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HIGHLIGHTS FEBRUARY 1999

2-1 SOMATIZATION RECONSIDERED: Incorporating The Patient's Experience Of Illness

"All illnesses in all patients have emotional and social considerations. While most physicians would agree with this, their clinical practice speaks otherwise." Rather than invoking emotions and social factors in only those illnesses whose solutions remain unexplained, simultaneously explore symptoms, pathological findings, life context, and emotions in all cases. Archives Int Med February 8,1999; 159: 215-222.

2-2 PREVALENCE AND EXTENT OF ATHEROSCLEROSIS IN ADOLESCENTS AND YOUNG PEOPLE: Implications for Prevention from the Pathobiological Determinants of Atherosclerosis in Youth (PADY) Study

Atherosclerosis begins in youth. Fatty streaks and clinically significant raised lesions increase rapidly in prevalence and extent during the 15 to 34-year age span. Primary prevention of clinically manifest atherosclerotic disease must begin in childhood or adolescence. JAMA February 24, 1999; 281: 727-35

2-3 HEALTH LITERACY AMONG MEDICARE ENROLLEES IN A MANAGED CARE ORGANIZATION

Elderly managed care enrollees may not have the literacy skills necessary to function adequately in the health care environment. This may limit ability to care for their health problems. JAMA February 10, 1999; 281: 545-51

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Oral sildenafil was an effective and well-tolerated treatment for ED in men with diabetes.
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The presence of so called venous symptoms was extremely high in this population, especially in women. However, agreement between symptoms and signs of varicose veins is so poor that it may be of little value in determining whether symptoms are of venous origin, or whether surgery will relieve them. BMJ February 6, 1999; 318: 353-56

2-6 EFFECTS OF THYROXINE AS COMPARED WITH THYROXINE PLUS TRIIODOTHYRONINE IN PATIENTS WITH HYPOTHYROIDISM

In patients with hypothyroidism, partial substitution by triiodothyronine for thyroxine may improve mood and neuropsychological function. This suggests that the normal thyroidal secretion of triiodothyronine is physiologically important. NEJM February 11, 1999; 340: 424-49

2-8 SINGLE BLIND, RANDOMISED, CONTROLLED TRIAL OF PELVIC FLOOR EXERCISES, ELECTRICAL STIMULATION, VAGINAL CONES, AND NO TREATMENT IN MANAGEMENT OF GENUINE STRESS INCONTINENCE IN WOMEN

Training of the pelvic floor muscles with exercise was superior to electrical stimulation and vaginal cones in treatment of genuine stress incontinence. BMJ February 20, 1999; 318: 487-93

2-9 ACUTE PHASE PROTEINS AND OTHER SYSTEMIC RESPONSES TO INFLAMMATION

"Acute phase changes reflect the presence and intensity of inflammation. They have long been used as a clinical guide to diagnosis and management. For this purpose, determination of serum C-reactive protein has advantages over the traditional strategy of measuring the erythrocyte sedimentation rate." NEJM February 11, 1999; 340: 448-54

2-10 WOULD CLONED HUMANS REALLY BE LIKE SHEEP?

Why a clone cannot be a clone. Read the original! NEJM February 11, 1999; 340: 471-75

2-11 IMPROVED DETECTION OF CORONARY ARTERY DISEASE BY EXERCISE ELECTROCARDIOGAPHY WITH USE OF RIGHT PRECORDIAL LEADS

Exercise electrocardiography incorporating the combination of right leads along with the standard left leads greatly improved sensitivity for the diagnosis of coronary artery disease. NEJM February 4,1999; 340; 340-45

2-12 THE VALUE OF THE RIGHT PRECORDIAL LEADS OF THE ELECTROCARDIOGRAM

Right ventricular infarction carries a marked increase in mortality during hospitalization. Identification of right ventricular infarction by right chest leads may select those who would benefit most from reperfusion. NEJM February 4, 1999; 340: 381-83

2-13 LACK OF EFFECTIVENESS OF BED REST FOR SCIATICA

Among patients with symptoms and signs of lumbosacral radicular syndrome, bed rest was not a more effective therapy than watchful waiting. NEJM February 11, 1999; 340: 418-23

2-14 LOOKING BEYOND THE NEXT PATIENT: Sociology and Modern Health Care

Exclusion, isolation, and helplessness can be harmful to health. An assault must be made on factors that affect the human psyche — those that make people feel undervalued and excluded. THE LANCET February 6, 1999; 353: 486-89

2-15 CAN RANDOMISED TRIALS INFORM CLINICAL DECISIONS ABOUT INDIVIDUAL PATIENTS?

The paradox of RCTs is that they are the best way to assess whether an intervention works, but it is a poor way to assess who will benefit. "Clinical decision making requires evidence of applicability from clinical trials and evidence of applicability to individual patient from observational studies." "Most general practice depends on 'interpreting personally unique patterns of illness, rather than recognizing generalized patterns of disease'." There are grey zones where scientific evidence is incomplete or conflicting. "What is black and white in the abstract may become grey in practice". THE LANCET February 27,1999; 353: 743-46

2-16 APPLICATION OF EVIDENCE FROM RANDOMISED TRIALS TO GENERAL PRACTICE.

"There is no simple answer to the question as to whether all advice or interventions provided by family physicians should be evidence based." Using a patient-centered approach to clinical practice is most likely to achieve the best possible outcome for evidence based medicine.

THE LANCET February 20,1999; 353: 661-64

2-17 INCREASED PULSE PRESSURE AND RISK OF HEART FAILURE IN THE ELDERLY

In this prospective study of community-based elderly, PP was independently and linearly associated with risk of HF. JAMA February 17, 1999; 281: 634-39

2-18 CHRONIC STRESS IN ELDERLY CARERS OF DEMENTIA PATIENTS AND ANTIBODY RESPONSE TO INFLUENZA VACCINE

Elderly carers of spouses with dementia have increased activation of the hypothalamic-pituitary-adrenal axis and a poor response to influenza vaccine.

Carers may be more vulnerable to infectious disease. THE LANCET February 20, 1999; 353: 627-31

2-19 SUCCESSFUL TREATMENT OF LATRODECTISM WITH ANTIVENIN AFTER 90 HOURS

Anecdotal report which reminds us of the availability and use of antivenin. NEJM February 25, 1999: 340: 657

2-20 THE NATIONAL DIABETES EDUCATION PROGRAM: Changing the Way Diabetes is Treated.

These emerging findings have prompted the National Institutes of Health and the Centers for Disease Control and Prevention to sponsor a major national initiative, the National Diabetes Education Program. This will develop strategies to improve diabetes care, promote early detection, and ultimately prevent the onset of the disease.

The Web site: http://NDEP.NIH.gov Annals Int. Med. February 16, 1999; 130: 324-26

2-21 THE MENOPAUSE

Review article. THE LANCET February 13, 1999; 353: 571-80

RECOMMENDED READING

2-10 WOULD CLONED HUMANS REALLY BE LIKE SHEEP?

2-15 CAN RANDOMISED TRIALS INFORM CLINICAL DECISIONS ABOUT INDIVIDUAL PATIENTS?

2-16 APPLICATION OF EVIDENCE FROM RANDOMISED TRIALS TO GENERAL PRACTICE.

REFERENCE ARTICLES

2-1 SOMATIZATION RECONSIDERED

REFERENCE ARTICLE

2-1 SOMATIZATION RECONSIDERED: Incorporating The Patient's Experience Of Illness

"Up to two thirds of patients in primary care settings have unexplained somatic symptoms. Many fulfill criteria for a somatization disorder according to the DSM-IV." Patients are frequently labeled "somatizers", not on the basis of specific symptom constellations, but because they repeatedly seek the council of physicians in search of understanding, and no satisfactory medical explanations can be found. These patients attribute their symptoms to malevolent physical causes that cannot be verified, and do not accept any psychological or social explanations for their distress.

This article challenges and recasts some assumptions related to patients with unexplained somatic symptoms who present to primary care. It proposes an alternative approach to care — a bio-psycho-social model, with contributions from the patient-centered clinical method.

Some patients with persistent somatic complaints feel blamed, coerced, devalued and misunderstood by any psychological inquiry. This may result from differences in ways of using language and understanding illness. After many visits and referrals, physician, patient, and family may be frustrated by the absence of a clear diagnosis. Family life may be disrupted. Care is expensive. Unless the physician and patient develop a shared understanding of the nature of the problem, the goals and methods of treatment are at odds.

The bio-psycho-social model considers all significant illness involves bodily functioning, and emotions, and social relationships. The bio-psycho-social model and the patient-centered method require attention to emotions and relationships in every case. Some patients labeled as "somatizers" are survivors of childhood abuse and neglect. They may use bodily language to express the "unspeakable". Being again blamed for one's distress can be destructive.

The strategy of "ruling out" organic disease before exploring psychosocial dimensions of illness is based on a hierarchical notion of the primary importance of physical disease, and the belief that mental and physiological phenomena can be neatly separated. For many illnesses the correlation between observed pathological changes and symptoms is poor. Differences in sensitivity to painful stimuli are both biologically and psychosocially conditioned. (Some patients are stoic; some sensitive.) It is normal to experience emotions in the body, and for bodily symptoms to be accompanied by emotional distress. Modern medicine often distinguishes between somatic and psychological symptoms. This is incorrect. Patients who experience bodily symptoms often do not regard their mind as the primary cause of their distress, and may be fearful of psychological explanations. "Much of the conflict between patients with somatic distress and their physicians revolves around the inability to agree on a name (and, by implication, a cause) for the illness." [1]

Primary care physicians constantly deal with illnesses requiring long-term follow-up and expect relapses and remissions for non-curable conditions. This reorients medical practice toward care rather than cure while avoiding the pitfalls of overtreatment, undertreatment, and iatrogenic harm. Successful treatment can reduce symptoms and improve functioning by accepting the patient's experience of symptoms without trying to change it, and by providing support and developing coping skills. At the same time, physicians must recognize and tolerate uncertainty. A cascade of consultations commonly amplifies and fragments the problem by providing a series of partial explanations and hypotheses within each organ system without addressing the larger integrated whole.

Recommendations

* Understand and accept the patient's suffering: (Ask for concerns and listen. Know the patient's story.
* Do not deny the reality of the symptoms. When all tests are normal do not tell the patient there is nothing wrong. "I know you are in distress.")
* Legitimize the patient's suffering: (Giving the condition a name (eg, fibromyalgia, chronic fatigue syndome, irritable bowel) may help. But, "in the present state of medical knowledge we do not have tests that diagnose the cause of your symptoms".)
* Be patient; recognize uncertainty:[2] ("We do know there is something amiss in your nervous system which makes you more sensitive to pain and other symptoms. We remain uncertain as to the exact cause. " Avoid "head", "brain", and "mind", "imaginary", "psychiatric".)
* Limit referrals and iatrogenic harm: ("I cannot recommend further testing. We will follow-up and keep an eye on you.")

* Reassure. Remove any sense of blame: ("The tests so far have revealed nothing serious. I can assure you there is nothing to indicate a condition serious enough to shorten your life or cause significant disability.")
* Help the patient cope and improve functioning: ("Many patients with disabilities which we cannot cure, cope and live productive lives despite continuing discomfort. You can do the same. Keep going.)
* Empower patients to manage the illness themselves: (Involve patients in their own care. Accept bad days and be thankful for good days.)
* Direct attention to care rather than cure.

Some medications may help. "Bodily therapies such as diet, meditation, physiotherapy, relaxation techniques, biofeedback, massage and exercise are generally well accepted by patients."

"All illnesses in all patients have emotional and social considerations. While most physicians would agree with this, their clinical practice speaks otherwise." Rather than invoking emotions and social factors in only those illnesses whose solutions remain unexplained, simultaneously explore symptoms, pathological findings, life context, and emotions in all cases.

The dichotomy — the emotional vs the physical aspects of illness — is unique to Western medicine.
" Attempts to force the problem of unexplained somatic complaints into 19th-century pathologically based diagnostic system have not been successful."

Archives Int Med February 8,1999; 159: 215-222. "Special Article", commentary, first author, Ronald M Epstein, Highland Hospital, University of Rochester School of Medicine an Dentistry, NY

Comment:

Italics are mine — editor

1. Is labeling always bad? Cannot "fibromyalgia " and "chronic fatigue syndrome" help some to cope?

2. Uncertainty is a domain of primary care.

For a related article see: "Patient's Perceptions of Medical Explanations for Somatisation Disorders" Qualitative Analysis" BMJ February 6, 1999; 318: 371-76

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2-2 PREVALENCE AND EXTENT OF ATHEROSCLEROSIS IN ADOLESCENTS AND YOUNG PEOPLE: Implications for Prevention from the Pathobiological Determinants of Atherosclerosis in Youth (PADY) Study

Atherosclerosis has been shown to be present in young adults. Previous studies have reported that the conditions predicting risk of clinically manifest coronary heart disease **(CHD)** are associated with the extent and severity of atherosclerotic lesions in youth. This article summarizes the natural history of aortic and coronary atherosclerosis among adolescents from the PADY study

The objective of this study was to document the extent and severity of atherosclerosis in adolescents and young adults in the US.

Conclusion: Atherosclerosis begins in youth.

STUDY

1. Multicenter study entered 2876 subjects in the 15 to 34-year old age group who died of external causes. Autopsy was performed in all. Examined the aortas and the right coronary artery in detail.
2. Determined extent, prevalence, and topography of atherosclerotic lesions.
3. Fatty streaks (innocuous) are prevalent in the young. Fibrous plaques (raised lesions, clinically significant) begin to appear later.

RESULTS

1. Intimal lesions appeared in all the aortas and more than half of the coronary arteries of the youngest age group (15-19 years)
2. The lesions increased in prevalence and extent with age through the oldest group (30-34).
3. Area involved was greater in blacks than in whites.

DISCUSSION

1. The existence of altherosclerosis in children and adolescents has been recognized for years. (Atherosclerosis does begin in childhood.)
2. In another study, more than 50% of children age 10-14 had lesions characterized by accumulations of macrophage foam cells, lipid-containing smooth muscle cells, and thinly scattered extracellular lipid. This represents the microscopic counterpart of gross fatty streaks.
3. These lesions progress to fibrous plaques which are known to be associated with clinical disease.
4. Raised low density cholesterol levels are positively associated with both fatty streaks and raised lesions. Levels of high density lipoprotein cholesterol are negatively associated with prevalence of raised lesions. Raised glycohemoglobin, hypertension, and raised body mass index are also associated with lesions.
5. Atherosclerosis begin in childhood. The risk factors for adult CHD and other clinical syndromes resulting from atherosclerosis determine to a large degree its rate of progression.

CONCLUSION

Atherosclerosis begins in youth. Fatty streaks and clinically significant raised lesions increase rapidly in prevalence and extent during the 15 to 34-year age span. Primary prevention of clinically manifest atherosclerotic disease must begin in childhood or adolescence.

JAMA February 24, 1999; 281: 727-35 Original investigation by the Pathobiological Determinants of Atherosclerosis in Youth (PADY) Study, first author Jack P Strong, Louisiana State University Medical Center, New Orleans.
Comment: The message is obvious. RTJ

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2-3 HEALTH LITERACY AMONG MEDICARE ENROLLEES IN A MANAGED CARE ORGANIZATION

In 1993, the National Adult Literacy Survey reported that 44% of adults over age 64 scored in the lowest reading level, meaning they could not perform the basic reading tasks necessary to fully function in society. Other surveys reported that the majority of English speaking patients over age 60 had inadequate health literacy. They could not correctly read basic items

commonly encountered in the health care setting, such as prescription bottles and appointment slips. Another study of low income community-dwelling adults over age 60 found mean skills at the fifth-grade level.

This cross-sectional study determined the prevalence of low functional health literacy among community-dwelling Medicare enrollees.

Conclusion: Many patients had inadequate or marginal health literacy.

STUDY

1. Interviewed over 3000 new Medicare enrollees over age 64. The great majority spoke English; some spoke Spanish.
2. Measured functional health literacy by the Short Test of Functional Literacy in Adults. (Reference # 29) The test is available in both English and Spanish. It takes no more than 12 minutes to administer. It uses actual materials that patients might encounter in the health care setting, measures ability to read and understand prose passages written at grade level 4 explaining instructions for preparation for an upper GI tract radiographic procedure. It also tests ability to comprehend directions for taking medicines, monitoring blood glucose levels, and keeping appointments.

RESULTS

1. Overall, 40% of English-speaking and 52% of Spanish-speaking respondents had inadequate or marginal health literacy.
2. Reading ability declined dramatically with age, even after adjusting for years of school completed and cognitive impairment. The adjusted odds ratio for having inadequate or marginal health literacy was 9 for enrollees aged over 84 compared with individuals age 65-69.
3. Health literacy and years of school completed were strongly associated: 17% of respondents with a high school education and 10% with more than a high school education had inadequate health literacy.

DISCUSSION

1. Among these Medicare enrollees, more than one third of respondents had inadequate or marginal health literacy.
2. There was a striking difference in the prevalence of inadequate health literacy across the 4 sites. Much of this was because of differences in race/language, and socioeconomic status across sites. Practitioners need to assess health literacy levels in their own setting.
3. The data suggest that inadequate health literacy continues to increase beyond age 65. This suggests that reading ability declines with age and that the elderly may have difficulty in completing the test within the allotted time. They may do better when no time limit is set for completion. They may also do better if the test is done at a time when they are not fatigued.[1]
4. Clinicians need to be aware of the prevalence of health literacy problems and need to identify patients with poor literacy skills. As a first step, one may determine (compassionately) how many years of school they have completed. For those who have not completed high school, additional questions (Do you know the names of the medicines you are taking?) may raise concerns.

5. Managed care programs should be aware of the prevalence of health illiteracy in their members.
Illiteracy, especially among the elderly, who use care more frequently, may reduce effectiveness of care and increase costs.

CONCLUSION

Elderly managed care enrollees may not have the literacy skills necessary to function adequately in the health care environment. This may limit ability to care for their health problems.

JAMA February 10, 1999; 281: 545-51 Original investigation, first author Julie A Gazmararian, Prudential Center for Health Care Research, Emory University School of Medicine, Atlanta, GA.

1. The goal of treatment of patients is to ensure understanding, trust, and concurrence between patient and doctor in the treatment plan. Some individuals, especially the elderly, may require additional time and patience.

We cannot expect concurrence unless the patient understands. RTJ

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2-4 SILDENAFIL FOR THE TREATMENT OF ERECTILE DYSFUNCTION IN MEN WITH DIABETES

Erectile dysfunction **(ED)** is common and distressing in men with diabetes. It is often associated with neuropathy and peripheral vascular disease.

Penile erection is a hemodynamic event dependent on relaxation of smooth muscle cells in the arteries and corpus cavernosum of the penis. It is mediated by Nitric oxide (NO) which is released in the penis in response to sexual stimuli. NO induces a guanosine compound which leads to the smooth muscle relaxation. Sildenafil (*Viagra*) acts by inhibiting the enzyme which hydrolyzes the relaxing compound. Thus the action of NO is enhanced. The plasma half life of sildenafil is about 4 hours.

This study assessed efficacy and safety of sildenafil in the treatment of ED in men with diabetes.

Conclusion: Sildenafil was effective and well tolerated.

STUDY

1. Multicenter randomized, double-blind, placebo-controlled trial entered 268 men (mean age 57) with a mean duration of diabetes for 12 years duration and ED for 6 years.
2. Randomized one hour before anticipated sexual activity to: 1) sildenafil, or 2) placebo.
3. Starting dose of sildenafil was 50 mg, with the option of adjusting dose to 25 mg or 100 mg.
4. Duration of study = 12 weeks.

RESULTS

1. Ninety four percent completed the study.
2. At 12 weeks, 56% of sildenafil patients reported improved erections vs 10% of the placebo patients.
3. Ability to achieve and maintain an erection occurred only "sometimes". Most men did not achieve this on all occasion.
4. Sixty one percent of sildenafil group reported at least one successful attempt at sexual intercourse vs 22% of placebo group.

5. Adverse events occurred in 16% of sildenafil group (headache 11%, dyspepsia 9%, respiratory tract disorder [predominantly sinus congestion or drainage] 6%).
6. Cardiovascular events occurred equally in both groups — 3% sildenafil ; 5% placebo.

DISCUSSION

1. Sildenafil had been reported to be effective in men with organic, psychogenic and mixed erectal dysfunction. ED in men with diabetes is predominantly caused by organic factors.
2. Since there is a degree of risk associated with sexual activity in men with cardiovascular disease, their status in this regard should be determined before starting treatment.

CONCLUSION

Oral sildenafil was an effective and well-tolerated treatment for ED in men with diabetes.

JAMA February 3, 1999; 281: 421-26 Original investigation, first author Marc S Rendell, Creighton Diabetes Center, Omaha, Neb.

An editorial in this issue (pp 465-66) comments: The FDA has mandated labeling to warn men who have had a heart attack, stroke, or life-threatening arrhythmia within the previous 6 months; have a BP under 90/50 or over 170/110; have a history of heart failure, unstable angina, or retinitis pigmentosa; about possible serious adverse effects. Men taking nitrates are at increased risk.

Some institutions routinely evaluate cardiovascular risk factors and perform exercise stress testing before the drug is prescribed. This may be especially appropriate in patients with diabetes.

Comment:

There was no mention of quality-of-life benefits in the study. In men with long standing ED due to diabetes, the quality-of-life benefits may be high indeed. RTJ

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2-5 WHAT ARE THE SYMPTOMS OF VARICOSE VEINS? Edinburgh Vein Study Cross Sectional Population Survey

Varicose veins **(VV)** are commonly stated to be responsible for a wide range of lower limb symptoms such as heaviness, swelling, aching, restless legs, cramps, itching, and tingling. The presence of symptoms together with clinical or ultrasound evidence of main stem saphenous reflux is generally accepted as an indication for surgery.

But, a cause and effect relation between uncomplicated trunk VV and symptoms has not been proved. There is little evidence that removing the VV improves the symptoms.

This study aimed to define any relation between age, sex, lower limb symptoms, and the presence of trunk VV.

Conclusion: Most lower limb symptoms have a non-venous cause. Surgery is unlikely to ameliorate symptoms in most patients.

STUDY

1. Cross sectional study of 12 general practices entered over 1500 patients selected from computerized age-sex registers. (Equal numbers of men and women; age range = 18 to 64) The aim was to determine prevalence of all grades of VV in a randomly selected age-stratified sample of the adult population.
2. A self administered questionnaire asked about presence of lower limb symptoms.
3. Physical examination determined presence and severity of VV.

RESULTS

1. Twenty seven percent of the cohort had trunk varices defined as dilated, tortuous trunks of the long or short saphenous vein, or their first or second order branches.
2. Prevalence of lower limb symptoms increased with age. In older men, a feeling of swelling and cramps; in older women, a feeling of aching, swelling, restless legs, and itching.
3. Women were more likely to report a wide range of lower limb symptoms.
4. In men, only itching was significantly related to the presence and severity of trunk varices.
5. In women there was a significant relation between trunk varices and symptoms of heaviness or tension, aching, and itching.
6. However, the level of agreement between the presence of symptoms and trunk varices was too low to be of clinical value.
7. There was no significant association between symptoms and the presence and grade of intradermal varices (venous telangiectasia).

DISCUSSION

1. Lower limb symptoms, often attributed to varicose veins, were extremely common in the general population.
2. All these symptoms tended to increase with age and were significantly more common in women.
3. In men there was no significant relation between trunk varices and any symptom except itching.
4. In women, even though there was an apparently strong relation between heaviness, aching, and itching and the presence of trunk varices, this may be of limited clinical value. Aching was present in 45% of women without varices, and 63% of those with grade 2 and 3 trunk varices, a difference of only 18%.
5. Thus, many patients with VV are asymptomatic, and others without VV have a whole range of lower limb symptoms.
6. "Although tens of thousands of varicose vein operations are performed each year, the scientific basis for this activity is lacking."
7. There is little evidence that operating on simple varicose veins before skin changes have developed reduces the burden of venous ulceration compared with a strategy of postponing surgery until the early skin changes of chronic venous insufficiency become apparent.

CONCLUSION

The presence of so called venous symptoms was extremely high in this population, especially in women. However, agreement between symptoms and signs of varicose veins is so poor that it may be of little value in determining whether symptoms are of venous origin, or whether surgery will relieve them.

BMJ February 6, 1999; 318: 353-56 Original investigation, first author Andrew Bradbury, University of Edinburgh, UK

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2-6 EFFECTS OF THYROXINE AS COMPARED WITH THYROXINE PLUS TRIIODOTHYRONINE IN PATIENTS WITH HYPOTHYROIDISM

There are two thyroid hormones, thyroxine and triiodothyronine. The daily production of thyroxine is about 100 ug, all produced by the thyroid gland. The daily production of triiodothyronine is about 30 ug, of which 20% is produced by the thyroid gland, and 80% by deiodination of thyroxine in extrathyroid tissues.

Triiodothyronine is the active form of the hormone.

Not all tissues that need thyroid hormone are equally able to convert thyroxine to triiodothyronine.

Most patients with hypothyroidism are treated with only thyroxine (levothyroxine; [Synthroid]). Although this treatment is effective some patients so treated are not entirely well.

This study compared the effects of: 1) thyroxine alone with 2) thyroxine plus triiodothyronine on thyroid hormone actions on the brain, pituitary gland, and other organs in patients with hypothyroidinsm.

Conclusion: Partial substitution of triiodothyronine for thyroxine may improve mood and neuropsychological functioning in some patients.

STUDY

1. Compared effects of thyroxine alone with thyroxine + triiodothyronine in 333 patients with hypothyroidism.
2. Treatment was divided into 2-five week periods. During one period, patients received the usual dose of thyroxine; during the next, 50 ug thyroxine of the usual dose of thyroxine was replaced by 12.5 ug of triiodothyronine.

RESULTS

1. During the dual treatment period patients had lower serum free total thyroxine concentrations, and higher serum triiodothyronine concentrations compared with the thyroxine alone period.
2. Serum thyrotropin (pituitary TSH) concentrations were similar after both treatments.
3. Among 17 scores of cognitive performance and assessments of mood, 6 were better or closer to normal after dual treatment.
4. Among 15 visual-analogue scales indicating mood and physical status, 10 were significantly better during the dual treatment periods.
5. BP and serum lipids were similar after both treatments.

DISCUSSION

1. Patients benefited when 12.5 ug of triiodothyronine was substituted for 50 ug of their usual dose of
2. thyroxine. They performed better on standard neuropsychological tasks, and their psychological state improved.
2. Pulse rates and serum sex hormone-binding globulin concentrations were higher during dual therapy, indicating a slightly greater effect on heart and liver.

3. No test was better after thyroxine alone.
4. "It seems clear that treatment with thyroxine plus triiodothyronine improved the quality of life for most patients."
5. The combined therapy was not sufficient treatment for depression. The four depressed patients in the cohort did not improve.
6. The dose of triiodothyronine somewhat exceeded the normal glandular production.

CONCLUSION

In patients with hypothyroidism, partial substitution by triiodothyronine for thyroxine may improve mood and neuropsychological function. This suggests that the normal thyroidal secretion of triiodothyronine is physiologically important.

NEJM February 11, 1999; 340: 424-49 Original investigation, first author, Robertas Bunevicius, Kaunas Medical University, Kaunas, Lithuania

Comment: We could easily confirm the putative benefits of this iconoclastic observation in individual patients with an N-of-1 trial. RTJ

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2-7 THYROID HORMONE REPLACEMENT -- ONE HORMONE OR TWO?

(This editorial comments and expands on the preceding.)

Thyroxine (T4) is converted to triiodotyronine (T3) by widespread peripheral monodeiodination.

The American Thyroid Association states that the goal of therapy (with thyroxine) is to restore most patients to the euthyroid state and to normalize serum thyroxine and thyrotropin ` concentrations.

However, a substantial minority of patients with hypothyroidism say they do not feel as well as they would like to while taking thyroxine in doses sufficient to restore their serum thyrotropin concentrations to normal. They have the desired sense of well-being only if thyroxine is given in a dose that is 50 ug per day greater than the dose needed to restore normal TSH secretion. Many physicians are therefore content to allow patients to have serum thyroxine concentrations at the upper limit of the reference range or even slightly higher, and low serum TSH concentrations, but normal serum triiodothyronine concentrations.

In view of the preceding study, should physicians begin to treat hypothyroidism with the combined hormones? The editorialist says "Not yet, for several reasons": Most hypothyroid patients taking a dose of thyroxine that satisfies recommendations of the American Thyroid Society have no complaints about their medication. Most currently available preparations of combined thyroid hormones contain as excess of triiodothyronine as compared with thyroxine. The ideal combination would contain approximately 100 ug of T4 and 10 ug of T3, the later in slow-release form to avoid adverse cardiac effects.

NEJM February 11, 1999; 340: 469-70 Editorial by Anthony D Toft, Royal Infirmary, Edinburgh, Scotland.

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2-8 SINGLE BLIND, RANDOMISED, CONTROLLED TRIAL OF PELVIC FLOOR EXERCISES, ELECTRICAL STIMULATION, VAGINAL CONES, AND NO TREATMENT IN MANAGEMENT OF GENUINE STRESS INCONTINENCE IN WOMEN

Stress incontinence is the most common type of urinary incontinence in women. It is defined as the involuntary loss of urine during coughing, sneezing, sporting activities, or sudden changes in position.

"Genuine" stress incontinence is urodynamically proved involuntary loss of urine when the intravesical pressure exceeds that of the urethra when, at the same time, there is no detrusor contraction.

This study compared the effect of the 4 modalities noted above.

Conclusion: Pelvic floor muscle exercise was superior.

STUDY

1. Entered 107 women (mean age 50; mean duration of symptoms, 11 years) with clinically and urodynamically proved genuine stress incontinence.
2. Randomized to the 4 groups noted.
3. Exercise group: pelvic floor exercise comprised about 10 high intensity (close to maximum) contractions 3 times daily at home. Once a week, exercise was done in groups with skilled physical therapists. Training was performed in lying, standing, kneeling, and sitting positions with legs apart to emphasize specific strength training of pelvic flood muscles.
4. Electrical stimulation group: vaginal intermittent stimulation 30 minutes daily
5. Vaginal cones group: used cones for 20 minutes daily.
6. Untreated group: offered use of continence guard.
7. Measured muscle strength by vaginal squeeze pressure once a month.
8. Follow-up = 6 months

RESULTS

1. Improvement in muscle strength was significantly better in the exercise group.
2. Reduction in leakage on pad test was greater in the exercise group.
3. On completion of the trial one participant in the control group, 14 (56%) in the exercise group, 3 in the electrical group, and 2 in the vaginal cone group no longer considered themselves as having a problem.
4. No adverse effects were reported in the exercise group.

DISCUSSION

1. "Pelvic floor exercise should be the first choice of treatment for women with genuine stress incontinence."
2. The method was safe and effective.

CONCLUSION

Training of the pelvic floor muscles with exercise was superior to electrical stimulation and vaginal cones in treatment of genuine stress incontinence.

BMJ February 20, 1999; 318: 487-93 Original investigation, first author Kari Bo, Norwegian University of Sport and Physical Medicine, Oslo

Comment:

Behavioral treatment has also been reported superior to drug therapy for "urge" incontinence ("overactive bladder" — as opposed to stress incontinence due to sphincter disability). The two types often occur together. JAMA December 16. 1998; 280: 1995-2000

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REFERENCE ARTICLE

2-9 ACUTE PHASE PROTEINS AND OTHER SYSTEMIC RESPONSES TO INFLAMMATION

A large number of changes, distant from the sites of inflammation and involving many organ systems, may accompany inflammation.

C-reactive protein was so named because it reacts with the pneumococcal C-polysaccharide during the acute phase of pneumococcal pneumonia.

Acute phase changes include production of acute phase proteins (APP), defined as those whose plasma concentration increases (positive response), or decreases (negative response) by at least 25% during inflammatory disorders. They include proteins of the complement system, coagulation, and fibrinolytic systems, and many others. . (See a long list Table 1 p 449.) APPs are largely produced by hepatocytes.

Substantial changes in APPs accompany infection, trauma, surgery, burns, and other inflammatory conditions. It is assumed that APPs are beneficial.

Cytokines are inter-cellular signaling polypeptides produced by activated cells. Most have multiple targets and multiple functions. Cytokines that are produced during, and participate in, the inflammatory process are stimulators of APPs. Interleukin-6. is the chief stimulator of most APPs. Measurement of cytokines is costly, and of limited availability, and standardization is not available. They are not applicable clinically.

Despite lack of diagnostic specificity, APPs are useful to clinicians because their changes reflect the presence and intensity of an inflammatory process. They are useful in managing the patient’s disease since the concentration. often reflects the response to, and need for, therapeutic intervention. They also have prognostic value. Measurement of C-reactive protein can help differentiate inflammatory from non-inflammatory conditions.

The most widely used indicators of the response of APPs are the sedimentation rate and the plasma C-reactive protein. The sed rate depends largely on the plasma concentration of fibrinogen. It has the advantage of simplicity, familiarity, and a long history of use. But, it is an indirect measurement of APP concentration, and can be influenced by the size, shape, and numbers of erythrocytes. . The sed rate increases or decreases slowly in response to inflammation. It increases steadily with age. Consequently the results are imprecise and sometimes misleading. Some regard the sed rate as archaic. It is no longer needed since fibrinogen can be measured directly .

C-reactive protein has advantages: concentrations change rapidly; it is not influenced by age.

"Acute phase changes reflect the presence and intensity of inflammation. They have long been used as a clinical guide to diagnosis and management. For this purpose, determination of serum C-reactive protein has advantages over the traditional strategy of measuring the erythrocyte sedimentation rate."

NEJM February 11, 1999; 340: 448-54 "Mechanisms of Disease" review article, first author, Cem Gabay, University of Colorado Health Sciences Center, Denver.

Fascinating! Read the original! Why a clone cannot be a clone

2-10 WOULD CLONED HUMANS REALLY BE LIKE SHEEP?

The successful cloning of sheep and mice has led to discussions about the ethics of cloning humans. Bans on mammalian cloning have been called for.

"From the standpoint of biologic science, a ban on such laboratory experiments would be a severe setback for research in embryology."

"From the standpoint of moral philosophy, the ethical debate has been so obscured by incorrect assumptions about the relation between a potential human clone and its adult progenitor that the scientific issues must be reexamined in order to clarify the relation between genotype and phenotype. There are powerful biologic objections to the use of cloning to alter the human species, objections that make speculations about the ethics of the process largely irrelevant."

A clone is the aggregate of the asexually produced progeny of an individual organism. A colony of bacteria constitutes a clone if its members are descendants of a single bacterium that has undergone asexual fission. The myriad bacteria in the clone each have precisely the same genetic complement as the progenitor cell, and are indistinguishable from each other.

In mammals at least some of the nuclei in fully differentiated mammalian cells contain the full complement of potentially active genetic material that is present in the zygote. Turning genes "off" or "on" leads to differentiation of specific cells. (Ie, forming a liver cell or a muscle cell.)

Cloning humans would involve transferring a human ovum to a test tube, removing its nucleus, replacing it with the nucleus of a somatic cell, allowing the ovum to differentiate to the blastula stage, and then implanting it in a "host" uterus. The resultant person, on attaining maturity would be an identical genetic twin of the adult nuclear donor. This hypothetical outcome has given rise to speculation about the psychological, ethical, and social consequences of cloning humans.

Restricting genetic diversity:

One negative consequence of very wide scale cloning is that it would lead to a marked restriction in the diversity of the human gene pool. Such a limitation would endanger the ability of our species to survive major environmental changes. For example, the "green revolution" in agriculture led to the selective cultivation of grain seeds chosen for high yield under modern conditions of fertilization and pest control. But this has made world-wide food production highly vulnerable to new blights because of our reliance on a narrow range of genotypes. The same threat would hold for humans, were we to replace sexual reproduction with cloning. "The extraordinary biologic investment in sexual reproduction (as compared with asexual replication) provides a measure of its importance to the evolution of species."

Cloning yesterdays people for tomorrows problems:

The choice of whom to clone could be made only on the basis of phenotypic characteristics, when the persons considered for cloning have come to maturity. This requires choosing the genotype we wish to preserve. Even if we agree on the genotype we wish to preserve, we face a formidable barrier. We know so little of the environmental features necessary for the flowering of that genotype that we cannot specify in detail the environment we would have to provide to ensure a phenotype outcome identical to the complex of traits we seek to perpetuate. Even if we could specify the environment necessary for the flowering of a specified phenotype so admirably suited to the world in which it matured, the environment a generation hence will be different.

The traits leading a person to be creative or to exhibit leadership at one moment in history may not be appropriate for another. Social evolution demands new types of men and women. Cloning would condemn us always to plan the future on the basis of the past (since the successful phenotype cannot be identified sooner than adulthood).

The connection between genotype and phenotype:

The potential of a given genotype can only be estimated from the varied manifestations of the phenotype over as wide a range of environments as are compatible with its survival. The wider the range of environments, the greater the diversity

observed in the manifestations of one genotype. Human populations possess an extraordinary range of variability. Cloning requires identity between environmental interactions. It cannot do this.

Postnatal environmental effects on the human brain:

The human species is notable for the proportion of brain development that occurs postnatally. From birth to maturity, the human brain increases in weight by a factor of 3 to 4. The elaboration of pathways and interconnections is highly dependent on the quantity, quality, and timing of intellectual and emotional stimulation. Nature and nurture jointly mold the structure of the brain. The basic plan of the central nervous system is laid down in the human genome, but the detailed pattern of connections results from competition between axones for common target neurons. Interaction between organism and environment leads to patterned neuronal activity that determines which synapses will persist. Experience molds the brain in a process that continues throughout life.

Becoming human:

Human traits are polygenic rather than monogenic. Similar outcomes can result from the interaction between different genomes and different social environments. To produce another Mozart, we would need not only Mozart's genome, but his mother's uterus, his father's music lessons, his parent's friends and his own, the state of music in 18th century Austria, Haydn's patronage, and on and on in ever-widening circles. We have no right to assume that his genome, cultivated in another world at another time, would result in the same musical genius.

In sum, cloning would be a poor method indeed for improving the human species. Proposals for human cloning as a method for "improving" the species is biological nonsense. The real moral issue is the way in which the genetic potential of humans born into impoverished environments is stunted and thwarted.

NEJM February 11, 1999; 340: 471-75 "Sounding Board" commentary by Leon Eisenberg, Harvard Medical School, Boston, Mass.

Comment:

If the donor nucleus is placed in the ovum of a person different from the donor, the DNA present in the mitochondria of the cytoplasm will differ from the mitochondria of the donor. Thus, in this sense, the offspring is not a complete clone.
RTJ

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2-11 IMPROVED DETECTION OF CORONARY ARTERY DISEASE BY EXERCISE ELECTROCARDIOGAPHY WITH USE OF RIGHT PRECORDIAL LEADS

The sensitivity of standard exercise testing for single-vessel coronary disease is low. It detects only about 1/3 to 2/3 of cases. Its sensitivity for detection of right coronary disease is even lower.

This study attempted to improve the diagnostic accuracy of exercise testing by using a combination of left and right precordial leads.[1] (Purists might prefer to label the leads chest leads since they are really not precordial, unless dextrocardia is present. We understand what the authors mean.)

Conclusion: Combined left and right leads greatly improved sensitivity of exercise testing.

STUDY

1. Studied 245 patients who underwent exercise treadmill testing. All received the standard 12-lead ECG with V3R, V4R and V5R added. All also received thallium scintigraphy and coronary arteriography.

2. The exercise ECG was considered positive by: 1) a horizontal or downsloping ST depression of at least 1 mm 60 msec after the J point; 2) upsloping ST segment with a depression of at least 1.5 mm 80 msec after the J point: 3) in the presence of ST depression at rest, an additional 2 mm of ST depression ; or 4) an ST elevation of at least 1 mm at the J point as compared with the base-line ECG recorded at rest.

RESULTS

1. On the basis of arteriography, 34 patients had normal arteries; 85 had single-vessel disease; 84 had 2-vessel disease; and 42 had 3-vessel disease.
2. Sensitivity of tests using arteriography as the gold standard:

	Exercise ECG 12 lead only	Exercise ECG 12 lead + right leads	Thallium scintigraphy
Single vessel disease	52%	89%	87%
Two-vessel disease	71%	94%	96%
Three vessel disease	83%	95%	98%
Any coronary disease	66%	92%	93%

DISCUSSION

1. Combining data on ST-segment changes from both left and right leads provided excellent sensitivity for detection of coronary disease, similar to that of thallium scintigraphy.
2. The technique significantly improved ability to detect single-vessel disease, especially clinically significant stenosis of the right coronary and the left circumflex.
3. ST-segment elevation in the right leads during evolving inferior infarction indicates right ventricular involvement.
4. In another trial of acute myocardial infarction, ST-segment elevation of at least 1 mm in the V4R lead had a sensitivity of 100% for detection of proximal occlusion of the right coronary and a specificity of 87%: **2**

	Proximal right occlusion (Disease present)	No proximal right occlusion (Disease absent)
ST shift present (Test positive)	100 % (True positive % = Sensitivity)	13% (False positive)
ST shift not present (Test negative)	0% (False positive)	87% (True negative % = Specificity)

5. The contribution of the 3 right leads to the detection of single vessel disease and to the identification of the diseased vessel was prominent for both right coronary disease and disease of the left circumflex artery.
6. Exercise induced ST-segment changes in V3R and V4R, or both (but not V5R) may identify right coronary disease.

7. Exercise induced ST-segment changes in V4Rand V5R, or both (but not V3R) may identify disease in he circumflex artery.
8. In those whose standard 12-lead exercise ECG failed to detect disease, the addition of the right leads increased detection of single-vessel disease of the left anterior descending artery by 14%; the right coronary artery by 64%; and the left circumflex by 41%.

CONCLUSION

Exercise electrocardiography incorporating the combination of right leads along with the standard left leads greatly improved sensitivity for the diagnosis of coronary artery disease.

NEJM February 4,1999; 340; 340-45 Original investigation, first author Andreas P Michadlides, University of Athens Medical School, Athens, Greece

1. For positioning the right leads, see standard texts
2. I like to construct two-by-two tables occasionally to refresh my memory. RTJ

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2-12 THE VALUE OF THE RIGHT PRECORDIAL LEADS OF THE ELECTROCARDIOGRAM

(This editorial comments and expands on the preceding.)

Several studies have shown that recording additional right leads is helpful in the detection of ischemia or infarction of the right ventricle. Indeed, V4R is a reliable marker of the site of coronary occlusion in acute inferoposterior infarction — either proximal or distal right artery, or the circumflex. Occlusion of the proximal right artery obviously leads to right ventricular involvement.

Diagnosing right ventricular infarction (RVI) is important. RVI may lead to hemodynamic consequences including decreased compliance of the right ventricle, and lowering of both cardiac output and systemic blood pressure. Right-sided pressures are elevated, and left ventricular filling is decreased.

Right ventricular infarction occurs in about 1/3 of patients with acute infero-posterior infarctions. Hemodynamic abnormalities become clinically important in only 10%. Recognition is important because of the need for volume expansion and the occasional use of dobutamine.

Another problem is the high incidence (about 50%) of advanced atrio-ventricular block in cases of right ventricular infarction.

Right ventricular infarction carries a marked increase in mortality during hospitalization. Identification of right ventricular infarction by right chest leads may select those who would benefit most from reperfusion.

The editorialist believes that pharmacologic reperfusion or angioplasty should be performed in patients who are seen within 6 hours after an acute inferoposterior infarction and who have evidence of proximal occlusion of a dominant right coronary artery. This is shown by the presence of substantial ST segment elevation in the inferior leads, and ST depression in the left precordial leads. Finding concurrent ST elevation in V4R suggests that there is proximal occlusion of a dominant right coronary artery.

"The right precordial leads enlarge the electrocardiographic window to include the right ventricle."

NEJM February 4, 1999; 340: 381-83 Editorial by Hein J J Wellens, Academic Hospital Maastricht, Netherlands.

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2-13 LACK OF EFFECTIVENESS OF BED REST FOR SCIATICA

Sciatica usually improves over time. Conservative therapy has been proposed, with bed rest as a mainstay. There are few data to support this view. Its effectiveness has not been established.

This study assessed effectiveness of bed rest for lumbosacral radicular syndrome.

Conclusion: Bed rest was no more effective than watchful waiting.

STUDY

1. Entered 183 patients with lumbosacral radicular syndrome (back pain radiating to one lower extremity below the gluteal fold). Symptoms were of sufficient severity to justify treatment with bed rest.
2. All had at least two of the following: radicular pain distribution; increased leg pain on coughing, sneezing or straining; decreased muscle strength; sensory loss; reflex loss; or a positive straight leg raising test. None had indications for immediate surgical intervention (morphine-dependent intractable pain; rapidly progressing paresis; or cauda equina syndrome).
3. Over half of the patients had nerve root compression on MRI.
4. Randomized to: 1) bed rest, or 2) watchful waiting for two weeks.
5. Bed rest group was instructed to stay in bed , supine or lateral recumbent position with one pillow under the head for 2 weeks. They were permitted to get out of bed to use the toilet and to bathe. Mean time in bed = 21 hours daily.
6. Watchful waiting group were instructed to be up and about whenever possible, but to avoid straining the back or provoking pain. They were allowed to go to work. Bed rest was not prohibited. Mean time in bed = 10 hours daily.
7. All were allowed to take acetaminophen (with codeine if needed), or naproxin. Tamazepam was prescribed for insomnia.

RESULTS

1. At two weeks, 70% of bed rest group reported improvement vs 65% of the watchful waiting group
2. At 12 weeks, 87% of both groups reported improvement.
3. There were no significant differences between groups in intensity of pain, bothersomeness of symptoms, and functional status. Use of acetaminophen and codeine were similar.
4. Extent of absenteeism from work and rates of surgical intervention were similar between groups.
5. The number of hours spent in bed had no relation to the likelihood of improvement.

DISCUSSION

1. The study found no evidence that bed rest is an effective treatment for sciatica.
2. There were no significant differences in effectiveness of bed rest between patients with MRI evidence of nerve root compression and those without.

CONCLUSION

Among patients with symptoms and signs of lumbosacral radicular syndrome, bed rest was not a more effective therapy than watchful waiting.

NEJM February 11, 1999; 340: 418-23 Original investigation, first author Patrick C A J Vroomen, Maastricht University Hospital, Maastricht, Netherlands

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2-14 LOOKING BEYOND THE NEXT PATIENT: Sociology and Modern Health Care

"The medical profession needs a keener understanding where it fits into the broader organization of society."

Social variables remain the most important determinants of health. The most lasting relation identified has been that between poverty and health. Sociologists have long argued over the importance of relative or absolute deprivation and its impact on health status.

There is good evidence that wealth does not trickle down to the very poorest people (or trickles down very slowly). This strengthens the argument in favor of some targeted redistribution of resources.

In developed countries the link between deprivation and ill-health is subtle. A persistent vein of sociological research has shown that social isolation or exclusion lies behind much ill-health. Social isolation is linked with suicide — one reason why suicide is less common during periods of greater social cohesion, such as wartime. Chronic illness causes a vicious circle of increasing isolation. Women without close confidants to provide support show greater vulnerability to depression. Good-quality marriages are related to lower rates of depression. Divorce is associated with adverse outcome for parents and children which persist for life.

Thus, exclusion, isolation, and helplessness can be harmful to health. An assault must be made on factors that affect the human psyche — those that make people feel undervalued and excluded.

One method to achieve long-term benefit is to improve general education. The general education level for women in developing countries has greater effect on family health than any other single factor. One spectacular study concerned children of deprived single-parent homes. They were randomly assigned to attend or not attend nursery school. Children were followed up to 27 years. Those who attended school consistently had better health, higher educational achievements, higher earnings, and lower rates of crime. Social patterning starts early.

There is a radical shift in the relationship between all professions and the people they serve. As people become more questioning and information is more widely available, inequality between professionals and the population becomes much less pronounced. Many changes are being driven by increasingly knowledgeable and assertive customers.

Influential narrative (eg, "One Flew Over the Cuckoo's Nest) had some part in accelerating decarceration, one of the most radical reforms of health services in recent years.

Conclusion: The care that patients get depends on many factors: knowledge and attitudes of clinicians, organizations and the services provided, the legislative framework, and the attitudes of society itself. Health-care professionals do not treat patients one at a time on the basis of textbook, evidence-based algorithms.

THE LANCET February 6, 1999; 353: 486-89 Review article, commentary, first author Jiri Chard, University of Bristol, UK

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RECOMMENDED READING

2-15 CAN RANDOMISED TRIALS INFORM CLINICAL DECISIONS ABOUT INDIVIDUAL PATIENTS?

Primary care physicians agree that clinical medicine (including remedies handed down through clinical folklore) should be subject to empirical assessment. They recognize the importance of randomized-controlled trials (RCT) in the assessment of

clinical effectiveness. But, they are also becoming increasingly concerned about the crude applications of evidence from RCTs to practice.

Evidence-based medicine has been accused of diminishing the importance of human relationships by ignoring consideration of the unique problems and concerns of individual patients.

RCTs provide statistical evidence of likely effects of an intervention, usually based on the "average" outcome aggregated across all patients in the trial. This is frequently expressed as the number needed to treat (NNT) to achieve one unit of benefit. (It may also be expressed as the number needed to harm [NNH]). Clinicians then are concerned about whether and how to apply the NNT and NNH to individual patients. Are the results of the trial generalizable, such that the individual will respond to the intervention in a way similar to trial participants? Can the statistical prediction based on the "average" give a prediction of the outcome in the individual?

Generalization:

Participants in trials are seldom representative of the general population. They are usually healthier, younger, and of higher social status. In some applications this matters little. In some it matters a lot. For example, primary care clinicians accept that warfarin will prevent strokes in patients with atrial fibrillation with a reasonable risk of harm. But most trials excluded patients with social problems, or significant comorbidity, (most elderly have some), and advanced age. The clinician is concerned about the harm to these individuals. Application to an individual requires a qualitative judgement about whether possible benefit outweighs the possible harm and the fixed costs.

The precision of individual prediction:

If the intervention is easy to replicate and the individual patient is similar to the trial participants, is this the solution to the question of generalization? For the clinician it is not, because most clinical trials display substantial heterogeneity of effect for individuals. If the likelihood of a positive outcome is 20% in the intervention group, and 5% in the control group, the NNT is 7 to lead to benefit in one. There is variation in treatment effect depending on variations in baseline risk. Patients wish to be the one who benefits, but there is no way of telling whether they will be the one, or among the 6 who do not benefit.

Patients' perceptions and values are important, but this is difficult to identify in the context of a clinical trial.

Randomized trials are not an ideal way to address heterogeneity.

Implications:

The paradox of RCTs is that they are the best way to assess whether an intervention works, but it is a poor way to assess who will benefit. "Clinical decision making requires evidence of applicability from clinical trials and evidence of applicability to individual patient from observational studies." In order to apply the results of RCTs to individuals, there must be a parallel investment in observational studies. These studies provide assessment of baseline risk needed to model the absolute benefit for an individual, to characterize the patient's experience, the frequency of long-term adverse effects, the effect on outcomes of patient characteristics such as preference, the effect of intervening at different stages of the disease, and the feasibility of implementing the intervention effectively in practice.

"Most general practice depends on 'interpreting personally unique patterns of illness, rather than recognizing generalized patterns of disease'." There are grey zones where scientific evidence is incomplete or conflicting. "What is black and white in the abstract may become grey in practice". The use of evidence from RCTs is frequently subsidiary to the process of understanding the patient's condition and implementing treatment within a good doctor-patient relationship. Clinical decisions involve people and, particularly in primary care, understanding the person in his or her social context is as important as understanding the probable effectiveness of an intervention. Clinical decision making should involve "the conscientious, explicit, and judicious use of current best evidence".

"Randomized, controlled trials are primarily about medical interventions and not patients." The methodological minimization of information on effectiveness in relation to the individual patient leaves an evidence gap for clinicians.

The editorialist calls on the research community to value observational methods, and to see that applicability is an issue as important to trial design as statistical power. "Does this intervention work for this patient?"

THE LANCET February 27,1999; 353: 743-46 "Evidence and Primary Care" commentary by David Mant, University of Oxford, UK

Comment:

I believe one way to assess applicability of an intervention to an individual patient is to determine the number of individuals screened for entrance into a RCT. If the number is high in proportion to the number completing the trial, the intervention is unlikely to be broadly applicable. RTJ

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2-16 APPLICATION OF EVIDENCE FROM RANDOMISED TRIALS TO GENERAL PRACTICE.

"The low prevalence of most disorders seen in general practice and the long natural history of some diseases makes the randomized controlled trial **(RCT)** impractical, both financially and logistically, for finding answers to important questions." About 40% of all new disorders in a general practice do not evolve into conditions that meet accepted criteria for a diagnosis. The preferred management of undifferentiated disorders is "watchful waiting", a step that requires a trusting relationship between the physician and the patient.

The absence of clear definitions of many disorders makes exploring their management methodologically difficult in the purest world of RTCs.

Management of a person and his problems is the core intervention — not the management of a single diagnosis (as in the case in most RCTs). "There should always be a tension between evidence based on a population perspective and its application to individuals in patient-centered general practice."

Economic factors have a major effect on the application of evidence. Each country or health insurance company must decide what is acceptable within their value system, where to draw the line on expenditure based on evidence or political considerations. On an individual basis, patients on a limited budget may not be willing to fill a prescription for a drug after being told that 128 people will need to take the drug for 5 years to prevent one heart attack. The primary care physician must provide guidance on the quality of the evidence available and its relevance to the individual's personal context.

Social context and values, including religion, also influence application.

Patient's satisfaction with their relationship with the physician is highest when they take full part in decision making. Their compliance (concordance is a better term) with the agreed upon strategy is best when decisions are made in partnership.

"There is no simple answer to the question as to whether all advice or interventions provided by family physicians should be evidence based." Using a patient-centered approach in clinical practice is most likely to achieve the best possible outcome for evidence based medicine.

THE LANCET February 20,1999; 353: 661-64 "Evidence and Primary Care" Commentary by Walter W Rosser, University of Toronto, Canada.

Comment:

At times, applying an intervention to an individual based on the best evidence from RCTs may be bad medicine indeed, regardless of the strength of the conclusions. RTJ

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2-17 INCREASED PULSE PRESSURE AND RISK OF HEART FAILURE IN THE ELDERLY

The incidence of heart failure **(HF)** doubles in each decade after age 45. HF is the leading hospital diagnosis in persons over age 65.

Pulse pressure (PP) is the difference between systolic BP **(SBP)** and diastolic BP **(DBP).** Pulse pressure rises markedly after the fifth decade due to age-related arterial stiffening. The SBP rises progressively and the DBP falls as the elastic capacity of the aorta diminishes. Arterial stiffness increases afterload and myocardial oxygen demand, impairs ventricular relaxation, and causes subendocardial ischemia even in the absence of coronary arteriosclerosis.

Measures of arterial stiffness are strongly associated with left ventricular hypertrophy.

This study addressed the hypothesis that increased arterial stiffness, as measured by the PP, contributes to HF in the elderly.

Conclusion: PP was an independent predictor of risk of HF in this elderly cohort.

STUDY

1. Prospective, community-based, cohort study entered over 1600 persons (mean age 78).
2. All were free of HF at baseline.
3. Determined SBP and DBP at baseline. Follow-up for 4 years, ascertaining incidence of HF by hospital discharge diagnosis and death certificate.

RESULTS

1. After controlling for age, mean BP, history of coronary disease, diabetes and other possible confounders PP was an independent predictor of HF.
2. Systolic BP had a graded relationship with increased risk of HF, with a 12% increase in risk for every 10 mm Hg rise.
3. Diastolic BP had a U-shaped relationship with HF. Compared with subjects with DBP 70-79, those with DBP less than 70 were 1.6 times more likely to develop HF; those with DBP 80-89, 1.1 times more likely; and those with DBP over 90 1.7 times more likely.
4. For each 10 mm elevation in PP, risk of HF increased by 17%.
5. Risk rose by 75% in those with the highest tertile of PP (> 67mm Hg) compared with those in the lowest tertile (< 54 mm Hg).
6. PP had a significant linear relationship with HF risk.

DISCUSSION

1. PP is easily measured. It correlates with arterial stiffness and pulsatile hemodynamic load. It is an independent predictor of risk of HF, and provides additional predictive information independent of SBP alone.
2. A low DBP correlates with increased large artery stiffness and is independently associated with increased risk of HF.

3. PP reflects the complex interaction between intermittent cardiac ejection and the dynamic properties of large arteries. The dispensable, elastic aorta transiently stores part of the stroke volume during systole and transmits this volume forward in diastole. This limits end-systolic BP and wall tension and maintains diastolic pressure
4. Loss of aortic compliance with age results in elevation of SBP and decrease in DPP, and increased PP.
5. This imposes a greater load on the left ventricle, reduces ejection fraction, and icreases myocardial oxygen demand. The increased systolic load and myocardial work, coupled with the fall in diastolic coronary perfusion pressure results in subendocardial ischemia.

CONCLUSION

In this prospective study of community-based elderly, PP was independently and linearly associated with risk of HF.

JAMA February 17, 1999; 281: 634-39 Original investigation, first author Claudia U Chae, Brigham and Woman's Hospital, Boston Mass.

Comment:

I abstracted this article chiefly because of the interesting pathophysiology it describes. At first, I thought there is little to we can do to about stiff aortas. On reflection perhaps we can do much. Cannot the progression of stiffness with age be retarded by reducing likelihood of atherosclerosis? Once present, will not stiffness be lowered by therapy with diuretics to remove some sodium from the walls of large vessels?

Increased PP may just be another definition of "isolated systolic BP". We can do much to lower risk of complications of ISBP. RTJ

2-18 CHRONIC STRESS IN ELDERLY CARERS OF DEMENTIA PATIENTS AND ANTIBODY RESPONSE TO INFLUENZA VACCINE

"The task of caring for a significant other with a dementing illness is arduous and prolonged." The care of people with dementia often falls on partners (spouse or others) who themselves are elderly and often ill-prepared for the demanding physical and emotional burdens. Increased psychological morbidity in carers may persist for several years after the partner has been taken into full time care.

This study investigated whether antibody responses to influenza vaccine differ between carers and non-carers, and the relation of the antibody response to the hypothalamic-pituitary-adrenal axis.

Conclusion: Elderly carers had increased activation of the axis, and poor antibody response.

STUDY

1. Case-control study entered 50 spousal carers (mean age 73; 3.5 mean years of care) of demented patients and 67 non-carers as controls.
2. Measured 1) anxiety-depression, and stress by 2 different scales, 2) salivary cortisol concentrations, and 3) IgG antibody responses to influenza vaccine.

RESULTS

1. Scores of emotional distress were higher in the carers.
2. Mean salivary cortisol concentrations were higher in carers.

3. There was an inverse relation between cortisol levels and antibody responses — 16% of carers had a 4-fold increase in IgG titers vs 37% of controls.

DISCUSSION

1. Other studies have reported reduced natural-killer-cell activity and increased cortisol concentrations in bereaved women.
2. Psychiatric inpatients who describe themselves as more distressed and isolated also have higher cortisol concentrations and poorer proliferative responses of T cells.
3. The increased levels of distress in carers were related to significantly raised concentrations of cortisol (chronic activation of the hypothalamic-pituitary-adrenal axis), and also associated with significantly impaired antibody responses to influenza vaccine.
4. The prophylactic benefits of vaccination depend on the host's ability to generate a 4-fold increase in antibody titers. This may place chronically distressed persons to higher risk of infection.

CONCLUSION

Elderly carers of spouses with dementia have increased activation of the hypothalamic-pituitary-adrenal axis and a poor response to influenza vaccine.

Carers may be more vulnerable to infectious disease

THE LANCET February 20, 1999; 353: 627-31 Original investigation, first author Kav Vedhara, University of Bristol, UK

Comment:

Carers are vulnerable to chronic fatigue and depression. Primary care clinicians have the opportunity to engage carers in conversation about their level of stress. Simply acknowledging this may help them. Clinicians who are primarily caring for a demented or chronically ill patient may have an opportunity to suggest some sort of relief for their carers. RTJ

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Anecdotal report

2-19 SUCCESSFUL TREATMENT OF LATRODECTISM WITH ANTIVENIN AFTER 90 HOURS

This account describes the course of a 13-year old boy who was bitten by a black widow spider. Symptoms were severe and continued for 4 days. Symptomatic treatment gave only minor relief. He became unable to walk.

The correspondents saw him on the 4th day and administered one vial of Latrodectus mactans antivenin. Relief of symptoms was rapid. Ten minutes after the infusion he was able to dress himself. Strength in the extremities returned to normal and he was able to walk.

The American Association of Poison Control Centers reported over 13 000 black widow bites in 1997. Over 1300 moderate or severe – no deaths.

L mactans is found in every state except Alaska. They migrate indoors during cold weather. The protein component causing symptoms is alpha-latrotoxin. It binds to specific receptors at the neuromuscular end plate, resulting in increased synaptic concentrations of catecholamines. This results in migratory muscle cramps and spasm, nausea, vomiting, hypertension, weakness, and tremors. Symptoms can last days, up to a week.

The correspondents suggest the rapid recovery of the boy indicates the anti-venin is effective.

NEJM February 25, 1999: 340: 657 Letter to the Editor, first correspondent Gerald F O'Malley, Rocky Mountain Poison and Drug Center, Denver, CO

Comment:

This is a good example of the potential value of anecdotal reports. In uncommon conditions, randomized control trials are impossible. We must at times rely on anecdote. If the therapy seems biologically plausible, we would be more likely to accept it.

I welcomed the review of black widow spider bites, and the reminder that an antivenin is available.

Antivenin is available from Merck. It is produced from horses immunized against the antivenin. Thus precautions, including skin testing, must be taken. Have epinephrine on hand. Other treatments (PDR 1999; p 1734) include warm baths, iv calcium gluconate, morphine (observe for respiratory paralysis). Serum sickness may occur for up to 12 days after administration.

In otherwise healthy individuals age 16 to 60, anitvenin may be deferred and treatment with muscle relaxants considered.

Venin? Venom? Anti-venin? Anti-venom? There must be a subtle difference between the terms. I found them used interchangeably. RTJ

2-20 THE NATIONAL DIABETES EDUCATION PROGRAM: Changing the Way Diabetes is Treated.

Evidence that glycemic control can prevent or markedly reduce microvascular complications of diabetes is now overwhelming. The Diabetes Control and Complications Trial, of patients with type 1 diabetes, reported that for every 10% reduction in HbA1c, a corresponding 40% reduction in retinopathy occurred. Similar reductions were also found in nephropathy and neuropathy.

For type 2 diabetes the United Kingdom Prospective Diabetes Study reported that a relatively small reduction in HbA1c from 7.9% to 7.0% resulted in significant reductions in microvascular complications.

What about macro-vascular (atherosclerotic) disease complications? The data are less clear. The studies did not find intensive treatment of glycemia associated with any significant reduction in incidence of macro-vascular disease; but also no deleterious effect. However, evidence is accumulating that treatment of traditional risk factors for atherosclerotic disease (hypertension and lipid disorders) is as beneficial (if not more so) for patients with diabetes as it is for those without the disease.

"These data should motivate us to treat hyperglycemia more intensively in all patients with diabetes, with the goal of achieving an overall hemoglobin A1c level of 7%."

These emerging findings have prompted the National Institutes of Health and the Centers for Disease Control and Prevention to sponsor a major national initiative, the National Diabetes Education Program. This will develop strategies to improve diabetes care, promote early detection, and ultimately prevent the onset of the disease.

The Web site: http://NDEP.NIH.gov

Annals Int. Med. February 16, 1999; 130: 324-26 Commentary by Charles M Clark, Indiana University School of Medicine, Indianapolis.

Comment:

This recalls the National Cholesterol Education Program which I believe has been successful. RTJ

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REFERENCE ARTICLE

2-21 THE MENOPAUSE

This article reviews definitions; symptoms; relation to coronary heart disease, hypertension, osteoporosis; treatment, bleeding patterns; contraindications and precautions with hormone therapy

"Menopause is diagnosed after 12 months of amenorrhea resulting from permanent cessation of ovarian function. The mean age at menopause is 51. The perimenopause, a time of changing ovarian function, precedes the final menopause by several years. Some symptoms, such as hot flashes, certainly begin in the perimenopause.

"Postmenopausal hormone therapy is a complex intervention that produces some positive and some detrimental health effects. Most decision analyses conclude that the benefits of therapy — unopposed oestrogen of combination therapy — outweigh the risks.

"Observational studies of mortality in hormone users, compared with non-users, report a 30-50% reduction in mortality among users compared with non-users.

"The value that each woman places on the various health outcomes associated with hormone- replacement differs. The decision to use hormone-replacement therapy should be made jointly by the woman and her health care provider, should account for all known and possible benefits and risks, and should assess each woman's health history and accommodate her personal point of view."

THE LANCET February 13, 1999; 353: 571-80 "Seminar". Review article, first author Gail A Greendale, University of California, Los Angeles.