

CORRESPONDENCE

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Sexual behaviour at the millennium

Sir—In your series on sexual health and lifestyles, Kevin Fenton and colleagues (Dec 1, p 1851)¹ report a prevalence of chlamydial infection of 1.5% in a population-based sample of 2055 UK women aged 16–44 years.

We looked at risk factors in women attending inner-city general practices for cervical smears, and noted age younger than 25 years, two or more sexual partners in the preceding year, and AfroCaribbean ethnic origin to be independent predictors of chlamydial infection². In a further study of chlamydial infection in 1125 newly pregnant women (mean gestation 49 days) aged 16–48 years attending 32 practices in south London, UK, we noted a prevalence of 2.0% (95% CI 1.2–2.9). We analysed self-administered vaginal swabs and first pass urine. Despite possible anxieties about screening during pregnancy, women were able and willing to do their own swabs. Of 1080 women responding to a postal questionnaire, 63% said that providing a self-taken swab was at least as easy as providing a urine sample.

In an accompanying Dec 1 Commentary, Ralph DiClemente³ states that an important but under-used access point in promotion of sexual health is during provision of health care. Making nucleic acid amplification techniques for chlamydial detection more widely available in the UK might improve the role of general practice.

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- 1 Fenton KA, Korovessis C, Johnson AM, et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital *Chlamydia trachomatis* infection. *Lancet* 2001; **358**: 1851–54.
- 2 Oakeshott P, Kerry S, Hay S, Hay P. Opportunistic screening for chlamydial infection at time of cervical smear testing in general practice: prevalence study. *BMJ* 1998; **316**: 351–52.
- 3 DiClemente R. Development of programmes for enhancing sexual health. *Lancet* 2001; **358**: 1828–29.

Sir—In their report on early heterosexual experience, Kay Wellings and colleagues (Dec 1, p 1843)¹ highlight the complex and wide-ranging issues that surround maintenance of sexual health in the millennium.

Independent predictors such as education, drugs, religious or parental choices, poverty, and alcohol are deemed to affect sexual activity and risk-taking behaviour. Targeting these known risk factors may be more appropriate than combating their disease-based outcomes.

Research has shown a trend of decreasing age of first sexual intercourse; Wellings and colleagues believe this trend has now stabilised. Over the past decade, Barnsley District in South Yorkshire, UK, has consistently shown teenage conception rates to be twice the national average.² In our analysis of 617 female patients (aged 14–50 years) attending the genitourinary clinic at Barnsley District General Hospital, 30% reported sexual experience at younger than 16 years.³ For patients in the younger age-groups, age at first sexual experience was much lower than in the older age-groups. 60% first had intercourse at younger than 16 years compared with fewer than 15% in patients 40 years and older.

However, by contrast with Wellings and colleagues' findings, we noted that patients reporting first sexual experience at younger than 16 years had a higher rate of current sexually transmitted infections (STIs) than did those with first experience at older than 16 years (53 vs 45%). We also noted, as do Wellings and colleagues, that individuals younger than 20 years used barrier methods of contraception more than those in any other age-group. This difference might explain the lower rates of previous STIs in this group. Although the disparity in the STI results may well reflect a local trend, of all the patients who reported early first sexual intercourse, 74% had an STI and were more likely to be single and have had three or more sexual partners.

Can this generational change be associated with earlier onset of sexual activity that can persist into the fourth and fifth decade? In addition to the prevalent prevention strategies,

methods, strategies, and resources to encourage teenagers towards starting sexual activity later are needed.

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- 1 Wellings K, Nanchahal K, Macdowall W, et al. Sexual behaviour in Britain: early heterosexual experience. *Lancet* 2001; **358**: 1843–50.
- 2 Public health common data set 1993–95, and OPCS monitors FM1 95/2, 95/3, 96/2, 97/2 and 98/1. London: HMSO.
- 3 Dhar J, Westlake L, Bray L. Coital debut and sexually transmitted infections: is there a relationship? Spring Meeting of the Medical Society for the Study of Venereal Diseases, Athens, May 1998: 19.

Sir—In his Dec 1 Commentary, Ralph DiClemente¹ draws attention to the toll on individuals and ultimately on society exacted by unintended pregnancy and sexually transmitted infection.

As he points out, this burden is not least due to the sometimes potentially fatal consequences. He rightly draws attention to the need to rely on assessed programmes for prevention and to intervene effectively with high-risk groups.

However, for those working with young people, especially young substance users, there is a sense of déjà vu. In this case, there is a focus exclusively on sexual behaviour, as if sexuality was separate from other parts of the life of young people. In fact, risky sexual behaviour, like substance abuse, is highly correlated with other risks: failure at and drop out of school, petty crime, personal misery, and perhaps self-harm. Such a broad syndrome of risk has been identified many times and is well known to child and youth health and mental health practitioners, and indeed teachers and social workers.

In addition, although DiClemente does focus on youth, he does not mention the notion of development. Actually, the antecedents of the sexually risky behaviours he discusses are frequently identifiable, arising from complex interactions of intrinsic vulnerabilities and environmental circumstances. The developmental context also requires that adults have a duty of care in relation to young people. For instance, is this early sexual activity a

manifestation of poor availability of warmth and affection from parents, as well as poor supervision? Should there be activation of child-protection mechanisms? Are these young people being adequately educated, not just in terms of sexual knowledge, but in basic academic education? Success or failure in the latter will determine much of their life opportunities. What is the state of their mental health, so crucial to quality of life? DiClemente raises none of these issues.

A report by the Health Advisory Service² recommends that substance-use services for young people should be embedded in health services for children and young people. In this way, those trained to address the general needs of vulnerable young people are at hand, cooperating with those who have specialised knowledge. There should not be parallel services nor services attempting to treat children and young people as small adults. The same principles apply to sexual health, perhaps even more so. It is a paradox that in a liberal society we have such separation of sexuality from overall consideration of health and development. The forthcoming National Service Framework should consider some of these issues.

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- 1 DiClemente RJ. Development of programmes for enhancing sexual health. *Lancet* 2001; **358**: 1828–29.
- 2 Gilvarry E, Christian J, Crome I, Johnson P, McArdle P, McCarthy S. The substance of young needs. London: Health Advisory Service, 2001.

Sir—Your sex at the millennium series provides a solid basis for the need of elaborate strategies to control sexually transmitted diseases (STDs), especially for chlamydia. Ralph DiClemente¹ suggests that medical staff have an important and influential opportunity for sexual-health promotion during the provision of health care. Most opportunities will occur in a primary-care context.

However, seizing the chance to bring up sexual-health matters is not easily done. STD counselling in primary care is rarely done and is frequently inadequate.^{2,3}

We carried out a survey in Antwerp, Belgium, to identify difficulties family physicians encounter in relation to STD counselling. 75.6% of physicians reported they provide STD advice once monthly or less. Absence of genital symptoms was pointed out as a major barrier by 78.8% of respondents.

This finding is crucial, and suggests that the shift towards largely symptomless STDs such as chlamydia, HIV, and hepatitis B, has left physicians unadapted to their new role in STD management. Physicians, trained to diagnose and treat well defined clinical STD syndromes, are now faced with patients without or with insidious genital complaints, with whom it is difficult to raise sexual matters seemingly out of the blue. Substantial skills are needed for sexual counselling under such circumstances.

For primary-care-based STD control programmes to have a chance of success, education of physicians must change. Whether establishing intensive training facilities would be cost effective has yet to be studied. Alternatives such as family physicians referring patients to a telephone service with trained doctors are worth considering.

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- 1 DiClemente RJ. Development of programmes for enhancing sexual health. *Lancet* 2001; **358**: 1828–29.
- 2 Temple-Smith MJ, Mulvey G, Keogh L. Attitudes to taking a sexual history in general practice in Victoria, Australia. *Sex Transm Infect* 1999; **75**: 41–44.
- 3 Haley N, Maheux B, Rivard M, Gervais A. Sexual risk assessment and counselling in primary care: how involved are general practitioners and obstetrician-gynecologists? *Am J Public Health* 1999; **89**: 899–902.

Sir—Anne Johnson and colleagues (Dec 1, p 1835)¹ describe increased reporting of risky sexual behaviours in the UK, particularly in people younger than 25 years. Kevin Fenton and colleagues² note that more than 10% of the population aged 16–44 years have been diagnosed with an STI; they also discovered a significant burden of undiagnosed genital chlamydial infection.

In a survey done in an English medical school last year, we noted that even medical students (most of whom were in their final year of training) had little knowledge about important sexual health issues. 96% of the 213 respondents underestimated the failure rate of condoms. Less than half knew (or correctly guessed) that prevalence of chlamydia has risen by more than 10% in the past 3 years, with the rest believing that it had risen by a smaller percentage, had not changed, or even fell. Almost half the respondents overestimated the proportion of women in whom chlamydial infection is

symptomatic, with 15% believing that most infected women have symptoms.

Many of our respondents had alarmingly poor knowledge about certain important sexual health issues. If this knowledge is poor among medical students, it is probably worse in the general population.

Our findings support Ralph DiClemente's conclusion³ that there is a greater need for sexual health-promotion programmes for young people in Britain. Such a strategy is crucial if we are to reduce the substantial morbidity and potential mortality related to STIs, including HIV and unwanted teenage pregnancies.

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- 1 Johnson AM, Mercer CH, Erens B, et al. Sexual behaviour in Britain: partnerships, practices, and HIV risk behaviours. *Lancet* 2001; **358**: 1835–42.
- 2 Fenton KA, Korovessis C, Johnson AM, et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital *Chlamydia trachomatis* infection. *Lancet* 2001; **358**: 1851–54.
- 3 DiClemente RJ. Development of programmes for enhancing sexual health. *Lancet* 2001; **358**: 1828–29.

BCG efficacy and tuberculin skin testing

Sir—Frank Cobelens and Martien Borgdorff, in their Dec 15 commentary,¹ discuss in depth the best time for reading of tuberculin skin testing in BCG-vaccinated health-care workers. Unfortunately, they do not discuss two other important issues, the usefulness of BCG vaccination in prevention of new infections, disease, or both, and the correlation between successful BCG vaccination and tuberculin skin testing positivity.

The protective efficacy, if any, of BCG increases with increasing distance from the equator and seems to be higher in developed countries than in developing countries.^{2,3} Hence, in populations with high infection rates who need an effective vaccine the most, BCG offers no protection against adult forms of bacillary (highly infectious) pulmonary tuberculosis and offers a low level of protection in children.⁴ Consequently, tuberculosis remains common in many populations who have received BCG vaccine.

Furthermore, tuberculin reactivity after BCG vaccination does not correspond to protective immunity;

evidence for this was provided as far back as in 1944 by Arnold Rich, and the best confirmation came from the British Research Council trial.⁵ Delayed-type hypersensitivity and protection against tuberculosis sometimes emerge in parallel after BCG vaccination or infection with *Mycobacterium tuberculosis*, but they reflect different immune responses. Protective cellular immunity produces activation of macrophages with killing properties against mycobacteria, whereas delayed-type hypersensitivity is associated with tissue damage, including caseation.

Despite these notions, in most countries, for a BCG vaccine produced by a particular manufacturer to be licensed, regulatory bodies require that tuberculin skin tests convert to positive for at least 90–95% of vaccine recipients. Therefore, strains that lose their ability to produce tuberculin reactions are discarded. There is no way of selecting strains on the basis of their immunogenic activity or protective efficacy in the persisting absence of a good correlate of protective immunity to *M tuberculosis*, after the initial enthusiasm for *M tuberculosis*-stimulated whole blood production of interferon gamma has waned.

Finally, the policy of revaccination of tuberculin-negative individuals (including health-care workers) with BCG has no serious scientific basis.

Despite decades of worldwide widespread use of BCG, tuberculosis is still the leading worldwide cause of death from one infectious disease. Rigorous carefully implemented studies are urgently needed to better understand the biology and immunology of tuberculosis in human beings, and the social, genetic, and environmental factors affecting the spread of infection and its clinical expression, and to find new vaccines effective in high-risk regions of the world. Ideally, these vaccines should stimulate development of protective immunity with no effect on tuberculin reactivity.

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- 1 Cobelens F, Borgdorff M. Boosting, BCG, and time of reading in tuberculin skin testing. *Lancet* 2001; **358**: 2014.
- 2 Colditz GA, Brewer TF, Berkey C, et al. Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. *JAMA* 1994; **271**: 698–702.
- 3 Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; **346**: 1339–45.
- 4 Tuberculosis Research Centre (ICMR), Chennai. Fifteen year follow up of trial of BCG vaccines in south India for tuberculosis

prevention. *Indian J Med Res* 1999; **110**: 56–69.

- 5 Hart PD, Sutherland I, Thomas J. The immunity conferred by effective BCG and vole bacillus vaccines, in relation to individual variations in tuberculin sensitivity and to technical variations in the vaccines. *Tubercle* 1967; **48**: 201–10.

Polyclonal intravenous immunoglobulin to prevent brain injury in preterm infants

Sir—P Duggan and colleagues' observations (Nov 17, p 1699)¹ that cerebral lesions on magnetic resonance imaging (MRI) in very preterm infants were preceded by a fetal inflammatory response with T-cell activation have important implications.

Controlled trials in multiple sclerosis and case reports in acute demyelinating encephalomyelitis have shown that polyclonal intravenous immunoglobulin (IVIg) is of therapeutic benefit in inflammatory diseases of the central nervous system.² Polyclonal IVIg has several anti-inflammatory properties, including down-regulation of inflammatory cytokines via Fc-receptor blockade, provision of idiotype antibodies, and interference with the activation of T cells, B cells, the cytokine network, and complement. This might partly explain why polyclonal IVIg is reported to lower mortality by 40% in adult sepsis.³ Importantly, polyclonal IVIg may modulate the local immune reaction in the central nervous system, suppressing phagocytosis and helping to prevent or repair damage to oligodendrocytes.² In a crossover study, some longstanding cerebral lesions on MRI disappeared after IVIg treatment,⁴ raising the possibility that antenatal cerebral lesions might respond to postnatal intervention.

Enhancement of endogenous protection against brain injury in the fetus and newborn is a logical strategy. The International Neonatal Immunotherapy study is a placebo-controlled trial of polyclonal IVIg as an adjunct to antibiotics in neonatal sepsis of early or late onset, which aims to recruit about 5000 infants of all gestations. This study has the support and endorsement of the Medical Research Council, the Scottish National Blood Transfusion Service, and the Australian Red Cross Blood Service. The main measure of outcome will be survival free from neurodevelopmental impairment at 2 years, assessed by parental and professional questionnaires. Detailed assessment of neurodevelopmental and

psychometric status with the Bayley II Scales is planned for infants in Australia and New Zealand.

Sepsis of antenatal and early postnatal origin is probably underdiagnosed in preterm infants and newer techniques may be useful.⁵ In Duggan and colleagues' series of infants of less than 30 weeks' gestation, one-third had early cerebral lesions and an early inflammatory response consistent with antenatal infection. It would be helpful to know how many of these infants compared with the others were born after spontaneous preterm labour or after preterm premature rupture of the membranes, and how many were ventilated. This information could facilitate a substudy of neurodevelopmental outcomes for similar infants who are entered in the International Neonatal Immunotherapy study.

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- 1 Duggan PJ, Maalouf EF, Watts TL, et al. Intrauterine T-cell activation and increased proinflammatory cytokine concentrations in preterm infants with cerebral lesions. *Lancet* 2001; **358**: 1699–1700.
- 2 Stangel M, Compston A. Polyclonal immunoglobulins (IVIg) modulate nitric oxide production and microglial functions in vitro via Fc receptors. *J Neuroimmunol* 2001; **112**: 63–71.
- 3 Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock (Cochrane Review). In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 2001.
- 4 Sorensen PS, Wanscher B, Jensen CV, et al. Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* 1998; **50**: 1273–81.
- 5 Krueger M, Nauck MS, Sang S, Hentschel R, Wieland H, Berner R. Cord blood levels of interleukin-6 and interleukin-8 for the immediate diagnosis of early-onset infection in premature infants. *Biol Neonate* 2001; **80**: 118–23.

Sir—P Duggan and colleagues' data¹ for involvement of intrauterine antigen exposure and inflammation in the pathogenesis of brain injury of preterm infants is of special concern because infections are a leading cause of preterm delivery, with a high rate of morbidity and mortality in infants at less than 30 weeks' gestation.

The rate of cerebral lesions was much higher than reported in previous studies.² The higher sensitivity of MRI than of cranial ultrasonography may account for this difference. However, whether all detected cerebral lesions

	Fetuses	Adults	p
Cytokine			
Interleukin 6	33.2% (9.1)	51.8% (11.5)	<0.01
Interleukin 8	89.0% (3.6)	68.9% (8.1)	<0.0001
TNF α	14.3% (2.9)	33.8% (15.7)	0.02

TNF α =tumour necrosis factor α .

Mean (SD) proportion of cytokine-positive monocytes

will be clinically relevant is unknown. Therefore, long-term follow-up of all these infants is advisable. The meaning of the study would be increased if clinically relevant cerebral lesions instead of lesions documented on MRI only related directly to intrauterine antigen exposure and inflammation.

Nevertheless, we strongly support Duggan and colleagues' hypothesis. Our own data challenge the current view that neonates have a reduced capability to produce proinflammatory cytokines.³ We have shown a higher percentage of monocytes positive for interleukins 6 and 8 directly at the cell level by flow cytometry in term and preterm infants compared with adults.⁴ In very low-birthweight infants with proven infection, the amount of cytokine-positive cells increased greatly compared with that in infants without infection.⁴

To show the fetal inflammatory response we analysed fetal blood samples after written consent obtained by cordocentesis from six pregnancies undergoing prenatal diagnosis (median 24.6 weeks' gestation, range 21.6–27.0). After stimulation with lipopolysaccharide, the amount of monocytes positive for interleukin 6 and tumour necrosis factor α was lower than that of adults, whereas the amount of interleukin-8-positive monocytes was strikingly higher (table). These preliminary data indicate that fetuses were able to produce substantial amounts of proinflammatory cytokines early in gestation.

Maternal endotoxin administration induces a dose-dependent cytokine increase in fetal rat brains, and proinflammatory cytokines cause brain injury in animals.⁵ The documented inflammatory response in fetuses (table) and preterm infants,⁴ and the potentially harmful effects of proinflammatory cytokines suggest that the fetal inflammatory response will be more important in the pathogenesis of cerebral lesions than previously suspected. Duggan and colleagues add useful new data to this issue, supporting a direct relation between the fetal inflammatory response, activation of immunological memory in utero, and the occurrence of cerebral damage. These data have major implications in the understanding of

neonatal brain injury and may offer a basis for preventive strategies.

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- 1 Duggan PJ, Maalouf EF, Watts TL, et al. Intrauterine T-cell activation and increased proinflammatory cytokine concentrations in preterm infants with cerebral lesions. *Lancet* 2001; **358**: 1699–700.
- 2 Zupan V, Gonzalez P, Lacaze-Masmonteil T, et al. Periventricular leukomalacia: risk factors revisited. *Dev Med Child Neurol* 1996; **38**: 1061–67.
- 3 Kilpatrick L, Harris MC. Cytokines and the inflammatory response. In: Polin RA, Fox WW, eds. Fetal and neonatal physiology. Philadelphia: WB Saunders, 1997: 1967–78.
- 4 Schultz C, Rott C, Temming P, Schlenke P, Möller JC, Bucsky P. Enhanced interleukin-6 and interleukin-8 synthesis in term and preterm infants. *Pediatr Res* 2002; **51**: 317–22.
- 5 Brett FM, Mizisin AP, Powell HC, Campbell IL. Evolution of neuropathologic abnormalities associated with blood-brain barrier breakdown in transgenic mice expressing interleukin-6 in astrocytes. *J Neuropathol Exp Neurol* 1995; **54**: 766–75.

Authors' reply

Sir—William Tarnow-Mordi and colleagues request some additional data with respect to our study. 38 of 50 infants delivered spontaneously. 29% of these had abnormal MRIs, a proportion similar to the whole sample. However, of 25 infants with sustained rupture of membranes, 60% had lesions visible on MRI—a significant proportion ($p<0.01$). This finding is not surprising given the association of intrauterine infection and membrane rupture. Almost all infants were intubated for surfactant administration and received at least short-term mechanical ventilation. Median time of intubation in those without brain lesions was 18 h (range 0–408) and in those with abnormalities 48 h (0–960). Although this trend was not significant, it might be worth some consideration since systemic fetal inflammation predisposes to chronic lung disease.¹ Intrauterine inflammation may predict widespread tissue injury; in our study inflammation was greater in infants who died or developed severe chronic lung disease ($p<0.05$).

The data presented by Schultz and colleagues are useful because they contradict the commonly held belief that the immature immune system is intrinsically hyporesponsive. Investigation of how the immune response is controlled in preterm infants may elucidate mechanisms of tissue injury, especially since normal-term fetal blood contains large numbers of CD4 and CD25 regulatory lymphocytes, which, in mice, prevent autoimmune tissue injury.²

In this context, Tarnow-Mordi and colleagues' imaginative suggestion that intravenous immunoglobulin might have a specific neuroprotective effect through down-regulation of the inflammatory response is interesting. Cerebral white matter abnormalities are common in preterm infants,³ and infection can cause immune-mediated demyelination in the immature brain,⁴ so a treatment effective in demyelinating disorders may be a logical treatment for some white-matter disease. We would be delighted if the International Neonatal Immunotherapy Trial allowed this to be tested.

However, some thought may be needed about the substudy endpoint. Preterm infants have multiple risks for diverse postnatal and prenatal brain injuries. Schultz and colleagues point out that we used MRI rather than neurodevelopmental impairment as an endpoint. We used this approach specifically to reduce the effect of later injury and allow a proof of principle examination of intrauterine effects. However, if the investigators in the International Neonatal Immunotherapy Trial assess neurodevelopmental outcome, this will naturally encompass all types of brain injury. The relative proportion of prenatal and postnatal damage, of ischaemic, inflammatory, and developmental effects, is unknown and probably varies in different clinical contexts. There might be a case for use of biomarkers of inflammation such as the C-reactive protein concentration, which, surprisingly, we noted was predictive of cerebral lesions.⁵

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- 1 Yoon BH, Romero R, Kim KS, et al. A systemic fetal inflammatory response and the development of bronchopulmonary dysplasia. *Am J Obstet Gynecol* 1999; **181**: 773–79.
- 2 Ng WF, Duggan PJ, Ponchel F, et al. Human CD4(+)CD25(+) cells: a naturally

- occurring population of regulatory T cells. *Blood* 2001; **98**: 2736–44.
- 3 Maalouf E, Duggan PJ, Rutherford MA, et al. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. *J Pediatr* 1999; **135**: 351–57.
 - 4 Jorens PG, VanderBorgh A, Ceulemans B, et al. Encephalomyelitis-associated antimyelin autoreactivity induced by streptococcal exotoxins. *Neurology* 2000; **54**: 1433–41.
 - 5 Duggan PJ, Maalouf E, Watts TL, et al. Intrauterine T cell activation and increased pro-inflammatory cytokine concentrations in preterm infants with cerebral lesions. *Lancet* 2001; **358**: 1699–700.

- 1 Disdier P, Granel B, Serratrice S, Weiller P-J. A teenager with rash and fever. *Lancet* 2001; **358**: 2046.
- 2 Kawasaki T. Adult type MCLS. *Med Technol* 1997; **5**: 845.
- 3 Yoganathan K, Goodman F, Pozniak A. Kawasaki like syndrome in an HIV positive adult. *J Infect Dis* 1995; **30**: 165–66.
- 4 Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Paediatrics* 1974; **54**: 271–76.
- 5 Stevens DL, Tanner MH, Winship J, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin. *N Engl J Med* 1989; **321**: 1–7.

A teenager with rash and fever

Sir—Patrick Disdier and colleagues (Dec 15, p 2046)¹ report a case of a teenager with rash and fever. However, they do not mention two important differential diagnoses—adult Kawasaki syndrome and toxic shock syndrome.

In 1977, Kawasaki reported the first case of a man aged 22 years with Kawasaki syndrome.² The syndrome has since been increasingly reported worldwide, including cases in patients with HIV.³ Kawasaki syndrome is a diagnosis of exclusion and is made by noting presence of five of six major clinical criteria. These are fever of unknown cause of more than 5 days' duration that does not respond to antibiotics, bilateral conjunctival erythema, non-suppurative cervical adenopathy, erythematous macular eruption, regions of desquamation in the lower extremities, and erythema of the lips and oral cavity.^{3,4}

Disdier and colleagues' 16-year-old patient had the first five of these criteria, but they do not mention whether lesions of the oropharynx or lips were present. Their patient also had subsidiary features of Kawasaki syndrome—ie, leucocytosis with raised C-reactive protein. Most importantly, apart from administration of minocycline, no other cause for the illness could be identified. If the patient has Kawasaki syndrome, the possibility of life-threatening coronary arteritis should be considered and appropriate investigations done.

In addition, toxic shock syndrome should be excluded since this disorder can mimic Kawasaki syndrome and is commonly associated with hypotension and multiple-organ failure.⁵ The fact that cefuroxime had been given to Disdier's patient without response makes this diagnosis less likely.

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Priority-setting decisions for new cancer drugs

Sir—The study by Douglas Martin and colleagues (Nov 17, p 1676)¹ is a model of how not to make decisions on resource allocation for expensive drugs. As John Crown,² in his Nov 17 Commentary, points out, the basis for the decisions was informed common sense, but Martin and colleagues' report shows how fickle such an approach, or indeed such a concept, is.

Without the intellectual rigour imposed by proper cost-effectiveness analysis, the Cancer Care Ontario Policy Advisory Committee's processes seem to have simply disintegrated. Whereas at the outset it intended to consider only high-quality clinical trial data from randomised trials, eventually the Committee accepted data from non-randomised studies. This approach was at odds with their aim to ensure benefit to patients, since it did not recognise the proneness of the latter to produce biased results.

The justification for funding also degenerated from survival advantage to softer supposed benefits. Decision-making eventually became off the cuff (ie, criteria were progressively "discovered"). Therefore, the Committee's decisions were essentially arbitrary and amounted to a positive recommendation for any drug with any benefit, irrespective of cost.

Given this conclusion, the claim that decisions of a group of fair-minded people in a committee setting have some inherent moral force must be rejected. Such an argument leads to the clearly erroneous conclusion that a committee's decisions are defensible on moral grounds, irrespective of process or outcome, if only the members are fair-minded.

The Committee did not manage the selection and introduction of new drugs within the funds provided because the Ontario Government simply increased

the size of the budget on demand. Both parties were therefore able to avoid the hard economic and political questions of resource allocation, including where the money should come from—in other words, which group will sacrifice benefit so that cancer patients will benefit?

Martin and colleagues do not seem to grasp the importance of this question, or appreciate that cost-effectiveness analysis is an objective attempt to reach decisions on competing funding claims, and is ultimately justified on moral grounds. Instead, they worked on the basis of the novel economic notions that priority setting can occur "in relation to resource mobilisation", that ". . . the pies are seldom fixed", and that budget restrictions can be addressed "by advocating for sufficient funds to implement . . . decisions". Such concepts have zero economic, social, or moral credibility, and served to avoid them having to occasionally say no.

Martin and colleagues compounded avoidance of formal economic analysis by permitting an uninformed amateur version of the same without bothering to analyse the underlying moral or philosophical implications.

The difficulty with cytotoxic drugs that are modestly effective but expensive is being grappled with worldwide. Perhaps the Canadian approach was worth a try, but that it has failed is hardly in doubt after reading these researchers' report.

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- 1 Martin, DK, Pater, JL, Singer PA. Priority-setting decisions for new cancer drugs: a qualitative case study. *Lancet* 2001; **358**: 1676–81.
- 2 Crown J. A "bureaucratic" view of cancer drug rationing. *Lancet* 2001; **358**: 1660.

Authors' reply

Sir—Alasdair Millar criticises the approach to priority setting we describe, arguing that it is fickle and lacks the intellectual rigour imposed by proper cost-effectiveness analysis, and adds that cost-effectiveness analysis is an objective attempt to reach decisions on competing funding claims, and is ultimately justified on moral grounds. This presents us with an opportunity to debunk the widely held myth that health economics is the solution to the difficulty of priority setting.

Health economics provides necessary but insufficient tools (eg, cost-effectiveness analysis, programme

budgeting, and marginal analysis¹) to aid priority-setting decision makers. Our study accords with others of actual priority setting, showing that these tools have only limited effect on decision making, and the analyses are frequently unavailable when needed.² Moreover, the values emphasised in the studies are, to say the least, controversial.³ The Institute of Medicine Panel on Cost-Effectiveness in Health and Medicine argue that the cost-effectiveness analysis should be used as an aid to decision makers who must weigh the information it provides in the context of other values.

Those, like Millar, who promote cost-effectiveness analysis implicitly argue that the key value underlying priority setting is efficiency. Other values important to priority setting include equity, the health of individuals as against communities, the rule of rescue, and democratic decision making.⁴ These values help to clarify choices, but reasonable people, having diverse moral views, disagree about what constitutes fair allocation of resources to meet competing health care needs. In the absence of consensus on guiding principles, the difficulty of priority setting becomes one of procedural justice—legitimate institutions using fair processes.⁵ We describe one group addressing the issue of priority setting by attending to the fairness of their priority-setting processes.

Rather than continuing to worship at the altar of cost-effectiveness analysis, we propose that Millar might take a more ecumenical approach to the complex, multidisciplinary difficulty of priority setting in health care.

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- 1 Scott A, Currie N, Donaldson C. Evaluating innovation in general practice: a pragmatic framework using programme budgeting and marginal analysis. *Fam Pract* 1998; **15**: 216–22.
- 2 Ham C, Coulter A. Explicit and implicit rationing: taking responsibility and avoiding blame for health care choices. *J Health Serv Res Policy* 2001; **6**: 163–69.
- 3 Loughlin M. Rationing, barbarity, and the economist's perspective. *Health Care Anal* 1996; **4**: 146–56.
- 4 Daniels N. Four unsolved rationing problems. *Hastings Center Report* 1994; **24**: 27–29.
- 5 Daniels N, Sabin J. Limits to health care: fair procedures, democratic deliberation, and the legitimacy problem for insurers. *Phil Public Affairs* 1997; **26**: 303–50.

Sir—D Martin and colleagues¹ claim that, based on evidence of equal quality, pamidronate provides better symptom relief and prevention of complications than clodronate, specifically, bone pain and fractures, in myeloma. Their ethical decision about allocation of resources was based on an epistemological argument related to the interpretation of research evidence. What was this evidence?

We have published as a Cochrane Review a systematic meta-analysis of all the available published data from randomised trials of bisphosphonate treatment in myeloma.² This analysis provides no evidence that pamidronate is better than clodronate. For pain, in clodronate trials the odds ratio was 0.50 (95% CI 0.34–0.73), and for pamidronate trials was 0.61 (0.40–0.93). A test for interaction showed no difference between these results ($p=0.5$). For vertebral fractures, the clodronate odds ratio was 0.55 (0.38–0.82), and for pamidronate was 0.50 (0.32–0.79), again with no difference between results ($p=0.7$). Non-vertebral fracture rates were not reduced by clodronate or pamidronate.

Martin and colleagues also report that one trial of pamidronate showed a survival benefit.³ This result was actually in a subgroup. One clodronate trial has also reported a survival benefit in a subgroup, but no mention of this is made by Martin and colleagues.⁴ The dangers of such subgroup analyses are well known, and both these apparent benefits should be interpreted with great caution. Our meta-analysis shows no evidence of a survival benefit for bisphosphonates overall (0.99, 0.88–1.12), with no difference between clodronate and pamidronate ($p=0.9$).

Thus, we think the decision of Cancer Care Ontario to fund pamidronate but not clodronate for myeloma patients was made on the basis of data that are incomplete, flawed, or both. We wonder how many other such dubious decisions are made around the world because of the lack of appropriate assessment of available evidence with systematic and quantitative methods. Science and ethics both crucially depend on an understanding of these methods.

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- 1 Martin DK, Pater JL, Singer PA. Priority-setting decisions for new cancer drugs: a qualitative case study. *Lancet* 2001; **358**: 1676–81.

- 2 Djulbegovic B, Wheatley K, Ross J, et al. Bisphosphonates in multiple myeloma (Cochrane Review). In: *The Cochrane Library*. Issue 4. Oxford: Update Software, 2001.
- 3 Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. *J Clin Oncol* 1998; **16**: 593–602.
- 4 McCloskey EV, Dunn JA, Kanis JA, et al. Long-term follow-up of a prospective, double-blind, placebo-controlled randomized trial of clodronate in multiple myeloma. *Br J Haematol* 2001; **113**: 1035–43.

HIV-1 shedding in genital tract of infected women

Sir—Andrea Kovacs and colleagues (Nov 10, p 1593)¹ present results from a cross-sectional study on the determinants of genital HIV-1 shedding in women. We agree that the genital tract may function as a separate reservoir of HIV-1.

We measured HIV-1 RNA in paired plasma and cervicovaginal fluid samples of 122 Italian white women with no clinical evidence of sexually transmitted disease by ultrasensitive assay. We did not attempt viral isolation because of the low sensitivity of cultural methods when cervicovaginal secretions are tested.²

Women were asked to avoid sexual intercourse and douching for the 48 h before the gynaecological visit. We did cervicovaginal lavages by irrigating the vaginal walls and fornix with 3 mL sterile phosphate-buffered saline. No woman was menstruating, had vaginal discharge, genital bleeding, or signs or symptoms of sexually transmitted disease. Swabs for *Mycoplasma* spp and fungi cultures were also done. The cervicovaginal lavage samples were centrifuged and the cell-free supernatant tested for quantitative HIV-1 RNA. We used univariate and multivariate logistic models to calculate odds ratios for presence of HIV-1 RNA in plasma and in lavage samples, respectively. Only variables significant at the univariate level were included in the multivariate model. HIV-1 RNA was judged undetectable at lower than 80 copies/mL.

79 women were symptom-free at sampling; 43 had a previous or concurrent diagnosis of AIDS. 75 women were not receiving antiretrovirals. 94 women had detectable plasma viraemia. HIV-1 RNA was quantified in the lavage samples of 87 (71%). 80 had detectable and seven undetectable plasma viral load. At univariate analysis, absence of genital shedding correlated with increased CD4 cell count and antiretroviral therapy,

whereas no correlation was found with disease stage (AIDS *vs* symptom-free), exposure (drug users *vs* sexual partners) or presence of symptomless vaginal mycoplasma or candida infection.

Only a raised CD4 cell count and HAART treatment were significantly associated with undetectable vaginal HIV-1 RNA. Therefore, women taking HAART were significantly more unlikely to shed HIV-1 through the vaginal mucosa than those treated with non-HAART regimens or those untreated, independent of their plasma HIV-1 RNA concentrations.

In agreement with Kovacs and colleagues' conclusions and those of our previous study on a small cohort of infected pregnant women,³ we suggest that plasma viraemia may not be an accurate predictor of sexual and mother-to-child infectivity. In fact, HIV-1 replication in the female genital tract might not coincide with that in the blood, thus supporting the idea of distinct anatomical compartments in which viral evolution proceeds separately. HIV-1 in the female genital tract certainly affects the likelihood of HIV-1 transmission and its compartmentalisation could hinder the complete eradication of HIV-1 infection.

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- 1 Kovacs A, Wasserman SS, Burns D, et al. Determinants of HIV-1 shedding in the genital tract of women. *Lancet* 2001; **358**: 1593–601.
- 2 Saracino A, Di Stefano M, Fiore JR, et al. Frequent detection of HIV-1 RNA but low rates of HIV-1 isolation in cervicovaginal secretions from infected women. *Microbiologica* 2000; **23**: 79–83.
- 3 Saracino A, Di Stefano M, Vimercati A, et al. Cervicovaginal HIV-1 shedding in pregnant women near delivery. *Antiviral Ther* 2001; **6**: 79–81.

Sir—Andrea Kovacs and colleagues¹ suggest that HIV-1 genital shedding was significantly lower than blood concentrations except in 3.6% of women who were hypersecretors, and, therefore, were much more contagious. They also report high concentrations of HIV-1 in some patients receiving antiretroviral therapy and conclude that a separate reservoir of HIV-1 replication must exist in some individuals.

Complementary evidence to validate that female genital tracts have the potential to produce their own differential replication of HIV-1 can be found with the herpes simplex virus. Presence of herpes simplex virus DNA

sequences have been isolated from epithelial tissues distant from the site of recurrent HSV infection.^{2,3} The replication of these epithelial DNA is the direct cause of erythema multiforme. The DNA persists in the skin despite antiviral therapy; however, outbreaks of erythema multiforme are greatly diminished by continuous prophylactic treatment.

Although screening for hypersecretors may be useful, Kovacs and colleagues' study concedes that antiretroviral therapy alone does not eliminate transmission, and better protective methods are needed.

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- 1 Kovacs A, Wasserman SS, Burns D, et al. Determinants of HIV-1 shedding in the genital tract of women. *Lancet* 2001; **358**: 1593–601.
- 2 Brice SL, Krzemien D, Weston WL, et al. Detection of herpes simplex virus DNA in cutaneous lesions of erythema multiforme. *J Invest Dermatol* 1989; **93**: 183–87.
- 3 Miura S, Smith CC, Burnett JW, et al. Detection of viral DNA within skin of healed recurrent herpes simplex infection and erythema multiforme. *J Invest Dermatol* 1992; **98**: 68–72.

Sir—Pietro Vernazza, in his Nov 10 Commentary,¹ stresses the hazards of unprotected sex and criticises the studies of Andrea Kovacs and colleagues² on female genital shedding of HIV-1 RNA despite successful antiretroviral therapy. He criticises the work partly because the researchers do not take into account cell-associated HIV-1 RNA. I have some additional points to make.

Encapsulated cell-free HIV-1 remains to be shown microscopically in human blood, semen, uterine secretions, and maternal milk.

Variably integrated HIV-1 RNA in lymphocyte DNA fulfills Koch's postulates, especially the first and fourth, as the cause of AIDS.³

Whether or not infected with retroviruses, small cytoplasm-depleted lymphocytes, generated from rapidly dividing large germinal centre lymphocytes in organised lymphoid tissues and migrating in blood, semen, endocervical secretions, and maternal colostrum, normally number $2\text{--}5 \times 10^6/\text{mL}$, $2 \times 10^{5\text{--}6}/\text{mL}$, $2 \times 10^{4\text{--}5}/\text{mL}$, and $2.5 \times 10^6/\text{mL}$, respectively.^{3,4} During the latent stages of HIV/AIDS after prodrome, provirus-infected small cytoplasm-depleted lymphocytes in lymphoid tissues and circulating blood make up 0.5% of the total, with 0.5% containing linear integrated HIV-1 RNA in transcriptionally silent form, 0.05% in

transcriptionally silent circular form, and 0.005% in replication-competent linear form. Thus, 25 000 small cytoplasm-depleted lymphocytes per mL are capable of spreading HIV/AIDS.

During latency, the serum viral load, estimated by PCR analyses for soluble HIV-1 RNA, is generally lower than 500 copies/mL. Some explanations for low viral load are that the plasmalemma of infected large germinal centre lymphocytes form the capsule for HIV-1.⁵ With the appearance of circulating anticapsular antibodies, the retroviral RNA is precipitated in the form of amorphous antigen-antibody complexes between the large germinal centre lymphocytes and follicular dendritic cells.³ During the late stages of HIV/AIDS infection, when the large germinal centre lymphocytes disappear and their small cytoplasm-depleted lymphocytes progeny fall to lower than $2\text{--}5 \times 10^3/\text{mL}$, the serum viral RNA load rises, roughly proportionally to small cytoplasm-depleted lymphocyte depletion.^{3,4}

Owing to customary emperipoletic migrations through tissues, other cells and body secretions for sustaining homeostasis, infected small cytoplasm-depleted lymphocytes are ideal vectors for HIV/AIDS.⁴

Emperipoletic migrations and random^{3,4} error-prone⁵ integration of HIV-1 RNA into the DNA of small cytoplasm-depleted lymphocytes can explain why AIDS includes such a wide spectrum of signs and symptoms, why strains resistant to highly active antiretroviral treatment continually develop, and why formulation of effective vaccines remains elusive.^{3–5}

Given worldwide statistics on the heterosexual spread of HIV/AIDS, Kovacs and colleagues' study and Vernazza's comment are most timely. One might conclude that methods for protecting one another from transmission via infected small cytoplasm-depleted lymphocytes, cell-free RNA, or both during sex are imperative.

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- 1 Vernazza PL. Genital shedding of HIV-1 despite successful antiretroviral therapy. *Lancet* 2001; **358**: 1564–65.
- 2 Kovacs A, Wasserman SS, Burns D, et al. Determinants of HIV-1 shedding in the genital tract of women. *Lancet* 2001; **358**: 1593–601.
- 3 Shields JW. The XI AIDS Conference and HIV-1 lymphopathy. *Lymphology* 1997; **30**: 137–54.
- 4 Shields JW. Lymphspiration: lymph, lymphomania, lymphotrophy and HIV 1 lymphocytopathy: an historical perspective. *Lymphology* 1994; **27**: 21–40.
- 5 Barré-Sinoussi F. HIV as the cause of AIDS. *Lancet* 1996; **348**: 31–35.

The African challenge

Sir—Richard Horton, in his Dec 22/29 news item,¹ evokes many memories of our 4 years working as lecturers at the Komfo Anokye Teaching Hospital, Kumasi, Ghana. As Horton points out, Ghana's healthcare challenges are enormous, as is the case in much of sub-Saharan Africa. In a "cash and carry" healthcare system, many patients have little cash and, therefore, cannot carry. Even disorders as cheap to treat as cerebral malaria commonly present a financial challenge to families. Although there are undoubtedly opportunities for great satisfaction working in such a setting, the daily frustrations for healthcare staff are also huge: lack of infrastructure, facilities, basic equipment and drugs, and sometimes even loss of hope that health care and health outcomes will one day improve. Soaring inflation, a faltering national currency, and inadequate public sector wages fuel an ever present urge for the best and brightest healthcare workers to seek greener pastures abroad. This so-called brain drain is inevitable when local opportunities for postgraduate training, research, and professional development are sorely lacking.

Despite the immensity of the challenges, there are solutions. Although provision of facilities and equipment are certainly needed, a vital part of the solution is investing in key local healthcare staff who are committed to stay and struggle for improved health outcomes and equity. How can child health in Ghana improve if only a handful of Ghanaian doctors have postgraduate qualifications in paediatrics? How can the National Tuberculosis Control Programme succeed if senior staff frequently leave to work for organisations in Europe and the USA? Sadly, much development aid comes in the form of short-term donor-driven programmes that divert the energetic and experienced workers into short-term non-sustainable programmes. These often do little to build capacity within the national health-care system.

This brings the challenge to us. Health-care staff in industrialised countries have access to a wealth of information and opportunities. Although Horton rightly points out the substantial inequalities in healthcare provision that exist between different regions within Ghana, these internal inequalities are less than the huge disparities that exist between industrialised nations and countries in Africa. We can, and indeed must, form partnerships with our colleagues in

Africa to help develop clinical, laboratory, and public-health services, and assist in building capacity for research. More opportunities for professional and personal progress would have a positive effect on the satisfaction-frustration balance, empowering nationals to stay, to persevere, and to make solutions work. Improved local opportunities at home may also encourage the return of some of the many African health-care workers currently working abroad.

There are many ways that we in industrialised countries can contribute, including providing access to information and training, equipping laboratory staff, facilitating strategic short-term learning attachments in the UK for healthcare workers, engaging in relevant research activities, and promoting long-term partnerships between academic units. The answers to Africa's health challenges will come from within Africa, but the question for us in richer countries is not whether to be challenged, but how to respond.

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Sir—Richard Horton¹ mentions the public-health problem caused by snake bite in the village of Tabale, near Tamale, northern Ghana. Snake bite was the eighth most frequent cause of admission to Bolgatanga Regional Hospital and caused 6% of hospital deaths in 2000. In this region of Ghana in 1999, snake bite led to more than 1100 admissions and 30 deaths in health centres or hospitals. One health centre alone dealt with more than 500 bites (personal communication).

As in many other parts of West Africa's savannah belt, snake bite (mostly from the saw-scaled viper, *Echis ocellatus*) is a serious public-health problem in Ghana. Results of a population-based study in Senegal suggested that yearly mortality is as high as 14 per 100 000 population,² and worldwide snake bite mortality has been estimated at 125 000 deaths per year.³ Many victims of snake bite do not reach formal health-care facilities because of difficulties getting to a hospital, or a preference for traditional treatments.

Research on clinical and epidemiological features of snake bite is neglected in most parts of the world. Snake bites affect mainly the rural

poor such as subsistence farmers, therefore they cause social and economic effects as well as being medically important. In Africa, the problem of treating snake bites is compounded by the high cost and scarcity of antivenoms. With the exception of one South African company, all the major manufacturers of antivenom for Africa have suspended or curtailed production. Our experience in Nigeria and Ghana is that many imported antivenoms are inappropriate because they are manufactured with venoms from Indian snakes and do not effectively neutralise venoms of west African species, or control symptoms.

Although it is appropriate to concentrate research efforts on the major diseases affecting Ghana, we must not forget other less-well-recognised but important problems. Research is urgently needed to assess the true burden and economic effect of snake bite, and to improve the development and supply of suitable antivenoms.

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- 1 Horton R. Ghana: defining the African challenge. *Lancet* 2001 **358**: 2141–49.
- 2 Trape JF, Pison G, Guyavarch E, Mane Y. High mortality from snakebite in south-eastern Senegal. *Trans R Soc Trop Med Hyg* 2001; **95**: 420–23.
- 3 Chippaux JP. Snake-bites: appraisal of the global situation. *Bull World Health Organ* 1998; **76**: 515–24.

Sir—Richard Horton's news item¹ contains familiar passages relating to health-care delivery in underprivileged circumstances. He writes of Buruli ulcer, an ulcerative skin disease caused by *Mycobacterium ulcerans*, that is seen in several west African countries, including scattered foci in the southern parts of Ghana.^{2,3} Epidemiology and transmission of this disease are poorly understood. During our investigations, we have been led to scattered areas in the southern part of Ghana, where Buruli ulcer affects mainly underprivileged rural people. We witnessed situations similar to those described by Horton in the northern regions: illiteracy, extreme poverty, poor access to health-care facilities, and difficulties in attracting and retaining well-trained healthcare staff.

Epidemiological data have typically been based on hospital records, but we met patients who were not registered at any health-care facility. We realised that

under-reporting is more common than registrations in two or more hospitals.

Access to the health-care system is not limited only by economic restraints. Patients reported fearing the mutilating features of the treatment, and they said they were reluctant to seek treatment outside their own community. Many patients with Buruli ulcer practise self-treatment, or visit traditional healers.^{4,5} Stigma surrounding the disease may also prevent patients from reporting early to healthcare facilities. Fortunately, educational programmes seem to have lowered perception of stigma.⁴

Horton describes how in southern Ghana, health-care facilities are concentrated in the cities of Accra and Kumasi. Many people living outside populated centres have limited access to health-care facilities.

Apart from beliefs and attitudes, the present treatment options for Buruli ulcer do little to encourage patients to report to hospitals. We need to improve existing treatment options, and develop better treatment strategies.

Our follow-up data suggest that extensive surgical excision improves the chance of healing, but adjuvant antimycobacterial treatment might be a confounder. Many doctors prescribe antibiotics, especially rifampicin, although there is no evidence to support this practice.² If treatment with antibiotics are not beneficial, then their continued use is draining resources from the tuberculosis service. A well designed clinical trial with sufficiently long follow-up is needed to address this question. Small short-term studies, as referred to by Horton, are unlikely to help answer this important question of how to best treat Buruli ulcer.

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- Horton R. Ghana: Defining the African challenge. *Lancet* 2001; **358**: 2141–49.
- van der Werf TS, van der Graaf WT, Tappero JW, Asiedu K. *Mycobacterium ulcerans* infection. *Lancet* 1999; **354**: 1013–18.
- Amofah GK, Sagoe-Moses C, Adjei-Acquah C, Frimpong EH. Epidemiology of Buruli ulcer in Amansie West district, Ghana. *Trans R Soc Trop Med Hyg* 1993; **87**: 644–45.
- Stienstra Y, van der Graaf WTA, Asamoah K, Van Der Werf TS. Beliefs and attitudes towards Buruli ulcer in Ghana. *Am J Trop Med Hyg* (in press).
- Guédénon A, Zinsou C, Josse R, et al. Traditional treatment of Buruli ulcer in Benin. *Arch Dermatol* 1995; **131**: 741–42.

Mathematical significance

Sir—The concept of mathematical significance is a good one, but I have frequently thought that when dealing with biological systems, to ignore calculations that approach significance is to lose the possibilities of a half-open door, since things like the background genome, disease, or stress might just flip the physiology into a new pathway.

Discussing this with friends labels me as a lunatic or worse but too much rigidity does disturb my naïvety.

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Private health in India

Sir—Mukund Uplekar and colleagues (Sept 15, p 912)¹ touch on the important issue of private practitioners in tuberculosis control, although the title of his report could well have read “Private practitioners and public health: weak links”.

Health care outside the public sector in India is provided by people ranging from untrained quacks to highly accomplished, trained professionals. Under Indian laws, those trained in alternative and indigenous systems of medicine such as ayurveda, unani, and homoeopathy are allowed to practise their system of medicine. Unfortunately, they frequently also have an extensive unqualified practice of allopathic medicine, with disastrous consequences.

A similar practice is also done by people whose only experience may have been to work as a dresser or pharmacist for a doctor for several months. Others in practice include nursing orderlies, operation theatre technicians, and so on, who have been employed at large hospitals.

This problem is further compounded by the prevalence of a dispensing practice wherein written prescriptions are not provided. The rationale for this practice is to avoid revealing the secret of cures. Patients’ pressure for rapid results leads to widespread dispensing of steroids since they produce an early sense of wellbeing.

Strict laws to prevent sale of all but over-the-counter drugs exist. Yet the reality is that almost any drug, including opioids, steroids and antibiotics are freely available for sale without a prescription.

Such practitioners and practices are especially common in slums and rural areas. These are the very regions at which most public-health programmes are targeted. Difficulties such as these

contribute substantially to the failure of India’s public-health programmes. They also lead to difficulties such as drug resistance. Stricter enforcement of existing laws would, probably, greatly improve health care in India.

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- Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. *Lancet* 2001; **358**: 912–16.

Medical waste

Sir—In her Jan 5 news item,¹ Karen Birchard reports on the so-called problem of medical waste. I think her report deserves comment.

An unnamed WHO source is quoted as saying that health-care waste is a reservoir of potentially harmful micro-organisms and that there are other potential infectious risks. Birchard quotes her source as saying these risks have been poorly studied.

Potential infection risks are ubiquitous, including regular household waste or a spoonful of soil from London’s Hyde Park. The absence of data associating medical waste to diseases is rather reassuring.

Furthermore, the report links medical wastes with known industrial chemical hazards such as organophosphates and the Love Canal incident in New York, USA. This association is utterly irrelevant, needlessly alarmist, and perpetuates the misconception that medical waste is in the same category as chemical wastes. Medical wastes are hazardous to our sensibilities, but probably not to our health.

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- Birchard K. Out of sight, out of mind . . . the medical waste problem. *Lancet* 2002; **359**: 56.

DEPARTMENT OF ERROR

Cardioprotection by nicorandil—In this Talking point of April 13, the fourth sentence should have read: “After a mean of 1.6 years, 13% of the patients on nicorandil and 16% on placebo had died of coronary heart disease or had had a non-fatal myocardial infarction or been admitted to hospital for cardiac chest pain.”

Hepatocyte transplantation as a treatment for glycogen storage disease type 1a—In this Research letter by Maurizio Muraca and colleagues (Jan 26, p 317), the third sentence of the fourth paragraph should have read “Purified hepatocytes were suspended in Ringer lactate adjusted to pH 7.4 at a concentration of 1.5 million cells per mL.”