

CORRESPONDENCE

e-mail submissions to correspondence@lancet.com

Insulin-like growth factor-I genotype and birthweight

Sir—Norbert Vaessen and colleagues (March 23, p 1036)¹ report that a polymorphism in the gene for insulin-like growth factor-I (IGF-I), previously implicated in type 2 diabetes and myocardial infarction, is associated with low birthweight. Birthweight was lower by an average of 215 g in those who did not have the wild type (192 bp) allele than in those homozygous for the allele.

We have previously assessed this genotype in 627 men and 426 women, representing the Hertfordshire, UK, cohorts in which the birthweight associations with late onset diseases were first identified.² Our previous hypotheses focused on measures of weight and length or height at birth, 1 year, and in late adulthood. We coded three genotypes, based on whether the allele is or is not 192 bp, and applied ANOVA.

We have reassessed our data to correspond directly with Vaessen and colleagues' analyses. In men and women, mean weights did not differ between groups (table). We measured weight at 1 year, and weight, height, and body-mass index in later life. We also used the quartiles classification applied by Vaessen and colleagues to classify postnatal gain in weight during life (ie, a crude assay of weight centile increment), and measured birth to 1 year change and birth to adult change. There were no positive trends. Finally, on a subset of 225 men and

133 women in whom glucose tolerance tests had been done, opposite homozygote groups for the 192 bp allele did not differ.

Why do Vaessen and colleagues' report that our findings do not seem consistent for this genotype of IGF-I? The genetic marker itself is a microsatellite length polymorphism in the promoter region of the *IGF-I* gene. It seems not to be functional, but is thought to act as a proxy marker for common IGF-I haplotypes. Indeed the distribution of the rarer alleles (188, 190, 194, 196, and 198 bp) in earlier reports by Vaessen and colleagues is similar to our observations. It seems unlikely then that the spectrum of common genetic variation at this locus and gene differs between the Rotterdam study, of which Vaessen and colleagues' study is a substudy, and our study. Subject ascertainment and phenotype acquisition do differ between the two studies. Ours benefits from prospectively and very accurately recorded birthweight and 1-year weight archives. Vaessen and colleagues' study focused on diabetes pathogenesis and depended on questionnaire acquisition of birthweight data and diabetes family history, and the selection included 93 individuals with diabetes. Within our study, 42% of participants' weight rose in quartile between birth and late life, twice to three times the equivalent percentage for the same phenotype in Vaessen and colleagues' study; the basis of this large difference remains obscure. Mean birthweight is also around 10% higher in our study.

Additional questions concern the significance level attained ($p=0.04$ and $p=0.03$ in Vaessen and colleagues' report with a test focused on participants with no 192 bp allele), the previous hypotheses, and number of tests done and genetic models assumed.

There needs to be better mechanisms to publish positive and negative gene association studies, specific hypothesis tests and descriptive hypothesis formation, and substudies, and to include sufficient detail to combine and meta-analyse traditionally substantial study sizes. In

this instance, further replication studies might usefully focus on very large studies in diabetic samples.

Ian N M Day, Tabitha H T King, Xiao-he Chen, Anca M Voropanov, Shu Ye, Holly E Syddall, Avan Aihie Sayer, Cyrus Cooper, David J Barker, and David I W Phillips were all involved in the writing of the letter.

Ian N M Day, on behalf of all authors

Human Genetics Division, School of Medicine, Southampton University Hospital, Southampton SO16 6YD, UK
(e-mail: I.N.M.Day@soton.ac.uk)

- 1 Vaessen N, Janssen JA, Heutink P, et al. Association between genetic variation in the gene for insulin-like growth factor-I and low birthweight. *Lancet* 2002; **359**: 1036–37.
- 2 Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989; **2**: 577–80.

Authors' reply

Sir—Ian Day and colleagues report no association between the polymorphism in the promoter region of the *IGF-I* gene and birthweight. Neither could they detect any association between this polymorphism and glucose tolerance. There are several explanations for these inconsistent findings.

First, we often think of effects of genes as fixed effects, but they are not. The variation in birthweight explained by the IGF-I polymorphism may depend on the variability of other genetic or environmental factors. As reported, our participants were initially selected for a case-control study focusing on risk factors for diabetes. Consequently, our population consists of many individuals who have diabetes (20%), impaired glucose tolerance (20%), and obesity (41%). Therefore, Day and colleagues' population probably differs from ours for glucose and insulin concentrations as well as for concentrations of IGF-I binding proteins. All these factors affect IGF-I expression.

This difference in population background may also explain the lack of association of the IGF-I polymorphism with glucose tolerance in the Hertfordshire study. Evidence suggests that IGF-I is involved in

	Mean (SD) birthweight (g)	p*
IGF-I genotype		
Male		
Homozygous 192 bp allele (n=293)	3521 (528)	0.38
Heterozygous 192 bp allele (n=260)	3554 (503)	
No 192 bp allele (n=74)	3614 (609)	
Female		
Homozygous 192 bp allele (n=187)	3444 (489)	0.08
Heterozygous 192 bp allele (n=190)	3350 (524)	
No 192 bp allele (n=49)	3495 (443)	

*On 2 df from one-way ANOVA.

Association of IGF-I-promoter microsatellite polymorphism with birthweight

pancreatic islet development during embryogenesis but also promotes compensatory β -cell proliferation and survival in situations of increasing insulin demands, as occurs in insulin resistance or obesity.¹ Also, our data (unpublished) suggest an effect of the polymorphism on β -cell function. The effect of the IGF-I polymorphism on glucose tolerance will probably, therefore, become apparent only in a population with a high frequency of insulin resistance and obesity.

Second, given the population-based approach of our study, we cannot distinguish whether this polymorphism itself is involved in regulation of IGF-I expression. The polymorphism we investigated has been associated with serum IGF-I concentrations in several studies. The direction of this association, however, varies between populations. Thus the polymorphism itself may not be functional but merely serve as a marker for a nearby genetic variant functionally involved in IGF-I expression. Day and colleagues argue that it is very unlikely that the spectrum of common genetic variation at the IGF-I locus differs between our and their study. However, as for other promoter polymorphisms, even within Europe, both allele frequencies and the extent of allelic association may differ across populations.²

Despite the inability to reproduce our results in the Hertfordshire study, the findings on the IGF-I promoter polymorphism in the Dutch population are very consistent. We have previously shown that absence of the wild-type allele of the IGF-I polymorphism is associated with low IGF-I serum concentrations and reduced body height at older age.³ The relation between this polymorphism and body height has been confirmed in another Dutch cohort.⁴ In addition, in a group of Dutch children, born small for gestational age, absence of the wild-type allele of a nearby polymorphism in the promoter region of the *IGF-I* gene has been associated with low serum concentrations of IGF-I, and with reduced birth length, birthweight, and head circumference.⁴

The consistency of these findings strongly suggests that the IGF-I polymorphism can be used as a marker of IGF-I expression in the Dutch population.

Norbert Vaessen, Joop A Janssen,
Huibert A Pols, Ben A Oostra,
*Cornelia M van Duijn

*Genetic Epidemiology Unit, Department of Epidemiology and Biostatistics, Department of Clinical Genetics, and Department of Internal Medicine, Erasmus Medical Center, PO Box 1738, 3000 DR Rotterdam, Netherlands (e-mail: vanduijn@epib.fgg.eur.nl)

- 1 Bonner-Weir S. Perspective: postnatal pancreatic beta cell growth. *Endocrinology* 2000; **141**: 1926–29.
- 2 Roks G, Cruts M, Bullido MJ, et al. The -491 A/T polymorphism in the regulatory region of the apolipoprotein E gene and early-onset Alzheimer's disease. *Neurosci Lett* 1998; **258**: 65–68.
- 3 Vaessen N, Heutink P, Janssen JA, et al. A polymorphism in the gene for insulin-like growth factor-I: functional properties and risk for type 2 diabetes mellitus and myocardial infarction. *Diabetes* 2001; **50**: 673–42.
- 4 Arends N, Johnston L, Hokken-Koelega A, et al. Polymorphism in the IGF-I gene: clinical relevance for short children born small for gestational age (SGA). *J Clin Endocrinol Metab* 2002; **87**: 2720–24.

Sir—Norbert Vaessen and colleagues¹ describe the interesting observation that a polymorphism of the *IGF-I* gene is closely associated with low birthweight and an increased incidence of type 2 diabetes mellitus.

It is relevant in this context that a phenotypic association between low birthweight and increased incidence of type 2 diabetes is supported by a large Scandinavian study.² From their results, Vaessen and colleagues propose that a specific *IGF-I* polymorphism is related to the extent of plasma IGF-I expression, a key factor in the development of pancreatic insulin-secreting cells. This proposal is supported by previous animal knock-out and transgenic models in which the concentration of plasma IGF-I is a determinant of the development and maturation of the insulin secreting β cells in fetal life, which consequently affects insulin-secreting properties of the β cells in adult-life.³ Most IGF-I in plasma is bound to IGF-binding protein-3 (IGFBP-3).

Due to the heritability of expression of IGF-I and IGFBP-3 (more with respect to IGFBP-3 than IGF-I⁴), we have assessed whether the relation between plasma IGF-I concentration and IGFBP-3 expression in insulin-secreting cells, or both, is conserved in adult-life. We did a standard oral glucose tolerance test (75 g glucose), and a hyperglycaemic clamp (10 mmol/L during 180 min) with measurement of first and second (average plasma insulin in 140–80 min period) phase insulin secretion in 53 non-diabetic individuals (mean age 46 years, SD 6; 13 men, 40 women; mean body-mass index 25.9 kg/m², SD 3.8).

Plasma IGF-I concentrations were not related to variables of insulin secretion, but plasma concentrations of IGFBP-3 were significantly correlated with second-phase insulin

secretion ($p=0.025$) in the clamp, and with baseline ($p=0.056$) and 120-min plasma insulin after the oral glucose tolerance test ($p=0.037$). Multiple linear regression showed that the effect of IGFBP-3 on insulin secretion could be accounted for by body-mass index.

Thus, IGFBP-3 concentrations are closely related to insulin secretion in the adult pancreas. Several factors, including growth hormone status, age, nutrition, and hepatic function affect plasma concentrations of IGFBP-3. However, the variation between individuals of concentrations of IGFBP-3 in the circulation seems to be largely determined by a genetic component.⁴ Hence, at least to a certain extent, IGFBP-3 concentrations at the tissue level are also affected by genetic factors. IGFBP-3 plays an important part in the modulation (inhibitory or stimulatory) of IGF action at the cellular level.

During fetal development, local concentrations of IGF and IGFBP-3 may affect the balance between cell apoptosis and the maturing of functional β cells,³ and hence the insulin secretory capacity in adult life. This may explain the intriguing finding that a relation exists between plasma IGFBP-3 and insulin secretion by the adult pancreas. The apparent effect of body-mass index on this relation remains puzzling. Considered together with the data of Vaessen and colleagues, we also suggest that pancreatic β -cell function may be primarily determined early in life.

ThBT has received personal financial support from the foundation De Drie Lichten and a grant from the Dutch Association of Science (NWO).

Th B Twickler,
M G M de Sain-van der Velden,
J van Doorn, *T W van Haeften

Departments of *Internal Medicine and Metabolic and Endocrine Diseases, University Medical Centre Utrecht (UMCU), PO Box 85500, 3508 GA Utrecht, Netherlands; and INSERM Unité 551, Hôpital Pitié Salpêtrière, Paris, France (e-mail: T.W.vanHaeften@azu.nl)

- 1 Vaessen N, Janssen JA, Heutink P, et al. Association between genetic variation in the gene for insulin-like growth factor-I and low birthweight. *Lancet* 2002; **359**: 1036–37.
- 2 Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VW, Osmond C, Barker DJ. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia* 2002; **45**: 342–48.
- 3 Hill DJ, Petrik J, Arany E. Growth factors and the regulation of fetal growth. *Diabetes Care* 1998; **21**: B60–69.
- 4 Harrela M, Koistinen H, Kaprio J, et al. Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. *J Clin Invest* 1996; **98**: 2612–15.

Effect of angiotensin-converting-enzyme inhibitors

Sir—Fernando Boix (March 30, p 1157)¹ refers to the effect of angiotensin-converting-enzyme (ACE) inhibitors being due partly to an increase in the action of bradykinin on its B2 receptor.

We have tested this hypothesis with various techniques in our laboratory in isolated organs or cultured cells in the past 5 years.²⁻⁴ We attributed potentiation of the bradykinin peptide to a protein-protein interaction—a heterodimer formation between ACE and the B2 receptor—which leads to an increase in prostaglandin and nitric-oxide release.

Boix suggests that it would be interesting to see whether vaso-peptidase inhibitors could also increase the bradykinin activation of the B2 receptor. We have noted that this mechanism is correct.⁵ Omapatrilat and another neprilysin inhibitor also strongly potentiated kinin action on the B2 receptor. We tested cultured cells that constitutively expressed human neprilysin and B2 receptor or were transfected with them. We measured potentiation by rise in intracellular calcium.

The kinin agonist in the latter experiments was a bradykinin analogue resistant to inactivation by both ACE and neprilysin. Consequently, the combined inhibitors of ACE and neprilysin can potentiate kinins in cells that express ACE or neprilysin, provided that the B2 receptor is also present on the cell membrane.

Peter A Deddish, *Ervin G Erdős

University of Illinois College of Medicine,
Department of Pharmacology, 835 S Wolcott
Avenue, Chicago, IL 60612, USA
(e-mail: egerdos@uic.edu)

- 1 Boix F. Vasopeptidase inhibitors: a bradykinin link. *Lancet* 2002; **359**: 1157–58.
- 2 Minshall RD, Tan F, Nakamura F, et al. Potentiation of the actions of bradykinin by angiotensin I converting enzyme (ACE) inhibitors: the role of expressed human bradykinin B2 receptors and ACE in CHO cells. *Circ Res* 1997; **81**: 848–56.
- 3 Marcic B, Deddish PA, Jackman HL, Erdős EG. Enhancement of bradykinin and resensitization of its B₂ receptor. *Hypertension* 1999; **33**: 835–43.
- 4 Marcic B, Deddish PA, Skidgel RA, Erdős EG, Minshall RD, Tan F. Replacement of the transmembrane anchor in angiotensin I-converting enzyme (ACE) with a glycosylphosphatidylinositol tail affects activation of the B2 bradykinin receptor by ACE inhibitors. *J Biol Chem* 2000; **275**: 16110–18.
- 5 Deddish PA, Marcic BM, Tan F, Jackman HL, Chen Z, Erdős EG. Neprilysin inhibitors potentiate effects of bradykinin on B2 receptor. *Hypertension* 2002; **39**: 619–23.

Helicobacter pylori infection in elderly patients

Sir—Hoda Malaty and colleagues (March 16, p 931)¹ do not recognise that *Helicobacter pylori* infection poses a great risk to elderly patients with previous peptic ulcer disease. Their conclusion that eradication should be targeted at children will direct focus away from this already neglected group.

Although *H pylori* is associated with gastric cancer and lymphoma, the incidence of these diseases is in decline, and in developed-country populations particularly the absolute risk is small.² The major burden on health-care resources from *H pylori* infection results from peptic ulcer disease and its complications. Older patients are most at risk, since mortality rates for peptic ulcers rise from around one per million at age 20 years, towards 200 per million at age 70 years.³ Elderly people with previous peptic ulcer disease benefit from eradication therapy.

There is no consensus to date about how best to identify these patients, but primary-care screening is ineffective.⁴ We have found a simple hospital-based strategy for screening by history and serology to be effective, showing 85% seropositivity for *H pylori* in patients with a history of peptic ulcer disease.

We reviewed the histories of consecutive patients who we saw for

	Number of patients
Diagnosis	
Duodenal ulcer	8
Gastric ulcer	2
Undifferentiated	9
Duodenal and gastric ulcer	1
Method	
Gastroscopy	7
Barium meal	8
Emergency surgery	3
Unknown	2
Years since diagnosis	
0–9	6
10–19	4
20–29	3
≥30	6
Unknown	1
Reported history of H pylori eradication	
	0
Risk factors for ulcer recurrence	
Smoker	5
Ulcerogenic treatment* (without proton-pump-inhibitor cover)	3
Smoker plus ulcerogenic treatment	2
Current ulcer-healing or dyspepsia therapy	
Proton-pump inhibitor	6
H ₂ -receptor antagonist	8

*Aspirin, non-steroidal anti-inflammatory drugs, serotonin reuptake inhibitors, cyclo-oxygenase 2 inhibitors.

Time and method of diagnosis of ulcer disease and risk factors for ulcer recurrence

non-ulcer-related medical disorders. All those with previous peptic ulcers underwent serological testing for *H pylori* IgG, and we recorded details of date and method of diagnosis, current symptoms, and ulcer risk factors.

With an assumed infection prevalence of 75% among cases, we calculated that audit of the first 20 patients would provide sufficient clinical information to assess the usefulness of the proposed strategy (95% CI 56–94).

The table shows the diagnoses, estimated duration of disease, and proportion of patients with current risk factors for ulcer disease. The mean age of patients was 67 years (range 48–88) and seven were men. 85% (95% CI 69–100) of patients with a history of ulcer disease were *H pylori* positive. No patient gave a history of *H pylori* eradication.

If current guidelines were followed, all patients should have negative serology for *H pylori*. Around 80% (62–98) were still symptomatic or requiring acid suppression treatment, and 50% (28–72) were current smokers or taking ulcerogenic medication. Research shows synergism, with *H pylori* infection increasing the risk of peptic-ulcer disease in patients taking non-steroidal anti-inflammatory drugs up to 3.53 times higher than the risk associated with NSAID use alone.⁵

Eradication treatment lowers the risk of recurrent ulcer disease, complications, and drug costs. A hospital-based approach to screen for *H pylori* in patients with documented peptic ulcer disease involves little investment in time and money. Compared with children, adults admitted to hospital are in a higher risk group, and eradication efforts should be directed at them.

*J Younger, A Duggan

Department of Gastroenterology, John Hunter Hospital, Locked Bag 1, Hunter Region Mail Centre, Newcastle, NSW 2310, Australia (e-mail: jonnyounger@bigpond.com)

- 1 Malaty HM, El-Kasabany A, Graham DY, et al. Age at acquisition of *Helicobacter pylori* infection: a follow-up study from infancy to adulthood. *Lancet* 2002; **359**: 931–35.
- 2 Fuchs CS, Mayer RJ. Medical progress: gastric carcinoma. *N Engl J Med* 1995; **333**: 32–41.
- 3 Banks L, Wright JP, Marks IN. Peptic ulcer: a follow-up study. *J Clin Gastroenterol* 1986; **8**: 381–84.
- 4 Duggan A, Bilku J, Ledger C, Scaffardi R, Hawkey CJ. Eradicating *H pylori* in patients with a past history of documented peptic ulcer: is the juice worth the squeeze? *J Qual Clin Pract* 2001; **21**: 76–79.
- 5 Huang JQ, Subbaramiah S, Hunt RM. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic ulcer disease: a meta-analysis. *Lancet* 2002; **359**: 214–25.

Author's reply

Sir—J Younger and A Duggan have unfortunately missed our message for directing management strategies of *H pylori* infection towards children.

We agree that *H pylori* infection poses the greatest risk to elderly patients. Most, if not all, such patients have acquired *H pylori* during childhood, since infection is primarily acquired during childhood.^{1,2} Unless the infection is treated, it persists throughout life.

Younger and Duggan, as do many others, confuse the prevalence and the incidence of a disease. Prevalence is the proportion of a population that has a particular disease at a particular time. As a measurement of the burden of peptic ulcer disease, the prevalence is the measure of the frequency and complication of the disease process. However, incidence is the rate of development of newly acquired infection (here *H pylori*) in a population over time rather than a burden of an existing disease. To prevent the burden of such a disease, we must prevent its development—ie, for *H pylori*, infection in childhood, since the acquisition in adulthood is extremely rare.³ Our epidemiological study aimed to identify the incidence and age of acquisition of *H pylori* infection and how accordingly to achieve long-term eradication of the infection and how to reduce the incidence of peptic ulcer disease worldwide.

Despite it being only 20 years since *H pylori* was discovered, intensive work worldwide has advanced our understanding of this infection's epidemiology and its causal role in peptic ulcer disease and gastric cancer. Epidemiological models of the interrelation between *H pylori* infection and associated diseases can differentiate, but not separate, the clinical from the preventive perspectives. From a clinical perspective, treatment and screening of *H pylori*-infected adults with previous peptic ulcer disease is a must to prevent further complications.

From a preventive perspective, the targeting and treatment of infected children with *H pylori* will reduce the infection transmission and ultimately reduce the incidence of peptic ulcer disease and gastric cancer in generations to come since the reinfection rate of *H pylori* is low among children older than 5 years.⁴

The lessons learned from the epidemiology of poliomyelitis, syphilis, and smallpox are applicable to *H pylori* infection and provide preventive strategies to make *H pylori* infection,

and thus peptic ulcer disease, part of the past.

Hoda M Malaty

Department of Medicine, Baylor College of Medicine, and Veterans Affairs Medical Center, 2002 Holcombe Boulevard, Houston, TX 77030, USA
(e-mail: hmalaty@bcm.tmc.edu)

- 1 Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. *Gut* 1994; **35**: 742–45.
- 2 Malaty HM, Graham DY, Wittingty WA, Srinivasan SR, Osato M, Berenson GS. *Helicobacter pylori* acquisition in childhood: a 12-year follow-up cohort study in a biracial community. *Clin Infect Dis* 1999; **28**: 279–82.
- 3 Cullen DJ, Collins BJ, Christiansen KJ, et al. When is *Helicobacter pylori* infection acquired? *Gut* 1993; **34**: 1681–82.
- 4 Rowland M, Kumar D, Daly L, O'Connor P, Vaughan D, Drumm B. Low rates of *Helicobacter pylori* reinfection in children. *Gastroenterology* 1999; **117**: 336–41.

The right to buy or sell a kidney

Sir—Michael Friedlaender (March 16, p 971)¹ and Hans Schlitt, in his March 16 Commentary,² make important contributions to the hot debate on paid non-related living organ donation.

Schlitt is to be congratulated for a thoughtful, objective, and non-emotional approach to this sensible issue. As he states, solutions to the donor shortage do exist and strictly controlled non-directed live donation of kidneys, as described by Matas and colleagues,³ may be one of them.

Friedlaender, on the other hand, does not know whether he is a humanitarian or an utilitarian and, therefore, needs some help. His Viewpoint suggests that he is neither, and his hesitation should be placed between cynical and opportunist.

Can any normal, intelligent human being—which Friedlaender certainly is—honestly believe that young, able-bodied men aged 25–35 years, who receive about US\$700 for a kidney in a starved country, are fully informed and autonomous donors? Is there a definition of autonomy for the developed countries only that makes us paternalistic when we judge the motivation and values of other peoples and cultures? What needs to be understood here is not so much the motivation of poor and easily exploitable people, but that of their exploiters.

In the context of terminal illness, the reaction of some desperately sick patients may be explainable. Physicians should not, however, encourage them to buy a kidney abroad under the pretext

that there is no increase in mortality after donation in developed areas, and no evidence suggesting that the situation is different in less-developed countries. There is indeed no evidence either that the standards of developed countries are met in poorer regions, and common sense would suggest not. In addition, it is hard to be naive to the point of believing that the donor recruiters and organ brokers are driven by anything other than profit: legalisation of their activities on an international basis to prevent uncontrolled trade and transplantation tourism seems, therefore, at best, wishful thinking.

Such an attitude is illustrated by the behaviour of the government in Friedlaender's country, who sponsors the citizens who buy kidneys abroad but prohibits paid donation within its own boundaries. Evidently, the definition of human rights, like that of humanitarianism, is not the same everywhere.

François Mosimann

Service de Chirurgie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland
(e-mail: Francois.Mosimann@chuv.hospvd.ch)

- 1 Friedlaender MM. The right to sell or buy a kidney: are we failing our patients? *Lancet* 2002; **359**: 971–73.
- 2 Schlitt HJ. Paid non-related living organ donation: Horn of Plenty or Pandora's box? *Lancet* 2002; **359**: 906–07.
- 3 Matas AJ, Garvey CA, Jacobs CL, Kahn JP. Nondirected donation of kidneys from living donors. *N Engl J Med* 2000; **343**: 433–36.

Sir—Our experience of unrelated renal transplantation done overseas differs from that of Michael Friedlaender,¹ especially in the Indian subcontinent.²

Our region has a large Indo-Asian subpopulation in which there is a high demand for renal transplantation. For several reasons members of this community have a limited chance of receiving a cadaveric transplant,³ with the result that some patients travel to Indo-Asia, against medical advice, to receive unrelated transplants. This so-called transplant tourism in our region was highlighted some years ago, with some successes being noted.⁴ However, increasingly this trade is becoming associated with unacceptable risks.

In our own unit, some patients, most of whom are deemed unsuitable for transplantation, have travelled to India and undergone transplantation from unrelated donors. All have returned to the UK prematurely and, on their return, have invariably required major resuscitation. Furthermore, the overall results in these circumstances have been poor. Of six patients returning four have died (mostly sepsis and multiorgan

failure on the background of widespread cardiovascular disease); only two patients have functioning grafts, both after considerable intervention.

On the basis of these results we have done a questionnaire audit of the experience of other UK units. Of 17 UK transplant units responding, 12 reported patients who had been transplanted overseas. In total, 23 patients were identified, all of whom had been transplanted against UK medical advice. Eight of the 23 patients died from causes directly related to transplantation (35% mortality) and graft loss occurred in a further five patients (overall graft loss 56%). In only one instance was any information provided by the transplanting centre and no donor details, including donor outcomes, were ever provided (unpublished data).

These results reinforce the standpoint that organ trading is associated with variable results and exploitation based on the selection of patients by monetary rather than clinical criteria—we know of no patients who were turned down because they were deemed unsuitable—and the promise of an outcome that cannot be fulfilled. Even the most desperate dialysis patient would probably not knowingly undergo a transplant associated with a one in three chance of dying and a 50% chance of graft loss.

We have found no audits of results in paid donors, who must be presumed to consent to operation with little information of outcomes. We cannot endorse this practice and advise our patients against it in the strongest terms. However, we do have sympathy with Friedlaender's view that the subject of paid donation per se should not be excluded from future discussions, but this should be separated from transplant tourism. We would prefer discussions to focus on compensated donation, limited to donors within the UK where regulation and accepted clinical guidelines would prevent exploitation and maintain standards for donors and recipients.

N G Inston, *A R Ready

Department of Renal Transplantation Surgery,
Queen Elizabeth Hospital, Birmingham
B29 6JD, UK
(e-mail: Andrew.Ready@University-
b.wmids.NHS.UK)

- 1 Friedlaender MM. The right to sell or buy a kidney: are we failing our patients? *Lancet* 2002; **359**: 971–73.
- 2 Friedlaender MM, Gofrit O, Eid A. Unrelated-living-donor kidney transplantation. *Lancet* 1993; **342**: 1061–62.
- 3 Ready AR. Transplanting an ethnic community: approaches to the crisis. *Nephrol Dial Transplant* 1998; **13**: 2490–93.
- 4 Odum J, Rylance PB, Jackson MA. From Wolverhampton to Bombay. *Lancet* 1996; **343**: 191–95.

Author's reply

Sir—François Mosimann is completely correct in suggesting that I need some help. That was the underlying reason for my Viewpoint.

Much as I sympathise with his dislike of people who participate in illegal transplantations, closer reading might have allowed him to realise that the patients will continue to seek to save their own lives regardless of his moral outrage, and certainly without any recommendation from me. I also endorse his approval of Hans Schlitt's Commentary, which I did not find to be in any direct contradiction to my views. Unfortunately, there is little evidence that unrelated altruistic donation, non-directed or otherwise, has wide appeal and thus it is unlikely to alleviate the current shortage of donor kidneys. Is the donor to be the only one in the equation who does not get paid?

I did not mention legalisation of the unregulated activities of brokers and organ recruiters. My suggestion was to pre-empt the uncontrolled trade and transplant tourism with a legal trade that, hopefully, would be established in the patients' own countries and meet only the highest medical standards. Such a trade already exists de facto in top university centres in the USA and Europe; foreign donors and recipients are well rehearsed, probably by the brokers, to give adequate answers to cursory questions.

International understanding of the issue would be a move in the right direction, but censure achieves nothing. A Turkish father sold a kidney to pay for medical treatment for his son. Consider if the son had required a kidney and he had donated the kidney to his son. Mosimann seems to find fault not only with the unregulated exploiters but also with the father's autonomy to seek the money to pay for his son's treatment. We do not live in a perfect world. Perhaps I should tell patients to die without protest, ask Saddam Hussein to pay his citizens more, and campaign to abolish the profit incentive.

However, I would reserve the word cynical for people who prefer the status quo and perhaps also for a reader who derides the reimbursement of medical expenses to the sick and questions humanitarianism. Patients also have rights.

Michael Friedlaender

Nephrology and Hypertension Services,
Hadassah University Hospital, PO Box 12000,
Jerusalem 91120, Israel
(e-mail: fried@cc.huji.ac.il)

Infection with unexpected micro-organisms in splenectomised patients

Sir—Carsten Ziske and Thomas Müller (March 30, p 1144)¹ emphasise no pneumococcal vaccination and infection with unexpected penicillin-resistant *Streptococcus pneumoniae* as a cause of the unfortunate outcome of their patient with overwhelming postsplenectomy infection (OPSI). However, it is not clear if guidelines for management of asplenic or hyposplenic patients² had been followed, whether the outcome would have been different.

Failure of pneumococcal vaccination³ and vaccination plus prophylactic penicillin^{4,5} to prevent OPSI is well known. In a study from the UK, 25% of *S pneumoniae* isolates from 49 patients with OPSI were serotypes not covered by the current 23-valent vaccine; in 17 of 22 patients who received pneumococcal vaccine, *S pneumoniae* caused infection. On the other hand, in 13% of 77 reported cases, the pathogens that caused OPSI differed from *S pneumoniae*.

Therefore, in more than a third of the patients with postsplenectomy infection, the microorganism that caused infection might not be covered by a current vaccine or may not be susceptible to proposed first-line antibiotics such as penicillin or erythromycin.

In our clinic, a boy aged 9 years who had β -thalassaemia and had undergone splenectomy 2 years earlier, presented with general malaise, fever, vomiting, and mild abdominal pain. He had been immunised with pneumococcal vaccine after splenectomy. At admission he was feverish, with a temperature of 38.5°C, and had no signs of acute abdomen or meningism. Systolic blood pressure was 90 mm Hg, heart rate 108 beats per min, and breathing rate 28 breaths per min. Laboratory assessment showed haemoglobin 98 g/L, leucocytosis of $20.6 \times 10^9/L$, urea 13.9 mmol/L, creatinine 121.7 $\mu\text{mol/L}$, aspartate aminotransferase 545 U/L, and alanine aminotransferase 465 U/L. We diagnosed sepsis with shock, took blood samples for culture, and started fluid resuscitation along with intravenous cefazolin and amikacin.

6 h after admission, the patient became oliguric. Repeated laboratory assessment showed hypoxaemia, leucocytosis of $12.1 \times 10^9/L$, urea 18.4 mmol/L, creatinine 209 $\mu\text{mol/L}$, aspartate aminotransferase 934 U/L, and alanine aminotransferase 697 U/L. Despite treatment, the patient died within 16 h of admission in irreversible

septic shock with multipleorgan failure. Blood cultures grew *Acinetobacter* sp microorganisms.

Despite data showing that nearly 90% of OPSI are caused by *S pneumoniae*,³ other pathogens cannot be excluded. We speculate that in every case of postsplenectomy infection a broad-spectrum reserve antibiotic (or antibiotic combination) must be used at first line, dependent on regional or hospital data of antibiotic resistance—this is our current practice. It seems that awaiting mainly penicillin-susceptible strains of *S pneumoniae* to cause overwhelming postsplenectomy syndrome is no longer justified. Aggressive antibiotic treatment and resuscitation measures provided in intensive care with close monitoring could lower the high mortality rate in these patients.

*Alexander Julianov, Slavena Palijska, Nikolai Nedkov

Department of General Surgery, Thracian University Hospital, 6000 Stara Zagora, Bulgaria
(e-mail: a_julianov@yahoo.com)

- 1 Ziske CG, Müller T. Partial splenectomy. *Lancet* 2002; **359**: 1144.
- 2 Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ* 1996; **312**: 430–34.
- 3 Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. *J Clin Pathol* 2001; **54**: 214–18.
- 4 Klinge J, Hammersen G, Scharf J, Liufficken R, Reinert RR. Overwhelming post splenectomy infection in vaccine type *Streptococcus pneumoniae* in a 12 year old girl, despite vaccination and antibiotic prophylaxis. *J Infect* 1997; **35**: 368–71.
- 5 Shetty N, Aurora P, Ridgway GL. A failure of anti-pneumococcal vaccine and prophylactic penicillin in the splenectomised patient. *J Infect* 1998; **37**: 87–88.

Author's reply

Sir—Alexander Julianov and colleagues make important points about prophylactic vaccination for patients who are at increased risk of OPSI and adequate antibiotic treatment for patients with OPSI. After OPSI is diagnosed, mortality rates as high as 50–70% are reported despite appropriate antibiotic and medical management.

Encapsulated organisms are frequently involved in sepsis in patients who have undergone splenectomy. Around 50% of cases are caused by *S pneumoniae*, and 25% by *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pyogenes*. Rarer pathogens, making up the last 25%, include gram-negative organisms such as

Pseudomonas sp.¹ Variation in resistant species is reported by geographical region and by population of patients, as well as between different *S pneumoniae* serotypes. Pneumococci exhibit more non-β-lactamase-mediated resistance to penicillin and other β-lactam antibiotics than they previously did, but they also show more resistance to non-β-lactam antimicrobials.² In several European reports, resistance of pneumococcal isolates to tetracycline hydrochloride of 71% has been reported, to a combination of trimethoprim and sulfamethoxazole of 53%, and for erythromycin up to 51%.

Treatment for suspected pneumococcal illness, irrespective of population, should be based on whether the site of infection is meningeal or non-meningeal. The drugs of choice for suspected bacterial meningitis are ceftriaxone or cefotaxime, based on their bactericidal activity and penetration into the cerebrospinal fluid. If the organism is sensitive or has intermediate resistance to penicillin (minimum inhibitory concentration >0.1–1.0 ng/L), cephalosporin treatment alone is justified. If high-level resistance (minimum inhibitory concentration >2.0 ng/L) is encountered, vancomycin is recommended. Non-meningeal infections with intermediate resistance to penicillin may be treated with high-dose penicillin G, or, if that is ineffective, cefotaxime or ceftriaxone may be used. Again, if high-level penicillin resistance or resistance to cephalosporins is encountered, vancomycin may be needed.³

Prevention of infection is important for patients who are immunocompromised. The pneumococcal vaccine includes 23 serotypes that cause 85–88% of pneumococcal infections. Currently, it is estimated that only 10% of patients for whom vaccination is recommended actually receive the vaccine,⁴ despite many indications existing for vaccination.

Our case is somewhat different, because it was not obvious that our patient was at increased risk, since only a partial splenectomy had been done years previously. Little is known about the risk of OPSI in patients after spleen-preserving surgery. Because the spleen is not necessarily readily dispensable, various alternatives to total splenectomy have been developed to preserve functioning. Splenorrhaphy, partial splenectomy, or autoimplantation of splenic fragments into omental pockets have been done. Autoimplantation does not protect against OPSI,⁵ but vascular supply to the implants is not critical because small multiple peripheral vessels grow in from the

omentum. Radionuclide uptake by the remaining spleen may not correlate with normal immunological functioning and cannot be estimated with the hitherto used tests. Partial splenectomy may not protect against OPSI, and it remains unclear how much spleen must remain to prevent this syndrome.

We conclude that all patients with even a spleen-preserving operation should receive immunisation to avoid an OPSI.

Carsten G Ziske

Medizinische Klinik und Poliklinik I, Rheinische Friedrich-Wilhelms-Universität, 53105 Bonn, Germany
(e-mail: tuohimaa@gmx.de)

- 1 Brigden ML. Postsplenectomy sepsis syndrome: how to identify and manage patients at risk. *Postgrad Med* 1985; **77**: 215–18.
- 2 Lister PD. Multiply-resistant pneumococcus: therapeutic problems in the management of serious infections. *Eur J Clin Microbiol Infect Dis* 1995; **14** (suppl 1): S18–25.
- 3 Pallares R, Linares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *N Engl J Med* 1995; **333**: 474–80.
- 4 Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. *JAMA* 1993; **270**: 1826–31.
- 5 Moore GE, Stevens RE, Moore EE, Aragon GE. Failure of splenic implants to protect against fatal postsplenectomy infection. *Am J Surg* 1983; **146**: 413–14.

Leishmania spp infection in injecting drug users

Sir—I Cruz and colleagues (March 30, p 1124)¹ report that *Leishmania* spp were detected by PCR in 32–52% of the syringes discarded by Spanish injecting drug users. Moreover, they note shared restriction fragment length polymorphisms in roughly 20% of the samples tested, which suggests that clones of leishmania may spread through the sharing of needles.

Their results agree with the previous finding of positive leishmania serology and skin reaction against leishmanin in a high proportion of HIV-1-seronegative Spanish injecting drug users.² However, the data contrast apparently with the fact that the frequency of overt visceral leishmaniasis is declining in our area, mainly because the rate of this disease in HIV-1-coinfected injecting drug users has fallen sharply in the past few years.³

A high number of patients with parasitaemic active infection should exist to explain the proportion of syringes in which leishmania has been

detected. Theoretically, these parasitaemic patients should show symptomatic visceral leishmaniasis, but the number with this disorder is currently low in Spain. However, in one study,⁴ leishmania was detected in peripheral blood samples from a striking proportion of blood donors living in the Mediterranean area. According to these results, frequent occurrence of leishmania parasitaemia might be identified among HIV-1-seronegative asymptomatic injecting drug users living in Spain if a sensitive PCR is used, but this hypothesis has not yet been investigated.

In an epidemiological survey, we collected serum samples from 93 asymptomatic HIV-1 seronegative injecting drug users who shared equipment. All participants lived in Seville. We tested for leishmania antibodies with an immunofluorescent antibody test. 23 (25%) of these individuals had antibody titres of 1/40 or more. Whole blood samples, cryopreserved at -70°C , from these leishmania seropositive individuals were tested for *Leishmania infantum* kDNA by PCR,⁵ and seven were positive. Thus, 7.5% of the total injecting drug users group harboured *L. infantum* in blood without symptoms of overt visceral leishmaniasis. Since all of them shared injection equipment routinely, they could be spreading the infection.

These results are in line with those of Cruz and colleagues and explain why a high proportion of shared syringes contain leishmania, whereas the frequency of overt visceral leishmaniasis declines. Likewise, the previous finding of a high prevalence of indirect markers of leishmania infection² would also be explained. Since asymptomatic parasitemic injecting drug users who share injecting devices seem to be a suitable reservoir for *L. infantum*, an artificial anthroponotic cycle would be completed. Needles and syringes would be the vectors and uninfected injecting drug users the receptors.

*Juan A Pineda, J Martín-Sánchez, J Macías, F Morillas

*Servicio de Medicina Interna, Hospital Universitario de Valme, 41014 Sevilla, Spain; and Departamento de Parasitología, Facultad de Farmacia, Universidad de Granada, Granada (e-mail: japineda@nacom.es)

- 1 Cruz I, Morales MA, Noguera I, Rodríguez A, Alvar J. Leishmania in discarded syringes from intravenous drug users. *Lancet* 2002; **359**: 1124–25.
- 2 Pineda JA, Macías J, Morillas F, et al. Evidence of increased risk for *Leishmania infantum* infection among HIV-seronegative intravenous drug users from Southern Spain. *Eur J Clin Microbiol Infect Dis* 2001; **20**: 354–57.

- 3 de la Rosa R, Pineda JA, Delgado J, et al. Incidence of and risk factors for symptomatic visceral leishmaniasis among human immunodeficiency virus type-1 infected patients from Spain in the era of highly active antiretroviral therapy. *J Clin Microbiol* 2002; **40**: 762–67.
- 4 Le Fichoux I, Quaranta JF, Aufeuve JP, et al. Occurrence of *Leishmania infantum* parasitemia in asymptomatic blood donors living in an area of endemicity in southern France. *J Clin Microbiol* 1999; **37**: 1953–57.
- 5 Martín-Sánchez J, López-López MC, Acedo-Sánchez C, Castro-Fajardo JJ, Pineda JA, Morillas-Márquez F. Diagnosis of infections with *Leishmania infantum* using PCR-ELISA. *Parasitology* 2001; **122**: 607–15.

Health status and subjective economic satisfaction in West Papua

Sir—Richard Horton's March 23 Commentary¹ leads us to ponder the concept of Americanised globalisation.

We have done a medical assessment, in cooperation with a local Christian Hospital, in indigenous people living in Senggo, a rural village in West Papua/Irian Jaya, Indonesia, where the population is about 2000. Senggo is a tidal swampland on the south coast of West Papua, with abundant sago palms, birds, and fish. Economic conditions are generally poor. Birth rates seem to be high but average life expectancy is low.

We used questionnaires to assess subjective quality of life, did physical

examinations, and measured total cholesterol and haemoglobin concentrations. Subjective quality of life was rated on a 100 mm visual analogue scale (worst on the left, best on the right). We asked participants to mark on the scale the level of their economic condition. We defined the distance from the left (mm) to the marked position as the quality of life score.^{2,3}

227 indigenous people (115 men, 112 women, mean age 36.4 years [SD 13.5]) participated. 153 agreed to undergo blood tests. The mean concentrations of total cholesterol (3.7 mmol/L [1.0]) and haemoglobin (104 g/L [19]) were lower than those of healthy Japanese men aged 30–39 years (5.2 mmol/L [0.9], and 151 g/L [9.7]).

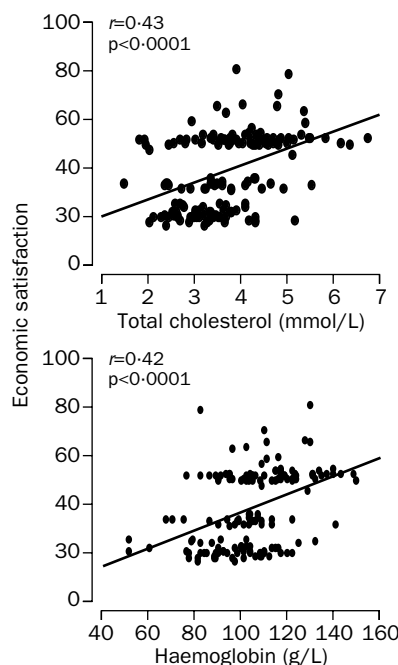
One of the explanations of lower concentrations of total cholesterol and haemoglobin may be widespread and chronic infections of malaria, tuberculosis, and parasites on top of general poor nutrition. There was significant linear association between total cholesterol and haemoglobin concentrations, and, more surprisingly, they both correlated significantly with subjective economical satisfaction (figure). These correlations were stronger among men than women. Total cholesterol and haemoglobin, therefore, seem to be indicators of objective nutritional and chronic infectious state in such regions.

Although economical conditions are recognised as being associated with health and nutritional state, asymptomatic medical disturbances such as cholesterol or haemoglobin concentrations were closely associated with subjective economical satisfaction in West Papua. Although our findings relate to a specific area, they may lead to a more global way of thinking when designing strategy for public health in developing countries.

*Taizo Wada, Koza Matsubayashi, Kiyohito Okumiya, Eva Garcia Del Saz, Toru Kita

*Department of Geriatric Medicine, Kyoto University, Graduate School of Medicine, Kyoto 606-8507, Japan; Centre for Southeast Asian Studies, Kyoto University; and Departments of Medicine and Geriatrics, Anatomy and Cell Biology, Kochi Medical School, Kochi (e-mail: taizow@kuhp.kyoto-u.ac.jp)

- 1 Horton R. The health (and wealth) of nations. *Lancet* 2002; **359**: 993–94.
- 2 Matsubayashi K, Okumiya K, Osaki Y, Fujisawa M, Doi Y. Quality of life of old people in the community. *Lancet* 1997; **350**: 1521–22.
- 3 Morrison DP. The Crichton visual analogue scale for the assessment of behavior in the elderly. *Acta Psychiatr Scand* 1983; **68**: 408–13.



Association of total cholesterol and haemoglobin concentrations with subjective economic status

Screening in clinical trials

Sir—We support the statement by David A Grimes and Kenneth F Schulz (March 9, p 881)¹ that certain features of screening tests are frequently overlooked. However, we disagree with their definition of screening as being tests done among apparently well people to identify those at an increased risk of a disease or disorder. They distinguish between screening and case finding by classifying the latter as looking for additional illnesses in patients with existing medical disorders. These definitions do not match the screening situation in identifying the diagnosis of inborn errors of metabolism, a specialty that is primarily associated with paediatrics, but also important for other areas.

Limited numbers of such inherited diseases (including phenylketonuria, which Grimes and Schulz mention as an example) are detected in the neonatal screening programmes now offered in most industrialised countries. These programmes are compatible with the definition of screening they provide.

However, metabolic screening includes not only general neonatal screening, but also selective screening done because of clinical indications in symptomatic individuals.^{2,3} Selective screening is not looking for additional illnesses, but rather aiming to identify the primary diagnosis and trying to reveal the underlying cause of clinical symptoms. This is done by analyses of several groups of metabolites.²

Selective screening for genetic metabolic disorders is offered by an increasing number of laboratories throughout the world.⁴ The proportion of diagnoses identified by selective screening is generally not higher than a few percent of the patients studied. This rate, however, depends very much on the expertise of the clinicians selecting the patients to be screened.

A case-finding approach⁵ rather than selective screening may be appropriate only if the clinical suspicion is strong for a certain inborn error of metabolism.

SPG is a recipient of a fellowship of the Österreichischer Austauschdienst (ÖAD).

*Jörn Oliver Sass, Sara Pascoe-González, Willy Lehnert.

*Stoffwechsellabor, Zentrum für Kinderheilkunde und Jugendmedizin, Universitätsklinikum Freiburg, D-79106 Freiburg, Germany; and Universitätsklinik für Kinder- und Jugendheilkunde, Innsbruck, Austria (e-mail: sass@kikli.uni-freiburg.de)

- 1 Grimes DA, Schulz KF. Uses and abuses of screening tests. *Lancet* 2002; **359**: 881–84.
- 2 Lehnert W. Long-term results for selective screening for inborn errors of metabolism. *Eur J Pediatr* 1994; **153** (suppl 1): S9–13.
- 3 Sass JO, Sewell AC. Gas chromatography-

mass spectrometry for selective screening for inborn errors of metabolism. In:

Niessen WMA, ed. Current practice of gas chromatography-mass spectrometry. New York: Marcel Dekker, 2001: 341–54.

- 4 Hoffmann GF. Selective screening for inborn errors of metabolism: past, present and future. *Eur J Pediatr* 1994; **153** (suppl 1): S2–8.
- 5 Shah V, Friedman S, Moore AM, Platt BA, Feigenbaum ASJ. Selective screening for neonatal galactosemia: an alternative approach. *Acta Paediatr* 2001; **90**: 948–49.

Sir—David A Grimes and Kenneth F Schulz¹ describe the distortion that can be produced by the presence of lead-time and length biases when seeking to assess the benefits of cancer screening.

These biases arise when the survival experience of people who have cancers detected by screening is compared with that of other people with the same form of cancer. The remedy proposed by Grimes and Schulz is just what is called for—a comparison of mortality rates for people who have (not just cases) and have been not been screened. However, I take issue with their contention that the only way to avoid these pervasive biases is to do randomised controlled trials, since I believe unbiased comparisons of cancer mortality in screened and unscreened groups sometimes can be made without randomisation.

For example, although there have been no randomised trials of the efficacy of screening for cervical cancer, we can be reasonably confident that such efficacy is present given the sharp decline in mortality from cervical cancer in the specific countries and the specific age groups in which screening has become widespread.^{2,3}

Some case-control studies can probably provide an unbiased estimate of the mortality from a given cancer between screened and unscreened groups.⁴ For example, compared with controls, a far smaller proportion of people who died of cancer of the rectum or sigmoid colon were noted to have a history of screening sigmoidoscopy.⁵ Since in the same study controls and people who died from cancer of the ascending or transverse colon did not differ, the evidence that screening sigmoidoscopy leads to life-saving treatment in some people is strong.

Grimes and Schulz accurately refer to randomised trials of screening as a massive and hugely expensive enterprise. I suggest that in some instances the data from non-randomised studies will be sufficiently compelling to make such an enterprise unnecessary.

Noel S Weiss

University of Washington, 1959 NE Pacific St, Rm F263, Box 357236, Seattle, WA 98195, USA (e-mail: nweiss@u.washington.edu)

- 1 Grimes DA, Schulz KF. Uses and abuses of screening tests. *Lancet* 2002; **359**: 881–84.
- 2 Day NE. Effects of cervical cancer screening in Scandinavia. *Obstet Gynecol* 1984; **63**: 714–18.
- 3 Sigurdsson K. Effect of organized screening on the risk of cervical cancer. *Int J Cancer* 1993; **54**: 563–70.
- 4 Weiss NS. Application of the case-control method in the evaluation of screening. *Epidemiol Rev* 1994; **16**: 102–08.
- 5 Selby JV, Friedman GD, Quesenberry CP, et al. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992; **326**: 653–57.

Authors' reply

Sir—Jörn Oliver Sass and colleagues disagree with our definition of screening as testing done among apparently well people. This definition was established in 1951 by the US Commission on Chronic Illness and has been accepted internationally since.¹ Moreover, as we noted in our report on screening, this definition is used by Cuckle and Wald,² who have done extensive work in neonatal screening.

Noel Weiss suggests that unbiased estimates of the benefits of screening, such as for colorectal cancer, can be derived from observational studies. Whereas case-control studies can provide strong level II-2 evidence of the benefit of screening,³ we believe that level I evidence from randomised controlled trials is more compelling.^{4,5} Case-control studies cannot eliminate bias, since people who elect to undergo inconvenient and expensive screening, such as flexible sigmoidoscopy, probably differ in important (and unmeasured) ways from those who choose not to be screened.

David A Grimes, *Kenneth F Schulz
Family Health International, PO Box 13590,
Research Triangle Park, NC 27709, USA
(e-mail: KSchulz@fhi.org)

- 1 Last JM, ed. A dictionary of epidemiology, 2nd edn. New York: Oxford University Press, 1988.
- 2 Cuckle HS, Wald NJ. Principles of screening. In: Wald NJ, ed. Antenatal and neonatal screening. Oxford: Oxford University Press, 1984: 1–22.
- 3 US Preventive Services Task Force. Guide to clinical preventive services, 2nd edn. Baltimore: Williams and Wilkins, 1996.
- 4 UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002; **359**: 1291–300.
- 5 Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut* 2002; **50**: 29–32.

Positive effect of meningococcal C vaccination on serogroup replacement in *Neisseria meningitidis*

Sir—Clinical observation and experimental studies suggest that capsule switching in *Neisseria meningitidis* and in other capsulated bacteria as pneumococci may occur in vivo.

Meningococci of different serogroups, B and C, but with identical serotype and electrophoretic type were detected in the Czech Republic,¹ Canada,² and the Pacific Northwest,³ which suggests that capsule switching with serogroup replacement may be more common than previously expected.

The Basque Country, Northern Spain (2 107 300 inhabitants), is a moderate endemic area of meningococcal disease. For 1988 to 2002, the annual incidence was 3.4–6.2 cases per 100 000 inhabitants. An epidemic outbreak of serogroup C meningococci occurred in Spain in 1997⁴ and a vaccination campaign with the polysaccharide vaccine A+C started in people aged 18 months to 20 years (coverage 88.6%). At the start of 2000, a meningococcal C conjugated vaccine was introduced in the immunisation schedule for children aged 2 months to 6 years, with coverage of 94.9%.

From January to April, 2002, a cluster of meningococcal disease was detected in a region of the Basque Country. The analysis of these isolates showed meningococci (serotype, serosubtype, and multilocus sequence type) 2a:P1.5,

ST-11 that belonged to the ET-37 complex, and were genetically distant from the strains that caused the 1997 outbreak.

Since 2000, strains 2a:P1.5, ST-11 have been detected in 39 people with meningococcal disease in the Basque Country, 19 strains of serogroup C and 20 of serogroup B. The first meningococcus B was isolated 7 months after the first meningococcus C appeared. In most places, meningococci 2a:P1.5, ST-11 are mainly serogroup C.

A detailed study of 26 of 19 serogroup C and seven serogroup B strains made clear the presence of a unique clone. In addition to the same phenotype and multilocus sequence type, all the strains had the same variable region of the porine A (VR1:5) and had almost identical pulsed-field gel electrophoresis patterns (figure).

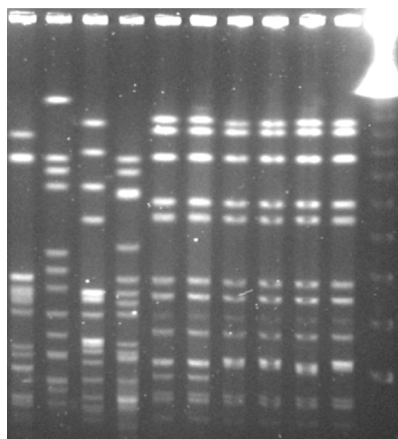
In the Czech Republic¹ and in Canada,² the capsule switching between serogroups B and C were seen in similar isolates (2a:P1.5,2; ST-11, ET-37 complex) to those detected by us, and in both places this switching occurred in a context where the meningococcal C vaccine was being used. Therefore, meningococci 2a:P1.5,[2], ST-11 might have high facility to switch capsule. Moreover, in a population immunised against meningococci C but not meningococci B, replacement of serogroup C 2a:P1.5, ST-11 by serogroup B 2a:P1.5, ST-11 meningococci might easily occur.

Although, probably, meningococcal C vaccination (particularly with the meningococcal conjugated vaccine) produces more advantages than no vaccination, we should be aware of the appearance of variants of meningococci for which there are not yet available vaccines.

*Emilio Pérez-Trallero, Diego Vicente, Mila Montes, Ramón Cisterna

*Servicio de Microbiología, Basque Country Reference Laboratory for Meningococcal Infections, Hospital Donostia, 20014 San Sebastián, Gipuzkoa, Spain; Microbiology Department, Hospital Basurto, Bilbao, Spain, and Basque Country University, Spain (e-mail: mikrobiol@terra.es)

- 1 Kriz P, Giorgini D, Musilek M, Larribe M, Taha MK. Microevolution through DNA exchange among strains of *Neisseria meningitidis* isolated during an outbreak in the Czech Republic. *Res Microbiol* 1999; **150**: 273–80.
- 2 Kertesz DA, Coulthart MB, Ryan JA, Johnson WM, Ashton FE. Serogroup B, electrophoretic type 15 *Neisseria meningitidis* in Canada. *J Infect Dis* 1998; **177**: 1754–57.
- 3 Swartley JS, Marfin AA, Edupuganti S, et al. Capsule switching of *Neisseria meningitidis*. *Proc Natl Acad Sci USA* 1997; **94**: 271–76.
- 4 De Mateo Ontañón S. Enfermedad meningocócica en España, 1990–1997: cambio del patrón epidemiológico. *Rev Esp Salud Publica* 2000; **74**: 387–96.



Pulsed-field gel electrophoresis patterns (after *NheI* restriction) of 10 *N meningitidis* isolates

Lanes 1–4: four non-related isolates of serogroups C, B, W135, and B, respectively; lanes 5 and 6: two *N meningitidis* B 2a:P1.5 isolates; lanes 7–10: four *N meningitidis* C 2a:P1.5 isolates; lane 11: DNA size standard (lambda-ladder, Biorad).

WHO: the casualties and compromises of renewal

Sir—Richard Horton discusses WHO's role in health and human development (May 4, p 1605).¹ Although we will not comment on WHO policy, on behalf of the research-based pharmaceutical industry I would like to respond to his negative views of the industry and clarify a few points on access to medicines and the industry's global responsibilities.

You state that the demands of the private sector trump public-health principles; yet the pharmaceutical industry contributes to global health care in many ways. Primarily, it creates and develops the medicines that save and improve the lives of millions of people.

Furthermore, our companies continuously expand their efforts in improving access for patients to the drugs they need through an increasing number of partnerships with governments and other organisations. Companies are currently engaged in more than 50 separate partnerships around the world, working through individual company contributions or groups of companies in collaboration with international bodies such as WHO and others. Since 1998, the industry has contributed US\$1.9 billion in donations of products to developing countries through partnerships. In addition, we are engaged in many initiatives that provide education, infrastructure, and technical assistance to developing countries.

Some examples of vital public-private partnerships include the Accelerating Access Initiative, which addresses the HIV/AIDS crisis. This initiative involves several companies, UN agencies, and other international institutions working together to supply products at greatly discounted costs to patients in a growing number of countries in Africa and worldwide. By the end of March, 2002, 78 countries had indicated their interest in this scheme, including 41 countries in Africa. 18 countries have already concluded memorandums of agreement with companies, including 13 in Africa. One company is offering a drug for opportunistic HIV/AIDS infections at no cost in the 50 least developed countries, as defined by the United Nations. Furthermore, industry has also played a leading part in the establishment of the Medicines for Malaria Venture, one of the first public-private partnerships focusing on affordable product development for a

disease prevalent in developing countries. Companies are now contributing their skills and expertise to the objective of bringing forwards one new antimalarial medicine every 5 years. We are also an active partner in the Global Alliance for Vaccine and Immunisation (GAVI), which is boosting immunisation rates and reducing the gap in vaccine access among children in developing countries.

Thus, the extent of the pharmaceutical industry's support goes well beyond the realms of traditional philanthropy, and places the industry in a leading position among all industries in addressing the issue of limited access to medicines.

Harvey Bale Jr

International Federation of Pharmaceutical Manufacturers Associations, 1211 Geneva 13, Switzerland
(e-mail: admin@ifpma.org)

- 1 Horton R. WHO: the casualties and compromises of renewal. *Lancet* 2002; **359**: 1605–11.

How to survive the survival plots

Sir—Stuart Pocock and colleagues (May 11, p 1686)¹ provide an excellent and timely highlight of the common pitfalls encountered in survival analysis, which is widely used in the clinical trials of chronic diseases. This practical guide is the best I have seen on how to critically appraise survival plots since those provided by Peto and colleagues.² However, two further issues frequently confuse general readers such as myself.

First, the terms relative risk and risk reduction are sometimes used in survival analyses.³ These parameters are not, however, derived from the event rates of the treatment groups at the end of follow-up. Rather, they are related to the hazard ratio of the survival plots, such that relative risk is equal to hazard ratio, and risk reduction is equal to one minus the hazard ratio. This derivation may not be familiar to many readers and most reports do not emphasise this distinction.

Second, the number needed to treat (NNT) in survival analysis ideally should incorporate the time-dependent nature of the data by being calculated from the hazard ratio,⁴ but this has not been a common practice. Some appraisers simply ignore the survival plots and calculate the NNT based on the difference in event rates between treatment groups at the end of follow-up.⁵

Evidence-based medicine requires a

basic understanding of how to critically appraise statistical interpretation of clinical data. I hope that experts in survival analysis will continue to offer practical advice in this important area.

Mário L de Lemos

Systemic Therapy Program, British Columbia Cancer Agency, Vancouver, BC, Canada V5Z 4E6
(e-mail: mdelemos@bccancer.bc.ca)

- 1 Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet* 2002; **359**: 1686–89.
- 2 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient, II: analysis and examples. *Br J Cancer* 1977; **35**: 1–39.
- 3 Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**: 709–17.
- 4 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999; **319**: 1492–95.
- 5 New drugs, V: spironolactone (Aldactone®). In: Anon. Therapeutics letter, 34. Vancouver: University of British Columbia, 2000.

Where health care is not a right

Sir—You are right in your June 1 Editorial,¹ that “it is difficult to understand how such a scandalous situation can be tolerated in the USA, a country of such great wealth and resources”. However, you only touch the problem.

First, there is no health-care system in the USA, rather we have an exceedingly complex and inefficient medical industry whose sole purpose is to generate money. The system is driven by market forces rather than by social need. It is a system in which multiple parties are competing for the same dollar and where care has fallen by the wayside. How can you provide health care when health insurance companies profit by limiting and denying medical services.

The inequities in the distribution in health care go far beyond the uninsured. In many areas of the USA, including the capital, the treatment a patient receives is largely affected by ethnic origin and wealth.²

American's were shocked when the Institute of Medicine claimed that more than 44 000 Americans die each year from medical errors, and that serious and widespread quality issues exist throughout US medicine.³ The US health system spends a higher portion of its gross domestic product than any

other country, but according to the WHO World Health Report, ranks only 37th according to its performance.⁴ Furthermore, US medical researchers are among the best in the world, yet most Americans do not benefit from their brilliance since evidence-based medicine is perceived as being a violation of the physicians' first-amendment right.⁵

I am proud to be an American (naturalised). The USA is a great country, but God help you if you are sick. Our health system requires immediate resuscitation if we plan to provide high-quality equitable health care for all our countrymen.

Paul Marik

Department of Critical Care Medicine, University of Pittsburgh Medical School, 640A Scaife Hall, 3550 Terrace Street, Pittsburgh, PA 15261, USA
(e-mail: maripe@ccm.upmc.edu)

- 1 Editorial. Where health care is not a right. *Lancet* 2002; **359**: 1871.
- 2 Fiscella K, Franks P, Gold MR, Clancy CM. Inequality in quality: addressing socioeconomic, racial, and ethnic disparities in health care. *JAMA* 2000; **283**: 2579–84.
- 3 Kohn LT, Corrigan JM, Donaldson MS. To err is human: building a safer health system. Washington: National Academy Press, 2000.
- 4 WHO. World Health Report Statistics 2000. <http://www.who.int/whr/2000/en/statistics.htm> (accessed July 24, 2002).
- 5 Rich MW. From clinical trials to clinical practice: bridging the GAP. *JAMA* 2002; **287**: 1321–23.

DEPARTMENT OF ERROR

Tobacco money: up in smoke?—In this Viewpoint by Steven Woloshin and colleagues (June 15, p 2108), the last sentence of the last paragraph on page 2108 should be, “To do so, investigators are recruiting 10 000 individuals who are aged 60 years or older, have at least a 10 pack-year smoking history (at least one packet a day for 10 years, or two packets for 5 years), report no history of cancer, and are fit to undergo screening with spiral CT.” Also, the second sentence in the fifth paragraph on page 2110 should be “About 5% of patients assessed for lung reduction surgery had unsuspected lung cancer detected during preoperative examination.”¹⁶

Blunt and penetrating injuries caused by rubber bullets during the Israeli-Arab conflict in October, 2000: a retrospective study—In this Article by Ahmad Mahajna and colleagues (May 25, p 1795), figure 1 should have appeared as below.

