**CORRESPONDENCE**

**Interpretation of Thrombosis Prevention Trial**

Sir—In the report of the Thrombosis Prevention Trial (Jan 24, p 233) 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 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.

With legal barriers ludicrously absent, the industry has established nicotine addiction on such a large scale that it 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 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 concerned about just minor side-effects.

For its survival, 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.

Sir—The Thrombosis Prevention Trial 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. As others have demonstrated for cholesterol-lowering drugs, absolute benefit 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 concerned about just minor side-effects.

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 concerned 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 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 concerned 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.

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 concerned 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.

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 concerned 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.

**CORRESPONDENCE**


*Jayant S Vaidya*  
Department of Surgery, University College London, London W1P 7LD, UK

2 Scandinavian Simvastatin Survival Study

*Tom Fahey, Tim J Peters*  
Division of Primary Care and Department of Social Medicine, University of Bristol, Canynge Hall, Bristol BS8 2PR, UK
Sir—The Thrombosis Prevention Trial1 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 differently 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,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 cholesterol-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.

Licia Iacoviello,* Maria Benedetta Donati
Department of Vascular Medicine and Pharmacology, Istituto di Ricerche Farmacologiche Mario Negri, Corzorizzo Mario Negri Sud, 66030 Santa Maria Imbaro, Italy


Sir—Although evidence from the Thrombosis Prevention Trial1 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 commonly 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.3 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.

OMP Jolobe
Department of Medicine for the Elderly, Tameside General Hospital, Ashton under Lyne OL6 9RW, UK

the reduction of IHD than either agent on its own.7 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.

*John G F Cleland, Ian Ford
Clinical Research Initiative in Heart Failure, University of Glasgow, Glasgow G12 8QQ, UK


Sir—The report of the Thrombosis Prevention Trial7 implied that our letter in The Lancet7 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, our letter was intended more 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 (INR) 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 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. 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.

*Roger E Peverelli, Richard W Harper, Joseph J Smolich
Centre for Heart and Chest Research, Monash Medical Centre and Monash University, Clayton, Victoria 3168, Australia


Sir—The Thrombosis Prevention Trial 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 aspirin differs from conventional formulations. These observations caution against extending the results of this study to conventional formulations of aspirin.

*Garret A Fitzgerald, William N Charman
Department of Pharmacology, Center for Experimental Therapeutics, University of Pennsylvania Medical Center, Philadelphia, PA 19104, USA; and Victorian College of Pharmacy, Monash University, Parkville, Victoria, Australia


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. At the same time, other studies suggest that aspirin may attenuate the presentation of severity of cardiac ischaemia.

Roger Peverill and his colleagues agree that anticoagulant regimens we used appears effective. The CARS trial 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 1·2 to which they refer, 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. 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.

*W Meade, P Brennan

MRC Epidemiology and Medical Care Unit, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, UK


**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 superseded 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) 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 mid trimester 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 trying small 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 AMEM 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.

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
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 midgestation.

We thank the Cytogenetics Laboratory at Columbia's Children's Hospital, Vancouver, British Columbia's Biochemical Diseases Laboratory, British Columbia's Children's Hospital, Vancouver, BC V6H 3V4, Canada (e-mail: applegar@unixg.ubc.ca).

J R Toone, *D A Applegarth, H D Vallance, R D Wilson
Biochemical Diseases Laboratory, British Columbia's Children's Hospital, Vancouver, BC V6H 3V4, Canada

1 The Canadian Early and Mid-Trimester Amniocentesis Trial (CIMAT) Group.

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 Africa 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 recorded 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 only performed 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.1 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.

Rosalind Coleman
8 St James's Avenue, London E2 9JD, UK


Sir—We agree with Richard Cooper and colleagues1 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 sub-Saharan Africa initiated the Adult Mortality and Morbidity 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 population groups 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 HIV/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 and those from stroke substantially higher than in North American or European populations.4 In addition to these data, population-
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 thrombocytopenia is frequently seen in patients with HCV infection and correlates to the presence of antiphospholipid antibodies.4 The presence of viral genome in platelets suggests that HCV is directly involved in the pathogenesis of the thrombocytopenia.

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.5 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.6 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, ribavirin can be used in some patients with symptomatic cryoglobulinaemia associated with chronic C hepatitis, who are intolerant or non-responders to interferon.7

J M Durand
Service de Médecine Interne, Hôpital Sainte-Marguerite, 13274 Marseille, France


Sir—Readers of Adrian Di Bisceglie’s seminar on hepatitis C might be further 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.8 Nosocomial transmission—unequivocally shown by molecular virology—results mainly from poor hand hygiene by staff members and the sharing of objects between patients.9 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.10

Nosocomial transmission has also been reported in other hospital settings, such as haematology wards and even, more recently, during consultations.11 The prevention of nosocomial transmission of all bloodborne pathogens including HCV remains a major challenge for all health-care workers.

Michel Jadoul
University of Louvain Medical School, Cliniques Universitaires St-Luc, Department of Nephrology, 1200 Brussels, Belgium


Sir—In his description of hepatitis C related extrahepatic manifestations, Adrian Di Bisceglie1 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.2,3,4

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
CORRESPONDENCE

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. Moreover, Nagao and co-workers 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 coagulopathy. He was positive for HLA-DRB1*0101 allele is responsible for HLA susceptibility to lichen ruber planus. Eur J Immunogenet 1994; 21: 425–28.

Antiepileptic drugs in developing countries

Sir—Deb Pal and colleagues (Jan 3, p 19) 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 appropriate comparison group.

Phenytoin is a bad choice as a first-line antiepileptic drug for developing countries: it has zero-order kinetics in children with absence seizures; and has adverse interaction with major antiparasitic drugs such as praziquantel. 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 alternative therapies.

Connors’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. 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.

*Edwin Trevathan, Marco T Medina, Amanda Madrid
Comprehensive Epilepsy Centre, Departments of Neurology and Paediatrics, University of Kentucky College of Medicine, Lexington, Kentucky, USA; Department of Research, National University of Honduras, Tegucigalpa, Honduras; and PREDISAN, Cataramas, Honduras


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. 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 developing 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. Newer and sometimes older antiepileptic drugs may be more expensive in developing than in developed countries because of differential pricing. 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.

*Deb K Pal, Brian GR Neville, Gautam Chaudhury, Tulika Das, Anthony Johnson
*Neurosciences Unit, Institute of Child Health, London WC1N 2AP, UK; Sanchar-Arod, vill & PO Pallian, West Bengal; and MRC Biostatistics Unit, Institute of Public Health, Cambridge

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.

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.

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, 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=0·0005) 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

Lack of specificity of procalcitonin for sepsis diagnosis in premature infants

Sir—M Hatherill and colleagues (Dec 13, p 1749) 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. 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...
CORRESPONDENCE

bacterial infections in this paediatric population.

*Alexandre Lapillonne, Eliane Basson, Guillaume Monneret, Jacques Bienvenu, Bernard L Saile


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 and in the USA. 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 intrinsically 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 vanG3 on PCR amplification of DNA. Pulse-field gel electrophoresis of SmaI restriction digests 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) described the selection of subpopulations of VISA colonies from previously vancomycin-sensitive strains at a frequency of one per 105 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 indicate that they are not related, though a genetic analysis is in progress. 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.

*MC Ploy, C Grélaud, C Martin, L de Lumley, F Denis


Height measurements and stretching

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

The well known diurnal variation in height is mainly due to loss of fluid from the intervertebral discs rather than postural changes. 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. 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.

Jeremy Fairbank
Nuffield Orthopaedic Centre, Headington, Oxford, OX3 7LD, UK

**Fish consumption and major depression**

Sir—WHO estimates that major depression is the greatest single cause of disability worldwide. The annual prevalence of major depression shows nearly a 60-fold variation across countries, 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 concentrations of a marker of brain 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 are among the most reliable cross-national data available. The rigorous methodologies used in these studies—large sample size (35 000), random population-sampling methods, 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), as well as higher ratios of eicosapentaenoic acid to arachidonic acid in plasma (r=−0·73, p<0·01), 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 correlative relation.

Joseph R Hibbeln
Outpatient Clinic, National Institute on Alcohol Abuse and Alcoholism, Rockville, MD 20852, USA


**Food rations for refugees**

Sir—Barbara Reed and Jean-Pierre Habicht (Jan 10, p 129) 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 caloric 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 1·2% in Nyamithutu camp. A case-control study showed that refugees dependent on relief rations were most at risk of the disease. In November, 1997, the caloric content of refugee rations was increased by the World Food Program.

**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.
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.

*Umberto Tirelli, Michele Spina
Division of Medical Oncology and AIDS, Centro di Riferimento Oncologico, 33081 Aviano (PN), Italy
(e-mail: oma@ets.it)

1 Simini B. Public warned about HIV-1 positive prostitute in Italy. Lancet 1998; 351: 580.

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 Berga1 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.

Roger A Fiskin
Friargate Hospital, Northallerton Health Services, National Health Service Trust, Northallerton, North Yorkshire DL7 6JG, UK


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 = cr, where c is the consultant and r is the registrar to whom the task is delegated.

*Steve Prescott, Martin Mayfield
Pyrah Department of Urology, St James’s University Hospital Trust, Leeds, LS9 7TF, UK