

# Letters

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## New consultant contract marks huge step forward

EDITOR—You report that your 22 respondents were unanimous in their condemnation of the proposed new consultant contract.<sup>1</sup> As the regional roadshows roll out and the detail is explained, views are changing.

We have succeeded in securing a contract that gives consultants a substantial pay rise, a time limited contract, recognition of emergency work, payment for being on-call, extra payments for working beyond 40 hours per week, protected time for teaching, research, audit and continuing professional development, and a major boost to their pensionable salary. There is a lot at stake here. I make no apologies for trying to persuade my colleagues that they should accept it.

Respondents complain of excessive management control. Consultants asked us to deliver a more time limited contract. If your hours are defined and limited, it is inevitable that trust managers will want to be sure that they are getting what they are paying for. It will be in the best interests of the vast majority of consultants to have a defined job plan because then trusts will have to start paying for all the extra work currently donated to the NHS by the consultant body and reducing our hours.

### Advice to authors

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Responses should be under 400 words and relate to articles published in the preceding month. They should include  $\leq 5$  references, in the Vancouver style, including one to the BMJ article to which they relate. We welcome illustrations.

Please supply each author's current appointment and full address, and a phone or fax number or email address for the corresponding author. We ask authors to declare any competing interest. Please send a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected.

Letters will be edited and may be shortened.

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The prime minister and the chancellor are making great play that further investment in the public services must be coupled with reform. For Health Secretary Alan Milburn that translates to greater control for trust managers over how they deploy consultants, but the new contract does not give them any powers they do not already have. Retaining the old contract is no proof against managerial zeal. A properly defined contract and job plan will be. We will provide support to consultants negotiating their job plans.

There is complaint that consultants are not being paid at premium rates for working at nights and weekends. Currently most of us are not paid even at plain time rates. We are not paid at all. We have tried to build a contract that is fair to all specialties and allows people to change their working patterns without sacrificing extra payments and incentives. That means putting the maximum possible into the basic contract.

It is claimed that the new contract is not family friendly. This poses a genuine difficulty as patients' illness is inherently unpredictable, we have long waiting lists, and it is unsatisfactory that so many patients mark time over the weekends because test results cannot be obtained or treatment regimens started.

In principle an evening clinic is no more family unfriendly than an evening ward round or an emergency operating session. To meet genuine patient need and legitimate expectation, we must have sufficient consultants to share the unsocial work more equitably and achieve a reasonable balance between life and work.

If an evening session is agreed well in advance and is not too frequent, it may well suit many consultants to have free time during the day for other commitments. The contract also gives scope for annualised hours, which will help those consultants who want to avoid working in school holidays.

Currently many part time consultants are getting the worst of both worlds, reduced pay but the same level of on-call commitment and a huge amount of unpaid work. The new contract, by defining their commitments and recognising their emergency work, should make life much more manageable.

There are some elements still to be resolved but the health departments have made it abundantly clear that they have learnt lessons from the juniors' negotiations.

Reopening the fundamentals of what has been negotiated so far is not possible. It does not need to be. It is a good contract.

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<sup>1</sup> Davies S. Summary of responses. *BMJ* 2002;325:100-2. (13 July.)

## Different sex ratios at birth in Europe and North America



ARMEN KACHATURIAN/PHOTONICA

### Does it matter?

EDITOR—Grech et al seem to confuse statistical significance with practical significance.<sup>1</sup> They found highly significant differences in sex ratios among the regions they studied not because of large differences in the sex ratios but because of their large sample sizes. In any case, the use of significance testing in this context is questionable: the purpose of significance testing is to make inferences about a population from a sample, and here whole populations are being studied. What is the population about which Grech et al are trying to make inferences?

In all regions that Grech et al studied I would expect 51 boys out of every 100 live births. Do differences in sex ratio at the third decimal place and beyond really have any practical significance?

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### Latitude has important role

**EDITOR**—In their ecological study of 27 countries Grech et al reported a higher male to female ratio at birth for southern Europe than for central and Nordic Europe.<sup>1</sup> A reversed latitudinal relation emerged for North America, with Mexico and the United States yielding lower sex ratios than any European country; Canada's sex ratio (although not stated) was somewhat higher. The authors were unable to explain this cross continental pattern reversal and concluded that a temperature related (or latitudinal) effect on sex ratios is unsupported. Here we show that cross continental differences are likely to be artefacts and that there is a latitudinal effect on sex ratios.

Firstly, the study periods differ noticeably: whereas European data are for 1950-99, North American data are for 1958-97. Sex ratios peaked internationally after the second world war,<sup>2</sup> and different onsets of study periods may thus account for observed cross continental differences in sex ratios.

Secondly, Canada, the United States, and Mexico are too large for ecological analysis. Their combined area equals 4.8 times the combined area of the 24 European countries investigated. Noticeable differences in sex ratios within countries have been reported for Canada<sup>3</sup> and may well extend to the United States and Mexico.

Thirdly, the authors obscured the relation between latitude and sex ratio by aggregating the 24 European countries' sex ratios into three latitude bands. We reanalysed only the European data presented, since the reported North American sex ratios were not suitable (see above). Regressing the latitude of the countries' capital city on their sex ratio yielded 22% variance in sex ratios explained by latitude ( $P=0.021$ ). Subsequent entry of a squared latitude term into the regression model explained an increase of a further 27.7% variance in sex ratios ( $P=0.003$ ). The regression equation is sex ratio = 0.542 - 0.001064 \* latitude + 0.000009982 \* latitude squared.

Within Europe the lowest sex ratios are found in moderate latitudes, where the amplitudes of seasonal change in climate are most pronounced. In contrast, higher sex ratios are found in both Nordic and southern Europe, where less ambient seasonality is experienced. Our finding of a curvilinear relation of latitude and sex ratio is consistent with an effect related to photo-period, as has been put forward for numerous other observations, such as seasonality in the incidence of suicide<sup>4</sup> and the ratio of the length of the index finger to that of the ring finger.<sup>5</sup>

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### Maternal cytomegalovirus seropositivity affects sex determination

**EDITOR**—Grech et al report that significantly more male than female infants were born in southern latitudes in Europe, with the reverse finding in North America.<sup>1</sup> The reasons for this are unexplained. We have made an incidental finding that maternal cytomegalovirus seropositivity is associated with an increased proportion of female infants.

We pooled data from two studies from which the prevalence of cytomegalovirus infection in women of childbearing age in Northern Ireland could be calculated. The first study related to the prevalence of viral infections in infancy.<sup>2</sup> Cord blood was collected at birth for 236 consecutive mothers and analysed for cytomegalovirus IgG by standard immunofluorescence. The cord samples (analysed as described) from the second study were taken as part of a study of fetal loss associated with parvovirus B19 infection.<sup>3</sup>

In the first study 96 (41%) samples of cord serum were positive for cytomegalovirus. Altogether, 123 male infants and 113 female infants were delivered to this group of women. The sex ratio (male:female) was 1.08:1. A relation between cytomegalovirus seropositivity in cord blood and female sex was noted (odds ratio 1.9, confidence interval 1.12 to 3.21,  $P=0.017$ ). In the second study 625 consecutive samples were tested; 268 (43%) were positive for cytomegalovirus. There were 311 male infants and 314 female infants (sex ratio (male:female) 0.99:1). Cytomegalovirus seropositivity was again associated with female sex (odds ratio 1.46, 1.06 to 2.00,  $P=0.02$ ). Pooling the data from both studies gave a cohort of 861 with a male:female ratio of 1.02:1; 364 (42.3%) cord blood samples were positive for cytomegalovirus.

A highly significant relation between cytomegalovirus seropositivity in cord blood and female sex was obtained, with an odds ratio of 1.6 (1.19 to 2.06,  $P=0.001$ ). Maternal cytomegalovirus seropositivity most probably occurs before pregnancy, as seroconversion rates during pregnancy are low. There is an association between cytomegalovirus seropositivity and unmarried status and social deprivation.

The cervix is thought to harbour latent cytomegalovirus, and cytomegalovirus shedding has been shown in vaginal secretions.<sup>4</sup> Cytomegalovirus may influence sex determination by effects on the quantity and quality of cervical mucus (for example, facilitating penetration of sperm carrying the X chromosome or blocking penetration of sperm carrying the Y chromosome), sperm

motility, success of implantation, and selective male fetal loss.

Any attempt to explain a change in the sex ratio and variation among different racial groups should consider the possible influence of the prevalence of cytomegalovirus infection.<sup>5</sup>

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### Consumer demand for caesarean sections in Brazil

#### Demand should be assessed rather than inferred

**EDITOR**—Several recent papers present evidence that in Brazil consumer demand for caesarean sections is much lower than previously assumed.<sup>1,2</sup> Langer and Villar<sup>3</sup> state that the results reported by Béhague et al contradict these findings.<sup>4</sup> We are surprised by this assertion.

Despite using the term consumer demand in their title, Béhague et al do not present an estimate of the demand for caesarean sections in the population they studied—mothers giving birth in 1993 in a medium sized city in southern Brazil. The only statistic that relates to demand is the proportion of a subsample of mothers (32/80) who stated that when they went to the hospital they expected to deliver by caesarean section. But the type of delivery that a woman expects may not be the type of birth she would prefer, especially in the private sector, where most caesareans are scheduled.

Also puzzling is Béhague et al's failure to distinguish their sample by sector of care. Studies in Brazil and elsewhere have shown dramatic differences in caesarean section rates depending on whether the woman

delivered in the public sector (rate of 25-30%) or private sector (rate of 70%).<sup>5</sup>

Our most striking finding was that despite these large differences in rates there were no significant differences in women's preference for vaginal delivery, which was about 80% in both sectors.<sup>2</sup> Although the remainder who prefer caesarean section are by no means the majority, we commend Béhague et al for giving voice to them. Notably absent from their discussion, however, is tubal ligation—one of the primary reasons why women, especially poor women, actively seek to deliver by caesarean section in Brazil.

Among most of the approximately 3000 women in the new studies who stated their preference for vaginal delivery, the most frequently expressed reason from both rich and poor women was that vaginal delivery affords a faster recovery (followed by "it's more natural").<sup>1, 2</sup> A faster recovery is important for poor women, who know that they would have little support while recovering from a caesarean section.

Perhaps the most troubling aspect of the analysis by Béhague et al is that, lacking a direct assessment of demand for caesarean delivery and information on how and when the decision to operate was taken, they seem to infer demand from differentials in caesarean rates. Recent research has shown that such differentials may be misleading.<sup>1, 2, 5</sup>

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### Demand is affected by mothers' perception of good health care

EDITOR—Béhague et al highlighted mothers' preferences for caesarean section on the basis of their perception of poor quality of care for vaginal deliveries.<sup>1</sup> Data from two birth cohorts born 15 years apart (1978-9 and 1994) in Ribeirão Preto, one of the richest areas in Brazil, showed that the caesarean section rate increased from 30.3% to 50.8%.<sup>2</sup> Over the same period the rate of low birth weight increased from 7.2% to 10.6% and of preterm births from 7.6% to 13.6%.<sup>3</sup> Thus maternal beliefs that caesarean section is good quality care may not be supported by evidence.

We were concerned that Béhague et al did not fully explore the influence of doctors' convenience on mothers' preferences.<sup>1</sup> In our studies caesarean section was more commonly performed in daylight hours and evenings among women attended by the same doctor during prenatal care and

delivery and who had more antenatal visits than others did.<sup>2</sup>

Similar results were found in 1997 in São Luís, in one of the poorest regions in Brazil.<sup>4</sup> The caesarean section rate was 33.7%, and the risk was higher for primiparous, married, and better educated mothers; those attended by the same doctor during prenatal care and delivery; deliveries done in private hospitals, daylight hours, or evenings; and mothers who had adequate prenatal care.

These findings are consistent with a recent report showing that, contrary to popular belief, nearly all women wanted a vaginal delivery despite the higher caesarean section rate among women in the private sector (72%) than in the public one (31%).<sup>5</sup> The differences in births by caesarean section between the two groups were due to higher rates of unwanted caesarean section among private patients rather than to differences in preferences about type of delivery.

We believe that by focusing on maternal preferences Béhague et al are dealing with the effect rather than the cause of the problem. Maternal preferences regarding delivery by caesarean section may be related to the mother's perception of doctors' behaviour during the antenatal and delivery period. Scheduling caesarean sections is how obstetricians accommodate their working and leisure time. Although caesarean sections are commoner among private patients, the trend to caesarean sections may have a knock-on effect on the socially unprivileged women seeking what they perceive to be good health care during delivery.

Efforts should be made to change doctors' behaviour and the healthcare context in which they operate. We fear that education alone, regardless of target population, will be ineffective.

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### Episiotomy rates may change after evidence based intervention

EDITOR—Althabe et al report on caesarean section rates among women in Brazil.<sup>1</sup> In 1984 a retrospective study in one maternity hospital in Dublin showed an episiotomy rate of 54% in primigravida women having normal deliveries. The practice of 20 experienced labour ward midwives was found to differ significantly ( $\chi^2=72.4$ ,  $df=38$ ,  $P<0.001$ ), with episiotomy rates varying from 6% to 84%.<sup>2</sup>

Full results of the study, with accompanying literature showing that the only indication for episiotomy in a normal delivery is fetal distress, were presented to staff both orally and in written form. Much discussion ensued, and many of the midwives requested their own confidential data in order to learn their position in the table ranking midwives according to the rate of "no suture."

Six months later a follow up study was carried out over a further six months. The episiotomy rates had decreased from 54% to 34% in primigravidas, from 25% to 7% in the para 1 group, and from 5% to 2% in the para 2 or greater group. There was no increase in second degree lacerations (defined as those requiring suturing) in the primigravida or para 1 group, and there was a significant decrease in second degree lacerations in the para 2 or greater group, from 18% to 11%.<sup>2</sup>

Providing evidence relating to practitioners' performance compared with that of their peers, together with research based rationales for changing, has led to major changes in midwives' practice in this hospital.

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### Cost of nitric oxide is exorbitant

EDITOR—Evidence based medicine is the gold standard for practice, and pharmaceutical companies appreciate the power of evidence based medicine. A positive result in a randomised controlled study produces pressure to use a specific agent regardless of cost.

High costs seem to predominate in intensive care. Over the past 10 years several expensive treatments have been launched and subsequently failed. Inhaled nitric oxide (iNO) was the reverse, being initially inexpensive, and is of proved efficacy in reducing morbidity.

Recently, two randomised controlled studies have shown improved oxygenation<sup>1</sup> and a reduction in the need for extracorporeal membrane oxygenation with the use of inhaled nitric oxide in neonates with persist-

ent pulmonary hypertension and hypoxic respiratory failure.<sup>2,3</sup> As a result, the use of inhaled nitric oxide was approved by the US Food and Drug Administration in 1999 and the European Medical Equipment Agency in 2001. As a consequence of these reports and the need to practise evidence based medicine the use of inhaled nitric oxide in persistent pulmonary hypertension is now almost mandatory.<sup>1</sup>

In the early 1990s a patent was granted in the United States for the use of inhaled nitric oxide in persistent pulmonary hypertension. This was then sold to industry. Currently INOTherapeutics has the franchise and marketing authorisation for Europe and the United States.

When medical grade inhaled nitric oxide first became available in the United Kingdom the cost was minimal (\$1.99/h (£1.28/h)).<sup>5</sup> Currently, British Oxygen Company supplies us with inhaled nitric oxide. Once the brand is established, however, BOC will have to stop providing us with inhaled nitric oxide. The licensed pharmaceutical grade product will be available only from INOTherapeutics. Each cylinder will have a gas meter attached, and we will be charged the American predicted rate of \$125/h (£80/h). This could equate to a cost of up to £102/h (including value added tax) per patient, with a ceiling of 96 h per patient (£10 000 per patient maximally). INOTherapeutics have now quoted a sliding scale of costs depending upon national usage and indicated that above a certain threshold of usage the cost could come down to about £26/h. This is still a 20 fold increase.

Our use of inhaled nitric oxide during 2001-02 amounted to 7200 h in 164 children, at a cost of £31 000. Should the proposed changes in price be implemented we would be looking at a possible projected cost of around £600 000/year for inhaled nitric oxide. As a result of evidence based studies we are obliged to prescribe inhaled nitric oxide. Is this enormous change in cost an unforeseen consequence of level 1 evidence?

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## Psychological stress and cardiovascular disease

### Rose questionnaire is not what it seems

EDITOR—Macleod et al's paper on stress and cardiovascular disease tells us two things.<sup>1</sup> Firstly, the Rose angina questionnaire rather inconveniently does not just measure angina in the sense understood by cardiologists.<sup>2</sup> Instead it measures chest pain as understood by everyone else.

Most cases of chest pain in the general population are not due to heart disease, and even in middle aged Scottish men the prevalence of coronary heart disease is low, so the positive predictive value of the Rose questionnaire will be poor.<sup>3</sup> The relation between stress and chest pain that the questionnaire measures is only a "bias" in as much as it does not fit into the view of cardiovascular epidemiologists. The effect is real (and has important clinical implications to cardiologists) in that the Rose questionnaire is a superb measure of anxiety in young people but will mislead those who interpret its results too credulously.<sup>3</sup> The effect probably accounts for anomalies such as the higher rates of angina in women despite their lower rates of coronary heart disease.<sup>4</sup>

The second thing the paper tells us is that a weak measure of stress is a poor predictor of cardiovascular events many years later. Contrary to the statement in "This week in the BMJ," the findings of the study do not do much to "cast doubt over the associations between psychosocial measures and disease outcomes."

Many studies indicate a higher mortality for people with depression and other psychiatric disorders.<sup>5</sup> Though there may be important residual confounders (or explanatory pathways) to explain these effects, they still need explaining.

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### Paper doesn't clarify things

EDITOR—The notion that responses to four questions provide an accurate measurement of stress levels is as naive as the counterintuitive conclusion reached by Macleod et al.<sup>1</sup> A wealth of literature confirms a causative or aggravating contribution of anxiety, depression, sudden emotional shock, and other

stressors to coronary morbidity and mortality, sudden death, and congestive failure.<sup>2</sup> Two articles in one issue of *Psychosomatic Medicine* were devoted to discussing novel pathways by which such stress related effects may be mediated.<sup>3,4</sup>

Having worked in stress research for over 50 years, I would question the value and alleged "wide" use of the four question Reeder stress inventory. The fact that this inventory has not been much used may explain why it is no longer in vogue. In one study (not cited), this assessment was not consistent with validated instruments such as two anxiety inventories.<sup>5</sup>

In addition, high scores with responses to these questions may reflect increased neuroticism, which would essentially exclude men with type A behaviour, which is as significant a risk factor for coronary heart disease as cholesterol concentration, hypertension, and cigarette smoking.

There is little doubt that reporting bias can influence putative associations between emotions and health, but this paper hardly negates numerous studies showing a relation between "stress" and coronary events and is not likely to shed light on this controversial subject.

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### Authors' reply

EDITOR—Hotopf seems to agree that artefactual associations between self reported psychosocial exposures and self reported symptoms of angina are almost inevitable. However, he seems to suggest that this point is self evident and barely worth making. We disagree. It is hardly a naive minority who seem to give credence to these associations. Indeed, the *BMJ* and the *Lancet* regularly report such associations as evidence of substantive effects.<sup>1,2</sup> Our point is that bias may influence all effect estimates derived in this way, as becomes apparent when subjective outcomes are compared with objective ones. The accompanying table presents our results alongside those from the Whitehall II study on effects of job control to illustrate this.<sup>3</sup>

We agree that the Rose questionnaire is not a precise diagnostic instrument. It is a widely used epidemiological survey tool. And clearly it has some validity: coronary mortality was almost trebled in subjects who had positive results on the questionnaire.

Associations between stress and job control and subjective and objective outcomes in West of Scotland collaborative study and Whitehall II study

Outcome type	Effects in collaborative study (95% CI)	Effects in Whitehall II study (95% CI) <sup>3</sup>
Fully subjective <sup>*</sup>	High exposure 2.66 (1.61 to 4.41) Medium exposure 1.37 (0.91 to 2.08) Low exposure 1.00	High exposure 2.02 (1.22 to 2.34) Medium exposure 1.44 (0.86 to 2.39) Low exposure 1.00
Fully objective <sup>†</sup>	High exposure 0.67 (0.36 to 1.26) Medium exposure 1.03 (0.71 to 1.49) Low exposure 1.00	High exposure 1.17 (0.8 to 1.8) Medium exposure 1.16 (0.8 to 1.7) Low exposure 1.00 <sup>‡</sup>

<sup>\*</sup> Rose angina in both studies. <sup>†</sup>Electrocardiographic abnormalities (Minnesota coding system) in both studies. All estimates adjusted for age, social position, and cardiovascular risk factors other than <sup>‡</sup> (only unadjusted estimates were reported in the paper).

We agree that the Reeder inventory can be criticised on several grounds but reiterate that our points about problems interpreting observational evidence in psychosocial epidemiology are independent of the status of the instrument we used to illustrate these issues. Furthermore, by the conventions of psychometric validation this instrument seems as robust as many of its more modern and popular counterparts.<sup>4</sup>

Relations between depression (or other psychosocial factors) and coronary mortality are certainly unlikely to be the product of reporting bias. However, they may well be the product of confounding (for example, by socioeconomic factors or disease severity), as suggested by results of the only large experimental study so far to address this issue.<sup>5</sup>

Rosch states that a wealth of literature confirms a causal relation between psychological exposures and heart disease and cites one of his own editorials (devoid of references) in support of this statement. Despite Rosch's assertions, however, the American Heart Association does not currently accept "type A behaviour," or any other psychosocial exposure, as an established coronary risk factor. Unlike smoking, hypertension, and cholesterol concentration, type A behaviour basically stopped being a coronary risk factor when diagnosed heart disease stopped being more common among the middle class. This perhaps explains why contemporary studies prefer to focus on "hostility"—the component of type A behaviour most reliably associated with disadvantage and hence now with heart disease.<sup>6</sup>

We suggest that more light than heat could be shed on the important questions that psychosocial epidemiology seeks to explore if researchers in the field were as critical of evidence that ostensibly supports their cherished theories as that which challenges them.

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### Off label prescribing in children



MIKE BLUESTONE/ISPL

EDITOR—We read with interest the articles regarding off licence prescribing in children and agree that prescribing in children must improve.<sup>1-4</sup> It will be difficult to change the prescribing habits of doctors treating children. If only licensed drugs were prescribed, it would greatly restrict the pharmaceutical choice for that age group. We found it of particular interest that the formulary approved by the Royal College of Paediatrics and Child Health (*Medicines for Children*) states that doctors who prescribe for a child should choose the medicine that offers the best prospect for the child, with due regard to cost and that in general it is not necessary to obtain the explicit consent of parents, carers, or child patients to prescribe or administer licensed medicines for unlicensed applications or unlicensed medicines.<sup>5</sup>

In stark contrast to this the *Small Animal Formulary* (4th ed) approved by the British Small Animal Veterinary Association states that when using non-authorized products informed written consent should be obtained from clients, to reduce any liability that may fall on veterinary surgeons if any problems arise subsequently, and to protect them against claims of negligence.<sup>6</sup>

Does this mean that doctors giving advice on prescribing for children are less fearful of litigation than veterinary surgeons, or that we are more concerned about the

welfare of animals than children? If paediatricians needed to have written consent for every unlicensed drug prescribed, this would accentuate the already copious amount of paperwork and so further pressurise busy working days.

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### It is easy to be cynical

EDITOR—With reference to the editorial by Banner, the proportion of medicines prescribed for children that are for an "off label" indication should come as no surprise.<sup>1</sup> A high prevalence of off label prescribing in paediatrics has been shown for many years,<sup>2-4</sup> and the only nation to make any serious attempt to address the issue has been the United States.

Despite the encouragement of patent extensions, however, the data presented in support of paediatric labelling has been of a poor standard, and mostly limited to children over the age of 2 years. Yet differences in the disposition, efficacy, and safety of medicines would be expected to be most marked in the age group under 2 years. This has not stopped pharmaceutical companies from reaping the benefits of the patent extensions. A suspension of the "paediatric rule" by the Food and Drug Administration may represent an acknowledgement of its failure.

The realities are that children have little economic or political power, and the regulatory process is fuelled by money and influence. Children have little to benefit from the major advances in the treatment of impotence, obesity, and baldness that currently obsess big pharmaceutical companies. Their pocket money would not pay for them anyway. They don't vote, so there is little incentive for elected governments to address the issue seriously.

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### Children's human rights are violated

EDITOR—Not only in the United States but also in the European Union drug regulations fail a significant proportion of the population, namely children.<sup>1</sup> Companies develop a product in such a way as to get earliest returns on their research investment. Where a paediatric indication is not envisaged for a new drug, studies in this population are not mandated. Thus, in contrast to adults, children are unable to benefit from therapeutic agents that have been shown to be adequately safe and effective for their own requirements. This violates their human rights.<sup>2</sup>

The European Union directives allow a doctor to prescribe outside the approved indications on his or her own responsibility.<sup>3</sup> This gives children access to important medicines that would otherwise be denied them, but puts an additional legal and ethical burden on the prescribing doctor. In the absence of controlled and validated paediatric studies, doctors have to make their own professional assessment of the available data, possibly anecdotal or theoretical in nature. Use by other specialists or inclusion in a hospital formulary gives only prima facie evidence of satisfying the legal standard of care. In addition, it is even more difficult than usual to determine the level of disclosure of relevant information that would ensure valid (informed) consent. Although the fact that a product does not have regulatory approval for the proposed use probably constitutes a significant risk that would affect the judgement of a reasonable patient,<sup>4</sup> it is less certain how many patients or their parents would fully understand the implications of this information.

Until it gains regulatory approval for a given indication or patient population, a drug is technically an experimental entity. A doctor must decide whether it is ethically more acceptable to withhold such a product or to treat the patient essentially as a subject in an uncontrolled clinical trial. The use of experimental treatment in children clearly should be subject to a higher level of ethical review.

The Food and Drug Administration has been trying to remedy this situation since 1994, but the European Union has only recently issued a consultative document.<sup>1,5</sup> Doctors and their paediatric patients have existed in this regulatory vacuum for too long. It is imperative that the legislators expedite the legal framework for mandatory paediatric studies, for both new and generic compounds. Until then, we must hope that the increasingly global nature of pharmaceutical development will result in studies from other regulatory areas providing the necessary reassurance that children are receiving adequately researched drug treatment.

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### Why does NICE not recommend laparoscopic herniorrhaphy?



### Patients must consider potential serious complications

EDITOR—The juxtaposition of Motson's article and the review of marrow transplantation for breast cancer is intriguing.<sup>1,2</sup> Both articles refer to new technologies, strongly supported by interest groups. In the case of supra-lethal chemotherapy with marrow transplant rescue the evidence has now been discredited. For the repair of groin hernias the case is not clear cut. Certainly, patients should be informed of the laparoscopic option, with its short term advantages of reduced postoperative pain and time off work.

There is a downside, however. The review article that Motson quotes includes data on the small risk of potentially serious complications, which were more frequent with the laparoscopic operations in a ratio of 15:4.<sup>3</sup> Informed consent must surely include mention of the possibly devastating intra-abdominal injuries, even though the incidence is only of the order of 2.5 per 1000 for laparoscopic compared with 0.25 per 1000 for open hernia repair. Shouldn't the patient then decide whether the advantages of the laparoscopic operation offset this risk?

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### Article implies that vested interest and prejudice operate

EDITOR—Motson disagrees with the recommendation that laparoscopic herniorrhaphy has a limited role.<sup>1</sup> But he managed to write the whole of his article without mentioning the fact that the Lichtenstein open mesh repair needs only a local anaesthetic.<sup>2</sup> Instead, he makes the odd comment that "if the patient was unfit for general surgery then they would be limited to open operation under general anaesthetic." Once you remove the need for a general anaesthetic open repair is far more cost effective.

Even more alarmingly, however, he does not include the use of local anaesthetic in his section on telling patients the options. Since local anaesthesia has many advantages this omission is surprising. His final statement, unsupported by any evidence other than a personal communication from another enthusiast for laparoscopy, implies that well informed patients will request laparoscopic repair. I could equally well state that well informed patients wish to avoid the expense and morbidity of general anaesthesia. Both statements reflect only vested interest and prejudice.

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### French institute and NICE arrived at similar conclusions

EDITOR—Motson comments on the National Institute for Clinical Excellence's conclusion on hernia repair.<sup>1</sup> In France a similar institute—the Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES)—made similar recommendations in 2000. The group, which included 10 surgeons, concluded that the laparoscopic approach is feasible, is associated with less postoperative pain and earlier return to work, but leads to specific, potentially severe complications; these findings are in accordance with those of the main British trial.<sup>2</sup>

I agree with both panels' conclusions. They were based on an objective assessment of papers and cannot be suspected of having partisan views. The results of four meta-analyses, three systematic reviews, and 100 randomised trials (list on request) suggest that mesh repair is probably the gold standard and that the differences between laparoscopy and open mesh repair are less than those between laparoscopy and non-mesh repair. Motson wrote that contralateral hernia can be identified and repaired, which implies that a transabdominal approach should be used for laparoscopy, but no trial has shown any advantage of this approach over the more logical totally extraperitoneal approach. On the other hand, whether a contralateral hernia should be systematically repaired is controversial.<sup>3</sup>

Motson also criticised the cost calculation by the National Institute for Clinical Excellence. He omitted to discuss the cost utility analysis showing that laparoscopy may be a viable alternative only when reusable equipment is used.<sup>4</sup> But is this practical when the use of disposable surgical instruments is highly recommended to avoid iatrogenic transmission of diseases?<sup>5</sup> Laparoscopic herniorrhaphy will probably remain a costly procedure.

Finally, Motson wrote that patients prefer laparoscopy. Several university surgical departments in France do not perform laparoscopic herniorrhaphy because of the lack of evidence regarding its superiority. French patients (like those in the United Kingdom) often say that they would like the laparoscopic approach, but we have no difficulty in convincing them to undergo open mesh repair. The more the surgeon is convinced about the benefits and drawbacks of laparoscopy the easier it is to convince the patient to undergo the alternative approach.

Fortunately, doctors in France have some scientific organisations to evaluate the emerging procedures objectively; their conclusions are based on the best available evidence.

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## Another way of screening for familial hypercholesterolaemia

EDITOR—We would like to suggest that there is an easier and more cost effective method of screening the population for hyperlipidaemia than that discussed in Marks et al's paper.<sup>1</sup>

The diagnosis of familial hyperlipidaemia requires a family history. In primary care one would expect patients to have a check of blood pressure at least every five years. A screen of family history might on average add 30 seconds to this consultation.

In our practice (list size 5200), using a cost of £25/h, this would produce an additional cost of £436 if the 2097 eligible patients (aged over 25 and under 55) were screened. From the 95% we have screened we found 670 patients with a family history of coronary heart disease, of whom 22 have a cholesterol concentration of >7.5 mmol/l. Using the published figure for opportunistic screening in primary care on the 670, we calculate a cost of £6927, or

£2487 per case (using the detection rate of 1 in 938), as compared to the £9072 in the paper.

By using this method we have found 16 patients who have family history, fasting cholesterol concentration >7.5 mmol/l, and low density lipoprotein >4.9 mmol/l concentration—considerably higher than the suggested incidence of 1 in 938. Genetic testing is not available to us, so we are unable to confirm that these people have familial hyperlipidaemia, although many have convincing family histories.

It would seem obvious that genetically determined conditions will occur in clusters, and therefore the incidence may vary in different areas. This needs further research to determine optimal screening protocols. However, it would seem to us that a combination of opportunistic screening in primary care and targeted testing could identify 95% of those at risk within five years, as we have done in our practice. It would also give the primary care team valuable information on its practice population so that other coronary heart disease prevention targets can be integrated.

We use a computerised screening programme, which allows us to educate patients on the reduction of all their risk factors for coronary heart disease, and have achieved considerable reductions in these. The reduction in smoking in our practice, for example, is probably enough to pay for the screening in terms of life years added. In effect, this means that detection of familial hyperlipidaemia is achieved at no extra cost.

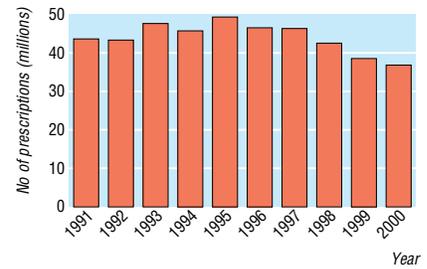
We believe that if these methods were generally adopted the plan to detect all cases of familial hyperlipidaemia in patients aged over 25 by 2010 could be achieved at a cost that could easily be justified.

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## Antibiotic prescribing rates in England are falling

EDITOR—The figure in Dobson's short article in the news roundup shows that Greek doctors prescribe the most antibiotics.<sup>1</sup> In contrast, general practitioners in England have responded to concerns about the overuse of antibiotics by reducing their antibiotic prescribing rates.<sup>2</sup> The number of antibiotic prescriptions dispensed in the community decreased by 25% between 1995 and 2000, from 49.4 to 36.9 million prescriptions (figure). A more detailed analysis of prescribing data from 210 practices in 1994-8 showed that the largest reductions in antibiotic prescribing rates were seen among children.<sup>2</sup> Large falls in these rates among children have also



Decrease in antibiotic prescribing by general practitioners in England, 1991-2000

occurred elsewhere—for example, in the United States.<sup>3</sup>

The change in prescribing practice in England predates the Department of Health's initiative (launched in 1998) to reduce community antibiotic prescribing rates ([www.claphamhealth.org.uk/Clinical/Antibiotic.html](http://www.claphamhealth.org.uk/Clinical/Antibiotic.html)). This suggests that general practitioners were already aware of the need to reduce antibiotic prescribing and of the limited effectiveness of antibiotics for many common community infections and had begun to change their prescribing practice to reflect this. The large decline seen among children may be because many of the guidelines on antibiotic prescribing are for upper respiratory tract infections and otitis media, both of which are common in children.<sup>4,5</sup>

We know less about trends in antibiotic prescribing in hospitals because these data are not collected centrally. This is paradoxical because the problem of antibiotic resistance is greatest in hospitals. This deficiency needs to be addressed if we are to monitor the impact of initiatives to reduce antibiotic prescribing in hospitals in the same way that is already possible for antibiotic prescribing in the community.

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### Rapid responses

Correspondence submitted electronically is available on our website