

PRACTICAL POINTERS

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HIGHLIGHTS AND *EDITORIAL COMMENT*

2-1 ANTIHYPERTENSIVE TREATMENT BASED ON BLOOD PRESSURE MEASUREMENT AT HOME OR IN THE PHYSICIAN'S OFFICE.

Intermittent, self-measurement of BP with an inexpensive ocillometric reader at home accomplishes several of the advantages of 24-hour ambulatory monitoring.

This study compared BP measurements taken in the physician's office with those self-measured at home in patients with hypertension. The goal was a diastolic between 80 and 89.

HomeBP led to less intensive drug treatment and marginally lower costs. It determined presence of white-coat hypertension (office BP higher than home BP), and led to discontinuation of drug therapy in twice as many patients as officeBP measurement. But slightly poorer long-term BP control. It may also help identify masked hypertension (home BP higher than office BP).

Should primary care clinicians offer home BP recordings to their patients with hypertension?

I believe it would be helpful. The greatest benefit would be in eliminating or reducing drug therapy in a sizable number of patients. It would also increase compliance and interest in treatment, and reduce the number of office visits. The downside might be slightly less adequate control.

BP goals would differ depending on the individual patient. The great majority of older patients with hypertension have isolated systolic hypertension.

Would patients accept and comply with this approach? They might, with difficulty. Enthusiastic support will be required. Machines would have to be recalibrated periodically. RTJ

2-2 POPULATION-BASED STUDY OF EARLY RISK OF STROKE AFTER TRANSIENT ISCHAEMIC ATTACK OR MINOR STROKE.

Ischemic strokes are frequently preceded by a transient ischemic attacks (TIA). This warning gives an opportunity to prevent stroke. This study determined frequency of stroke following a TIA or minor stroke.

	7 days	1 month	3 months
Stroke after a TIA (%)	8	12	17
Recurrent stroke after minor stroke. (%)	12	15	19

“For stroke prevention to be most effective, patients will need to be seen within the first few hours or days.”

Many of these patients had risk factors for stroke at baseline (previous TIA, hypertension, smoking, diabetes, angina, previous myocardial infarction, and hyperlipidemia).

They were a high risk group. Interventions (primary prevention) prior to the incident TIA or minor stroke would have lowered the risk considerably. RTJ

2-3 SECONDARY PREVENTION FOR STROKE AND TRANSIENT ISCHAEMIC ATTACKS

Epidemiologic studies show no demonstrable floor exists for the relationship between BP and risk of stroke. Risk continues to halve for every 10 mm Hg fall in diastolic even if initial BP is within conventionally normal limits.

“Definitions of hypertension and hypercholesterolemia in any patient with stroke or TIA seem artificial.” Irrespective of starting levels, almost all patients may benefit from reduction of BP and cholesterol.

A general therapeutic principle is emerging. There is no cut-point below which risk is eliminated. Try to reduce BP, LDL-cholesterol, HbA1c, body mass index, abdominal girth and other risk markers to as low a level as reasonable without encountering adverse effects. The cut-point for smoking is an exception. One cannot reduce risk further than cessation—if cessation is permanent. RTJ

2-4 NARRATIVE MEDICINE

More health care professionals are recognizing the importance of the stories patients tell about their illnesses. Not only is the diagnosis encoded in the narrative, but also deep and therapeutic understandings of the persons who bear the symptoms are made possible through the stories they tell. Only in the telling is the patient’s suffering made evident.

Narrative competence, defined as the set of skills required to recognize, absorb, interpret, and be moved by the stories one hears, is increasingly recognized as a basis for diagnosis and therapy.

Primary care practice bears the greatest opportunity and responsibility for understanding and responding to patients’ stories. Some writers term this making a “connexion” with the patient.

It is the “worried well” and the patient with chronic illness whose narratives should be developed and understood over time as a basis of therapy and support.

Patently listening and understanding narratives will benefit our family members, children, associates, and friends as well as patients. The art of listening and responding empathetically is a difficult, life-long quest. RTJ

2-5 B-TYPE NATRIURETIC PEPTIDE—A Biomarker For All Seasons?

Recently, natriuretic peptides have been introduced as biomarkers:

- 1) In patients presenting to the emergency department with acute dyspnea, elevated BTNP was helpful in discriminating between heart failure and other causes of dyspnea (chiefly COPD)
- 2) In asymptomatic middle-aged persons, BTNP was prognostic of future death, heart failure, and stroke over a mean of 5 years. Levels of BTNP higher than 20 pg/mL (above the 80th percentile) were associated with an increase of over 60% in the long-term risk of death. There was also a significant prognostic gradient of BTNP levels—low (under 4 pg/ml), intermediate (4 to 13), and high (over 13)—with respect to risk of heart failure, and stroke. This is remarkable because levels below 100 pg/mL are considered to rule out heart failure.

The first use may be of value to the primary care clinician in making triage decisions.

Investigators struggle to find more meaningful and accurate risk markers for cardiovascular disease. I believe we already have enough risk markers to act upon (and often do not) in order to improve prognosis. When the BTNP is elevated what does one do to reduce risk? — just revert to measurement and treatment of the traditional risk factors. RTJ

2-6 EXPERTS URGE EARLY INVESTMENT IN BONE HEALTH

The American Academy of Pediatrics has issued a policy statement urging physicians to contact schools in their communities and push for the elimination of sweetened soft drinks. Carbonated soft drink consumption has increased by 16% since 1970; milk consumption has decreased by an equal amount. In addition to displacing milk in the diet, the phosphorus content of soft drinks may impair absorption of calcium. Milk is the main source of calcium in the typical American diet. Milk consumption—and therefore calcium intake—decreases as soft drink consumption increases.

Much of the focus was on the contribution of sugary (high fructose) beverages to the obesity crisis.

Prevention of osteoporosis begins in childhood and adolescence. This is one of the most important preventive measures primary care clinicians can offer their patients.

Anyone living in a retirement home will realize how common and disabling the kyphotic-osteoporotic spine can become. Development of osteoporosis can largely be prevented or retarded. I believe it is a major prevention opportunity for primary care clinicians. Prevention begins in childhood.

Commercial interests have intruded into our school system in subtle ways. Vending machines dispense not only soft drinks, but high calorie snacks. Textbooks are not an exception; advertising enters them in apparently innocuous ways. TV and radio programs provided for children in school contain commercial messages. Children can not perceive the hype. RTJ

2-7 ASSESSMENT OF DEPENDENCE AND MOTIVATION TO STOP SMOKING

Whether a smoker succeeds in stopping smoking depends on the balance between: 1) motivation to stop, and 2) degree of dependence. Clinicians must be able to assess both of these characteristics. Motivation is important because “treatments” to assist with smoking cessation will not work unless the smoker is highly motivated. Dependence is especially important in smokers who do not wish to stop. The degree of dependence influences the choice of intervention.

The practical objective of assessing motivation is to identify smokers who are ready to make a quit attempt. The main value of measuring dependence is to judge the need for pharmacotherapy.

Motivation to stop can be assessed by simple direct questions about the interest in stopping and intention to quit. However, the degree of motivation seems to play a small role in success; once a quit attempt is made, markers of dependence are far stronger determinants of success.

I believe primary care clinicians should frequently assess smoker’s motivation to quit. If the patient expresses no interest in stopping there is no benefit in pursuing the subject. Raise the question again at a later consultation. Don’t give up.

Smokers who develop angina, have an MI, or stroke, or other serious illness are more likely to quit. This is a great opportunity. It is amazing, however, how many relapse after a time. RTJ

2-8 USE OF SIMPLE ADVICE AND BEHAVIORAL SUPPORT

The most effective method of helping smokers quit is to combine drug therapy (nicotine or bupropion [Zyban]), with advice and behavioral support.

Simple advice: “The best thing you can do for your health is to stop smoking. I would advise you to stop as soon as possible.” The success rate of brief advice, however, is modest, achieving cessation in about 1 in 40. Nevertheless, it is one of the most cost effective interventions in medicine because the cost is so low. It takes only 1 to 2 minutes in routine consultations.

Behavioral support: Intensive behavioral support is provided outside routine clinical care by trained counselors. About 1 in 13 smokers who are motivated enough to attend counseling sessions are likely to quit. No one type of intensive behavioral support is clearly more effective than any other.

The most effective interventions combine behavioral support with drug treatment.

Primary care clinicians are already aware of the great benefits of quitting smoking. Yet, I believe few routinely ask about smoking and fewer still attempt to offer help. They then miss “The greatest opportunity to improve their patient’s health”

We should persist. Don’t be discouraged by the poor success rate. I believe obtaining one success in cessation is a benefit equivalent to one coronary by-pass. RTJ

2-9 NICOTINE REPLACEMENT THERAPY

Nicotine products are available to all smokers who want to stop smoking. The purpose is to blunt withdrawal symptoms. Nicotine replacement therapy (NRT) is most effective when used in conjunction with behavioral and other types of non-pharmacological-cessation interventions.

NRT makes cigarettes less rewarding. It does not completely eliminate symptoms of withdrawal, possibly because none of the available delivery systems reproduce the rapid and high levels of nicotine in the brain achieved by inhaling cigarette smoke.

The most recent Cochrane review data suggest that NRT doubles achievement of cessation.

NRT should be offered to any regular cigarette smoker who is prepared to make a quit attempt.

It is less harmful than continued smoking even in pregnancy and cardiovascular disease. Increased efforts to quit should be made in these patients,

2-10 BUPROPION AND OTHER NON-NICOTINE PHARMACOTHERAPIES

It is as effective as nicotine replacement when given in association with intensive behavioral support, achieving a 19% long-term abstinence. It also seems to attenuate the weight gain associated with cessation of nicotine. Use beyond the recommended 8 weeks may confer further protection against relapse.

One study suggested that combined bupropion-nicotine patch produces higher quit rates.

Nicotine replacement is still the treatment of first choice.

2-11 COUGHING CAN REDUCE PAIN OF INJECTION

The British Journal of Plastic Surgery reports that, when patients cough vigorously as the needle comes into contact with the skin, the pain of injection is decreased.

There is little doubt that distraction works. It may be explained by the gate-control theory. Stimuli traveling over fast nerve fibers partially override painful sensations traveling along slower nerve fibers.

Coughing may also decrease pain when blood is being drawn.

2-12 PROZAC (FLUOXITINE) DROPPED AS INDICATION FOR PREMENSTRUAL DYSPHORIC DISORDER.

Last summer, a European committee reported that “PMDD is not a well-established disease entity”. It is listed in the DSM IV only as a research diagnosis. The committee strongly criticized two key trials of the selective serotonin reuptake inhibitor fluoxetine (*Prozac*), noting that in one study almost half of the participants dropped out, and, in the second study, little attempt was made to distinguish between mild and severe health problems. There was concern that women with less severe premenstrual symptoms might receive the diagnosis and be treated inappropriately.

Some researchers welcomed the decision, saying that PMDD (which was only recently described) was an invented illness—a strong example of the medicalization of ordinary life.

Prozac was first approved for PMDD in 2000 by the FDA. An aggressive promotional campaign followed.

This leaves us with PMS (“premenstrual syndrome”). PMS can be severe and accompanied by depression. A variety of lifestyle changes and drugs, including hormonal therapy, have been suggested.

I believe many MDs will continue to prescribe selective serotonin reuptake inhibitors (including Prozac) off label at low dose (20 mg as a trial therapy for select patients). PMS can be disabling. There are few effective alternative therapies. RTJ

2-13 TREATMENTS OF HOMOSEXUALITY IN BRITAIN SINCE THE 1950s - AN ORAL HISTORY

In Britain, “treatments” to change homosexuals into heterosexuals peaked in the 1960s and early 1970s. “Some participants chose to undergo treatments instead of imprisonment.” (Sexual behavior in private between adult men was not decriminalized in Britain until 1967.) DSM classified homosexuality as a disease until 1973.

Treatments included behavioral aversion therapy with electroshock (including electroconvulsive therapy) and apomorphine (one died of side effects); psychoanalysis; estrogen to reduce libido; religious counseling; and hypnosis.

No participant benefited from treatment. “There is no evidence that treatments were effective at changing sexual orientation.”

“Social and political assumptions sometimes lie at the heart of what we regard as mental pathology and serve as a warning for future practice.” “Assumptions about public morality and professional authority can lead to the medicalization of human differences and the infringement of human rights.”

We are not as far removed from barbarism as we think we are. (Note the eugenics movement in the USA in the 20th century.)

In the USA as elsewhere, social mores, religion, politics, and culture still influence medical decisions, and override some of the established benefits scientific medicine brings for both individuals and the general population. RTJ

2-14 HABITS (Hormonal Replacement Therapy After Breast Cancer - Is It Safe?)

In this 2-year randomized study, 12% of women in the HRT group experienced a new BC vs 4% in the no-HRT group. In the HRT group, 11 were local recurrences; 5 were contralateral BC; and 10 were distant metastases. In the no-HRT group 2; 1; and 5. (One in 8 women taking HRT developed recurrence of BC vs 1 in 25 in the no-HRT group.)

Women with a history of BC should not receive HRT. Those already receiving HRT should be advised to discontinue.

For women with history of BC, what can be advised for menopausal-symptom relief other than HRT? The North American Menopause Society suggests several non-hormonal therapies:

Antidepressants venlafaxine (Effexor), paroxetine (Paxil), and fluoxetine (Prozac; generic). Start at very low doses and gradually increase. Cessation requires gradual tapering off.

Gabapentin (Neurontin) may be considered in women older than 65

Clonidine is less effective than gabapentin. RTJ

2-15 SEX, LIES, AND NIAGRA

All capsules of an “all natural” remedy for erectile dysfunction (*Actra-R*) contained sildenafil (*Viagra*), an average of about 55 mg per capsule.

Charlatanism remains alive. Nostrums fill the shelves of our pharmacies. Fraud pervades “alternative/complementary” medicines and the “all-natural herb” industry. Some products have been found toxic (eg, ephedra). Some are ineffective (eg, echinacea for upper respiratory infections in children). I remember one report of an “all natural” topical preparation for dermatitis which was found to contain hydrocortisone. RTJ

2-16 FACTS VERSUS IDEOLOGY IN THE CLONING DEBATE

HUMAN CELLS FROM CLONED EMBRYOS IN RESEARCH AND THERAPY.

Korean investigators recently reported derivation of stem cells from a cloned human embryo. This may lead to development of ability to study genetic diseases in entirely new ways. “Experience will be needed to learn how such cells should best be used.” The investigators strongly condemned efforts to clone a human.

2-17 STRUCTURE OF THE 1918 FLU VIRUS

Scientists at the Medical Research Council (UK) have discovered a crucial structural change in the avian influenza virus that resulted in the death of 20 million people worldwide in 1918.

The hemagglutinin molecule protrudes from the surface of the flu virus as a series of spikes. A change in the configuration of the spikes enabled the avian flu virus to lock on the surface of human cells. Usually, bird viruses cannot be transmitted to humans. But, in 1918 this subtle change in shape of HA gave the virus the ability to attach to receptors on human cells as well as bird cells. The virus then spread rapidly from human to human to infect an estimated billion people—half of the world's population at the time.

All of the devastating flu pandemics of the last century were caused by viruses that came from birds.

Could this happen again? Many believe so. Eternal vigilance and vaccine adjustment will hopefully blunt the epidemic.
RTJ

2-18 ANTIBIOTIC USE IN RELATION TO THE RISK OF BREAST CANCER

This case-control study compared 2266 cases of primary invasive breast cancer (**BC**) with 7953 matched controls without BC in regard to their use of antibiotics. Antibiotic use was ascertained by computerized pharmacy records. Observation period ranged from 10 years to 23 years.

Increasing cumulative days of antibiotic use were associated with increased incident BC.

The investigators report the risk as odds ratios of breast cancer. By this measure, the chance of developing BC in high-dose uses of antibiotics is twice that of non-users.

Is this a clinically important point? Certainly, other risks are more important. To make clinical sense, readers must take the time and trouble of converting odds ratios into absolute risk. Few do. According to my unadjusted calculations, an extraordinarily high use of antibiotics use was associated with a 1% higher risk of developing BC. Patients using antibiotics for less than 500 days (the great majority) had an increased risk of 2 in 1000. Editors and investigators should plainly state absolute risks in their discussion. And editors should insist upon it. RTJ)

Self Measurement Of BP Is Increasingly Used In Clinical Practice

2-1 ANTIHYPERTENSIVE TREATMENT BASED ON BLOOD PRESSURE MEASUREMENT AT HOME OR IN THE PHYSICIAN'S OFFICE.

Self measurement of BP is increasingly used in clinical practice. How does it affect treatment?

Previous studies have reported that *24-hour ambulatory* monitoring of BP instead of conventional measurements in the physician's office, led to less intensive drug treatment with preservation of BP control, general well-being, and inhibition of left ventricular enlargement.

If applied in a standardized way, intermittent, self-measurement of BP with an inexpensive ocillometric reader at home accomplishes several of the advantages of 24-hour ambulatory monitoring: a greater number of BP measurements; elimination of white-coat hypertension; and lack of observer bias. It may increase compliance with antihypertension therapy, and may lead to fewer clinic visits.

This study compared use of BP measurements taken in the physician's office (**OfficeBP**) with those self-measured at home (**HomeBP**) in patients with hypertension.

Conclusion: HomeBP led to less intensive drug treatment and marginally lower costs. It determined presence of white-coat hypertension.

STUDY

1. Multicenter, blinded, randomized, controlled trial entered 400 patients (mean age 53) with hypertension. All had diastolic BP over 94 mm Hg (range = 95 to 114) as measured in the physician's office. About half were taking antihypertension drugs at baseline. Randomized to 1) HomeBP, or 2) OfficeBP.
2. HomeBP averaged 6 daily measurements (3 between 6 – 10 AM and 3 between 6 – 10 PM) the week before an office visit. Monthly or bimonthly physician's office visits averaged 3 BP measurements. HomeBP patients used a battery operated ocillometric device which was calibrated by the manufacturer.¹ HomeBP was considered to be the average of all reading collected during the preceding 7 days.
3. In both groups, OfficeBP and HomeBP were recorded and compared each month.
4. Physicians either intensified drug treatment (if diastolic above 89); did not change drug treatment if diastolic was between 80-89; and reduced or discontinued it if diastolic was below 80. The target BP was diastolic 80-89.
5. Treatment was based either on HomeBP or on OfficeBP, starting with monotherapy with lisinopril (*Prinivil*; generic), and then stepped-up by adding hydrochlorothiazide (generic), then adding amlodipine (*Norvasc*) and/or prazosin (*Minipres*; generic). [See text p 956] Follow-up = 1 year.

RESULTS

1. OfficeBP and HomeBP both decreased after randomization

2. At end of one year	HomeBP	OfficeBP	Absolute diff	NNT (1 year)
Stopping antihypertension drugs	26%	11%	15%	6
Progressing to multiple drugs	39%	45%	6%	16

(More patients in the HomeBP group were able to stop drugs completely because their diastolic stabilized below 80. Treatment was slightly more intensive in the OfficeBP.)

3. But, BP reductions were greater in the OfficeBP treated group than in the HomeBP group by 7 /4 mm Hg vs 5/3 mm Hg.
4. Calculated costs were lower in the home group
5. No difference between groups in left ventricular mass, and reported symptoms.

DISCUSSION

1. HomeBP led to less intensive drug therapy and marginally lower costs, but also slightly less adequate long-term BP control.
2. HomeBP led to discontinuation of drug therapy in twice as many patients. Self-measurement helped identify patients with white-coat hypertension (office BP higher than home BP). It may also help identify masked hypertension (home BP higher than office BP).

CONCLUSION

Adjustment of BP by HomeBP measurement led to: 1) less intensive drug therapy, and 2) diagnosis of patients with white-coat hypertension in whom drugs could be discontinued.

[JAMA February 25, 2004; 291: 955-64](#) Original investigation by the Treatment of hypertension based on Home or Office blood Pressure (THOP) Trial Investigators, first author Jan A Staessen, University of Leuven, Belgium.

1 Omron HEM-705CP device (Omron, Kyoto, Japan) Cost = \$100

Comment:

I found the article difficult to abstract. Baseline BP differed between the 2 groups. I do not know why. I believe, however, that I abstracted the main points adequately.

Should primary care clinicians offer home BP recordings to their patients with hypertension?

I believe it would be helpful. The greatest benefit would be in eliminating or reducing drug therapy in a sizable number of patients. It would also increase compliance and interest in treatment, and reduce the number of office visits. The downside might be slightly less adequate control.

Some clinicians might prefer periodic 24-hour ambulatory recordings.

BP goals would differ depending on the individual patient. The great majority of older patients with hypertension have isolated systolic hypertension.

Would patients accept and comply with this approach.? They might, with difficulty. Enthusiastic support will be required.

Machines would have to be recalibrated periodically. RTJ

“For Stroke Prevention To Be Most Effective, Patients Will Need To Be Seen Within The First Few Hours Or Days.”

2-2 POPULATION-BASED STUDY OF EARLY RISK OF STROKE AFTER TRANSIENT ISCHAEMIC ATTACK OR MINOR STROKE.

About 15% of ischemic strokes are preceded by a transient ischemic attack (**TIA**). This warning gives an opportunity to prevent stroke.

We do not know how urgently patients must be seen for prevention to be effective. The North American guidelines recommend that assessment and investigations should be completed within one week

This study estimated the risk of very early stroke risk after a TIA or minor stroke (**MS**) in order to plan effective stroke prevention.

Conclusion: Early risks of stroke are much higher than commonly quoted.

STUDY

1. Recruited 174 patients (mean age 74) with TIA or minor stroke.¹
2. Calculated actuarial survival free of stroke for 3 months from time of onset.
3. Main outcome measures = risk of recurrent stroke at 7 days, one month, and three months after initial TIA or minor stroke.

RESULTS

1. Recurrent stroke (%)	7 days	1 month	3 months
After a TIA	8	12	17
After a minor stroke	12	15	19

DISCUSSION

1. Other studies have reported high risk of stroke after a first ever TIA.
2. Patients with TIA or minor stroke have a high risk of stroke. They should receive urgent preventive treatment. This is particularly important for patients in whom specific treatments are needed (cardiac embolism or carotid stenosis). Patients with atrial fibrillation require immediate anticoagulation. Benefit from carotid endarterectomy falls rapidly with time.
3. A substantial number of patients will have a stroke within one week. "For stroke prevention to be most effective, patients will need to be seen within the first few hours or days."

CONCLUSION

The estimated risk of stroke after a TIA or minor stroke is 8-12% at 7 days. Patients should be educated to seek medical attention urgently. Medical services should be organized accordingly.

[BMJ February 7, 2004; 328: 326-28](#). Original investigation, by the Oxford Vascular Study, first author A J Coull, Radcliffe Infirmary Oxford, UK.

1 Defined minor stroke as a score of 3 or less on the National Institutes of Health stroke scale. This neurological scale includes measures of levels of consciousness, hemianopsia, eye movements, facial weakness, motor function of extremities, ataxia, sensory function, dysarthria, and aphasia

www.sagas.org.sa/English%20Progress/Physician%20pages/Protocols/NIHSS.HTM

Comment:

Many of these patients had risk factors for stroke at baseline (previous TIA, hypertension, smoking, diabetes, angina, previous myocardial infarction, and hyperlipidemia).

They were a high risk group. Interventions (primary prevention) prior to the incident TIA or minor stroke would have lowered the risk considerably. RTJ

"Even patients with normal BP and cholesterol levels may benefit."

2-3 SECONDARY PREVENTION FOR STROKE AND TRANSIENT ISCHAEMIC ATTACKS

Risk of stroke can be lowered by controlling BP and lipids. This editorial comments on *secondary* prevention of stroke after a stroke or a TIA. To what extent should BP and cholesterol be lowered to obtain maximal protection?

Blood pressure:

Epidemiologic studies show no demonstrable floor exists for the relationship between BP and risk of stroke. Risk continues to halve for every 10 mm Hg fall in diastolic even if initial BP is within conventionally normal limits.

The PROGRESS study ¹ randomized over 6000 patients who had experienced a stroke or TIA to: 1) the ACE inhibitor perindopril (*Aceon*) alone, with or without added non-thiazide diuretic indapamide (*Generic*) vs 2) placebo. Most also received aspirin and continued other antihypertension drugs. As expected, lowering BP in the subset of patients considered to be hypertensive (160/90 and over) reduced risk of recurrent stroke. In the subset of over 3000 patients considered to be non-hypertensive at baseline (mean BP = 136/79), treatment reduced mean BP to 127/75, and was associated with an identical reduction in risk of recurrence. (4.3%; NNT 4 years = 23)

Treatment of the lowest tertile of BP at entry resulted in an identical absolute reduction in stroke compared with the higher tertiles.

Cholesterol:

The Heart Protection Study ² entered over 20 000 high-risk individuals. A subset of over 3000 had prior Stroke or TIA. Lowering LDL-cholesterol with simvastatin from 116 to 78 was just as effective as lowering from 134 to 96. Benefits were in addition to use of aspirin, beta-blockers and ACE inhibitors. Major vascular events were reduced by 5% over 5 years. (NNT = 20)

“Definitions of hypertension and hypercholesterolemia in any patient with stroke or TIA seem artificial.” Irrespective of starting levels, almost all patients may benefit from reduction of BP and cholesterol.

Overall, combined ACE inhibitor and diuretic treatment has had the best supporting evidence of effectiveness.

TIA and minor stroke are medical emergencies. However, whether secondary prevention by drug therapy of BP and cholesterol extend to the very early period (1 to 4 weeks) is not known.

Acute cerebrovascular syndromes merit treatment as aggressive as that of acute coronary syndromes.

[BMJ February 7, 2004; 328: 297-98](#) Editorial by Keith W Muir, Southern General Hospital, Glasgow, UK

1 Randomized Trial Of A Perindopril-Based Blood-Pressure Lowering Regimen Among 6105 Individuals With Previous Stroke Or Ischaemic Attack. PROGRESS: Perindopril Protection against Recurrent Stroke Study
Lancet 2001;358: 1033-41 . (See abstract Practical Pointers September 2001)

2 Heart Protection Study Of Cholesterol Lowering With Simvastatin In 20 536 High-Risk individuals
Lancet July 6, 2002; 360: 7-22 (See abstract Practical Pointers July 2002)

Comment:

I am surprised that lowering levels of BP and cholesterol from low levels to still lower levels is just as beneficial as lowering them from high levels to lower levels. It would seem to me that the latter would bring more benefit since risk of complications is higher in this group.

Practical Pointers has published many articles about both primary and secondary prevention of stroke. I made a check list of interventions:

Immediate

Rule out hemorrhage. Check for atrial fibrillation (start warfarin and possibly ximelagatran)

Check for carotid bruit and narrowing (50%-99%). Aspirin (possibly added clopidogrel)

BP control. Immediate thrombolysis only under protocol conditions

Ongoing

Aspirin (+ clopidogrel?). BP control (including isolated systolic hypertension) Lipid control Weight control
Diet (eg, DASH plus diet; omega-3 fatty acids; fish) Smoking cessation Alcohol--one drink daily
Diabetes control Warfarin for atrial fibrillation (INR ~ 2.5) Physical activity Flu vaccine

These ongoing measures are also relevant to primary and secondary prevention of coronary atherosclerosis and peripheral atherosclerosis. RTJ

The Art Of Listening Is A Life-Long Quest.

2-4 NARRATIVE MEDICINE

More health care professionals are recognizing the importance of the stories patients tell about their illnesses. Not only is the diagnosis encoded in the narrative, but also deep and therapeutic understandings of the persons who bear the symptoms are made possible through the stories they tell. Only in the telling is the patient's suffering made evident.

More attention is being paid to developing narrative competence, defined as the set of skills required to recognize, absorb, interpret, and be moved by the stories one hears. When a doctor practices medicine with narrative competence, he or she can quickly and accurately hear and interpret what a patient tries to say. The doctor uses the time of a clinical interaction efficiently, wringing all possible medical knowledge from what a patient conveys about the experience of illness and how he or she conveys it.

The patient is told the doctor needs to learn as much as possible about his health. He asks the patient to tell whatever he thinks the doctor should know about his situation. Then the doctor *remains silent* and absorbs all the patients tell about his life and health. The doctor listens not only to the content of the narration, but for its form—its temporal course, its images, its associated subplots, its silences, where the patient chooses to begin telling of himself, how he sequences symptoms with other life events. The doctor pays attention to the narrator's performance—body positions, tone of voice, gestures, expressions.

The doctor with narrative skills habitually confirms the patient's worth in the process of attending seriously to what he or she tells. The doctor demonstrates concern for a patient while concentrating on what the patient says, and as a result achieves the genuine intersubjective contact required for an effective therapeutic alliance. Narrative competence includes an awareness of the ethical complexity of the relationship between teller and listener, a relationship marked by duty toward privileged knowledge, and gratitude for being heard. The practice of medicine sometimes lacks attunement to the patient's individuality, sensitivity to emotional and cultural dimensions of care, and ethical commitment to the patient. Narrative competence of doctors might help them to achieve the elusive goal of humanism by providing them with skills in adopting patients' points of view, imagining what they endure, and deducing what they need.

Of course, this takes time.

The patient's narrative reveals the connection among his symptoms, his illness, his literacy, his failings as a breadwinner, his familial losses, and his life in an alien culture, . The doctor can confirm the gravity of all the patient tells and can share an optimism that things could improve.

Narrative studies can provide the “basic science” of a story-based medicine that can honor the patients who endure illness and nourish the physicians who care for them.

[NEJM February 26, 2004; 350: 862-63](#) “Perspective”, commentary by Rita Charon, from the Programme in Narrative Medicine, College of Physicians and Surgeons, Columbia University, New York.

Comment:

Dr Charon has written extensively on what she calls “Narrative-based Medicine”. She recommends that physicians *read* stories of patients and their suffering and feelings about illness as depicted in some great novels. And to *write* about their own feelings and emotional experiences they encounter in practice.

Primary care practice bears the greatest opportunity and responsibility for understanding the patients’ stories. Some writers term this making a “connexion” with the patient.

What about the time involved? Making the “connexion” does take time. It need not and cannot be made in one visit. Listening can continue over time. It need not and should not be applied to all patients.

Those who consult occasionally for incidental illness such as respiratory infections and gastrointestinal upsets do not require an in-depth understanding of their life story. Over time, if the patient seeks occasional consultations, physicians as a matter of interest will learn more about their personal lives even if this does not pertain to their illness. It is the “worried well” and the patient with chronic illness whose narratives should be developed and understood as a basis of therapy and support.

Patiently listening and understanding narratives will benefit family members, children, associates, and friends as well as patients. The art of listening and responding empathetically is a difficult, life-long quest. RTJ

2-5 B-TYPE NATRIURETIC PEPTIDE—A Biomarker For All Seasons?

New biomarkers which promise to simplify clinical-decision making are often adopted enthusiastically by practitioners. In the emergency department (**ED**), for example, routine measurement of cardiac troponins reduces the need to struggle with medical histories and atypical presentations of acute coronary disease when making triage decisions.

Recently natriuretic peptides have been introduced as biomarkers.

B-type natriuretic peptide (**BTNP**) and atrial natriuretic peptide (**ANP**) are hormones released in response to myocyte stretch. BTNP is released primarily by the ventricles; ANP by the atria. Both augment urinary sodium excretion; relax smooth muscle; and inhibit the sympathetic nervous system and the renin-angiotensin-aldosterone system. These physiological effects improve loading conditions. BTNP has now been developed as a therapeutic agent for heart failure.

Rapid NP testing is available by high sensitivity, inexpensive, commercially-available assay kits. This has led to a number of studies providing diagnostic and screening information.

This issue of NEJM reports 2 provocative studies: ^{1,2}

1. *Evaluation of patients with acute dyspnea*: BTNP was evaluated as a diagnostic tool for assessment of the cause of acute dyspnea in patients presenting to the emergency department (**ED**)

This study randomized patients to a single measurement of BTNP vs no such measurement. A level below 100 pg/mL made heart failure (**HF**) unlikely. (A low level has a high negative predictive value.) A level

above 500 made HF highly likely. For intermediate levels, use of clinical judgment and adjunctive testing were encouraged. Use of BTNP testing in the ED was associated with a decrease in hospital admissions by 10%, a shortening of the length of stay by 3 days, and a savings of about \$1800, with no adverse effects on mortality or the rate of subsequent hospitalization. Effective therapy could be applied more quickly to reduce rate of complications. More expensive tests could be avoided.

2. *Prognostic screening in asymptomatic persons:* In asymptomatic middle-aged people, the level of BTNP and atrial NP independently predicted risk of death, heart failure, atrial fibrillation, and stroke over a mean follow-up of 5 years. Levels of BTNP higher than 20 pg/mL (above the 80th percentile) were associated with an increase of over 60% in the long-term risk of death. There was also a significant prognostic gradient of BTNP levels with respect to risk of heart failure, atrial fibrillation and stroke—low (under 4 pg/ml), intermediate (4 to 13), and high (over 13) This is remarkable because levels below 100 pg/mL are considered to rule out heart failure.

Slight elevations of BTNP may reflect early stages of pathological processes that precede the development of apparent cardiac manifestations. (Eg, left ventricular hypertrophy or early diastolic dysfunction.)

Interventions to improve prognosis in these patients, however, have not been identified.

[NEJM February 12, 2004; 350: 718-20](#) Editorial, first author Daniel B Mark, Duke University, Durham, NC.

1 Use Of B-Type Natriuretic Peptide In The Evaluation And Management Of Acute Dyspnea

NEJM February 12, 2004; 350: 647-54 Original investigation, first author Christian Mueller, University of Basel, Switzerland

2 Plasma Natriuretic Peptide Levels And The Risk Of Cardiovascular Events And Death

NEJM February 12, 2004; 350: 655-63 Original investigation, first author Thomas J Wang, Framingham Heart Study, Framingham Mass

Comment:

The first use may be of value to the primary care clinician when triaging patients.

Investigators struggle to find more meaningful and accurate risk markers for cardiovascular disease. I believe we have enough markers now to act upon to improve prognosis. When the BTNP is elevated what does one do to reduce risk? RTJ

Milk Consumption—And Therefore Calcium Intake—Decreases As Soft Drink Consumption Increases.

2-6 EXPERTS URGE EARLY INVESTMENT IN BONE HEALTH

The American Academy of Pediatrics has issued a policy statement urging physicians to contact schools in their communities and push for the elimination of sweetened soft drinks. Carbonated soft drink consumption has increased by 16% since 1970; milk consumption has decreased by an equal amount. In addition to displacing milk in the diet, the phosphorus content of soft drinks may impair absorption of calcium.

Much of the focus was on the contribution of sugary (high fructose) beverages to the obesity crisis. The policy also highlighted concern that, when soft drinks displace milk, it sets the stage for later osteoporosis and risk of fractures. The evidence suggests that swapping soda pop for milk has effects on bone and increases

fracture rate in teenage girls. Milk is the main source of calcium in the typical American diet. Milk consumption—and therefore calcium intake—decreases as soft drink consumption increases.

“Every single child needs to be exercising and consuming calcium.” However, once supplements are stopped, the benefits regress.

Other nutrients are also important for bone health: vitamin D, vitamin C, magnesium, and zinc.

Adolescence is a time for bone accretion, Up to 90% of bone mass is acquired by age 18 in females and by age 20 in males. After age 30 or so, bone mass is actually breaking down faster than it is created. “People may see their grandmothers with osteoporosis, and it seems a long way off. They don’t realize it’s a relevant issue for their child.”

“The curved spines and frequent bone fractures in individuals with osteoporosis may be in part caused by events as far back as childhood.” “You give supplemental calcium and vitamin D to people over age 65, and you can reduce their osteoporotic fracture risk over half.”

[JAMA February 18, 2004; 291: 811-12](#) “Medical News and Perspectives” commentary by Tracy Hampton, JAMA staff.

Comment:

Anyone living in a retirement home will realize how common and disabling the kyphotic-osteoporotic spine can become. Development of osteoporosis can largely be prevented or retarded. I believe it is a major prevention opportunity for primary care clinicians. Prevention begins in childhood.

Commercial interests have intruded into our school system in subtle ways. Vending machines dispense not only soft drinks, but high calorie snacks. Textbooks are not an exception; advertising enters them in apparently innocuous ways. TV and radio programs provided for children in school contain commercial messages. Children can not perceive the hype. RTJ

This month BMJ presents ABC of Smoking, a review of dependence and motivation to quit; use of simple advice and behavioral support; and use of nicotine replacement therapy and bupropion. It follows an article abstracted in Practical Pointers January 2004 on “Why People Smoke”.

None of this is new. I felt, however, that a reminder is worthwhile considering that “Cigarette smoking is the single biggest avoidable cause of death and disability, and one of the biggest threats of current and future world health”.

The Main Value Of Measuring Dependence Is To Judge The Need For Pharmacotherapy.

2-7 ASSESSMENT OF DEPENDENCE AND MOTIVATION TO STOP SMOKING

Whether a smoker succeeds in stopping smoking depends on the balance between: 1) motivation to stop, and 2) degree of dependence. Clinicians must be able to assess both of these characteristics. Motivation is important because “treatments” to assist with smoking cessation will not work unless the smoker is highly motivated.

Dependence is especially important in smokers who do not wish to stop. The degree of dependence influences the choice of intervention.

Motivation to stop and dependence are often related: heavy smokers may show low motivation because they lack confidence in their ability to quit; lighter smokers may show low motivation because they believe they can stop anytime they wish. Motivation to stop can vary considerably with time and be strongly influenced by the immediate environment. What smokers say about their wish to stop may not accurately reflect their genuine feelings.

	Motivation	
	Low	High
Dependence low	Unlikely to stop, but could do so without help	Likely to stop with minimal help. Goal is to trigger a quit attempt
Dependence high	Unlikely to stop. Primary intervention is to increase motivation to be receptive to treatment for dependence	Unlikely to stop without help, but would benefit from treatment

Measuring dependence:

The simplest approach to measuring dependence is to ask patients whether they would find it difficult to stop in circumstances in which they would ordinarily smoke, and whether they have made a serious attempt to stop and failed.

The Fagerstrom test (http://www.letitpass.com/16p_fagerstrom_1.html) is a quantitative measure of dependence. The most telling questions deal with the number of cigarettes smoked per day, and the need to smoke first thing in the morning. (The need for a cigarette first thing on awakening is a marker of dependence. This is because overnight, nicotine blood levels fall to zero, and craving demands immediate replacement.)

The main value of measuring dependence is to judge the need for pharmacotherapy.

Measuring motivation to quit:

About 2/3 of smokers declare that they want to stop. About 1/3 make an attempt to stop in any given years. Older smokers are less motivated than the young. Only a minority of those attempting to stop use cessation medication or attend specialist cessation service.

Motivation to stop can be assessed by simple direct questions about the interest in stopping and intentions to quit. However, the degree of motivation seems to play a small role in success; once a quit attempt is made, markers of dependence are far stronger determinants of success.

The practical objective of assessing motivation is to identify smokers who are ready to make a quit attempt.

Comment:

I believe primary care clinicians should frequently assess patient's motivation to quit. If the patient expresses no interest in stopping there is no benefit in pursuing the subject. Raise the question again at a later consultation. Don't give up.

Smokers who develop angina, have an MI, or stroke or other serious illness are more likely to quit. This is a great opportunity. Smokers who are facing elective surgery within 6 weeks or so can be told that the likelihood of complications from the surgery will be greatly lessened if they quit.

It is amazing; however, how many relapse after a time. Those who quit and later relapse can be told that many smokers make several attempts to quit before succeeding. RTJ

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“The Best Thing You Can Do For Your Health Is To Stop Smoking.”

2-8 USE OF SIMPLE ADVICE AND BEHAVIORAL SUPPORT

The most effective methods of helping smokers quit is to combine drug therapy (nicotine or bupropion [Zyban]), with advice and behavioral support.

Simple advice: “The best thing you can do for your health is to stop smoking. I would advise you to stop as soon as possible.” The success rate of brief advice, however, is modest, achieving cessation in about 1 in 40. Nevertheless, it is one of the most cost effective interventions in medicine because the cost is so low. It takes only 1 to 2 minutes in routine consultations.

Behavioral support: Intensive behavioral support is provided outside routine clinical care by trained counselors. About 1 in 13 smokers who are motivated enough to attend counseling sessions are likely to quit. No one type of intensive behavioral support is clearly more effective than any other.

Written self help materials^{1,2} are more effective than doing nothing, but are not as effective as simple advice.

The most effective interventions combine behavioral support with drug treatment.

[BMJ February 14, 2004; 328: 397-99.](#) “ABC of Smoking Cessation” by Tim Coleman, Queen's Medical Centre, Nottingham, UK

1 <http://cancercontrol.cancer.gov/tcrb/quitlines.html>

2 <http://www.myclearhorizons.com/>

Both refer to other helpful sites. I downloaded and printed The National Cancer Institute's “*Clearing the Air: Quit Smoking Today*” from the first web site. Combined with simple advice, the information and encouragement presented might help a few to consider cessation.

Comment:

Primary care clinicians are fully aware of the great benefits of quitting smoking. Yet, I believe few routinely ask about smoking and fewer still attempt to offer help. They then miss “The greatest opportunity to improve their patient's health”

We should be persistent. Don't be discouraged by the poor success rate. I believe obtaining one success in cessation is a benefit equivalent to one coronary by-pass. RTJ

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NRT Doubles Likelihood of Achieving Cessation

2-9 NICOTINE REPLACEMENT THERAPY

Nicotine products are available to all smokers who want to stop smoking. The purpose is to blunt withdrawal symptoms. Nicotine replacement therapy (**NRT**) is most effective when used in conjunction with behavioral and other types of non-pharmacological cessation interventions.

NRT makes cigarettes less rewarding. It does not completely eliminate symptoms of withdrawal, possibly because none of the available delivery systems reproduce the rapid and high levels of nicotine in the brain achieved by inhaling cigarette smoke. (This takes only a few seconds.) Nicotine replacement products take longer, and produce lower levels. Nasal and oral products take minutes to reach the brain. Patches take hours. There is no evidence that any one of the formulations is more effective than any other. The choice is generally guided by the smoker's preference. A higher dose product, however, is more effective. Combining products (eg, patch and nasal spray) may also be more effective.

The most recent Cochrane review data suggest that NRT doubles cessation achieved.

Intervention	Long term abstinence (%)
None (will power alone)	3
Brief, opportunistic advice	5
Plus NRT	10
Intensive support from specialist	10
Plus NRT	18

NRT should be offered to any regular cigarette smoker who is prepared to make a quit attempt. It should be prescribed in blocks (usually 2 weeks), and continued for 6 to 8 weeks in those maintaining abstinence—then discontinued if possible. Only about 5% of NRT users who quit successfully continue to use it regularly long term.

NRT is safer than smoking cigarettes. Long-term use is not thought to be associated with any serious harmful effects. NRT may have adverse effects on placental function and fetal development. It is likely to be far less harmful than smoking. About 30% of pregnant women succeed in stopping without pharmacological support. NRT is safe in patients with stable cardiovascular disease. It should be used with caution in patients with unstable angina, acute MI, or stroke. Nicotine is a vasoconstrictor. It is less harmful than continued smoking.

Smokers should be advised not to smoke while taking NRT.

[BMJ February 21, 2004; 328: 454-56](#) “ABC of Smoking Cessation”, clinical review by Andrew Molyneux, City Hospital, Nottingham, UK

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Also Seems To Attenuate The Weight Gain Associated With Cessation Of Smoking.

2-10 BUPROPION AND OTHER NON-NICOTINE PHARMACOTHERAPIES

Bupropion (*Zyban*) was first introduced as an antidepressant. Subsequently it was noted to reduce the desire to smoke cigarettes. Its chemical structure is similar to diethylpropion, an appetite suppressant. It inhibits reuptake of dopamine, noradrenalin, and serotonin in the central nervous system and is a non-competitive nicotine receptor blocker. Its anti-smoking action is not related to its antidepressant action. It acts equally well in non-depressed persons.

It is as effective as nicotine replacement when given in association with intensive behavioral support, achieving a 19% long-term abstinence. It also seems to attenuate the weight gain associated with cessation of smoking. Use beyond the recommended 8 weeks may confer further protection against relapse.

Suggested dose regimen:

Week 1	Days 1-5 150 mg daily
	Days 6-7 150 mg twice daily
	(Quit smoking between day 7 and day 14)
Weeks 2-8	150 mg twice daily.

Bupropion is contraindicated in persons with current or past epilepsy. (*See text for other cautions.*) It is metabolized in the liver by cytochrome P450. It is generally safe and well tolerated.

One study suggested that combined bupropion-nicotine patch produces higher quit rates.

Nicotine replacement is still the treatment of first choice.

The article mentions nortriptyline and other antidepressants and other drugs such as Clonidine. None is used routinely in specialist smoking-cessation clinics.

[BMJ February 28, 2004; 328: 509-11](#) “ABC of Smoking Cessation” clinical review by Elin Roddy, University of Nottingham, UK.

2-11 COUGHING CAN REDUCE PAIN OF INJECTION

Many tactics have been tried to distract from the pain of injections—cartoons, hypnosis, music, jokes, and counter pressure. *The British Journal of Plastic Surgery* reports that when patients cough vigorously as the needle comes into contact with the skin the pain of injection is decreased.

There is little doubt that distraction works. It may be explained by the gate control theory. Stimuli traveling over fast nerve fibers partially override painful sensations traveling along slower nerve fibers.

Pain may also be decreased when blood is being drawn.

[BMJ February 21, 2004; 328: 424](#) “News” by Roger Dobson, Abergavenny, UK

An “Invented Illness”?

2-12 PROZAC (FLUOXITINE) DROPPED AS INDICATION FOR PREMENSTRUAL DYSPHORIC DISORDER.

Last summer, a European committee found that “PMDD is not a well-established disease entity”. It is listed in the DSM IV only as a research diagnosis. The committee strongly criticized two key trials of the antidepressant drug, the selective serotonin reuptake inhibitor fluoxetine (*Prozac*; Lilly), noting that in one study almost half of the participants dropped out, and, in the second study, little attempt was made to distinguish between mild and severe health problems. There was concern that women with less severe premenstrual symptoms might receive the diagnosis and be treated inappropriately.

The drug company informed health professionals in the USA in December that it had removed PMDD as an indication for *Prozac*.

Some researchers welcomed the decision, saying that PMDD (which was only recently described) was an invented illness—a strong example of the medicalization of ordinary life.

Prozac was first approved for PMDD in 2000 by the FDA. An aggressive promotional campaign followed.

[BMJ February 14, 2004; 328: 365](#) “News”, commentary by Roy Moynihan, Washington DC

Comment:

The January 2003 issue of *Practical Pointers* abstracted a review article (NEJM January 30, 2003; 348: 433-38) which endorsed two selective serotonin reuptake inhibitors for treatment of PMDD. (*Prozac* and *Zoloft*)

A table in the article presents criteria for diagnosis. It does not mention that PMDD is a research diagnosis. The hallmark of the syndrome is its cyclic nature, with symptoms coinciding with the luteal phase. PMDD was described as being different from the more common premenstrual syndrome (PMS). PMDD is much more severe and can cause marked interference with social activities and exacerbation of depression. The author of the NEJM article recommends a trial of calcium carbonate or vitamin B6. If no benefit, *Prozac* may be prescribed during the luteal phase. If there is an improvement, it may be continued for at least 9 to 12 months

This leaves us with PMS (“premenstrual syndrome”) PMS can be severe and accompanied by depression. A variety of lifestyle changes and drugs, including hormonal therapy, have been suggested.

I believe many MDs will continue to prescribe selective serotonin reuptake inhibitors (including Prozac) off label at low dose (20 mg as a trial therapy for select patients). PMS can be disabling and there are few effective alternative therapies. RTJ

No Participant Thought They Had Benefited From Treatment

2-13 TREATMENTS OF HOMOSEXUALITY IN BRITAIN SINCE THE 1950--AN ORAL

HISTORY: The Experience Of Patients. The Experience of Professionals

In Britain, “treatments” to change homosexuals into heterosexuals peaked in the 1960s and early 1970s. This article describes the experiences of 29 persons in the UK who received such treatment.

Most of these persons were distressed by their attraction to their own sex. Those who confided in others were usually met with silence, condemnation, and rejection. People in whom they confided thought treatment was advisable.

“Although some participants chose to undergo treatments instead of imprisonment (sexual behavior in private between adult men was not decriminalized in Britain until 1967), or were encouraged through some form of medical coercion, most were responding to complex personal and social pressures that discouraged any expression of their sexuality.” Those who grew up between 1940 and 1970 commented that their same-sex attraction gave rise to considerable anxiety. One subject commented. . . “I felt bewildered that my entire emotional life was being written up in the papers as utter filth and perversity”. Treatments included behavioral aversion therapy with electroshock (including electroconvulsive therapy) and apomorphine (one died of side effects); psychoanalysis; estrogen to reduce libido; religious counseling; and hypnosis. Dating skills were

sometimes taught, and occasionally men were encouraged to find a woman with whom to try sexual intercourse. Therapists rarely questioned the prevailing assumption that same sex attraction was abnormal, or considered that people could adapt to their sexuality.

No participant thought they had benefited from treatment. “There is no evidence that treatments were effective at changing sexual orientation.” For many, it increased their sense of social isolation and shame. (*Some were driven to suicide RTJ*) Occasionally it enabled acceptance of their sexuality.

“Social and political assumptions sometimes lie at the heart of what we regard as mental pathology and serve as a warning for future practice.” “Assumptions about public morality and professional authority can lead to the medicalization of human differences and the infringement of human rights.”

[BMJ February 21, 2004; 328: 427-32](#) Original investigations, first authors Glenn Smith and Michael King, Royal Free and University College School of Medicine, London.

Comment:

One leader in the field of therapy was shocked to find his work publicly compared with brain washing and Nazi experimentation. DSM classified homosexuality as a disease until 1973. Even the most enlightened cultures still contain remnants of barbarism.

In the USA as elsewhere, social mores, religion, politics, and culture still influence medical decisions, and override some of the established benefits scientific medicine brings for both individuals and the general population. RTJ

Women With A History Of BC Should Not Receive HRT

2-14 HABITS (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?)

Increasing numbers of premenopausal women are surviving breast cancer (**BC**). They experience menopausal symptoms as they grow older. Is hormone replacement therapy (**HRT**) safe in these patients? Recent studies report that HRT increases risk of BC in women who have not had a history of BC.

This study investigated whether HRT is safe given to women with previously treated BC. All had less than 4 positive nodes and were free of recurrence at baseline. All had menopausal symptoms deemed by the patient and the doctor to need treatment. Adjuvant tamoxifen was allowed. The main end point was any new BC.

Choice of type of HRT was directed by local practice. Women with an intact uterus were recommended to receive combined estrogen/progestin. Hysterectomized women were recommended to receive a medium potency estrogen only.

Over 400 were randomized to HRT or no HRT; 345 were followed for 2 years.

RESULTS:

1. Over 2 years, 26 women (12%) in the HRT group experienced a new BC vs 8 (4%) in the no-HRT group. In the HRT group, 11 were local recurrences; 5 were contralateral BC; and 10 were distant metastases. In the no-HRT group 2; 1; and 5. [NNT (to harm over 2-y) =12]
2. The specific type of HRT (combined continuous, combined sequential, or estrogen alone) made no difference in recurrence rate.

3. Because of the unacceptable risk in the HRT group, the trial was discontinued early.

CONCLUSION:

Women with a history of BC should not receive HRT. Those already receiving HRT should be advised to discontinue.

[Lancet February 7, 2004; 363: 453-55](#) “Research Letter”, a report from the HABITS group, reported by (first author) L Holmberg, Lund University, Lund, Sweden.

Comment:

For women with history of BC, what can be advised for menopausal-symptom relief other than HRT? The North American Menopause Society suggests several non-hormonal therapies:

Antidepressants venlafaxine (*Effexor*) paroxetine (*Paxil*) fluoxetine (*Prozac*; generic). Start at very low doses and gradually increase. Cessation requires gradual tapering off.

Gabapentin (*Neurontin*) may be considered in women older than 65

Clonidine is less effective than gabapentin. RTJ

2-15 SEX, LIES, AND NIAGRA

An estimated 20 million men worldwide have been prescribed sildenafil (*Viagra*) for erectile dysfunction. There is a growing market for “natural” alternatives. One such product *Actra-R* (or *Niagra Actra-R*) has been advertised as “100% natural”.

These investigators obtained samples of *Actra-R* over the counter and directly from the vendor over the Internet. They used sophisticated chemical analyses to compare content of *Actra-R* with sildenafil.

All capsules of *Actra-R* contained sildenafil, an average of about 55 mg per capsule.

[JAMA February 4, 2004; 291: 560-62](#) “Research Letter” first author Alberto J Sabucedo, Florida International University, Miami.

Comment:

Charlatanism remains alive. Nostrums fill the shelves of pharmacies. Fraud pervades the “alternative/complementary” medicine and the “all-natural herb” industry. Some products have been found toxic (eg, ephedra). Some are ineffective (eg, echinacea for upper respiratory infections in children). I remember one report of an “all natural” topical preparation for dermatitis which was found to contain hydrocortisone.

2-16 FACTS VERSUS IDEOLOGY IN THE CLONING DEBATE

HUMAN CELLS FROM CLONED EMBRYOS IN RESEARCH AND THERAPY.

Korean investigators recently reported derivation of stem cells from a cloned human embryo. This may lead to development of ability to study genetic diseases in entirely new ways. "Experience will be needed to learn how such cells should best be used."

The method used was essentially the same as that used to produce Dolly, the cloned sheep. The investigators harvested human eggs and removed the nucleus (*23 chromosomes*). They then took nuclei from surrounding cumulus cells (*46 chromosomes*) and injected them into the enucleated egg to produce a cell genetically identical to the cumulus cell. A total of 30 of over 200 cloned cells developed normally for 6 days to reach the blastocyst stage. (Typically less than 5% of cloned embryos become viable offspring.) Cells were isolated from 20 of these embryos, and from these, one stable cell line was derived. The stable stem cells had the ability to grow for prolonged periods in culture and to form other cell types.

Methods for deriving specific cell types from stem cells are being established. It is not known if these cells will function normally after transfer. Immunologic rejection may occur. Some day, researches may grow from stem cells into immunologically matched replacement tissues to treat illness.

There is much misunderstanding, especially in the lay press, about the procedure. No human baby was made, let alone destroyed. No one made an "embryo" (as most people understand the term). The cell line was not derived from the union of sperm and egg. The "parents" of the undifferentiated, pluripotent stem cells were an unfertilized egg which provided the cytoplasm, and a cumulus cell which provided the nucleus. The resulting cells were genetically identical to the cumulus cells of the woman. The researchers were not able to clone a viable embryo containing genetic material from someone other than the original egg donor, Their only success came when they sucked the DNA from an adult cell donated by the same woman.

Left where they were, the cloned cells would not have become separate human beings.

Such an artificially created blastocyst, if implanted back into the uterus would perhaps have developed further, eventually as a new person—ie, reproductive cloning. The investigators in fact called on a world-wide ban on reproductive cloning.

It could be argued that this new technology is more "morally" acceptable than the current way in which embryonic stem-cell lines are produced from embryos derived from sperm and egg left over after in vitro fertilization.

[Lancet February 21, 2004; 363: 561](#) Editorial from the Lancet staff

[BMJ February 21, 2004; 328: 41516](#) Editorial by Ian Wilmut, Roslin Institute, Roslin, UK

Comment:

JAMA, in addition to BMJ and Lancet, commented on this work. The lay press also took note. I abstracted these news items because of their general interest, not for any practical importance.

The next generations may have the opportunity to benefit from this basic research. RTJ

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A Subtle Change In The Shape Of The Virus Killed 20 Million People.

2-17 STRUCTURE OF THE 1918 FLU VIRUS

Scientists at the Medical Research Council (UK) have discovered the crucial structural change the avian influenza virus underwent that resulted in the death of 20 million people worldwide in 1918. The 1918 virus was obtained from the body of an Inuit woman buried in the Alaskan tundra and from US soldiers who fought in WW I. Subtle alterations in the shape of a protein (hemagglutinin [HA]) on the virus allowed transmission from birds to human.

The HA molecule protrudes from the surface of the flu virus as a series of spikes. The change in the configuration of the spikes enabled the avian flu virus to lock on the surface of human cells. Usually, bird viruses cannot be transmitted to humans. But, in 1918 this subtle change in shape of HA gave it the capability to attach to receptors on human cells as well as bird cells. The virus then spread rapidly from human to human to infect an estimated billion people—half of the world’s population at the time.

All of the devastating flu pandemics of the last century were caused by viruses that came from birds.

[BMJ February 14, 2004; 328: 368](#) “News”, commentary by Debashis Singh, London UK.

2-18 ANTIBIOTIC USE IN RELATION TO THE RISK OF BREAST CANCER

This case-control study compared 2266 cases of primary invasive breast cancer (BC) with 7953 matched controls without BC in regard to their use of antibiotics. Antibiotic use was ascertained by computerized pharmacy records. Observation period ranged from 10 years to 23 years.

Increasing cumulative days of antibiotic use were associated with increased incident BC.

Risk adjusted for age and length of enrollment:

Days of use	Odds ratio of BC (Compared with controls)
0	1.00 (referent)
1-50	1.45
51-100	1.53
101-500	1.68
501-1000	2.14
Over 1000	2.07

Increased risk was observed in all antibiotic classes studied and in a subanalysis of having a BC fatality.

The investigators state that the study cannot determine if antibiotics are causally related to BC, or whether the indication for antibiotic use, overall weakened immune function, or other factors underlie the relationship.

[JAMA February 18, 2004; 291: 827-35](#) Original investigation, first author Christine M Velicer, University of Washington, Seattle.

Comment:

The investigators report the risk as *adjusted*-relative risks. What is the absolute risk?

By my calculations from their tables 3 (p 832):

Days of antibiotic use

	Controls (7948)	Cases (2266)	Absolute difference	Risk per 1000 patients
1-50	29.8 %	29.8 %	0	0
51-100	19.1 %	19.2%	0.1 %	1/1000
101-500	27.9 %	30.1 %	0.2%	2/1000
501-1000	2.7 %	3.7	1 %	10/1000
Over 1000	2.0 %	2.6 %	0.6 %	6/1000

(According to my unadjusted calculations, an extraordinarily high use of antibiotics use was associated with at most a 1% higher risk of developing BC. Patients using antibiotics for less than 500 days (the great majority) had little increased risk. RTJ)
