CHD.

This study hypothesized that raising HDL-c levels and lowering levels of triglycerides would improve prognosis in men with established CHD who have low levels of both LDL-c and HDL-c. (Secondary prevention.)

Fibric acid derivatives (eg, gemfibrozil — *Lopid*; generic) are the most likely agents to improve HDL-c and triglyceride levels, while having the least effect on LDL-c.

Conclusion: Gemfibrozil therapy reduced risk of major cardiovascular events in these patients.

STUDY

Double-blind trial entered over 2500 men (mean age = 64) who had a documented history of CHD.

At baseline, all had a HDL-c level of 40 mg/dL or less (mean = 32 mg/dL) and an LDL-c of 140 mg/dL or less (mean = 112 mg/dL). Triglyceride mean = 160 mg/dL.

Many patients were taking aspirin, nitrates, calcium blockers, ACE inhibitors, and beta-blockers. No mention of statin drug use.

Randomized to: 1) gemfibrozil 1200 mg daily, or 2) placebo.

Follow-up = 5 years.

RESULTS

At 1 year, mean HDL-c was 6% higher in the treatment group than in the placebo group (34 mg/dL vs 32 mg/dL); and mean triglyceride levels 31% lower (115 vs 166). Mean LDL-c levels remained unchanged from baseline and did not differ significantly between groups.

Over 5 years, non-fatal myocardial infarction and death from coronary disease (the primary outcome) occurred in 22% of the placebos group vs 17% of the gemfibrozil group. Overall reduction in risk = 4.4%. [NNT(benefit-5 years) = 23]

The benefit of gemfibrozil did not become apparent until about 2 years after randomization.

In the treatment group a significant reduction occurred in transient ischemic attacks (59%) and carotid endarterectomy (65%)

Gemfibrozil was generally well tolerated. At 5 years 71% of patients assigned were still taking the drug. It is inexpensive. It may prove highly cost effective.

DISCUSSION

2. The study suggests that raising HDL-c and lowering triglyceride levels, even if LDL-c is not reduced, reduces major coronary events in patients with CHD whose primary lipid abnormality is a low HDL-c.
3. The Helsinki Heart Study, a primary prevention trial with gemfibrozil suggested that an 8% increase in HDL-c would be expected to result in a 23% reduction in major cardiac events.
4. Gemfibrozil has favorable effects on decreasing the fraction of dense LDL particles (more oxidizable particles which increase risk) and improving clearance of triglyceride rich lipoproteins.
5. This and other secondary prevention trials give clinicians the data necessary to provide evidence based lipid therapy for individual patients according to their predominant lipid abnormality. For patients with moderate or high levels of LDL-c statin drugs effectively reduce incidence of major coronary events. “It is uncertain, however, whether statins are beneficial for patients with LDL cholesterol levels of less than 130 mg per deciliter.” For such patients who also have a low HDL-c, gemfibrozil therapy is associated with a significant reduction in risk of major cardiovascular events.
6. Raising HDL cholesterol levels and lowering triglyceride levels without lowering LDL-cholesterol may reduce rate of coronary events.

CONCLUSION

For secondary prevention in patient with demonstrated coronary heart disease whose primary lipid abnormality is a low HDL-c level (a finding commonly occurring in the context of central obesity, diabetes, and other features of the metabolic syndrome), gemfibrozil effectively prevented recurrence of myocardial infarction and death from coronary heart disease.

NEJM August 5, 1999; 410-18 Original investigation form the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group, first author Hanna Bloomfield Rubins, VA Medical Center, Minneapolis, Minn.

Comment:

The baseline LDL-c levels were remarkably low in a group with established CHD, especially considering statin drugs were not used. Statins probably would have reduced the LDL-c levels in this group of patients, and increased HDL-c and lowered triglycerides about as much.

The study's main message is a good one — raising HDL-c is important in reducing risk. I believe, however, that in this group lowering the LDL-c to below a mean of 112 would have increased benefits despite the statement by the authors that lowering LDL-c levels below 130 may not benefit.

Statins in secondary prevention may be preferred even in those with low HDL-c levels.

Study supported in part by Parke-Davis RTJ

REFERENCE ARTICLE

8-11 CHOLESTEROL LOWERING IN THE ELDERLY POPULATION

Smoking, hypertension, and diabetes remain major risk factors for coronary heart disease **(CHD)** in the elderly. Does high serum cholesterol continue to elevate the risk of CHD in the old as it does in younger persons.

This article reviews the available evidence related to this issue.

Conclusion: The National Cholesterol Education Program emphasizes the need to include the elderly (age 75-80+) in clinical management of high cholesterol. The elderly carry the highest risk for CHD and the highest burden of atherosclerotic heart disease.

Clinical trials of statin therapy indicate similar benefit in older and younger patients.
Because of the similar pathologic process of coronary atherosclerosis in middle-aged and older patients, the extrapolation of clinical trial data from the middle-aged patient to the elderly patient seems warranted.

For *secondary* prevention in the elderly who have established CHD, aggressive lowering of cholesterol seems fully justified. Inclusion of high risk old persons without clinical manifestations of CHD is also justified. In addition to the life-style measures, drug therapy can also be considered for elderly patients at highest risk.

Archives Int Med August 9/23 1999; 159: 1670-78 "Special Article" from the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, Bethesda MD. First author Scott M Grundy.

Comment:

Several years ago, I advised elderly patients not to be concerned about their cholesterol. (Some were unduly concerned.) I believed that, after a certain age, the benefit/harm-cost ratio of dietary and drug therapy would be low. Why not encourage the elderly to freely eat what they most enjoy? Why subject them to the cost, and possible adverse effects of drugs? My belief was based on the older view of pathogenesis of coronary atherosclerosis and coronary heart disease. "Heart attacks" were caused by large infiltrates of cholesterol-filled endothelium which almost occluded the lumen, on which thrombi wee likely to form due to hemodynamic factors. The process was only slowly progressive. Even the most rigorous therapy would do no more than prevent progression of the lesions, or at moat lead to slight regression. This would require 5 to 10 years of therapy. Since the remaining years of life were few, and co-morbidity high, therapy seemed of little benefit.

The new pathogenesis changed my thinking. Most myocardial infarctions occur because of disruption of an endothelial plaque which is not occlusive. The plaque ruptures and thrombosis forms on top of the rupture. This is the cause of the occlusion and the myocardial ischemia. Therapy is not directed at reduction in size of the cholesterol infiltrate, but at stabilizing the plaque. Stabilization is aided by lipid control and takes far less time — 1 to 2 years.

Thus, a subset of elderly who have established CHD, or are at high risk and have no serious co-morbidity, and a reasonably long projected life span, the benefit/harm-cost of therapy for lipid control may be high. RTJ

==========

8-12 A PROSPECTIVE STUDY OF WALKING AS COMPARED WITH VIGOROUS EXERCISE IN THE PREVENTION OF CORONARY HEART DISEASE IN WOMEN

Earlier guidelines recommended vigorous endurance exercise for at least 20 minutes three of more times a week. Recently, prestigious organizations have endorsed at least 30 minutes of moderate intensity physical activity on most, preferable all, days of the week.

This study assessed comparative effects of walking and vigorous exercise in the prevention of coronary events in a large cohort of women.

Conclusion: Brisk walking was associated with reductions in coronary events similar to the reductions associated with vigorous exercise.

STUDY

1. Prospectively examined the association between scores of walking and vigorous exercise and the incidence of coronary events among over 72 000 women age 40 to 65 (mean = 52) in 1986.
2. All were free of diagnosed cardiovascular disease at baseline. All completed serial detailed questionnaires about physical activity.
3. Physical activity was calculated in METS expended in walking and other physical activities per week. (One MET is the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram per hour at rest.) Brisk walking for an hour equals about 3 MET-hours. Brisk walking for 1/2 hour a day for 7 days would add up to about 7 MET-hours. Vigorous exercise for the same time would equal about 35 MET-hours

7. 4. Follow-up = 8 years.

RESULTS

1. Over 8 years documented 645 non-fatal myocardial infarctions and deaths from coronary disease.
2. There was a strong, graded *inverse* association between physical activity and risk of coronary events.
3. Compared with sedentary women, those expending 7 MET hours per week by walking briskly had a relative risk (RR) of 0.65 for coronary events. Women expending over 21 METs per week had a RR of 0.46.
4. Sedentary women who became active in middle or later life had a lower risk than women who remained sedentary.[1]
5. Even for women who smoked, brisk walking was associated with a lower risk than for women who smoked and remained sedentary. RR = 0.86

8. 6. Women who walked at an average pace (2.5 miles per hour) had a RR of 0.75 compared with women who walked at a casual pace (< 2 miles per hour). Women who walked briskly > 3 miles per hour had a comparative RR 0f 0.64.
9. 7."We did not observe a greater magnitude of risk reduction with vigorous exercise than with walking in this cohort when we compared those who walked with those who exercised a similar number of MET-hours per week."

DISCUSSION

1. Both walking and vigorous exercise were associated with substantial reductions in the incidence of coronary events.
2. The magnitudes of risk reduction associated with brisk walking and vigorous exercise were similar when the total expenditures were similar.
3. "Our results suggest that . . .brisk walking for three or four hours per week could reduce the risk of coronary events in women by 30 to 40 percent."
4. "One third of coronary events among middle aged women in the United States are attributable to physical inactivity."

5 The substantial reduction in risk among women who increased their activity level in later life, as compared with women who remained sedentary, suggests that risk can be modified through increased activity.

CONCLUSION

Both walking and vigorous exercise were associated with substantial reductions in the risk of coronary events. There was a strong, graded inverse relation between energy expenditure, either walking or vigorous exercise and the incidence of coronary events. Risk was reduced equally in women who walked briskly for at least 3 hours per week and women who exercised vigorously for 1.5 hours per week.

Enormous public health benefits would accrue from the adoption of moderate intensity exercise by those who are currently sedentary.

NEJM August 26, 1999; 650-58 Original investigation based on the Nurses' Health Study, first author JoAnn E Manson, Channing Laboratory, Harvard Medical School, Boston Mass.

Comment:

The authors state that over 40 epidemiological studies have addressed the relation between exercise and coronary disease. *Practical Pointers* has abstracted some of them. The clinical application is important.

Primary care physicians should take every opportunity to encourage physical activity for their patients — and set their own example. It is comforting to know that it is never too late to start.

Modest exercise, as in brisk walking, can reduce risk as much as vigorous exercise, but requires a longer time spent in the activity.

Of interest — even persons who have risk factors they cannot or will not remove (eg, smoking) will benefit from exercise.

==========

8-13 HEARTBURN TREATMENT IN PRIMARY CARE

Omeprazole [*Prilosec*], a proton pump inhibitor, has been used successfully in patients with gi-reflux disease. A prokinetic agent (eg, cisapride [*Propulsid*]) could represent an alternative treatment.

This study compared omeprazole with cisapride for treatment of heartburn.

Conclusion: Omeprazole was highly effective; cisapride was no more effective than placebo.

STUDY

1. Randomized, placebo-controlled, double-blind multicenter trial entered over 450 patients (median age 48) with heartburn.
2. Symptoms were present over 3 days a week in all patients. Heartburn was present every day in 50% of subjects and interfered with daily activities in more than 75%. The majority had other gi complaints as well.
3. Endoscopy performed in all. Patients with severe esophagitis were excluded.
4. Randomized to: 1) omeprazole 20 mg once daily, or 2) cisapride 20 mg twice daily or 3) placebo.
5. Follow-up = 8 weeks.

RESULTS

10.1. Adequate control of heartburn (defined as ≤ one day with no more than mild heartburn in the 7 days before the 4-week visit) was achieved in 71% of those taking omeprazole; in 22% of cisapride group; and 18% of the placebo patients.

11.2.Antacid use was 2 to 3 times greater in groups 2) and 3) than in group 1).

12.3. Significantly more patients in the cisapride group reported adverse effects.

13.4. Of interest — in patients taking omeprazole, symptom control was achieved more often in those positive for *H pylori.* (86% vs 65%). (*The authors made no further comment on this point. I do not know what to make of it. Ed.)*

14.5. Improvement in belching, epigastric pain, and regurgitation was significantly greater in the omeprazole group.

DISCUSSION

1. For young individuals with typical heartburn and absence of alarm symptoms, treatment on basis of symptom evaluation and treatment response is justifiable.
2. In the authors' experience, advice on diet, smoking cessation, and raising the head of the bed are often inadequate to control symptoms.
3. Cisapride increases lower esophageal sphincter resting pressure, and improves gastric emptying. "Low lower esophageal sphincter pressure and delayed gastric emptying may be uncommon in primary care patients."

CONCLUSION

Omeprazole should be considered as first choice in treating patients with heartburn in primary care. Cisapride was not effective.

BMJ August 28, 1999; 319: 550-53 Original investigation, first author Jan G Hatlebakk, University of Bergen, Norway.

8-14 DIETARY SUPPLEMENTATION WITH N-3 POLYUNSATURATED FATTY ACIDS AND VITAMIN E AFTER MYOCARDIAL INFARCTION

A diet rich in fish oils (n-3 polyunsaturated fatty acids — n-3 PUFA) derived from marine vertebrates, has been reported to protect against cardiovascular disease ever since 1976. Vitamin E (an anti-oxidant) has also been reported to be protective.

Controlled trials have reported conflicting evidence of benefits.

This trial assessed the independent and combined effects of n-3 PUFA and vitamin E on morbidity and mortality after myocardial infarction (secondary prevention).

Conclusion: Supplements of n-3 PUFA led to clinically important benefits. Vitamin E had no benefit.

STUDY

1. Multicenter trial entered over 11 000 patients who survived recent (within 3 months) myocardial infarction (MI). Continued recommended preventive treatments: aspirin, beta-blockers, ACE inhibitors. Statins were not supported by definitive data when the trial was started.
2. Randomized to: 1) supplements of N-3 acids (1 g daily) [1] ; 2) vitamin E 300 mg daily [1] ; 3) both; or 4) neither (controls).
3. Primary endpoint — combined death, non-fatal MI, and stroke.
4. Follow-up = 3.5 years

RESULTS

1. N-3 acids were associated with a 14% lower risk of the primary end-point and a 20% lower risk of fatal events. All the benefit was attributable to a decrease in risk of overall death and cardiovascular death.

2. Vitamin E had no benefit compared with controls.

DISCUSSION

1. Results obtained with n-3 acids are consistent with the DART study [2] which reported a 29% decrease over 2 years in overall mortality in men who ate fatty fish twice a week. The results with vitamin E did not support the strong epidemiological evidence of benefit available at the beginning of the trial.

2. This regimen of n-3 acids corresponds to a diet which contains a large amount of fatty fish — 100 g daily.

3. The dose of vitamin E used (300 mg/d — 200 tablespoons of olive oil) is much higher than currently recommended dietary allowances.

4. The population of patients in the study already had Mediterranean dietary habits and were treated with up to date preventive pharmacological interventions.

CONCLUSION

Dietary supplementation with n-3 PUFA led to a clinically important and statistically significant benefit in patients who recently had a myocardial infarction. (Secondary prevention) The benefit occurred in patients already receiving up to date pharmacological interventions.

Vitamin E had no benefit.

Lancet August 7, 1999; 354: 447-55 original investigation by the Gruppo Italiano per lo Studio della Sopravivenza nell'infarto Myocardico" — correspondence to Roberto Marchioli, Consorzio Mario Negri Sud, Imbaro, Italy

1. Eicosapentaenoic acid and docosahexaenoic acid; synthetic alpha tocopherol.

2. "Effects of changes in fat, fish, and fibre intakes on death and myocardial infarction: Diet and Reinfarction Trial (DART)" *Lancet* 1993; 328: 1450-56

Comment:

The results may be clinically important. Perhaps fish oils do work. But are they "worth it"? Is this clinically applicable to therapy in the US? I doubt that many patients would comply over a period of years, particularly since other measures (eg, statin therapy) are effective secondary prevention.

The study does support dietary habits that include more fatty fish.

The anti-oxidant hypothesis seems to be loosing steam. RTJ

REFERENCE ARTICLE

8-15 BRIEF ENCOUNTERS: Speaking With Patients

"The foundation of good medical care . . . is a comfortable, evolving relationship between patient and physician." For new physicians, learning this art requires a prolonged relationship with a role-model, then adapting the art to their own personalities and practices.

With the shift from physician paternalism to patient autonomy, renewed attention has been turned to the study of the patient-physician encounter. An examination of what happens in this encounter, and how it can be studied, taught, and learned, is of major importance.

The editorialist cites 4 books published in the past 12 years which address the issues of the changing nature of the patient-physician relationship:

Encounters between Patients and Doctors: An Anthology J D Stoekle, editor. MIT Press, Cambridge, Mass. 1987

The Medical Interview: A Primer for Students of the Art J L Coulehan, F A Davis, Philadelphia 1991

The Medical Interview: The Three-Function Approach S A Cohen-Cole Mosby-Year Book St Louis 1991

The Medical Interview: Clinical Care, Education, and Research. Springer-Verlag, New York 1995

The editorialist comments briefly on each book.

The interaction between patient and physician is bi-directional. Over time it can influence the relationship and the behavior of both participants.

Annals Int Med August 3, 1999; 131: 231-34 "Medical Writings" commentary by John A Balint, Albany Medical Center, New York.

Comment:

I have not read any of these books. However, on the basis that it is never too late to improve the art of connecting to, and listening to patients, I will look forward to reading at least one. It would be a good suggestion for your spouse when he/she asks — what would you like for your birthday? RTJ

8-16 HYPOGLYCEMIA AND THE DECISION TO DRIVE A MOTOR VEHICLE BY PERSONS WITH DIABETES.

Driving performance, as determined by using a driving simulator, deteriorates significantly when the blood glucose **(BG)** level is reduced to between 65 mg/dL and 47 mg/dL.* Even at these mild to moderate BG levels of hypoglycemia, steering was disrupted resulting in swerving, spinning, and increased time across the midline and off the road. On the simulator, global driving performance was impaired in about 1/3 of subjects with type 1 diabetes.

This study examined type 1 diabetic subjects' decisions to drive during their daily routine based on: 1) the subjects' perception of their BG levels, and 2) the actual measurements of BG

Conclusion: Persons with type 1 diabetes may not judge correctly when their BG is too low for safe driving.

STUDY

1. The investigators developed a hand-held computer to record data on symptoms, cognitive function, insulin dosage, food intake, activity, and estimated and actual BG levels
   (Actual BG measured by a glucose monitor.)
2. Entered 150 drivers (mean age 39) with type 1 diabetes (mean dose of insulin = 40 U/d).
3. Data were entered 3 to 6 times daily during a 3 to 4 week period.

RESULTS

1. Subjects stated they would drive over 40% of the times when they estimated their BG to be between 40 and 60.
2. About half of subjects decided to drive at least half of the times when their actual BG was less than 70 mg/dL.

DISCUSSION

1. Almost half of the time subjects with type 1 diabetes who estimated their BG to be in a range previously shown to be associated with deterioration in driving performance continued to drive.

2. Up to a third of the time subjects decided they would drive even though they estimated their BG to be dangerously low (< 40 mg/dL)
3. An accurate BG level determined by a glucose monitor did not guarantee that detection of a low BG would deter subjects from driving.
4. "These data should not be construed to mean that individuals with type 1 diabetes should not be permitted to drive, or that their privilege to drive should be restricted. Indeed, compared with non-diabetic persons, the frequency of motor vehicle crashes is not known to be higher among persons with type 1 diabetes." [1]
5. Persons with type 1 diabetes need to be cautious about driving. "The suggestion that individuals measure their BG and raise potentially low BG levels prior to driving does not seem unreasonable."
6. Drivers with diabetes should always carry rapid-acting glucose with them and plan their journeys to ensure that they will not be late for a meal.
7. Health care professionals should discuss safe driving practices with these patients.

CONCLUSION

Persons with type 1 diabetes may not judge correctly when their blood glucose levels are too low to permit safe driving. Many continue to drive when they are aware of low levels. Health care workers should be aware of the possible dangers and so counsel patients.

JAMA August 25,1999; 282: 750-54 Original investigation, first author William L Clarke, University of Virginia, Charlottesville.

1. Intuitively, impaired driving would be more likely in drivers who developed effects of hypoglycemia suddenly. I would be uneasy sitting as a passenger with such a driver.

This recalls risks of driving when drinking, and among patients with Alzheimer's disease.
Previous studies of Navy pilots reported that, a single alcoholic drink impairs high-tech performance.
Patients with Alzheimer's raise serious questions about driving — when and how to confront demented persons who insist on continuing to drive pose difficulties to both family and physician. The physician and family should act in concert to advise the patient. If the patient continues to drive, the physician should issue her or him a specific written prescription — "Do not drive". RTJ

(* To convert to mmol/L multiply by 0.0555)

==========

8-17 AZITHROMYCIN IN CONTROL OF TRACHOMA

Chlamydia trachomatis is is the world's leading cause of preventable blindness.

Programs to control trachoma are based on community-wide treatment with topical tetracycline. However the infection often rapidly re-emerges after topical treatment of active cases is discontinued.

Oral antibiotics are more effective since *C trachomatis* infects sites other than the conjunctiva — nasopharynx, throat, and rectum.

Azithromycin [*Zithromax*], a macrolide of the erythromycin family, is highly effective as single-dose oral therapy for genital chlamydial infections. It concentrates in cells, has a long half life, and offers an opportunity for better control of trachoma.

This study was carried out in villages in Egypt, The Gambia, and Tanzania, where trachoma is endemic.

Conclusion: Community-wide treatment markedly reduced infection and clinical trachoma.

STUDY

1. Randomized children and adults beyond childbearing age to: 1) oral azithromycin (3 doses at intervals of one week), or 2) 1% topical tetracycline ointment once daily for 6 weeks.
2. Dose of azithromycin — 1 g tablets for adults; for children an oral suspension, dose depending on weight–- 20 mg/kg.
3. Conducted clinical examinations at baseline and for up to 1 year.
4. Identified *C trachomatis* by ligase chain reaction.

RESULTS

1. About 30% of subjects with no active disease were positive for *C trachomatis.*
2. At 4 weeks, of persons initially positive for *C trachomatis* who received at least one dose of azithromycin, 95% were negative at follow-up vs 82% of those receiving topical tetracycline. Efficacy of azithromycin was greater in all 3 sites.
3. There was a greater reduction in clinical activity of trachoma after azithromycin than after tetracycline. (Although the study was aimed at prevention, not treatment, some treatment benefit was noted, especially in severe inflammatory disease in children under age 10.)

DISCUSSION

1. In light of its ease of once-weekly oral administration compared with daily topical tetracycline, azithromycin can play an important part in trachoma control.
2. A community-wide treatment approach is necessary. Good compliance can be achieved with the azithromycin regimen.
3. In some villages there may be resistance to treatment, mostly by men, because they have little personal perception of disease and the topical treatments blurred their vision. Nonetheless, infection rates fell during the period of observation. This was likely because infections in adults are likely to be short-lived, and aggressive treatment of the rest of the village, including children, who are the main reservoir, protected the men from reinfection.

CONCLUSION

Community-wide treatment with oral azithromycin markedly reduced *C trachomatis* infection and clinical trachoma in endemic areas. Oral treatment may have advantages over topical ointment.

Lancet August 21, 1999; 345: 630-35 Original investigation first author Julius Schachter, University of California, San Francisco.

8-18 ORAL CORTICOSTEROIDS IN PATIENTS ADMITTED TO HOSPITAL WITH EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

Guidelines for treating exacerbations of COPD have recommended clear indications for antibiotics and bronchodilators, but state that the use of oral corticosteroids is based on common practice, and is not evidence based.

When given to stable COPD patients, systemic cortocosteroids significantly increase FEV1 in only 10% of cases. Continued use is associated with corticosteroid myopathy.

This study assessed the role of oral corticosteroids in treating severe exacerbations of COPD. Conclusion: The data support use of low-dose corticosteroids.

STUDY

1. Recruited 56 patients (mean age 67) hospitalized with non-acidotic exacerbations. All had history of increasing breathlessness and combinations of increased frequency of cough, increased sputum volume or purulence, and increased wheeze.
2. All had a history of at least 20 pack-years cigarette smoking. (Mean = 55 pack-years)
3. At entry all had a FEV1 less than 70% predicted (mean = 25% before bronchodilation) and a FEV1/forced vital capacity ratio less than 75%.
4. All received conventional treatment including combinations of: inhaled beta-agonists, inhaled anticholinergics, inhaled corticosteroids, oral theophyllins, and oxygen. Almost all received antibiotics.
5. Randomized to: 1) oral prednisone 30 mg once daily, or 2) placebo

RESULTS

1. FEV1 *before* bronchodilation rose from 27% to 38% in the treated group — vs 21% to 31% in the placebo group. FEV1 *after* bronchodilation increased more rapidly in the treated group, rising from
2. Up to day five of hospital stay, FEV1 after bronchodilation increased by 90 mL daily — vs 30 mL daily in the placebo group
3. Hospital stays were shorter in the treated group — 7 days vs 9 days.
4. There were no differences between groups at 6 weeks.
5. Visual analogue scale scores indicated improvement in symptoms in both groups, with a trend toward greater improvement in the treated group.

DISCUSSION

1. Patients in this study were physiologically more severely affected and had worse health status than in other studies.
2. “We found significant differences in the rate of improvement in FEV1 before and after bronchodilation compared with placebo.”
3. Symptom improvement was greater in the corticosteroid group, but did not reach statistical significance.
4. The initial benefit of the corticosteroids did not extend beyond the early stages of recovery from the exacerbation.
5. No simple clinical indicator reliably distinguished responders from non-responders to the corticosteroids.

CONCLUSION

The data support the current practice of prescribing low-dose oral corticosteroids to all patients with non-acidotic exacerbations of COPD who require hospitalization.

Lancet August 7, 1999; 354: 456-60 Original investigation, first author L Davies, University of Liverpool, UK

Comment:

Recent studies have also reported benefit from inhaled corticosteroids, but only in a small minority.
Short-term oral corticosteroids do help COPD patients over the hump of an acute exacerbation. The benefit is transient. RTJ

8-19 LONG-TERM CLINICAL EFFECTIVENESS OF GRASS-POLLEN IMMUNOTHERAPY

Topical nasal corticosteroids and the newer non-sedating antihistamines are highly effective in treating hay fever (HF—IgE-mediated seasonal allergic rhinitis). Some patients respond poorly to these therapies. Immunotherapy (IT) is currently recommended for this group.

A previous study by these authors[1] demonstrated usefulness of IT in severe summer HF not controlled by drugs.

The present study asks: Does benefit persist after discontinuation of IT?

Conclusion: Benefit persists.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered 32 patients with severe HF
2. All had received IT for 3 to 4 years. It had been beneficial.
3. Randomized to: 1) discontinuation of IT, or 2) continued maintenance IT.
4. Followed 3) a third group of additional control patients who had not received IT
5. Follow-up = 3 years.

RESULTS

1. Use of rescue antiallergic medication (including prednisone) and scores of seasonal symptoms remained low in both groups 1) and 2).
2. No significant differences between the groups 1) and 2).
3. Symptom scores remained high in group 3).
4. A sustained reduction in objective measures of outcome occurred in both group 1) and 2) — [infiltration of T cells; T-cell derived cytokines].

DISCUSSION

1. Three to 4 years of IT remained effective for at least 3 years *after discontinuation* of the therapy.
2. The efficacy of grass-pollen IT in patients with seasonal HF has been confirmed in many controlled trials. IT is also effective, although less so, in patients with seasonal asthma.
3. In contrast, patients with perennial disease associated with sensitivity to multiple allergens are less responsive.
4. "Selection of patients is extremely important; the risk-benefit ratio is less favorable in patients with asthma than for those with allergic rhinitis. The rational for prescribing allergen immunotherapy depends on the degree to which symptoms can be alleviated by medication, and whether effective avoidance of the allergen is possible."

CONCLUSION

Immunotherapy for grass-pollen allergy induced prolonged clinical remission which continued for at least 3 years after discontinuation of therapy.

NEJM August 12, 1999; 341: 468-75 Original study, first author Stephen R Durham, Imperial College School of Medicine, London.

1. "Usefulness of Immunotherapy in Patients with Severe Summer Hay Fever Uncontrolled by Antiallergic Drugs" BMJ 1991; 302: 265-69

8-20 IMMUNOTHERAPY FOR ALLERGIC RHINITIS

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

Immunotherapy continues to be an attractive therapeutic option for selected patients because it provides benefits that cannot be achieved with pharmacotherapy. It is a specific antidote for allergen-specific immune responses. It is devoid of systemic toxic effects other than the risk of acute allergic reactions to the injections. Local swelling and tenderness may occur.

The study provides evidence that immunotherapy has long-term, and perhaps permanent, benefits. Interestingly, some patients who have excellent clinical results with immunotherapy are reluctant to stop treatment, even when it is reasonable to do so.

What about therapy for asthma? A recent study in children with moderate to severe asthma found no overall benefit when immunotherapy was added to pharmacotherapy and environmental measures. There was a trend for benefit in younger children and those with less severe disease. Patients with asthma are at greater risk for systemic allergic reactions to the vaccine than those with rhinitis. Most fatal allergic reactions to immunotherapy have occurred in patients with asthma. The editorialist states that, because of the increased risk and lack of readily demonstrable benefits in patients with moderate-severe asthma, such patients should not receive immunotherapy.

Immunotherapy works best when environmental controls are first implemented to minimize exposure to allergens, especially in the home. If patients sensitive to animal dander are unwilling to banish pets, immunotherapy may be a waste of time and money.

NEJM August 12, 1999; 341: 522-24 Editorial by N Franklin Adkinson, Johns Hopkins School of Medicine, Baltimore, MD.

REFERENCE ARTICLE

8-21 DRUG TREATMENT OF LIPID DISORDERS

This review discusses mechanisms of atherogenesis: target serum lipoprotein concentrations above which diet and drug therapy should be initiated; dietary treatment; drug treatment (statins, bile-acid-binding resins, nicotinic acid, fibrates); and other therapies (fiber, sitostanol, n-3 fatty acids, estrogen).

(I abstracted a few points. Ed.)

Statins:

Table 4 (p 501) presents characteristics of statins. Atorvastatin (*Lipitor*) 80 mg daily (the maximum dose) lowers LDL-cholesterol and triglycerides more effectively than the other statins. All statins except pravastatin are metabolized by the cytochrome P450 system in the liver. This may enhance or lower effectiveness of other drugs. (See table 6 p 503). Table 5 (p 503) lists side effects of statins.

Bile acids-binding resins:

The chief indication is to augment reduction of LDL-cholesterol in patients who are already receiving a statin.

Nicotinic acid:

At maximal doses, nicotinic acid raises HDL-cholesterol levels by up to 30% — more than any other drug. It also shifts LDL from small, dense particles (adverse form) to larger, more buoyant particles (more beneficial form). It has been reported to reduce myocardial infarction and total mortality over 15 years of therapy. It is more effective in preventing heart disease when given in combination with a bile-acid-binding resin or a fibrate.

Time-release formulations are more toxic to the liver at doses of 2000 mg/d.

Fibrates:

Are the most effective triglyceride-lowering drugs. Secondary prevention in men with a low serum HDL-cholesterol and normal LDL-cholesterol reduces frequency of heart disease.

NEJM August 12, 1999; 341: 498- 511 "Drug Therapy" review article by Robert J Knopp, University of Washington, Seattle.

REFERENCE ARTICLE

8-22 AN INTRODUCTION TO BAYESIAN METHODS IN HEALTH TECHNOLOGY ASSESSMENT.

Bayesian methods are necessary to adequately assess the probability that a positive test for the disease in question for an individual in a given cohort of patients truly indicates that the disease is present.

I have abstracted several articles dealing with Bayesian methods. The concept gives a simple and uncontroversial result in probability theory. It basic to assessing results of clinical studies of tests and treatments. Reading several accounts strengthened my understanding. Editor.

The authors suggest a definition of the Bayesian method: "The explicit quantitative use of *external* evidence in the design, monitoring, analysis, interpretation, and reporting of a health technology assessment."

The method is based on "external evidence"— ie, the "pretest" likelihood — the likelihood that the disease under investigation is present in the cohort studied. This is based on knowledge of the prevalence of the disease in the community and patients' symptoms. This is a bold step based on wide clinical experience. Estimates of the pretest likelihood may differ between experts.

After this is entered into the calculation, the evidence from the test applied to the disease will modify the likelihood that the disease is present or absent. This results in a 'post-test" likelihood that the disease is present. Will the analysis based on pretest likelihood modified by the diagnostic test change what we currently believe?

BMJ August 21, 1999; 508-12 Analysis , first author David J Spiegelhalter, Institute of Public Health, Cambridge, UK.

REFERENCE ARTICLE

8-23 DISSEMINATED INTRAVASCULAR COAGULATION

This article reviews incidence, associated causal clinical conditions, pathogenesis, diagnosis, clinical relevance, prognosis, and management.

" Disseminated intravascular coagulation is characterized by widespread activation of coagulation, which results in the intravascular formation of fibrin and ultimately thrombotic occlusion of small and midsize vessels. Intravascular coagulation can also compromise the blood supply to organs and, in conjunction with hemodynamic and metabolic derangements, may contribute to the failure of multiple organs. At the same time, the use and subsequent depletion of platelets and coagulation proteins resulting from the ongoing coagulation may induce severe bleeding. Bleeding may be the presenting symptom in a patient with disseminated intravascular coagulation, a factor that can complicate decisions about treatment."

NEJM August 19, 1999; 341:586-92 "Clinical Concepts", review article by Marcel Levi and Hugo ten Cate, University of Amsterdam, Netherlands.

==========

Read the Original !

8-24 PARTNERSHIP FOR GOOD DYING

A 52-year old woman facing death from metastatic adenocarcinoma of the lung wrote this editorial. After receiving the usual surgery, chemo, and radiation, and had been offered a complementary health regimen, she decided not to try any longer "to beat cancer and live". It didn't work.

She now comments on her acceptance of death and physicians' role in the dying process of their patients.

"When curing is no longer viable and this message is communicated to or intuited by the patient, a pregnant moment for healing arises for both physician and patient."

Years of training to heal and zeal to heal have focused the physician on doing anything and everything to save the patient. "Death is treated as the enemy." What use can I be if I cannot fix the problem? One may be tempted to withdraw.

The moment when death raises its specter is a crossroads. Herein lies the opportunity for physicians to go beyond their conventional model of relating to patients. Now conventional models of relating to patients can be set aside in favor of the most powerful contribution of all, physicians' *caring* itself. The only requirement is a willingness to extend listening and basic humanity to the dying. The simple act of visitation , of presence, of taking the trouble to witness can be a potent healing affirmation — a sacramental gesture received by the dying person who may be feeling helpless, diminished, and fearful.

Beyond pain control, three elements are most needed for dying patients: feeling cared about; being respected; enjoying a sense of continuity, be it in terms of relationships or in terms of spiritual awareness.

Here is a chance to embody the mandate "Physician, heal thyself" by looking within to contemplate one's own mission and one's own death.

Conscious listening is an impartial witnessing where people feel free to ramble in a non-linear way. Or they may simply be silent. Listening with non-judgmental acceptance brings relief from distress and isolation and foster pride in the dying person.

The time, effort and care the physician takes to be present will be a blessing in itself. A "blessing" can be a genuine , heartfelt well-wishing for the patient's equanimity. "May you find peace."

JAMA August 18, 1999; 282: 615-16 :A Piece of My Mind" Essay by Deborah T Fahnestock, MSW, Tucson. Arizona

==========

REFERENCE ARTICLE

8-25 PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

I mention this article without abstracting it for those who may wish an inclusive reference. The 23 pages and 175 references are indeed extensive. Editor.

Annals Int Med August 17, 1999; 131: 281-303 Review article by Ralph A DeFronzo, University of Texas Health Science Center, San Antonio

==========

8-26 PATIENTS' PERCEPTIONS OF INTENSIVE CARE

"Pain, noise, sleep deprivation, thirst, hunger, heat , cold, fear, anxiety, isolation, physical restraint, want of information, and absence of daylight were common memories of patients surviving intensive care.

Lancet August 14, 1999; 354: 571-72 "Research Letter" by Bruno Simini, Ospedale 55050 Lucca, Italy