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HIGHLIGHTS DECEMBER 2000

12-1 EFFECTS OF PRAVASTATIN IN 3260 PATIENTS WITH UNSTABLE ANGINA

Patients who survived myocardial infarction or unstable angina had equally unfavorable prognoses. They benefited from lipid-control therapy with pravastatin started some months after the event.

Starting statins immediately after an episode of MI or UA may be even more beneficial, and is becoming standard therapy.

12-2 HEALTH OUTCOMES ASSOCIATED WITH CALCIUM ANTAGONISTS COMPARED WITH OTHER FIRST-LINE ANTIHYPERTENSIVE THERAPIES

"Low-dose diuretics, which have proven efficacy and low cost, should continue to be the standard therapy for hypertension."   The use of long-acting calcium antagonists should be limited to patients who do not tolerate or do not respond to diuretics, beta-blockers, or ACE inhibitors.

12-3 SELECTION OF INITIAL ANTIHYPERTENSIVE DRUG THERAPY

Diuretics and beta-blockers should be used as first-line therapy of uncomplicated hypertension. ACE inhibitors may be especially useful in patients with high risk of heart failure. Caution is needed in recommending calcium antagonists as initial therapy in populations at high risk of coronary heart disease and heart failure.

12-4 RANDOMISED CONTROLLED TRIAL OF DUAL BLOCKADE OF RENIN-ANGIOTENSIN SYSTEM IN PATIENTS WITH HYPERTENSION, MICROALBUMINURIA, AND NON-INSULIN-DEPENDENT DIABETES

The ACE-inhibitor lisinopril and the angiotensin II blocker candesartan were equally effective in reducing BP and albumin excretion in diabetic patients with hypertension and microalbuminuria.

When the 2 drugs were combined, BP and albuminuria were further improved.

Combination treatment was well tolerated.

12-5 SHORT-TERM PROGNOSIS AFTER EMERGENCY DEPARTMENT DIAGNOSIS OF TIA.

Short-term risks of patients who presented to the ED with a TIA were substantial. Five factors stratified risk and would indicate immediate intervention — age greater than 60, diabetes, symptom duration longer than 10 minutes, weakness, and speech impairment

12-6   DOES THIS PATIENT HAVE STREP THROAT?

No single element of the history or physical examination is powerful enough to confirm the probability of strep throat. Instead, physicians should consider a combination of findings including tonsillar exudate, tender or enlarged anterior cervical nodes, absence of cough, and a history of fever.

 This clinical prediction rule can be useful and can help physicians make more informed use of rapid antigen tests and throat cultures.

12-7 BAYSEAN STATISTICAL METHODS.

PRE-TEST PROBABILITY; SENSITIVITY, SPECIFICITY, POSITIVE LIKELIHOOD RATIO, NEGATIVE LIKELIHOOD RATIO, POST-TEST PROBABILITY.

12-8 A PROSPECTIVE, OBSERVATIONAL STUDY OF POSTMENOPAUSAL HORMONE THERAPY AND PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE.

"In this large, observational, prospective study, the risk of major coronary events appeared to be substantially decreased among current users of hormone therapy."

Among women taking oral conjugated estrogen (eg, *Premarin*) the risk reduction was similar in those taking 0.3 mg/d and 0.625 mg /d. (RR = 0.54 and 0.58 compared with never-users.)

Primary care clinicians might be more willing to begin prescribing *Premarin* at the 0.3 mg dose. It would be reasonable to consider that breast and ovarian cancer may be lower in women taking this dose.

12-9 DIURNAL VARIATION IN FASTING PLASMA GLUCOSE: Implications for Diagnosis of Diabetes in Patients Examined in the Afternoon

Fasting blood glucose concentrations are higher in the early AM than in the PM. The early AM increase in glucose and insulin requirements have been attributed to the "dawn phenomenon". Nocturnal elevations of growth hormone and early morning increases in cortisol secretion have been cited as causes of a higher blood glucose in the early AM. They also report higher serum insulin and serum C peptide levels in the morning in non-diabetic subjects.

If current diagnostic criteria are applied to patients tested in the afternoon, many cases of undiagnosed diabetes will be missed. (Ie, FPG may be above 126 mg/dL in the early AM, and below 126 in the PM.) "Regardless of the time of day that patients are tested, physicians need to confirm the diagnosis by testing on a different day."

12-10 MANAGING DEPRESSION IN MEDICAL OUTPATIENTS

Two simple questions can be used for case-finding:

1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past month have you often been bothered by having little interest or pleasure in doing things?

12-11 LONGITUDINAL STUDY OF MODERATE WEIGHT CHANGE AND SLEEP-DISORDERED BREATHING

Even modest weight loss is likely to be effective in managing SDB and reducing new occurrence of SDB.

12-12 PEGINTERFERON ALFA-2A IN PATIENTS WITH CHRONIC HEPATITIS C

In patients with chronic HC, a regimen of peginterferon-alfa (interferon combined with polyethylene glycol) given once weekly was more effective than interferon alfa-2a given 3 times weekly.

This compound has sustained absorption, a slower rate of clearance, and a longer half-life than unmodified interferon. This maintains an antiviral effect on hepatitis C virus (**HCV**) and makes possible a once-weekly administration.

12-13 EFFICACY OF RIVASTIGMINE IN DEMENTIA WITH LEWY BODIES.

Rivastigmine produced clinically significant behavioral effects in patients with Lewy-body dementia, and seems safe and well tolerated if titrated individually.

12-14 CHOLINESTERASE INHIBITORS; EXPANDING APPLICATIONS

The behavioral improvement achieved with rivastigmine in the study is clinically relevant. Rivastigmine has pharmacological properties that distinguish it from other cholinesterase inhibitors, so the findings may not apply to other drugs in the class.

12-15 EFFICACY AND SAFETY OF GALANTAMINE IN PATIENTS WITH MILD TO MODERATED ALZHEIMER'S DISEASE

Compared with placebo, galantamine was effective and well tolerated in Alzheimer's disease.

12-16 EFFECT OF SIBUTRAMINE ON WEIGHT MAINTENANCE AFTER WEIGHT LOSS

An individualized management program with sibutramine and diet achieved weight loss in 77% of obese patients, and sustained the weight loss in most patients continuing therapy with sibutramine for 2 years.

12-17 UNCOMPLICATED ACUTE BRONCHITIS

Decreased rates of antibiotic treatment are not associated with increased utilization, return visits, or dissatisfaction with care. "The evidence is indisputable that *not* prescribing antibiotics to patients with uncomplicated bronchitis is safe, and does *not* result in excess morbidity."

Ruling out pneumonia is the primary objective in evaluating otherwise healthy adults with acute cough illness. (Pneumonia is unlikely if heart rate is < 100, respiratory rate is < 24, and temperature $< 38^0$C [101.5^0F]

RECOMMENDED READING

REFERENCE ARTICLES

12-1 EFFECTS OF PRAVASTATIN IN 3260 PATIENTS WITH UNSTABLE ANGINA

The admission rate of patients with unstable angina **(UA)** often is greater than the admission rate for myocardial infarction **(MI).** The role of lipid control in UA has received little attention. Most attention has been directed at patients with MI.

This *secondary* prevention study assessed long-term risks of major cardiovascular events in patients with UA and MI, and the effect of lipid-control with pravastatin (*Pravachol*) on subsequent events.

Conclusion: Patients who survived MI or UA have a similar long-term prognosis. Both benefited from lipid control with pravastatin.

STUDY

1. Randomized trial followed over 3000 patients with unstable angina, and over 5000 patients with acute MI. All events had occurred 3 to 36 months before randomization. Mean LDL-cholesterol = 150 mg/dL.
2. The study did not have strict criteria for diagnosis of UA, but relied on hospital discharge diagnosis.
3. Randomly assigned to: 1) 40 mg of pravastatin/d, or 2) placebo.
4. Follow-up = mean of 6 years for a range of cardiovascular events.

RESULTS

1. Survival of patients with UA and MI was similar in the placebo groups.
2. *MI group:* Relative risk reduction for mortality in the MI-pravastatin group vs placebo was 21%. Pravastatin significantly reduced the rates of all prespecified coronary end-points.
3. *UA group*: Relative risk reduction for mortality in the UA-pravastatin group vs placebo was 26%. Pravastatin significantly reduced coronary heart disease mortality, total mortality, myocardial infarction, need for coronary revascularization, and hospital admissions.

DISCUSSION

1. Patients who survive UA as well as those who survive MI have a similar adverse long-term prognosis. Over 6 years, there was a high rate of subsequent episodes of UA (25%) and MI (10%).
2. Over 6 years, pravastatin was associated with a similar improvement in prognosis in both groups.
3. In absolute terms, pravastatin therapy of 1000 patients with UA could prevent 33 deaths, 24 non-fatal MIs, and 26 coronary revascularizations.
4. The study did *not* include patients treated with statins immediately after the episode of MI or

UA. Observational studies suggest that patients with UA or MI who start statin drugs immediately (within a few hours) after the event have a better prognosis. Starting pravastatin some time after the occurrence of UA (3 to 36 months) also improved prognosis. Starting lipid-control therapy in the hospital may lead to better adherence to the therapy.

5. There are theoretical reasons, other than lipid control, why statins may benefit: improved endothelial function, suppressed inflammatory cell activity, and decreased thrombus formation.

CONCLUSION

Patients who survived MI or UA had an unfavorable prognosis. They benefited from lipid-control therapy with pravastatin started some months after the event.

Lancet December 2, 2000; 356: 1871-75 Original investigation by the "Long-term Intervention with Pravastatin in Ischemic Disease (LIPID)" study, first author Andrew M Tonkin, National Heart Foundation of Australia, Melbourne. **www.thelancet.com**

 Comment:

  Lipid control, of course, includes diet. Other risk factors should be reduced as well.

  Beginning statins immediately after an ischemic event is becoming standard therapy.

  Is there low cut-point for LDL-cholesterol for which statins would not be recommended?   I doubt it. The study included patients with total cholesterol levels as low as 4.0 mmol/L (150 mg/dL).   RTJ

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12-2 HEALTH OUTCOMES ASSOCIATED WITH CALCIUM ANTAGONISTS COMPARED WITH OTHER FIRST-LINE ANTIHYPERTENSIVE THERAPIES: A Meta-Analysis Of Randomized, Controlled Trials.

  Lowering BP with diuretics and beta-blockers as first-line agents reduces risk of major cardiovascular complications of hypertension.

  Are calcium antagonists inferior or superior? Several controlled trials of long-acting calcium antagonists, compared with other therapies, show similar BP-lowering potential, but trends toward higher cardiovascular event rates.

  This study assessed the effects of calcium antagonists and other anti-hypertensives on major cardiovascular events.

  Conclusion: Calcium antagonists were inferior to other types of first-line agents.

STUDY

1. Meta-analysis of 9 trials (27 000 patients) in which hypertensive patients were randomized to calcium antagonists (intermediate-acting and long-acting) or other anti-hypertensive drugs.
2. Follow-up = at least 2 years.

RESULTS

1. Calcium antagonists achieved control of both systolic and diastolic BP similar to other drugs.
2. Compared with patients assigned diuretics, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors. Those assigned to calcium antagonists had a significantly higher risk of acute myocardial infarction (odds ratio = 1.3), congestive heart failure (OR = 1.3), and major cardiovascular events (OR = 1.1).
3. No significant differences in risk of stroke and all-cause mortality.

DISCUSSION

1. Combined results of 9 trials showed that calcium antagonists were associated with a significantly higher risk of major complications of hypertension.
2. This was despite similar control of BP. Mechanisms not involving BP control are important in determining, at least in part, therapeutic effects.
3. Concentration on a single outcome in a hypertension trial (eg, BP control) may lead to an incomplete definition of the drug's therapeutic profile.
4. It is not evident whether calcium antagonists have a harmful effect on coronary heart disease and heart failure, or whether other drugs have special benefits. Another trial showed that the calcium antagonist nitrendipine (compared with placebo) had a lower risk of stroke. (BP control may have an especially important role in preventing stroke.)
5. Therapeutic decisions should be based on a drug's overall risks and benefits, the patient's risk profile, and the patient's preference. If, for an individual patient, prevention of stroke is the main or only concern, calcium antagonists may be equivalent of other drugs tested (*But, not superior. RTJ*) . However, for prevention of heart failure or combined major cardiovascular events, the findings of this study suggest that calcium antagonists are inferior to other drugs as first-line therapy.
6. The surrogate end-point, BP lowering, is not a consistent and valid marker of all the therapeutic benefits of anti-hypertensive agents.
7. The benefits of calcium antagonists as add-on therapy has not been assessed. "For a combination of antihypertensive therapies, reliance on the classes known to be superior — low-dose diuretics, beta-blockers, and ACE inhibitors — seems prudent."
8. "Low-dose diuretics, which have proven efficacy and low cost, should continue to be the

standard therapy for hypertension. The use of long-acting calcium antagonists and alpha-blockers should be limited to patients who do not tolerate or do not respond to diuretics, beta-blockers, or ACE inhibitors."

CONCLUSION

This large database suggests that calcium antagonists are inferior to other types of anti-hypertensive drugs as first-line agents to reduce risk of several major complications of hypertension.

Lancet December 9, 2000; 1949-54 Original investigation, first author Marco Pahor, Wake Forrest University, Winston-Salem North Carolina **www.thelancet.com**

 Comment:

Important point: BP lowering is not the *only* benefit of antihypertension drugs. ACE inhibitors (eg, ramipril) produce their most benefit by non-BP-lowering effects. BP per se is not the whole story. RTJ

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12-3 SELECTION OF INITIAL ANTIHYPERTENSIVE DRUG THERAPY

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

Diuretics; beta-blockers: Meta-analyses of diuretic and beta-blocker therapy (compared with placebo) report a reduction in coronary heart disease by 16%, stroke by 38%, cardiovascular death by 21%, and all-cause mortality by 13%.

ACE inhibitors: Compared with placebo, patients treated with ACE-inhibitors had a lower risk of stroke by 30%, coronary heart disease by 20%, major cardiac events by 20%, cardiovascular death by 26%, and total mortality by 16%. Risk of heart failure was reduced by 13% (not statistically significant). This benefit was impressive and was achieved in the context of a small difference in BP (3/1 mm Hg). The benefits were likely *not* mediated just by BP lowering. Benefits were also reported in non-hypertensive patients.

Calcium antagonists (compared with placebo) have also been reported to reduce risk of stroke, major cardiovascular events, and cardiovascular death. Compared with diuretics and beta-blockers, calcium antagonists have been associated with a 14% *reduction* in risk of stroke, but a 12%-15% *increase* in risk of coronary heart disease and heart failure. Compared with ACE inhibitors, calcium antagonists were also associated with increased risk of coronary heart disease and heart failure.

What are the implications for clinical practice? Diuretics and beta-blockers should be used as first-line therapy of uncomplicated hypertension. ACE inhibitors may be especially useful in patients with

high risk of heart failure. Caution is needed in recommending calcium antagonists as initial therapy in populations at high risk of coronary heart disease and heart failure.

Most patients with hypertension require more than one drug to achieve good BP control. "Therefore, a combination of diuretics, beta-blockers, ACE-inhibitors, and calcium antagonists, based on a patient's absolute level of risk for cause-specific cardiovascular disease, may provide the best approach."

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12-4 RANDOMISED CONTROLLED TRIAL OF DUAL BLOCKADE OF RENIN-ANGIOTENSIN SYSTEM IN PATIENTS WITH HYPERTENSION, MICROALBUMINURIA, AND NON-INSULIN-DEPENDENT DIABETES

The role of inhibitors of the renin-angiotensin system in preventing microvascular complications of diabetes, particularly nephropathy, has been clearly shown. In many patients with diabetic kidney disease and hypertension, angiotensin converting enzyme-inhibitors **(ACE)** alone fails to lower BP to target levels.

There is increasing evidence that angiotensin II, the effector molecule of the renin-angiotensin system, can be generated in pathways alternative to the ACE-inhibitors. The advent of angiotensin II blockers provides an alternative approach to blocking the renin-angiotensin system.

This study compared the effects of the ACE II blocker, candesartan (*Atacand*) and the ACE inhibitor lisinopril (*Prinivil;Zestril*) on BP and urinary albumin excretion in patients with type 2 diabetes and hypertension.

Conclusion: Both drugs used separately were equally effective in reducing BP and microalbuminuria. Combination therapy was more effective than either alone.

STUDY
1. Multicountry, randomized, parallel group, double-blind study followed almost 200 patients with type 2 diabetes and hypertension. (Mean age = 60; mean BP 163/96)
2. All had diastolic BP 90 to 110 mm Hg. and increased albumin excretion.
3. First randomization: Candesartan alone 16 mg/d, or 2) lisinopril alone 20 mg/d for 12 weeks.
4. Second randomization: Candesartan alone, or 2) lisinopril alone, or 3) both drugs combined.
   (Unless the patient had achieved a diastolic BP < 80 at 12 weeks.)

RESULTS

1. First randomization	Candesartan	Lisinopril
Mean reduction in diastolic BP (mm Hg)	-9.5	-9.7
Mean reduction in systolic BP (mm Hg)	-20	-20
Reduction in urinary albumin:creatinine ratio	-30%	-46%

2. Second randomization. Effects of candesartan + lisinopril	
Mean reduction in diastolic BP (mm Hg)	- 16.3
Mean reduction in systolic BP (mm Hg)	- 30
Reduction in urinary albumin:creatinine ratio	- 50%

3. Lisinopril alone and candesartan alone both reduced mean BP to 145/85. Combination therapy reduced BP to 135/80

4. Drugs were generally well tolerated. Cough in the lisinopril group occurred in less than 10% (3 patients withdrew) . 14 patients withdrew because of dizziness, weakness,

DISCUSSION

1. Both drugs reduced BP and urinary albumin excretion to an equal extent. The combination was more effective than either drug alone.

2. "We can confirm that dual blockade of the renin-angiotensin system, both at the level of ACE and at the level of the angiotensin II receptor, is associated with more effective reduction on BP than observed with a single agent." This observation extends to patients with diabetes.

4. The combination also had a beneficial effect on reducing albumin excretion.

5. The drugs were associated with an excellent safety profile.

6. Treatment of diabetic patients with hypertension should be aggressive, especially in the presence of renal disease. Dual blockade is particularly effective.

CONCLUSION

The ACE-inhibitor lisinopril and the angiotensin II blocker candesartan were equally effective in reducing BP and albumin excretion in diabetic patients with hypertension and microalbuminuria.

When the 2 drugs were combined, BP and albuminuria were further improved.

Combination treatment was well tolerated.

Comment:

The investigators stressed changes in *diastolic* BP as the beneficial result. Actually systolic is a better prognostic marker in hypertension-diabetes as well as in hypertension alone. The reduction in systolic with either drug alone was from 165 to 145. The reduction in systolic with the combination was from 165 to 135 — near the target range (130) for systolic in patients with diabetes. RTJ

Costs: My pharmacy quotes: Prinivil $30 for 30— 20mg tablets

Atacand $ 39 for 30 —16 mg tablets

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12-5 SHORT-TERM PROGNOSIS AFTER EMERGENCY DEPARTMENT DIAGNOSIS OF TIA.

About 15% of patients experiencing stroke report a history of transient ischemic attack (**TIA).** Effective prevention of subsequent stroke in patients with TIA could significantly reduce overall stroke incidence.

The need for urgent intervention is not clear for patients with TIA. They have usually returned to their baseline level of function by the time they are evaluated. Indeed, it is often impossible to confirm a diagnosis since symptoms are transient and may have other causes such as migraine, seizures, and syncope. Agreement on TIA diagnosis between independent observers is poor. Clinical decisions are often based on the final diagnosis of an emergency department **(ED)** physician.

Management of patients with TIA varies widely. Some institutions admit all patients; others proceed with outpatient evaluation. Lack of understanding natural history of TIA has led to variability in clinical practice. Determining the short-term prognosis and risk factors for stroke after TIA may provide guidance in determining which patients need rapid evaluation.

This study determined the short-term risk of stroke and other adverse events among patients after an ED diagnosis of TIA.

Conclusion: The short term risk of stroke is substantial. Some characteristics of patients may aid in decisions for expeditious evaluation and treatment.

STUDY
1. Multicenter cohort study followed over 1700 patients (mean age = 72) who had been identified by ED physicians as having had a TIA.
2. Determined the short-term risk of stroke and other adverse events.
3. Follow-up = 90 days.

RESULTS

1. Overall, stroke and other adverse events occurred in 25% of patients in the 90 day

   follow-up. These included cardiovascular events (2.6%); death (2.6%); and recurrent TIA (13%)

2. During follow-up, 10% returned to the ED with a stroke. About half of these strokes occurred within

   the first 2 days.

3. Five factors were independently associated with stroke:

	Odds Ratio
Age greater than 60.	1.8
Diabetes	2.0
Symptom duration longer than 10 minutes	2.3
Weakness	1.9
Speech impairment	1.5

4. Stroke-free survival varied from about 96% in those with 1 risk factor to 65% when all 5 were present.

DISCUSSION

1. TIAs carry a substantial short-term risk of stroke, hospitalization for cardiovascular events, and

   death. Half of the strokes occurred within 2 days of the TIA.

2. Diagnosis of TIA is problematic. Even among neurologists, there is a low inter-observer agreement.

3. Timing of presentation may be important. Since more than half the strokes occurred within 2 days,

   if a patient presents for evaluation after 3 days, the period of highest risk has passed.

4. Stratification of risk allows targeting expensive interventions (eg, hospitalization and urgent

   carotid ultrasound) to those at greatest risk.

CONCLUSION

   Short-term risks of patients who presented to the ED with a TIA were substantial. Five risk factors

stratified risk and would indicate immediate intervention.

 Comment:

   Will it turn out that the subset of patients with TIA at highest risk for stroke within 2 days might

benefit from immediate angiography and thrombolytic therapy ?

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12-6 DOES THIS PATIENT HAVE STREP THROAT?

Identifying beta-hemolytic streptococcus (group A) as the cause of sore throat is clinically important. Treatment with antibiotics decreases the severity of symptoms; reduces the duration and likelihood of suppurative complications and rheumatic fever (rare now in the US), and the risk of transmission.

This article reviewed the precision and accuracy of the clinical examination (history and physical examination) in diagnosing strep throat.

"Always doing a throat culture or rapid antigen test can lead to overtreatment of low-risk patients due to excessive false positive tests[1], and undertreatment of high-risk patients due to false negative tests."

By using the pre-examination (pre-test) probability of strep throat followed by the clinical examination, patients can be divided into 3 groups: 1) very high probability (these could receive immediate empiric antibiotic therapy), 2) intermediate probability (require further diagnostic testing), and 3) low probability (may require only symptomatic therapy and appropriate follow-up rather than further diagnostic testing or treatment).

This study found 9 relevant studies in a MEDLINE search about diagnosis of strep throat using history and physical examination.

Conclusion: No single element of the history or physical examination is sufficiently accurate to diagnose strep throat. A combination of findings can be used to categorize patients for immediate antibiotic therapy, further diagnostic tests (culture or rapid antigen test), or symptomatic therapy and follow-up.

STUDY

1. Considered 9 large blinded, prospective studies each with over 300 patients presenting with sore throat. All reported history and physical examination data.
2. All used throat culture as the reference standard for diagnosis.

RESULTS

1. Clinical presentation.

   A. Symptoms:

   Classically, onset of strep sore throat is sudden. It is typically described as severe. Fever is moderate. Systemic symptoms are usually present.

   B. Signs:

   Breath: characteristically foul.

   Skin: Rash (scarlet fever) may be present. Fine erythematous papules begin on the trunk

and spread to the extremities sparing the palms and soles. Rash may be accentuated in antecubital skin creases (Pastia sign). Rash blanches on pressure, and has a sandpapery feel. "Strawberry tongue" and circumoral pallor may be present. Desquamation of the skin may occur after a week or so.

Pharynx and uvula: may be erythematous and edematous (beefy and bright red with the color ending abruptly at the soft palate). Petechiae may be present on the soft palate. Lymphoid tissue in posterior pharynx may be hypertrophied. Posterior pharynx and tonsils are covered with a gray-white membrane or exudate. [Pharyngeal vesicles and ulcers are associated with viral infections. Their presence reduces the likelihood of beta-hemolytic strep (group A) being present.]

Lymph nodes: anterior cervical nodes are often enlarged and tender, especially at the angle of the jaw.

(*I enjoyed this review of the classical evolution of hemolytic strep infections and scarlet fever. The full blown picture must be rare now in the US. RTJ*)

2. Precision: In this context, the authors mean degree of concurrence between observers assessing various symptoms and signs (present or absent). Studies have reported the concurrence is high.

3. Diagnostic accuracy of symptoms and signs:

A. Diagnostic accuracy is measured by considering the pre-test probability of the presence of strep throat, sensitivity of diagnostic tests, specificity of diagnostic tests, the positive likelihood ratio, and the negative likelihood ratio, to arrive at a post-test probability that strep is the cause of the sore throat. (*See the following article for clarification. RTJ)*

B. The diagnostic points with the highest likelihood of *ruling in* strep throat were: presence of tonsillar exudate (positive likelihood ratio = 3.4); pharyngeal exudate (positive likelihood ratio = 2.1); and history of exposure to strep throat within the preceding 2 weeks (positive likelihood ratio = 1.9)

C. The diagnostic points with the highest likelihood ration of *ruling out* strep throat were: absence of tender anterior cervical nodes (negative likelihood ratio = 0.60); absence of tonsillar enlargement (negative likelihood ratio = 0.63); or absence of tonsillar exudate (negative likelihood ratio = 0.74)

4. No individual element of history or physical examination is accurate enough by itself to rule in or rule out strep throat.

5. Other validated clinical prediction rules have been described for adult populations. One of the best is a simple prediction rule developed by Centor. It considers 4 signs and symptoms:

Tonsillar exudate

Presence of swollen, tender cervical nodes

Absence of cough

History of fever

Presence of 3 or 4 of these increases the likelihood that strep is the cause. Those with none of the 4 are very unlikely to have strep as the cause.

6. An algorithm on page 2917 presents a method of evaluating adults with sore throat. It assesses the likelihood of risk (low, medium, and high).

DISCUSSION

1. Previous studies of the differential diagnosis of sore throat report that viral infections are by far the most common cause.

2. The investigators used Baysean statistical methods to arrive at the probability that strep throat is present:

This combines 1) pre-test probability, 2) calculation of sensitivity and specificity of the tests, 3) likelihood ratios of tests, to 4) arrive at a post-test probability that strep is the cause. (Note that a "test" may be an item in the history or examination as well as a laboratory test such as culture.)

CONCLUSION

No single element of the history or physical examination is powerful enough to confirm the probability of strep throat. Instead, physicians should consider a combination of findings including tonsillar exudate, tender or enlarged anterior cervical nodes, absence of cough, and a history of fever.

A well validated clinical prediction rule can be useful and can help physicians make more informed use of rapid antigen tests and throat cultures— presence of tonsillar exudate, tender cervical nodes, absence of cough, and history of fever.

JAMA December 13, 200; 284: 2912-18   "The Rational Clinical Examination", original investigation, first author Mark H Ebeell, Michigan State University, East Lansing **www.jama.com**

1. Treating the carrier state.

 Comment:

The authors concentrated on a quantitative assessment of the probability of the presence of strep throat. This was not successful. They fell back on a clinical guideline which combined a number of signs and symptoms which made arriving at the correct diagnosis more likely.

The latest issue of "Clinical Evidence" is not helpful. There is a short comment on treatment of "sore throat" (not strep throat).

See following article for a review of the Baysean statistical method the authors considered in the study. RTJ

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BAYSEAN STATISTICAL METHODS.

12-7 PRE-TEST PROBABILITY; SENSITIVITY, SPECIFICITY, POSITIVE LIKELIHOOD RATIO, NEGATIVE LIKELIHOOD RATIO, POST-TEST PROBABILITY.

The authors of the previous article discussed statistical applications which attempt to quantitate the probability of the presence or the absence of strep throat. I review them mainly for my own benefit. If I do not review these principles periodically, I forget them. Familiarity with the standard 2 X 2 tables clarifies the concepts. RTJ

Pre-test probability

Pre-test probability is the probability that a disease is present among patients entered into a trial on the basis of entrance criteria, and before any confirmatory tests are performed. Pretest probability is based on clinical judgement and the prevalence of the disease in the population considered. In the preceding article, the entrance criterion was the simple statement "I have a sore throat". The pre-test probability that strep caused the sore throat was based primarily on age, clinical setting, and the season — more common in children, more common in those seen in the emergency department than in the office, and more common in fall and winter.   A reasonable estimate of *pre-test* probability of strep throat in office-based patients presenting with sore throat is 5% to 10%.

Clinically, in an individual patient, there is always a judgement that a disease may be present (pre-test probability) which leads to testing. The exception may be screening, which by definition is performed in individuals who have no indication of the disease in question. Even here there is a pre-test probability that the disease may be present.

Tests are then preformed on each member of the cohort to strengthen the probability that the disease in question is or is not present. In the preceding article the tests were simply historical and physical examination observations. (Eg, pharyngeal exudate, cervical nodes.) Or the test may be an ECG, a chemical determination, radiography, and many others.

Sensitivity of a test:

	Disease present	Disease absent
Test positive	True positive (a)	

Test negative   False negative (c)

Sensitivity is the true positive percentage, or true positive (a) ÷ (true positive + false negative) [a ÷ (a + c)]

A. No test is perfect. Thus, there will be patients *who have the disease* who have a *positive* test (true positive tests). There will also be patients *who have the disease* who have a *negative* test (false negative tests). Sensitivity is the ratio (expressed as a percentage) between the number of patients who have a true positive test and the total number of patients who *actually have the disease.* (The ratio between the true positive tests and the sum of true positive tests plus false negative tests. The sum is always 100%.)

   If, of all patients tested who actually have the target disease, 85% of the tests are positive (true positive) and 15% are negative (false negative), the sensitivity of the test is 85 / 85 + 15; or 85/100; = 85%.

B. To calculate the sensitivity of a test:

   1) First determine the total number of patients in the trial *who have the disease* in question defined by the "gold standard". The sensitivity of a test concerns *only* those patients in the trial who *actually* have the disease.

   2) Determine the % of patients in this group who have a positive test. (True positive test percentage;

      or true positive tests ÷ (true positive tests + false negative tests)

   3) This is the sensitivity of the test.

C. Simply stated, sensitivity of a test is the percent of patients who have the disease who have a positive test.

Specificity of a test:

	Disease present	Disease absent
Test positive		**False positive (b)**
Test negative		**True negative (d)**

Specificity is the true negative percentage, or true negative (d) ÷ (false positive + true negative.)   [d ÷ (b + d)]

A. No test is perfect. Thus, there will be patients *who do not have the disease* who have a *negative* test (true negative tests). There will also be patients *who do not have the disease* who have a *positive* test (false positive tests). Specificity is the ratio between the number of patients who have a true negative test and the number of patients who *do not have the disease.* (The ratio

between true negative tests and the sum of true negative tests plus false positive tests. The sum is always 100%.)

If, of all patients in the cohort tested who actually do *not* have the target disease, 90% of the tests are negative (true negative) and 10% are positive (false positive), the specificity of the test is 90/10; or 90%

B. To calculate the specificity of a test:

 1) First determine the total number of patients in the trial *who do not have the disease* in question.

The sensitivity of a test concerns *only* those patients in the trial who *do not* have the disease.

2) Determine the % of the total patients in this group who have a *negative* test. (True negative %; or true negatives ÷ (true negatives + false positives.)

3) This is the specificity of the test.

C. Simply stated, specificity of a test is the % of patients who do *not* have the disease who have a *negative* test.

Likelihood ratios:

A. Positive likelihood ratio:

	Disease present	**Disease absent**
Test positive	**True positive (a)**	**False positive (b)**
Test negative		

Positive likelihood ratio is the ratio between true positive tests and false positive tests — (a) ÷ (b)

Positive likelihood ratio:

To determine the positive likelihood ratio, first determine all those in the cohort who have positive tests. The positive likelihood ratio concerns only those in the cohort who have positive tests (true positive + false positive). It estimates the likelihood that the target disease is present when the test is positive.

For example, a given test is *positive* in 90% (true positives) in those who have the target disease, and positive in 10% (false positives) in those who do not have the disease. The likelihood ratio of positive tests is 90/10 = 9.

Thus it is likely that about 9 out of every 10 patients who have a positive test will have the disease, and 1 out of 10 will not have the disease.

In this example, the accuracy of the positive test is high. The test helps to *rule in* the disease.

B. Negative likelihood ratio

	Disease present	Disease absent
Test positive		
Test negative	False negative (c)	True negatives (d)

Negative likelihood ratio is the ratio between false negative and true negatives — (c) ÷ (d)

Negative likelihood ratio:

To determine this ratio, first determine all those in the cohort who have negative tests. The negative likelihood ratio concerns only those in the cohort who have negative tests (false negative + true negative). It estimates the likelihood that the target disease is *not* present when the test is negative.

For example, a given test is *negative* in 10% (false negative) in those who have the disease, and negative in 90% (true negative) in those who do *not* have the disease. The likelihood ratio of negative tests = 10/90 = 0.11

Thus it is likely that about 9 of 10 who have a negative test will *not* have the disease, and about 1 in 10 with a negative test will have the disease.

In this example, the accuracy of the negative test is moderately high. The test helps to *rule out* the disease.

Accuracy of a test:

For help in *ruling in* the disease: The *greater* the *positive* likelihood ratio of the test, the more likely it is that the patient has the disease. A positive likelihood ratio of 2 to 5 provides weak accuracy for the diagnosis. A positive likelihood ratio of 5 to 10 provides moderate accuracy that the disease is present; over 10 provides strong accuracy.

For help in *ruling out* the disease: The *lower* the *negative* likelihood ratio of the test, the more likely it is that the patient does *not* have the disease. Eg, a negative likelihood ratio of 0.5 to 0.2 provides weak accuracy that the disease is *not* present; 0.2 to 0.1 provides moderate accuracy; less than 0.1 provides strong accuracy.

Post-test probability:

Is calculated from 1) pretest probability, and 2) likelihood ratios.

Clinical epidemiologists calculate the post-test probability by nomogram or by using odds ratios. This results in a spuriously "exact" probability. (Eg, patients with a given pre-test probability and a given

positive likelihood ratio might have a post-test probability of having the target disease of 96%; or with a given negative likelihood ratio might have a post-test probability of not having the target disease of 0.5%.) Considering the wide variation of estimates of pre-test probability and variations in the tests these estimates are far from exact.

In clinical medicine, I believe it is simpler to make a reasonable judgement about post-test probability by considering the pre-test probability and adjusting it by the likelihood ratios.

For example, if the likelihood ratio is 10, this increases the probability that the disease is present 10-fold. If the pre-test probability is high this almost assures that the disease is present. If the pre-test probability is low, doubt remains.

Comment:

Acquaintance with these calculations makes journal-reading more enjoyable. Sensitivity and specificity are frequently mentioned. The calculations are simple, but tricky. I have found several articles in which sensitivity and/or specificity were incorrectly stated. Indeed, I am not sure I always state them correctly.

Epidemiologists apply these calculations to groups of patients; primary care clinicians to individual patients. Clinicians constantly employ these concepts, most often intuitively.

Note that in the preceding study about diagnosis of strep throat, the positive likelihood ratio of one test was low (presence of tonsillar exudate = 3.4). This provides only weak accuracy of post-test probability of the diagnosis. When 4 symptoms or signs were present, the positive likelihood ratio was enhanced.

Primary care clinicians rely on multiple tests to arrive at a high probability of the disease being present (or absent). Every historical point of the illness, every sign, every lab test, will increase (or decrease) the probability that the illness is (or is not) present. In addition, clinicians usually have the advantage of continuing observation which clarifies the diagnostic probabilities. RTJ

Practical Pointers for Primary Care December 2000; 12-7 Commentary by Richard T. James Jr, Editor. Much of this commentary was based on articles in the ACP Journal Club, and in the small volume "Evidence-Based Medicine", Churchill-Livingston 19997, first author David L Sackett.

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The Debate Continues

12-8 A PROSPECTIVE, OBSERVATIONAL STUDY OF POSTMENOPAUSAL HORMONE THERAPY AND PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE.

"Whether to take hormone therapy (hormone-replacement therapy; **HRT)** is one of the most difficult medical decisions that healthy postmenopausal women face."

Most primary prevention studies have reported that long-term users are at lower risk for coronary events, but numerous questions remain.

This study investigated the duration, dose, and type of HRT in *primary* prevention of cardiovascular disease.

Conclusion: In *primary* prevention, HRT appeared to decrease risk of coronary disease, but not risk of stroke.

STUDY

1. The Nurses' Health Study followed over 70 000 women from 1976 to 1996.
2. Identified over 1250 major coronary events (non-fatal myocardial infarction or fatal coronary disease), and over 750 strokes.
3. Obtained data on postmenopausal HRT use.
4. Calculated relative risks between users and non-users.

RESULTS

1. When all cardiovascular risk factors were considered, the risk of major coronary events was lower among current users of HRT, including short-term users, compared with never-users. RR = 0.61. The reduction was similar between women taking oral conjugated estrogen alone, and those taking estrogen plus progestin.
2. Among women taking oral conjugated estrogen (eg, *Premarin*) the risk reduction was similar between those taking 0.3 mg/d and 0.625 mg /d. (RR = 0.54 and 0.58 compared with never-users.)
3. The risk of stroke was significantly *increased* among those taking 0.625 mg (RR = 1.35), and among those taking estrogen + progestin (RR = 1.45).

DISCUSSION

1. "In this large, observational, prospective study, the risk of major coronary events appeared to be substantially decreased among current users of hormone therapy."
2. Daily oral conjugated estrogen (both 0.625 mg and 0.3 mg) was associated with a reduced risk of coronary heart disease
3. Estrogen alone and estrogen combined with progestin were also associated with a reduced risk of coronary heart disease.
4. Among those taking conjugated estrogen 0.625 mg/d or more, and among those taking

estrogen + progestin there was an *increased* risk for stroke.

5. A recent study of hormone therapy for *secondary* prevention[1] reported an *increased* risk during the first year of therapy, followed by a *decreased* risk later. Another Nurses' Health Study (secondary prevention) also reported a higher rate of recurrent cardiovascular events with short term use.

6. This study of *primary* prevention observed a strong dose-response relation between estrogen and *increased* risk of stroke. Conjugated estrogen 0.3 mg/d may be safer than 0.625 mg/d. (And 0.3 mg/d is also strongly associated with a *reduced* risk of heart disease.)

7. The risk of adverse effects during the first year of *primary* prevention may be less than that during the first year for *secondary* prevention.

8. This study also found few substantial differences in lifestyle factors between women who took hormones and those who did not. All analyses were carefully adjusted for potential confounders including cigarette smoking and body mass index. "Confounding by lifestyle or health practice probably does not explain our observations." (Ie, evidence against the "healthy user" confounding effect.)

CONCLUSION

This study of *primary* prevention indicated that postmenopausal hormone therapy may be associated with prevention of coronary events. Low doses of estrogen (eg, 0.3 mg/d of conjugated estrogen) as well as estrogen combined with progestin may be equally effective in providing the benefit.

The risk of stroke appeared to be greater in those taking 0.625 mg/d or more of conjugated equine estrogen, and in those taking progestin in combination with estrogen.

Annals Int Med December 2, 2000; 133: 933-41 Original investigation, first author Francine Grodstein, Channing Laboratory and Brigham and Women's hospital, Boston Mass. **www.annals.org**

1 "Randomized Trial of Estrogen plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women" Heart and Estrogen/Progestin Replacement Study (HERS) JAMA 1998; 280: 605-13 **www.jama.com**

Comment:

So . . . what should the primary care clinician advise? Primary prevention of heart disease is *not* the prime reason for prescribing HRT. And it should not be prescribed solely for this purpose. It should be prescribed with caution, if at all, in women at high risk of coronary heart disease (including secondary prevention) because of the likelihood of increased risk during the first year or two. However, for women

at ordinary risk, low dose HRT prescribed at the time of menopause may be beneficial over the years in primary prevention.

The trend now is to prescribe lower doses (eg, 0.3 mg/d conjugated estrogen). At this dose benefits remain but risks are decreased. A recent study reported continuous 0.3 mg equine conjugated estrogen combined with low dose progesterone had a sparing effect on bone mass as compared with placebo. Calcium and vitamin D were added. Low dose therapy beginning at the menopausal onset may relieve some of the anxiety about adverse effects of estrogen, especially on risk of breast and ovarian cancer.

The confounding of the "healthy user" effect has been partially dispelled by this study.

Two observations make strong biological sense for the protective effect of estrogen: 1) the lower risk of CHD in the premenopause and the lag in risk of about 10 years between men and women, and 2) the beneficial effect of estrogen on the lipid profile. RTJ

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12-9 DIURNAL VARIATION IN FASTING PLASMA GLUCOSE: Implications for Diagnosis of Diabetes in Patients Examined in the Afternoon

Current diagnostic criteria for diabetes are based on fasting plasma glucose (**FPG**) levels (obtained in the morning after an overnight fast). A value of 126 mg/dL (7.0 mmol/L) or more indicates diabetes.

Many patients are seen in the afternoon with an uncertain state of fasting. Because plasma glucose levels are *higher* in the morning and *lower* in the afternoon, it is not clear whether these diagnostic criteria can be applied to patients tested in the afternoon.

This study analyzed data from the US population-based Third National Health and Nutrition Examination Study. It included persons over age 20 (n > 13 000) who had no previously diagnosed diabetes. They were randomized to morning or afternoon examinations. Those examined in the morning fasted for a median of 13 hours; those examined in the afternoon, 7 hours.

Results: Mean FPG in the morning was 97.4 mg/dL; in the afternoon 92.4 mg/dL. Median FPG levels dropped between 8 AM and 11AM from 96 mg/dL to 91 mg/dL. The prevalence of afternoon-examined participants with FPG of 126 mg/dL or greater (1.2%) was half that of those examined in the morning (2.8%). In the afternoon, a FPG level of 114 or greater would indicate diabetes. (*Note: from the figure on page 3158, median FPG fell to afternoon levels by 10 AM. Thus late morning samples may be misleading as well. RTJ*)

Conclusion: If current diagnostic criteria are applied to patients seen in the afternoon, many cases of undiagnosed diabetes will be missed. "Regardless of the time of day that patients are tested, physicians need to confirm the diagnosis by testing on a different day."

JAMA December 27, 2000; 284: 3157-59 Original investigation, first author Rebecca J Troisi, Social and Scientific Systems, Inc, Bethesda MD. **www.jama.com**

Comment:

As the authors mention, the early AM rise in glucose and insulin requirements have been attributed to the "dawn phenomenon". Nocturnal elevations of growth hormone and early morning increases in cortisol secretion have been cited as causes. They also report higher serum insulin and serum C peptide levels in the morning in non-diabetic subjects.

The recently lowered diagnostic cut-point for diabetes (126 mg/dL) makes re-testing much more necessary. RTJ

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REFERENCE ARTICLE

12-10 MANAGING DEPRESSION IN MEDICAL OUTPATIENTS

"Depression is second only to hypertension as the most common chronic condition encountered in general medical practice."

This review discusses diagnosis, assessment of the risk of suicide, need for treatment, options for treatment, selected internet resources, and prognosis.

Two simple questions can be used for case-finding:

1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past month have you often been bothered by having little interest or pleasure in doing things?

If "no" to both, the patient is not likely to have a major depression. If "yes" to either, proceed with a clinical interview. (Page 1943)

The *sensitivity* of this test (the 2 questions) is 96% when depression is present. (Ie, for every 100 patients with depression diagnosed by DSM-IV criteria, 96 responded positively (true positive) to one or both questions; 4 responded negatively to both questions (false negative).

The *specificity* of this test (the 2 questions) is only 56%. (Ie, for every 100 patients without depression by DSM-IV criteria, 56 responded negatively to both questions (true negative); 44 responded positively to one or both questions (false positive).

NEJM December 28, 2000; 343: 1942-50 Review article, first author Mary A Whooley, University of California, San Francisco. **www.nejm.com**

Comment:

Primary care physicians should use these simple screening questions more routinely. RTJ

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12-11 LONGITUDINAL STUDY OF MODERATE WEIGHT CHANGE AND SLEEP-DISORDERED BREATHING

Sleep-disordered breathing (**SDB**) is characterized by repeated episodes of apnea and hypopnea during sleep. It is highly prevalent and is associated with behavioral morbidity; hypertension, cardiovascular disease, and mortality.

Obesity is a strong correlate of SDB.

This study measured the association between weight change and severity of SDB.

Conclusion: Weight loss, even if moderate, was effective in managing SDB.

STUDY

1. Population-based, prospective cohort study randomly selected about 700 employed Wisconsin residents (mean age = 46; mean BMI = 30). All were evaluated twice at a 4-year interval for SDB. (High-quality polysomnography was used.)
2. Defined moderate-to severe SDB as over 15 events per hour of sleep.
3. Outcome measures included change in the apnea-hypopnea index (**AHI;** apnea events + hypopnea events per hour of sleep) and relationship of change in SDB with respect to change in weight.

RESULTS

1. Relative to a stable weight, a 10% weight *gain* predicted approximately 32% *increase* in AHI.
2. A 10% increase in weight predicted a 6-fold increase in the odds of developing moderate-to-severe SDB. A 20% increase in weight predicted an estimated increase in AHI of 70%.
3. A 10% weight *loss* predicted a 26% *decrease* in AHI. A 20% weight loss predicted a 48% decrease.

DISCUSSION

1. In persons with SBD there was a relation between weight gain and increase in SBD severity.
2. Weight loss was associated with a reduced severity of SDB and the likelihood of developing SDB.
3. The changes were independent of many other potential confounding factors.

CONCLUSION

Even modest weight loss is likely to be effective in managing SDB and reducing new occurrence of SDB.

 Comment:

We should remind overweight individuals that they do not have to gain "normal" weight to benefit. Loss of 10 pounds is a reasonable goal for many. RTJ

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12-12 PEGINTERFERON ALFA-2A IN PATIENTS WITH CHRONIC HEPATITIS C

 Interferon is an essential component of treatment of chronic hepatitis C **(HC)** . However, a sustained virologic response occurs in fewer than 20% of patients. With added ribavirin, response rate doubles.

 One reason for the marginal response to interferon is its short half-life (8 hours). This leads to wide fluctuations in plasma concentrations.

 Peginterferon is formed by covalent attachment of a polyethylene glycol moiety (*thus — peg*) to interferon. This compound has sustained absorption, a slower rate of clearance, and a longer half-life than unmodified interferon. This maintains an antiviral effect on the hepatitis C virus **(HCV)** and makes possible a once-weekly administration.

 This study compared clinical effects of peginterferon with interferon in initial treatment of chronic HC.

 Conclusion: Peginterferon given once weekly was more effective than interferon given three times weekly.

STUDY

1. Selected over 500 patients with chronic HC infection. All had a positive test for anti-HCV antibody, HCV RNA levels over 2000 copies per mL on polymerase chain analysis, serum alanine aminotransferase above upper normal on 2 occasions in the past 6 months, and liver biopsy consistent with chronic HC.

2. Randomized to: 1) peginterferon-alfa 180 ug subcutaneously once a week for 48 weeks, or
   2) interferon subcutaneously 6 million units three times weekly for 12 weeks, then 3 million units three times a week for 36 weeks.

3. Assessed at 72 weeks for a sustained virological response (an undetectable level of hepatitis C virus.)

RESULTS

1. At 72 weeks   Peginterferon   Interferon

Completed follow-up	76%	58%
Sustained virological response	39%	19%
Sustained normal ALT	45%	25%

2 Frequency and severity of adverse events were typical of those associated with interferon and were similar between groups. Depression the most serious. Fewer than 1% in each group discontinued because of laboratory abnormalities.

3. In general, peginterferon was well tolerated. In no patient was therapy discontinued because of neutropenia. Anemia and thrombocytopenia were rare.

DISCUSSION

1. Peginterferon was associated with a significantly higher rate of sustained virologic response as compared with interferon, possibly due to the sustained anti-viral effects associated with the enhanced pharmacokinetics of the molecule.

2. The response to peginterferon was similar to that previously reported for combination therapy with interferon and ribavirin.

3. Peginterferon was not associated with long-term adverse effects on the liver.

4. Sustained virological response from peginterferon was seen in patients in whom treatment has historically been unsuccessful — some patients with HCV genotype 1, and some with bridging fibrosis or cirrhosis.

CONCLUSION

In patients with chronic HC, a regimen of peginterferon-alfa given once weekly was more effective than interferon alfa-2a given 3 times weekly.

NEJM December 7 2000; 343: 1666-72 Original investigation, first author Stefan Zeuzem, Goethe Universitat, Frankfurt, Germany **www.nejm.com**

Comment:

See also "Peginterferon Alfa 2a in Patients with Chronic Hepatitis C and Cirrhosis" NEJM December 7 2000; 343: 1673-80 Peginterferon was significantly more effective than interferon in these patients with more advanced disease.

CONQUERING HEPATITIS C, STEP BY STEP

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

Hepatitis C virus **(HCV)** infection is the most common chronic blood-borne infection in the US. An estimated 2.7 million are infected, most undiagnosed. Many of those who have been diagnosed have not been treated.

The best current treatment is expensive, complex, relatively ineffective, and fraught with side-effects. Many physicians are reluctant to offer it to patients.

The infection progresses over decades to end-stage liver disease in a small percentage of patients. Nevertheless, a small percentage of a large number is still a large number. HCV-related disease is now the leading indication for liver transplantation. Unfortunately transplantation is not curative. The infection inevitably recurs.

At present, a combination of interferon + ribavirin is the treatment of choice. Response rate is double that of interferon alone. Even this therapy is none too good. Half the patients treated will continue to have viremia once treatment is stopped. Thus, hepatologists have adopted the language of oncologists, speaking of "response" rather than "cure". The preceding studies reported that peginterferon was associated with a sustained virological response (about 40%) — similar to that of combined interferon-ribavirin.

There are encouraging points: patients who do not have a virologic response may have a histologic response, indicated by a lessening of inflammation of the liver. Treated patients may be less likely to develop cancer of the liver even if they continue to carry the virus.

Prevention is still the best strategy through a change in behavior. An effective vaccine is not an immediate prospect for this genetically mutable RNA virus.

NEJM December 7, 2000; 343: 1723-24 Editorial by Daniel F Schafer and Michael F Sorrell, University of Nebraska Medical Center, Omaha. **www.nejm.com**

Comment:

These patients should avoid alcohol. Alcohol hastens progression.

Depression is the most common adverse effect of interferon. A recent study "Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alfa" NEJM March 29, 2001; 344: 961-66 reports that paroxetine (*Paxil*) appears to be an effective strategy for minimizing the depression induced by interferon. Paroxetine is an anti-depressant which acts by increasing serotonin concentrations. In addition to depression, it has been reported effective in treatment of social anxiety, obsessive-compulsive disorder, and panic disorder. RTJ

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12-13 EFFICACY OF RIVASTIGMINE IN DEMENTIA WITH LEWY BODIES.

"Dementia with Lewy bodies (Lewy body dementia; **LBD**) has been recognized during the past decade as a common form of dementia in the elderly. It accounts for 15-25% of dementia presentations. Fluctuating cognitive impairment and attention deficits are usually accompanied by recurrent visual hallucinations and parkinsonism. Delusions, depressed mood, sleep disturbance, auditory hallucinations unresponsiveness, and daytime somnolence also occur.

In this type of dementia. neuroleptic medication (anti-psychosis drugs, the mainstay of management of psychosis and behavioral problems in most other disorders) can provoke severe, irreversible, and often fatal sensitivity reactions.

LBD is accompanied by extensive deficits in cholinergic neurotransmission, more so than in Alzheimer's disease.

Rivastigmine (*Exelon*) is a cholinesterase inhibitor. It is safe and symptomatically effective in patients with Alzheimer's disease.

This study tested rivastigmine in a group of patients characterized *clinically* as having LBD

Conclusion: The drug produced clinically significant behavioral benefits.

STUDY

1. Randomized, placebo-controlled, double-blind, multicenter trial entered 120 patients with *clinically* diagnosed LBD (mild to moderate; mini-mental state examination score of 10 and above). Excluded those with severe extra-pyramidal symptoms.
2. Randomized to: 1) rivastigmine up to 12 mg daily, or 2) placebo for 20 weeks.
3. Assessed cognition and behavioral status. Follow-up = 20 weeks.

RESULTS

1. Only about 2/3 of patients assigned to rivastigmine completed the trial.
2. Rivastigmine patients were significantly less apathetic and anxious. Fewer had delusions and hallucinations.
3. Neuropsychological and cognitive tests showed a significantly faster and better response, particularly with the attentional component.
4. Adverse effects of cholinesterase inhibition (nausea, vomiting, anorexia) were more common in the rivastigmine group. More in the treatment group withdrew.
5. Safety and tolerability were judged acceptable. Parkinsonian symptoms did not worsen.
6. Effects were reversed rapidly on withdrawal of the drug.

DISCUSSION

1. Rivastigmine produced clinically relevant behavioral benefits in LBD. Patients were less apathetic, and less anxious, and had fewer delusions and hallucinations. In some patients improvement was substantial. **1**

2. Improvements in attention, responsiveness, and daytime somnolence were substantial. Hallucinations and psychotic features resolved almost completely in over half of the patients receiving rivastigmine.

3. Caregivers reported patients were more alert.

4. "Our study results suggest that cholinesterase inhibitors could be a more rational choice of treatment for Lewy-body dementia patients than neuroleptics, both on an efficacy and safety basis."

CONCLUSION

Rivastigmine produced clinically significant behavioral effects in patients with Lewy-body dementia, and seems safe and well tolerated if titrated individually.

Lancet December 16, 2000; 356: 2031-36 Originals investigation, first author Ian McKeith, University of Newcastle upon Tyne, UK **www.thelancet.com**

 Comment:

I abstracted mainly because of the description of the disease. I had not known much about LBD before this.

The risk associated with neuroleptics is important to keep in mind.

Neurofibrillary tangle deposition is absent in LBD

1 Individual response makes clinical trials with anti-cholinergics more acceptable in primary care. Although in general, benefits are modest if they occur at all, the possibility that an individual patient might be an outlier with substantial improvement makes a clinical trial reasonable in primary care. RTJ

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12-14 CHOLINESTERASE INHIBITORS; EXPANDING APPLICATIONS

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

The study expands the application of cholinesterase inhibitors to an non-Alzheimer disorder (Lewy-body dementia; **LBD**). The trial considered a change in neuropsychiatric symptoms as the primary outcome.

LBD had been recognized increasingly in the past decade. The characteristics are progressive dementia with at least 2 of 3 features: fluctuating cognition, visual hallucinations, and parkinsonism.

Post-mortem studies reveal neuritic plaques similar to those of Alzheimer's, but there are few neurofibrillary tangles. It is still not clear whether LBD is best regarded as a variant of Alzheimer's or as an independent neurological disorder sharing some of the histologic features of Alzheimer's.

These patients have a severe cholinergic deficit.

The behavioral improvement achieved with rivastigmine in the study was clinically relevant.

Several anti-cholinergic drug are now available to treat Alzheimer's disease: tacrine, donepezil, rivastigmine, and galantamine. Overall . . . "20% of patients treated with cholinesterase inhibitors show a treatment outcome superior to placebo."   A few respond with striking improvement. Responses tend to be more evident in patients with moderately advanced disease (Mini-mental State Examination score less than 18).

Rivastigmine has pharmacological properties that distinguish it from other cholinesterase inhibitors, so the findings may not apply to other drugs in the class.

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12-15 EFFICACY AND SAFETY OF GALANTAMINE IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE

Galantamine is a new drug that reversibly and competitively inhibits acetylcholinesterase.

This randomized, double-blind parallel group, placebo controlled trial evaluated safety and efficacy of galantamine.

At 6 months, compared with placebo, the group receiving galantamine had a significantly better outcome on a cognitive scale (the decline in cognition slowed), better functional ability (the decline in functional ability slowed), and showed improvement in the judgement of clinicians and caregivers. Activities of daily living were benefited significantly.

Compared with placebo, galantamine was effective and well tolerated in treatment of Alzheimer's disease.

Comment:

The FDA has approved galantamine (*Reminyl*). I have read it was originally derived from daffodil bulbs.

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12-16 EFFECT OF SIBUTRAMINE ON WEIGHT MAINTENANCE AFTER WEIGHT LOSS

Sibutramine (*Meridia*), a tertiary amine, was originally developed as a potential anti-depressant. It enhances effects of norepinephrine and serotonin. Weight loss occurs because of a resultant lowering of food intake as well as prevention of the decline in energy expenditure which occurs normally during weight loss.

It induces a dose-dependent weight loss and can amplify the effects of a very low calorie diet.

This study assessed the effect of sibutramine + diet in maintaining long-term weight loss.

Conclusion: Sibutramine sustained weight loss in most patients who continued to take it.

STUDY

1. Multicenter trial recruited over 600 obese individuals (BMI — 30 to 45). Most had repeatedly tried to lose weight in the past.

2. All entered into a 6-month period of weight loss with sibutramine (10 mg daily) and a diet calculated to be 600 kcal/d deficient based on measured resting metabolic rates.

3. The trial then entered those who had lost more than 5% of their weight during the 6 months. (N = 467).

4. Randomized to: 1) to 10 mg/d sibutramine, or 2) placebo for an additional 18 months.
   (Dose increased to 20 mg if weight regain occurred.)

RESULTS

1. Almost 50% of subjects in each group dropped out. (*Another discouragement regarding long-term weight-loss therapy. RTJ*)

2. Of those completing the trial: 43% of those in the sibutramine group maintained at least 80% of their original weight loss vs 16% of those in the placebo group. (Odds ratio = 4.6)

3. In the sibutramine group, substantial decreases occurred in triglyceride levels, VLDL cholesterol, insulin, and uric acid. HDL-cholesterol rose.

4. 3% of patients in the treatment group were withdrawn because of increase in BP. Mean pulse rate increased slightly.

5. Withdrawals due to adverse events: sibutramine — 14%; placebo — 5%.

DISCUSSION

1. "Almost all patients who persist with the management scheme . . . can achieve at least a 5% weight loss with sibutramine, and over half can lose more than 10% within 6 months."

2. The importance of sibutramine in maintaining a lower weight was shown by the immediate and steady increase in body weight once sibutramine was stopped.

3. Patients with hypertension were not excluded from the trial. In those taking sibutramine who achieved weight loss, BP remained unchanged.

CONCLUSION

An individualized management program with sibutramine and diet achieved weight loss in 77% of obese patients, and sustained the weight loss in most patients continuing therapy for 2 years.

 Comment:

This study can be interpreted as a failure (most subjects did not complete the trial), or as a success (some of those completing the 2 years did benefit).

Long-term effects are not known. Can patients continue on sibutramine indefinitely?

Study supported by BASF Pharma, makers of sibutramine. RTJ

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REFERENCE ARTICLE

12-17 UNCOMPLICATED ACUTE BRONCHITIS

Acute bronchitis is an acute cough illness in otherwise healthy adults that usually lasts 1 to 3 weeks. Practical points:

1. Respiratory viruses appear to cause most cases of uncomplicated bronchitis.

2. Pertussis infection is present in up to 10%-20% of adults with cough illness lasting more than 2 to 3 weeks.

3. Transient bronchial hyper-responsiveness appears to be the predominant mechanism for the bothersome cough.

4. Ruling out pneumonia is the primary objective in evaluating otherwise healthy adults with acute cough illness. (Pneumonia is unlikely if heart rate is < 100, respiratory rate is < 24, and temperature $< 38^0$C [101.5^{0}F])

5. Randomized, placebo-controlled trials do not support routine antibiotic treatment of uncomplicated bronchitis.

6. Inhaled albuterol (*Proventil; Ventolin; generic*) decreases the duration of the cough in adults with uncomplicated acute bronchitis. However, "Until more studies are conducted, reserving beta-agonist treatment for troublesome cough and evidence of bronchial hyper-responsiveness seems prudent."

7. Antibiotic treatment can be reduced by using a combination of patient and physician education. Decreased rates of antibiotic treatment are not associated with increased utilization, return visits, or dissatisfaction with care. "The evidence is indisputable that *not* prescribing antibiotics to patients with uncomplicated bronchitis is safe, and does *not* result in excess morbidity."

8. On an empirical basis, low-cost, low-risk actions such as elimination of environmental cough triggers (dust, dander) and using vaporized air treatments, particularly in environments with low humidity, are reasonable.

The authors propose an algorithm for evaluation and management on page 988.

 Comment:

   I believe patients as well as physicians are more willing to accept symptomatic therapy and to avoid antibiotic therapy for acute bronchitis, sore throat, and sinusitis as they become more aware of the lack of benefit, the risk of side-effects, and the increased likelihood of antibiotic resistance in themselves as well as in others. RTJ

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REFERENCE ARTICLE

12-18 THE DIAGNOSIS AND TREATMENT OF COUGH

   This review presents a systematic approach to managing cough in adults. "The cause of chronic cough can be determined in 88 to 100 percent of cases, and determination leads to specific therapies with success rates that range from 84 to 98 percent."

   Tables present guidelines for treating the most common causes of acute, subacute, and chronic cough.

   A table on page 1720 presents common pitfalls in managing the most common causes of chronic cough.

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REFERENCE ARTICLE

12-19 AGE RELATED MACULAR DEGENERATION

Laser treatments have become available for macular degeneration **(MD)** in the past few years. Laser can halt progression of the disease and the consequent loss of vision in some patients.

The treatment is limited to neo-vascular MD ("wet" or exudative— the less common variety) in which new vessels extend under the center of the retina. Treatment consists of intravenous verteporfin, a photoactivator, followed by laser applied over the entire neovascular area.

"The advent of effective photodynamic therapy makes even more important than before the need for primary care physicians to identify and educate the many people aged over 50 who have drusen about the risk of developing choroidal neovascularization."

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RECOMMENDED READING

12-20 NARRATIVE AND THE PRACTICE OF MEDICINE

"Clinicians spend their lives in the midst of narrative: listening to story fragments, interpreting word sequences, observing gestures, deciphering symptoms, ascribing causes, and suggesting treatments."

We are creatures who offer ourselves to each other as links in stories that go on and on. "Clinical practice is predicated upon recognizing and responding to such links — whether symptoms, signs, expression, mood, behavior pattern, or feeling."

Through stories we are able to imaginatively enter into other worlds, shift viewpoints, change perspectives, and focus on the experience of others. People generally seek medical advice as first-person narrators of snippets of life story, to which they invite responses and sometimes interpretation.

In searching for truths and meanings, detectives and doctors share similar narrative preoccupations.

"That story-telling processes lie at the heart of medical practice has long been recognised."   "Good historians, whether they like it or not, have the future in their bones. Besides the question, 'Why', the historian asks the question, 'Whither' — a question which also suffuses medicine."

General practitioners in the UK undertake some 8000 to 10 000 consultations every year. In a high proportion of these diagnosis is not the major concern and cannot be said to provide a key to the narrative fragments the patients bring to the consultation.

"Human beings are storytelling animals, and narrative is the most compelling form by which we recount our reality, understand events, and through which we make sense of our experiences and ourselves."

Lancet December 16, 2000; 356: 2086-89   "Literature and Medicine" Editorial by Brian Hurwitz, Imperial College of Science, Technology, and Medicine, London UK

Comment:

Story-telling is half of the process. Story-listening is the other half. As the editorialist states — "Clinical practice is predicated upon recognizing and responding to such links — whether symptoms, signs, expression, mood, behavior pattern, or feeling." This requires good listening. Perfecting the art of listening is a life-long quest. It requires a mature, experienced mind. Not easy, and mastered by few. RTJ

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RECOMMENDED READING

12-21 ERARITJARKTJAKA

Eraritjarktjaka is an archaic, poetic expression in a language of an aboriginal tribe in Australia. It means: "filled with desire for something which is lost".

Read the original to find out what the essayist has lost and for which he desires a return.

Lancet December 23/30 2000; 356: 2169-70 the Wakley prize assay by Joris Nauwelaers, Wijchmaal-Peer, Belgium **www.thelancet.com**

Comment:

The prize is awarded each year for the best essay, given in honor of the founder of The Lancet. RTJ

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RECOMMENDED READING

12-22 PUTTING WOMEN IN CONTROL: A Doctor Who Changed My Practice

This obstetrician comments on learning from an experienced mentor a new approach to examining women vaginally. It had never occurred to her before. It startled her.

"Many of the women coming for contraception, pregnancy testing, and abortion advice were young and had never had vaginal examinations or smears. They would be prepared on the couch as usual and then were given a speculum and asked to 'put it inside, please'. As if it were the most natural thing in the world that a doctor would ask a woman to insert a speculum!   And most did so with no fuss. I was shocked by the strangeness of what I was seeing and the topsy-turvy relationship between doctor and patient."

"All doctors find it hard to give up control. But sometimes it's beneficial for patients."

BMJ December 9, 2000; 321: 1454 Commentary by Susan Bewley, consultant obstetrician, London.
www.bmj.com/cgi/cintent/full/321/7274/1454

Comment:

I never thought of this before, either. RTJ

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RECOMMENDED READING

12-23 FROM RITES OF PASSAGE TO LAST RIGHTS

"Like everyone else who has lived a long time, I have come to the sad conclusion that at last I have become obsolete."

The essayist, a retired physician, divides the "golden years?" into 3 "rites".

1. The retirement years
2. The dwindling years
3. The final years.

JAMA December 27. 2000; 284: 3100-02 "A Piece of My Mind", essay by Louis F Sandock, MD
South Bend Indiana. **www.jama.com**

Comment:

We 80+ year olds will understand. The younger set should empathize.
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RECOMMENDED READING

20 FINALE FOR 2000

BMJ for 23-30 December 2000; 321: 1541-98 contains a pot-pourri of articles which differ from the usual. Many of them discuss "Happiness".

Example:

"Gore Vidal told a wonderful joke on the radio recently about the former British prime minister Harold Macmillan and a social visit he paid with his wife to the French president, Charles de Gaulle. At the end of a long and probably very boring meal, Macmillan turned to Madame DeGaulle and asked politely what she was looking forward to in her retirement. Quick as a flash the elderly lady replied: "A penis". Macmillan had been trained all his life never to appear shocked, but even he was a bit taken aback. After drawling out a series of polite platitudes —"Well, I can see your point of view", "Don't have much time for that sort of thing nowadays" — it gradually dawned on him to his intense relief that what the old girl had actually said was 'happiness'. "

BMJ December 23-30 321: 1576 "A New Definition" by Paul Foot. investigative journalist, London
www.bmj.com/cgi/content/full/321/7276/1576