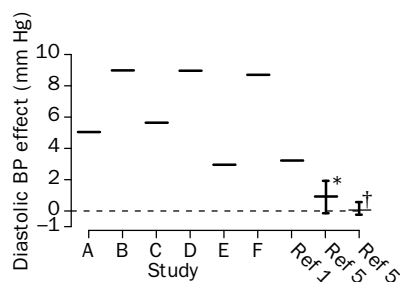


## CORRESPONDENCE

## Modest salt restriction in older people

SIR—Francesco Cappuccio and colleagues (Sept 20, p 850)<sup>1</sup> report that a modest salt restriction of 83 mmol per day in older people decreases blood pressure by 7.3/3.2 mm Hg. This is the seventh randomised study of the effect of salt restriction on blood pressure from St George's Hospital, London, all showing a remarkable effect. Cappuccio et al mention the meta-analysis by Law et al,<sup>2</sup> which also shows a large effect of salt restriction. That meta-analysis, however, includes both randomised and unrandomised studies. Other meta-analyses, including only randomised studies,<sup>3-5</sup> indicate a much smaller effect of 2–4/1–2 mm Hg. Cappuccio et al do not cite these meta-analyses. The figure compares the results from St George's Hospital with the mean of most other published randomised studies, as published in the last and largest meta-analysis.<sup>3</sup> In all seven studies from St George's Hospital the mean effect is higher than the upper 95% CI of the meta-analysis by Midgley et al. (Only English language studies were included in Midgley's study and since that strategy may cause a bias favouring significant studies, even the small effect found by Midgley et al may be an overestimation.)

Whatever the reason for the divergence, we think it is of general interest that the large effects obtained



**Mean effect of salt restriction on diastolic blood pressure in seven studies from St George's Hospital compared with meta-analysis of 28 hypertensive and 28 normotensive populations**

Studies A–F published between 1982 and 1994.\*

\*Hypertensives; †normotensives.

\*List of six references for studies A–F available from authors, on request

in the studies from St George's Hospital may not be generalisable.

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- 1 Cappuccio F, Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people. *Lancet* 1997; **350**: 850–54.
- 2 Law MR, Frost CD, Wald NJ. III—analysis of observational data among populations. *BMJ* 1991; **302**: 819–24.
- 3 Grobbee DE, Hofman A. Does sodium restriction lower blood pressure? *BMJ* 1986; **293**: 27–29.
- 4 Cutler JA, Follmann D, Elliott P, Suh I. An overview of randomised trials of sodium reduction and blood pressure. *Hypertension* 1993; **17** (suppl 1): 127–33.
- 5 Midgley JP, Matthew AG, Greenwood CMT, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275**: 1590–97.

SIR—The double-blind randomised study by Francesco Cappuccio and colleagues<sup>1</sup> is methodologically sound experimental work but their paper and the accompanying commentary by Paul Elliott (p 825)<sup>2</sup> suffer from data-to-conclusion dissociation.

Cappuccio et al measured sodium excretion and blood pressure in 47 elderly people. In a 2-month study, low and high salt intakes were randomly assigned in crossover fashion, each for 1 month. The difference between the low and high sodium intake was 177–94 (=83 mmol), and the low sodium group was associated with a mean difference of 2–3 mm Hg in diastolic pressure and a 30% increase in plasma-renin-activity.

Cappuccio et al and Elliott conclude that “sodium reduction of about 80 mmol/day is feasible and acceptable”. While that statement may be true, there is nothing in this study to support it. Indeed, these vigilant clinical investigators, dispensing sodium-free bread, produced only a 33 mmol/day drop (127–94) in sodium intake. What the study has shown is that a large difference (halving) of sodium intake yields a 2–3 mm Hg difference in diastolic pressure. The difference in

sodium intake was mostly (60%) due to the addition of sodium tablets and not dietary sodium restriction. These data might better support a warning against adding salt tablets to the regular diet, at least for the short term.

My guess is that readers will recognise these data for what they are—namely, solid scientific support for the view that large differences in sodium intake produce measurable differences in blood pressure, at least for a short time. The issue for doctors and patients, however, is whether the 33 mmol in-study reduction in sodium intake achieved through application of the clinical protocol used here would alter blood pressure. It might, but the evidence suggests that a much larger sodium reduction would be required.<sup>3,4</sup> In any event, it is an answerable question. Beyond that is the more momentous public-held issue of how such a modest change in sodium intake would affect the quality or duration of life. This careful study by Cappuccio and colleagues provides no guidance on these issues.

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- 1 Cappuccio F, Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people. *Lancet* 1997; **350**: 850–54.
- 2 Elliott P. Lower sodium for all. *Lancet* 1997; **350**: 825–26.
- 3 Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr* 1997; **65** (suppl): 643S–51S.
- 4 Midgley JP, Matthew AG, Greenwood CMT, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275**: 1590–97.

SIR—Francesco Cappuccio and colleagues point out<sup>1</sup> that a fall in supine blood pressure with reduced salt intake in normotensive and hypertensive older people has important implications for stroke prevention. However, the authors fail to address adequately compliance and satisfaction with a reduced salt diet, which are central to the efficacy of a population approach. They report that five out of 47 people were thought not to be compliant with their low-salt diet

because their 24 h urinary sodium excretion was not lowered. This may be an underestimate since patients may follow their diet more strictly immediately before a single measurement of 24 h urinary sodium. With closer monitoring of compliance (or a larger sample) the fall in standing blood pressure might also have reached significance.

This study shows the efficacy of a reduced salt diet in a small but highly selective population under experimental conditions. However, this does not prove the feasibility of such an intervention in "real life". The challenge now is to develop standard clinical protocols for such intervention for use by general practitioners rather than researchers, which address the acceptability and compliance of a dietary approach in the general population.

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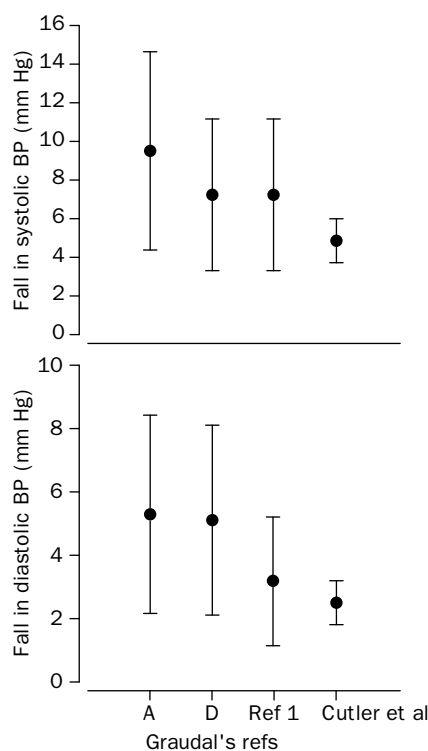
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1 Cappuccio F, Markandu ND, Carney C,  
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#### Authors' reply

SIR—Niels Graudal and colleagues draw attention to some (though not all) of the studies that we have done over the past 17 years at Charing Cross Hospital and at St George's Hospital, London, looking at the effects of changing salt intake on a variety of indices including blood pressure. However, we have done only three double-blind, randomised, crossover trials, of modest salt reduction (from 10 to 5 g) of 4 weeks' duration in untreated individuals. In one<sup>1</sup> we looked at the dose-response to 200, 100, and 50 mmol per day. Graudal et al compare the extreme levels and, not surprisingly, find a bigger fall in blood pressure with a larger reduction in sodium intake. However, if the changes from 200 to 100 mmol are used, falls in blood pressure comparable with those in the other trials are observed.

The results of these trials show similar significant reductions in blood pressure which are consistent with the average reduction in blood pressure estimated by Cutler and colleagues<sup>2</sup> in a more recent meta-analysis. The figure shows that the results of each trial are fully compatible with Cutler's estimate, as the 95% CIs (omitted by Graudal et al) overlap. Graudal et al cite two salt trials in patients on an angiotensin-



#### Mean (95% CI) changes in blood pressure in three trials of modest salt reduction and in more recent meta-analysis<sup>2</sup>

Three trials identified, as in Graudal and colleagues' letter.

converting-enzyme inhibitor. When angiotensin II production is blocked it is not surprising that the blood pressure fall with salt reduction would be greater. They also refer to two studies of 5 days' duration either from very low (25 mmol) or to very high (330 mmol) daily sodium intakes. These studies are irrelevant to our study in the elderly.

Michael Alderman focuses on diastolic blood pressure but in the elderly systolic blood pressure is a much stronger predictor of risk and outcome. We demonstrated that a modest reduction in salt intake (from 10 to 5 g per day) in the elderly irrespective of blood pressure levels causes significant falls in both systolic and diastolic pressure (7.2/3.2 mm Hg) which is similar to the recent Syst-Eur trial in the elderly (10.1/4.5 mm Hg).<sup>3</sup> Syst-Eur was terminated prematurely because of large significant reductions in stroke (42%) and cardiac endpoints (26%) in the actively treated group. Population studies have shown that salt intake in the UK and USA averages 10 g per day. Our purpose was to look at a reduction from this level of salt intake. Indeed, this fits with recent UK government and US recommendations, and allows our results to be generalised to the whole of the elderly population in those countries.

We do not agree with Alderman's suggestion that we should analyse our randomised crossover study by comparing the entry measurements (not blind) to one of the phases of the double-blind study. 24 h urinary sodium excretion at entry to the trial was 127 mmol, reflecting the awareness of people and patients around St George's Hospital of the importance of salt but this does not reflect average intake in the UK. If we analyse our data in the incorrect way that Alderman suggests, the fall in blood pressure is still 5.8/2.8 mm Hg. He ignores our previous work that showed a dose-response to salt restriction—ie, the further the salt intake is reduced the greater the fall in blood pressure—and that the long-term salt restriction continued to control blood pressure.<sup>1</sup>

Nicholas Brennan and colleagues address feasibility. We examined efficacy. When salt intake is reduced, the salt taste receptors become much more sensitive. Foods with less salt are preferred to the highly salted food consumed before and this ensures long-term compliance. Vast amounts of salt are added by the food industry at a sodium concentration equivalent to sea water (1.0 g sodium per 100 g water), examples being cornflakes (1.1 g per 100 g) and bread (0.5–1.2 g per 100 g).

Salt is the cheapest food ingredient and makes unpalatable food edible, allows large amounts of water to be added, thus increasing the weight at no cost, and, in temperate climates, is the main determinant of thirst (soft drinks). Since 80% of our salt intake now comes from processed food, the cooperation of the food industry is essential to reduce our high salt intake. The obstinate pursuit of purely commercial interests by the salt industry and some food companies is responsible for thousands of avoidable deaths and disability from stroke and coronary heart disease.

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## New-variant Creutzfeldt-Jakob disease and treatment of haemophilia

SIR—There is concern about the possibility that blood products might transmit the agent responsible for new-variant Creutzfeldt-Jakob disease (nvCJD). As a result of the recent directive from the Committee for Proprietary Medicinal Products two batches of factor VIII concentrate have been withdrawn in the UK by the manufacturer because they were produced from plasma containing donations from individuals who subsequently developed nvCJD.

The United Kingdom Haemophilia Centre Directors' Organisation (UKHCDO) executive committee has met with authorities on transmissible spongiform encephalopathies to review the medical and scientific evidence that blood and blood products might transmit the agent responsible for nvCJD.

From studies undertaken in the USA and the UK there is as yet no evidence of transmission to patients of the agent responsible for classic or sporadic CJD (spCJD) by blood or blood products. We are not aware of any cases of spCJD in persons with haemophilia.

In 1996, nvCJD was first identified by the CJD Surveillance Unit in Edinburgh.<sup>1</sup> Recently published data indicate that nvCJD and bovine spongiform encephalopathy (BSE) are caused by the same infectious agent.<sup>2,3</sup> nvCJD is clinically distinct and should be regarded as a separate condition from spCJD. nvCJD in man has probably arisen from ingestion of bovine products containing the agent responsible for BSE in cattle.

The largest epidemic of BSE has taken place in the UK, where nearly all the cases of nvCJD have arisen, and it is likely that more cases, currently symptom-free, will present clinically in the future. The finding of the abnormal prion-related protein (PrP) in the tonsils and spleen of patients with nvCJD raises the possibility that circulating lymphocytes in the blood of symptom-free individuals could transmit the agent responsible for nvCJD.<sup>4</sup>

For this reason the Spongiform Encephalopathies Advisory Committee (SEAC) recommended that consideration be given to leucodepleting blood in the UK, and a risk assessment by the Department of Health and a feasibility study by the National Blood Authority (NBA) is underway. If such a policy is accepted it will take a considerable time to implement, and meanwhile further cases of nvCJD in blood donors may

lead to further recalls of clotting factor concentrates manufactured from plasma donated in the UK.

In 1996 UKHCDO recommended that recombinant factor VIII (rVIII) concentrate was the treatment of choice for those with haemophilia A.<sup>5</sup> Further and new uncertainties about the safety of plasma products with respect to nvCJD requires that these recommendations are implemented with greater urgency. The executive committee therefore recommends that patients should be treated, as soon as possible, with rVIII manufactured without the use of bovine proteins or human albumin. Meanwhile we continue to recommend strongly the use of the current licensed rVIII concentrates for all people with haemophilia A. When rIX concentrate becomes licensed this will be the treatment of choice for those with haemophilia B. Consideration should be given to the use of rVIIa concentrate for patients with congenital factor VII deficiency, although it is not licensed for this purpose.

Patients for whom recombinant concentrates are not available will need treatment with plasma-derived products. The choice lies between concentrates manufactured from plasma collected in countries with cases of nvCJD and BSE, or in those geographical regions in which there are no recorded cases of either of these conditions. From our understanding of the epidemiology that nvCJD occurs almost exclusively in the UK, it is likely that any risk of transmission would be reduced by the use of concentrates prepared from donor plasma collected in other countries, such as the USA, where there are no recorded cases of nvCJD or BSE.

We should not underestimate the anxiety that nvCJD has created for those with haemophilia. The recent withdrawal of concentrates and other blood products in the UK means that patients will require counselling; not only recipients of these batches, but also others at risk from products derived from the same source plasma.

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## Hormone replacement therapy and biological aggressiveness of breast cancer

SIR—In the meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (Oct 11, p 1047)<sup>1</sup> hormone replacement therapy (HRT) was associated with an increased risk of breast cancer. In addition to this increased risk, the meta-analysis showed a tendency towards a higher proportion of localised tumours in HRT users. This is an important finding, because a less advanced clinical stage in breast cancer is usually associated with better survival and lower mortality. Thus the effect of HRT on breast cancer mortality (not examined in the meta-analysis) is probably less and may even be beneficial, as seen in two large cohort studies.<sup>2,3</sup> The less advanced clinical stage in HRT users has been explained by selection or surveillance bias, and by a biological effect of HRT on breast tumours. The data on tumour biology in HRT users is scarce and we fully agree with the conclusion of the Collaborative Group that it should be the focus of future investigations.

We have looked at the possible effect of HRT on tumour biology in a population-based cohort of 477 consecutive patients with breast cancer who were older than 50 years in the Tampere University Hospital district between 1992 and 1994. The use of HRT was determined by a structured interview and from prescriptions (171 [37%] of the patients had used HRT, of whom 44 [25%] were on oestrogen alone, 127 [73%] oestrogen and progestogen combination, and three [2%] on progestogen alone). Standard clinical and pathological information (age, tumour size, axillary nodal status, histological grade), and the method of diagnosis (screen detected or self-referral) were recorded for all patients. Indicators of biological aggressiveness included oestrogen and progesterone receptors, c-erbB<sub>2</sub> oncoprotein, ploidy, and tumour proliferation rate.

Our findings (table) indicated that

	Odds ratio (95% CI)*			p
Tumour size (>2 cm vs <2 cm)	0.47 (0.31-0.72)			0.0005†
Lymph-node status (-ve/+ve)	0.73 (0.47-1.2)			0.2†
Histological grade (I vs II vs III)				0.04‡
Oestrogen receptor	0.76 (0.46-1.2)			0.31†
Progesterone receptor	1.01 (0.85-1.5)			0.99†
C-erbB <sub>2</sub> oncoprotein (-ve/+ve)	1.60 (0.85-2.9)			0.15†
Ploidy (diploid vs aneuploid)	0.69 (0.45-1.1)			0.11†
Tumour proliferation rate¶	Never-user (n=228)	Ex-users (n=27)	Current users (n=91)	
	10.3 (7.4)	9.4 (5.8)	7.8 (5.9)	0.0001§

\*Never-user vs HRT users; † $\chi^2$  test; ‡ $\chi^2$  test for trend; §Wilcoxon test for trend; ¶mean s-phase fraction (%) (SD). Never-user=no use of HRT; ex-user=use of HRT for over 3 months but stopped at least 3 months before diagnosis of breast cancer; current user: use of HRT for over 3 months and until diagnosis of breast cancer; +ve=positive; -ve=negative.

### Association of hormone replacement therapy (HRT) with established prognostic factors in a population-based set of 477 consecutive postmenopausal patients with breast cancer

tumours from HRT users are biologically less aggressive. Use of HRT was significantly associated with small tumour size and low tumour proliferation rate (S-phase fraction by DNA flow cytometry). The latter association was found only if HRT was used at the time when breast cancer was diagnosed. This finding suggests that the lower proliferation rate is a specific and immediate effect of HRT on established breast tumours. The primary tumours were also significantly smaller in HRT users, which is in accordance with the meta-analysis.<sup>1</sup> Adjusting for the method of detection (171 cancers detected by mammography screening vs 306 by self-referral) had a minimum effect on the association between tumour size, proliferation rate, and HRT, suggesting that the detection of smaller tumours in HRT users was not due to surveillance bias. Tumour size and proliferation rate were significantly correlated ( $p < 0.0001$ ), and it is likely that the relation of HRT to tumour size is secondary to the effect of HRT on proliferation rate. Likewise, the modest association between HRT and histological grade can probably be at least partly explained by tumour proliferation, because number of mitoses is a key element in histological grading.

Although HRT increases the risk of breast cancer,<sup>1</sup> the overall effect of HRT on breast carcinogenesis and tumour progression remains to be fully evaluated. There is growing evidence for a more favourable tumour biology in HRT users,<sup>4,5</sup> and there are at least two large studies reporting decreased mortality due to breast cancer in HRT users.<sup>2,3</sup>

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### Ventricular remodelling in dilated cardiomyopathy

SIR—G D Angelini and colleagues (Aug 16, p 489)<sup>1</sup> reduce the diameter of the dilated ventricle in dilated cardiomyopathy (DCM) by excising a slice of myocardium, thus lessening wall tension and improving myocardial contractility.

The normal left ventricle at end-diastole resembles a prolate ellipsoid. As the ventricle dilates, it becomes more spherical.<sup>2,3</sup> Alteration of the ellipsoid shape to a more spherical one translates into an abnormal distribution of afterload, and both shape change and altered load distribution have been associated with a higher early mortality rate in one group of patients with DCM.<sup>3</sup> On the Laplace principle, left-ventricular wall stress is directly related to chamber dimension and pressure and inversely related to wall thickness.<sup>2</sup> Inadequate thickening of the ventricular wall in response to the increased internal diameter of the ventricular cavity is one of the important morphological features of

decompensating DCM,<sup>2-5</sup> so reduction of left-ventricular diameter in decompensating DCM is justifiable. However, the volume reduction will not be successful in every patient. How do you decide how much reduction of the ventricular diameter, for a particular heart, would bring a successful outcome—and should the myocardium be excised in all cases of DCM? To try to answer these questions we have received published data on ventricular dimensions and have analysed the probable causes of a negative outcome after volume reduction surgery.

With the concept in mind that a postoperative left-ventricular mass/left-ventricular end-diastolic volume (M/EDV) quotient of less than 0.95 will not indicate better prognosis after surgery—and since the chamber volume cannot be directly measured after ventriculotomy—preoperative data on M/EDV and on left-ventricular end-diastolic endocardial surface area (EDESA)/EDV should help in the surgical reduction of EDESA (corresponding to the EDV estimated preoperatively) to the desired level. Intraoperative measurement of the mass and ESA of the excised myocardium would be the best control for every step of ventricular wall excision.

For remodelling of the ventricle from a spherical to an ellipsoid shape, after ventriculotomy, the initial circumference of the endocardial surface ( $C_0$ ) at the level of minor axis (between the tips of mitral valve leaflets and the superior aspect of the papillary muscles) and wall thickness (h) should be measured. To normalise the thickness/radius quotient, for the given value of h, the desired circumference ( $C_d$ ) would be around  $14 \times h$  at the level of the minor axis of the ventricle. With the increase in left-ventricular end-diastolic diameter there was a thinning of the wall (h), from 10.2 to 9.2 mm in one group of patients with DCM.<sup>2</sup> Perhaps when h is 10 mm or less the myocardium should not be excised during the reduction of left-ventricular diameter. In this situation, conceivably, overlapping the surplus myocardium ( $0.5 [C_0 - C_d]$  from each ventriculotomy end) with reduction of the diameter to the desired level—ie, volume reduction plus cardiomyoplasty—would reduce the wall stress and thus improve the overall inotropic state of myocardium.

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SIR—In G D Angelini and colleagues' series<sup>1</sup> of 14 cases of reduction of left-ventricular volume (Batista's procedure) several procedures were done at the same time, including mitral valve surgery and coronary revascularisation. There were three deaths in hospital and one late sudden death. On average, short-term results are consistent with 17% reduction in left-ventricular diastolic dimension and a 55% increase in left-ventricular ejection fraction. The associated procedures prompt A Carpentier (Aug 16, p 456)<sup>2</sup> to doubt the efficacy of left-ventricular reduction volume in heart failure since mitral valve surgery and coronary revascularisation alone may improve clinical status in selected patients with end-stage heart failure.

In essence, Angelini et al confirm our work.<sup>3</sup> We demonstrated beneficial effects of Batista's procedure in patients with end-stage heart failure secondary to dilated cardiomyopathy. Seven consecutive patients in New York Heart Association functional class IV underwent partial ventriculectomy; mean left-ventricular diastolic dimension was 78.3 (SD 12.6) mm, mean left-ventricular ejection fraction 15 (5)%, and mean pulmonary vascular resistance 6.6 (3.2) Wood units. No patient had a ventricular aneurysm or localised ventricular dysfunction at catheterisation; all had a globally dilated heart. Neither coronary revascularisation nor mitral valve surgery were done. There were no hospital deaths. 60 days after the partial ventriculectomy, mean NYHA functional class was 1.71 (0.48) ( $p=0.009$ ) with a 15% reduction in left-ventricular diastolic dimension and a 50% increase in ejection fraction. The improvement was thought to be due to the ability of partial ventriculectomy not only to decrease left-ventricular elastic stiffness and wall tension but also to change left-ventricular shape.<sup>4</sup> At follow-up (12 [4] months) the improvement in symptoms, left-

ventricular diastolic dimension, and ejection fraction persist; two patients had died, one from gastrointestinal haemorrhage and one suddenly.<sup>5</sup>

Thus, in contrast to Carpentier's opinion,<sup>2</sup> partial ventriculectomy alone can improve clinical status in patients with end-stage heart failure. The magnitude of effects on left-ventricular diastolic dimension and ejection fraction suggests that patients with a left-ventricular diastolic dimension greater than 85 mm detected echocardiographically and left-ventricular ejection fraction below 15% should not be operated on because reduction surgery could be too dangerous. Patients with cardiogenic shock may not be suitable either, unless ventricular assistance is available, because three patients subsequently operated on by us died in the operating theatre.<sup>5</sup>

I agree with Angelini and colleagues and Carpentier that partial ventriculectomy cannot yet be recommended for end-stage heart failure. As for cardiomyoplasty, a controlled trial is necessary to prove that ventriculectomy prolongs life. Nonetheless, when heart transplantation is not indicated (eg, because of high pulmonary vascular resistance), partial ventriculectomy could be offered for selected patients with end-stage heart failure due to dilated cardiomyopathy.

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SIR—G D Angelini and colleagues<sup>1</sup> report an increase in cardiac index and ejection fraction concomitant with a decrease in left-ventricular end-diastolic diameter in 13 of 14 patients undergoing left-ventricular-volume reduction for end-stage heart failure. In nine patients, New York Heart Association (NYHA) functional class

improved, and overall survival was ten of 14. We appreciate the group's concerns that ventricular reduction surgery needs further evaluation before extended clinical application. Several shortcomings of their study should, however, be addressed.

Since left-ventricular function is improved by respiratory<sup>2</sup> and pharmacological support<sup>3</sup> we need further details to clarify the conditions under which cardiac index was measured. Assessment of exercise tolerance might help to evaluate improvement in cardiac performance more objectively. In heart transplant recipients, despite an improvement in NYHA functional class, systemic oxygen uptake can be substantially impaired.<sup>4</sup> Left-ventricular volume reduction surgery is still associated with significant perioperative mortality and more comprehensive evaluation of postoperative cardiac physiology is warranted.

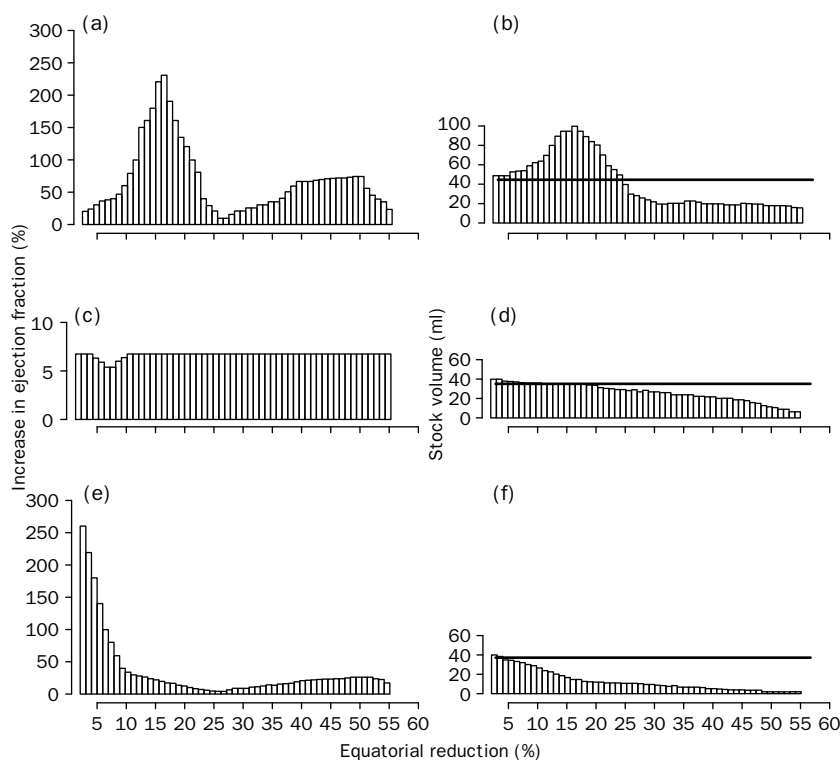
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#### Authors' reply

SIR—We agree with Jyotirmay Chanda, and Reinaldo Bestetti, and their colleagues, that left-ventricular volume reduction surgery is not successful in every case. We have tried to develop a method of patient selection on the basis of echocardiographic data. We use Sofheart Select, a computer program which makes use of preoperative data such as end-diastolic and end-systolic volumes and diameters and ejection fraction to rebuild the preoperative left-ventricular function. After progressive shortening (5%, 10%, 15% . . .) of the maximum equatorial circumference, postoperative function as the ventricular cavity changes from the spherical to the ellipsoid shape can be predicted. In addition, it is possible to identify the amount of circumferential shortening that will produce the greater increase in ejection fraction and stroke volume. The method is based on the principle that the surface of a sphere is



**Three shapes of curve predicting changes in ejection fraction (a, c, e) and stroke volume (b, d, f) after ventricular reduction surgery**

(a,b)= peaked curve; (c,d)=flat curve; (e,f)=monotonic decreasing curve.

greater than or equal to that of the corresponding ellipsoid. Then, for the same contraction, the best change of surface for an ellipsoid will be estimated, and the accumulated energy (ie, the work that can be done) will be proportional to the variation of the surface, given that the ellipsoidal model is more efficient than the spherical.

When this method was applied to 90 patients with end-stage failure and 15 healthy controls we obtained three types of curve. (1) The peaked curve (figure a and b) corresponds to an indication to perform ventricular reduction; on shortening the maximum equatorial circumference the ejection fraction and stroke volume increase. These patients have severe dilation of the left ventricle, severely reduced ejection fraction, a moderate degree of inadequate hypertrophy, a high value of maximum systolic stress, and a ventricular shape closer to the spherical than the ellipsoidal. (2) A flat curve (c and d) corresponds to a contraindication to volume reduction. Reducing circumference and end-diastolic volume does not alter the ejection fraction and stroke volume decreases. These patients differ from those with a peaked curve because they have clearly inadequate hypertrophy and the ventricular cavity is more

spherical. (3) A monotonic decreasing curve (e and f) is to an absolute contraindication because both ejection fraction and stroke volume will fall. These patients have moderate left-ventricular dilation, a moderate decrease in ejection fraction, adequate hypertrophy, and a ventricular shape closer to the ellipsoid. All the controls showed this monotonic decreasing curve.

The sensitivity and specificity of the method was tested prospectively using preoperative echocardiographic data on 29 patients undergoing ventricular reduction. Perioperative mortality was 21% and late mortality 13% with a follow-up of 31–579 days. Of the 19 patients with preoperative peaked curves, two died in the perioperative period (one from pulmonary artery bleeding, the other from irreversible heart failure) and two died later from a stroke and acute pancreatitis, for a total mortality of 21%. Of nine patients with flat curves, four died (44%), three in the early postoperative period (two from irreversible heart failure, one from bleeding) and one at late follow-up from heart failure. The remaining four patients showed a modest improvement. The only patient with a monotonic decreasing curve died in the postoperative period of heart failure. If we define postoperative failure as death

of cardiac origin or survival but with no improvement in cardiac function, the Sofheart Select program gives a sensitivity of 90%, a specificity of 100%, a positive predictive value of 93.75%, and a negative predictive value of 100%. Sensitivity would have been 100% if the patient with the peaked curve who died from cardiac failure, but in whom surgical reduction was greater than that predicted by the curve, is excluded.

This method may permit more accurate selection of patients with end-stage heart-failure for ventricular reduction surgery.

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## Meningococcal vaccine in sub-Saharan Africa

SIR—John Robbins and his colleagues (Sept 20, p 880)<sup>1</sup> recommend universal immunisation with unconjugated group A meningococcal vaccine in sub-Saharan Africa. This recommendation might not have the beneficial effect they intend.

Unconjugated polysaccharide vaccines are thought to induce T-cell-independent immunity and, therefore, do not induce immunological memory.<sup>2</sup> Without repeated immunisation, antibodies to group A antigens decline to levels found in unimmunised adults within 8 years.<sup>3</sup> Natural immunity to meningococci depends on the carriage of meningococci<sup>4</sup> as well as cross-reacting species such as *Neisseria lactamica* and enteric organisms. If a mass immunisation campaign suppressed meningococcal carriage, immune individuals would be deprived of the reimmunising effect of exposure to meningococci. Without revaccination, levels of immunity would decline and the susceptible proportion of the population would increase, eventually leading to an increase in disease.

It is even possible that the widespread use of vaccines in sub-Saharan Africa during the past 20 years has interfered sufficiently with carriage to allow the accumulation of susceptibles, which increases the intensity of subsequent epidemics. More needs to be known about the effect of vaccination on carriage and the importance of meningococcal carriage in maintaining immunity in adults,

before such a programme is considered. Conjugated vaccines under development are more likely to induce immunological memory, provide lasting immunity, and suppress carriage than current unconjugated vaccines.<sup>5</sup>

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SIR—We understand the frustration of John Robbins and colleagues<sup>1</sup> about the prevention of meningococcal disease in sub-Saharan Africa. These epidemics strike otherwise healthy people from infants to young adulthood and the disease often results in death or disability.

The current meningococcal polysaccharide vaccine is useful for control of epidemic meningococcal disease but it is a poor public-health tool for prevention of epidemics through routine childhood vaccination. A single dose of the serogroup A polysaccharide vaccine provides a limited duration of protection to children less than 4 years of age,<sup>2</sup> so multiple doses beyond 1 year of age will be needed, and that would require a new vaccine infrastructure because the Expanded Program for Immunization (EPI) only targets children aged 1 year or less.

Many studies have suggested that the vaccine does not substantially affect carriage of serogroup A meningococci 1 year after vaccination and that it does not provide herd immunity. Without herd immunity, epidemics could continue even with the regimen proposed by Robbins et al since EPI coverage is low in many of the highest risk countries and those over 5 years are likely to need periodic revaccination.

What public health approach should be used? First, because epidemics are unpredictable, a surveillance-based threshold disease rate that is sensitive and specific was identified and tested for early detection of epidemic disease and initiation of mass vaccination

campaigns.<sup>3</sup> This approach has not failed, as Robbins and co-workers suggest, for it has only just begun to be widely implemented among district health officers by the African regional office of WHO.

Second, development of conjugate serogroup A vaccines (similar to the successful *Haemophilus influenzae* serotype b [Hib] conjugate vaccines) should be vigorously pursued.<sup>4</sup> A study of a Pasteur-Mérieux Connaught conjugate serogroup A/C vaccine with a dose schedule compatible with EPI (ie, 6, 10, and 14 weeks) among infants in Niamey, Niger, showed levels of serogroup A meningococcal serum bactericidal antibodies far in excess of those elicited by the polysaccharide vaccine.<sup>5</sup> This provides early evidence that conjugate serogroup A vaccines may elicit longlasting immunity and provide protection from carriage of serogroup A meningococci, and therefore herd immunity, in the same way as conjugate Hib vaccines have been shown to do.

Until conjugate serogroup A meningococcal vaccines are licensed and widely available, countries will need to focus on early detection and prompt mass vaccination to reach high coverage in affected populations.

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- 1 Robbins JB, Towne DW, Gotschlich EC, et al. "Love's labours lost": failure to implement mass vaccination against group A meningococcal meningitis in sub-Saharan Africa. *Lancet* 1997; **350**: 880-82.
- 2 Reingold AL, Broome CV, Hightower AW, et al. Age-specific differences in duration of clinical protection after vaccination with meningococcal polysaccharide A vaccine. *Lancet* 1985; **ii**: 114-18.
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SIR—Although we agree with John Robbins and colleagues<sup>1</sup> that vaccination is the most costeffective intervention to control group A meningococcal disease and that short-term vaccine efficacy is high both in

children and adults, their recommendations are unrealistic. Mass vaccination of the entire population of the meningitis belt (250 million people) does not appear sustainable. It would probably result in very low vaccine coverage, it would not prevent outbreaks, and scarce resources would be wasted. Measles vaccination has been routine for infants in Africa for more than 10 years now and this vaccine is safe, has an efficacy of over 85%, provides life-long protection with only one dose, and results in herd immunity. Even so, measles is far from being eliminated and vaccine coverage remains stubbornly below 50% in many African countries.

The control of meningitis epidemics in sub-Saharan Africa is currently based on mass vaccination initiated on a threshold approach,<sup>2</sup> with an alert threshold usually as low as five cases per 100 000 per week. The rationale for this strategy is that outbreaks of group A meningococcal meningitis are irregular and unpredictable (every 5-12 years); the protection provided by the polysaccharide vaccine is waning after a few years; high-risk individuals have to be revaccinated every 3-5 years; and vaccination does not prevent carriage of *Neisseria meningitidis* so that carrier prevalence of 25% may exist without cases of meningitis.<sup>3</sup> Meningococcal meningitis is not regarded as eradicable by vaccination and herd immunity with this vaccine<sup>4</sup> has not been demonstrated in the field. Effort should be put into strengthening the threshold approach, which includes effective surveillance and early warning systems. Operational research should help refine the criteria for initiating mass vaccination. Epidemic preparedness has a crucial role, as does the positioning of stocks of drugs and vaccines. Efforts should also focus on the development of new and affordable vaccines to provide long-lasting immunity in infants.

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- 1 Robbins JB, Towne DW, Gotschlich EC, Schneerson R. "Love's labours lost": failure to implement mass vaccination against group A meningococcal meningitis in sub-Saharan Africa. *Lancet* 1997; **350**: 880-82.
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SIR—John Robbins and colleagues<sup>1</sup> present an optimistic view of the utility of the group A meningococcal polysaccharide vaccine and suggest a new immunisation strategy for sub-Saharan Africa. Unfortunately, many qualities they attribute to the vaccine, including efficacy in infants, long-term protection, and induction of herd immunity, are particularly questionable. For example, there are no published data demonstrating protective efficacy of the suggested infant regimen—neither of the two studies that directly address efficacy of infant regimens had adequate statistical power. The most recent concluded that efficacy in infants “remains unanswered”.<sup>2</sup> Similarly, duration of protection is unknown. Antibody levels decrease rapidly in younger children, and more gradually in adults. Only one study evaluates duration of protection against disease—protection disappeared in 3 years in children receiving a single dose at less than 4 years of age and declined steadily in older children within 3 years.<sup>3</sup> Finally, they say that the current vaccine yields herd immunity, presumably by eradication of colonisation. However, of the nine reports referenced as demonstrating herd immunity, three do not mention it at all (their references 3, 31, 34); one said it did not occur (26); three mention the possibility, but show only that disease declined after mass immunisation (21, 28, 29); and only two (separate publications about the same outbreak in Europe) attempt an analytic demonstration of this occurrence (13, 20). In that epidemic, the trend toward herd immunity was not statistically significant. Further, the statement that group A meningococcal vaccine inhibits colonisation is not supported by most publications from the meningitis belt. The only controlled study from Africa that showed decreased carriage after immunisation, showed no effect 2 years later.<sup>4</sup>

WHO is committed to optimum use of the current vaccines and development of new vaccines to control epidemic meningococcal disease. Since the recent epidemics in Africa, WHO has worked with countries to enhance the existing control strategy (rapid outbreak detection and emergency mass immunisation) and evaluation of alternative immunisation strategies, and to review immunisation programmes and develop plans for improved surveillance and response. In addition, an international coordinating group was formed to make the best use of the limited supply of vaccine.

To assess alternative prevention strategies with the current vaccine,

WHO is collaborating with partners to evaluate duration of vaccine efficacy in children immunised at age 5; immunogenicity and impact of an infant immunisation schedule; and, since most alternative strategies involve routine immunisation, vaccine delivery through the existing immunisation infrastructure. In these areas, the last scheduled visit to childhood immunisation clinics is between 9 and 12 months, and only a portion of children receive recommended immunisations. For example, in the five most severely affected countries, between 31% and 55% of children receive the complete recommended infant diphtheria/tetanus/pertussis regimen. No system exists for delivery of vaccine to older children. Thus, the immunisation schedules that Robbins et al suggest require substantial modifications to the immunisation infrastructure, and unless major improvements in coverage were to occur, substantially under half meningococcal cases would be prevented.

Finally, many of these difficulties could be addressed with improved group A vaccines, and WHO is actively supporting development of meningococcal polysaccharide-protein conjugate vaccines, which should provide long-term protection with a schedule that can be delivered in these countries.

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- 1 Robbins JB, Towne DW, Gotschlich EC, Schneerson R. “Love’s labours lost”: failure to implement mass vaccination against group A meningococcal meningitis in sub-Saharan Africa. *Lancet* 1997; **350**: 880–82.
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#### *Authors’ reply*

SIR—Group A meningococcal polysaccharide vaccine (GAMP) does induce booster responses up to the age of 2 years, herd immunity, and

longlived and protective antibody levels and immunity at all ages (as referenced in our paper). Two injections, starting at 3 months and given at least 1 month apart and an injection at 2 years and again at about 6 years confer a high degree of immunity in infants and young children. Although the numbers were small, GAMP injected according to this schedule induced 100% protection in infants.<sup>1,2</sup> Only one injection of GAMP in young adults induces protective antibody levels for at least 10 years.<sup>3</sup> The suggestion that GAMP could interfere with carriage, allow the accumulation of susceptibles, and increase the intensity of future epidemics is not based on data or experience.

Because GAMP was not used as recommended, conclusions about the degree and duration of efficacy elicited by one injection of the vaccine are not valid.<sup>4</sup> Would Bradley Perkins and colleagues recommend only one dose of diphtheria-tetanus-pertussis vaccine (DTP) or only one dose of conjugated GAMP for primary vaccination of young children? Of course not. All children should receive vaccines according to the recommendations based on the best scientific data. This was not the case in the report cited by Reingold et al.<sup>4</sup> Herd immunity after widespread use of GAMP has been observed in Europe, Africa, and New Zealand. Epidemics and high endemic rates of group A meningococcal in sub-Saharan Africa have persisted since they were first recognised in 1907. There were 150 000 cases with 15 000 deaths reported in Africa in 1996, and 65 000 cases reported for 1997 to date: the system of early detection followed by selective vaccination has obviously failed to control group A meningococcal epidemics in Africa.<sup>5</sup> A change in the infrastructure may be necessary to prevent group A meningococcal meningitis by vaccination.

J Wenger and colleagues reiterate inaccurate information about published data, including those that failed to use group A meningococcal vaccine as directed. They propose that WHO should continue rapid outbreak detection and emergency mass vaccination. But this strategy at best can prevent only 50% of cases, and adverse circumstances further diminish the value of this approach (epidemics in 1996 and 1997 occurred despite this strategy). Wenger et al would study again the duration of immunity (vaccine-induced serum antibodies) even after the careful and extensive studies of American (which include many children of African descent), European, and Middle-Eastern



children. Published work and worldwide and successful use of group A meningococcal vaccine suggest that this proposal is unconscionable.

Mass vaccination of the entire population and then routine vaccination of infants with GAMP according to the recommended schedule will eliminate endemic disease and prevent epidemics—and this should be the recommendation of WHO for the nations of the meningitis belt.

We can all look forward to conjugated GAMP vaccines but should we wait for a “better vaccine” when we have a highly effective, safe, inexpensive, and available vaccine? Ultimately it is the nations of Africa that must consider the loss caused by epidemic and endemic group A meningococcal meningitis against the cost of vaccinating their entire populations with GAMP.

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- 1 Peltola H, Mäkelä PH, Käyhty H, et al. Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children three months to five years of age. *N Engl J Med* 1977; **297**: 686–93.
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## Sickle-cell disease

SIR—I enjoyed reading the comprehensive review on sickle cell disease by Graham Serjeant (September 6, p 725).<sup>1</sup> However there is no mention of hepatic crisis or sickle-cell hepatopathy in Graham Serjeant’s seminar.

Hepatic crisis is characterised by nausea, abdominal pain, low-grade fever, raised bilirubin, slight increase in alkaline phosphatase, and intact coagulation functions. In his description of hepatic crisis, Diggs<sup>2</sup> claimed that 10% of patients with sickle-cell disease who seek medical attention have jaundice secondary to intrahepatic “regurgitant

jaundice”. This is attributed to the sudden trapping of sickled red cells in the liver, somewhat similar to acute splenic sequestration. The course is variable but there is usually resolution in 1–2 weeks.

Sickle cell intrahepatic cholestasis is characterised by severe right upper-quadrant pain, encephalopathy, extreme hyperbilirubinaemia, and coagulopathy associated with an enlarging liver and a precipitous drop in the haematocrit. Sickle-cell hepatopathy was first described by Green<sup>3</sup> and co-workers in 1953. Death from liver failure has been reported. In sickle-cell hepatopathy, there is sequestration of sickled red cells in the hepatic sinusoids with subsequent sinusoidal obstruction and dilation. Sinusoidal dilation and Kupffer cell erythrophagocytosis are common pathological findings unique to sickle-cell hepatopathy.<sup>3</sup> Although the finding of sickled red cells in hepatic sinusoids indicates an underlying sickling disorder, it may not always substantiate the diagnosis of sickle-cell hepatopathy, especially when liver tissue is preserved in formalin, which may potentiate sickling.<sup>4</sup> The only effective therapy for sickle-cell hepatopathy is exchange transfusion with both packed red cells and fresh plasma that can correct the coagulopathy and reverse the process of intrahepatic cholestasis. Avoidance of surgical intervention is also key to a successful outcome.<sup>5</sup>

Differential diagnosis of both hepatic crisis and sickle-cell hepatopathy should include other diseases such as viral hepatitis, autoimmune liver disease, sclerosing cholangitis, choledocholithiasis, and cholecystitis, all of which can be seen in patients with sickle-cell disease. Regular and scrupulous examination of hepatic size, particularly when there is a precipitous fall in haemoglobin concentration, should be a part of the management of patients with sickle-cell disease who are in crisis. Liver biopsy is important in establishing the correct diagnosis and in instituting appropriate management, though it should be borne in mind that the patient may have another distinct liver disease co-existing with sickle-cell disease.

These two clinical entities of hepatic crisis and sickle hepatopathy could be placed either under “vasoocclusion” or under “other” manifestations given in panel 2 in the seminar by Graham Serjeant.

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- 1 Serjeant GR. Sickle-cell disease. *Lancet* 1997; **350**: 725–30.
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## Continuing increase in invasive methicillin-resistant infection

SIR—We wish to report a continuing increase in the proportion of invasive *Staphylococcus aureus* infections caused by methicillin-resistant isolates (MRSA) in England. We reported previously<sup>1</sup> that the prevalence of MRSA among cases of *S aureus* bacteraemia or cerebrospinal fluid infection had increased from about 1.5% in 1989–91 to 13.2% in 1995. We have subsequently analysed data for 5946 isolates of *S aureus* obtained from blood culture or CSF in hospitals in England during 1996, and have found that MRSA consisted of 21.1% of the total. As before, most MRSA isolates were also resistant to ciprofloxacin (94%) and erythromycin (92%). Resistance rates to these drugs for methicillin-sensitive isolates were 6% and 8.2%, respectively.

This continuing increase in the prevalence of bacteraemia due to MRSA has implications for the empirical treatment of staphylococcal sepsis. A further worry is that this therapeutic problem will be compounded if strains of vancomycin-resistant MRSA, such as those reported recently from Japan<sup>2</sup> and America<sup>3</sup> spread to other countries, including the UK.

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## End-of-life decisions in Dutch paediatric practice

SIR—We wish to reply to the various responses (Sept 13, p 816)<sup>1</sup> to our July 26 paper<sup>2</sup> on end-of-life decisions in neonatology. Philip Howard refers inaccurately to our data. Among the infants in whom life-sustaining treatment was stopped, the percentage to whom drugs were administered with the explicit intention of hastening death was 14% (8% of 57%), and not 48% as Howard suggests. Furthermore, Howard suggests that only 23% of the neonatologists and 6% of the other paediatricians in our survey felt that decisions to administer drugs with the explicit intention of ending life should be reviewed after the death, but there were another 42% and 59%, respectively, who preferred review both before and after the act. The autonomy Dutch paediatricians are supposed to expect for end-of-life decisions is not reflected in our finding that 75% of the neonatologists and 59% of the paediatricians support review of these acts by a committee not restricted to medical professionals. Transparency of the decision-making process in this field is widely endorsed in our country where active euthanasia is emphatically not “tacitly approved”, but widely discussed.

We agree with A P Cole that doctors should “uphold the law where life is concerned”. According to Dutch jurisdiction, in exceptional circumstances the administration of a drug to an infant by a doctor with the explicit intention of ending life may be justified by medical necessity. Therefore, under Dutch law, doctors have a specific, professional responsibility towards the life and death of severely ill infants, and they are, in that respect, different from other groups of citizens.

We cannot find any clue for Marc Grassin and colleagues’ claim that the Dutch notification procedure for physician-assisted death is not used in most end-of-life decisions, “because patients are not regarded as incompetent to give consent”. However, we do agree that parents may endure lasting psychological effects as a result of the responsibility for an end-of-life decision for their child, although it is not clear to what extent psychological effects affect the decision-making process. Currently, we are examining parental opinions and feelings about medical decisions concerning the life and death of their child.

We believe that the widely endorsed need for medical professionals to discuss their increasing responsibilities towards the life and death of severely ill patients

is not done justice by Margaret White’s suggestion that without rigorous legal prosecution any sound practice is impossible.

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- 1 Howard PJ; Cole AP; Grassin M et al; White M. End-of-life decisions in Dutch medical practice. *Lancet* 1997; 350: 816–17.
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## Sex and examination results

SIR—A G Acheson (Sept 27, p 964)<sup>1</sup> reports that male medical students are at a disadvantage in medical examinations in UK. This is an important issue in terms of strategies in medical education. We studied the association between sex and the examination results in two Japanese national examinations: the national examination for medical practitioners which gives a licence of physician and the national bar examination which gives a licence of legal profession. The proportion of successful applicants in each examination was significantly higher among women than among men (national examination for physician: 93.5% *vs* 86.3%; national bar examination: 3.6% *vs* 2.7%).

I suppose that present-day female students are more diligent with regard to examination questions that have correct answers. However, it remains unknown whether sex has a role in solving problems for which there is not necessarily a correct answer, such as the questions physicians face in their daily clinical or research work.

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- 1 Acheson AG. Do male medical students face prejudice? *Lancet* 1977; 350: 964.

SIR—A G Acheson<sup>1</sup> and others<sup>2</sup> have shown that the gender and ethnic background of medical students affects their pass rates in some medical schools. In the Department of Child Health of the University of Queensland, where students do a 10-week posting in the final year, we have not found a significant difference in the male/female pass rates, but we have elicited other and interesting differences related to gender, age, and ethnic background.

Many of our medical students are from South-East Asia.

We have analysed the results of terminal examinations in the department for the four terms in each of the years 1993, 1994, and 1995—a total of 658 students. In each term examination there was a multiple-choice section, with 20 multiple true/false questions, each with four items (statements). Each statement could be answered true, false, or don’t know. We have calculated for each term the number of correct responses (true for a true statement, false for a false statement), wrong responses (true for a false statement and false for a true statement), and the number of don’t know responses. The numbers of responses were analysed with a method that sums the significance of the responses for each term to find the overall effect of gender, age, and mother tongue.

Some variables, for example, sex and first language English/non-English, were inherently binary. With each of the other variables, for example, age, number of correct responses, the median value was found for each of the 12 terms. For each term, we constructed two-by-two tables for each pair of variables by counting the number of responses on-and-above the median and the number below the median and putting these numbers in rows and columns. A modification of the Cochran test<sup>3</sup> was used to combine the results from the 12 terms into one value which gave the overall probability of the null hypothesis and the direction of the interaction. The inclusion of values on the median into the upper group has increased the expected number above the 50%, but this does not invalidate the results. For brevity, high means on-and-above the median, and low means below the median.

Compared with female students, male students had a trend towards fewer correct responses (50% men and high scores *vs* 56% women,  $p=0.053$ , significantly more wrong responses (60% men had high scores *vs* 49% women,  $p=0.003$ ), and significantly fewer don’t know responses (52% men had high scores *vs* 57% women,  $p=0.04$ ). Age had no significant effect on correct and don’t know responses, but older students had more wrong responses (older students had 62% high wrong responses *vs* 52% high wrong responses in younger students). The first language had no significant effect on correct and wrong responses, but those whose mother tongue was not English had fewer don’t know responses (56% of students with English as mother tongue had high don’t know responses *vs* 47% for those whose mother tongue

was not English,  $p=0.05$ ).

We suggest that willingness to admit ignorance rather than support a false statement is a desirable trait in medical graduates. If this examination finding is carried across into medical practice, does this make young female graduates better clinicians than their older male colleagues?

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- 1 Acheson AG. Do male medical students face prejudice. *Lancet* 1997; **350**: 964.
- 2 McManus IC, Richards P, Winder BC, Sproston KA. Final examination performance of medical students from ethnic minorities. *Med Educ* 1996; **30**: 195–200.
- 3 Dugdale AE. A simple method for analysing multifactorial data. *Am J Clin Nutrition* 1975; **28**: 788–92.

## Quality of essential drugs

SIR—I wish to confirm, given Ernst Lauridsen's disclaimer (Oct 11, p 1106)<sup>1</sup> about your Aug 30 editorial,<sup>2</sup> on quality control and essential drugs, that my concerns, as recounted in *Drugs Quarterly*,<sup>3</sup> relate only to events that occurred after September, 1990, when I assumed transient (and nominal) oversight of WHO's Drug Action Programme (DAP).

At that time, DAP advocated local manufacture throughout east Africa, despite evidence that many production facilities did not comply with good manufacturing practices. Overtures were also being made, I later found, to the International Trade Centre to set up the Market News Service (MNS) on bulk pharmaceutical materials. Subsequently, the staff member central to these activities was transferred to the International Trade Centre to promote the MNS within Africa, notwithstanding disciplinary charges against him including improper use of influence.

In 1994, a WHO Expert Committee, for which I was responsible, expressed serious concern that the MNS was "promoting outdated pharmaceutical specifications offered by unnamed sources under the WHO flag". Without reference to me, this criticism was deleted from the published report. I have since proposed in vain to the Director-General that regulators serving on this committee be invited to review the MNS. Instead, Jonathan Quick<sup>4</sup> shows that the Secretariat is in no mood to brook criticism from expert advisors.

But is his response convincing? Quick claims that the MNS "has never

served as a broker". Yet the International Trade Centre identifies itself as a "non-commercial broker" in the agreement with WHO; it emphasises that MNS is dependent "on good connections with traders and brokers", and it has expressed optimism that "links between buyers and sellers are starting to form". MNS is geared to trade interests, not to widespread dissemination of representative information on drug prices: commercial data on the availability of some 300 materials of undisclosed origin are mailed monthly to only a few hundred paying subscribers. Quick also "condemns the sale of outdated products". Yet in May, 1997, a third of MNS entries bore specifications of outdated editions of the British or United States *Pharmacopeia*. These editions have no status outside WHO which is now, apparently, determined to legitimise them explicitly to serve the needs of the MNS.

The result is that WHO is promoting life-saving drugs which have been in store, perhaps in uncontrolled premises, for up to 10 years. But WHO has not explained—even to its own governing bodies—on what basis brokers are selected; how it establishes that the materials they trade have been made and stored in compliance with good manufacturing practices; how possible degradation, contamination, adulteration, mixing of multiple lots, and relabelling have been excluded; and when identity and specification were last verified. Governments should take careful note. It is they who will foot the bill should tragedy supervene.

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- 1 Lauridsen E. Quality control of essential drugs. *Lancet* 1997; **350**: 1106.
- 2 Editorial. Quality control and essential drugs. *Lancet* 1997; **350**: 601.
- 3 Dunne J. Cavaeat emptor. *Drugs Quarterly* 1997; **1**: 39–41.
- 4 Quick J. Quality control of essential drugs. *Lancet* 1997; **350**: 1106.

## Terathanasia or teratothanasia?

SIR—In the discussion about folic acid, birth defects, and miscarriage (Nov 1, p 1322–24),<sup>1</sup> the use of terathanasia to describe the death of an embryo or fetus with malformation is wrong. Apparently, this term was introduced by Warkany in 1978.<sup>2</sup> However, this composition of the Greek words *thanatos* meaning death, and *teras*, meaning monster, does not

follow basic grammatical rules.

What is meant by the term is the death of an abnormal infant, which would need the genitive: Teratothanasia. Terathanasia would mean a *terrific death*, and not *the death of something terrifying*. Ironically, the correct use of *teras* in composite words is shown in the name of the journal in which Warkany first published his article: *Teratology*, which means the word or science (logos) of abnormal infants or monsters. By analogy, the development of a physically or mentally disabled infant is described by the term teratogenesis and drugs that lead to such a development are teratogenic. On the other hand, in our daily use we talk about *terahertz* or *terabytes*, which mean a *terrific amount* of hertz or bytes.

We were also impressed to see that in their contribution, John Burn and Nicholas Fisk did not use this term, but merely spoke of miscarriages, avoiding by that to qualify a disabled fetus as a *teras*.

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- 1 Hall JG, Burn J, Fisk NM, Schorah CJ, Smithells RW, Seller MJ, Hook EB. Terathanasia, folic acid, and birth defects. *Lancet* 1997; **350**: 1322–24.
- 2 Warkany J. Terathanasia. *Teratology* 1978; **17**: 187–92.

## DEPARTMENT OF ERROR

*Antioxidants and ischaemic heart disease*—In the third letter of the group under this title (Aug 30, p 667–68), the second author's name should have been L. Iuliano.

*Combination therapies for HIV infection and genomic drug resistance*—In this commentary by David Katzenstein (Oct 4, p 970) the missing references were:

- 6 The Delta coordinating committee. Delta: a randomized double blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996; **348**: 283–89.
- 7 Shafer RW, Iversen AKN, Winters MA, Aguiniga E, Katzenstein DA, Merigan TC, and the AIDS Clinical Trials Group 143 Virology Team. Drug resistance and heterogeneous long-term virologic responses of human immunodeficiency virus type 1-infected subjects to zidovudine and didanosine combination therapy. *J Infect Dis* 1995; **172**: 70–78.
- 8 Jody Lawrence, Shapiro J, Pesano R, et al. Clinical and genotypic resistance patterns of sequential therapy with nevirapine followed by didanosine in saquinavir/reverse transcriptase inhibitor/experienced patients. Abstract 64. Presented at the International Workshop on HIV Drug Resistance, Treatment strategies and eradication. 25–28 June, 1997. St Petersburg, Florida.