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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS***

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 years can be accessed at www.practicalpointers.org

Richard T. James Jr, M.D.
Editor/Publisher.

HIGHLIGHTS AND *EDITORIAL COMMENTS* OCTOBER 2005

This Is Fascinating!

10-1 PAIN STUDIES ILLUMINATE THE PLACEBO EFFECT

Recent studies based on MRI and PET scans of the brain provide the first direct evidence that the placebo effect is mediated by activation of the receptors in the endogenous opioid system. This demonstrates a mechanism through which patient's *expectation* of pain relief can alter their experience of pain and their emotional state.

This article cites a study in which a salt water solution was injected into the jaws of healthy male volunteers to maintain a steady state of pain. Brain imaging studies compared responses of 1) subjects received a placebo that was described as a medicine which might relieve pain, *vs* 2) subjects who did not receive the placebo. The images differed. In group 1) areas of the brain containing opioid receptors were activated. In group 2) they were not activated.

The mental events induced by placebo can activate mechanisms that are similar to those activated by drugs. There is a similarity between psychosocial and pharmacodynamic effects.

The Only Effective Application To Correct It Morbid Obesity

10-2 WEIGHING IN ON BARIATRIC SURGERY: Procedure Use, Readmission Rates, And Mortality

An estimated 5% of the adult population in the USA has a BMI greater than 40. (*Morbid obesity*.)
In recent years, as the prevalence of obesity has increased, use of bariatric surgery has increased dramatically.

Combinations of diet therapy, behavior modifications, prescribed exercise programs, and pharmacotherapy in various combinations are widely used. They generally accomplish some degree of weight loss, but unfortunately the loss is generally transient, particularly in persons with severe obesity. In contrast, over a 10-year period, bariatric surgery patients have demonstrated sustained weight loss which is sufficient to favorably affect obesity-related complications.

Despite the exponential increase in bariatric surgery, and despite surgery being the only effective application to correct morbid obesity, relatively few persons actually receive it.

The advent of laparoscopic surgical techniques and development of high-volume surgical centers has been associated with improved patient safety. Now, surgical capacity has increased and is no longer a limiting factor in some environments. Surgical techniques have improved and favorable outcomes occur in the majority.
"Experience and technique count."

"On a practical level, patients who present to their primary care physician with a breast mass or symptomatic gallstones are routinely referred for surgical consultation. In contrast, patients who present with severe obesity are routinely entered into medical treatment programs even if such programs have failed on multiple previous occasions."

"Morbid obesity is a significant health concern. Bariatric surgery offers a potentially effective and enduring treatment for weight reduction." It helps resolve co-morbidities of obesity, and provides a survival benefit. It has had increasing success.

The editorialist is an enthusiast.

When, if ever, should primary care clinicians consider advising bariatric surgery?

1) The patient is morbidly obese and is subject to medical complications and early death.

2) The patient should be relatively young and have little co-morbidity.

3) Repeated attempts to lose have failed miserably.

4) The clinician knows the consultant surgeons well, and understands that they have performed many procedures with long-term success, and little morbidity and mortality.

5) The patient wants desperately to lose weight, and is fully informed about outcomes, bad as well as good.

Would it be advisable to wait until the patient opens the subject? There may be good reason to do so. As with screening procedures, if the clinician opens the discussion he or she assumes greater responsibility for any adverse outcome. And yet, we do not wait for patients to open the possibility of surgery if they have gallbladder disease or a breast mass.

I suspect advice for bariatric surgery will be given with less reservation in the future.

10-3 REFINING THE EXERCISE PRESCRIPTION FOR HYPERTENSION

Guidelines for management of hypertension are likely to include advice to: "engage in regular aerobic activity such as brisk walking (at least 30 minutes a day) most days of the week".

This article states that there is enough published work on exercise and hypertension to refine aspects of this advice.

The authors present 19 points regarding benefits of exercise.

I am sure the effects of exercise on BP differ a great deal between individuals.

I was not aware of many of these points.

Primary care patients may find them helpful. That moderate exercise 3 times a week is as beneficial as more frequent, prolonged, and strenuous exercise may be welcome news to many. The flexibility and benefits of accumulating exercise in 10-minute sessions may increase compliance. The helpfulness of exercise independent of weight loss might encourage some.

Physical exercise instructors may post these points to foster continuing compliance with exercise programs they offer their clients.

The Proportional Reduction In The Event Rate Per Mmol/L Reduction In LDL-C Was Largely Independent Of The Pre-Treatment Level

10-4 EFFICACY AND SAFETY OF CHOLESTEROL-LOWERING TREATMENT: Prospective Meta-Analysis From 90 056 Participants In 14 Randomised Trials Of Statins

Observational studies indicate a continuous relationship between coronary heart disease (CHD) risk and low density lipoprotein cholesterol **(LDL-C**) concentrations. There is no definite threshold below which lowering LDL-c is not associated with lower risk.

This systematic meta-analysis was designed to remove uncertainty about over-estimating and under-estimating of effects of statin drugs on CHD, and other vascular or non-vascular outcomes.

Outcomes were reported as the effects per 39 mg/dl (1.0 mmol) reduction in LDL-c. Mean follow-up = 5 years.

Five-year absolute benefits per 39 mg/dL reduction in LDL-c:

A. Participants without previous CHD:

Outcomes avoided per 1000 participants:

Major coronary events	8
Coronary revascularizations	12
Stroke	5
Major vascular events	25

B. Participants with previous CHD:

Outcomes avoided per 1000 participants:

Major coronary events	30
Coronary revascularizations	27
Stroke	8
Major vascular events	48

Effects were evident during the first year. Benefits were greater in subsequent years. Absolute benefits increased with continuing treatment.

There was *no* evidence that lowering LDL-c by 39 mg/dL over 5 years increased the risk of non-vascular cause of death or any type of cancer. (*Statins remain among the safest of the major dugs used today. RTJ*)

The proportional reduction in the event rate per mmol/L reduction in LDL-c was largely *independent* of the pre-treatment level:

Lowering LDL-c from 156 to 117 reduces the risk of vascular events by about 23%

Lowering LDL-c from 117 to 78 also reduces (residual) risk by about 23%.

Treatment goals should aim chiefly to achieve substantial reductions in LDL-c (rather than to achieve particular target levels) since the risk reductions are proportional to the absolute LDL-c reduction.

LDL-c is only one of many risk factors for CVD. Even if LDL-c were controlled to the maximum, some risk would persist. The goal of therapy is to reduce all risk factors concomitantly I believe that benefits from lowering all factors to a modest degree (even if not reduced to "normal") would reduce risk more than lowering LDL-c maximally without concern for other risk factors.

Should The "Normal" FPG Be Lowered?

10-5 NORMAL FASTING PLASMA GLUCOSE LEVELS AND TYPE 2 DIABETES IN YOUNG MEN

The normal fasting plasma glucose **(FPG)** is now defined as less than 100 mg/dL. An "impaired FPG" is now considered to range between 100 and 125.

Persons with impaired FPG are at increased risk for type two diabetes **(DM2).**

Do FPG levels below 100 (especially those in the 90s) independently predict DM2 in young adults? Better and earlier identification of young adults at risk of DM2 may lead to interventions aimed at delaying onset of DM2.

This study followed over 13 000 men age 26 to 45 (mean = 33) for 14 years. All had baseline FPG under 100. None had DM2.

Primary endpoint = incidence of DM2 defined as FPG of 126 or more. Mean follow-up = 6 years.

Compared with FPG less than 82, risk of DM2 progressively increased as FPG rose from 82 to 99.

Hazard ratios for DM2 according to quintiles of normal fasting glucose:

	Quintile 1	2	3	4	5
Fasting plasma glucose	50-81	82-86	87-90	91-94	95-99
Number of incident DM2	20	24	37	50	77

Risk of DM2 increased when other risk factors were associated with FPG:

Hazard ratios for DM2 when TG and FPG were combined:

FPG	< 87	88-90	91-99
TG < 150	1.00	1.76	2.65
TG > 150	2.42	5.26	8.23

Hazard ratios for DM2 when BMI and FPG were combined:

FPG	< 87	78-90	91-99
BMI 24 and less	1.00	0.75	1.79
BMI 25-29.9	1.99	2.75	4.77
BMI 30 and more	3.42	7.78	8.29

In apparently healthy young adults, risk of developing DM2 rose across quintiles of FPG levels usually considered to be within normal range. A FPG in the high “normal” range may predict DM2.

Risk increases when other factors are associated with a high “normal” FPG: higher BMI and triglyceride levels,; age; family history; sedentary lifestyle; abdominal girth.

When clinicians inform a patient that her blood test is “normal”, this in no way indicates that risk of associated disease is absent—only that risk may be lower than in patients with an ” abnormal” test.

Patients should realize that risk increases when risk factors are combined even if they are all “normal”, especially if they are “high normal”. There is a continuum, not an absolute cutpoint. “Normal” is not necessarily normal anymore. It is relative. A given level of a risk factor may be normal for one patient and abnormal for another. It is the combination of risk factors, not the level of one, which determines risk.

This advances the concept that lowering all risk factors (BP, lipids, BMI, abdominal girth, FPG) is beneficial even if they are not reduced to “normal”.

The term “favorable” might replace “normal”.

The term “requires intervention” should be used more frequently.

10-6 DOES DIETARY FOLATE INTAKE MODIFY EFFECT OF ALCOHOL CONSUMPTION ON BREAST CANCER RISK: Prospective Cohort Study

High alcohol consumption is a known risk factor for breast cancer **(BC).** Although the association is modest, its adverse effect on BC is one of the most consistent findings among dietary risk factors.

Some studies report an inverse association between folate intake and risk of BC. This study asked: Is the association between alcohol consumption and risk of BC modified by intake of dietary folate?

This prospective cohort study recruited and followed over 17 000 women age 40-69 at baseline (mean = 55)

At baseline, obtained information about alcohol consumption. Calculated folate intake from a dietary questionnaire.

Hazard ratios for BC considering both alcohol and folate intake: For women who consumed 40 g alcohol per day and 400 ug of folate daily the rate of BC was half that of women who consumed 40 g alcohol per day and 200ug folate. (A suggestive protective effect.)

Women who had a high alcohol intake and a low folate intake had increased risk of BC. Women who had a high alcohol intake and a high folate intake were not at increase risk.

Value of a therapeutic intervention has been defined as the ratio between benefit/harm-cost.

Benefit depends on the absolute risk reduction (Number needed to treat to benefit one patient). It also depends on the type of benefit achieved. Preventing a BC may be considered a greater benefit than preventing a less ominous outcome.

Harm depends on the absolute number of adverse effects. (NNT to treat to harm one patient.) It also depends on the severity of the harm produced.

Cost is a basic consideration for primary care. It is seldom mentioned in scientific reports. Availability and accessibility are also cost considerations.

Folic acid has been reported to benefit (reduce risk of) neural tube defects, osteoporotic fractures, congestive heart failure, dementia and Alzheimer's disese. And now, BC in heavy alcohol consumers.

Consider the benefit/harm-cost ratio of a daily supplement of folic acid:

Benefit (except for reduction of risk of spina bifida) is not firmly established. Evidence of benefit is strongly suggestive.

Cost is nil. Harm is nil if B12 deficiency is not present. Availability and accessibility are high.

Because the absolute level of the denominator of the ratio (harm-cost) is so low, the benefit/harm-cost ratio may be very high.

I believe many primary care clinicians will prescribe daily folate (in a multivitamin capsule) for many patients on the basis of the high putative benefit and low harm-cost.

10-7 EFFICACY OF AN ACELLULAR PERTUSSIS VACCINE AMONG ADOLESCENTS AND ADULTS

During the past 50 years, routine immunization of children has dramatically decreased the burden of childhood pertussis.

Immunization of children has *not* decreased the incidence of disease in older persons, nor has it eliminated the transmission of infections to unimmunized children.

Infections among adolescents and adults result from waning immunity. Neither immunization nor natural infection induces long-term immunity. Most adult cases are not suspected.

This trial, sponsored by the National Institute of Health, aimed to ascertain the protective efficacy of acellular pertussis vaccine among adolescents and adults

Double-blind multicenter trial randomized over 2700 healthy subjects mean age 35 to 1) a single dose of acellular pertussis vaccine used alone, or 2) a control vaccine (hepatitis A).

A total of 2672 illnesses with cough lasting over 5 days were evaluated.

Ten cases met the criteria for pertussis:

Nine in controls.

One in vaccine group

The incidence of pertussis in the control group = 9 cases per 2444 persons over 2 years. (390 cases per 100 000 person-years. ~ 4 per 1000 between ages 15 to 65.)

Overall efficacy of the vaccine = 92%

Vaccine safety: Serious adverse events occurred in 140 of 1391 subjects—equally in both groups. None were deemed to be vaccine-related.

Pertussis in adults is not uncommon. Extrapolating the rate of pertussis reported in this study would result in an estimated 1 million cases each year in the USA. This does not include asymptomatic or mild infections.

Pertussis is one of the least well controlled illnesses that are preventable by vaccine. Immunization of adolescents between ages 10 and 19 may be the most beneficial initial strategy in view of ease of administration and costs.

The purified acellular vaccine is associated with fewer local and systemic reactions than the whole-cell vaccine.

Should Be Used Only When A Demented Patient Has An Identifiable Risk Of Harm To Themselves Or To Others.

10-8 ANTIPSYCHOTIC DRUGS IN DEMENTIA

Antipsychotic drugs are used to treat psychiatric and behavioral symptoms that affect the majority of persons with dementia. In nursing homes, where many residents have dementia, up to 25% of individuals receive such therapy.

In the 1990s, the introduction of atypical, or second-generation, antipsychotic drugs was met with enthusiasm because the rate of adverse effects (parkinsonism and tardive dyskinesia) was reported to be lower. However, in 2003 a study reported higher rates of cardiovascular adverse events and mortality in patients with dementia-associated agitation and psychosis who were treated with the newer antipsychotic risperidone (*Risperdal*) compared with placebo.

"Antipsychotic drugs should not be used when non-drug treatments are available and the risk of harm or significant distress is low."

"Patients with hallucinations and delusions that are neither distressing nor placing themselves or others at risk or harm should not be treated with antipsychotic drugs."

At present, we cannot say that there is a "safe" antipsychotic drug. And we cannot say that one drug is safer than another.

Primary care clinicians who follow nursing home patients should ask themselves__"Am I prescribing this antipsychotic to benefit the patient, or to benefit the staff and the family?"

10-9 EFFECT OF THE ADDITION OF A "HELP" QUESTION TO TWO SCREENING QUESTIONS ON SPECIFICITY FOR DIAGNOSIS OF DEPRESSION IN GENERAL PRACTICE

Two questions have been used as a screening test for depression:

1) During the past month have you often been bothered by feeling down, depressed, or hopeless?

2) During the past month have you been bothered by little interest or pleasure in doing things?

The sensitivity of the screen is high. If the patient is indeed depressed, one or two questions will be answered "yes". (True positive rate = > 90%.)

The specificity however, is relatively low (~ 60% to 85%). Many persons who are not actually depressed will answer "yes". (False positive rate ~ 15% to 40%)

This study adds a 3rd question.

"Is there something for which you would like help? "

Adding the help question improved specificity (increased true negative responses from 78% to 89%, and reduced false positive responses from 22% to 11%. This increased the likelihood that a positive screen does indeed denote depression.

I believe screening for depression in some groups of primary care patients should be applied universally. (Almost any serious condition with a prevalence of 5% requires screening.)

The authors of the study suggest the questions be put in writing for the patient to answer.

Will adding the "help" question aid the diagnosis? The study says so. It is simple and takes little additional time and bother.

What to do if the questions are answered positively? Certainly, not reach immediately for the prescription pad. Further conversation will allow patients to ventilate (which in itself may be helpful), and may lead to a better understanding of their problem and more willingness to seek help..

10-10 SENSITIVITY, SPECIFIFITY, POSITIVE LIKELIHOOD RATIO, NEGATIVE LIKELIHOOD RATIO OF SCREENING TESTS FOR DEPRESSION: Review by the Editor

Statistical analysis in now an essential component of studies presented by peer-reviewed journals. Primary care clinicians do not need to be expert statisticians, but they should know and be able to calculate several basic functions. Clinicians should be familiar with the meaning of sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio, and be able to calculate them from the data presented. This will enhance enjoyment of journal-reading and make it more meaningful.

Some articles present the opportunity to review these aspects of statistics as applied to general clinical practice. I enjoy calculating them.

Although I have calculated them many times from various studies, I still struggle to get them right, and then wonder if I did indeed get them right. A periodic refresher is required.

The preceding study allowed me to make these calculations from the data presented.

ABSTRACTS OCTOBER 2005

This Is Fascinating!

10-1 PAIN STUDIES ILLUMINATE THE PLACEBO EFFECT

Recent studies based on MRI and PET scans of the brain provide the first direct evidence that the placebo effect is mediated by activation of the receptors in the endogenous opioid system. This demonstrates a mechanism through which patient's *expectation* of pain relief can alter their experience of pain and their emotional state.

For decades, there has been evidence that the endogenous opioid system plays a key role in the mechanism of the placebo effect. The effect can be blocked by the opioid-inhibitor, naloxone.

This article cites a study in which a salt water solution was injected into the jaws of healthy male volunteers to maintain a steady state of pain. Brain imaging studies compared responses of 1) subjects received a placebo that was described as a medicine which might relieve pain, *vs* 2) subjects who did not receive the placebo. The images differed. In group 1) areas of the brain containing opioid receptors were activated. In group 2) they were not activated.

A picture on page 1750 illustrates the difference in images of brain activity when a subject received a pain stimulus alone vs a pain stimulus + a placebo. The difference is striking. "The study showed changes in opioid release occur directly in the brain in regions of the brain most closely associated with subjective feelings, reward, and pain experience."

"This emerging understanding of the placebo effect suggests that a patient's assessment of a situation could have important clinical implications." The mental events induced by placebo can activate mechanisms that are similar to those activated by drugs. There is a similarity between psychosocial and pharmacodynamic effects. Individuals who have a strong placebo response may have an adaptive advantage over those who do not.

There are implications of the physician-patient relationship—how physicians can influence patients' expectations.

To determine whether patients' expectations or beliefs about their treatment are affecting the outcomes of clinical trials, some researchers are designing studies that compare a drug's effects when: 1) Patients know they are receiving the drug vs 2) When the drug is given covertly. A review of overt-covert clinical trials of medications for pain, anxiety, and Parkinson disease reported that treatments were *less* effective when the patients did *not* know they were receiving the drug.

JAMA October 12, 2005; 294: 1750-51 "Medical News & Perspectives". Commentary by Bridget M Kuehn, JAMA Staff.

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The Only Effective Application To Correct Morbid Obesity

10-2 WEIGHING IN ON BARIATRIC SURGERY: Procedure Use, Readmission Rates, And Mortality

An estimated 5% of the adult population in the USA has a BMI greater than 40. (*Morbid obesity*.)
In recent years, use of bariatric surgery has increased dramatically as the prevalence of obesity has increased..

Combinations of diet therapy, behavior modifications, prescribed exercise programs, and pharmacotherapy in various combinations are widely used. They generally accomplish some degree of weight loss, but unfortunately the loss is generally transient, particularly in persons with severe obesity. In contrast, over a 10-year period, bariatric surgery patients have demonstrated sustained weight loss which is sufficient to favorably affect obesity-related complications.

The advent of laparoscopic surgical techniques and development of high-volume surgical centers has been associated with improved patient safety.

Despite the exponential increase in bariatric surgery, relatively few morbidly obese persons actually receive it.

"On a practical level, patients who present to their primary care physician with breast mass or symptomatic gallstones are routinely referred for surgical consultation. In contrast, patients who present with severe obesity are routinely entered into medical treatment programs even if such programs have failed on multiple previous occasions."

What explains the disparity between the recognition of the health consequences of severe obesity and . . . "the only effective application to correct it"? Primary care clinicians heretofore may have been reluctant to advise surgery because only a few surgeons were routinely performing bariatric surgery, and the awareness that bariatric surgery has the potential for adverse effects including mortality, rehospitalization, and disability. In addition, the same communication system that informs patients of the successes of surgery also provides anecdotal reports of adverse outcomes. There is a perception that weight loss achieved by bariatric surgery may be transient especially for certain procedures.

Now, surgical capacity has increased and is no longer a limiting factor in some environments. Surgical techniques have improved and favorable outcomes occur in the majority. "Experience and technique count."

Health care funding still constitutes a barrier to access, especially for those who are uninsured.

"Morbid obesity is a significant health concern. Bariatric surgery offers a potentially effective and enduring treatment for weight reduction." It helps resolve co-morbidities of obesity, and provides a survival benefit. It has had increasing success.

JAMA October 19, 2005; 294: 1960-63 Editorial, first author Bruce M Wolfe, Oregon Health and Science University, Portland.

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10-3 REFINING THE EXERCISE PRESCRIPTION FOR HYPERTENSION

Guidelines for management of hypertension are likely to include advice to: "engage in regular aerobic activity such as brisk walking (at least 30 minutes a day) most days of the week".

This article states that there is enough published work on exercise and hypertension to refine aspects of this advice:

1) One session of exercise can lower BP acutely for up to 24 hours. This requires only moderate-pace walking (at 40% of maximal capacity).

2) After three consecutive episodes of exercise, BP is reduced for a longer time, but returns to pre-exercise levels in 1 to 2 weeks.

3) Exercise in hypertensive patients results in a larger reduction in BP than in normotensive patients.

4) Regular exercise lowers BP in 75% of persons with hypertension by an average 11/8 mg Hg.

5) Exercise can reduce 10-year cardiovascular risk by at least 25% in the average patient with hypertension because of the effect on BP and other risk factors.

6) Exercising 3 times a week is as effective in lowering BP as exercising 5 times a week.

7) There seems to be little difference in effect on BP reduction between exercising at a rate of 373 kcal vs 1866 kcal a week (3 minutes of moderate walking a week vs 60 minutes brisk walking a week).

8) Cardiovascular fitness and lipid profiles can be improved in persons with hypertension by accumulating the required exercise in brief episodes of 10-minute sessions several times throughout the day.

9) The flexibility of accumulating exercise in 10-minute sessions throughout the day, and knowing that benefits start after the first day of exercise might improve exercise prescription uptake and motivation.

10) Aerobic exercise appears to be more effective than resistance exercise in lowering BP.

11) Any type of aerobic activity seems to work, including walking, jogging, or cycling. Cycling seems to be the most effective.

12) BP reduction with exercise is independent of weight loss. (Weight loss typically needs twice the energy expenditure to achieve.)

13) Low to moderate intensities of exercise are as effective, if not more effective, in lowering BP than vigorous exercise. Vigorous exercise can increase platelet activity and adhesion. This can increase risk of sudden death after exercise, especially in previously sedentary persons.

14) Platelet activity is inhibited by moderate exercise. Platelet adhesion is reduced by regular exercise.

15) Although BP often rises acutely during exercise, this response is attenuated by regular exercise.

16) Exercise is associated with reductions in cardiac output, stroke volume, and left ventricular end-diastolic pressure.

17) Regular exercise improves myocardial contractility, coronary perfusion, arterial compliance, and endothelial function.

18) Regular moderate exercise can also reverse left ventricular hypertrophy.

19) The recommended exercise prescription for lowering BP in patients with hypertension can be tailored, and can involve *any* intermittent or continuous aerobic activity of at least 30 minutes a day three or more times a week.

Lancet October 8, 2005; 366: 1248-49 "Comment", first author C Raina Elley, Otago University, Auckland, New Zealand.

The authors provide 14 references. They are certainly enthusiastic.

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The Proportional Reduction In The Event Rate Per Mmol/L Reduction In LDL-C Was Largely Independent Of The Pre-Treatment Level

10-4 EFFICACY AND SAFETY OF CHOLESTEROL-LOWERING TREATMENT: Prospective Meta-Analysis From 90 056 Participants In 14 Randomised Trials Of Statins

Observational studies indicate a continuous relationship between coronary heart disease (CHD) risk and low density lipoprotein cholesterol **(LDL-C**) concentrations. There is no definite threshold below which lowering LDL-c is not associated with lower risk.

This systematic meta-analysis was designed to remove uncertainty about over-estimating and under-estimating of effects of statin drugs on CHD, and other vascular or non-vascular outcomes.

Conclusion: Statin therapy safely reduced 5-year incidence of major coronary events, and stroke, irrespective of the initial lipid profile.

STUDY

1. This prospective meta-analysis obtained data from over 90 000 individuals in 14 randomized trials of statin therapy.
2. Main prespecified outcomes were: 1) all cause mortality, 2) CHD mortality. 3) non-CHD mortality.
   Secondary outcomes included effects on stroke, cancer, and vascular procedures.
3. Outcomes were reported as the effects per 39 mg/dl (1.0 mmol) reduction in LDL-c.
4. Mean follow-up = 5 years.

RESULTS

1. During follow-up there were over 8100 deaths; 14 000 major vascular events; 5000 cancers.
2. Mean LDL-c differences at 1 year was 42.5 mg/dL. At 5 years was 31 mg/dL. (The difference reflected non-compliance.)
3. Effects on mortality of a 39 mg/dL LDL-c reduction:

	Treatment (%) (n = 45 000)	Control (%) (n = 45 000)	Absolute difference (%)	NNT
CHD death	3.4	4.4	1.0	100
Stroke death	0.6	0.6	--	
Any vascular death	4.7	5.7	1/0	100
Any death	8.5	9.7	1.2	83

4. Effect on vascular events per 39 mg/dL reduction LDL-c:

Non-fatal MI	4.4	6.2	1.8	55

Major coronary event	7.4	9.8	2.4	42
Coronary revascularization	5.8	7.6	1.8	55
Ischemic stroke	2.8	3.4	0.6	166
Any major vascular event	14.1	17.8	3.7	29
Hemorrhagic stroke	0.2	0.2		

5. Five-year absolute benefits per 39 mg/dL reduction in LDL-c:

   A. Participants without previous CHD:

      Outcomes avoided per 1000 participants:

Major coronary events	8
Coronary revascularizations	12
Stroke	5
Major vascular events	25

   B. Participants with previous CHD:

      Outcomes avoided per 1000 participants:

Major coronary events	30
Coronary revascularizations	27
Stroke	8
Major vascular events	48

6. Effects were evident during the first year. Benefits were greater in subsequent years. Absolute benefits increased with continuing treatment.

7. Safety:

   A. There was *no* evidence that lowering LDL-c by 39 mg/dL over 5 years increased the risk of non-vascular cause of death or any type of cancer.

   B. The incidence of rhabdomyolyis was very low (0.1%). However, no trial used high doses of statins.

   C. Incidence of raised liver enzymes was not obtained.

   D. Adverse effects with treatment beyond 5 years must be studied.

DISCUSSION

1. There was an approximately linear relationship between the absolute reductions in LDL-c and the proportional reductions in coronary and other major vascular events. Larger LDL-c reductions produced larger reductions in vascular disease risk.

2. If all participants had been compliant, and had taken the statin regularly, benefits would have been greater by about 2%. Full compliance with statins can reduce LDL-c by substantially more than 39 mg/dL.

3. A reduction of LDL-c of 60 mg/dL with sustained statin therapy might be expected to reduce incidence of major vascular events by about one third.

4. The absolute reduction in LDL-c with a particular dose of statin tended to be smaller among those presenting with a lower LDL-c than among those with a higher LDL-c.

5. But, the proportional reduction in the event rate per mmol/L reduction in LDL-c was largely *independent* of the pre-treatment level:

Lowering LDL-c from 156 to 117 reduces the risk of vascular events by about 23%

Lowering LDL-c from 117 to 78 also reduces (residual) risk by about 23%.

A reduction of 78 mg/dL might be expected to reduce risk by as much as 40%

6. Treatment goals should aim chiefly to achieve substantial reductions in LDL-c (rather than to achieve particular target levels) since the risk reductions are proportional to the absolute LDL-c reduction.

CONCLUSION

Statin therapy safely reduced the 5-year incidence of major cardiovascular events by about one fifth for each 39 mg/dL reduction in LDL-c. Long-term therapy should be considered in all patients at high risk of any type of major vascular event.

Lancet October 8, 2005; 366: 1267-78 Original investigation by the Cholesterol Treatment Trialists' Collaborators, reported by the writing committee.

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Should The "Normal" FPG Be Lowered?

10-5 NORMAL FASTING PLASMA GLUCOSE LEVELS AND TYPE 2 DIABETES IN YOUNG MEN

The normal fasting plasma glucose **(FPG)** is now defined as less than 100 mg/dL. An "impaired FPG" is now considered to range between 100 and 125.

Persons with impaired FPG are at increased risk for type two diabetes **(DM2).**

This study asked: Do FPG levels below 100 (especially those in the 90s) independently predict DM2 in young adults? Better and earlier identification of young adults at risk of DM2 may lead to interventions aimed at delaying onset of DM2.

This study was based on determinations of FPG and data from physical examinations of men in the Israel Defense Forces age 26 to 45.

Conclusion: FPG levels within the high "normal" range were an independent risk factor for DM2 especially when combined with higher levels of other risk factors.

STUDY

1. Followed over 13 000 men age 26 to 45 (mean = 33) for 14 years. Women were not included.
2. All had baseline FPG under 100. None had DM2.
3. Primary endpoint = incidence of DM2 defined as FPG of 126 or more.
4. Two subjects developed type 1 diabetes. They were excluded from the study.
5. Mean follow-up = 6 years.

RESULTS

1. A total of 208 incident cases of DM2 occurred during over 74 000 person-years. All had FPG of 126 or more on two occasions.

2. Compared with FPG less than 82, risk of DM2 progressively increased as FPG rose from 82 to 99.

Hazard ratios for DM2 according to quintiles of normal fasting glucose:

	Quintile 1	2	3	4	5
Fasting plasma glucose	50-81	82-86	87-90	91-94	95-99
Number of incident DM2	20	24	37	50	77

3. Risk of DM2 increased when other risk factors were associated with FPG:

Hazard ratios for DM2 when TG and FPG were combined:

FPG	< 87	88-90	91-99
TG < 150	1.00	1.76	2.65
TG > 150	2.42	5.26	8.23

Hazard ratios for DM2 when BMI and FPG were combined:

FPG	< 87	78-90	91-99
BMI 24 and less	1.00	0.75	1.79
BMI 25-29.9	1.99	2.75	4.77
BMI 30 and more	3.42	7.78	8.29

DISCUSSION

1. In apparently healthy young adults, risk of developing DM2 rose across quintiles of FPG levels usually considered to be within normal range. A FPG in the high "normal" range may predict DM2.
2. Risk increases when other factors are associated with a high "normal" FPG: higher BMI and triglyceride levels; age; family history; sedentary lifestyle.
3. FPG levels are largely determined by hepatic glucose production. A relative overproduction of hepatic glucose which is exaggerated by obesity may exist early in the natural history of diabetes.

CONCLUSION

Higher FPG levels within the "normal" range may constitute a risk factor for DM2 in young men. Risk is enhanced by concomitant overweight, higher triglyceride levels, and other risk factors.

NEJM October 6, 2005; 355; 1454-62 Original investigation, first author Amir Tirosh, Sheba Medical Center, Tel-Hashomer, Israel.

An editorial by Ronald A Arky, Harvard Medical School, in this issue of NEJM (pp 1511-13) comments:

On the surface, patients asking "Are my laboratory results normal?" seems a benign, straightforward question which should lend itself to a simple answer. Over the past several decades, the complexity of this question has been compounded by the increased number of epidemiological studies that point out how differences in sex, ethnic backgrounds, age, and a multiplicity of other factors may determine what is "normal". There has been a redefinition of what is normal and what should be the desired level of interventions.

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10-6 DOES DIETARY FOLATE INTAKE MODIFY EFFECT OF ALCOHOL CONSUMPTION ON BREAST CANCER RISK: Prospective Cohort Study

High alcohol consumption is a known risk factor for breast cancer **(BC).** Although the association is modest, its adverse effect on BC is one of the most consistent findings among dietary risk factors.

Some studies report an inverse association between folate intake and risk of BC. This study asked: Is the association between alcohol consumption and risk of BC modified by intake of dietary folate?

Conclusion: An adequate intake of folate might protect against BC.

STUDY

1. This prospective cohort study recruited and followed over 17 000 women age 40-69 at baseline (mean = 55)
2. Followed for 9 to 13 years (mean = 10 years).
3. At baseline, obtained information about alcohol consumption. Calculated folate intake from a dietary questionnaire.
4. Divided alcohol consumption into 5 categories:
   Abstainers
   Ex-drinkers
   1-19 g/day
   20-39 g/day
   40 and 0ver g/day.
5. Main outcome measure = BCs diagnosed during follow up.

RESULTS

1. Diagnosed 537 incident BCs during follow-up.
2. Hazard ratios for BC considering alcohol intake alone:
   Hazard rate of BC increased by 1.03% for each 10g/day increase in alcohol consumption
   The highest hazard ratio occurred in women who consumed 40g/day or more.
   (This agrees with the many studies which have reported that high alcohol intake increase risk of BC.)
4. Hazard ratios for BC considering both alcohol and folate intake:
   For women who consumed 40 g alcohol per day and 400 ug of folate daily the rate of BC was half that of women who consumed 40 g alcohol per day and 200ug folate. (A suggestive protective effect.)

DISCUSSION

1. The authors cite a meta-analysis of 53 epidemiological studies comparing women who abstained from alcohol with those reporting an average intake of 45 g/d. The relative hazard of BC in the alcohol group was 1.46. The present study agrees with the increased alcohol-BC risk.
2. The study found a significant association between risk of incident BC and alcohol consumption and folate intake. Women who had a high alcohol intake and a low folate intake had increased risk of BC. Women who had a high alcohol intake and a high folate intake were not at increase risk.

3. The mechanism is not clear. The impact of alcohol consumption on hormonal status is likely to be a major contributor.

CONCLUSION

This study supports the hypothesis that alcohol consumption may increase the risk of BC through an interaction with folate. Some of the adverse effects of alcohol may be reduced by sufficient dietary folate intake.

BMJ October 8, 2005; 331: 807-10 Original investigation, first author Laura Baglietto, Cancer Epidemiology Centre, Victoria, Australia.

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10-7 EFFICACY OF AN ACELLULAR PERTUSSIS VACCINE AMONG ADOLESCENTS AND ADULTS

Bordetella pertussis causes whooping cough in non-immune persons. The illness is characterized by prolonged cough. The severity of the illness varies with age, immune status (prior immunization or infection), and probably the extent of the exposure and the virulence of the organism. Infections can be asymptomatic, mild, or classic in presentation.

During the past 50 years, routine immunization of children has dramatically decreased the burden of childhood pertussis.

Immunization of children has *not* decreased the incidence of disease in older persons, nor has it eliminated the transmission of infections to unimmunized children.

Infections among adolescents and adults result from waning immunity. Neither immunization nor natural infection induces long-term immunity. Most adult cases are not suspected. The possibility of adult infection is usually considered only when it occurs in association with classic whooping cough in children. Many factors contribute to the failure to detect pertussis: lack of clinical awareness, lack of availability and insensitivity of culture and polymerase-chain-reaction assay **(PCR),** difficulty in obtaining appropriate specimens, and absence of clear serologic diagnostic criteria.

Vaccines have not been recommended for persons over age 6. Consequently, pertussis continues to circulate among older persons. This creates a source of contagion for younger children.

Vaccines combining diphtheria and tetanus toxoids with acellular pertussis are safe and effective in children and have been routinely used worldwide. Two adult acellular vaccines have recently been licensed in the USA. They contain lower concentrations of pertussis toxoid than the pediatric vaccines.

This trial, sponsored by the National Institute of Health, aimed to ascertain the protective efficacy of acellular pertussis vaccine among adolescents and adults.

Conclusion: The vaccine was protective.

STUDY

1. Double-blind multicenter trial randomized over 2700 healthy subjects mean age 35 to

1) a single dose of acellular pertussis vaccine used alone, or 2) a control vaccine (hepatitis A).

2. The pertussis vaccine contained 3 different acellular antigens. The total vaccine content was about 1/3 that of the acellular pertussis vaccine usually given to children. Dose = 0.5 mL.
3. Monitored subjects over 2.5 years for illness with cough lasting over 5 days.
4. Evaluated each illness by culture and PCR of nasopharyngeal aspirates, and serum samples for changes in antibodies to 9 different *B pertussis* antigens.
5. Defined cases of pertussis:
   A. Cough over 5 days.
   B. Positive culture for *B pertussis;* or positive PCR; or stringent serological evidence of infection (increase in titer of antibody to pertussis toxin by a factor of two or more).

RESULTS

1. A total of 2672 illnesses with cough lasting over 5 days were evaluated.
2. Ten cases met the criteria for pertussis:
   A. Nine in controls.
   B. One in vaccine group (Serological evidence only.)
3. The incidence of pertussis in the control group = 9 cases per 2444 persons over 2 years; 390 cases per 100 000 person-years; ~ 4 per 1000 between ages 15 to 65.
3. Overall efficacy of the vaccine = 92%
4. Vaccine safety: Serious adverse events occurred in 140 of 1391 subjects—equally in both groups. None were deemed to be vaccine-related.

DISCUSSION

1. Illness with cough lasting over 5 days is common and is associated with substantial morbidity and costs.
2. Immunization prevented pertussis, but did not decrease the overall burden of prolonged illness. This was because pertussis constituted only a small proportion of the illnesses.
3. However, pertussis in adults is not uncommon. Extrapolating the rate of pertussis reported in this study would result in an estimated 1 million cases each year in the USA. This does not include asymptomatic or mild infections.
4. Immunity to pertussis wanes with time. The control of the disease will probably require immunization of all adolescents and adults as well as children.
5. Pertussis is one of the least well controlled illnesses that are preventable by vaccine. Immunization of adolescents between ages 10 and 19 may be the most beneficial initial strategy in view of ease of administration and costs.

CONCLUSION

The acellular pertussis vaccine was protective among adolescents and adults. Routine use might reduce the overall burden of the disease and transmission to children.

NEJM October 13, 2005; 353: 155-63 original investigation, first author Joel I Ward, David Gelfin School of Medicine, UCLA, Torrance, California.

An editorial in this issue of NEJM (pp 1615-17 by Scott A Halperin, comments and expands on the study:

In the USA, children routinely receive 5 doses of vaccine between ages 2 to 18 months. The overall burden of illness due to *B pertussis* is increasingly shifting toward adolescents and adults, due in large part to waning vaccine-induced immunity

The clinical severity in adults increases with age.

Two formulations of acellular pertussis vaccine are now licensed in the USA . Both are combined with an adult formulation of diphtheria and tetanus toxoids (dTap). The vaccine is highly immunogenic after a single dose in adolescents and adults.

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Should Be Used Only When A Demented Patient Has An Identifiable Risk Of Harm To Themselves Or To Others.

10-8 ANTIPSYCHOTIC DRUGS IN DEMENTIA

Chlorpromazine (*Thorazine*), the first antipsychotic drug, was introduced into clinical practice over 50 years ago. It revolutionized psychiatry and neurology. The efficacy of this drug and others in the phenothazine class demonstrated that a disease considered a "mental illness" could respond to a biologically mediated therapy.

Antipsychotic drugs are used to treat psychiatric and behavioral symptoms that affect the majority of persons with dementia. In nursing homes, where many residents have dementia, up to 25% of individuals receive such therapy.

In the 1990s, the introduction of atypical, or second-generation, antipsychotic drugs was met with enthusiasm because the rate of adverse effects (parkinsonism and tardive dyskinesia) was reported to be lower. However, in 2003 a study reported higher rates of cardiovascular adverse events and mortality in patients with dementia-associated agitation and psychosis who were treated with a second-generation antipsychotic drug risperidone (*Risperdal*) compared with placebo. "These findings should have a direct effect on clinical practice." They do not contraindicate use in patients with dementia who have psychotic symptoms and agitation. Instead, they change the risk-benefit analysis such that antipsychotic drugs should be used only when the demented patients have an identifiable risk of harm to themselves or to others. Or when the distress caused by the symptoms is significant, when alternate therapies have failed, and symptom relief would be beneficial.

"Antipsychotic drugs should not be used when non-drug treatments are available and the risk of harm or significant distress is low."

"Patients with hallucinations and delusions that are neither distressing nor placing themselves or others at risk or harm should not be treated with antipsychotic drugs."

Once these drugs have been prescribed, careful assessment and documentation of the need for continuation should be reassessed.

JAMA October 19, 2005; 294: 1963-65 Editorial, first author Peter V Rabins, Johns Hopkins Medical Institutions, Baltimore, MD.

The risk of newer antipsychotic agents may be just as great as the older "conventional" agents. NEJM December 1, 2005; 353: 2335-41 "Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications" The article lists 6 newer "atypical antipsychotic agents, and 14 older "conventional" agents. This is a reflection of widespread use.

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10-9 EFFECT OF THE ADDITION OF A "HELP" QUESTION TO TWO SCREENING QUESTIONS ON SPECIFICITY FOR DIAGNOSIS OF DEPRESSION IN GENERAL PRACTICE

Depression is common in primary care practice. The diagnosis is often missed. Quality-of-life and productivity are lowered to an extent comparable to that of major physical illnesses.

Depressed patients often present with a variety of physical symptoms (somatization), leading to excess use of medical services. The suicide rate of depressed persons is at least 8 times higher than in the general population.

Two questions have been used as a screening test for depression:

1) During the past month have you often been bothered by feeling down, depressed, or hopeless?

2) During the past month have you been bothered by little interest or pleasure in doing things?

The sensitivity of this screen is high. If the patients in the group studied are indeed depressed, one or two questions will be answered "yes" by over 90%. . (Sensitivity of the test = > 90%)

The specificity however, is relatively low (~ 60% to 85%). Many persons who are not actually depressed will answer "yes". (False positive rate ~ 15% to 40%)

This study adds a 3rd question:

"Is there something for which you would like help? "

Conclusion: Adding the help question improved specificity (increased the true negative responses from 78% to 89%, and reduced false positive responses from 22% to 11%). This increased the likelihood that a positive screen does indeed denote depression.

STUDY

1. Cross sectional study involved 19 general practitioners in 6 clinics.
2. Screened over 1000 patients for depression. None were receiving psychoactive drugs.
3. Determined the sensitivity, specificity and likelihood ratios of various combinations of the questions.
   All questions were answered in writing, not verbally.
4. Considered these responses to indicate depression:
   A. If the patient answered "yes" to either or both of the two screening questions. .
   B. If patients responded "yes" to either or both screening question plus "yes" to the help question.
5. The general practioners could ask further questions. They then gave their opinion whether the patient was depressed
6. Subjects completed the mood module of the composite international diagnostic interview. This was considered the reference standard for depression.

RESULTS

1.	Sensitivity	Specificity	Positive likelihood ratio (Ratio of positive tests)	Negative likelihood ratio (Ratio of negative tests)
Two screening questions alone	96%	78%	4.4	0.05
Screening questions plus a "help" question	96%	89%	9	0.05

(See the following for a more detailed explanation RTJ)

2. When general practitioners considered answers to the screening questions plus the help and then added their own questions about depression, their accuracy of diagnosing depression was increased.

DISCUSSION

1. The addition of a help question to two screening questions improved specificity of the test for detecting depression from 78% to 89%. (Increased the % of true negative responses, and reduced the % of false positive responses.)
2. Importantly, the accuracy of the general practioners' diagnosis of depression after seeing the patients' responses to the classical screening questions plus the help question increased from the 35% often reported to 79%.
3. The two screening tests are shorter than other questionnaires for depression, and have similar likelihood ratios. This enables clinicians to immediately pursue the issue of depression with the help question.
4. In practice, any patient who answers yes to one or both screening questions, and yes to the help question, should be questioned further about depression.

CONCLUSION

After asking two classical questions about depression, adding a question inquiring if help is wanted improves the specificity of the tests (increased the rate of true negative responses, and reduced the rate of false positives . It improved the accuracy of general practitioner's diagnosis of depression.

BMJ October 15, 2005; 331: 884-86 Original investigation, first author B Arroll, University of Auckland, New Zealand.

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10-10 SENSITIVITY, SPECIFIFITY, POSITIVE LIKELIHOOD RATIO, NEGATIVE LIKELIHOOD RATIO OF TESTS FOR DEPRESSION: Review by the Editor

Statistical analysis in now an essential component of studies presented by peer-reviewed journals. Primary care clinicians do not need to be expert statisticians, but they should know and be able to calculate several basic functions. Clinicians should be familiar with the meaning of sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio, and be able to calculate them from the data presented. This will enhance their enjoyment of journal-reading,

Some articles present the opportunity to review these aspects of statistics as applied to general clinical practice. I enjoy calculating them.

Although I have calculated them many times from various studies, I still struggle to get them right, and then wonder if I did indeed get them right. A periodic refresher is required.

The preceding study allowed me to make these calculations from the data presented.

TO BEGIN:

The calculations are best made from the classical 2 X 2 table. The table must be set up correctly, Otherwise, results will be confusing.

On the top row place disease present and disease not present as determined by a "gold standard" which defines the disease.

In the left column place whether the test is positive, or negative

	Disease present	Disease not present
Test positive	(a)	(b)
Test negative	(c)	(d)
Total	(e)	(f)

I applied the data from page 885 of the preceding study to make the calculations:

	Depression present	Depression not present
Test positive		
Two screening questions	(a) true positive test	(b) false positive test
One or two answered "yes"	n = 45	n = 196
	96%	22%
Test negative		
Two screening questions	(c) false negative test	(d) true negative test
Both answered "no"	n = 2	n = 697
	4%	78%
Total	(e) = 45 + 2 = 47	(f) = 196 + 697 = 893

1. SENSITIVITY is calculated from the "disease present" column:

A. In the preceding study the 'disease': was depression. :

	Depression present	Depression not present
Test positive		
Two screening questions	(a) true positive test	----
One or two answered yes	n = 45	
	96% = SENSITIVITY	

Test negative

Two screening questions	(c) false negative test	----
Both answered “no”	n = 2	
	4%	
Total	(e) = 47	

Sensitivity = (a)/(e) = 45/47 = 96%

2. SPECFICITY is calculated from the “disease not present column”:

	Depression present	Depression not present
Test positive		
Two screening questions	----	(b) false positive test)
One or two answered yes		n = 196
		22%
Test negative		
Two screening questions	----	(d) true negative test
Both answered “no”		n = 697
		78% = SPECIFICITY
Total		(f) = 893

Specificity = (d)/(f) – 697/893 = 78%

3. LIKELIHOOD RATIOS

1. Positive likelihood ratio:

This is better defined as the ratio between true positive and false positive tests.

It is calculated from the top row

	Depression present	Depression not present
Test positive		
Two screening questions	(a) true positive	(b) false positive test)
One or two answered “yes”	96%	22%
Test negative		
Two screening questions	----	----
Both answered “no”		

The ratio of positive tests = (a)/(b) = 96/22 = 4.4

This means that whatever the pre-test probability of depression is, a ratio of positive tests of 4 will modestly enhance the post-test probability that depression is present. (Any value above 1.0 will do so.)

2. Negative likelihood ratio:

This is better defined as the ratio between false negative and true negative tests

It is calculated from the bottom row

	Depression present	Depression not present
Test positive	----	----
Test negative		
Two screening questions	(c) false negative test	(d) true negative
Both answered “no”	n = 2	n = 697
	4%	78%

The ratio of negative tests = (c)/(d) = 4/78 = 0.05.

This means that whatever the pre-test probability of depression is, a ratio of negative tests of 0.05 will greatly enhance the post-test probability that depression is absent. (Any value below 1.0 will do so.)

For further information about likelihood ratios go to: www.cebm.net/likelihood_ratios.asp

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