# CORRESPONDENCE

## Interpretation of Thrombosis Prevention Trial

Sir—In the report of the Thrombosis Prevention Trial (Jan 24, p 233)[1] there is no multivariate analysis of the recognised aetiological factors for ischaemic heart disease (IHD), the most important of which is smoking. The differential effects of aspirin and/or warfarin in smokers (41% of the study population) *vs* non-smokers should have been reported since, apart from being an independent prognostic variable, smoking may interfere with the therapeutic effects of trial drugs by increasing platelet aggregability. Were smokers advised to quit? How many succeeded—and how many were perhaps inhibited from quitting because they thought they were being offered an antidote? Was it made clear to the smokers that the trial drug(s) were neither an antidote to the detrimental effects of smoking nor an alternative to quitting.

The ultimate aim is to reduce deaths from IHD. In his commentary on this trial (Jan 24, p 227) Freek Verheugt[2] mentions "a change of lifestyle" but smoking is not a lifestyle, it is a very powerful addiction. The tobacco industry knows that it does not have to worry about quitters. For its survival, it needs to replenish 3 million dead customers every year with new recruits, inevitably children and adolescents.[3] With legal barriers ludicrously absent, the industry has established nicotine addiction on such a large scale that it is renamed as "lifestyle"—and then the concept of personal choice is thrown in, effectively rationalising the addiction and removing all blame from the industry.

Being a non-smoker has the highest value-for-effort risk-reducing ability, and taking aspirin will never reduce the IHD risk of a smoker to that of a non-smoker. Smoking increases the risk of IHD five-fold[4] and this effect is cumulative and irreversible.[5] If the risk is 100 for a smoker, it would be 80 for a smoker taking aspirin but only 20–30 for a non-smoker. We must remember that the abolition of the tobacco industry will pay the highest dividends for the health of the nation.

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1 The Medical Research Council's General Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; **351:** 227–28.
2 Verheugt FWA. Aspirin, the poor man's statin? *Lancet* 1998; **351:** 227–28.
3 Josefson D. Tobacco company targeted marketing campaign at teenagers. *BMJ* 1998; **316:** 329.
4 Parish S, Collins R, Peto R, et al. Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14000 cases and 32 000 controls in the United Kingdom. *BMJ* 1995; **311:** 471–77.
5 Howard G, Wagenknecht LE, Burke GL, et al, for the ARIC Investigators. Cigarette smoking and progression of atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. *JAMA* 1998; **279:** 119–24.

Sir—The Thrombosis Prevention Trial[1] provides evidence that primary prevention of ischaemic heart disease (IHD) is possible by treating high-risk men with low-intensity oral anticoagulation with warfarin and low-dose aspirin. However, we have reservations about how the results of this trial can be applied to individuals.

For the primary endpoint, prevention of IHD, treatment with warfarin plus aspirin led to a proportional rate reduction of 34% when compared with placebo Assuming that there were no serious differences between these groups in the distribution of follow-up times, this translates to an annual NNT of 221 (NNT=number of patients who need to be treated for one year to prevent one episode of IHD). The number of side-effects from warfarin plus aspirin also varied, with corresponding annual NNHs (numbers needed to treat for one year to produce a harmful event) of 1019 (major), 174 (intermediate), and 37 (minor), again assuming similar follow-up profiles. For the individual, the acceptability of warfarin/aspirin is critically dependent on the value he or she places on the benefits of preventing an IHD event compared with the risk of side-effects of treatment. The likelihood of being helped is 4·6 times greater if a person is unconcerned about intermediate and minor side-effects and 1·5 times greater if unconcerned about just minor side-effects. Conversely, the likelihood of being harmed is 7·5 times more likely if a person is concerned about any (major, intermediate, or minor) side-effect.

Furthermore, without knowing whether the relative benefits of treatment are constant across strata of cardiovascular risk, it is very difficult to estimate for an individual patient the likely risk/benefit ratio for warfarin/aspirin. As others have demonstrated for cholesterol-lowering drugs, absolute benefit is critically dependent on the baseline risk of individual patients.[2-4] Given that the side-effects of treatment of warfarin/aspirin are substantial, knowledge of baseline risk is critical for informed decision making with individual patients.

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1 The Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; **351:** 233–41.
2 Scandinavian Simvastatin Survival Study

Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study. *Lancet* 1995; **345:** 1274–75.
3 Vandenbroucke JP, Westendorp RGJ. Are the effects of cholesterol lowering drugs always equal? *Lancet* 1996; **347:** 1267–68.
4 Davey Smith G, Song J, Sheldon T. Cholesterol lowering and mortality: the importance of considering initial level of risk. *BMJ* 1993; **306:** 1367–73.

Sir—The Thrombosis Prevention Trial[1] shows that low-intensity oral anticoagulant therapy protects against ischaemic heart disease (IHD), reducing mortality in high-risk men. Low-dose aspirin was also effective, but only against non-fatal events. Thus both treatments had an independent effect in primary prevention and, presumably, protected different types of high-risk men. Primary prevention implies the treatment of very large numbers, even if at high risk, to avoid a small number of events; indeed, in this trial, 1000 men were treated with either warfarin or aspirin to avoid 6 events. Both treatments carry a small but real chance of bleeding. Progress in primary prevention could be achieved through the identification of subgroups who might differentially benefit from either warfarin or aspirin.

Recent work on genetic determinants of the risk of IHD may help here. Indeed, it has been suggested that some genetic variants of coagulation factor VII protect against myocardial infarction.[2] These variants were associated with lower plasma levels of factor VII in the same range as those obtained pharmacologically with low-dose warfarin in the Thrombosis Prevention Trial. The "protective" alleles were found in almost one-third of the Italian population tested (21% and 36% for each variant); these naturally protected individuals, if carrying other risk factors, could preferentially benefit from treatments different from warfarin. The frequency of such genetic variants in Italians was significantly higher than in northern European populations,[2,3] contributing to the decreasing north-south gradient of myocardial infarction incidence in Europe. Low-intensity oral anticoagulation may be less effective than other therapies (eg, low-dose aspirin) in primary prevention among high-risk individuals from Italy or other southern European populations, who are more likely than British men to have a "naturally" lower potential for clotting.

Genotyping may also help to define the responders to treatment, as with cholesteryl-ester transfer protein gene and statins.[4] Further studies are needed to identify polymorphic variants in candidate genes for IHD that are related to the risk of the disease and/or the efficacy of antithrombotic therapy. In the planning of future primary prevention trials the inclusion of genotyping might contribute to the treating with greater efficacy of a smaller population. Genotyping large numbers of people is expensive, though technically easy; its results are not subject, as biochemical tests are, to day-to-day variability and environmental modulation. The cost-effectiveness of genotyping could be judged by carefully considering the possibility that future trials could be smaller.

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1 The Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; **351:** 233–41.
2 Iacoviello L, Di Castelnuovo A, De Knijff P, et al. Polymorphism in the coagulation factor VII gene as an inherited protective factor for myocardial infarction. *N Engl J Med* 1998; **338:** 79–85.
3 Bernardi F, Arcieri P, Chiarotti F, et al. Contribution of factor VII genotype to activated FVII levels: differences in genotype frequencies between Northern and Southern European populations. *Arterioscl Thromb Vasc Biol* 1997; **17:** 2548–53.
4 Kuivenhoven JA, Jukema JW, Zwinderman AH, et al. The role of a common variant of cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. *N Engl J Med* 1998; **338:** 86–93.

Sir—Although evidence from the Thrombosis Prevention Trial[1] supports the proposition that, for high-risk men, primary prevention of coronary thrombosis is better with prescription of warfarin plus aspirin than with either agent alone. However, the claim is not necessarily valid that "simultaneous modification of platelet activity and of fibrin formation may be more effective than modifying either process alone" in the context of secondary prevention in patients of either sex, with a target INR of 2·5–4·8.[2,3] Warfarin, in this context,[2,3] currently occupies an unassailable position in the hierarchy of antithrombotic therapies because, unlike aspirin, whose evidence base is metaanalysis,[4] its justification is founded on well-powered prospective studies, yielding numbers needed to treat to prevent one myocardial infarction ranging from 42 to 45, as opposed to the NNT of 83 emerging from the comparison with aspirin.[5] The way forward is to explore the risk/benefit profile of INR intensities of the order of 2–3, so that patients with coexisting atrial fibrillation can derive antithrombotic benefits superior to those conferred by aspirin for either indication without incurring risks such as haemorrhagic stroke and gastroduodenopathy inherent in the coprescription of this agent.

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1 The Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; **351:** 233–41.
2 Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1990; **323:** 147–52.
3 Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. *Lancet* 1994; **343:** 499–503.
4 Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106.
5 Miller DB. Secondary prevention for ischemic heart disease: relative numbers needed to treat with different therapies. *Arch Intern Med* 1997; **157:** 2045–52.

Sir—The Thrombosis Prevention Trial group[1] rightly states that the results give limited, if any, encouragement for the general use of aspirin in primary prevention regardless of risk, which is in marked contrast with the accompanying commentary[2] which suggests that aspirin was effective. 600 (3·81%) patients of 15 734 randomised to aspirin have died in primary prevention studies compared with 639 (4·53%) of 14 106 randomised to control (not significantly different).[2] The risk of major bleeding has been doubled by aspirin. Since myocardial infarction is a condition associated with a 30-day mortality of about 50% and since half or more deaths in these studies were cardiovascular the lack of a mortality difference suggests that the effects of aspirin on non-fatal events in primary prevention studies may only be cosmetic.[3] Drugs that reduce only non-fatal myocardial infarction may achieve this by masking symptoms or increasing the risk of sudden death, both possibilities with aspirin.

It is difficult to accept the conclusion that "Combined treatment with warfarin and aspirin is more effective in

the reduction of IHD than either agent on its own." The combination was the only regimen to show a significant reduction in the primary endpoint compared with placebo but the effects of the combination on the primary endpoint did not appear significantly greater than those of either agent used alone, and for several other outcomes, including all-cause mortality, the results seem worse. Moreover, a substantial increase in major and moderate bleeds, including haemorrhagic stroke, was observed with the combination compared with either agent used alone. These data add to those from several other trials that suggest that monotherapy, with aspirin or warfarin, is superior or at least not inferior to combination therapy. The Thrombosis Prevention Trial suggests that the safest and most effective regimen for reducing mortality may be warfarin alone and that low and moderate intensity anticoagulation now need to be compared. How to monitor treatment in an acceptable and cost-effective manner remains the major barrier to wider use.

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1 The Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; **351:** 233–41.
2 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106.
3 Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas A, Pajak A. Myocardial infarction and coronary deaths in the World Health Organisation MONICA project. *Circulation* 1994; **90:** 538–612.

Sir—The report of the Thrombosis Prevention Trial[1] implied that our letter in *The Lancet*[2] had asserted that low-intensity anticoagulation had been proved to be of no clinical benefit in the prevention of arterial thrombosis. That is a significant misinterpretation of the issues we raised. While we acknowledged the absence of evidence for a benefit of fixed or adjusted low-dose warfarin in the then published trials, the main point of our letter was to propose an explanation for the apparent failure of the fixed low-dose warfarin regimen, used in the CARS trial to reduce the risk of thrombosis.[3] We were not suggesting that the result of the CARS trial was due to the use of low-dose warfarin per se but that it was related to the minor prolongation of the international normalised ratio (≤1·2) seen in patients in that trial and that this ratio may have been too low.[4] A corollary of this explanation is that low-dose warfarin with an INR>1·2 could be an effective treatment for the prevention of arterial thrombosis, a proposition which now appears to be supported by the finding in the Thrombosis Prevention Trial that adjustment of the warfarin dose to produce a mean INR of 1·47 was accompanied by a significant reduction in death due to ischaemic heart disease

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1 The Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; **351:** 233–41.
2 Peverill RE, Harper RW, Smolich JJ. CARS trial: warfarin and thrombin generation. *Lancet* 1998; **350:** 1177–78.
3 Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomized double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. *Lancet* 1997; **350:** 389–96.
4 Feinberg WM, Cornell ES, Nightingale SD, et al. Relationship between prothrombin activation fragment F1.2 and international normalized ratio in patients with atrial fibrillation. *Stroke* 1997; **28:** 1101–06.

Sir—The Thrombosis Prevention Trial[1] presents the first clearcut evidence for benefit from low-dose aspirin in the primary prevention of cardiovascular disease. However, the potential relevance of the formulation of aspirin used was barely discussed.

The coincident acetylation of platelets and inhibition of vascular prostacyclin is a common feature of clinically-effective doses of conventional, immediate release aspirin. The development of the 75 mg controlled-release preparation used in this trial was based on the discovery that acetylation of platelets in the presystemic circulation offered a potential approach to avoiding inhibition of prostacyclin formation in the systemic vasculature. Taking advantage of the high first-pass metabolism of aspirin to salicylate (a weak and readily reversible inhibitor of cyclooxygenase), we studied a range of doses and rates of aspirin delivery to optimise selective presystemic platelet acetylation.[2] A controlled release 75 mg preparation was as efficient in inhibiting serum thromboxane $B_2$ as the same dose of an immediate-release tablet but, unlike the conventional tablet, it did not depress the bradykinin-stimulated increment in excretion of a major urinary prostacyclin metabolite, an index of stimulated systemic prostacyclin biosynthesis.[3]

Given recent evidence from mice deficient in the receptor of prostacyclin[4] —suggesting that formation of this platelet inhibitory, vasodilator eicosanoid which is increased in human syndromes of platelet activation,[5] ameliorates the response to prothrombotic stimuli in vivo—it is certainly possible that a controlled-release aspirin differs from conventional formulations with respect to the prevention of morbidity from vascular occlusive syndromes, such as those recorded in the Thrombosis Prevention Trial. Furthermore, the gastrointestinal epithelium would be exposed to much lower local concentrations of aspirin compared with immediate-release formulations. These observations caution against extending the results of this study to conventional formulations of aspirin.

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1 The Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; **351:** 233–41.
2 Charman W, Charman SA, et al. Biopharmaceutic characterization of a low dose (75 mg) controlled-release aspirin formulation in man. *Br J Clin Pharmacol* 1993; **36:** 470–73.
3 Clarke RJ, Price P, Mayo G, FitzGerald GA. Preservation of systemic prostacyclin synthesis by controlled release, low dose aspirin: selectivity for thromboxane $A_2$. *N Engl J Med* 1991; **325:** 1137–41.
4 Murata T, Ushikubi F, Mtsuoka T, et al. Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. *Nature* 1997; **388:** 678–82.
5 FitzGerald DJ, Catella F, FitGerald GA. Platelet activation in unstable coronary disease. *N Engl J Med* 1986; **315:** 983–89.

### *Authors' reply*

Sir—We share Jayant Vaidya's concern about smoking. However, pharmacological intervention in those at increased risk has to be considered for those unable to modify their lifestyles. Smoking did not confound the results because randomisation ensured that its effects were all the same in all four groups. Men were encouraged to stop smoking (and were advised on other prudent living measures) and there was no evidence that the many smokers who wanted to stop

relied on trial treatment instead. During the first three years of participation, the proportion of smokers fell from 41% to 33%. In deriving their NNH (treat to harm) figure for major bleeding, Tom Fahey and Tim Peters appear to assume that the non-significant difference between combined warfarin plus aspirin treatment and placebo is real and precise, whereas it is at least subject to a very wide confidence interval because of the, fortunately, small numbers. We pointed out that decisions about treatment involve considerations other than potential benefits. We will be reporting on treatment effects in the subgroups suggested by Vaidya and by Fahey and Peters, with the qualifications necessary for analyses of this sort.

We agree with the emphasis Licia Iacoviello and Maria Benedetta Donati place on improving the definition of risk and thus on reducing the numbers requiring treatment. Meanwhile, if coronary deaths are to be reduced, the high case fatality of first major attacks and the difficulty of predicting which will be fatal inevitably mean that in primary prevention many more people must be treated than would be the case in a setting of secondary prevention.

O M P Jolobe is correct in drawing attention to the clear value of anticoagulant therapy in secondary prevention but the evidence now available from all the clinical settings in which the combination of platelet-active and fibrin-modifying agents has been used leaves little doubt that it is more effective than either approach on its own.

We agree with John Cleland and Ian Ford that further thought should be given to the use of low-intensity anticoagulation with warfarin alone, not only because of its potential value but also because traditional (indeed, almost knee-jerk) objections to warfarin need to be reconsidered in the new context of low-intensity treatment. There were 18 sudden coronary deaths in those allocated to aspirin compared with 11 in the placebo group (main effect). (Corresponding numbers for warfarin were 16 and 22.) In the US Physicians Study there were 22 sudden deaths in the aspirin group and 12 in the placebo group.[1] At the same time, other studies suggest that aspirin may attenuate the presentation of severity of cardiac ischaemia.[2,3]

Roger Peverill and his colleagues agree that the anticoagulant regimen we used appears effective. The CARS trial[4] does add to evidence suggesting that minor prolongation of INR with both "fixed and adjusted low-dose warfarin" does not reduce the risk of thrombosis but, as they also note, the INR of 1·47 we achieved, hitherto also considered low, is more than the 1·2 to which they refer.

We used the controlled-release aspirin on the basis of the thromboxane inhibition/prostacyclin sparing hypothesis that Garret FitzGerald and William Charman describe. The benefit it conferred is similar to that observed with considerably higher doses in the overview of two other primary prevention trials.[5] The explanation of any advantage in reducing the risk of bleeding is just as likely to be the aspirin dose as its formulation. Perhaps our results raise some doubts as to the validity of the thromboxane/prostacyclin hypothesis, at least in clinical terms.

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1 Steering Committee of the Physicians Study Research Group. Final report on the aspirin component of the ongoing physicians study. *N Engl J Med* 1989; **321:** 129–35.

2 Garcia-Dorado D, Théroux P, Tornos P, et al. Previous aspirin use may attenuate the severity of the manifestation of acute ischemic syndromes. *Circulation* 1995; **92:** 1743–48.

3 Col NF, Yarzebski J, Gore JM, Alpert JS, Goldberg RJ. Does aspirin consumption affect the presentation of severity of acute myocardial infarction? *Arch Intern Med* 1995; **155:** 1386–89.

4 Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. *Lancet* 1997; **350:** 389–96.

5 Hennekens CH, Burning JE, Sandercock P, Collins R, Peto R. Aspirin and other antiplatelet agents in the secondary and primary prevention of cardiovascular disease. *Circulation* 1989; **80:** 749–56.

## Early amniocentesis for biochemical genetic prenatal diagnosis

Sir—Prenatal diagnosis of biochemical genetic diseases was initially done by mid-trimester amniocentesis from about 15 weeks of gestational. This approach was largely superceded by chorionic villus testing which offers the advantage, for most disorders, of assays of direct tissue and cultured cells with results available before 15 weeks of gestation. The Canadian Early and Mid-Trimester Amniocentesis Trial (CEMAT) Group (Jan 24, p 242)[1] assessed amniocentesis at 11 to 13 weeks of gestation. However, the feasibility of biochemical genetic testing on samples from early amniocentesis has not been assessed.

We obtained 45 cell lines from the CEMAT group after cytogenetic analysis was complete. We monitored further culture to assess the time required to obtain about 10 million cells, the best medium for the successful continuation of culture and the cell types that grew. Harvested cells were assayed by standard techniques for midtrimester samples to establish normal values for 13 lysosomal enzymes.

All cell cultures were initiated in Amniomax (Gibco BRL, Burlington, Canada) and the effect of switching to a medium containing 20% fetal calf serum with minimum essential medium (aMEM, Gibco BRL) was assessed by trypsinising pairs of T25 flasks into Amniomax and aMEM containing 20% fetal calf serum and comparing the growth rates; no difference in growth rates was seen.

T25 flasks cultured from an initial sample of about 0·5 mL amniotic fluid (total sample volume for early amniocentesis in our centre is usually 8–11 mL) were grown in aMEN plus 20% fetal calf serum. We obtained sufficient cells after 3–4 weeks to provide a more-or-less confluent T75 flask from each initial T25 flask. Three cell lines were contaminated after removal of antibiotics (present in the initial Amniomax medium) and three cell lines showed poor growth and were discarded. No extraordinary measures were taken to stimulate slow-growing cells or to treat potentially contaminated cells with antibiotics. The early amniocentesis cells had similar morphology to midtrimester amniocentesis cells and could be classified as predominantly fibroblastic or epithelial or mixed cultures. Early amniocentesis cell lines (11–13 weeks of gestation) were mostly epithelial and growth rates were a little faster than for midtrimester cells, which may be because the initial cultures were started in Amniomax.

Cells from each confluent T75 flask were pelleted and stored at –70°C before assay of 13 cellular lysosomal enzymes. Iduronate sulphatase was measured in early amniocentesis amniotic fluid (frozen to –20°C before assay). The enzymes tested in amniotic fluid cells were α-iduronidase, iduronate sulphatase, heparin sulphamidase, α-N-acetyl glucosaminidase, β-glucuronidase, aryl sulphatase A, galactocerebrosidase, agalactosidase, β-galactosidase, α-glucosidase, β-glucosidase, sphingomyelinase, and acid lipase. We did not observe any significant differences in enzyme activity between cells harvested at 11–13 weeks of gestation and those harvested at 15–16 weeks of gestation.*

Our study shows that sufficient cells from biochemical lysosomal prenatal diagnosis can be obtained from a small

*Detailed findings from the authors or *The Lancet*, on request.

sample volume within 1 month of cell culture after early amniocentesis. Culture in Amniomax is not necessary after the initial cultures are established. In the small number of cell lines that we investigated, no gestational age correlation was found with lysosomal-enzyme-specific activity at 11–13 weeks of gestation. No correlation of cell type with enzyme-specific activity was seen except for aryl-sulphatase-A activities in which epithelial cells had almost double the mean value of fibroblastic or mixed cultures. We were unable to detect measurable amniotic-fluid activity of iduronate sulphatase in early amniocentesis fluid to provide a secondary test for prenatal diagnosis of Hunter syndrome. With that single exception, we believe that for biochemical analysis of lysosomal enzymes early amniocentesis at 11–13 weeks of gestation is similar to results obtained by amniocentesis at midtrimester.

We thank the Cytogenetics Laboratory at Vancouver Hospital Health Sciences Centre for providing early amniocentesis cell cultures.

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1 The Canadian Early and Mid-Trimester Amniocentesis Trial (CEMAT) Group. Randomised trial to assess safety and fetal outcome of early and midtrimester amniocentesis. *Lancet* 1998; **351:** 242–47.

## Disease burden in sub-Saharan Africa

Sir—Richard Cooper (Jan 17, p 208)[1] concludes that the inaccuracies involved in extrapolating data from South Africa to sub-Saharan Africa weaken the global burden of disease study (GBD) so that the results should not be used in the region. Relevance of data is as important as accuracy in programme planning, and depends on an understanding of disease processes, including the role of risk factors. Calculation of the burden attributable to different risk factors based on inappropriate models of disease causation will result in misdirected disease-prevention strategies.

The calculation in the GBD of the burden due to hypertension in sub-Saharan African populations is an example of such misdirection. Exposure to hypertension in this region apparently causes cardiac-ventricular failure but is rarely associated with the cardiac ischaemia seen in other countries.[2,3] In the GBD, many cardiovascular deaths coded under garbage (*sic*) codes, including heart failure, were recoded as due to ischaemic heart disease for the purpose of analysis.[4] It is more likely that those deaths originally coded as heart failure were secondary to hypertensive hypertrophy and not related to ischaemia. By denying its role in cardiac mortality, the burden due to hypertension in sub-Saharan Africa could have been underestimated. (The details of the pathology attributed to hypertension when determining the morbidity it causes are not available.)

Assessment of the impact of hypertension in sub-Saharan Africa is not only a matter of knowing which diseases it relates to. Hypertension causes cerebrovascular disease, renal failure, and visual impairment, as well as myocardial hypertrophy, and all these conditions can have alternative causes. If limited technology means that investigation of these conditions is by clinical signs and symptoms alone, then it is difficult to accurately determine the proportion of each that is due to hypertension.

The GBD was a first step in predicting the future of health, and it was hoped that the methods used and assumptions made would be challenged and debated.[5] Research at dedicated and representative sites is needed to clarify which of the complications due to hypertension should be measured to determine the disease burden it causes. Then the GBD will have acted as a catalyst to further understand health needs in sub-Saharan Africa.

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1 Cooper RS, Osotimehin B, Kaufman JS, Forrester T. Disease burden in sub-Saharan Africa: what should we conclude in the absence of data? *Lancet* 1998; **351:** 208–10.
2 Seedat YK, Mayet FG, Latiff GH, Joubert G. Study of risk factors leading to coronary heart disease in urban Zulus. *J Hum Hypertens* 1993; **7:** 529–32.
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5 Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; **349:** 1498–504.

Sir—We agree with Richard Cooper and colleagues[1] that the model-based methods adopted by the Global Burden of Disease study are blighted by their necessary assumptions. These are well described by the original authors whose estimates of adult mortality are often based on small-scale infant mortality surveys combined with life-expectancy data from the region. In the absence of other information, it is appropriate and helpful to use such model-based estimates, but these methods are not effective monitoring devices and their limitations will continue in the absence of quality data collection on adult health in developing countries.

However, we take issue with Cooper's assertion that "there is little quantitative data about the health of adults in sub-Saharan Africa . . . [and] nothing which meets the standards of public-health science acceptable in developed countries". In 1991, the recognition of the need for such data on adult health in Tanzania initiated the Adult Mortality and Mortality Project (AMMP), a collaboration between the University of Newcastle upon Tyne, the Tanzanian Ministry of Health, and the UK Government's Department for International Development. The continued monitoring of deaths from all causes in a population of more than 300 000 people from three different areas of Tanzania has given estimates of cause-specific and all-cause mortality among adults.[2] During the first 5 years of the project, we have recorded the deaths of more than 22 000 adults.[3] These data have allowed us to estimate the relative burden of major causes of death for three large populations in Tanzania, including statistics on the use of health care by people before death. This information is of direct use to public-health planners locally, and data from this work have already been used by other governments in East Africa.

Results of our work include the importance of infectious diseases, particularly AIDS, malaria, tuberculosis, and gastroenteritis, which account for most premature deaths among adults aged 15–59 years. There are also differences in the burden of disease between rural and urban areas. 90% of women who die during their reproductive years die from causes not related to childbirth. The importance of non-communicable diseases has also been noted, accounting for 15–30% of adult deaths. In Tanzania, age-specific death rates from diabetes seem to be similar[4] and those from stroke substantially higher[3] than in North American or European populations.[3] In addition to these data, population-

based studies of the prevalence of diabetes, hypertension, and other cardiovascular risk factors have been published from Tanzania.[5]

The future of adult-health surveillance in Tanzania is to integrate data collection on adult health through a national sentinel district system to inform local health-service planners. Coordination of data collection with health-care planning in this fashion is true public health in action and will allow rational health planning, which will be the envy of many so-called developed countries. We agree with Cooper that more information is needed for sub-Saharan Africa, but data are beginning to emerge and should not be ignored.

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## Hepatitis C

Sir—Adrian Di Bisceglie (Jan 31, p 351)[1] points out that some extrahepatic manifestations have been reported in hepatitis C virus (HCV) infection. We agree that only a few associations have become established and many may be only coincidental. I believe, however, that HCV infection should be viewed as a generalised disease, rather than an isolated hepatic disorder.

Di Bisceglie does not mention the possible association between HCV and diabetes, polyarteritis nodosa, or thrombocytopenia. A high prevalence of HCV infection has been detected in diabetic patients, and the absence of any specific epidemiological factor for HCV infection among diabetics suggests that HCV could have a direct role in the development of diabetes.[2] I also believe that patients with autoimmune thrombocytopenia should be tested for HCV infection.[3] A high prevalence of HCV markers (10–20%) has been reported in several series of patients with autoimmune thrombocytopenic purpura, and thrombocytopeania is frequently seen in patients with HCV infection and correlates to the presence of antiphospholipid antibodies.[2] The presence of viral genome in platelets suggests that HCV is directly involved in the pathogenesis of the thrombocytopenia.[2]

We assume that interferon treatment for chronic hepatitis C need not be systematically avoided just because of thrombocytopenia, and could be useful in thrombocytopenia associated with HCV infection.[4] A high prevalence of HCV markers (5%–20%) has been reported in several series of patients with polyarteritis nodosa, suggesting that HCV, as does hepatitis B virus infection, may occasionally cause this disorder.[2] As a final point, I agree that the management of the patients with extrahepatic manifestations related to HCV infection is difficult because the response to interferon is usually transient. However, ribavirine can be used in some patients with symptomatic cryoglobulinaemia associated with chronic C hepatitis, who are intolerant or non-responders to interferon.[5]

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Sir—Readers of Adrian Di Bisceglie's seminar[1] on hepatitis C might be falsely reassured by the suggestion that iatrogenic transmission of HCV results only from the use of non-disposable needles (for example, in Egypt) or from traditional healing practices.

Although Di Bisceglie mentions one report of HCV transmission from an infected surgeon, he makes no mention of the thousands of haemodialysed patients who become infected with HCV every year. In the era of virtually safe transfusions, it is troubling that annual rates of HCV seroconversion frequently exceed 3% (up to 15%) in patients who undergo haemodialysis.[2] Nosocomial transmission—unequivocally shown by molecular virology—results mainly from poor hand hygiene by staff members and the sharing of objects between patients.[3] Fortunately, careful adoption of universal precautions, as advocated by the Centers for Disease Control and Prevention (Atlanta, USA) should prevent HCV transmission as shown by a zero frequency of HCV seroconversion in the past 18 months of a large prospective study in patients undergoing haemodialysis.[4]

Nosocomial transmission has also been reported in other hospital settings, such as haematology wards and even, more recently, during colonoscopy.[5] The prevention of nosocomial transmission of all bloodborne pathogens including HCV remains a major challenge for all health-care workers.

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Sir—In his description of hepatitis C related extrahepatic manifestations, Adrian Di Bisceglie[1] does not include lichen planus. Since the development of reliable diagnostic assays for HCV infection in the early 1990s, several studies have shown an association between hepatitis C and lichen ruber planus.[2,3]

The reported prevalence of anti-HCV in patients with lichen planus shows wide geographical variations. The high prevalence of HCV RNA in patients with lichen planus might suggest an aetiological role of HCV in the pathogenesis of the disease, but no

convincing correlation has been reported between genotype/subtype and the presence of lichen planus. Neoplastic transformation of lichen planus is rare but there is some evidence that HCV-associated oral lichen planus may have a clinically significant premalignant potential.[2,4] Moreover, Nagao and co-workers[2] found a high incidence of oral precancerous lesions in a hyperendemic area of HCV infection.

In my clinical practice, a patient presented with squamous-cell carcinoma of the tongue in HCV-associated erosive oral lichen planus. The patient, a 65-year-old Sardinian man, had chronic hepatitis C with portal vein thrombosis, large gastro-oesophageal varices, and severe coagulopathy. He was positive for antinuclear antibodies and speckled immunofluorescent staining pattern for IgG (1/1280) and IgM (1/320) were detected by immunofluorescence on HEp-2 cells, as well as IgG to centromere. Because of the high operative risk, we carried out lesional laser $CO_2$ excision. The histopathological evaluation revealed a well excised squamous-cell carcinoma of the tongue, and after 6 months of follow-up no oral neoplastic recurrence has occurred. Unfortunately, the patient has now developed lichen planus of the penis.

The precise cause of this association between lichen planus and hepatitis C is not known. Host factors induced by HCV infection could be more important than viral factors in the pathogenesis of HCV-related lichen planus. Immune dysregulation in chronic HCV infection might have a major role in lichen planus development, since the rate for antinuclear-antibody positivity is significantly higher in patients with chronic hepatitis C and lichen planus than in patients with HCV infection alone, and some association to HLA-DRB1*0101 has been showed in a Sardinian population.[3,5] I advise the periodic examination of the oral cavity in patients with HCV and monitoring of patients with oral lichen planus for malignant transformation once every year.

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1 Di Bisceglie AM. Hepatitis C. *Lancet* 1998; **351:** 351–55.
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## Antiepileptic drugs in developing countries

Sir—Deb Pal and colleagues (Jan 3, p 19)[1] conclude that phenobarbital is an acceptable first-line antiepileptic drug for children in developing countries, since it did not differ significantly from phenytoin in rural India. However, children treated with phenytoin are not an appropraite comparison group.

Phenytoin is a bad choice as a first-line antiepileptic drug for developing countries: it has zero-order kinetics in countries where plasma concentrations of antiepileptic drugs are not routinely available; has low efficacy against and potential exacerbation of myoclonic and absence seizures; and has adverse interaction with major antiparasitic drugs such as praziquantel.[2] Moreover, it causes gingival hypertrophy in countries where dental caries and associated medical and nutritional disorders are public-health concerns. Thus, Pal and co-workers' statement that phenobarbital is equal to phenytoin in India is a weak endorsement of phenobarbital.

Pal's study also has several sources of bias. Children with absence, myoclonic, and multiple seizure types were randomly allocated phenytoin or phenobarbital but were not included in the analysis. (Children with absence and myoclonic seizures would not have a favourable response to either drug.) The investigators were not able to control for compliance or the use of various alternative therapies.

Connor's parent rating scale and the preschool behaviour screening questionnaire data were obtained by parents who were aware of treatment allocation. Results of these subjective outcome measures should be interpreted in light of the fact that Pal and colleagues' findings conflict with major studies from developed countries that document the cognitive side-effects of phenobarbital.[3–5]

Clinical trials of antiepileptic drugs should be conducted to address the needs of developing countries. The best antiepileptic drug for developing countries would be a broad-spectrum drug that could be used where there are no neurologists or electroencephalographic facilities, does not reduce bioavailability of antiparasitic drugs, has a good pharmacokinetic profile in people with malnutrition and parasitic diseases, and has fewer cognitive and addictive side-effects than phenobarbital. If a broad-spectrum antiepileptic is proven better as first-line treatment than phenobarbital, on the basis of clinical trials in developing countries, then it should be bought in large quantities at discount and distributed to epilepsy-treatment programmes in developing countries.

Although some people argue that the distribution programmes should be developed first, we believe that the question of the best therapy should be addressed first. The choice of treatment may affect the characteristics of the distribution programmes in various developing countries. The epilepsy and public-health communities can do better than phenobarbital or phenytoin for the world's 34 million people with epilepsy who live in the developing world.

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### *Authors' reply*

Sir—Edwin Trevathan and colleagues dispute our conclusions about the acceptability of phenobarbital for childhood epilepsy in rural India. They believe phenytoin to be an

unsuitable comparison antiepileptic drug. We chose phenytoin because it is the only other first-line antiepileptic of similar cost to phenobarbital and has no demonstrable difference to other antiepileptic drugs in efficacy for partial and generalised tonic-clonic seizures. In real terms, therefore, phenytoin is the only available choice for the rural poor in India. The pharmacokinetics and side-effects are well known. Adverse interaction with praziquantel is a theoretical risk for phenobarbital and carbamazepine, but none of our patients were on praziquantel, which is too expensive for most patients and is of doubtful benefit for neurocysticercosis.[1] Doctors who prescribe praziquantel should in any case be aware of this interaction.

Trevathan's other misgivings disappear on careful reading of our manuscript. Children with myoclonic, absence, and multiple seizure types were excluded from entry to the trial; compliance was equivalent in each treatment group; and the use of alternative therapies was handled by randomisation and intention-to-treat analysis. Difficulties with children's behaviour are by definition subjective observations by parents, and the Connor's parent rating scale is one of the most commonly used ways to measure side-effects in antiepileptic drug trials in children. Parents were not blinded for ethical reasons, and any possible bias that resulted from this would be expected to relate to excessive behavioural problems with phenobarbital, which did not occur. We did not set out to compare cognitive side-effects, and pointed out that a separate trial is necessary for this comparison. The rationale for our study was that clinical trials in developed countries are not necessarily applicable to developing countries and Trevathan and colleagues fail to appreciate this fundamental precept. Moreover, we have shown that clinical trials in epilepsy can successfully be mounted in developing countries to answer questions of regional importance.

Trevathan and co-workers describe the ideal antiepileptic drug for developing countries. We agree with the qualities they suggest but sadly no such drug exists, and their idea that this hypothetical drug should be "bought at discount and distributed to epilepsy-treatment programmes in developing countries" suggests a disturbing naivety about the realities of health economics, commercial interests, public health and policy, and logistics of service delivery in developing countries. In any case, comparative trials of phenobarbital versus carbamazepine have shown no difference in efficacy or side-effects in two other continents.[2,3] Newer and sometimes older antiepileptic drugs may be more expensive in developing than in developed countries because of differential pricing.[4] Our aim was to put the currently recommended WHO first-line antiepileptic therapy to the test in a well-designed clinical trial, to provide evidence for strategies of epilepsy management. Drug treatment is only one component of this strategy, but we have shown that a drug that is already widely available, cheap, and effective, is also well tolerated in a typical rural Indian setting. We welcome more research into service delivery to provide appropriate, sustainable services for people with epilepsy in developing countries.

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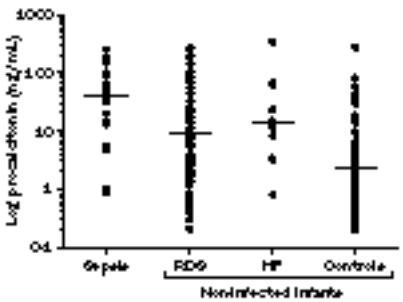
## Lack of specificity of procalcitonin for sepsis diagnosis in premature infants

Sir—M Hatherill and colleagues (Dec 13, p 1749)[1] emphasised the use of procalcitonin in differentiating conditions that may mimic septicaemia. They highlight procalcitonin as a specific marker of bacterial sepsis in paediatric intensive care units. However, to our knowledge, the specificity of this new marker has not been evaluated in premature infants.[2,3] We have therefore looked at the use of serum procalcitonin as a discriminating prognostic factor in severe septic states in such a paediatric population.

We report serum concentrations of procalcitonin, assessed by a specific immunoluminometric assay (Lumitest PCT, Brahms Diagnostica GMBH, Berlin, Germany), in 150 newborn babies (gestational age 25–41 weeks) at risk of bacterial infection during the first 10 days of life (mean postnatal age [SD, range] 2·3 [2·4, 0–10] days). On the basis of clinical and laboratory findings, 19 newborn babies with a positive bacteriological result in blood or cerebrospinal fluid cultures or with characteristic clinical symptoms of infection, were defined as having infection. Differences between groups were assessed with the Mann Whitney *U* test.




**Individual values of serum procalcitonin in 150 premature and term infants at risk of bacterial infection according to major diagnosis**

Sepsis (n=19), respiratory distress syndrome (RDS, n=66), haemodynamic failure (HF, n=12), and controls (n=53). Horizontal lines=median values.

Serum procalcitonin values were significantly higher in the infected group than in the non-infected group (median 42·0 *vs* 4·5 ng/mL, respectively; p=0·0004). These values varied greatly in both groups. With a threshold value of 5 ng/mL,[1,3] sensitivity for the diagnosis of bacterial infection was 84% whereas specificity was strikingly low (50%). The lack of specificity was in part explained by significantly higher procalcitonin in non-infected infants with respiratory distress syndrome (p=0005) or haemodynamic failure (p=0·002) than in non-infected infants who had neither of these conditions; Serum PCT values were highly variable in this latter group (figure). No significant effect on PCT of birthweight, gestational age, sex, mode of delivery, or perinatal asphyxia could be detected.

We suggest that serum PCT concentrations should be interpreted with caution in premature and term infants admitted to a neonatal intensive care unit. Our findings show that specific events (eg, respiratory distress syndrome and haemodynamic failure) determine serum concentration of PCT during the first 10 days of life, independently of any

bacterial infections in this paediatric population.

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## First clinical isolate of vancomycin-intermediate *Staphylococcus aureus* in a French hospital

Sir—Low level vancomycin resistance was recently described in clinical isolates of meticillin-resistant *Staphylococcus aureus* (MRSA) in Japan[1] and in the USA.[2] To our knowledge, no French isolate of MRSA with reduced susceptibility to vancomycin has been reported.

In November, 1995, blood cultures and a central line from a 2-year-old girl admitted to hospital for leukaemia grew an MRSA strain (LIM-1) which was susceptible to vancomycin (minimum inhibitory concentration [MIC] 2 mg/L. Treatment with vancomycin 35 mg/kg daily and amikacin 15 mg/kg daily for 10 days was not effective. The fever continued and she developed a purulent discharge from the central line site. The girl was given teicoplanin 10 mg/kg daily and amikacin 15 mg/kg daily for 18 days. During the first 2 days of teicoplanin therapy, an *S aureus* strain intermediately resistant to vancomycin (VISA) was isolated from blood cultures. This strain (LIM-2) had stable low-level resistance to vancomycin (MIC=8 mg/L) by the agar dilution method and crossresistance to teicoplanin (MIC 16 mg/L), and was susceptible to only pristinamycin and trimethoprim-sulfamethoxazole.

Culture of the purulent discharge also yielded a VISA isolate (LIM-3). Teicoplanin plus amikacin was not successful. The fever continued, the patient developed secondary localisations (pleural effusion, subcutaneous abscess) and, 15 days later, blood cultures again grew the VISA strain (LIM-4). Successful treatment consisted of drainage of purulent discharges and administration of the investigational antimicrobial agent quinupristin plus dalfopristin for 10 days. The LIM-2 strain was negative for *vanA, vanB, vanC1, vanC2,* and *vanC3* on PCR amplification of DNA. Pulse-field gel electrophoresis of *Sma* I restriction digestions from all susceptible and resistant isolates revealed an identical pattern, suggesting that the VISA isolate was selected from the previously vancomycin-susceptible MRSA strain LIM-1.

Hiramatsu and colleagues (Dec 6, p 1670)[3] described the selection of subpopulations of VISA colonies from previously vancomycin-sensitive strains at a frequency of one per $10^6$ cells. Moreover, these heterogeneous subclones and the homogeneous vancomycin-resistant *Staphylococcus aureus* strain Mu 50 have pulse-field-gel-electrophoresis patterns similar to an ubiquitous clonotype of MRSA in Japan, suggesting a common clonal ancestry. In the USA, VISA strains came from different geographic areas, which indicates that they are not related, though a genetic analysis is in progress.[4] These subpopulations express various levels of vancomycin resistance (MIC 3–8 mg/L) which makes it difficult to identify them in the clinical laboratory by standard methods such as disk-diffusion and MICs. These heterogeneous VISA strains could be involved in vancomycin therapeutic failure, especially in deep-seated or wound MRSA infections, given the weak tissue concentrations of vancomycin.

Emergence of VISA strains generally occurs in patients on multiple courses of vancomycin. For this child, however, neither previous episodes of *S aureus*-associated infections nor vancomycin therapy were reported. This emergence of VISA strains emphasises the importance of prudent use of antimicrobial and infection-control measures to reduce the incidence of VISA strains and to prevent their transmission.[5]

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## Height measurements and stretching

Sir—I am sure that most spine surgeons would disagree with George Werther's Jan 31 commentary[1] on L D Voss and B J R Bailey's paper.[2] The careful recording of height as an indicator of growth and development is important in the management of adolescent idiopathic scoliosis.[3]

The well known diurnal variation in height is mainly due to loss of fluid from the intervertebral discs rather than postural changes.[4] Most loss of height occurs in the first 2 h of the day, and would require stretching of medieval dimensions or several hours strict bedrest to reverse this loss in the juicy discs of adolescents. Neither "gentle upward pressure on the mastoid" nor "a short nap" will reverse this process with any reliability, nor are such measures practical within the constraints of a growth or scoliosis clinic. In children with scoliosis, an additional confounding factor is increasing curvature of the spine during the day.[5]

It is counter-intuitive to advocate uncontrolled stretching of children which can only add uncertainty to the measurement of height. I support Voss and Bailey's contention that stretching adds inaccuracy, and cannot believe that further research is needed beyond their well designed study. Their suggestion is that, ideally, all growth (and scoliosis) clinics should be held in the afternoon. I agree.

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## Fish consumption and major depression

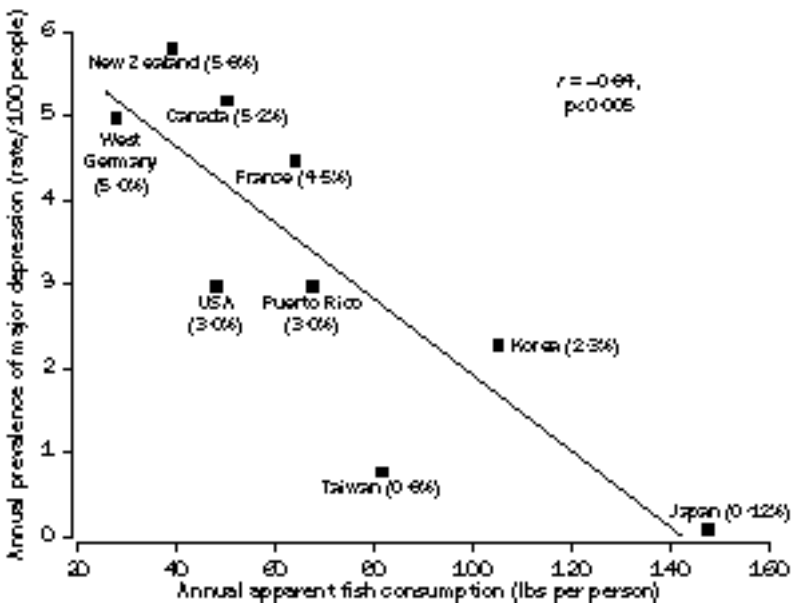
Sir—WHO estimates that major depression is the greatest single cause of disability worldwide.[1] The annual prevalence of major depression shows nearly a 60-fold variation across countries,[2] in a pattern similar to cross-national differences in mortality from coronary artery disease, which suggest that similar dietary risk factors could be important.

Among healthy volunteers, low plasma concentrations of an essential fatty acid found in fish, docosahexaenoic acid, predict low concentrations of a marker of brain serotonin turnover, cerebrospinal fluid 5-hydroxyindolacetic acid (CSF 5-HIAA).[3] The finding that low concentrations of CSF 5-HIAA are strongly associated with depression and suicide have been widely replicated. Since docosahexaenoic acid is selectively concentrated in neural tissues and important for nervous-system function, we tested the hypothesis that a high consumption of fish could be correlated with a lower annual prevalence of major depression (figure).

The cross-national comparisons of the prevalence of major depression reported by Weissman and colleagues[2] are among the most reliable cross-national data available. The rigorous methodologies used in these studies—large sample size (35 000), random prospective design, repeat sampling techniques, multiple community sampling, and use of a structured clinical interview with uniform internationally accepted diagnostic criteria—create confidence in the validity and comparability of these data. The structured interviews were independently verified as culturally appropriate for each community. The core biological symptoms that define major depression were the main factors used to determine the differences in prevalence of major depression across countries, rather than mood ratings which are prone to cultural bias. The economic data on apparent fish consumption was calculated by fish catch plus imports minus exports and are not as reliable as data from direct dietary surveys or tissue analyses, but do provide a comparable estimate across countries. The data on the annual prevalence of major depression reported by the Ministry of Welfare in Japan included 130 000 individuals, but did not use structured instruments for diagnosis or randomised population-sampling methods. However, exclusion of these Japanese data did not significantly affect the correlation analysis ($r$=0·77, p<0·03).

The direction and power of the correlation between apparent fish consumption and major depression accords with recent clinical reports of individuals that higher concentrations of docosahexaenoic acid in red-blood-cell membranes ($r$=−0·80, p<0·01),[4] as well as higher ratios of eicosapentaenoic acid to arachidonic acid in plasma ($r$=−0·73, p<0·01),[5] predict less severe symptoms of depression.

This correlation between apparent fish consumption and lower annual prevalence of major depression does not show that fish consumption can cause differences in the prevalence of major depression or that eating fish or fish oils are useful in treatment. Various cultural, economic, social, and other factors can confound this simple correlational relation.




**Fish consumption and prevalence of major depression**

Simple correlational model with Pearson product moment analysis indicates a potentially substantial interaction between the nearly 60-fold range in annual prevalence rates of major depression and the over 100-fold range of apparent fish consumption, in a multinational comparison.

1 lb=0·4536 kg.

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## Food rations for refugees

Sir—Barbara Reed and Jean-Pierre Habicht (Jan 10, p 129)[1] highlight the gap between policy and practice in the distribution of food aid. Refugees generally receive a cereal, an erratic supply of pulses or beans, vegetable oil, and sometimes salt. Most rations are deficient in overall calorie content and inadequate in micronutrient content.

In September, 1990, in the forest region of Guinea, a beriberi epidemic occurred in the Thuo refugee camp among Liberian adults who claimed to have consumed exclusively white rice and vegetable oil, the only rations received for months. Similarly, in 1989 and 1990, pellagra epidemics occurred among Mozambican refugees in Malawi. The attack rate was 0·5% among self-settled refugees and 13·2% in Nyamithutu camp. A case-control study showed that refugees dependent on relief rations were most at risk of the disease.[2]

In November, 1997, the caloric content of refugee rations was increased by the World Food

Programme (WFP) and the UN High Commissioner for Refugees to 2100 kcal per person daily to be in line with recommendations by WHO. However, consideration of energy, protein, and micronutrient content alone are not sufficient. Preparation and cultural acceptability should be taken into account if high rates of malnutrition and regular outbreaks of micronutrient deficiency diseases are to be avoided.

In the Dadaab camps of Kenya, the health of the refugees deteriorated when the ration was decreased from 2100 to 1800 kcal per person daily and the cereal changed to maize. Maize was new to the refugees and they found it unpalatable. Focus groups revealed that the maize was perceived as the main cause of ill-health: "diseases are brought by the bitter maize which UN gives us".[3] Selling of maize to buy rice resulted in net calorie loss of 25% per kg sold. A similar situation occurred in Guinea in 1995, when WFP switched from distributing rice to maize, under pressure from donors to reduce programme cost and fraud. Consequently, many refugees sold maize to buy rice at a loss. On average 5 kg of maize flour was traded for 1–2 kg of rice.

Although, in 1988, a conference held in Geneva[4] conceded that refugees frequently sell rations to improve their diet or to meet non-food needs, this has not changed the attitudes of donors, as Reed and Habicht point out. Donors should tolerate sales, and not interpret them as an indicator of excess. Refugee's own coping strategies should be encouraged and not condemned, and other more rational strategies should be explored, such as cash distributions,[5] which would facilitate farming or other forms of employment, whenever possible.

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## HIV-1 infection and prostitutes

Sir—In his Feb 21 news item, Bruno Simini (p 581),[1] states that prostitution is illegal in Italy and that about half the prostitutes are HIV-1 positive. Prostitution is not illegal in Italy, but only its exploitation. In Europe, prostitution is illegal only in Ireland, Iceland, and Malta. As far as the rated HIV-1 seroprevalence among prostitutes in Italy, only 131 (16%) of 802 female prostitutes working in Italy and tested within a cooperative study were HIV-1 positive.[2] However, 95 (39%) of 244 prostitutes who were also intravenous-drug users and 18 (37%) of 48 African prostitutes tested were HIV-1 positive.

We believe that health-information campaigns that suggest the use of condoms to prevent the spread of HIV-1 infection among prostitutes and their clients is inadequate. In fact, prostitutes conscious of their HIV-1 seropositive status are unlikely to use the condom and their clients frequently offer more money to have unprotected sex despite the risk of HIV-1 infection.

We propose that the HIV-1 test should be mandatory for prostitutes and that only those who are HIV-1 negative and do not have other sexually transmitted diseases should be allowed to practise prostitution. This approach could convince prostitutes to always use a condom to continue to practise, whereas HIV-1 positive prostitutes would not be allowed to continue to practise prostitution.

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## Need for holistic view of illness

Sir—I wonder why in the UK we are so fixed in our belief that there is a rigid separation between mind and body, between organic and psychological causes of disease. Two conditions in your Feb 14 issue fall into this trap.

In her Feb 14 commentary, Sarah Berga[1] elegantly describes recent advances in the neurochemistry that underlies the premenstrual syndrome, but concludes that these findings "validate [a woman's] sense of having an organic disturbance". Why on earth should it be necessary to validate someone's sense of having an organic rather than a psychological disturbance?

The clue to answering this question comes in Janet Fricker's news item (p 503)[2] in the same issue on repetitive strain injury (RSI). The insulting headline to this item—Repetitive strain injury is real, it's official—clearly implies that if the basis of RSI were found to be psychological rather than in the peripheral nerves, the disorder would not be "real". I suppose this means that obsessive-compulsive disorder and phobic anxiety are not real. Incidentally, the findings on RSI do not prove that abnormalities in peripheral-nerve function cause RSI. According to the report, patients with RSI and office-keyboard workers without RSI both had similar kinds of abnormalities in peripheral-nerve function, which suggests that repetitive use causes neurophysiological abnormalities but does not tell us whether such work causes RSI.

Many patients, especially those with RSI, chronic fatigue syndrome, and other recently described disorders seem preoccupied with the idea that they must find a physical basis for their disorder so as to, in Berga's terms, validate their illness. Such an approach seems also to have infected doctors. This view is based on a grossly naive view of the relation between mind and body, is a hindrance to the proper understanding of disease processes, and should be abandoned.

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## Futility and surgeons

Sir—In reply to Kenneth Rockwood's question (Jan 3, p 70)[1] the number of surgeons required to operate the audiovisual equipment can be predicted by the formula $n=c+r$, where $c$ is the consultant and $r$ is the registrar to whom the task is delegated.

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