

CORRESPONDENCE

Detection of HCV RNA in semen

Sir—The detection of hepatitis C virus (HCV) RNA in seminal fluid from eight (38%) of 21 men in Marianne Leruez-Ville and colleagues' report (July 1, p 42)¹ could be seen to strengthen the argument for a large proportion of HCV cases being sexually acquired. The Centers for Disease Control and Prevention, for example, has estimated the proportion to be 20% in the USA.² There are, however, several reasons why Leruez-Ville and colleagues' findings do not necessarily support the sexual transmissibility of HCV.

First, the load of seminal plasma HCV RNA was low (<200 copies/mL) in three men, and undetectable on quantitative viral load assessment (<100 copies/mL) in the other five men positive on qualitative assessment. These loads contrast with those for two other blood-borne viruses, HIV-1 and hepatitis B virus (HBV), in which 100 000–1 million copies/mL are frequently present in semen,³ and which have clearly proven epidemiological sexual transmissibility. Second, as Leruez-Ville and colleagues acknowledge, the HCV RNA detected might not represent infectious virus with cell-culture and animal-model systems required to assess infectiousness. Third, other settings exist in which the presence of detectable virus in bodily fluids does not translate to important infectiousness. The relatively low level for detection of HIV-1 RNA in saliva in about 50% of people with detectable serum HIV-1 RNA,⁴ for example, does not imply a notable risk of oral-to-oral or oral-to-genital transmission.

A more valid assessment of the efficiency of sexual transmission of HCV is through longitudinal studies of discordant couples. Such studies show an extremely low to negligible risk. Cross-sectional studies of partners of people with HCV infection, in whom other risk factors are unlikely, such as the female partners of male haemophiliacs with hepatitis C, are consistent with an extremely low risk of sexual transmission.⁵ Sexual practices that involve blood-to-blood contact are an exception to this general rule. The proponents of a reliable frequency of sexual transmission of HCV reference

studies in which up to 20% of people report multiple sexual partners as their only risk factor for HCV infection.² Those studies, based on self-reported risk behaviour, almost certainly are biased by the presence of residual confounding by under-reporting of non-sexual risk behaviours, such as injecting drug use.

Although the detection of HCV RNA in semen is of biological interest, it should not change counselling of people with HCV infection and their partners. The message should continue to be that the risk of sexual transmission of HCV is extremely low.

*Gregory J Dore, John M Kaldor

*National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney 2010, Australia; and St Vincent's Hospital Hepatitis Clinic, Sydney (e-mail: gdore@ncher.unsw.edu.au)

- 1 Leruez-Ville M, Kunstmann J-M, De Almeida M, Rouzioux C, Chaix M-L. Detection of hepatitis C virus in the semen of infected men. *Lancet* 2000; **356**: 42–43.
- 2 Alter MJ. Epidemiology of hepatitis C. *Hepatology* 1997; **26** (suppl 1): 62–65.
- 3 Dyer JR, Kazembe P, Vernazza PL, et al. High levels of human immunodeficiency virus type 1 in blood and semen of seropositive men in sub-Saharan Africa. *J Infect Dis* 1998; **177**: 1742–46.
- 4 Shepard RN, Schock J, Robertson K, et al. Quantitation of human immunodeficiency virus type 1 RNA in different biological compartments. *J Clin Microbiol* 2000; **38**: 1414–18.
- 5 Brettler DB, Mannucci PM, Gringeri A, et al. The low risk of hepatitis C virus transmission among sexual partners of hepatitis C-infected hemophilic males: an international, multicenter study. *Blood* 1992; **80**: 540–43.

Authors' reply

Sir—We agree with Gregory Dore and John Kaldor that epidemiological data published on sexual transmission of HCV are inconsistent. There are, however, epidemiological arguments for transmission between spouses that cannot be completely ignored.^{1,2}

The main argument against HCV sexual transmission is the absence of HCV recovery in semen.³ We show that, with adapted techniques, low HCV RNA load can be recovered frequently from semen. The detection of HCV RNA does not prove that the virus present in semen is infectious or consistent with sexual transmission of

HCV, as seen for hepatitis B virus and HIV-1, and the overall risk of HCV sexual transmission is probably low. HCV is, however, probably present in seminal fluid because of passive transport of the virus from the systemic compartment to the genital tract. Therefore patients with a very high blood viral load might have a higher semen viral load and be at increased risk of sexual transmission. Isolation of a subgroup of men, at potential risk of transmitting the virus sexually, might be possible.

Our results and those of Levy and colleagues⁴ should be considered when deciding the management of HCV-infected infertile couples seeking assisted reproduction. Assisted reproduction techniques in HCV-infected patients with potentially HCV-infected gametes could lead to contamination of a couple's embryos or, through unsafe manipulation of infected samples, gametes or embryos originating from non-infected couples.

Finally, we agree with Dore and Kalder that our results should not be used to change the counselling of couples with one seropositive partner, such as no recommendations for barrier methods of contraception in stable monogamous relationship.⁵ From a scientific point of view, our results should not be ignored and further studies are needed to evaluate HCV viral load in the semen of a larger population of infected men.

*Marianne Leruez-Ville,

Christine Rouzioux, Marie-Laure Chaix

Service de Bactériologie, Virologie Parasitologie, Hygiène, Groupe Hospitalier Necker-Enfants Malades, 75743 Paris, France

- 1 Mele A, Stroffolini T, Tosti ME, et al. Heterosexual transmission of hepatitis C in Italy. *J Med Virol* 1999; **57**: 111–13.
- 2 Salleras L, Bruguera M, Vidal J. Importance of sexual transmission of hepatitis C virus in seropositive pregnant women: a case control study. *J Med Virol* 1997; **52**: 164–67.
- 3 Semprini AE, Persico T, Thiers V, et al. Absence of hepatitis C virus and detection of hepatitis G virus/GB virus C RNA sequences in the semen of infected men. *J Infect Dis* 1998; **177**: 848–54.
- 4 Levy R, Tardy JC, Bourlet T, et al. Transmission risk of hepatitis C virus in assisted reproductive techniques. *Hum Reprod* 2000; **15**: 810–16.
- 5 Wejstal R. Sexual transmission of hepatitis C virus. *J Hepatol* 1999; **13** (suppl): 92–95.

Growth and autoantibodies to IA-2 in children with type 1 diabetes

Sir—G J Bruining and colleagues (Aug 19, p 655)¹ report the association between infant growth before onset of type 1 diabetes and autoantibodies to IA-2 (tyrosine phosphatase pancreatic β -cell-like protein) at diagnosis. Their major conclusion is that increased body-mass index in the first year of life and accelerated linear growth in the second and third year of life are risk factors for earlier development of diabetes.¹

We have investigated growth, insulin-like growth factor (IGF) system, metabolic status, and autoantibodies in 60 children (mean age 6.4 years [95% CI 5.4–7.4]) with type 1 diabetes at onset of disease. We analysed blood samples taken within 24 h of diagnosis. The relations between growth, IGF system and acidosis have been described in detail elsewhere.² However, we saw a close relation between stature (expressed as SD score) and autoantibodies to IA-2 ($r=0.36$, $p=0.01$) that puzzled us, and we omitted mentioning this association in the report so we could wait for a plausible explanation and further confirmation. Bruining and colleagues' finding, therefore, prompted us to reconsider our data. According to their results, stature in our children at diagnosis correlated with IA-2 but not with antibodies to glutamic acid decarboxylase ($p=0.98$); however, we have found no significant correlation between body-mass index and IA-2 antibodies.

In attempting to interpret their results, Bruining and colleagues quote the report of E Sabbah and colleagues, in which they report an inverse correlation between IA-2 antibodies and C-peptide concentrations.³ Sabbah and co-workers speculate that, since IA-2 antibodies seem to reflect the decay of β -cell function, increased growth in infancy may lead, through a higher production of IA-2 autoantibodies, to a more rapid exhaustion of β -cells. Contrary to this hypothesis, we saw no correlation between IA-2 antibodies and C-peptide concentrations at diagnosis.

Our results confirm the close correlation between linear growth and autoantibodies to IA-2, but the explanation of this relation and its pathophysiological meaning remain, in our view, unclear.

*S Cianfarani, R Bonfanti, M L Manca Bitti, G Chiumello, B Boscherini

*Departments of Paediatrics, "Tor Vergata" University, 00133 Rome, Italy, and Istituto Scientifico H S Raffaele, Milan (e-mail: stefano.cianfarani@uniroma2.it)

- 1 Bruining GJ, for the Netherlands Kolibri study group of childhood diabetes. Association between infant growth before onset of juvenile type-1 diabetes and autoantibodies to IA-2. *Lancet* 2000; **356**: 655–56.
- 2 Cianfarani S, Bonfanti R, Manca Bitti ML, et al. Growth and insulin-like growth factors (IGFs) in children with insulin-dependent diabetes mellitus (IDDM) at onset of disease: evidence for normal growth, age dependency of the IGF system alterations and presence of a small (~18 kDa) IGFBP-3 fragment in serum. *J Clin Endocrinol Metab* 2000; (in press).
- 3 Sabbah E, Savola K, Kulmala P, et al. Diabetes-associated autoantibodies in relation to clinical characteristics and natural course in children with newly diagnosed type 1 diabetes. *J Clin Endocrinol Metab* 1999; **84**: 1534–39.

Randomisation in the SYMPHONY trial

Sir—The report by the SYMPHONY investigators (Jan 29, p 337)¹ is explicit about how treatments were assigned to participants. Full and clear reporting of methods, as recommended by the CONSORT statement,² allows readers to assess and critically appraise the methods used in a randomised trial.

Randomisation in SYMPHONY was done in blocks of six, stratified by whether patients had had a myocardial infarction or unstable angina. There were separate randomisation schemes for each of three regional randomisation centres. These procedures should have led to a close balance in the numbers of patients in each of the three treatment groups and in each clinical group. Specifically, each block of six should have included two patients on each of the three treatments, so the maximum possible imbalance between the numbers in any pair of treatments is 12 (two per group in each stratum and in each randomisation centre). Within strata, the maximum imbalance is six.

The numbers actually randomised (table) show much larger imbalances than could be possible with the randomisation system described, overall and in each of the two strata. Can the investigators say whether the imbalance arose in all three centres, and explain the large discrepancy between their stated methods and the numbers actually randomised?

	Aspirin (control) (n=3089)	Low-dose sibralfiban (n=3105)	High-dose sibralfiban (n=3039)	Maximum difference (n=66)
Myocardial infarction	2239	2218	2209	30
Angina	839	879	817	62

Numbers randomised overall and within strata¹

Also, some patients (11, eight, and 13 in the treatment groups, respectively) seem to have had neither indication used to define the randomisation strata—how were they randomised?

Douglas G Altman

ICRF Medical Statistics Group, Centre for Statistics in Medicine, Institute of Health Sciences, Headington, Oxford OX3 7LF, UK (e-mail: d.altman@icrf.icnet.uk)

- 1 The SYMPHONY investigators. Comparison of sibralfiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. *Lancet* 2000; **355**: 337–45.
- 2 Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT Statement. *JAMA* 1996; **276**: 637–39.

Authors' reply

Sir—Douglas Altman raises interesting issues about randomisation in clinical trials and highlights the importance of careful reporting of methods and results. Although there are many methods for developing a randomisation scheme, we used a standard procedure to stratify by site, with a block size of six. We also stratified by indication, but because of limited space we did not report routine stratification by site. When the randomisation scheme was generated, we confirmed that it was balanced, with each block consisting of an equal number of treatment assignments. In the study, 670 sites enrolled patients in up to two strata, which led to 1123 strata with at least one patient. Three randomisation centres were used (Duke Clinical Research Institute, USA, Leuven Coordinating Center, Belgium, and the National Health and Medical Research Council Clinical Trials Center, Sydney). The table shows the observed treatment assignment.

Although the block size for randomisation was six, many sites enrolled fewer than six patients per indication. In addition, there were incomplete blocks for sites that enrolled more than six patients per indication, which led to imbalance in the overall number of patients assigned each treatment. These imbalances should cancel out across the strata, so we performed simulations to calculate the probability of the observed imbalance.

In the simulation, we created 1000 replicate randomisation schemes with the original randomisation algorithm, each with a different random seed number for the random-number generator. We applied each of the 1000

Centre	Number of sites	Low-dose sibralfiban	High-dose sibralfiban	Control	Total	Maximum difference
DCRI						
MI	359	1304 (33.9%)	1258 (32.7%)	1285 (33.4%)	3847	46
Angina	251	379 (34.3%)	352 (31.9%)	373 (33.8%)	1104	27
All	367	1683 (34.0%)	1610 (32.5%)	1658 (33.5%)	4951	73
LCC						
MI	230	738 (32.7%)	769 (34.1%)	749 (33.2%)	2256	31
Angina	176	419 (33.2%)	423 (33.5%)	419 (33.2%)	1261	4
All	244	1157 (32.6%)	1192 (33.9%)	1168 (33.2%)	3517	35
NHMRC						
MI	59	205 (34.2%)	194 (32.3%)	201 (33.5%)	600	11
Angina	48	60 (36.4%)	43 (26.1%)	62 (37.6%)	165	19
All	59	265 (34.6%)	237 (31.0%)	263 (34.4%)	765	28
Total						
MI	648	2247 (33.6%)	2221 (33.1%)	2235 (33.3%)	6703	26
Angina	475	858 (33.9%)	818 (32.3%)	854 (33.8%)	2530	40
All	670	3105 (33.6%)	3039 (32.9%)	3089 (33.5%)	9233	66

DCRI=Duke Clinical Research Institute; LCC=Leuven Coordinating Center; NHMRC=National Health and Medical Research Council Clinical Trials Center; MI=myocardial infarction.

Randomisation for SYMPHONY trial

randomisation schemes to the observed Duke Clinical Research Institute enrolment pattern as for the original randomisation and recorded the treatment assignment. Among the replicates, the 50th percentile for the maximum difference was 26, and 99% of the replicates had maximum differences of 68 or less. The maximum difference of 73 seen at Duke Clinical Research Institute was very unusual. Only four replications had a maximum difference of 73 or more.

Although the imbalance in the numbers of patients assigned to each group seen in SYMPHONY was an unusual result of the randomisation scheme and patterns of enrolment, we are confident that a true random assignment occurred.

*L Kristin Newby, Manju V Bhopkar, Kerry L Lee, Robert M Califf, for the SYMPHONY Investigators

Duke Clinical Research Institute, Duke University Medical Center, PO Box 17969, Durham, NC 27715, USA

Medical ethics

Sir—Your editorial (Aug 19, p 607)¹ debates a serious and urgent problem: direct-to-consumer advertising. In the USA, the Food and Drug Administration relaxed their guidelines in August, 1997, and the experience since then is not encouraging. *American Medical News*, a publication of the American Medical Association, reported after 1 year that 80% of patients (>12 million) who requested a drug they saw advertised received a prescription for that drug from their physician.² Drug advertising officials therefore, replace doctors as medical treatment decision-makers. Patients have now requested that the US Congress makes pharmaceutical direct-

to-consumer advertising illegal, just as that for alcohol and cigarettes.

Unfortunately, your editorial does not address other, equally important related issues facing the medical profession and society. Producers of the cholesterol-reducing drugs, statins, have accelerated a new form of direct-to-consumer advertising campaign. Members of that group voiced their opinion that some statins should be available to consumers as over-the-counter (OTC) drugs without prescription, which was not criticised by the medical community. At two international major conferences, speakers from academia, and not industry, supported such a strategy. Reuters Health circulated a story entitled *OTC generic availability of statins predicted to expand use greatly*. Statins are currently estimated to be used by more than 12 million people in the USA alone, and half of the adult US population could eventually be taking statins.

One of the claimed attractions for the public of OTC statins is lower prices. However, payments in the USA by Medicare and most insurance companies would be discontinued and the financial burden faced by the consumer.

Statins are well established as useful drugs for some forms of cardiovascular disorders. Yet, the other side of the coin, frequently neglected, is that statins can cause serious adverse effects, such as myopathies and rhabdomyolysis with renal failure. Data suggest that these drugs are also implicated in hepatic toxicity, cataracts, neoplasia, and some psychiatric disturbances, directly or indirectly related to lowered cholesterol concentrations.³ Furthermore, the six approved statins were introduced in the USA only 3–9 years ago and we do not

know the long-term side-effects. Patients on statins should be assessed periodically for liver function, raised creatine kinase, and blood lipid profiles.

The complex effects of statins, referred to as pleiotropic effects, influence various major systems, and include vasodilative, antithrombotic, antioxidant, antiproliferative, anti-inflammatory,⁴ immunosuppressive and bone-growth stimulation. Most pleiotropic effects are added automatically, without critical assessment, to the extended list of beneficial effects. Only few clinicians regard some effects as controversial or even adverse.⁴

Furthermore, statins restrict cholesterol biosynthesis and other end products of the same mevalonate pathway, such as dolichols and coenzyme Q, which contribute to various vital functions. The deficiency of these end products may aggravate further the side-effects of statins.³

To expect that hyperlipidaemic patients will try diet and lifestyle changes and will visit their physicians regularly for years for laboratory assessment during their statin treatment, is naïve. Many patients will jump on the OTC-statin bandwagon for the duration of this lengthy and expensive treatment, with negative consequences.

The close physician-industry relation has been long overlooked but was addressed in a short report.⁵ An analysis at the University of California, USA, of studies on heart drugs showed that 96% of investigators who had drug-company ties declared the tested drug to be safe, compared with only 37% of those with no ties.

The results of many published surveys still place physicians high on the ethical and moral scales of professionals. Let us keep it that way!

Emile G Bliznakov

Biomedical Research Consultants, 2821 North Course Drive (H-205), Pompano Beach, FL 33069, USA

- 1 Editorial. Experimenting with direct-to-consumer advertising. *Lancet* 2000; **356**: 607.
- 2 Gianelli D. Prescription for persuasion: direct-to-consumer ads. *Am Med News* 1998; **Nov 23/30**: 8–10.
- 3 Bliznakov EG, Wilkins DJ. Biochemical and clinical consequences of inhibiting coenzyme Q biosynthesis by lipid-lowering HMG-CoA reductase inhibitors (statins): a critical overview. *Adv Therapy* 1998; **15**: 218–28.
- 4 Davignon J, Laaksonen R. Low-density lipoprotein-independent effects of statins. *Curr Opin Lipidol* 1999; **10**: 543–59.
- 5 Business in brief: bias in drugmaker-financed studies. *Am Med News* 2000; **Sept 4**: 18.

Onchocerciasis control strategies

Sir—Frank Richards and colleagues (May 13, p 1663)¹ raise strategic issues relating to the onchocerciasis control programmes. The strategy of the African Programme for Onchocerciasis Control (APOC) is based on annual mass treatment with ivermectin. Richards and colleagues state that APOC accepts that this strategy “will not stop transmission” and that “treatment may need to be continued indefinitely”. However, community trials have shown that mass treatment with ivermectin results in a major reduction in onchocerciasis transmission and that repeated ivermectin treatment reduces the productivity of adult *O. volvulus*.^{2,3} Computer simulations indicate that interruption could be achieved after 15–25 years of annual treatment.⁴

The objective of APOC is to establish sustainable, community-directed treatment with ivermectin by 2007, when the programme will come to an end, with the goal of eliminating onchocerciasis as a public health and socioeconomic problem throughout Africa. APOC does envisage an endpoint for yearly ivermectin treatment but the required duration is being determined by the establishment of a monitoring system to assess the decline in infection and transmission levels.

In most of the area covered by the Onchocerciasis Control Programme in West Africa (OCP) that has been under effective control, the parasite has been virtually eliminated. In these areas, vector control ceased in 1989 and although the vector returned to pre-control densities within weeks, transmission has remained interrupted and no further intervention has been needed. OCP established a surveillance system for early detection of possible recrudescence and had developed an intervention strategy that aims to quickly stop transmission by ivermectin treatment. Thus, for much of the OCP area, surveillance by national teams will be the only intervention when OCP comes to an end in 2002. Contrary to Richards and Colleagues' assumptions, only the OCP areas that have not fully benefited from vector control, will switch to the APOC strategy. In an isolated focus in Senegal, ivermectin treatment

was given biannually in an attempt to interrupt transmission. Preliminary results indicate that this aim has been achieved after 9 years of intervention. If confirmed, these results might warrant further experimentation with 6-monthly treatment in large hyperendemic areas in Africa.

Richards and colleagues also refer to 6-monthly treatment in Guatemala and Ecuador. However, experiences in Africa and South America are difficult to compare because of differences in vectors and numbers of people affected.

Doubling the number of treatments would have major implications, and Richards and colleagues do not recognise the logistics and costs of additional treatment. These include geopolitical realities of distribution in complex emergencies; the need to continue expansion of APOC into the remaining hyperendemic and mesoendemic areas; and the uncertainties about onchocerciasis transmission in hypoendemic areas.

Whatever the frequency of treatment, a definite solution will be difficult with ivermectin alone. Research on alternative drugs that would kill or sterilise the adult worms is going ahead. Promising results have been obtained with moxidectin.⁵ Work on the effect of albendazole 400 on onchocerciasis, whether alone or in combination with ivermectin (the same dose as recommended for lymphatic filariasis elimination), shows that albendazole 400 had no effect on the viability or reproductive capacity of adult *O. volvulus*.

We agree the lymphatic filariasis programme offers synergy and reinforcement of control. But annual treatment with albendazole and ivermectin is unlikely to have more effect on onchocerciasis than ivermectin alone.

Adenike Abiose, Mamoun Homeida, Bernhard Liese, *David Molyneux, Hans Remme

Expert Advisory Committee of the Onchocerciasis Control Programme in West Africa, National Eye Institute, PMB 2267, Kaduna, Nigeria; Technical Consultative Committee of the Africa Programme for Onchocerciasis Control, University of Khartoum, Sudan; Human Development, Africa Region, World Bank, Washington, DC 20433, USA; *Liverpool School of Tropical Medicine, Liverpool L3 5QA, UK; and World Health Organization, 1211 Geneva 27, Switzerland

1 Richards F, Hopkins D, Cupp E. Programmatic goals and approaches to onchocerciasis. *Lancet* 2000; **355**: 1663–64.

- 2 Boussinesq M, Prod'hon J, Chippaux JP. *Onchocerca volvulus*: striking decrease in transmission in the Vina valley (Cameroon) after eight annual large scale ivermectin treatments. *Trans R Soc Trop Med Hyg* 1997; **91**: 82–86.
- 3 Plaisier AP, Alley ES, Boatman BA, et al. Irreversible effects of ivermectin on adult parasites in onchocerciasis patients in the Onchocerciasis Control Programme in West Africa. *J Infect Dis* 1995; **172**: 204–10.
- 4 Plaisier AP, van Oortmarssen GJ, Habbema JD, Remme J, Alley ES. ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis. *Comput Methods Programs Biomed* 1990; **31**: 43–56.
- 5 World Health Organisation. A suitable macrofilaricide? *TDR News* 2000; **62**: 11.

Authors' reply

Sir—Adenike Abiose and colleagues underscore the need for a better scientific basis for post OCP and ongoing APOC activities in long-term control of *Onchocerca volvulus* in Africa. The central idea we tried to communicate is that increasing treatment in time or space during the African programmes may decrease the risk of returning to where they started after 75 years.

OCP will end in 2002, after which all onchocerciasis control in Africa will depend primarily on the success or failure of annual ivermectin treatment. Published ONCHOSIM (computer simulation programme) modelling results show that 25 years of annual ivermectin treatment in hyperendemic communities without concurrent vector control has a high risk of failure.^{1,2} Habbema and colleagues state “. . . long-term annual ivermectin administration may be appropriate for the control of blindness and related morbidity in a community, but not for eradicating the parasite”.¹ The model predicts that after 25 years of mass annual ivermectin therapy, onchocerciasis morbidity in hyperendemic areas would return to preintervention levels 50 years after mass treatment ends. There has been interest in whether more frequent ivermectin treatments could completely interrupt transmission. 6-monthly ivermectin treatment for 12.5 years in hyperendemic communities, modelled by ONCHOSIM, was reported to have a good probability of successfully interrupting transmission without recrudescence, assuming no reintroduction of infection as a result of immigration of infected people or flies.³ On the basis of

another model, (SIMON), ivermectin treatment at 6-monthly intervals for 18 years could allow cessation of treatment without recrudescence.⁴ Abiose and colleagues note what has been an apparently successful 6-monthly treatment regimen for interrupting transmission in Senegal, and state that the post-OCP strategy to stop recrudescence is based on surveillance and rapid intervention through mass ivermectin treatment twice or three times a year. We are perplexed by their statement: "a premature change to 6-monthly treatment may just increase the cost for the same outcome".

Abiose and colleagues are against treating in hypoendemic areas because of the "uncertainties about the role of hypoendemic areas in onchocerciasis transmission". WHO's onchocerciasis community endemicity classifications were developed by OCP with ocular morbidity in mind, not parasite transmission.⁴ However, hypoendemic communities may have prevalence of skin microfilaria that reach 39% of residents (and an onchocercoma prevalence of up to 19%). Uncertain transmission of a vector-borne infectious agent does not lead to 39% infection rates in at risk populations. There was entomological evidence of transmission of *O. volvulus* in hypoendemic areas in Guinea Bissau, which has now been stopped by mass ivermectin administration.⁵

APOC's lack of support for treatment in hypoendemic areas reflects an ivermectin delivery strategy aimed fundamentally at morbidity control. Annual treatment may reduce transmission in hyper- and mesoendemic areas, and APOC may one day define and implement a routine monitoring system to show this, but the exclusion of hypoendemic areas from the programme means that APOC is unlikely to completely interrupt parasite transmission in the countries APOC assists.

The new lymphatic filariasis (LF) elimination programme might provide combined annual albendazole/ivermectin treatment in many hypoendemic onchocerciasis areas without an increased cost to APOC. We should use this opportunity to monitor the impact of the LF Programme on *O. volvulus* transmission where these infections are coendemic.

*Frank Richards, Donald Hopkins,
Ed Cupp

Global 2000 River Blindness Program, The Carter Center, Atlanta, GA 30307, USA; and Department of Entomology and Plant Pathology Auburn University, Auburn, Alabama

- 1 Habbema JDF, Alley ES, Plaiser AP, van Oortmarssen GJ, Remme JHF. Epidemiological modeling for onchocerciasis control. *Parasitol Today* 1992; **8**: 99–103.
- 2 Plaiser AP. The use of ONCHOSIM for the evaluation and prediction of OCP operations: past, present and future. Report to the 20th session of the OCP Expert Advisory Committee, Item 20.3. Ouagadougou, 7–11 June, 1999: 46.
- 3 WHO Expert Committee on Onchocerciasis, third report. Technical Report Series 752, World Health Organization, Geneva, 1987: 120–21.
- 4 Davies JB. Description of a computer model of forest onchocerciasis transmission and its application to field scenarios of vector control and chemotherapy. *Ann Trop Med Parasitol* 1993; **87**: 41–63.
- 5 Boatman BA, Hougard JM, Alley ES, et al. The impact of Mectizan on the transmission of onchocerciasis [suppl]. *Ann Trop Med Parasitol* 1998; **92** (1): S47–60.

OPUS and routine angiography

Sir—The full results of the OPUS trial reported by W Douglas Weaver and colleagues (June 24, p 2199)¹ had an important impact on routine angioplasty worldwide, prompting interventional cardiologists to use systematic stenting of any discrete lesion located on vessels of more than 3 mm diameter and, thereby encouraging the use of direct stenting.

Provisional stenting is of potential interest. In subgroups of the BENESTENT trial,² a randomised study,³ and some registries from high-volume centres, stent-like results obtained with regular balloon angioplasty could have immediate and long-term effects similar to those seen after stenting with no increase in the number of in-stent re-stenosis lesions. Nonetheless, the publication of the results of the OPUS 1 trial in a journal such as *The Lancet* might be taken to be the final word on the subject. However, Weaver and colleagues' report should be read with great care and attention, as it has some serious limitations.

If the aim of the study was to show that provisional stenting would result in clinical evolution comparable with that seen with systematic stenting, an equivalence trial would have been more appropriate. The acceptable limits of the difference in clinical

evolution between the two strategies could have then been defined. Such a trial could have started without a predefined sample size of 2000 patients, and avoided being forced to stop prematurely because of low recruitment rate.

The definition of the primary endpoint is questionable. In most studies comparing clinical evolution after angioplasty, the primary endpoint includes non-Q wave infarction defined by enzyme release at 12–24 h. Weaver and co-workers made no effort to track creatine kinase release after angioplasty, despite this marker's important prognostic value for survival and target-lesion revascularisation at 6 months.^{4,5}

The lack of core laboratory analysis of quantitative coronary angiography data before and after angioplasty means comparison of this study with other studies is not possible, and precludes clear definition of the nature of the immediate results in the so-called optimum PTCA group.

The OPUS trial addresses a very important issue. There are, however, some serious limitations in the methods that call into question the validity of the results.

*François Schiele, Jean-Pierre Bassand

Department of Cardiology, Pôle Coeur Poumon, University Hospital Jean-Minjoz, 25030 Besançon Cedex, France (e-mail: francois.schiele@ufc-chu.univ-fcomte.fr)

- 1 Weaver D, Reisman M, Griffin J, et al. Optimum percutaneous transluminal coronary angioplasty compared to routine stent strategy trial (OPUS-1): a randomised trial. *Lancet* 2000; **355**: 2199–203.
- 2 Foley DP, Serruys PW. Provisional stenting: stent-like balloon angioplasty—evidence to define the continuing role of balloon angioplasty for percutaneous coronary revascularisation. *Semin Interv Cardiol* 1996; **1**: 269–73.
- 3 Rodriguez A, Ayala F, Bernardi V, et al. Optimal coronary balloon angioplasty with provisional stenting versus primary stent (OCBAS): immediate and long-term follow-up results. *J Am Coll Cardiol* 1998; **32**: 3151–57.
- 4 Saucedo JF, Mehran R, Dangas G, et al. Long-term clinical events following creatine kinase: myocardial band isoenzyme elevation after successful coronary stenting. *J Am Coll Cardiol* 2000; **35**: 1134–41.
- 5 Narins CR, Miller DP, Califf RM, Topol EJ. The relationship between periprocedural myocardial infarction and subsequent target vessel revascularization following percutaneous coronary revascularization: insights from the EPIC trial—evaluation of IIb/IIIa platelet receptor antagonist 7²³ in Preventing Ischaemic Complications. *J Am Coll Cardiol* 1999; **33**: 647–53.

Author's reply

Sir—The rationale for our provisional stent trial was based on the results of the BENESTENT trial cited by François Schiele and Jean-Pierre Bassand, which showed that “stent-like” results obtained by balloons were equivalent at preventing angiographic restenosis compared with implantation of coronary stents. We felt it appropriate, therefore, to do a prospective trial based on the null hypothesis, designed to detect a 25% absolute difference in clinical restenosis.

The difference was larger for the 6-month composite event rate (death, myocardial infarction, and revascularisation of the target artery) in patients undergoing routine stent implantation than for those undergoing initial balloon angioplasty, and provisional stenting, despite a 30% crossover to stenting. Myocardial infarction was defined according to WHO criteria.

The references that Schiele and Bassand point out showing the importance of asymptomatic increases of enzyme concentrations after percutaneous coronary intervention are fairly new observations. When the study was designed, there was great debate as to the relevance of raised enzymes and, thus, we used endpoints that were generally considered “hard” and clinically meaningful.

We did quantitative coronary angiography in a subset of patients to characterise the optimum result and to look at the reasons for crossover. Angiography was routinely done during follow-up, since we believe that angiographic and clinical restenosis are two different entities. The OPUS I trial was thus designed to look at target vessel revascularisation driven by clinical symptoms and not by findings from routine follow-up angiography.

Our results clearly show that the routine implantation of coronary stents for single large vessels is better than balloon angioplasty and provisional stenting, when visual assessment of the optimum result is used to judge the need for provisional stenting, which is typical current practice. We recognise that other methods, such as doppler flow and repeat assessments to detect elastic recoil can alter these results, but such methods are not routinely used. Stents are now commonly used in multiple vessels, long lesions, and vessels

less than 3 mm in diameter; many studies suggest that restenosis rates for stents could be much higher in such cases.

W Douglas Weaver

Division of Cardiovascular Medicine, Henry Ford Heart and Vascular Institute, 2799 West Grand Boulevard, Detroit, MI 48202, USA

Realistic priorities for AIDS control

Sir—While agreeing with much of what Martha Ainsworth and Warnya Teokul (July 1, p 55)¹ have to say on the limited effectiveness of national AIDS control programmes in less developed countries and the need for priority setting, they neglect to mention several key issues. While rightly pointing out the reluctance of some national governments to take responsibility for prevention of spread of HIV-1, they do not mention two important points—namely, the significant contribution of the World Bank's Structural Adjustment Policies (SAPs) to undermining health systems across the developing world, and the ongoing problem of third world debt.

SAPs were introduced in the 1980s to facilitate debt repayments by curbing government expenditure and resulted in widespread health and education spending cuts in many countries. They also led to the introduction of user fees for health services, cuts in wages, and price rises for food and medicines. The impact on a range of socioeconomic variables (food security, access to health care, migration of health professionals) has been well documented and tracked for several years.^{2,3} More recently, research has hinted at a link between SAPs and the resurgence of malaria⁴ and tuberculosis⁵ in some parts of the world. It is reasonable to wonder what part SAPs may have played in the spread of HIV infection.

When discussing the “failure to prioritise in resource-scarce settings”, Ainsworth and Teokil make no reference as to why countries are pressured into spending what little they have on debt repayments. This is an issue that will continue to undermine the development of health systems (including HIV and AIDS prevention and control) in developing countries, unless dealt with by governments (including western ones) and international development organisations.

By failing to acknowledge the significant impact of the World Bank's

SAPs and debt on the health of people in developing countries, Ainsworth and Teokul neglect the wider political, economic, and social realities within which people in developing countries live. In doing this, they place the entire burden of responsibility on the countries themselves, and assist the World Bank in covering up its part in the story. Ainsworth and Teokul call for a “breaking of the silence”, but their own failure to inform us fully contributes to the perpetuation of that silence.

*Shailen Nandy, Robert Scott

*School for Policy Studies, University of Bristol, Bristol BS8 1TZ, UK, and Institute of Neurology, London
(e-mail: s.nandy@bristol.ac.uk)

- 1 Ainsworth M, Teokul W. Breaking the silence: setting realistic priorities for AIDS control in developing countries. *Lancet* 2000; **356**: 55–60.
- 2 Loewenson R. Structural adjustment and health policy in Africa. *Internat J Health Serv* 1993; **23**: 717–30.
- 3 Wakhweya AM. Structural adjustment and health. *BMJ* 1995; **311**: 71–72.
- 4 Manfredi C. Can the resurgence of malaria be partially attributed to structural adjustment programmes? *Parasitologia* 1999; **41**: 389–90.
- 5 Chaulet P. After health sector reform, whither lung health? *Internat Tuberc Lung Disease* 1998; **2**: 349–59.

Sir—Martha Ainsworth, a World Bank economist, and her colleague Waranya Teokul (July 1, p 55)¹ provide superficially attractive suggestions for reducing the impact of the HIV-1/AIDS pandemic. But the analysis is dangerous and dishonest since it omits any assessment of the World Bank's own role in driving the AIDS epidemic. For over the past 20 years, with its sister organisation the International Monetary Fund, the World Bank has weakened governments of resource-poor countries and eroded public health policy.

The liberalisation of economies, promoted by the World Bank, has increased unemployment, widened the rich-poor divide, cut subsidies for basic foods, and shifted agricultural policy to promote exports. The promotion of markets has not been capable of promoting pro-poor growth, namely generating employment, encouraging public-health policy, or improving the equality of sexes with the female literacy and empowerment necessary for better health.²

Cuts and underfinancing of public-health spending associated with structural-adjustment programmes in the 1980s have led to severe deterioration in health-care delivery systems, especially in Africa. The whole

public-health agenda (information surveillance, epidemiology, research, and behavioural surveillance) has been reduced to a skeleton, whereas cost recovery for health care has continuously been promoted by the Bank. As a result, HIV-1 testing, condoms, treatment for sexually transmitted diseases, tuberculosis, and co-infections of HIV-1 are subject to user-charges and, therefore, are unaffordable to many. In Zambia, where the HIV-1 prevalence is 19.5%, half the children are now malnourished, and consequently have lowered resistance to all diseases.

Structural adjustment programmes, debt repayments, cuts in aid budgets (especially by the USA), discrimination against African trade, increasing malnutrition, and the Cold War games played by the world's powers have all played a substantial part in fanning the AIDS pandemic. Reference to Uganda's gross national product per person of \$310 in 1998, with an average annual public and private expenditure of \$14 on health care over the past decade, is incomplete without reference to the fact that 40% of Ugandan government expenditure is spent on debt servicing—more than double the amount spent on health care and education combined.

Criticism of delayed action to the epidemic by African governments is misplaced when the more-developed countries have been equally slow to acknowledge the enormity of the crisis in Africa and elsewhere. Such countries have viewed HIV-1 and AIDS as a difficulty solved by throwing money at it in the form of expensive drugs whose long-term effects on the pandemic are unknown, especially without the backing of well-organised, well-funded health services.

Although we agree that the relation between AIDS and poverty is complex, plagues seldom arise in wealthy populations.³ Ainsworth¹ emphasises the need for governments to be sensitive to the needs of their citizens. The IMF and the World Bank have embraced good governance to guide their objectives in many countries. Others have suggested that there is a need for changing the constitutional rules and other features of the IMF and World Bank to promote good governance and accountability within these institutions themselves.⁴

A longer version of this response is available on *The Lancet* website at www.thelancet.com

Dorothy E Logie, *Solomon R Benatar

*Department of Medicine, University of Cape Town, South Africa; and Cheriote View, Bowden, Melrose, Scotland

- 1 Ainsworth M, Teokul W. Breaking the silence: setting realistic priorities for AIDS control and less-developed countries. *Lancet* 2000; **356**: 55–60.
- 2 Abbasi K. The World Bank and World Health. *BMJ* 1999; **318**: 1132–35
- 3 McNeil WH. Plagues and peoples. New York: Anchor Books, 1976.
- 4 Woods N. The challenge of good governance for the IMF and World Bank themselves. *World Devel* 2000; **28**: 823–41.

Vasopeptidase inhibition in heart failure

Sir—Renal function frequently deteriorates during the progression of chronic heart failure, and studies have shown that renal impairment is one of the most powerful predictors of prognosis in this syndrome.¹ Although angiotensin-converting-enzyme (ACE) inhibitors have become the most important drugs in the treatment of chronic heart failure, they are commonly withheld or prescribed in only low doses because of fear of deterioration of renal function.

Jean L Rouleau and colleagues (Aug 19, p 615)² compare the effects of the neutral endopeptidase inhibitor omapatrilat with the ACE inhibitor lisinopril in 573 patients with chronic heart failure. Although they show no difference between the two groups for the primary endpoint, exercise tolerance, omapatrilat has a significant benefit in the composite endpoint of death, admission, or discontinuation of study treatment for worsening heart failure. Moreover, the rate of renal dysfunction (5 vs 17 patients, or 1.8 vs 6.1% for plasma creatinine, $p=0.009$) differs significantly, favouring omapatrilat.

Although the number of patients in the study is low, the mechanism of action of omapatrilat makes it likely that this finding is true, rather than due to chance. Omapatrilat, by inhibiting neutral endopeptidase, inhibits the breakdown of the natriuretic peptides (especially atrial and brain natriuretic peptides). This mechanism leads to increased plasma concentrations of these peptides, thereby improving renal function.³ Renal function is increasingly being recognised as an important factor in chronic heart failure and new drugs are being developed that are primarily targeted at preserving kidney function.⁴ Also, polypharmacy is common in patients with chronic heart failure, and some agents (especially analgesics that inhibit prostaglandin, but also diuretics) can increase vulnerability for renal impairment, particularly in the elderly.⁵ The fact that omapatrilat has a more

favourable effect on the kidney than ACE inhibitors might be of potential importance in patients with chronic heart failure.

*Dirk J van Veldhuisen, Wiek H van Gilst
Department of Cardiology, Thoraxcenter, University Hospital Groningen, 9700 RB Groningen, Netherlands
(e-mail: d.j.van.veldhuisen@thorax.azg.nl)

- 1 Hillige H, Girbes ARJ, De Kam PJ, et al. Renal function, neurohormonal activation and survival in patients with chronic heart failure. *Circulation* 2000; **102**: 203–10.
- 2 Rouleau JL, Pfeffer MA, Stewart D, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000; **356**: 615–20.
- 3 Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998; **339**: 321–28.
- 4 Gottlieb SS, Skettino SL, Wolff A, et al. Effects of BG9719 (CVT-124), an A₁-adenosine receptor antagonist, and furosemide on glomerular filtration rate and natriuresis in patients with congestive heart failure. *J Am Coll Cardiol* 2000; **35**: 56–59.
- 5 Gottlieb SS, Weir MR. Renal effects of angiotensin-converting enzyme inhibition in congestive heart failure. *Am J Cardiol* 1990; **66**: 14–12D.

UK-style postgraduate examinations in mainland Europe

Sir—I wonder whether it is possible for UK authorities to assess the training of those coming from mainland Europe to work. Some candidates will have an Specialist Registrar (SpR) post and follow UK training, including the relevant examinations to acquire their Certification of Completion of Specialist Training (CCST). In some specialties, however, the relevant Royal College examination is a prerequisite for obtaining an SpR post and poses a major hurdle.

In the specialty of anaesthesia, this issue was recognised¹ and, in 1978, the European Academy of Anaesthesiology was founded with the aim of becoming the academic organisation for anaesthesia in Europe.² One of the academy's first activities was to introduce a two-part postgraduate diploma examination, broadly based on examinations set by the UK Royal Colleges.³

The examination, known as the European Diploma in Anaesthesiology and Intensive Care (EDA) was a gamble since it had no official status. Nevertheless, an annual multilingual, two-part examination was introduced in 1984. Part one is an MCQ examination and part two is an oral

examination based on traditional UK vivas. Each part can be completed in English, French, German, Italian, or Spanish. The exam now attracts more than 400 candidates a year.

A multinational examination committee sets the questions and handles the translations. The first part is held synchronously in 21 European cities, and the second is currently held in four cities. All part-two examiners speak English and one or two of the other EDA languages. Each pair of examiners, however, are of different nationalities. There are four vivas so each candidate is assessed by eight different examiners. Examiners do not assess their own trainees.

The entry criterion for the part-one examination is a medical qualification registrable in a European country. For the part two, however, candidates must have passed the part I, have been registered as a medical practitioner for 6 years, of which four in anaesthesia or intensive care), and must be eligible for registration as a specialist anaesthetist in a European country. Thus, UK anaesthetists are not eligible to sit part two until they have acquired their CCST.

European anaesthetists thus sit a postgraduate examination that has no official status because of departmental policy, to improve their curriculum vitae, because of perceived value of a paper qualification by potential emigrants, and the personal satisfaction of acquiring a widely recognised title of distinction. Successful candidates, of which there are now more than 1000, are known as diplomats of the European Academy of Anaesthesiology (DEAA).

The introduction of a postgraduate examination in anaesthesia had improved education and training throughout continental Europe. Perhaps this experience will encourage other specialties to follow suit. Despite the costs involved this examination is now self-financing. Mutual exemption arrangements now exist with the Royal College of Anaesthetists and the College of Anaesthetists in Ireland, whereby holders of the EDA are exempt from the part one examination of these colleges, and fellows of either college are exempt from part one of the EDA. Thus, UK authorities wishing to appoint DEAA anaesthetists from mainland Europe can be reassured about their training.

John S M Zorab

Holmray Cottage, Iron Acton, Bristol, BS37 9UJ
(e-mail: JZorab@compuserve.com)

1 Editorial. European diploma in anaesthesia and intensive care. *Lancet* 1991; **338**: 219.

- 2 Zorab JSM, Vickers MD. The European Academy of Anaesthesiology: 1992 and beyond. *J R Soc Med* 1991; **84**: 704–08.
- 3 Zorab JSM. The European diploma in anaesthesiology and intensive care of the European Academy of Anaesthesiology. *Acta Anaesth Scand* 1995; **39**: 570–81.

Health systems' performance and ethical yardsticks

Sir—The World Health Report 2000, *Health systems: improving performance*¹ has received much media attention, especially the suggested ranking of health systems. However, some of the report's key conclusions are ill understood by the general public. We aim to clarify key assumptions and concepts.

Important assumptions underlying WHO's refined analysis relate to the ethical theory, the economic outcome measure, and the perspective of assessment. First, for assessment of activities, such as the services of a health system, various ethical standpoints are possible. The World Health Report 2000 calculates utilities for the comparison of health systems, with weightings derived from the rating of a selected panel of multinational key informants. Domains of these utilities are health, responsiveness, and fair financial contribution, receiving 50%, 25%, and 25% of the total weight, respectively. Health and responsiveness are further separated into an overall or average rating and distribution or equality. The underlying ethical theory is best described as "utilitarian", and is aimed at the greatest good for the highest number of people.²

Performance is chosen as an economic outcome measure. The focus is the efficiency of health systems—their output relative to the money put in, not the effectiveness of systems (their absolute capacity to deliver services or achieve health gains). A health system with high quality services may, therefore, score badly because of poor financial management compared with a system with lower service standards but efficient management.

The societal or public interest viewpoint is taken in accordance with economic theory⁴ as the perspective of assessment. This viewpoint by necessity is systematically different from viewpoints such as individual sick citizens.

This ranking of health systems depends critically on the presented premises. The choosing of different

assumptions results in a different ranking and can add to a balanced understanding of health systems. In an ethical discussion, a utilitarian view favours the delivery of cost-effective services, with benefit for everybody's quality of life, such as dental care. The approach of egalitarian ethics, in contrast, focuses on the worst-off in society and their rights, and disproportionate allocation of resources to these individuals such the provision of dialysis, is seen as fair.⁵ Some systems may, therefore, score low under one ethical theory, but high under another.

The WHO report has chosen performance to judge outcome and looks at a system's output relative to spent resources, not a system's absolute achievement. This outcome measure is important from an economist's perspective, but it may be secondary for politicians and patients. For example, a perspective based on health rights might well accept some wasteful consumption of resources, such as for research and development or as a function of decreasing marginal effectiveness, as long as the overall effectiveness meets standards. Health-system administration, health politics, and individual citizens might have confronting interests in this perspective. Public administration could be inclined to allocate funds technocratically, based on league tables of decreasing cost-effectiveness, to achieve maximum overall utility.

Health politics and especially sick individuals may value the appropriateness of funds allocated to health care and the improvement of their quality of life differently. The ethical yardstick used in the comparison of health systems must be chosen carefully. Moreover, the ranking of health systems will change according to who is reading the yardstick.

*Manfred Wildner, Anne Brunner

*Bavarian Public Health Research Centre and Institute for Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-University, Munich D-81549, Germany; and Catholic University, Eichstaett, Germany (e-mail: wil@ise.med.uni-muenchen.de)

- 1 WHO. The World Health Report 2000. Geneva: WHO, 2000.
- 2 Kymlicka W. Contemporary political philosophy: an introduction. Oxford University Press, 1991.
- 3 Drummon M, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. Oxford: Oxford Medical Publication, 1993.
- 4 Gold M, Siegel J, Russel L, Weinstein M. Cost-effectiveness in health and medicine. Oxford: Oxford University Press, 1996.
- 5 Rawls J. A theory of justice. Cambridge, MA: Harvard University Press, 1971.

Terminology and gastric epithelial dysplasia

Sir—An important practical difficulty for gastric epithelial dysplasia is the interpretation by clinicians of the terminology used by pathologists.^{1,2} The use of different terminology may also partly explain the different behaviour of surgeons and endoscopists in European countries and in Japan.

In Europe, the recommendation for terminology of gastrointestinal epithelial tumours includes dysplasia in neoplastic lesions, and distinguishes low-grade and high-grade dysplasia (including carcinoma in situ).³ In the Japanese classification of gastric epithelial lesions the term dysplasia does not appear and is replaced by lesions strongly suspected for carcinoma and carcinoma. The most common clinical follow-up in Europe is endoscopy, whereas in Japan, endoscopic and surgical resection are more frequent.

Although gastric epithelial dysplasia is a fairly rare lesion in many geographic areas, this lesion is prevalent in some places, as in Japan. We believe that this difference in clinical behaviour has arisen not only because of the prevalence of the lesion itself, but also because of terminology. An international agreement to allow comparisons between Japanese and European investigators is needed.⁴

For this reason pathologists from different countries who have a special interest and substantial experience in the diagnosis of gastric cancer precursors have developed a new international system in Padova.⁵ The classification, however, uses the term dysplasia and, in our opinion, this might continue to confuse clinicians. It should not be forgotten that endoscopy and surgery are linked to numerous medicolegal problems; most western surgeons would not operate if pathologists did not clearly declare the presence of a non-invasive cancer. On this basis, we sent a questionnaire to 69 chief surgeons who decide operative interventions in their divisions. The questions and answers are reported in the table.

Most of the surgeons believe that terminology strongly affects their choices; they would prefer pathologists to use the term carcinoma in situ, and would agree to operate more frequently if, instead of the term high-grade dysplasia, pathologists use a term more clearly indicating the presence of cancer. Nevertheless, many of the interviewed surgeons declared that they are inclined to undertake an operation or endoscopic resection in the case of a high-grade dysplasia.

Question	Score
Although the terms high-grade dysplasia and carcinoma in situ in the stomach mean the same condition, do you believe that the use of a term instead of the other one can influence the behaviour of the surgeons?	41 yes/ 26 no
Which one of those terms do you prefer pathologists to use?	
High grade dysplasia	9
Carcinoma in situ	48
Non invasive malignant lesion	8
If the pathologists would use one of the other terms instead of the term dysplasia, do you believe that the more surgeons would agree to the surgical operation?	38 yes/27 no
Which is your actual behaviour when a high grade dysplasia is diagnosed?	
Endoscopic resection	12
Endoscopic follow-up	9
Surgical operation	40

Results of survey

The responses support a change in terminology. Surgeons should not need to know perfectly the different classifications of gastric epithelial dysplasia, and pathologists should take full responsibility for their reports.

We would like to thank all the chief surgeons who answered our questionnaire.

**Michele Caselli, Francesca Freguglia, Francesca Greco, Marco Ruina, Vittorio Alvisi*

Postgraduate School of Gastroenterology, University of Ferrara, I 44100, Ferrara, Italy

- Lewin KJ. Nomenclature problems of gastrointestinal epithelial neoplasia. *Am J Surg Pathol* 1998; **22**: 1043–47.
- Riddell RH, Iwafuchi M. Problems arising from Eastern and Western classification system for gastrointestinal dysplasia and carcinoma: are they resolvable? *Histopathology* 1998; **33**: 197–202.
- Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardised classification with clinical implications. *Hum Pathol* 1983; **14**: 931–38.
- Japanese Research Society for Gastric Cancer. Japanese classification of gastric carcinoma. Tokyo: Kamehara and Co, 1995.
- Rugge M, Correa P, Dixon MF, et al. Gastric dysplasia: the Padova international classification. *Am J Surg Pathol* 2000; **24**: 167–76.

Klinefelter's syndrome

Sir—Alison Wright, a physician who is now working in Sheffield, sent me a copy of John K Amory's report (July 22, p 333)¹ on Klinefelter's syndrome. This doctor is a friend, she was one of the first people I spoke to after I was diagnosed as having Klinefelter's syndrome. She therefore understands my insatiable desire to learn all I can about the disorder.

I found the report interesting and could identify with some of the symptoms described.

I was diagnosed as having Klinefelter's syndrome after I asked my doctor for sildenafil, once it became available through the National Health Service. That time my doctor listened to my plight of still being a virgin at age 47 years.

I had asked for help in 1981, but my former doctor told me to find a

prostitute. I tried unsuccessfully to explain that my new partner and I were having problems. As a result, I changed my doctor and moved to another family physician's practice.

If I had known why my partner and I were unable to have sex and that I was sterile, we could have adopted or tried to adopt, but we never went down this path because the embarrassment of trying to explain the situation was too painful to contemplate. Alternatively, my wife, as she became, could have undergone donor insemination.

We also went to the local National Health Service hospital and the British Pregnancy Advisory Service who assessed my wife. At no time was I assessed or asked to have a sperm count. They gave us a self-insemination kit, which I have, unused, to this day.

After I was diagnosed, fortunately for me, a friend found on the Internet, the Klinefelter Organisation (www.klinefelter.org.uk), formerly the KSCUK, which I joined. The Klinefelter Organisation is a self-help group of people who are prepared to talk about the disorder to professional and other people. Since then I have spoken to three people who have similar symptoms to mine, and six others with classic Klinefelter symptoms.

My understanding and current feeling of wellbeing was greatly assisted by spending a week with two people who have Klinefelter's syndrome, to laugh and cry about it.

It took me almost a year to get sildenafil and in the fullness of time, I hope it will be of use to us both. My current family physician is very supportive.

Arnold John Wilkes
Chester UK
(e-mail: arnoldwilkes@telco4u.net)

- Amory JK. Klinefelter's syndrome. *Lancet* 2000; **356**: 333.

DEPARTMENT OF ERROR

Dopamine and schizophrenia—proof at last?—In this Commentary (Sept 16, p 959), the author's name should be Paul J Harrison.