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HIGHLIGHTS NOVEMBER 2000

11-1 INTRATHECAL METHYLPREDNISOLONE FOR INTRACTABLE POST HERPETIC NEURALGIA.

Intrathecal administration of methylprednisolone was an effective treatment for severe, persistent PHN.

11-2 A NEW TREATMENT FOR POSTHERPETIC NEURALGIA

The editorialist, an experienced observer of PHN, comments that treatment should start with the simplest and safest approaches (see text). However, he found the results of the trial remarkable. Replication is necessary.

Primary care clinicians may be willing to consult with expert anesthesiologists to ask their opinion and willingness to try this new procedure in a highly distressed patient.

11-3 RHYTHM OR RATE CONTROL IN ATRIAL FIBRILLATION — Pharmacological Intervention in Atrial Fibrillation (PIAF): A Randomized Trial

Rate control and rhythm control yielded similar symptomatic improvement.

Rate control with diltiazem and digoxin had the advantage of fewer adverse effects and fewer hospitalizations; but the disadvantage of continuing warfarin prophylaxis to prevent embolic stroke.

Rhythm control had the advantage of improving exercise tolerance. But the disadvantages of often requiring electrical conversion and continuing amiodarone prophylaxis. Hospital admissions and withdrawals due to drug adverse effects were more frequent. Almost half failed to maintain normal sinus rhythm over 1 year.

"It seems appropriate to choose the best therapeutic strategy according to the needs of the individual patient."

Primary care clinicians may choose the simplest approach — rate control with added aspirin or warfarin.

11-4 SAFETY AND COSTS OF INITIATING ANGIOTENSIN CONVERTING INHIBITORS FOR HEART FAILURE IN PRIMARY CARE: Analysis Of Individual Data From Studies Of Left Ventricular Dysfunction

ACE inhibitors delay progression and reduce mortality in patients with HF due to left ventricular systolic dysfunction.

These drugs are underused in primary care practice.

Fewer than 2% of patients receiving a small test dose of enalapril reported side effects severe enough to discontinue. (More likely in older patients with more severe HF).

Continuing the drug at gradually increasing doses for prevention or treatment of HF was safe — overall, no difference between enalapril and placebo in withdrawals.

Primary care clinicians should use ACE inhibitors routinely in patients with HF or a reduced ejection fraction.

11-5 THE ROLE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

We should listen less to the opinions of those who either overtly promote or stubbornly reject complementary medicine. The many patients who use CM deserve better. Patients and health care providers need to know which forms of CM are safe and effective. Its future should be determined by unbiased scientific evaluation.

Meanwhile, "The complete physician must be sensitive to the values and beliefs of those who live in different worlds, working with them, not against them."

Primary care physicians can learn from some practitioners of CM that there is much more to practice than technical management of disease. We need to concentrate more on the patient as a whole.

11-6 SEVEN LEGAL BARRIERS TO END-OF-LIFE CARE" Myths, Realities, And Grains Of Truth

"Many legal barriers to end-of-life care are more mythical than real, but sometimes there is a grain of truth. Physicians must know the law of the state in which they practice."

See text for a discussion of 7 legal myths regarding end--of-life care.

Primary care clinicians must be equipped to give their terminal patients the best of palliative care.

11-7 USEFULNESS OF ULTRASONOGRAPHY IN THE MANAGEMENT OF THYROID DISEASE.

Ultrasonography altered the clinical management of 2 out of every 3 patients referred because of detection of a thyroid nodule by physical examination. Clinical examination does not detect all nodules, many of which should have fine-needle aspiration.

Ultrasound should be routine in patients with thyroid nodules.

11-8 TREATMENT OF WARFARIN-ASSOCIATED COAGULOPATHY WITH ORAL VITAMIN K

Low oral dose (1 mg) was more effective than placebo for rapidly lowering high INR values (5 to 10) in patients taking warfarin.

Primary care clinicians must always consider the cause of the increase in the INR.

11-9 ASSOCIATION BETWEEN CIGARETTE SMOKING AND ANXIETY DISORDERS DURING ADOLESCENCE AND EARLY ADULTHOOD.

Heavy cigarette smoking during adolescence was associated with a higher risk of development of agoraphobia, generalized anxiety disorder, and panic disorder in early adulthood.

Primary care clinicians should recognize the youths who may be crying out for help.

11-10 SMOKING AND MENTAL ILLNESS: A Population-Based Prevalence Study

Persons with mental illness were about twice as likely to smoke as persons without mental illness. Primary care clinicians should consider smoking a possible marker for mental illness, especially in those who start at an early age.

11-11 RISK OF GASTROINTESTINAL HAEMORRRHAGE WITH LONG TERM USE OF ASPIRIN: Meta-Analysis

Long-term therapy with aspirin is associated with a clinically significant increase in incidence of GI hemorrhage. No evidence that low dose or enteric coating reduces risk.

Primary care clinicians should alert patients taking long-term low-dose aspirin of this uncommon, but important adverse effect. On the basis of common sense, many clinicians might continue to use enteric coated aspirin (eg, 80 mg daily) despite the lack of any protective effect reported by this study.

11-12 ASPIRIN, LIKE ALL OTHER DRUGS, IS A POISON

The hope was that reducing the dose and providing different formulations of aspirin would reduce the risk of hemorrhage. The preceding meta-analysis negates this hope.

11-13 STRATIFIED CARE VS STEP CARE STRATEGIES FOR MIGRAINE.

Go at once to the most effective therapy based on individual trial and error experience.

11-14 THE IMPORTANCE OF INJECTING VACCINES INTO MUSCLE

Injecting a vaccine into the layer of subcutaneous fat, where poor vascularity may result in slow mobilization and processing of the antigen, is a cause of vaccine failure. Needles should be long enough to reach muscle.

11-15 STATINS AND THE RISK OF DEMENTIA

Individuals over age 50 who were prescribed statins had a substantially lowered risk of developing dementia.

This preliminary report needs replication. Patients who ask about it should be told statins should not be prescribed solely for this purpose. It may be an added benefit.

11-16 A COMPARISON OF ETANERCEPT AND METHOTREXATE IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

"Etanercept (tumor necrosis factor inhibitor) represents an important new therapeutic option to decrease disease activity and slow joint damage in patients with active rheumatoid arthritis."

As compared with oral methotrexate alone, subcutaneous etanercept alone acted more rapidly to decrease symptoms and slow joint damage in patients with early active RA.

"Preventing the damage that occurs early in the course of the disease may be the key to better long-term functional outcomes."

11-17 INFLIXIMAB AND METHOTREXATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

In patients with persistently active RA despite methotrexate therapy, repeated doses of infliximab (an antibody against tumor necrosis factor) in combination with methotrexate provided clinical benefit and halted the progression of joint damage.

At present, primary care clinicians should inform patients with RA of the benefit/harm-cost of TNF inhibitors and refer those interested to a rheumatologist.

11-18 EXERCISE TESTING IN CLINICAL MEDICINE

"Brief, inexpensive, and done in most cases without the presence of a cardiologist, the exercise test offers the highest value for predictive accuracy of any of the non-invasive tests for coronary artery disease."

Primary care clinicians may wish to add a treadmill to their practice.

11-19 TREATMENT POSSIBILITIES FOR UNSTABLE ANGINA

An excellent reference treatment plan is outlined on page 1272.

Most of the interventions can be prescribed by primary care clinicians.

RECOMMENDED READING

11-5 THE ROLE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE.

REFERENCE ARTICLES

11-6 SEVEN LEGAL BARRIERS TO END-OF-LIFE CARE" Myths, Realities, And Grains Of Truth

11-18 EXERCISE TESTING IN CLINICAL MEDICINE

11-19 TREATMENT POSSIBILITIES FOR UNSTABLE ANGINA

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11-1 INTRATHECAL METHYLPREDNISOLONE FOR INTRACTABLE POST HERPETIC NEURALGIA.

Interleukin 8 is associated with the pain induced by inflammatory reactions. High concentrations are present in the cerebrospinal fluid of patients who have intractable postherpetic neuralgia **(PHN)**

Postmortem studies of patients with prolonged postherpetic neuralgia reveal marked inflammation around the spinal cord, with massive infiltration and accumulation of lymphocytes.

The inflammatory component of PHN suggests that suitably timed anti-inflammatory treatment may help reverse the syndrome.

This study assessed treatment with intrathecally administered methylprednisolone to reduce pain in patients with intractable PHN.

Conclusion: The treatment was effective in reducing pain.

STUDY

1. Enrolled over 250 patients with intractable PHN — defined as burning and lancinating pain that was accompanied by allodynia[1], restricted to the dermatomes involved in the original eruption. Patients with involvement of the cranial nerves were excluded.
2. All had pain lasting over a year.
3. All had pain resistant to conventional treatments: antidepressants; anticonvulsants; epidural local anesthetics; topical anesthetics.
4. Randomized to: 1) intrathecal (lumbar space) methylprednisolone (60 mg) with lidocaine (3 mL of 3%), or 2) lidocaine alone, or 3) no treatment. Injections were given for once a week for up to 4 weeks. (*See text for technique of injection.*)
5. Follow-up = 2 years

RESULTS

1. Minimal change in degree of pain occurred in the lidocaine-alone and the untreated control groups.
2. 90% of the methylprednisolone group vs 4% to 6% of the other 2 groups reported good or excellent relief. The intensity and area of pain decreased; the use of NSAIDs declined. The pain relief lasted throughout the 2 years of follow-up.
3. Interleukin concentrations in the cerebrospinal fluid decreased by 50% in the methylprednisolone-lidocaine group.
4. No complications were noted.

DISCUSSION

1. Interleukin 8 is a potent mediator of inflammation. The high concentrations of interleukin 8 in the cerebrospinal fluid indicated a prolonged spinal inflammatory reaction in these patients. The inflammation responded to the methylprednisolone. The degree of decrease in the interleukin 8 concentrations was correlated with the degree of pain relief.
2. The methylprednisolone-lidocaine solution was hyperbaric. When the patient was tilted in a head-down position, the solution which had been injected into the lumbar region spread to the thoracic and cervical regions. This allowed effective treatment of neuralgia in these regions. The risk of injections associated with cervical or thoracic intrathecal injections was avoided.

CONCLUSION

In this trial, the intrathecal administration of methylprednisolone was an effective treatment for

severe, persistent PHN.

NEJM November 23, 2000; 343: 1514-19 Original investigation, first author Naoki Kotani, University of Hirosaki School of Medicine, Hirosaki, Japan **www.nejm.org**

1. Allodynia is pain caused by non-noxious stimuli. It can last for years in PHN.

Comment:

If confirmed, this intervention will bring relief to many who suffer dreadfully from long-lasting PHN. We eagerly await follow-up study. I can imagine that some patients in the U.S., after being fully informed would now be willing to receive these injections given by an expert anesthesiologist. RTJ

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11-2 A NEW TREATMENT FOR POSTHERPETIC NEURALGIA

Along with painful diabetic neuropathy, postherpetic neuropathy **(PHN)** is one of the chief models for the clinical investigation of treatment of neuropathic pain, or pain from nerve injury. Successful therapies for PHN may be applicable to other neuropathic conditions. [1]

PHN may have a variety of features: steady, burning pain; paroxysmal pain like an electric shock; exquisite sensitivity of the skin, often with allodynia. Quality of life is diminished. Patients may become reclusive, unable to bear even the slightest contact with clothing.

About half of patients with PHN do not respond to the usual drug treatments or are unable to take them because of adverse effects.

Currently it is reasonable to begin therapy with the lidocaine skin patch. This does not have any serious adverse effects. If that is not successful, go on to use of antidepressants such as nortriptyline (*Generic*) which, at a low dose — 10 to 20 mg/d— has fewer side-effects than amitryptyline (*Elavil*). The dose is taken at bedtime with gradual increases. Or, one may start with gabapentin (*Neurontin*) also at low dose, gradually increasing to a maximum 3500 mg/d or until adverse effects occur.

Treatment of acute herpes zoster within 72 hours of onset with valacyclovir (*Valtrex*) of famciclovir (*Famvir*) has a moderate benefit in reducing severity of PHN. Use of amitryptyline, nerve blocks, or opioids soon after onset of acute herpetic pain may lessen the sensitization of the central nervous system and may reduce severity of PHN. (The value of this is not proved.) Corticosteroids early in the treatment of herpes zoster have finally been considered *without* benefit in preventing PHN when given in addition to antiviral agents.

The editorialist, an experienced observer of PHN, found the results of the trial remarkable. Replication is necessary.

Treatment should start with the simplest and safest approaches.

NEJM November 23, 2000; 343: 1563-65 Editorial by C Peter N Watson, University of Toronto Canada. **www.nejm.com**

1 Will application of the intrathecal prednisolone reduce severity of diabetic neuropathy?

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11-3 RHYTHM OR RATE CONTROL IN ATRIAL FIBRILLATION — Pharmacological Intervention in Atrial Fibrillation (PIAF): A Randomized Trial

Atrial fibrillation **(AF)** causes symptoms and impairs quality of life. In addition, AF is associated with serious complications such as systemic embolization, hemodynamic dysfunction, and tachycardia-mediated cardiomyopathy.

In many institutions, the aim of treatment is to restore and maintain sinus rhythm. (*Rhythm control*). Heart rate control (*Rate control*) is usually pursued only when rhythm control fails.

With electrical conversion, sinus rhythm can be re-established in many patients. But maintenance of sinus rhythm is not assured. (Maintenance of sinus rhythm occurs in only 30% of patients who do not receive continuing drug therapy.) Preventive anti-arrhythmic drug therapy is often mandatory.

However, recognition of the hazards of anti-arrhythmic therapy, particularly proarrhythmia, has led to serious reconsideration of this treatment strategy. Control of ventricular rate in patients with persistent AF has been proposed as an alternative strategy.

This study compared differences between rate control and rhythm control.

Conclusion: Rate and rhythm control both yielded similar clinical results overall. With rhythm control, exercise tolerance was better, but hospital admissions were higher, and adverse drug reactions more frequent.

STUDY

1. Randomized trial entered over 250 patients with AF of 1 week to 1 year duration.
2. Randomized to:

   Group A) <u>Rate control</u> with diltiazem (*Cardizem* , a calcium blocker) as first line therapy.

   No attempt was made to terminate AF. The goal was to control symptoms by rate control alone.

   Group B) <u>Rhythm control:</u> Patients first received pharmacological or electrical cardioversion followed by rhythm control with amiodarone (*Cordarone*), aimed at prevention of recurrence of AF.
3. About 75% of patients in both groups were receiving digoxin at baseline. This was continued.

   The addition of diltiazem led to a small, but significant further decrease in heart rate.
4. All patients were anticoagulated throughout the study period.
5. Primary end-point = improvement in symptoms. (Palpation, dyspnea, dizziness)

RESULTS

1. In the rhythm control group, restoration of sinus rhythm occurred in 23% of patients on amiodarone alone. The remaining required electrical conversion.

2. At 1 year:	Rate control (Group A)	Rhythm control (Group B)
In sinus rhythm	10%	56%
Hospital admissions	24%	69%
Adverse drug reactions	15%	25% (Leading to a change in therapy.)

3. Over the year, a similar number of patients (63% vs 58%) reported symptom improvement. There was no difference in reported quality of life.
4. Walk test was better in the rhythm control group.

DISCUSSION

1. In the rhythm control group many more were in sinus rhythm at 1 year (56% vs 10%) [*But note that almost half failed to maintain normal sinus rhythm over 1 year. RTJ*]
2. Amiodarone loading in the rhythm control group restored sinus rhythm in 23%. The majority required electroconversion.
3. Neither of the 2 therapeutic strategies was superior to the other in terms of AF symptom control. "The results may have important implications for the care of individual patients who are treated mainly for symptomatic control."
4. Once converted, over half the patients could be maintained in sinus rhythm by continued low-dose amiodarone. However, amiodarone was discontinued in 25% of patients due to presumed side-effects.
5. Any advantage of rate control is counteracted in part by the need for continued anticoagulation.
6. "Careful control of the ventricular rate in atrial fibrillation can result in a substantial benefit for the patient." This includes lower costs related to a reduced rate of hospitalization.
7. "It seems appropriate to choose the best therapeutic strategy according to the needs of the individual patient."

CONCLUSION

Rate control and rhythm control yielded similar symptomatic improvement.

Rate control had the advantage of fewer adverse effects and fewer hospitalizations; the disadvantage of continuing warfarin prophylaxis to prevent embolic stroke.

Rhythm control had the advantage of improving exercise tolerance; but the disadvantages of requiring electrical conversion and continuing amiodarone prophylaxis. (Almost half failed to maintain normal sinus rhythm over 1 year.) Hospital admissions and withdrawals due to drug adverse effects were more frequent.

"It seems appropriate to choose the best therapeutic strategy according to the needs of the individual patient."

Lancet November 25, 2000; 356: 1789-94 Original multicenter investigation by the PIAF investigators, , first author Stefan H Hohnloser **www.thelancet.com**

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11-4 SAFETY AND COSTS OF INITIATING ANGIOTENSIN CONVERTING INHIBITORS FOR HEART FAILURE IN PRIMARY CARE: Analysis Of Individual Data From Studies Of Left Ventricular Dysfunction

The use of angiotensin converting enzyme inhibitors **(ACE)** in patients with heart failure **(HF)** is supported by good evidence of effectiveness and cost. A meta-analysis estimated that treatment with ACE inhibitors resulted in a 17% reduction in death.

Despite the evidence, ACE inhibitors are underused in primary care. This may be due to uncertainty resulting from the lack of availability of diagnostic investigations, particularly echocardiography.

A recent trial of ramipril (*Altace*)[1] in 10 000 patients at increased cardiovascular risk, but without signs of left ventricular systolic dysfunction, indicated modest benefits may be achieved even in *primary* prevention. "And so some imprecision in diagnosis may be acceptable."

Many clinicians may be concerned about ACE-induced renal damage and hypotension, which were reported in early trials. This was caused by too high a dose.

This paper examined the risks associated with *starting* ACE inhibitor treatment (enalapril; *Vasotec*) in a large cohort of patients (the SOLVID trial)[2], some with left ventricular dysfunction without heart failure, and some with clinical heart failure. In addition, the paper examined the need for reduction in dose and discontinuation of the drug with continuing use during the first year of therapy.

Conclusion: Treatment with an ACE inhibitor can be safely started and continued for both patients with left ventricular systolic dysfunction and for those in clinical HF.

STUDY

1. Entered about 7500 patients under age 80. All had an ejection fraction below 35%.
2. All were challenged with a dose of enalapril 2.5 mg twice daily for 2 to 7 days.
3. Treatment was continued with gradually increasing dose over one year, either for prevention or treatment of HF.

RESULTS

1. Initial treatment: Initial test dose of 2.5 mg twice daily for one week:
    - 8% reported side effects. (Most common— hypotension, altered taste, and rash.
        (No mention of cough)
    - Only 2% reported the side effects severe enough to discontinue.
    - Older patients with severe HF and severely impaired ejection fractions and anemia were more likely to discontinue.
2. Continuing treatment: Dose reduction of enalapril in the first year was most likely due to hypotension, although overall there was no difference between enalapril and placebo in withdrawals.

DISCUSSION

1. Patients should be started on small doses of an ACE inhibitor with the goal of reaching the dose used in large scale trials (eg, enalapril 10 mg twice daily)
2. Older patients should be observed for several hours after the first test dose.

BP, renal function, and electrolytes should be monitored. Since many patients seen in primary care with HF are over age 80, special care must be used.

3. "Introduction of ACE inhibitors rarely causes problems. None of 7500 patients in the initiation phase had a lasting or life threatening event." In the first year, withdrawal and dose reduction were similar for enalapril and placebo.

4. The validity of a clinical diagnosis of HF in primary care is low (25%-50% accuracy). Diagnosis requires objective evidence — at least echocardiography. However, an entirely normal electrocardiogram will usually exclude HF.

8. Estimated costs of diagnosis and starting treatment in the UK = equivalent of about $500.

9. "Doctor's perceptions of the risks of these drugs in patients with HF are exaggerated."

CONCLUSION

ACE inhibitors delay progression and reduce mortality in patients with HF due to left ventricular systolic dysfunction.

These drugs are underused in primary care practice.

Fewer than 2% of patients receiving a small test dose of enalapril reported side effects severe enough to discontinue. (More likely in older patients with more severe HF).

Continuing the drug at gradually increasing doses for prevention or treatment of HF was safe — overall, no difference between enalapril and placebo in withdrawals.

BMJ November 4, 2000; 321: 1113-1116 Original investigation, first author James Mason, University of York, UK **http://www.bmj.com/cgi/content/full/321/7269/1113**

1 "Effects of an Angiotensin-Converting Enzyme Inhibitor, Ramipril, on Death from Cardiovascular Causes, Myocardial Infarction, and Stroke in High-Risk Patients." NEJM 2000; 342: 145-53

2 "Effects of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure." NEJM 1991; 325: 293-302 A secondary prevention trial.

ACE inhibitors and beta-blockers have been major contributors to therapy. Both are underused. As usual, start low and go slow. Avoid the first dose hypotensive effect.

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RECOMMENDED READING

11-5 THE ROLE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE.

Complementary medicine **(CM**) and alternative medicine are defined as "diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy, or by diversifying the conceptual framework of medicine."

It comprises a confusingly large and heterogeneous array of techniques, with both therapeutic and diagnostic approaches. "At present much of complementary medicine is still opinion based."

Use of CM is frequent and popular — estimated around 20% of persons use it yearly.

The exact reasons for the popularity of complementary and alternative medicine are complex; they change with time and space; they may vary from therapy to therapy; and they are different from one individual to another. "Reporting on complementary medicine in the British daily press is considerably more enthusiastic than that for conventional medicine."

CM is largely practiced privately. There is a positive correlation between affluence and the sales figures of commercial complementary medicine products. (Ie, those with more disposable income use more.)

No single determinant of popularity of CM exists. There is a broad range of interacting positive and negative motivations. Some amount to a biting criticism of our modern healthcare system. "Mainstream medicine would be well advised to consider it seriously."

CM lacks both a research tradition and a research infrastructure and therefore fails to attract experienced researchers. Funding of research for CM is dismal.

The author extracted all CM therapies recommended for defined medical conditions in 7 recent and seemingly authoritative books. More than 100 therapies were recommended for asthma. Systematic reviews failed to back up a single treatment. There was little agreement between the 7 books. Surprisingly, less than half the books recommended St John's wort for depression, which happens to be proved. (*Once a CM is adopted into mainstream medicine, do practitioners of CM lose interest in it? RTJ*)

Only well designed clinical investigations can establish the truth. Those who would prefer to bypass rigorous research — for example by shifting the discussion towards patients' preference — and hope to integrate unproved treatments into routine health care are unlikely to succeed in the long run. "Those who believe that regulation is a substitute for evidence will find that even the most meticulous regulation of nonsense must still result in nonsense." Those who insist that the evidence to support CM can legitimately be softer than in mainstream medicine will have to reconsider their position.

The principle of "new benefit" should also include costs. CM is not cheap.

If research really shows that a complementary medicine (eg, aromatherapy) has no adverse effects, and helps people through powerful non-specific (placebo) effects, the medical community should start considering the power of placebos. The research question then shifts to how non-specific effects might be optimized so that more patients can profit from them.

Conclusion: We should listen less to the opinions of those who either overtly promote or stubbornly reject complementary medicine. The many patients who use CM deserve better. Patients and health care providers need to know which forms are safe and effective. Its future should be determined by unbiased scientific evaluation.

BMJ November 4, 2000; 321: 1133-35 "Education and Debate" commentary by E Ernst, Director of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, UK.
www.bmj.com/cgi/content/full/321/7269/1133

Comment:

"The complete physician must be sensitive to the values and beliefs of those who live in different worlds, working with them, not against them."

Consider a bio-science based western-style physician who goes to a developing country, attempting to bring some "scientific" medical applications to the population. He encounters the local folk healer (shaman?; witch doctor?). The western physician must recognize the long relation between the folk healer and those for whom he intervenes. The folk healer is trusted, and brings much solace and comfort to the afflicted. The western doctor might believe that the folk doctor's interventions are nonsense and bring no true benefit. But he should not denigrate the folk healer and thus diminish the trust placed in him. Indeed, CM is best applied where behavioral, emotional, social, and spiritual factors have a dominant role in causing disease. It is in this area that our traditional western medicine has often failed.[1] When we ask — "Does CM work?", we must qualify — "Work for what?".

A large segment of Americans also live in a different world. The American public does not spend money without expectation of something in return. The large sums spent on CM indicate that the public receives some benefit. What is the benefit? I believe it is mostly due to 2 factors: 1) the placebo effect, and 2) the personal interest, empathy, and support given by practitioners of CM to their patients. In some ways the public trusts CM in a manner similar to the trust placed in the folk healer. The placebo effect is powerful. Indeed, individuals who are most trusting and compliant with placebos achieve the most benefits from them. If a person using a CM practitioner or herb improves, belief in the CM is strengthened by post-hoc, ergo propter hoc reasoning. "It helped me."

The western physician, however, must be aware of the harms CM might bring:

1) When CM impedes access to the benefits of western interventions.
   (Eg, denying or delaying treatment of diabetic keto-acidosis, acute appendicitis, myocardial infarction, meningococcemia.)
2) When the herb is toxic, or incompatible with prescription drugs. (This is a major reason primary care clinicians should keep up with studies of CM.)

Primary care clinicians should understand that many of their patients use CM, be uncritical about it, and encourage their patients to openly discuss it. RTJ

1 See "The Role of Traditional Medicine" Lancet Perspectives December 2000; 356: issue s1 page 3 **www.thelancet.com**

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REFERENCE ARTICLE

11-6 SEVEN LEGAL BARRIERS TO END-OF-LIFE CARE" Myths, Realities, And Grains Of Truth

The American College of Physicians-American Society of Internal Medicine End-of-Life Consensus panel was convened to identify clinical, ethical, and policy problems in end-of-life care, to analyze critically the available evidence and guidelines, and to offer consensus recommendations on how to improve care of the dying.

The object was to provide practical clinical and other guidelines to clinicians who are not specialists in palliative care.

This article examines current legal myths, realities, and grains of truth in end-of-life care. Legal myths about end-of-life care can undermine good care and ethical medical practice. At times ethics, clinical judgement, and the law conflict. Families and physicians can find themselves considering clinical actions that are ethically appropriate, but raise legal concerns.

There are 7 major legal myths regarding end-of-life care: (*See text for details about the myths.)*

1. Forgoing life-sustaining treatment for patients without decision making capacity requires that there be evidence that this was the patient's actual wish.
2. Withholding or withdrawing artificial fluids and nutrition from terminally ill or permanently unconscious patients is illegal.
3. Risk management personnel must be consulted before life-sustaining medical treatment may be terminated.
4. Advance directives must comply with specific forms, are not transferable between states, govern all of a patient's future treatment decisions; oral advance directives are unenforceable.
5. If a physician prescribes or administers high doses of medication to relieve pain or other discomfort in a terminally ill patient and this results in death, the physician will be criminally prosecuted.
6. When a terminally ill patient's suffering is overwhelming despite excellent palliative care, and the patient is requesting a hastened death, there are no legally permissible options to ease suffering.
7. The 1997 Supreme Court decision outlawed physician-assisted suicide.

"Many legal barriers to end-of-life care are more mythical than real, but sometimes there is a grain of truth. Physicians must know the law of the state in which they practice."

JAMA November 15, 2000; 284: 2495-2501 first author Alan Meisel, University of Pittsburgh School of Law, Pittsburgh, PA**. www.jama.com**

Comment:

See also: **www.bmj.com/cgi/content/full/321/7271/1282** for a review of "The Courts' Role in Decisions about Medical Treatment" — a British view.

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11-7 USEFULNESS OF ULTRASONOGRAPHY IN THE MANAGEMENT OF THYROID DISEASE.

"Approximately 4% to 7% of adults have palpable thyroid nodules. Up to 70% of adults have thyroid nodules visible on ultrasonography, many of which are less than 1 cm in diameter." (*Ie, the thyroid is a nodular gland. RTJ*)

Fine needle aspiration is the standard diagnostic test for evaluating a palpable nodule in euthyroid patients. Diagnostic accuracy of biopsy is improved when ultrasonography is used for guidance. Ultrasound guidance is required for aspiration of non-palpable nodules.

This investigation evaluated the role of routine ultrasonography in the management of nodular thyroid disease.

Conclusion: Ultrasonography altered the clinical management of 63% of patients referred because of thyroid nodules.

STUDY

1. Retrospective chart review of over 150 patients referred to a thyroid nodule clinic.
2. All patients with suspected nodular thyroid disease or suspected recurrent thyroid cancer received ultrasonography and ultrasonographic-guided fine needle aspiration biopsy of nodules at least 1 cm in diameter.
3. Compared ultrasonography findings with the referring physician's findings.

RESULTS

1. A total of 209 fine-needle aspirations were performed in 156 patients.
2. Among 114 patients referred for a solitary nodule:
   A. Ultrasound detected additional non-palpable nodules of at least 1 cm in diameter in 23%.
   B. Ultrasound determined that no nodules required aspiration in 20%.
3. Among 59 patients referred for a diffuse goiter or a multinodular gland, ultrasound detected a discrete nodule of at least 1 cm in diameter in 39, and determined that aspiration was not necessary in 20.

DISCUSSION

1. "We routinely use ultrasonography and ultrasonography-guided fine-needle aspiration in patients referred to our Thyroid Nodule Clinic for suspected thyroid nodules.
2. Almost half referred for a solitary nodule on physical examination were found to have multiple nodules. Many required aspiration of a non-palpable nodule.
3. More than 50% of those with suspected diffuse or asymmetric goiter had discrete nodules requiring fine needle aspiration.
4. About 25% of patients had no nodule equal or greater than 1 cm, despite abnormal findings on physical examination.
5. "The occurrence of malignancy was similar in patients with solitary and multiple nodules."
6. Non-palpable nodules are often at least 1 cm in diameter. "It is difficult to predict which patients will benefit from ultrasonography on the basis of physical examination."
7. The presence of cancer in thyroid nodules is independent of the number of nodules. In 4 of the 12 patients with thyroid cancer, the malignant nodules were not palpated by the referring physician and would not have been detected at the time of referral without ultrasonography.

8. "Since the prognosis of thyroid cancer is partially dependent on its size at surgery, earlier detection is probably beneficial."

CONCLUSION

Ultrasonography altered the clinical management of 2 out of every 3 patients referred because of detection of a thyroid nodule by physical examination in primary care.

Annals Int Med November 7, 2000; 133: 696-700 First author Ellen Marqusee, Brigham and Woman's Hospital, Boston Mass. **www.annals.org**

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11-8 TREATMENT OF WARFARIN-ASSOCIATED COAGULOPATHY WITH ORAL VITAMIN K

In practice, increases above the normal therapeutic range of the international normalized ratio **(INR),** without symptoms, frequently occur in patients receiving warfarin (*Coumadin*). These patients face risk of hemorrhage, even when the increase in INR is moderate. This study asked: in asymptomatic (non-bleeding) patients with a modest above-normal increases in INR, which is preferable, the passive approach of simply withholding warfarin, or an active approach by giving vitamin K?

Conclusion: Giving vitamin K *in small doses.*

STUDY

1. Multicenter, double-blind, placebo-controlled randomized trial entered 92 patients (mean age = 65). All were receiving warfarin and had an INR between 4.5 and 10.0 (mean = 5.7)
2. None had an indication for immediate normalization of the INR. Warfarin was withheld.
3. Randomized to: 1) 1 mg vitamin K, or 2) placebo
   (Note the vitamin K was given orally.)
4. Primary outcome = INR on the day after treatment.

RESULTS

1. Patients given vitamin K had a more rapid decline in INR: 56% had an INR of 1.8 to 3.2 the next day compared with 20% of the placebo patients.
2. Patients receiving vitamin K had a significant decrease in the number of minor bleeding episodes in a follow up of 3 months.
3. One deep-vein thrombotic episode occurred at 22 days in the placebo group; one myocardial infarction at 3 days in the treatment group.

DISCUSSION

1. Giving the small dose of vitamin K not only brought the INR from 4.5-10.0 to a treatment range

more quickly than simply withholding treatment, but did so without causing warfarin resistance.

2. Patients receiving 1 mg vitamin K did not have persistently lower INR values than those who received placebo.
3. The authors state that the inclusion criteria of the study would capture a representative population of patients with this common clinical complication.
4. Many clinicians do not give vitamin K to symptomless patients even with an INR of 8.0, preferring simply to withdrawing warfarin. "Our findings provide a strong case for the routine use of vitamin K in patients with a symptomless increase in INR."

CONCLUSION

Low oral dose (1 mg) was more effective than placebo for the rapid lowering of raised INR values in patients taking warfarin.

Lancet November 4, 2000; 356: 15551-53 Original investigation, first author Mark A Crowther, McMaster University, Hamilton, Ontario, Canada**. www.thelancet.com**

Comment:

The challenge is to lower the INR quickly without overshooting and leading to thrombosis. The small dose of vitamin K is the secret in this subset of patients

This is only part of the solution. The larger problem is — what caused the increase in the INR? To maintain constancy in coumadin therapy, the patient must remain constant in all respects. Any change in health status, diet, or medication (the list is long indeed, including over-the-counter), has the potential to change the power of the anticoagulation. I wonder how patients manage to keep stable. Many do, but many also get into trouble. RTJ

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11-9 ASSOCIATION BETWEEN CIGARETTE SMOKING AND ANXIETY DISORDERS DURING ADOLESCENCE AND EARLY ADULTHOOD.

Previous research has demonstrated an association between cigarette smoking and anxiety disorders. Two hypotheses have been proposed to account for the association:

1) Anxious individuals are at elevated risk for smoking initiation because of peer pressure, facilitation of social interaction, and presumed calming effects of smoking. Research findings supporting this hypothesis have indicated that adolescents with symptoms of anxiety or depression were at higher risk for smoking initiation and that adolescents with social fears had an increased risk of onset of nicotine dependence. Smoking in the presence of a disturbing stimulus may reduce anxiety.
2) An alternative hypothesis suggests that cigarette smoking contributes to the development of anxiety disorders, possibly due to the presumed anxiogenic effects of nicotine. Some clinical studies have indicated that cigarette smoking preceded the onset of panic disorder among patients with panic disorder.

Prospective epidemiological research can investigate both hypotheses, asking whether anxiety disorders predict risk of smoking, and/or whether chronic smoking is associated with later development of anxiety disorder. This study investigated the longitudinal association between cigarette smoking and anxiety disorders among adolescents and young adults.

Conclusion: Cigarette smoking may increase later onset of certain anxiety disorders.

STUDY

1. "The Children in the Community Study" (1991-92), a prospective longitudinal investigation followed over 650 youths at a mean age of 16 in 1985-86 (adolescents) , and later at a mean age of 22 (young adults).
2. Determined prevalence of cigarette smoking and psychiatric disorders.

RESULTS

1. Heavy cigarette smoking (> 20/d) during adolescence was associated with higher risks of psychiatric disorders during early adulthood

	Heavy smokers	Non-smokers
Agoraphobia	10%	2%
Generalized anxiety disorder	21%	4%
Panic disorder	8%	0.6%

2. Anxiety disorders during adolescence were not significantly associated with later chronic use of cigarettes during early adulthood. (15% of participants with, and 15% of participants without, anxiety in adolescence smoked at least 20 cigarettes during early adult hood.)

DISCUSSION

1. Heavy cigarette smoking during adolescence was associated with an increased risk of agoraphobia, generalized anxiety disorder, and panic disorder during early adulthood.
2. The findings do not support the hypothesis that anxiety in adolescents is related to an elevated risk of smoking later in life.

CONCLUSION

Heavy cigarette smoking during adolescence was associated with a higher risk of development of agoraphobia, generalized anxiety disorder, and panic disorder in early adulthood.

JAMA November 8, 2000' 284: 2348-51 Original investigation, first author Jeffrey G Johnson, Columbia University, New York **www.jama.com**

Comment:

Which comes first is not the important question. The significance lies in the association. RTJ

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11-10 SMOKING AND MENTAL ILLNESS: A Population-Based Prevalence Study

This investigation hypothesized that persons with mental illness smoke at higher rates than persons without mental illness, have lower quit rates, and comprise a large proportion of the US tobacco market.

Conclusion: Persons with mental illness were about twice as likely to smoke as persons without mental illness.

STUDY

1. The National Comorbidity Study (1991-92), a nationally representative multistage probability study, analyzed data on over 4400 respondents age 15-54 for presence or absence of mental illness.
2. Defined mental illness as: major depression; bipolar depression; panic disorder; agoraphobia; social phobia; simple phobia; generalized anxiety disorder; alcohol abuse; alcohol dependence; drug abuse; drug dependence; antisocial personality; conduct disorder; or non-affective psychosis such as schizophrenia.
3. Determined rates of smoking according to the type of psychiatric diagnoses.
4. Determined rates of cessation.

RESULTS

1.

	Current smoking	Lifetime history of smoking
No mental illness	23%	39%
Lifetime mental illness	35%	55%
Past month mental illness	41%	59%

2. Odds ratios for smoking in persons with mental illness vs respondents without mental illness, adjusted for age, sex, and region of country = 2.7.
3. Self-quit rates = 37% of those with any mental illness; 30% of those with past-month mental illness; 42% of those without mental illness.
4. "Persons with mental illness in the past month consumed approximately 44% of cigarettes smoked by this nationally representative sample."

DISCUSSION

1. Persons with mental illness were about twice as likely to smoke as persons without mental illness.
2. However, more than one third of those with mental illness had quit smoking at the time of the survey.
3. Except for the group of persons dependant on alcohol and drugs, the quit rates of others with mental illness were similar to those without mental illness.

4. Why do persons with mental illness smoke more? As a means of self-medication for their psychiatric symptoms? This would imply that the mental illness causes smoking. However, there is data suggesting that smoking comes first and may be followed by depression, panic disorder, and anxiety. A recent study found that smoking preceded onset of schizophrenia in the majority of persons with schizophrenia who smoked.
5. Internal documents suggest that the tobacco industry has identified psychologically vulnerable persons as a part of their market.

6. These findings emphasize the importance of focusing on smoking prevention and cessation efforts of the mentally ill.
7. "The fact that smokers with mental illness are able to quit should offer hope."

CONCLUSION

Persons with mental illness were about twice as likely to smoke as persons without mental illness

JAMA November 22/29. 2000: 284: 2606-10 Original investigation, first Author Karen Lasser, Harvard Medical School, Cambridge, Mass**. www.jama.com**

Comment:

See the following abstract.

Primary care clinicians should consider smoking a possible marker for mental illness, especially in those who start at an early age. These youths may be crying out for help. RTJ

==========

11-11 RISK OF GASTROINTESTINAL HAEMORRRHAGE WITH LONG TERM USE OF ASPIRIN: Meta-Analysis

The benefit of aspirin in the prevention of cardiovascular disease is well established. An estimated 50 000 000 Americans have started taking aspirin for this reason over the past 2 decades.

But, aspirin has harmful effects, especially gastrointestinal bleeding. Recently the trend has been toward use of lower doses in the hope that they might offer a better safety profile. Likewise, "modified release " (enteric coated) formulations have been developed for the same reason.

This meta-analysis reviewed the safety of aspirin, and considered the effect of dose and formulation.

Conclusion: Long-term aspirin is associated with a clinically significant increase in incidence of GI hemorrhage. No evidence that reducing the dose or changing the formulation reduces risk.

STUDY

1. Included 24 randomized, controlled trials (about 66 000 participants; predominantly male and middle-aged.).

2. All trials compared aspirin with placebo, or no treatment for one year or more.
(Mean = 28 months) Doses of aspirin varied from 50-1500 mg/d.
3. Indications for aspirin extended from primary prevention in "healthy" individuals to
secondary prevention after stroke.
4, Excluded individuals with history of peptic ulcer, previous GI hemorrhage, or intolerance to aspirin.
5. Main outcome measure = GI hemorrhage.

RESULTS

1. GI hemorrhage	Aspirin	Control	Odds ratio	Odds ratio modified release
	2.47%	1.42%	1.68	1.93

2, Number needed to harm = 106 over 28 months.
3. No relation between dose of aspirin and hemorrhage. At doses below 163 mg/d, GI
hemorrhage occurred in 2.3%
4. No reduction when modified release aspirin was used.

DISCUSSION

1. Long-term aspirin, even at low dose, carries a risk of GI hemorrhage. (Number to harm = 248
per year).
2. Benefits must be weighed against harms. For secondary prevention of stroke, an estimated 2
recurrent strokes would be prevented at a risk of one hemorrhage. For primary prevention of myocardial
infarction (MI) , 2 to 3 GI hemorrhages (depending on baseline risks) would occur for each MI prevented.
3.Since there are relatively few deaths after GI hemorrhage, a trade-off with MI may be
worth considering. (*Again depending on baseline risk. RTJ*)
4. Neither reducing the dose or changing the formulation of aspirin offered clear benefits.

CONCLUSION

Long-term therapy with aspirin is associated with a clinically significant increase in incidence of GI hemorrhage. No evidence that low dose or enteric coating reduces risk.

BJM November 11, 2000; 321: 1183-87 Original investigation by Sheena Derry and Yoon Kong Loke, University of Oxford, Radcliffe Infirmary Oxford, UK **www.bmj.com/cgi/content/full/321/7270/1183**

Comment:

No mention of cerebral hemorrhage. Increased incidence of cerebral hemorrhage related to aspirin (although small) was evident in the large primary prevention trial of myocardial infarction US physicians.

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11-12 ASPIRIN, LIKE ALL OTHER DRUGS, IS A POISON

(This editorial comments and expands on the preceding meta-analysis RTJ)

A single dose of aspirin irreversibly inhibits the normal aggregation of platelets by suppressing the cyclo-oxygenase mediated synthesis of prostaglandins, including the platelet-aggregating prostaglandin thromboxane.

Aspirin also inhibits the prostaglandins that normally protect the mucosa of the stomach.

Thus, the possible benefit of aspirin in reducing tendency to clot formation is balanced by the possible harm in producing increased bleeding.

It has been suggested that aspirin should be given as prophylaxis against myocardial infarction to all men over age 50, and to all women after the menopause. Enthusiasm is dampened by the excess tendency to bleed and an increased risk of GI hemorrhage.

The hope was that reducing the dose and providing different formulations of aspirin would reduce the risk of hemorrhage. The preceding meta-analysis negates this hope.

So, clinicians must ask — Who should receive aspirin — at what dose, and for how long?

BMJ November 11, 2000; 321: 1170-71 Editorial by Martin R Tramer, Geneva University Hospital, Switzerland.
www.bmj.com/cgi/content/full/321/7270/1170

Comment:

There are two actions of aspirin which increase the risk of aspirin in causing GI bleeding: 1) a systemic effect in blocking production of prostaglandins which protect the mucosa of the stomach, and 2) a local damaging effect.

I still have difficulty understanding why eliminating or reducing the local damaging effect (by smaller doses and by enteric coating) would not lower the risk of bleeding from the stomach.

I believe the benefit/harm-cost ratio of aspirin is the highest of any drug. Many patietns will benefit greatly despite the risk of bleeding. We can make some estimates balancing benefit vs harm.

Patients with peptic ulcer disease and gastro-esophageal regurgitation , as well as smokers and dyspeptics, should be given long-term aspirin with caution. Patients over the long-term may develop new stomach ulcers. Some may begin to take other NSAIDs over the counter, which combined with aspirin greatly increase risk. Patients and clinicians have much to consider.

I believe, however, that for some the potential benefit of aspirin will be so great that the risk is worth taking. It might be well to consider concomitant protection of the stomach by adding a therapeutic prostaglandin such as misoprostol (*Cytotec*)

If other NSAIDs are prescribed in addition to low-dose prophylactic aspirin, give a COX-1 sparing, COX-2 inhibiting drug. RTJ

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11-13 STRATIFIED CARE VS STEP CARE STRATEGIES FOR MIGRAINE.

Clinicians and patients now have an unprecedented range of treatments for migraine.

Various guidelines have proposed at least 3 different acute treatment strategies for selecting and sequencing initial care:

1) Step care across attacks: Patients begin with a non-specific therapy (ie, a simple or combination analgesic). After treating several attacks, if the treatment is not satisfactory, treatment is escalated. The process is continued until a satisfactory treatment result is achieved. (This approach is often advocated by managed care guidelines.)

2) Step care within attacks: Patients begin treatment with a non-specific therapy. At a specific time point (eg, 2 hours) patients assess their response and, if needed, take another medication, often migraine specific.

3) Stratified care: Patients select initial treatment based on their own treatment needs.

This study compared the clinical benefits of the 3 strategies.

Conclusion: Stratified care provided significantly better clinical outcomes than either step-care strategies.

STUDY

1. Multicenter, randomized, controlled parallel -group trial entered over 800 adult patients (mean age = 38). All had an established diagnosis of migraine based on the International Headache Society's criteria . All had 1 to 8 migraine attacks monthly with severity ranging from II, III, and IV.

2.Randomized to:

1) Step care across attacks:

First 3 attacks treated with aspirin + metoclopramide. If inadequate relief step up to zolmitriptan (*Zomig*) as first drug for the next 3 attacks.

2) Step care within attacks:

First treatment = aspirin + metoclopramide for all attacks. If inadequate relief in 2 hours, step up to zolmitriptan. (In practice, step care will include other multiple steps — one simple analgesic, followed by various combinations of analgesics , isometheptene (*Midrin*), or a barbital-containing agent, and finally a triptan. Thus effective treatment may be delayed.)

3) Stratified care:

A. Grade II (Mild or infrequent disability) attacks received aspirin 800 to 1000 mg + metoclopramide 10 mg.

B. Grade III (moderate disability) and IV (severe disability) attacks received zolmitriptan 2.5 mg orally as initial treatment of all attacks.

RESULTS

1. Headache response at 2 hours was clinically better in the stratified care group.
2. Disability time was shorter, but the incidence of adverse events was higher. (Most adverse events were of mild-to-moderate intensity.)

DISCUSSION

1. Stratified care is based on the principle that patient characteristics (ie, headache disability) can be used to help determine the patient's treatment needs, thereby increasing the chance for successful therapy from the outset.
2. One difficulty with step-care is the delay which can occur in instituting effective treatment.
3. Severity of the headache predicts treatment need. Aspirin-metoclopramide effectively treats only about 25% of patients with severe migraine.

CONCLUSION

Measured by headache response and disability time, stratified care (going immediately to the most effective drug based on the severity of the headache) was clinically superior to step-care approaches

JAMA November 22/29. 2000; 284: 2599-605 Original investigation by The Disability In Strategies Of Care (DISC) Study , first author Richard B Lipton, Albert Einstein College of Medicine, Bronx, New York

www.jama.com

Comment:

Most patients with recurrent migraine discover the most effective treatment — usually going directly to the drug(s) of choice.

Metoclopramide (*Reglan; Generic*) stimulates motility of the upper GI tract. It increases gastric contractions, relaxes the pylorus and hastens gastric emptying. (It has been used to treat gastro-esophageal reflux disease and diabetes-associated gastric paresis.) It is used in migraine combined with aspirin to hasten aspirin absorption.

Zolmitriptan is one of the triptan drugs which is now used extensively to treat migraine. It acts by constricting the dilated cerebral vessels.

The ACE-inhibitor lisinopril has recently been reported effective treatment for migraine. No mention of beta-blocker or ergotamine therapy.

Main message: Go at once to the most effective therapy based on individual trial and error experience. RTJ

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A REMINDER

11-14 THE IMPORTANCE OF INJECTING VACCINES INTO MUSCLE

Most vaccines should be given via the intramuscular route into the deltoid or the anterolateral thigh. This optimizes immunogenicity and minimizes adverse reactions at the injection site.

Injecting a vaccine into the layer of subcutaneous fat, where poor vascularity may result in slow mobilization and processing of the antigen, is a cause of vaccine failure.

Traditionally, the buttocks were thought to be an appropriate site, but there the layers of fat do not contain the appropriate cells that are necessary to initiate the immune response (phagocytic or antigen-presenting cells). In addition, the antigen may take longer to reach the circulation after being deposited in fat, leading to a delay in processing. Thicker skinfolds are associated with a lowered antibody response.

The needle should be long enough to reach the muscle.

BMJ November 18, 2000; 321: 1237-38 Editorial by Jane N Zuckerman, Royal Free and University College of Medicine, London. **www.bmj.com/cgi/content/full/321/7271/1237**

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11-15 STATINS AND THE RISK OF DEMENTIA

Vascular and lipid-related mechanisms are thought to have a role in the pathogenesis of Alzheimer's disease and vascular dementia This epidemiological study assessed the potential effect of statin drugs and other lipid-lowering agents on dementia.

Conclusion: Individuals over age 50 for whom statins (Hydroxy-methylglutaryl-coenzyme A reductase inhibitors) were prescribed had a substantially lower risk of developing dementia.

STUDY

1. Multicenter, population-based, case-control study determined all individuals who had a first-time diagnosis of dementia during the study. (The cases; N = 284; all over age 50)
2. Matched each case with up to 4 controls from the same population base. (N=1080)
3. Determined use of statins and other lipid-controlling drugs in both cases and controls.
4. Duration of use of the drugs for the majority was less than 4 years.

RESULTS

1. After control for confounders:

	Cases (dementia)	Controls (no dementia)
Current use of statins	4.6%	9.3%
Past use of statins	0%	1.4%

(Ie, use of statins was less common in patients who developed dementia; more common in those who did not develop dementia. Ie, a protective effect of statins)

2. Adjusted relative risk estimate = 0.29 (95% confidence interval = 0.13 to 0.63)
   (*By my calculation, NNT for up to 4 years to be associated with prevention of one case of dementia = 16*)
3. People who were prescribed non-statin lipid-lowering agents did not have a reduced risk for dementia. (Ie, the benefit seems to be limited to statin drugs.)

DISCUSSION

1. People in the UK who are prescribed statins have a risk of dementia estimated as much as 70% lower (but at least 39% lower) than those who are not receiving statins.
2. The authors speculate that statins may have beneficial effects of the microvasculature,

including increasing endothelial nitric oxide synthase, and reducing endothelin-1, thereby dilating capillaries and increasing blood flow.

3. The available data did not distinguish between Alzheimer's disease and other forms of dementia.
4. "These findings suggest that the use of statins could substantially reduce the risk of dementia in the elderly, either by delaying its onset, or by opposing . . . age-related changes that result in cognitive impairment."

CONCLUSION

Individuals over age 50 who were prescribed statins had a substantially lowered risk of developing dementia over a subsequent 4 years. (*NNT over 2 to 4 years = 16 to prevent one case of dementia. RTJ*)

Lancet November 11, 2000; 356: 1627-31 Original investigation, first author H Jick, Boston University School of Medicine, Lexington Mass. **www.thelancet.com**

Comment:

The authors comment that they are aware of the substantial potential consequences of the study. The study must be replicated.

A similar study has been reported in Archives of Neurology, 2000: 57; 1439 (Citation # 34)

This is not a conclusive study by any means. I abstracted it because of its provocative hypothesis. We will watch for follow-ups. RTJ

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11-16 A COMPARISON OF ETANERCEPT AND METHOTREXATE IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS.

(*This article is a companion to the preceding. This study differs in that the anti-TNF was compared with methotrexate, not combined with methotrexate. And it was used in early RA, not in chronic RA RTJ*)

Etanercept (*Enbrel*) is a soluble tumor necrosis factor **(TNF)** blocker. It binds and inactivates TNF, the proinflammatory cytokine overproduced in the joints of patients with rheumatoid arthritis **(RA).** TNF also stimulates the production of other pro-inflammatory cytokines.

Early intervention in patients with disease-modifying anti- RA drugs is considered essential to retard joint destruction.

This study assessed efficacy of etanercept given to patients with early RA as compared with methotrexate. (They were not given together.)

Conclusion: Etanercept alone was more beneficial than methotrexate alone.

STUDY

1. Entered over 600 patients with early RA (no more than 3 years duration; no other important

concurrent disease; never treated with methotrexate) These patients were considered at risk for rapidly progressive joint damage.

2. Randomized to: 1) etanercept (10 or 25 mg subcutaneously twice-weekly), or 2) oral methotrexate weekly (mean 19 mg).
3. Follow-up = 1 year.

RESULTS

1. Etanercept 25 mg group (compared with methotrexate group) had a more rapid rate of improvement during the first 6 months.
2. Mean increase in joint erosion score in etanercept group at 1 year was 0.47 vs 1.03 in the methotrexate group. 72% of etanercept patients had no increase in erosion score vs 60% of methotrexate group. Both drugs prevented joint-space narrowing.
3. Both drugs were well tolerated. Most adverse effects were mild or moderate. Fewer adverse events and fewer infections occurred in the etanercept group. The most common adverse effect of etanercept was a reaction at the injection site.

DISCUSSION

1. Early intervention in slowing or arresting the joint damage is important. "Preventing the damage that occurs early in the course of the disease may be the key to better long-term functional outcomes."
2. Both the clinical benefits and the decrease in the rate of radiographic evidence of progression occurred more rapidly in the group receiving 25 mg etanercept.
3. Other studies have reported that etanercept can be safely administered with methotrexate.
4. "Etanercept represents an important new therapeutic option to decrease disease activity and slow joint damage in patients with active rheumatoid arthritis."

CONCLUSION

As compared with oral methotrexate alone, subcutaneous etanercept alone acted more rapidly to decrease symptoms and slow joint damage in patients with early active RA.

NEJM November 30, 2000; 343: 1586-93 Original investigation, first author Joan M Bathon, Johns Hopkins University, Baltimore MD. **www.nejm.com**

Comment: We await more information about which drug(s) in which combination(s) provide the most efficacious treatment. TNF blockers are major breakthroughs in therapy. As noted they must be given early in the course of the disease to benefit the most.

Etanercept has an advantage of being self-administered subcutaneously.

Both are very expensive. Neither is a cure.

Patients with chronic, recurrent, or active infections have been excluded from trials because of concern that reduction of the normal anti-infection property of TNF may enhance infections. RTJ

An editorial in this issue (p 1640) comments:

In addition to being approved for RA, etanercept has been approved for juvenile RA, and infliximab for active Crohn's disease and fistulas due to Crohn's disease.

It seems reasonable to start TNF inhibitors as early as possible in all patients with documented RA. The chief barrier is cost — about $10 000 per month.

These drugs have surprisingly few adverse effects.

Disease activity is suppressed only during treatment. Relapses are inevitable once treatment is discontinued, regardless of the duration of treatment.

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11-17 INFLIXIMAB AND METHOTREXATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Tumor necrosis factor alpha **(TNF)** has a central role in the pathogenesis of rheumatoid arthritis **(RA).** Two new drugs are available to neutralize the destructive effects to TNF on patients with RA — infliximab (*Remicade*), a monoclonal antibody against TNF, and etanercept (*Enbrel*), a TNF receptor blocker. Both have demonstrated effectiveness when used alone, and when used in conjunction with methotrexate.

This study assessed the long-term efficacy of infliximab added to methotrexate when the RA activity persisted despite treatment with methotrexate alone.

Conclusion: The combination treatment provided clinical benefit and halted progression of the disease.

STUDY

1. Entered over 400 patients with active RA. All continued to have active disease despite continuing methotrexate therapy.
2. Randomized to: 1) Infliximab (*Remicade*) 3 mg/kg intravenously every 4 or 8 weeks plus continued oral methotrexate ; 2) infliximab 10 mg/kg every 4 or 8 weeks plus continued oral methotrexate; or 3) methotrexate plus placebo.
3. NSAIDs and prednisone were continued as before.
4. Follow-up to 54 weeks.

RESULTS

1. Combination infliximab and methotrexate was well tolerated. It resulted in a greater sustained reduction in symptoms and signs of RA than the effect of methotrexate alone. The lowest dose of infliximab was effective; the higher dose more effective.
2. Radiographic evidence of joint damage did not increase in the combination group; did increase in the methotrexate-alone group. (Mean change in radiographic score = 0.6 vs 7.0)

3. Adverse events were common in all treatment groups — at least one in 9 out of ten treated. Most were minor. Serious adverse effects similar across the 2 groups.

DISCUSSION

1. Combination of infliximab + methotrexate for 1 year provided sustained clinical benefit in patients with active RA.
2. Quality of life was improved and symptoms and signs of the RA also improved.
3. Progression of joint damage halted, even in those with extensive damage.
4. The frequency of infections requiring antimicrobial-drug therapy was 44% in the combination group vs 35% in the methotrexate-alone group. ("Serious" infections occurred in 8% vs 6%.)

CONCLUSION

In patients with persistently active RA despite methotrexate therapy, repeated doses of infliximab in combination with methotrexate provided clinical benefit and halted the progression of joint damage.

NEJM November 30, 2000; 343: 1594-602 Original investigation by "The Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group", first author Peter E Lipsky, University of Texas Southwestern Medical Center, Dallas. **www.nejm.com**

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REFERENCE ARTICLE

11-18 EXERCISE TESTING IN CLINICAL MEDICINE

"Exercise-induced changes in the electrocardiogram have been used to identify coronary artery disease for almost a century. Clinicians now increasingly focus on newer and more expensive diagnostic tools, believing them to offer improved diagnostic accuracy."

"In fact, by incorporating historical data, the simple exercise test can in most cases outperform newer tests."

"Brief, inexpensive, and done in most cases without the presence of a cardiologist, the exercise test offers the highest value for predictive accuracy of any of the non-invasive tests for coronary artery disease."

"Far from fading away, the technique first proposed in 1932 as an aid to the diagnosis of angina is in the process of being reborn."

Lancet November 4, 2000; 356: 1592-97 "Seminar". review article, first author Euan A Ashley, University of Oxford, UK. **www.thelancet.com**

Comment:

How many of you remember the "Master Two-step test"? RTJ

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REFERENCE ARTICLE

11-19 TREATMENT POSSIBILITIES FOR UNSTABLE ANGINA

Articles on unstable angina and myocardial infarction without ST elevation appear regularly in the journals I abstract. Primary care clinicians often will be the first contact. Early risk assessment and treatment are essential. This is a concise review. An excellent reference treatment plan is outlined on page 1272.

In earlier days, treatment of unstable angina mainly consisted of bed rest and nitroglycerin.

Now we add:

Dietary advice
Exercise advice
Smoking cessation
Other forms of nitrates
Heparin
Aspirin
Glycoprotein IIb/IIIa inhibitors
Beta-blockers
Statins
ACE inhibitors
PTCA and CABG and stents

Treatment is much more complex and expensive. RTJ

BMJ November 18, 2000; 321: 1269-75 "Clinical review" by Ajay Manhapra and Steven Borzac, Henry Ford Heart and Vascular Institute, Detroit MI. **www.bmj.com/cgi/content/full/321/7271/1269**

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