Table 1—Cost per life year gained with diuretic and β blocker treatment (thousands of Swedish crowns at 1992 prices; 10 Swedish crowns = £1). *With permission³

Diastolic blood pressure (mm Hg)	Age (years)					
	<45		45-69		≥70	
	Men	Women	Men	Women	Men	Women
90-94	681	1805	26	122	13	8
95-99	551	1328	CS	56	3	CS
100-104	438	931	CS	CS	CS	CS
≥105	283	422	CS	CS	CS	CS

CS = Cost saving.

*Assuming a discount interest rate of 5% for costs and life years, an annual pharmaceutical cost of 900 Swedish crowns (annual treatment cost 2300 Swedish crowns), a treatment period of one year, and a reduction in risk of coronary heart disease of 16% and of stroke of 38%.

blood pressure in Sweden.³ The report contains a critical review of the literature focusing on the absolute treatment effects attained and a series of cost effectiveness analyses of treating high blood pressure in Swedish men and women with and without other risk factors.

The total annual cost of treating hypertension in Sweden in 1992 was about 1.6 billion Swedish crowns (£160m). Cost effectiveness analyses calculating the cost per life year gained showed that this cost decreased with increasing age in both sexes, as table 1 shows for treatment with diuretics and β blockers. The cost was also lower at a higher initial blood pressure. It is reasonable to assume that even more expensive drugs are cost effective for their special indications, provided they have an effect on morbidity and mortality, which remains to be proved, and no major side effects.³

We agree with Jackson and Sackett that it is time to put more emphasis on absolute treatment effects than on relative ones. An alternative (which may be easier to explain to patients) to the numbers needed to treat to prevent an unwanted event is to give the chances over, say, five years of remaining free of an unwanted event (for example, a stroke) in those actively treated and those not treated or treated with placebo. This has been done in the report by the Swedish Council on Technology Assessment in Health Care, with a set of tables from most of the major studies on the risks and benefits of antihypertensive treatment.³

The report may be requested (free) from the Swedish Council on Technology Assessment in Health Care, PO Box 161 58, S-103 24 Stockholm, Sweden (fax +46 8 611 79 73).

LARS H LINDHOLM
Chairman of project committee

LARS WERKÖ
Chairman of board of Swedish Council on Technology Assessment in Health Care

Department of Community Health Sciences,
Lund University,
S-223 54 Lund,
Sweden

1 Fahey TP, Peters TJ. What constitutes controlled hypertension? Patient based comparison of hypertension guidelines. *BMJ* 1996;313:93-6. (13 July.)

2 Jackson RT, Sackett DL. Guidelines for managing raised blood pressure. *BMJ* 1996;313:64-5. (13 July.)

3 Swedish Council on Technology Assessment in Health Care. Moderately elevated blood pressure. *J Intern Med* 1996;238(suppl 737):1-225.

Technical difficulties may have affected study's results

EDITOR,—We agree with the main conclusion of T P Fahey and T J Peters—namely, that hypertension guidelines vary considerably and that guidelines should explicitly target those people with higher absolute levels of cardiovascular risk.¹ Yet we are not convinced by many of the detailed arguments in the authors' paper.

Why did the authors choose to study patients who had already been labelled in their notes as hypertensive and were currently taking anti-hypertensive treatment? This group is not defined by any of the guidelines. It will include some who have never had hypertension by any guideline and will exclude some whom all the guidelines would have included. It is not a group to generate generalisable conclusions.

The authors found that the different guidelines produced large discrepancies in the number of patients whose blood pressure seemed to be controlled, and hence in the number who required treatment. There are at least two explanations for this observation. The first—and the only possibility considered by the authors—is that other risk factors need to be taken into account and that guidelines differ in their ability to do this. The second, and potentially major, explanation is that technical difficulties get in the way. Fahey and Peters's assessment of blood pressure control is flawed for at least three reasons.

Firstly, most guidelines demand numerous readings before treatment is started. In their study the authors used single readings, and never more than three in total. It is then an error to use a risk table from a guideline without first correcting for regression dilution bias, which is the weakening of the apparent relation between risk and blood pressures based on few readings.

Secondly, digit preference in recording² and perseverence in subsequent measurements³ make the interpretation of small threshold changes perilous.

Thirdly, the distribution of blood pressures determines the comparison of control based on a threshold method with control measured by absolute risk. The distribution of blood pressure in these patients will be peculiar to the behaviour of the patients and physicians in Oxfordshire and may be quite different elsewhere.

Altogether, 2.1% of subjects did not have their blood pressure recorded and were excluded. How many patients had no documentation about other risk factors, and how were the guidelines interpreted when additional risk factors were not recorded? The conclusion of the paper depends crucially on the coincidence of blood pressure and risk factors in the same patients: missing data can have a profound effect.

STUART BARTON

Senior lecturer in primary care therapeutics

MIKE CRANNEY

General practice research fellow

TOM WALLEY

Professor of clinical pharmacology

Department of Pharmacology and Therapeutics,
University of Liverpool,
Liverpool L69 3BX

1 Fahey TP, Peters TJ. What constitutes controlled hypertension? Patient based comparison of hypertension guidelines. *BMJ* 1996;313:93-6. (13 July.)

2 Wen SW, Kramer MS, Hoey J, Hanley JA, Usher RH. Terminal digit preference, random error, and bias in routine clinical measurement of blood pressure. *J Clin Epidemiol* 1993;46:1187-93.

3 Hense HW, Kuulasmaa K, Zaborskis A, Kupsc W, Tuomilehto J. Quality assessment of blood-pressure measurements in epidemiologic surveys—the impact of last digit preference and the proportions of identical duplicate measurements. *Rev Epidemiol Sante Publique* 1990;38:463-8.

Authors' reply

EDITOR,—We agree with Lars H Lindholm and Lars Werkö that guidelines that focus on the absolute risks and cost effectiveness of treatment are likely to make management of hypertension more rational. Stuart Barton and colleagues suggest that misclassification may have occurred because of incompleteness in recording of blood pressure and risk factors. In our study four fifths of patients had three records of blood pressure and 98% had evidence of a blood pressure record in the previous five years. Validation of computer records in a sample of patients showed that 11% of patients had additional blood pressure records in their notes. The completeness of records of other risk factors varied greatly (body mass index 83%, cholesterol concentration 24%, smoking status 89%). If a factor was not recorded then it was deemed not to be present; thus misclassification was always in the direction of underestimating absolute risk, making such estimates conservative.

Our study was a pragmatic one. We accept that digit preference and more frequent recordings may alter threshold measurements and subsequent estimation of control in guidelines that rely primarily on blood pressure alone. In contrast, blood pressure is only a small determinant of overall absolute cardiovascular risk^{1,2}; therefore measurement error and digit preference are far less important when determining control of hypertension according to an absolute risk standard. Indeed, we found that high blood pressure alone, in this group of patients, is a poor predictor of absolute risk.³

T P FAHEY
Lecturer in primary care

T J PETERS
Senior lecturer in medical statistics

University of Bristol,
Department of Social Science,
Bristol BS8 2PR

1 Anderson KM, Wilson PWF, Odell PW, Kannel WB. An updated coronary risk profile. A statement for health professionals. *Circulation* 1991;22:312-8.

2 Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham study. *Stroke* 1991;22:312-8.

3 Fahey TP, Peters TJ. A general practice based study examining the absolute risk of cardiovascular disease in treated hypertensive patients. *Br J Gen Pract* (in press).

St John's wort for depression

EDITOR,—The meta-analysis about the use of St John's wort (*Hypericum perforatum*) for depression¹ and the accompanying editorial highlight² two important points. The first is the growing interest in phytotherapy in Britain and the large amount of scientific data that still needs to be collected to confirm the anecdotal evidence about the safe and effective use of such preparations (which are often used for self treatment). There is a serious shortage of funds available for the necessary work to be carried out at all levels, but there is also a need for more clinicians in Britain to be willing to participate in clinical trials of well authenticated herbal material.

The second important point is that plants to be used for phytotherapy need to be identified correctly. The illustration in the editorial is not of *Hypericum perforatum* but of another species of *Hypericum*.² *H. perforatum* does not have the leaf shape or fruits shown in the figure. Correct identification of species is extremely important because use of the wrong plant may result in lack of effect or even toxicity. A large number of toxicological effects that are attributed to particular

herbal medicines are in fact the effects of other herbal material used in error. This type of mistake is typified by the irritatingly common practice of naming vincristine and related anticancer compounds as *Vinca* alkaloids although they are derived from *Catharanthus roseus*. Unfortunately, classical taxonomists and phytoanalysts do not have the same glamour and potential to attract money as some other scientists and so are an endangered species. Their demise will result in mistakes more serious than the one in the editorial.

PETER J HOUGHTON
Senior lecturer in pharmacognosy

Department of Pharmacy,
King's College London,
London SW3 6LX

- 1 Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression—an overview and meta-analysis of randomised clinical trials. *BMJ* 1996;313:253-8. (3 August.)
- 2 De Smet PAGM, Nolen WA. St John's wort as an antidepressant. *BMJ* 1996;313:241-2. (3 August.)

Iron deficiency anaemia and febrile convulsions

Possible confounding factors include lead toxicity ...

EDITOR,—Alfredo Pisacane and colleagues report that they found an association between iron deficiency anaemia and febrile seizures in Neapolitan children.¹ They apparently failed, however, to consider the confounding possibility of lead poisoning in these children with hypochromic, microcytic anaemia and low serum iron concentrations.² lowers the seizure threshold,² and could easily account for the apparent association between "iron deficiency" and seizures in these children. Was this potential confounder adjusted for, or even considered, by the authors?

Additionally, the study began with 156 subjects, yet only 146 were commented on. What became of the missing 10 children? Were they excluded for some reason?

Finally, even if an association between iron deficiency anaemia and febrile seizures does exist, a case-control study cannot prove causation (which is hinted at in the concluding paragraph).

WILLIAM M WIKE
Family practice intern
W R KISER
Specialty adviser to the surgeon general

Department of Family Practice,
United States Naval Hospital,
Jacksonville, FL 32214-5227,
USA

- 1 Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, et al. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. *BMJ* 1996;313:343. (10 August.)
- 2 Rudolph AM, ed. *Rudolph's pediatrics*. 20th ed. Stamford, CT: Appleton and Lange, 1996.
- 3 Johnson KB, ed. *The Harriet Lane handbook*. 13th ed. St Louis, MO: Mosby, 1993:222.

... and coeliac disease

EDITOR,—Alfredo Pisacane and colleagues report an increased incidence of iron deficiency anaemia in children under the age of 2 years presenting with febrile convulsions.¹ Although they considered confounding variables, they do not seem to have considered a known and linking condition for anaemia and fits. The literature, in both children^{2 3} and adults,⁴ documents an association between epilepsy, coeliac disease, and, intriguingly, intracerebral calcification. Some of this association may, of course, be due to the associated hypomagnesaemia and hypocalcaemia. Although the frequency of

coeliac disease in unselected patients with epilepsy is low (1%), we suspect that in an anaemic population it would be much higher. Because control of epilepsy improves with treatment,⁵ we would suggest that the authors screen the anaemic group for coeliac disease.

C E MACDONALD
Research registrar
R J PLAYFORD
Professor

University Division of Gastroenterology,
Leicester General Hospital NHS Trust,
Leicester LE5 4PW

- 1 Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, et al. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. *BMJ* 1996;313:343. (10 August.)
- 2 Fois A, Vascotto M, Di Bartolo RM, Di Marco V. Celiac disease and epilepsy in pediatric patients. *Childs Nerv Syst* 1994;10:450-4.
- 3 Piattella L, Zamponi N, Cardinali C, Porfiri L, Tavoni MA. Endocranial calcifications, infantile celiac disease and epilepsy. *Childs Nerv Syst* 1993;9:172-5.
- 4 Ambrosetto G, Antonini L, Tassinari CA. Occipital lobe seizures related to clinically asymptomatic celiac disease in adulthood. *Epilepsia* 1992;33:476-81.
- 5 Cernibori A, Gobbi G. Partial seizures, cerebral calcifications and celiac disease. *Ital J Neurol Sci* 1995;16:187-91.

Authors' reply

EDITOR,—The suggestion that potential confounders such as lead poisoning and coeliac disease might be responsible for the association that we reported between iron deficiency anaemia and febrile convulsions is important. Because of the characteristics of our study, however, no data are available from the clinical records that might indicate whether lead poisoning or coeliac disease was present in some of the cases.

Nevertheless, even though iron deficiency anaemia has been associated with both these conditions, febrile convulsions have not. Seizures without fever can occur as a clinical manifestation of lead encephalopathy and of coeliac disease in association with cerebral calcification. However, children with febrile seizures are usually children who are well before and after the fit, and afebrile convulsions are uncommon among them.

We are now studying prospectively a large group of children admitted with their first febrile seizure to some hospitals in greater Naples. All of them had a good nutritional status both at the time of the seizure and one year later, with no clinical signs of lead poisoning or coeliac disease. Moreover, when only those children with a haemoglobin concentration of >110 g/l were considered, iron deficiency was considerably more common among cases than controls. That could mean that iron deficiency rather than anaemia is associated with febrile seizures. Obviously, the points raised in the letters about our report need attention, and no claim of causation should be made before more studies have been carried out.

Finally, we regret that the reason for the exclusion of 10 cases (the fact that no haematological data were available from the clinical records) did not appear in the final manuscript.

ALFREDO PISACANE
Senior lecturer
RENATO SANSONE
Postgraduate trainee
NICOLA IMPAGLIAZZO
Postgraduate trainee
ANGELO COPPOLA
Postgraduate trainee

Dipartimento di Pediatria,
Università Degli Studi di Napoli Federico II,
5-80131 Naples,
Italy

PAOLO ROLANDO
Paediatric consultant
ALFONSO D'APUZZO
Paediatrician
CIRO TREGROSSI
Paediatrician

Divisione di Pediatria,
Ospedale di Castellammare di Stabia,
Naples

Hormone replacement therapy for all?

Women must choose for themselves

EDITOR,—Philip Tooze-Hobson and Linda Cardozo assert that "there are three main reasons why many who would benefit do not take oestrogen supplementation," but they offer no evidence to support this assertion.¹ They then state that women who believe that the menopause is a natural event are wrong. Aside from being irrelevant to the merits or otherwise of using hormone replacement therapy, this view ignores the fact that the word "natural" has no defined meaning when applied as a descriptive epithet to biological processes. It simply conveys some of our health beliefs concerning the event. In other words, people may disagree about whether a process is natural or not according to what they understand by natural. The fact that the authors reject all other interpretations of the word but their own does not augur well for their sensitivity towards lay health beliefs or their patients' autonomy. My own belief is that to regard the biological processes of one phase of life as more or less normal than those of another is problematic. Indeed, recasting the menopause as a medical event by definition makes symptoms out of what might otherwise be experiences.

The central issue is whether the advantages of hormone replacement outweigh the disadvantages. It has been noted that the potential reduction in cardiovascular disease would have the greatest impact on health outcomes.² Clearly, relief of symptoms (if there are any symptoms and these are perceived as problematic) and a reduced incidence of stroke and fracture are also important. The disadvantages include possible increased risks of breast cancer, medicalisation, resumption of bleeding, and cost. People may be expected to give different weight to these risks and benefits, especially those concerning medicalisation. We should not be surprised that different women will make different choices or even disagree with our assessments. It is up to women to make these choices themselves. For clinicians to impose their view rather than to advise encroaches on patients' autonomy and exceeds the mandate of the doctor-patient relationship.

TOM MARSHALL
Registrar in public health

Northamptonshire Health Authority,
Northampton NN1 5DN

- 1 Tooze-Hobson P, Cardozo L, Jacobs HS. Hormone replacement for all? *BMJ* 1996;313:350-2. (10 August.)
- 2 Daly E, Roche M, Barlow D, Gray A, McPherson K, Vessey M. HRT: an analysis of benefits, risks and costs. *Br Med Bull* 1992;48:368-400.

Arguments should be based on ratio of benefits to risks

EDITOR,—Philip Tooze-Hobson and Linda Cardozo assert that "some women believe that the menopause is a natural event and that taking medication (hormones) should be avoided. These women are wrong: oestrogen deficiency is the unnatural state."¹ Oestrogen concentrations normally change in childhood, the reproductive years, and postmenopausally, but nobody is suggesting that prepubertal girls are oestrogen deficient, so why should all older women be? It seems extraordinary that these gynaecologists wish to define all women over a certain age as being diseased and "wrong" if they do not concur with their diagnosis. The historical argument about increasing life expectancy is specious because the increase is largely due to falls in infant mortality, and women who have reached 50 have always had a life expectancy well beyond their menopause.